STUDIES TOWARD THE SYNTHESIS OF 3,6-BIS-(5-CHLORO-2-PIPERIDYL)-2,5-PIPERAZINEDIONE

by

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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September, 1979

ABSTRACT

The naturally occurring compound 3,6-bis-(5-chloro-2-piperidyl)-2,5-piperazinedione (1) is a promising new antitumor drug. The mechanisms of action of antitumor alkylating agents, particularly the nitrogen mustards and sesquiterpene lactones, suggest possible modes of antitumor activity of compound 1. A possible synthetic scheme for compound 1 is developed by consideration of methods of synthesis of piperidines, α-substituted-α,β-unsaturated esters, and β-amino alcohols.

A synthesis of α-chloro-α,β-unsaturated esters from carbonyl compounds and t-butyl α-chloro-α-trimethylsilyl acetate is developed. Oxyamination of the terminal double bond of t-butyl 2-chloro-2,6-heptadienoate occurs by epoxidation and reaction with an amine or azide ion and by osmium tetroxide catalyzed reaction with Chloramine T. The piperidine ring is formed by an internal Michael reaction of t-butyl 2-chloro-6-t-butyldimethylsilyloxy-7-tosylamino-2-heptenoate. The amino acid (1-tosyl-5-hydroxy-2-piperidyl) glycine is synthesized and found to be unstable to acidic esterification conditions.

Strategies for overcoming the problems encountered in the synthesis are discussed.

SOMMAIRE

Le composé naturel bis(chloro-5 pipéridyl-2)-3,6-piperazinedione-2,5 (1) est une nouvelle drogue aux effets prometteurs contre le cancer. Les méchanismes d'action des agents alkylants antitumeurs, particulièrement les ypérites azotées et les lactones sesquiterpènes, suggèrent des modes possibles pour l'activité du composé 1. Un schéma synthétique possible pour préparer le composé 1 est développé par considération des méthodes pour la synthèse des pipéridines, des esters α-substitués-α-éthyléniques, et des alcools β-aminés.

Une synthèse des esters α-chlorés-α-éthyléniques commençant avec les composés carbonylés et l'α-chloro-α-trimethylsilylacétate de t-butyle est developpé. L'oxyamination de la double-liaison terminale du chloro-2 heptadiène-2,6-oate de t-butyle a lieu par l'époxidation et réaction avec une amine ou l'ion azoture ou par réaction avec la chloramine-T catalysée par le tétroxyde d'osmium. L'anneau pipéridinique se forme par une réaction de Michael interne du chloro-2 t-butyldiméthylsilyloxy-6 tosylamino-7 heptèn-2 oate de t-butyle. L'amino-acide (tosyl-1 hydroxy-5 pipéridyl-2)glycine est synthetisé, mais on trouve qu'il est instable en milieu acide.

Des stratégies pour surmonter les problèmes rencontrés pendant la synthèse sont présentées.

Acknowledgements

I wish to express my gratitude to all those whose assistance made it possible for me to bring this work to a successful conclusion.

The patience and indefatigable optimism of Dr. T.H. Chan in directing this research made it possible for me to persevere. My colleagues in Room 25 provided helpful discussions and diversions. Dr. O. Mamer and Ms. J. Montgomery prepared the mass spectra. Dr. Bennett Falk provided moral support and a philosophy of thesis writing. Mr. Dennis Mullins deserves special thanks for his help in the final deposition of the thesis.

This work is dedicated to Ferrin and Hazel Moreland, my parents.

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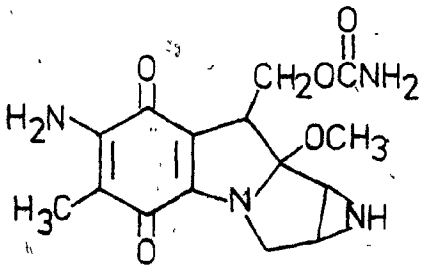
CHAPTER I

ALKYLATING AGENTS IN CANCER CHEMOTHERAPY

Chemotherapy is an established method of cancer treatment, but it is a field in which research continues in the search for new drugs and the study of their mechanisms of action. Cancer chemotherapy depends upon the selective destruction of tumor cells with minimal effect on normal cells. The primary difference between normal cells and tumor cells is rate of growth, so many antitumor drugs act by blocking those reactions which are most important in rapidly dividing cells, primarily RNA and DNA synthesis. When this is the only mechanism of specificity, normal rapidly growing cells, such as cells of the bone marrow and the lining of the gastrointestinal tract, are also susceptible to the drug. Chemotherapy is used mostly in the treatment of disseminated cancers (the hematologic cancers and metastatic tumors) which are difficult to treat by surgery or radiation. The kinetics of action of the antitumor drugs makes them most effective against a relatively small tumor cell population.[1] Most chemotherapeutic agents produce a first order kinetic cell kill; that is, a fixed percentage of cells are killed per dose of drug, not a fixed number per dose. This means that administration of the repeated doses which would be necessary to eliminate a large tumor mass might not be possible because of the toxic effects of the drug.

The main classes of anticancer drugs are the antimetabolites, alkaloids, antibiotics, hormones, and alkylating agents.[2] The antimetabolites include purine and pyrimidine antagonists which inhibit nucleotide synthesis by blocking the active sites of enzymes or, as with 6-thioguanine, by incorporation into the product DNA, making it dysfunctional.[3] Folate antagonists inhibit purine synthesis by blocking the enzyme dihydrofolate reductase. The plant alkaloids used as antitumor drugs act as mitotic inhibitors (colchicine derivatives, vincristine, and vinblastine), or by inhibition of DNA or RNA synthesis. The antitumor antibiotics generally bind non-covalently with DNA to block RNA production. However, mitomycin C forms covalent bonds and cross-links DNA strands.[4]



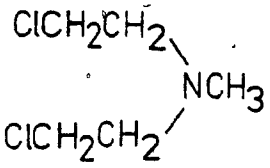
Mitomycin-C

Alkylating Agents

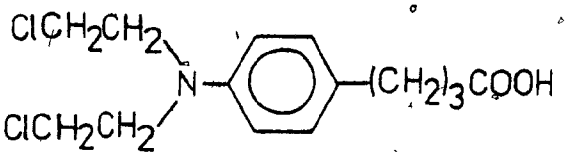
The crosslinking of DNA is also the primary mode of action of many of the alkylating agents. The alkylating agents which are in clinical use include nitrogen mustards, methanesulfonates, aziridines, and nitrosoureas.[5] (Figure 1) The compound commonly called nitrogen mustard, methyl-bis-(β-chloroethyl)amine, was first synthesized in 1935.[6] Other compounds of this class have been developed to provide increased selectivity and decreased toxicity. Cyclophosphamide, which is inactive until the ring structure is metabolized, was developed with the thought that it would be activated by phosphoramidases in tumor cells; however, activation has been found to occur in the liver.[7] The aziridines and methanesulfonates are not used clinically as much as the nitrogen mustards, though busulfan is used in the treatment of chronic myelogenous leukemia. The nitrosoureas have been developed more recently; their mechanism of action is somewhat different from the older alkylating agents. They cross the blood-brain barrier more easily and are often active against tumors resistant to other alkylating agents.

All the alkylating agents which are active as antitumor drugs have two reactive groups which can react with nucleophilic groups in the cell. The nitrogen mustards readily cyclize to form an aziridinium ion which is the active electrophilic species.[5]

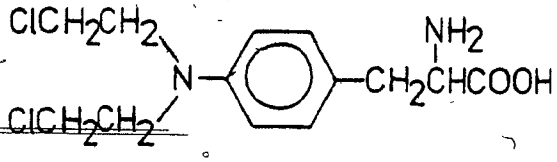
Nitrogen Mustards



Nitrogen mustard

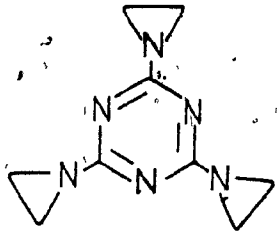


Chlorambucil

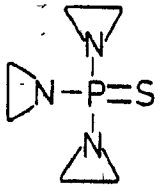


Melphalan

Aziridines

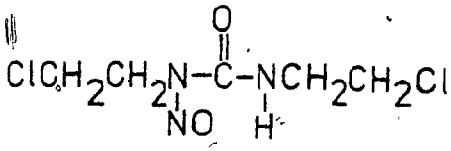


Triethylenemelanine

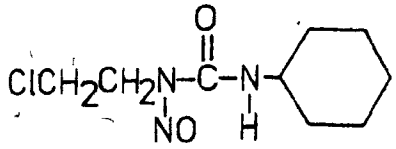


Triethylenethiophosphoramide

Nitrosoureas

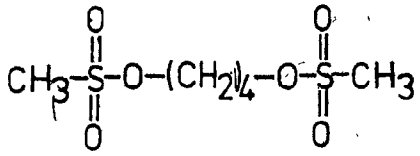


bis-chloroethyl nitrosurea
(BCNU)



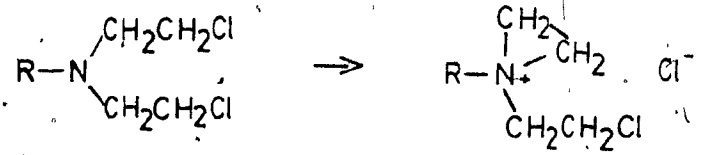
chloroethyl cyclohexyl nitrosourea
(CCNU)

Methanesulfonates

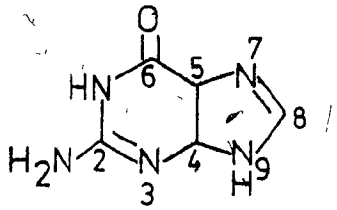


Busulfan

Figure 1. Alkylating Agents in Clinical Use.



They can react with a variety of nucleophiles in the cell including phosphate, amino, sulfhydryl, hydroxyl, carboxyl, and imidazole groups, but the most susceptible site is the 7-position of guanine.



When the two electrophilic groups of the drug react with two different guanine residues in DNA, either intrastrand or interstrand bridges are formed. Interstrand bridges prevent separation and replication of the DNA. Other cellular constituents are affected by alkylating agents, but DNA is most susceptible at low concentrations.

Since the main action of these drugs is disruption of DNA replication, cells are most sensitive when in a phase where DNA synthesis is occurring or is about to start. Cells go through several phases between mitotic divisions.[1] G_1 is a resting phase following division in which RNA and protein synthesis proceed normally, but no DNA synthesis for replication occurs, though some DNA repair takes place. At the end of G_1 a burst of RNA synthesis occurs and the cell enters G_2 where DNA synthesis stops and RNA and protein syntheses continue. During mitosis RNA and protein synthesis

also stop. Another phase, G_0, is an extended resting phase which may not be a separate phase, but a prolongation of G_1. The late G_1 and S phases are the most susceptible to alkylating agents, since damage done to DNA in other phases may be repaired before transcription occurs.

The two main problems in cancer chemotherapy are toxicity and development of resistance. Resistance of a tumor to a drug may develop through decreased permeability of the cell membrane to the drug, increased degradation of the drug within the cell, or by accelerated repair of damaged DNA.[9] This resistance is sometimes specific for the drug which has been used and sometimes extends to other compounds of the same class.

Cyclophosphamide

The problem of toxicity would be helped by a drug which would be inactive until metabolized by the tumor cell. The presence of high phosphoramidase activity in some tumors prompted the synthesis of cyclophosphamide. It was found that activation occurs in the liver rather than the tumor,[7] but cyclophosphamide still has greater selectivity toward tumor cells than most other nitrogen mustards. Its metabolism has been studied and its suggested breakdown is shown in Figure 2.[10] The acid derivative is the main metabolite and the 4-keto derivative has also been identified as a metabolite, but neither of these compounds is cytotoxic.

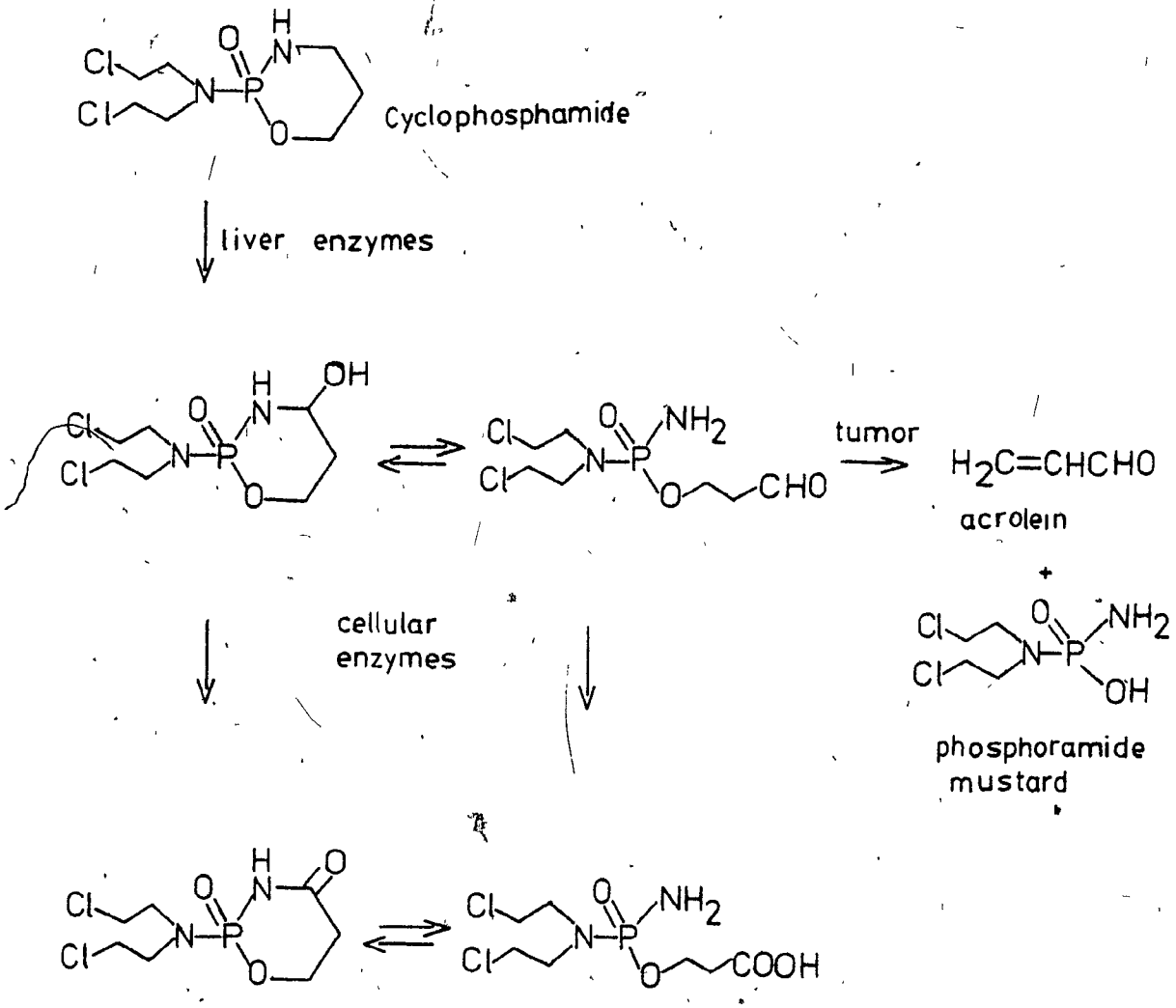
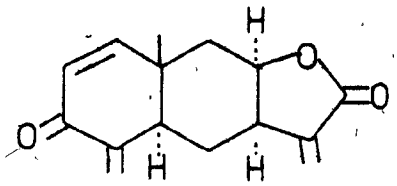


Figure 2. Metabolism of Cyclophosphamide

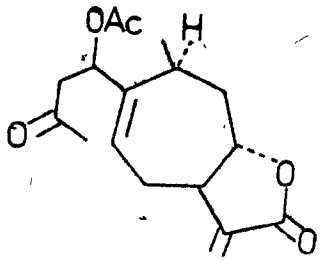
It has also been shown that acrolein and phosphoramide mustard are formed from cyclophosphamide. The assumption is, then, that after an initial oxidation in the liver to the 4-hydroxy compound, enzymes in normal cells cause further oxidation to the inactive metabolites, but in tumor cells lacking the necessary enzymes acrolein and phosphamide mustard are formed. Both these compounds are cytotoxic;[11] phosphamide mustard alkylates as a typical nitrogen mustard. Acrolein can react with nucleophiles in the cell by a Michael addition to cause alkylation.

Antitumor Sesquiterpenes

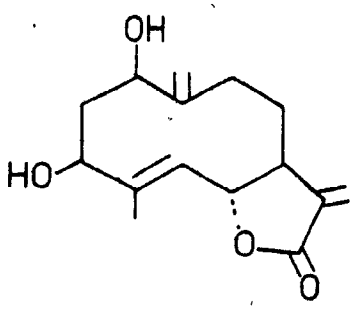
The alkylation of cellular nucleophiles by a Michael reaction has been shown to occur with a group of compounds which have antitumor activity, but are not in clinical use.[12,13] These compounds are sesquiterpenes which have an α,β-unsaturated carbonyl group present as either an α-methylene lactone or an α,β-unsaturated cyclopentenone. (Figure 3) The mechanism of cytotoxicity of the sesquiterpenes is different from that of the nitrogen mustards. They do not react with DNA, guanine, or adenine, but they do inhibit DNA synthesis.[12] The inhibition of several enzymes (DNA polymerase,[12] phosphofructokinase,[14] and glycogen synthetase[15]) by members of this group has been demonstrated. These enzymes all have sulfhydryl groups which are essential to their activity, and in the case of phosphofructokinase



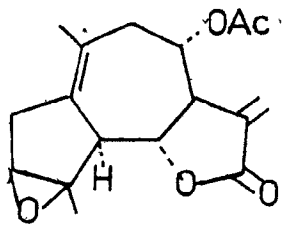
Encelin



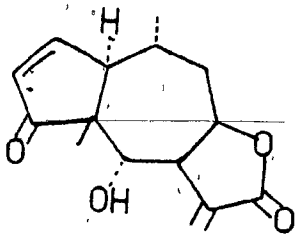
Xanthinin



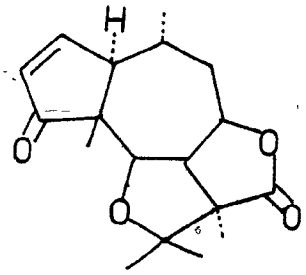
Ridentin



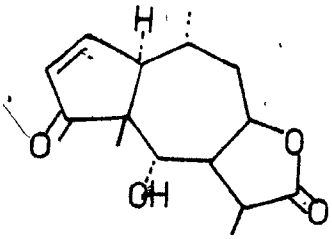
Arteglasin-A



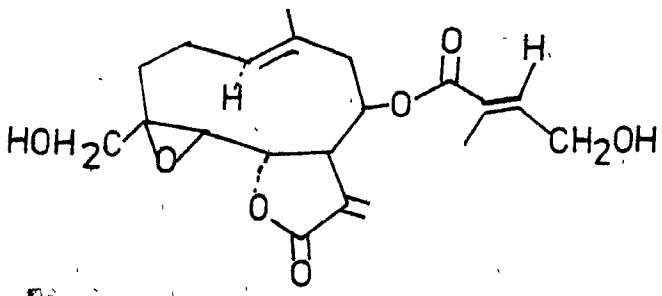
Helenalin



Tenalin



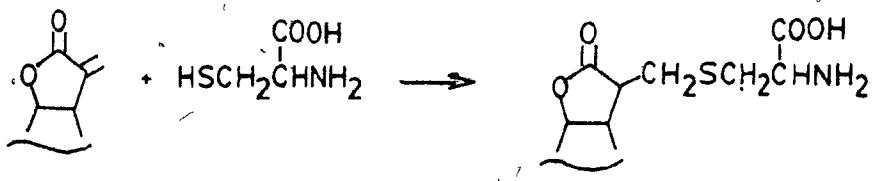
Plenolin



Eupahyssopin

Figure 3. Sesquiterpene Antitumor Agents.

it was shown that inhibition was related to reaction of the sesquiterpene with the -SH groups. The drugs have been shown to react by a Michael reaction with cysteine and reduced glutathione.[12,13]

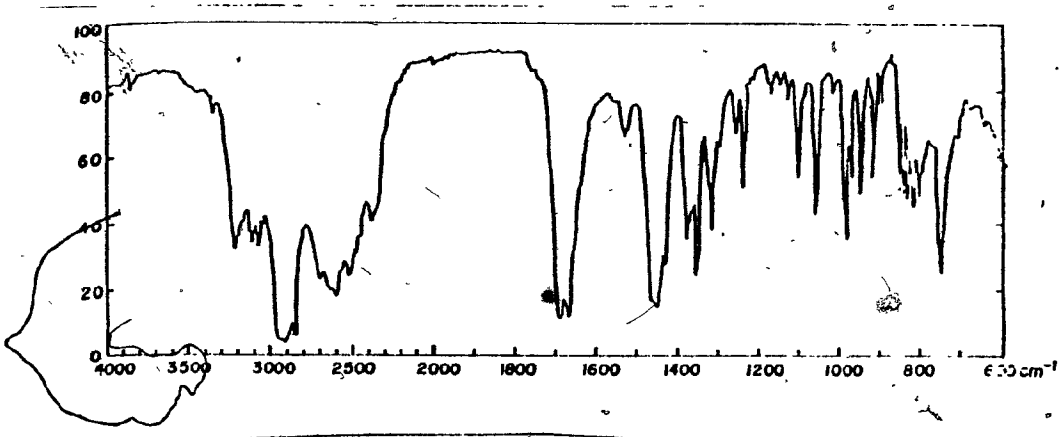


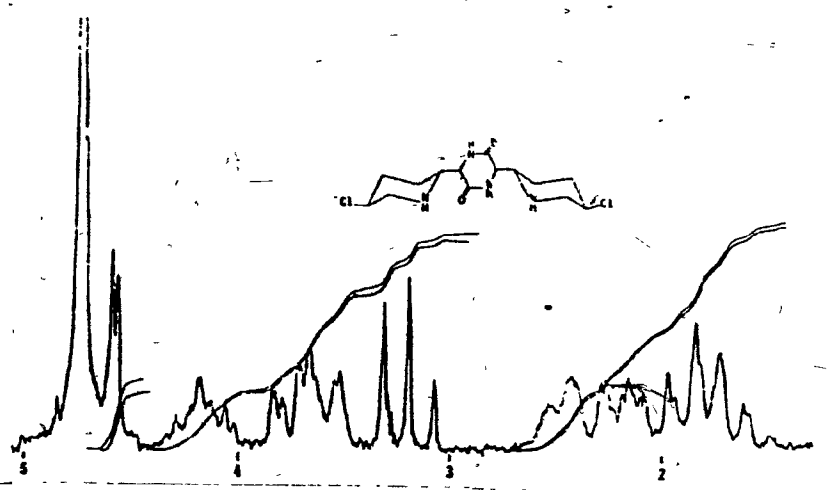
The cytotoxic effect of these compounds is due to enzyme inhibition caused by Michael addition to sulfhydryl groups, rather than alkylation of DNA as with the alkylating agents which react by substitution reactions.

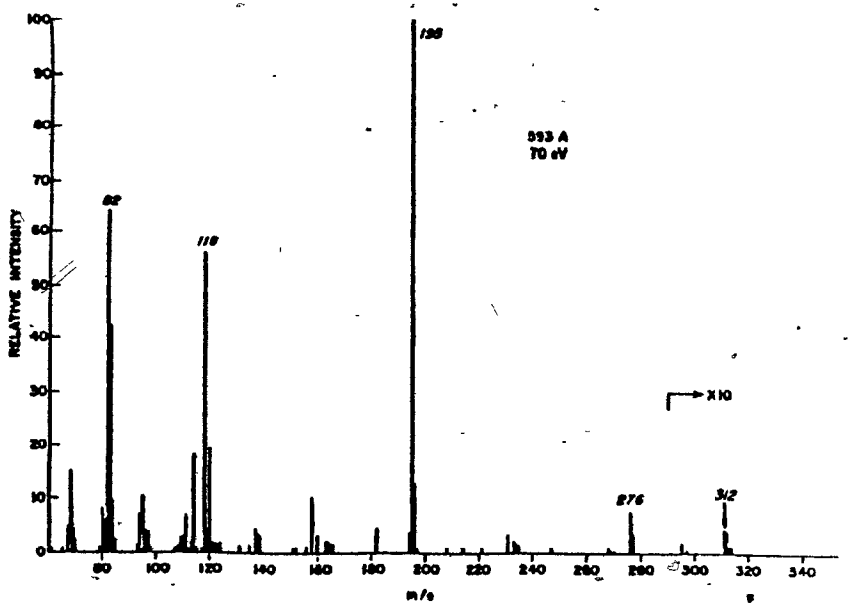
A number of compounds with antitumor activity have shown a positive correlation between their antitumor activity and inhibition of aerobic respiration in tumor cells.[17] Aerobic respiration is inhibited by sesquiterpenes which also have antitumor activity and it is postulated that this may be caused by reaction with sulfides and sulfhydryl groups in cytochromes and Krebs cycle dehydrogenases.[18]

3,6-bis(5-chloro-2-piperidyl)-2,5-piperazinedione

Recently a compound isolated from the fermentation broth of a culture of *Streptomyces griseoluteus* was identified as the first naturally occurring antitumor agent with a β-chloroamino group similar to that of the nitrogen mustards.[20] The report of its isolation gave only its elemental analysis and infrared spectrum. Later its structure was deduced[20]







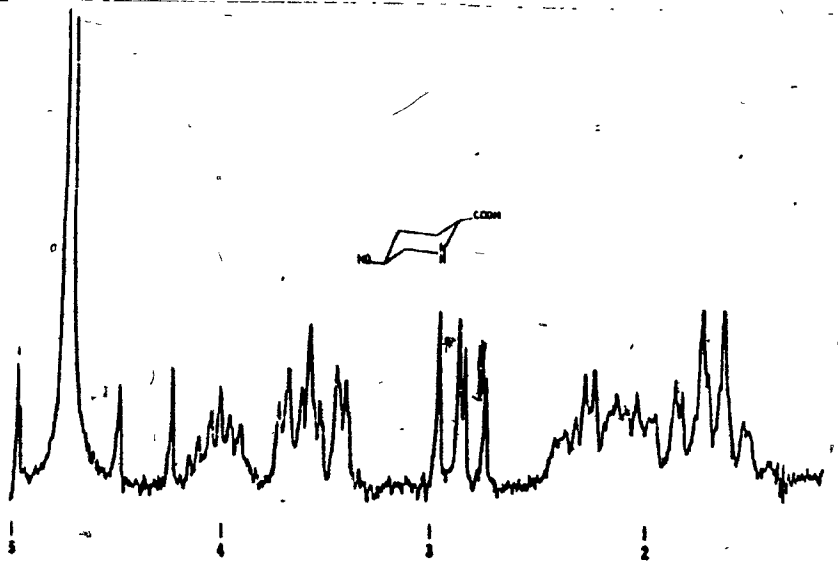
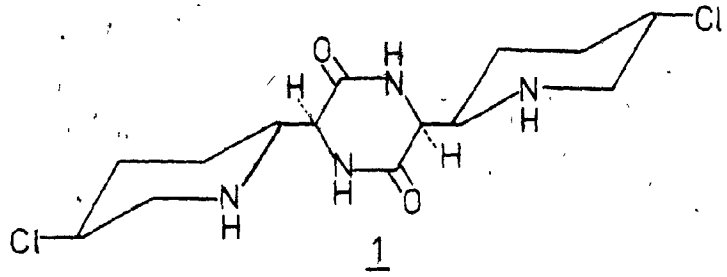


Figure 4. Spectra of 3,6-bis-(5-chloro-2-piperidyl)-2,5-piperazinedione.

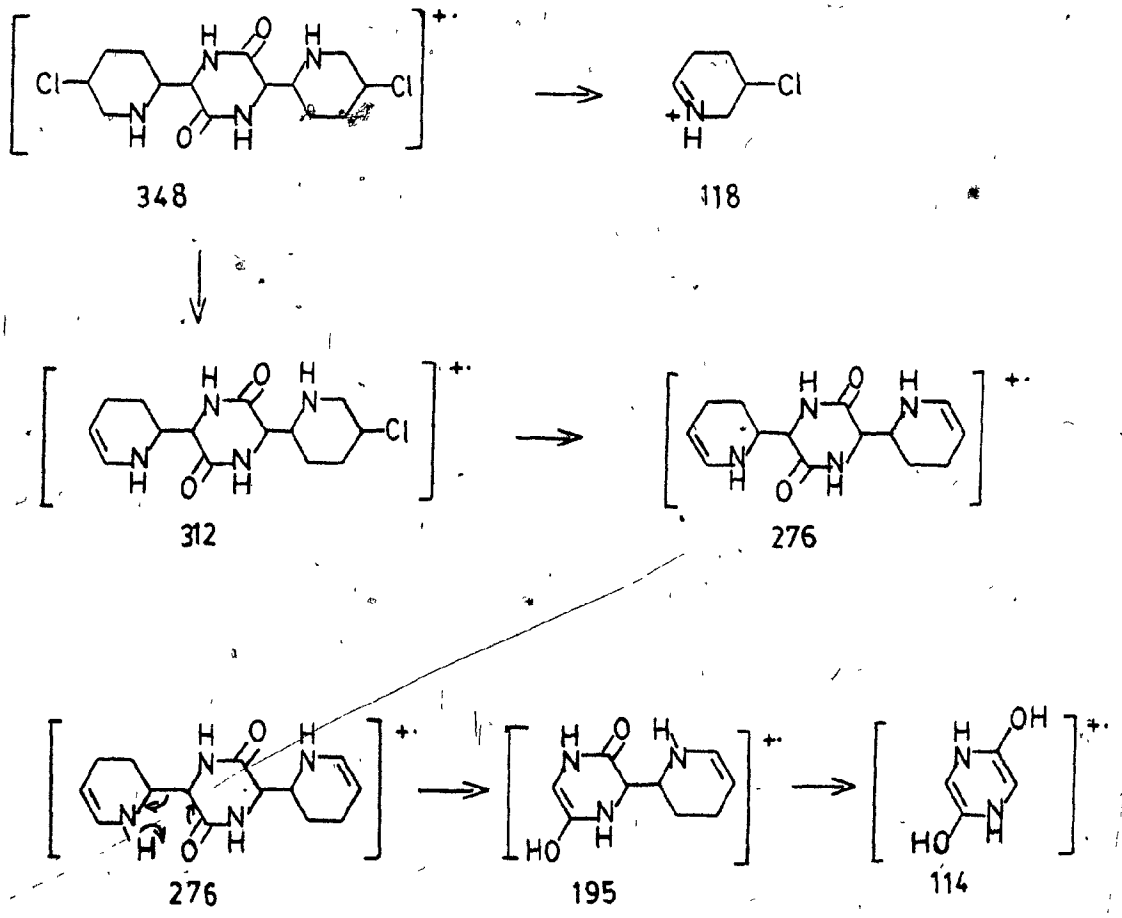
from the nmr spectrum and mass spectrum to be 3,6-bis(5-chloro-2-piperidyl)-2,5-piperazinedione (1). This structure was subsequently confirmed by x-ray crystallography.[21]



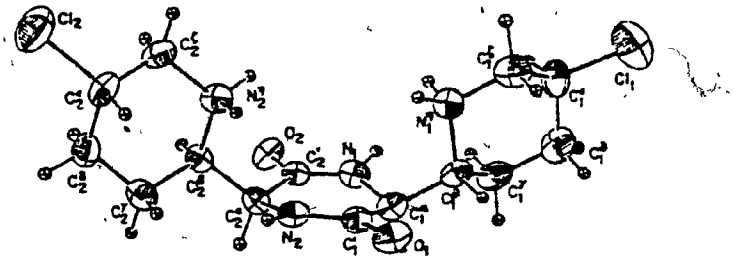
1

The elemental analysis of the hydrochloride salt gave an empirical formula of $C_7H_{12}ON_2Cl_2$ or $C_7H_{11}ON_2Cl$ for the free base. The IR showed peaks at 3070 cm^{-1}, 3110 cm^{-1}, and 3210 cm^{-1} (NH and/or OH); 2400-2700 cm^{-1} (NH^+); and 1685 cm^{-1} and 1665 cm^{-1} (carbonyl). The nmr was rather complex; the variety of coupling constants and moderate line broadening of some signals suggest a cyclic structure. Comparison of this nmr with the nmr spectrum of 5-hydroxy pipecolic acid showed a marked similarity, so the conclusion was drawn that the new compound was a 2,5-disubstituted piperidine with both substituents equatorial. The similarity of chemical shifts indicates that the substituents have similar shielding effects to the carboxyl and hydroxyl groups. The doublet at $\delta 4.58$ was shown by spin decoupling experiments to be a proton on a carbon attached to position 2 of the piperidine ring.

The mass spectrum of the compound had the highest mass peaks as a cluster at m/e 312-315 in a pattern indicating one chlorine atom. A peak at m/e 276 had no chlorine. The mass spectrum showed, then, that the empirical formula (MW 176) derived from the elemental analysis was not the molecular formula. Doubling the molecular weight given by the empirical formula gives a molecular weight of 348 from which loss of HCl would give 312 and loss of two HCl would give 276. This suggested the dimer structure 1 which fits the IR spectrum and the remaining peaks in the mass spectrum.



The arguments for the structure proposed were quite convincing, but could not be considered unequivocal, particularly in the absence of a molecular ion in the mass spectrum. The structure was confirmed and the absolute configuration determined by x-ray crystallography.[21] The sulfate salt pentahydrate of the compound was used for the study. Of the six chiral centers the two carbons of the piperazinedione ring and the two carbons bearing the chlorines were S and carbon-2 of each piperidine ring was R.

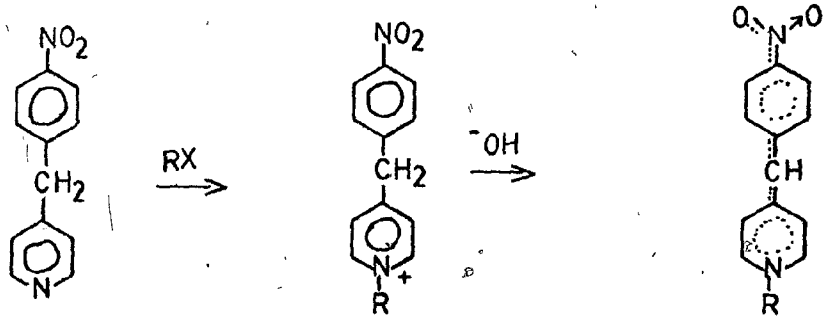


Compound 1 is assumed to be derived from the amino acid (5-chloro-2-piperidyl)glycine for which the trivial name streptolutine was proposed.[21] Compound 1 could then be called cyclo-(streptolutyl-streptolutyl).

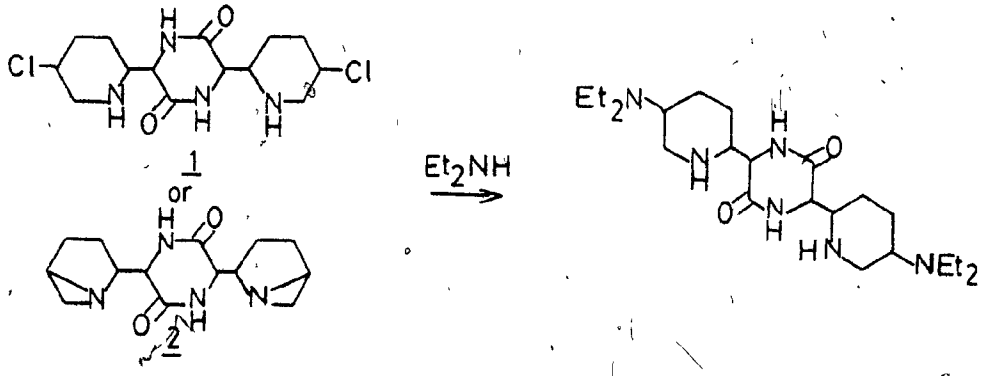
It was the antitumor activity of this compound which led to its isolation.[19] The antitumor activity was first detected in the fermentation broth of a culture of *Streptomyces griseoluteus* with the human tumor-egg host system using human adenocarcinoma #1 in the embryonated egg. This system was used to guide the isolation procedure. The lyophilized broth was first extracted with absolute ethanol and the ethanol solution evaporated to dryness.

The residue after evaporation was dissolved in water and extracted at pH 7.0 with butanol. Concentration of the butanol extract gave a crystalline material which was recrystallized from methanol. This crystalline compound had a 400-fold greater activity in the test system than the lyophilized broth. When the structure was elucidated, it was presumed that the biological action of this new compound would be similar to that of the nitrogen mustards.[21]

The mode of action of 3,6-bis(5-chloro-2-piperidyl)-2,5-piperazinedione has been investigated by *in vitro* studies. Reaction with 4-(p-nitrobenzyl)pyridine has been used as a test for alkylating activity.[22] The alkylating agent forms the pyridinium salt which, in an alkaline medium, loses a proton to form a blue colored compound.

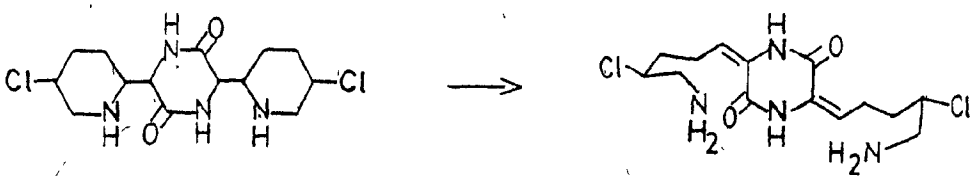


Both compound and the bis-aziridine (2) prepared from it were found[23] to react with 4-(p-nitrobenzyl)pyridine. Both these compounds also reacted with diethylamine.



In cell cultures compound 1 was found to inhibit DNA synthesis and cell proliferation, but not RNA or protein synthesis.[24,25] The bis-aziridine 2 also inhibited DNA synthesis, but its activity was lower. For the same inhibitory effect on DNA synthesis ten times as much bis-aziridine was required as compound 1. This suggests that either the chloro-compound does not cyclize before alkylation occurs or that it also reacts in some other way not open to the aziridine. In synchronous cell cultures compound 1 caused chromosome aberrations in all cells in S phase and 42% of cells in G_2 phase.[25] All these observations are indicative of a mechanism of action similar to that of the nitrogen mustard compounds.

In a study which correlated antitumor activity and inhibition of aerobic respiration[17] it was shown that compound 1 inhibits aerobic respiration in mitochondrial preparations. The reaction causing this inhibition was not studied, however. In view of the findings with the sesquiterpenes which were found to react with sulfhydryl groups of enzymes,[18] it might be tempting to propose a similar reaction for compound 1. Opening of the piperidine ring would give a compound which could undergo a Michael addition.



1 3

This possibility has not been studied, but 3 probably would not be as reactive as the sesquiterpenes. The double bond in compound 3 would be less electrophilic than either an α-methylene lactone or an α,β-unsaturated cyclopentenone. Also, it has been shown that substitution on the exocyclic carbon of α-methylene lactones decreases their antitumor activity.[26]

Animal studies showed compound 1 to retard the growth of Erlich and Taper liver ascites neoplasms and of Walker sarcoma 256 with some complete remissions seen.[27] It was also active against L1210 mouse leukemia, even those strains which were resistant to cyclophosphamide or BCNU.[28]

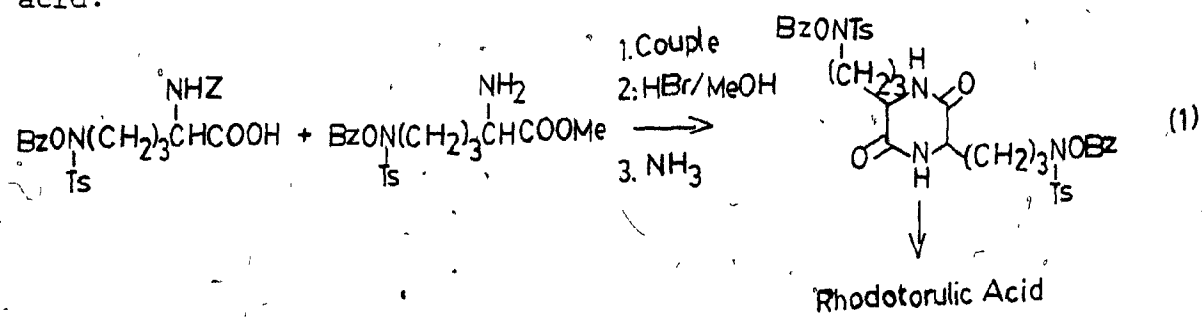
Clinical trials in humans have begun with some encouraging results. The greatest success has been with leukemias[29,30] and Hodgkin's disease.[31] Some response has been seen with non-Hodgkin's lymphomas[31] and metastatic breast cancer.[32] It has had no effect in trials with multiple myeloma,[31,33] metastatic renal carcinoma,[34] or metastases of other solid tumors.[29,33] Generally hematopoetic toxicity was the dose limiting factor with maximal effect on granulocytes and platelets seen 2 $\frac{1}{2}$ weeks after a dose.[30]

The promising results of these clinical trials make 3,6-bis-(5-chloro-2-piperidyl)-2,5-piperazinedione an interesting target for chemical synthesis. Also, preparation of analogs could aid in the clarification of its mechanism of action.

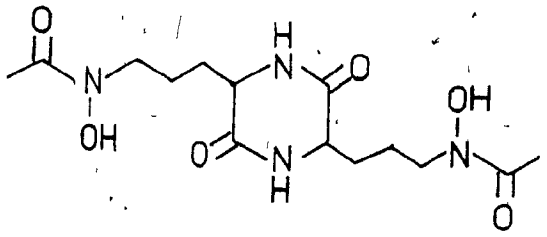
CHAPTER II

METHODS OF PIPERIDINE SYNTHESIS

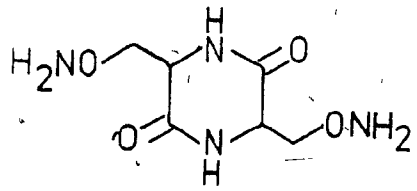
In considering 3,6-bis-(5-chloro-2-piperidyl)-2,5-piperazinedione from a synthetic viewpoint the major features are the diketopiperazine ring and the piperidine rings. Diketopiperazines, anhydro-dimers of α-amino acids, have been isolated from various natural sources, most commonly from cultures of yeast, lichens, and fungi.[35] Some of these are symmetrical, including rhodotorulic acid, cycloserine dimer, and cyclo-phenylalanyl-phenyalanyl; but most are more complex unsymmetrical structures. (See Figure 5) The symmetrical diketopiperazines are most often synthesized by dimerization of the amino acid ester. This dimerization often occurs spontaneously in solution.[36] They can also be prepared by heating the free amino acid in ethylene glycol.[37], β-naphthol,[38] or phenol.[39] The unsymmetrical diketopiperazines are usually synthesized from a dipeptide derivative. Unprotected dipeptides can be cyclized by heating in β-naphthol[38] or phenol,[39] and dipeptide ester hydrochlorides cyclize on treatment with ammonia.[40,41] The latter method was used in the synthesis of a symmetrical diketopiperazine, rhodotorulic acid.[42]



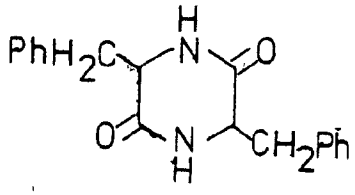
(1)



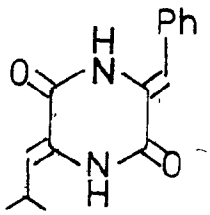
Rhodotorulic Acid



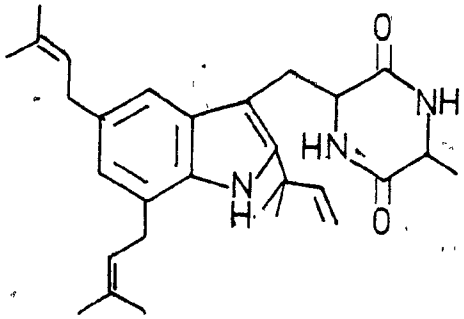
Cyclosèrine Dimer



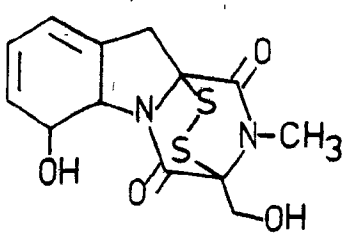
Cyclo phenylalanyl-
phenylalanyl



Albonoursin



Echinulin



Gliotoxin

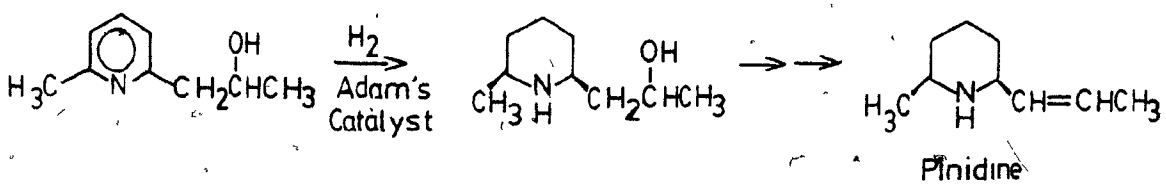
Figure 5. Naturally Occurring Diketopiperazines

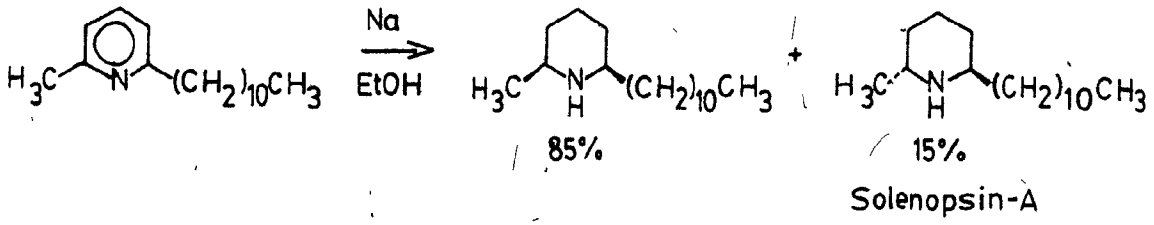
Since diketopiperazines, especially the symmetric compounds, are usually synthesized from the component amino acids or derivatives thereof, the synthetic target becomes the amino acid. Thus, in the case of 3,6-bis-(5-chloro-2-piperidyl)-2,5-piperazinedione, the objective is (5-chloro-2-piperidyl)glycine, and the piperidine ring becomes a major synthetic concern.

Many methods of piperidine ring formation are available which can produce rings with various substitution patterns. The method chosen for this synthesis will have to give a 2,5-disubstituted ring.

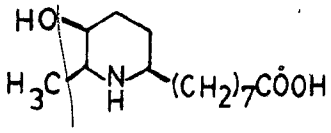
Pyridines

One of the commonest methods of piperidine ring synthesis is the reduction of pyridines. This method has been used in the synthesis of several piperidine alkaloids, including pinidine[43] and solenopsin-A.[44]



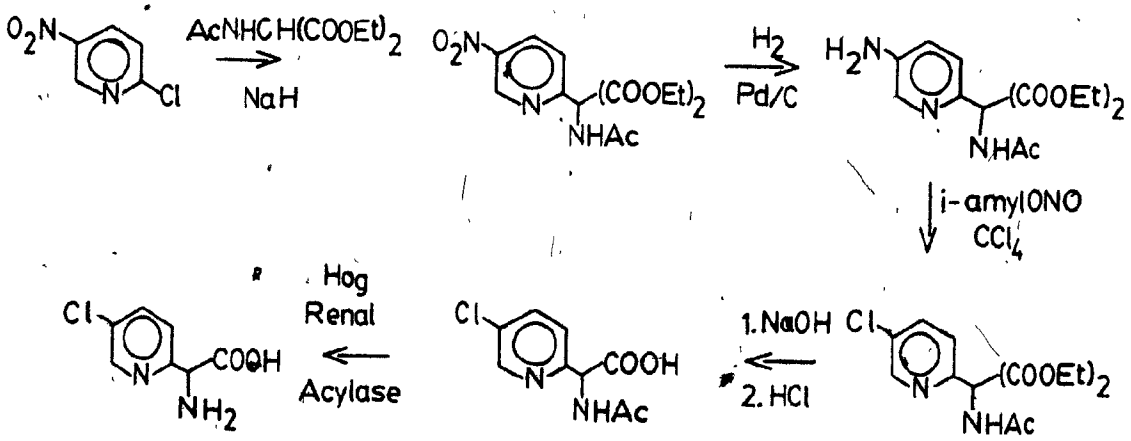


These alkaloids are 2,6-disubstituted piperidines and the cis isomers (diequatorial) are more stable than the trans isomers (axial-equatorial) so reduction of pyridines tends to give the cis isomers. This method was less successful with trisubstituted compounds such as carpamic acid,[45] with three asymmetric centers.



Piperidines which are 2,5-disubstituted are more stable as the trans isomers than as the cis isomers. Reduction of 2,5-disubstituted pyridines generally gives a mixture of the cis and trans piperidines with the ratio of isomers dependent upon the method of reduction. For example, catalytic hydrogenation of 2,5-dimethyl pyridine using Raney nickel gives a cis to trans ratio of 27:73.[46]

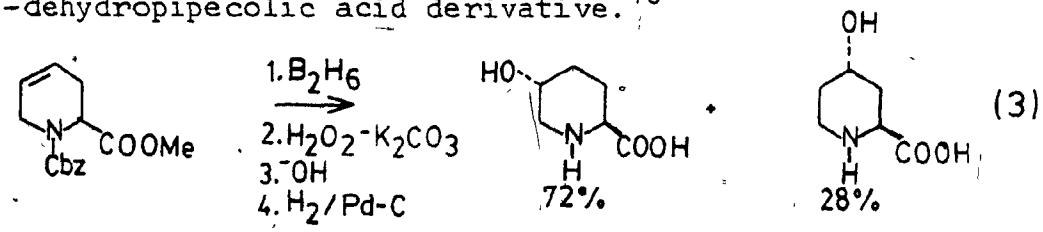
In an attempted synthesis of 3,6-bis(5-chloro-2-piperidyl)-2,5-piperazinedione the amino acid (5-chloro-2-pyridyl)-glycine was prepared as in scheme 1.[47]



Scheme 1. Synthesis of (5-chloro-2-pyridyl)glycine

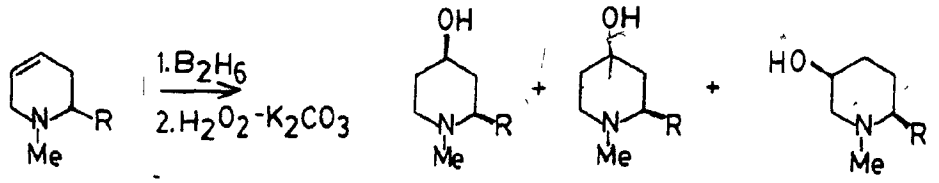
This pyridine derivative proved not to be a useful intermediate since all attempts at reduction of the pyridine ring also caused hydrogenolysis of the 5-chloro substituent.

Partially reduced pyridines have also been used in the synthesis of substituted piperidines, mostly by addition reactions. A naturally occurring piperidine, 5-hydroxy pipecolic acid, has been synthesized by hydroboration of a 4,5-dehydropipecolic acid derivative.[48]



(3)

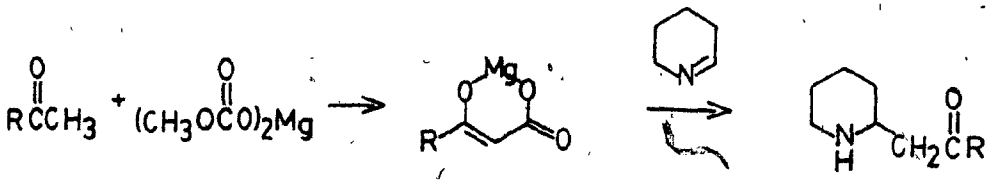
In this reaction the natural, and more stable, trans isomer of the 2,5-disubstituted compound was the major product. This was not the case with other 4,5-dehydropiperidines, however.[49]



(4)

Hydroboration of 1-methyl-2-alkyl-4,5-dehydropiperidines gave no trans-2,5-disubstituted product and only a small amount of the cis disubstituted product.

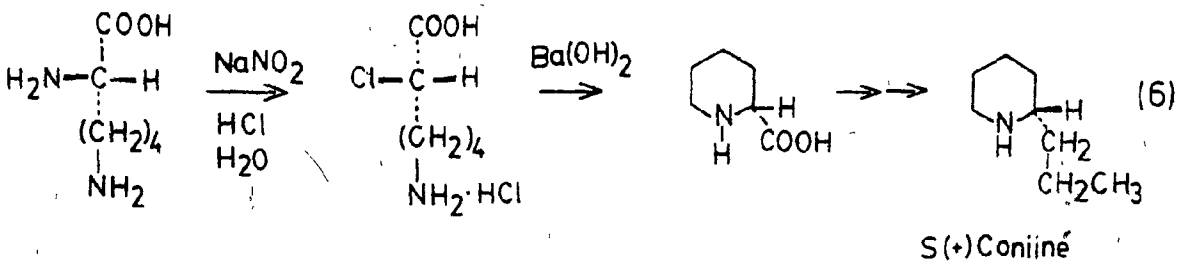
2-Piperidylmethyl ketones have been synthesized by the reaction of 1,2-dehydropyridines and the complex of magnesium methyl carbonate with a methyl ketone.[50]



(5)

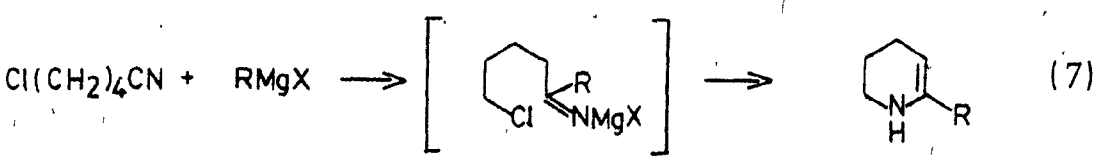
Cyclization at Nitrogen

The reactions discussed above have involved modifications of previously formed ring systems. Piperidines can also be formed from acyclic precursors. Perhaps the simplest reaction of this type is the cyclization of 5-haloamines, which occurs spontaneously on neutralization of the acid salt of the amine. This cyclization was used in a synthesis of the alkaloid coniine from lysine.[51]



(6)

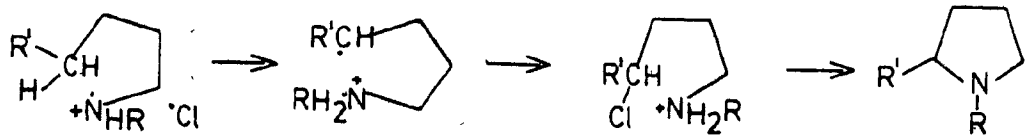
Similar cyclizations are the reactions of 1,5-dihalides with ammonia or amines and treatment of 5-hydroxyamines with HBr.[52] Grignard reagents react with δ-chlorovaleronitrile to give 2,3-dehydropiperidines.[53]



(7)

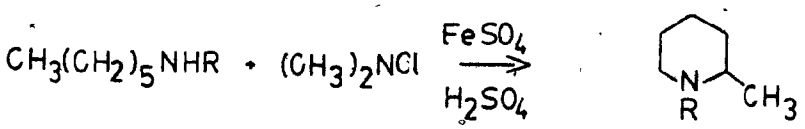
The Hofmann-Löffler reaction, the cyclization of an N-haloamine, forms piperidines in small amounts, but the major product is a pyrrolidine.[54] This reaction has been used in

the synthesis of pyrrolidine alkaloids.[55,56] The reaction involves an intramolecular radical chlorination which generally occurs at the 5-carbon.



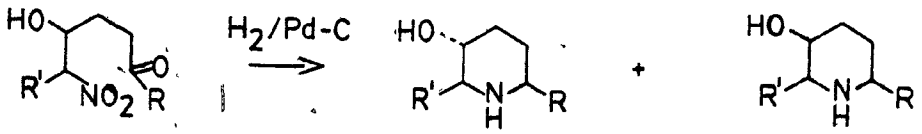
(8)

When the hydrogen abstraction occurs intermolecularly, the chlorination occurs predominantly at the position next to the end of the alkyl chain,[57] so piperidines are formed from n-hexylamines.[58]



(9)

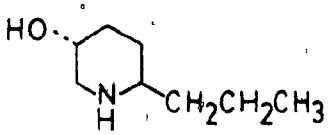
A number of piperidine alkaloids have been synthesized using another reaction of cyclization at the nitrogen. The reductive cyclization of a δ-nitroketone was part of the preparation of pseudo-conhydrine,[59] carpamic acid,[60] and aximic acid.[61] The method is general for the preparation of 3-hydroxypiperidines substituted at the 2 and/or 6 positions.



(10)

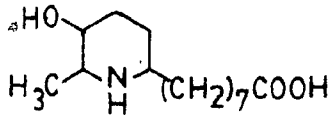
The product always has the 2 and 6 substituents cis, but the 3-hydroxyl may be exclusively cis, exclusively trans, or a mixture may be formed, depending upon the particular

substituents. The reaction gave pseudoconhydrine with the natural trans geometry exclusively.[59]

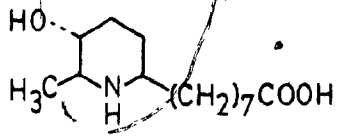


Pseudoconhydrine

Carpamic acid was formed as a mixture with 3-isocarpamic acid.[60]

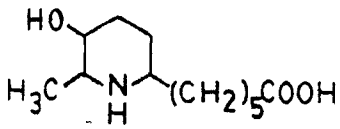


Carpamic Acid 1 : 2

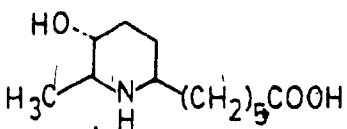


3-iso Carpamic Acid

Azimic acid was formed as a mixture with 5'-epi-azimic acid.[61]



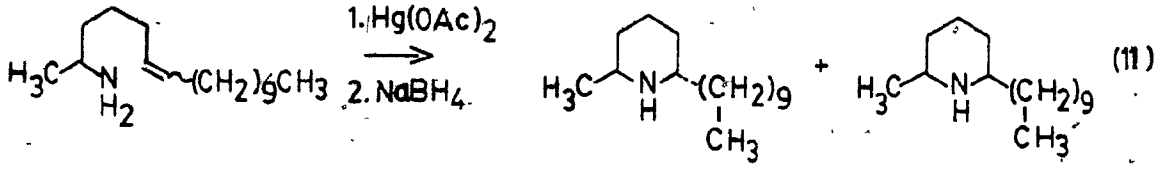
Azimic Acid 45%



35% 5'-epi Azimic Acid

In other compounds cyclized in this manner, (Equation 10), where R was benzyl, R'=H gave mostly cis hydroxyl, R'=methyl gave a mixture of cis and trans hydroxyl, and R'=ethyl gave exclusively cis hydroxyl.[62] When R was methyl, R'=methyl gave mostly cis hydroxyl and R'=ethyl or n-propyl gave exclusively cis.[63]

In a recent synthesis of solenopsin-A, a constiuent of fire ant venom,[44] the piperidine ring was formed by an intramolecular aminomercuration of a double bond.[64]



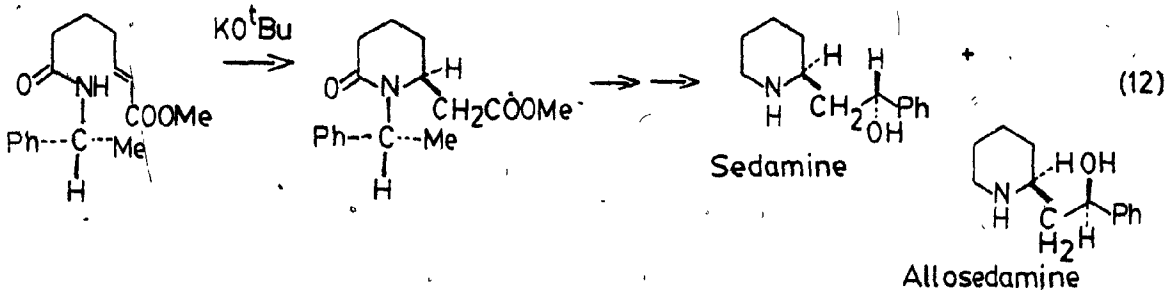
Solenopsin-A 11%

iso Solenopsin-A 43%

(11)

The unnatural trans isomer was the major product, but some of the natural cis isomer was also formed.

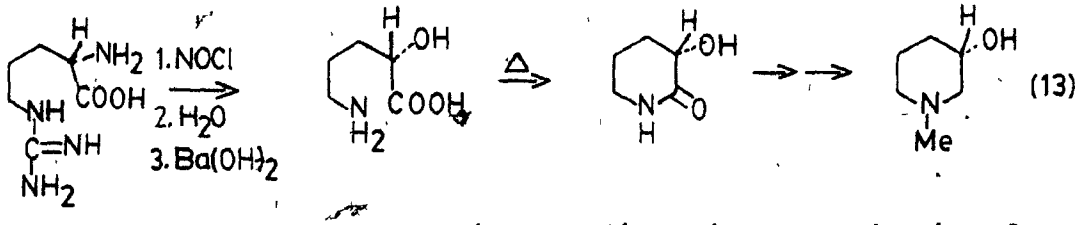
An asymmetric synthesis of the alkaloids sedamine and allosedamine was recently reported[65] in which an optically active piperidine derivative was formed by an intramolecular Michael addition of an amide ion to an α,β-unsaturated ester.



(12)

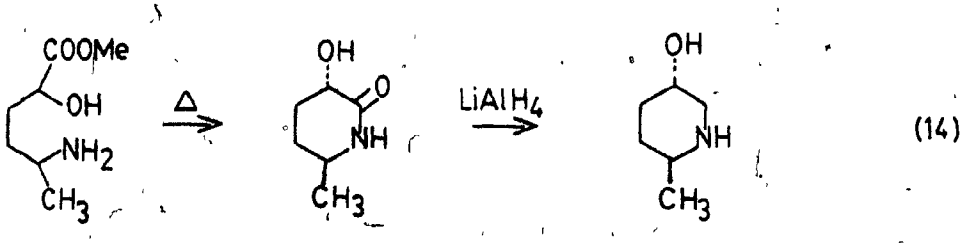
The lactam was hydrolyzed in removing the chiral directing group, but was easily re-formed. This synthesis illustrates that δ-lactams can be precursors of piperidines.

A synthesis of S-1-methyl-3-hydroxypiperidine starting from arginine used lactam formation as the ring closure reaction.[66]



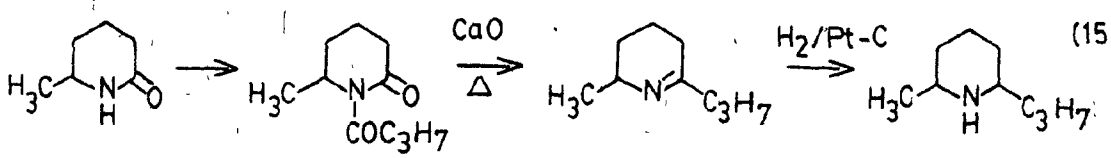
(13)

A lactam was also an intermediate in a synthesis of trans-2-methyl-5-hydroxypiperidine.[67]



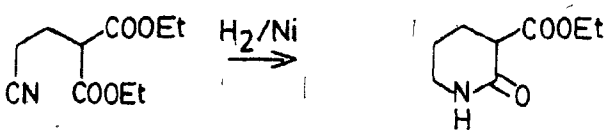
(14)

A lactam was used in a recent synthesis of dihydropinidine to allow introduction of the n-propyl group by N-acyl lactam rearrangement.[68]



(15)

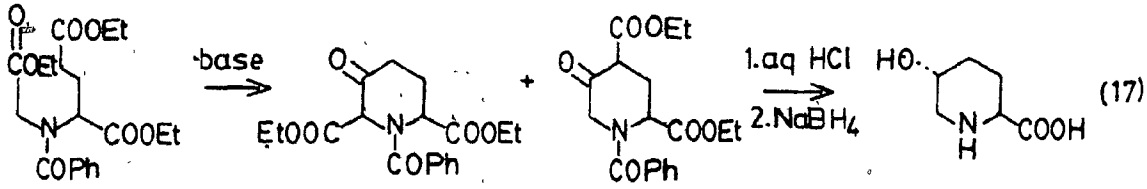
Lactam formation also occurs when γ-cyanoesters are catalytically reduced.[69]



(16)

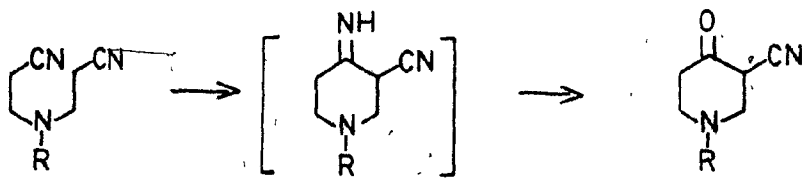
Cyclization at Carbon

All the cyclizations discussed above involve formation of a carbon-nitrogen bond, but piperidines can also be formed by ring closure between two carbon atoms of a secondary or tertiary amine. The Dieckmann condensation was used in a stereospecific synthesis of trans-5-hydroxypipecolic acid.[70]



(17)

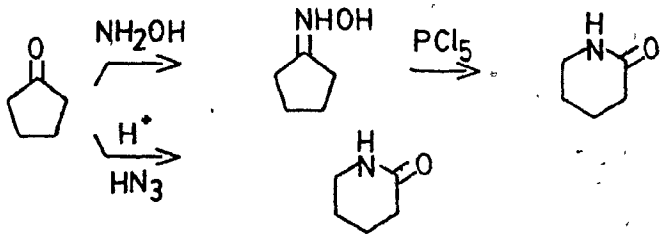
A similar condensation used cyano rather than ester groups.[71]



(18)

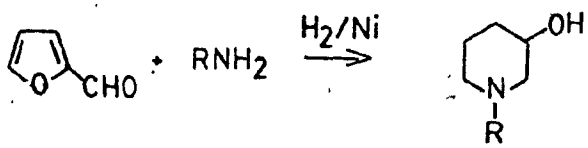
Transformation of Other Rings

Piperidines can also be formed by transformation of other ring systems. Cyclopentanone can be transformed by either the Beckman rearrangement or the Schmidt reaction to a lactam which can then be reduced to the piperidine.



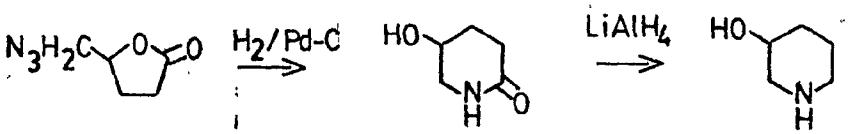
(19)

The catalytic hydrogenation of a mixture of furfural and a primary amine gives a 3-hydroxypiperidine.[72]



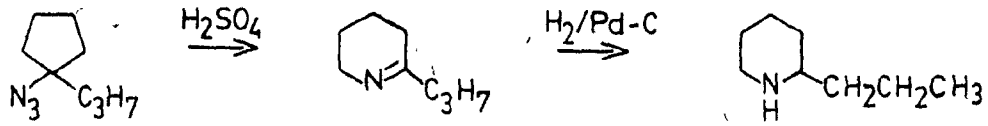
(20)

Hydroxypiperidines can also be formed by catalytic hydrogenation of a γ-lactone with γ-azidomethyl group.[73]



(21)

Tertiary cyclopentane azides when treated with acid give α-substituted piperideines which can be reduced to piperidines. This reaction was used to synthesize coniine and dihydropinidine.



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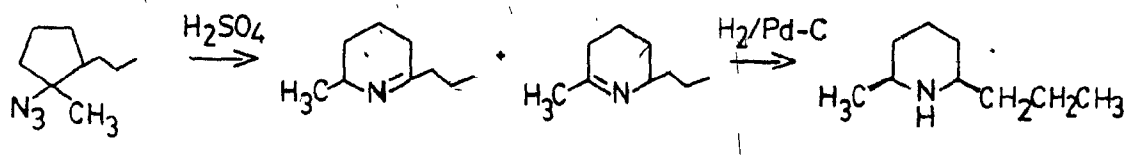
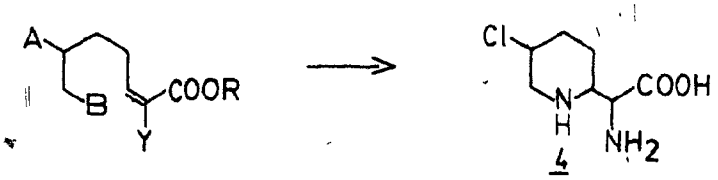
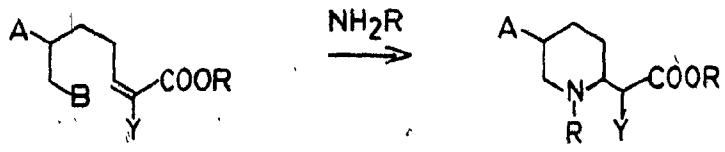


In the primary synthetic target of this work, (5-chloro-2-piperidyl)glycine, carbon-2 of the piperidine ring is β to the carboxylic acid. This means that an intramolecular Michael-type cyclization similar to that used in the synthesis of sedamine[65] (Equation 12) should be applicable to this synthesis. The acyclic precursor then, should be a 2-heptenoic acid derivative which has, or will allow the introduction of, the chlorine at C-6 and the amino group at C-7.

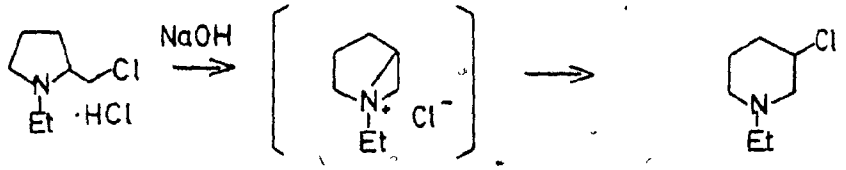


4

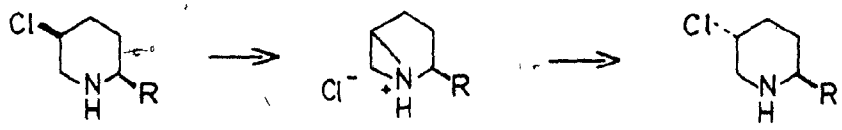
If group B is not an amino group then the substitution at C-7 and the Michael addition could possibly occur at the same time.



The stereochemistry of the substituents on the piperidine ring in compound 1 is trans, but it is not necessary that this geometry be introduced in the cyclization. Even if the cis compound is formed in the cyclization reaction, when the chlorine is introduced, isomerization to the trans compound can occur. When 1-ethyl-2-chloromethyl pyrrolidine hydrochloride is neutralized with base to form the free amine, it spontaneously rearranges,[148] through a bicyclic aziridinium ion,[149] to 1-ethyl-3-chloropiperidine.



This same sort of aziridinium ion formation would allow isomerization of a cis-2-substituted-5-chloropiperidine to the corresponding trans compound.

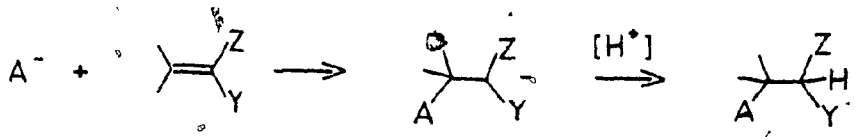


The trans diequatorial isomer would be more stable than a cis axial-equatorial isomer.

CHAPTER III

SYNTHESIS OF α-SUBSTITUTED-α,β-UNSATURATED ESTERS

The Michael reaction is the addition of a nucleophile to an alkene bearing an electron withdrawing substituent (Z).

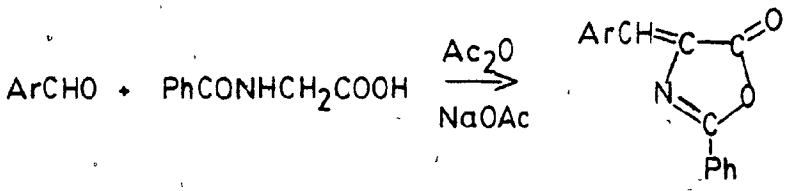


(1)

The group Z must be able to stabilize the intermediate carbanion. α,β-unsaturated esters are fairly good Michael acceptors, though not as good as α,β-unsaturated ketones or nitro compounds. The α,β-unsaturated ester chosen for this synthesis must have an α-substituent (Y) which can become the amino group of the final product, but which will not interfere with the Michael reaction. Thus, Y cannot be the amino group since this would deactivate the double bond to nucleophilic attack. (Enamines generally react with electrophiles at the β-carbon.) Possibilities for Y would be an imine (-N=C) or an acylated amino group (-NHCOR), which would be less likely to interfere with the Michael reaction; or a nitro group, azido group, or a halogen, which would increase the susceptibility of the double bond to nucleophilic attack. The substituent at the β-position of the α,β-unsaturated ester should contain the remaining four carbons needed for the piperidine ring and suitable functionality at the 6 and 7-positions as discussed in the previous chapter.

α,β-unsaturated-α-amino Acids

First, methods of forming α,β-unsaturated-α-substituted esters will be considered. Two methods are available for the direct synthesis of α,β-unsaturated-α-amino acid derivatives from carbonyl compounds. The Erlenmeyer azlactone[75] synthesis, a variation of the Perkin reaction, is the reaction of an aromatic aldehyde with hippuric acid in the presence of acetic anhydride and sodium acetate.

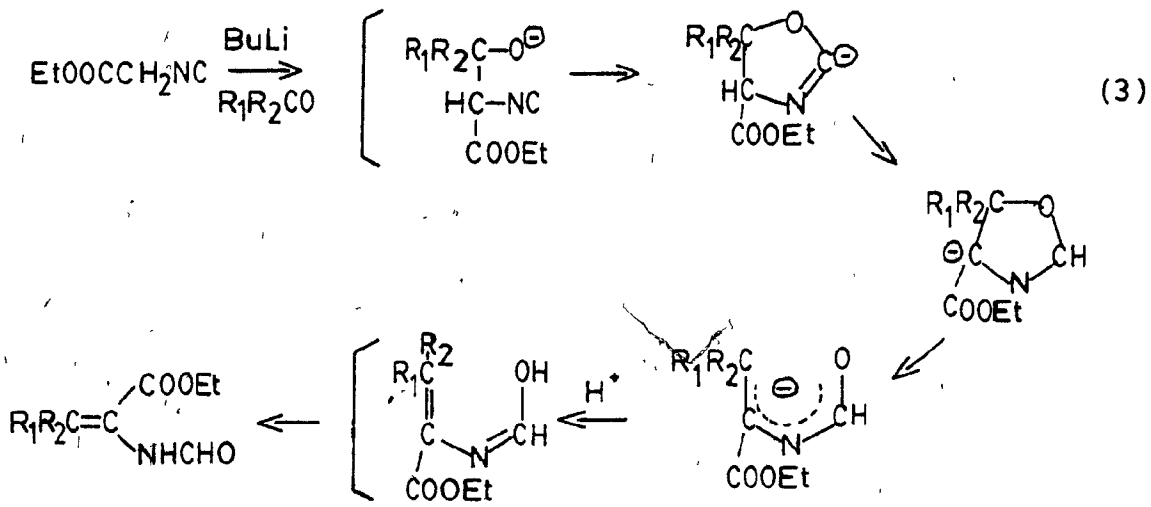


(2)

The reaction probably involves formation of the azlactone before condensation with the aldehyde. Facts supporting this reaction path are that the Erlenmeyer reaction occurs under milder conditions than the Perkin reaction, and that benzoyl-N-methyl glycine (which cannot form an azlactone) condenses with aldehydes much less readily than hippuric acid.

The original reaction gives good yields only with aromatic aldehydes, but Robinson[76] extended the reaction to aliphatic aldehydes and ketones by doing the reaction in refluxing tetrahydrofuran and using lead acetate instead of sodium acetate.

In the presence of base isocyanoacetic esters condense with carbonyl compounds and then rearrange to form α,β-unsaturated-α(formylamino)-esters.[77]

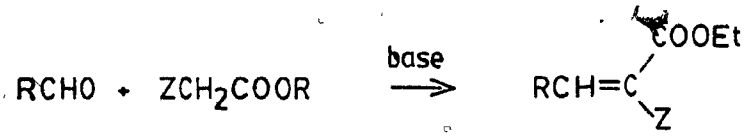


(3)

Both aromatic and aliphatic aldehydes and ketones give this reaction.

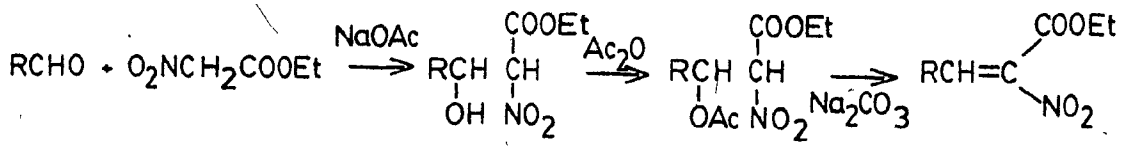
Knoevenagel Condensation

The Knoevenagel condensation can form α,β-unsaturated esters from condensation of compounds of the type ZCH_2COOR with aldehydes.



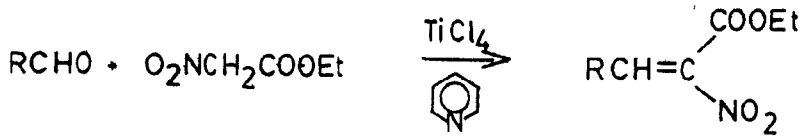
(4)

Nitroacetic esters have been used in this reaction[78,79] to form α-nitro-α,β-unsaturated esters. When ethyl nitroacetate reacted with an aldehyde in the presence of sodium acetate, the product isolated was the β-hydroxy-α-nitro ester.[78] The unsaturated ester was formed by acetylation of the hydroxyl group, followed by treatment with sodium carbonate.



(5)

The α,β-unsaturated ester was produced directly when the reaction was carried out in the presence of titanium tetrachloride and a tertiary amine.[79]

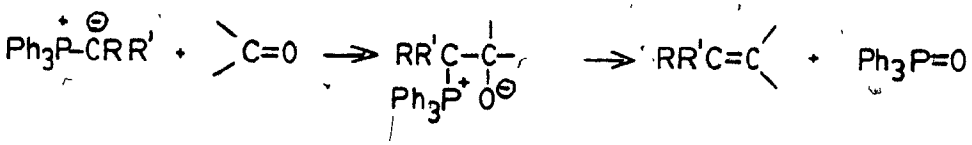


(6)

When the aldehyde has an α-hydrogen, its aldol condensation is a possible side reaction.

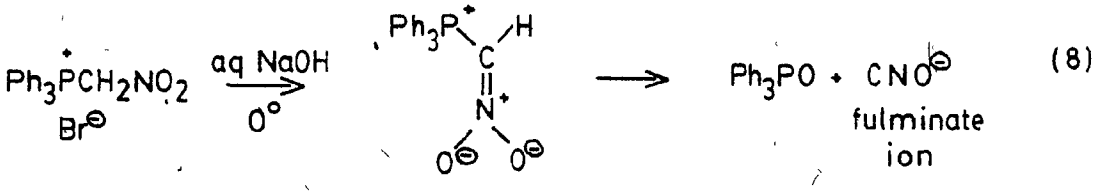
Organophosphorus Reactions

A more general method of forming carbon-carbon double bonds from carbonyl compounds is the Wittig reaction.[80]



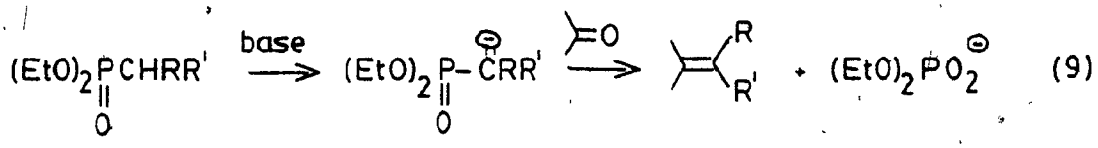
(7)

The phosphorus serves both to stabilize the carbanion which attacks the carbonyl compound and to remove the oxygen. The reaction is compatible with many functional groups in either the ylid or the carbonyl compound. The substituents, R and R', on the ylid carbon may be hydrogen, alkyl, aryl, halogen, -COR, -CHO, -CN, -COOR, or -OR. The ylid may not contain an α-nitro group, however, as these compounds decompose.[81]



(8)

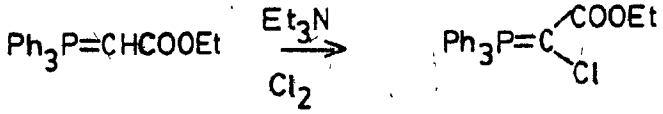
When there is an electron withdrawing substituent on the ylid carbon, the ylid is less reactive. The ylid in this case may react only with aldehydes and not with ketones. A variation of the Wittig reaction, the Horner-Emmons reaction, can overcome this problem. This reaction uses a phosphonate carbanion rather than the phosphonium ylid of the Wittig reaction.



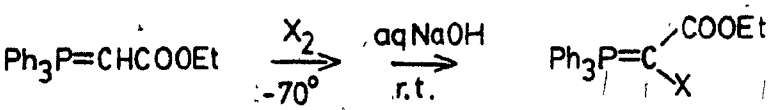
(9)

A phosphonate carbanion with an electron withdrawing group on the carbon is more nucleophilic than the corresponding phosphonium ylid, and reacts readily with ketones as well as aldehydes.[82]

These reactions have been used to prepare α,β-unsaturated-α-halo esters. The α-halo phosphonium ylids can be formed either by halogenation and dehydrohalogenation of the α-carbalkoxy ylid[83] or by reaction of two equivalents of triphenyl phosphine with a trihaloacetate.[84]



(10)



(11)

(12)

These ylids are not very reactive because of the stabilizing effect of the ester and halogen substituents, and have only been reported to react with aromatic aldehydes. The method of generating the ylid shown in equation (12)' is operationally very simple, but has the disadvantage of consuming two moles of aldehyde for each mole of the desired product formed since the Ph_3PX_2 also reacts with carbonyl compounds.

$$Ph_3P{=}CXCOOR + Ph_3PX_2 \xrightarrow{2\,RCHO} RCH{=}CXCOOR + RCHX_2 + 2\,PhPO \qquad (13)$$

The formation of α-halo-α,β-unsaturated esters from a wide variety of carbonyl compounds is made possible by the use of the Horner-Emmons reaction.[82] In this case the phosphonoacetate is halogenated similarly to the reaction in equation (10) before reaction with the carbonyl compound.

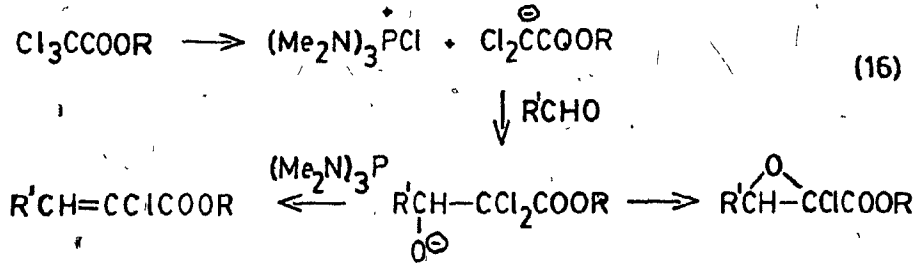
$$(EtO)_2\overset{O}{\overset{\|}{P}}CH_2COOEt \xrightarrow[3.NaH]{1.NaH\ 2.Br_2} \left[(EtO)_2\overset{O}{\overset{\|}{P}}-\underset{\ominus}{\overset{Br}{\overset{|}{C}}}COOEt\right] \xrightarrow{>C=O} >C{=}CBrCOOEt + (EtO)_2PO_2^{\ominus} \qquad (14)$$

A variation of the Horner-Emmons reaction which also forms α-chloro-α,β-unsaturated esters was recently reported.[85] Instead of halogenation of a phosphonoacetate, this method involves introduction of the ester group into diethyl trichloromethanephosphonate.

$$ClCP(OEt)_2 \xrightarrow[2.ClCOOEt]{1.nBuLi} (EtO)_2\overset{O}{\overset{\|}{P}}-\overset{Cl}{\overset{|}{\underset{Cl}{\overset{|}{C}}}}COOEt \xrightarrow[2.\,RCHO]{1.nBuLi} RCH{=}CClCOOEt \qquad (15)$$

Diethyl trichloromethanephosphonate undergoes lithium-chlorine exchange with n-butyllithium, then the lithio compound reacts with ethyl chloroformate. The α,β-dichlorophosphonoacetate is then treated with another equivalent of n-butyllithium followed by an aldehyde, giving the α-chloro-α,β-unsaturated ester. This reaction can be done all in one pot by treating the trichloromethanephosphonate with two equivalents of n-butyllithium at -100° followed by ethyl chloroformate, then warming to -60° before addition of the aldehyde. Both aliphatic and aromatic aldehydes and strongly electrophilic ketones (e.g. cyclohexanone) undergo this reaction at -60°.

Another synthesis of α-chlorovinyl esters has been reported[86] which also involves an organophosphorus compound, but differs from the Wittig reaction and its variations in that no ylid is formed. The first step is the reaction of tris-dimethylamino phosphine with a trichloroacetate.



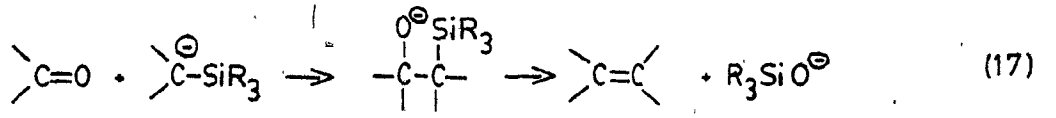
(16)

The amino phosphine removes a positive chlorine ion from the trichloro ester, forming an anion which reacts directly with the aldehyde. In the presence of a second equivalent of amino phosphine elimination occurs to give the α,β-unsaturated-α-chloro ester. When only one equivalent of

amino phosphine is present, however, the alkoxide ion cyclizes with loss of chloride to give the α,β-epoxy-α-chloro ester. In order to minimize epoxide formation the aldehyde is mixed with two equivalents of tris-dimethylamino phosphine and the trichloroester is added to the mixture. Even using this procedure, only aromatic aldehydes were reported to give good yields of the vinyl ester.

Organosilicon Reactions

Though the olefination of carbonyl compounds by the Wittig reaction and its variations is very widely used, organophosphorus compounds are not unique in forming alkenes from carbonyl compounds. A more recently developed method is the reaction of carbonyl compounds with α-silyl carbanions. In this reaction the silicon atom performs an analogous function to the phosphorus atom in stabilizing the carbanion and promoting elimination of the oxygen.



(17)

This method of alkene formation was first described by Peterson.[87] It has proven to be particularly useful in the preparation of strained alkenes, such as allene oxides,[88] cyclopropenes,[89] and bridgehead alkenes,[90] and hetero-substituted alkenes.[91]

The elimination of R_3SiO^- from the adduct to form the alkene is usually spontaneous, but in some cases, particularly terminal alkenes, the β-hydroxysilane can be isolated. When the elimination is not spontaneous, it can be brought about under either acidic or basic conditions[92] or by treatment with thionyl chloride or acetyl chloride.[93]

In general α-silyl carbanions are more reactive toward carbonyl compounds than the corresponding phosphonium ylids and give fewer side reactions than the phosphonate carbanions. The silicon method has been used to prepare α,β-unsaturated esters from both aldehydes and ketones.[94]

$$Me_3SiCH_2COOR \xrightarrow{LiNR'_2} Me_3SiCHCOOR \quad (Li) \xrightarrow{>C=O} >C=CHCOOR \qquad (18)$$

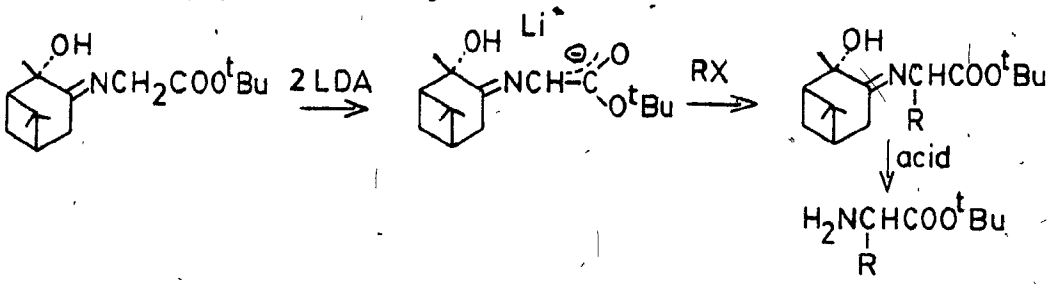
The reactivity of α-silyl carbanions and their success in forming hetero-substituted alkenes made this an attractive method for the synthesis of an α,β-unsaturated ester with an α-nitrogen functionality.

Alkylation of Glycine Derivatives

There have been a number of recent reports of the preparation of amino acids from Schiff base derivatives of glycine esters. These reactions usually involve the alkylation of the anion of the glycine derivative with alkyl iodides or benzyl or allyl bromides. If the anion were to react with trimethylsilyl chloride instead of an alkyl halide the silyl glycine could then be used in the olefination

reaction to give an α,β-unsaturated amino acid derivative. Various glycine Schiff bases have been described which have somewhat different reactivities.

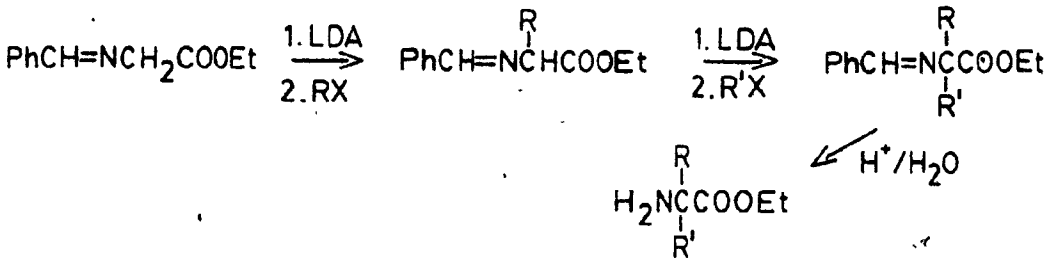
An asymmetric amino acid synthesis has been reported using the Schiff base formed from (1S,2S,5S)-2-hydroxypinan-3-one and glycine t-butyl ester.[95]



(19)

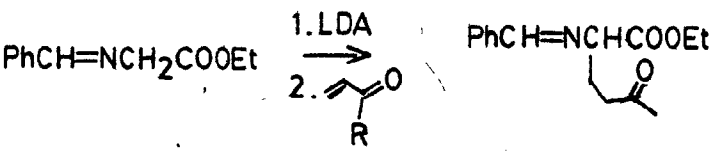
Monoalkylation occurred with several alkylating agents, but dialkyation did not occur even when an excess of alkylating agent was used.

A report by Stork appeared shortly after this one, which described the mono- and dialkylation of the benzylidene derivative of glycine ethyl ester.[96]



(20)

Dialkylation could be carried out in two steps using two different alkyl halides. In addition to reacting with alkyl halides the anion gave Michael addition with α,β-unsaturated esters and ketones.



(21)

Bey and Vevert reported the alkylation of the benzylidene derivative of amino acid methyl esters other than glycine.[97] The results were similar to those reported by Stork for the glycine derivatives, but there was no mention of Michael additions.

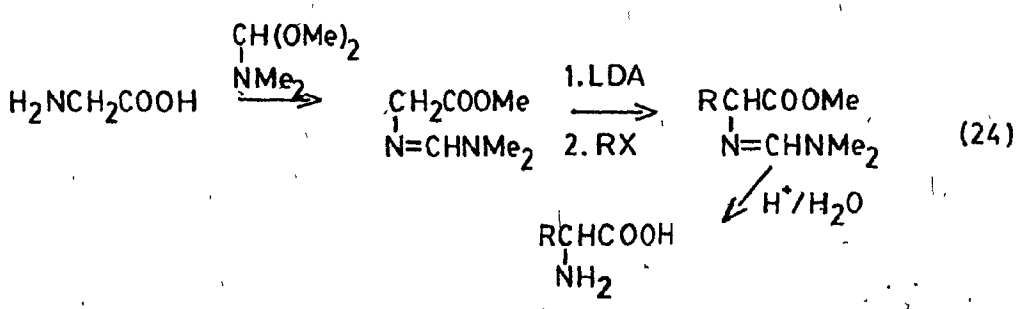
A more stable Schiff base of glycine ethyl ester from condensation with benzophenone was also reported to undergo alkylation.[98]

$$Ph_2C{=}NCH_2COOEt \xrightarrow[2.RX]{1.LDA} Ph_2C{=}N\underset{R}{C}HCOOEt \longrightarrow H_2N\underset{R}{C}HCOOEt \qquad (22)$$

In this case only monoalkylation occurred. In addition to alkylation of the anion under the usual anhydrous conditions this alkylation could be carried out using phase transfer catalysis at room temperature.

$$Ph_2C{=}NCH_2COOEt + RX \xrightarrow[10\%.NaOH/CH_2Cl_2]{nBu_4N^+HSO_4^-} Ph_2C{=}N\underset{R}{C}HCOOEt \qquad (23)$$

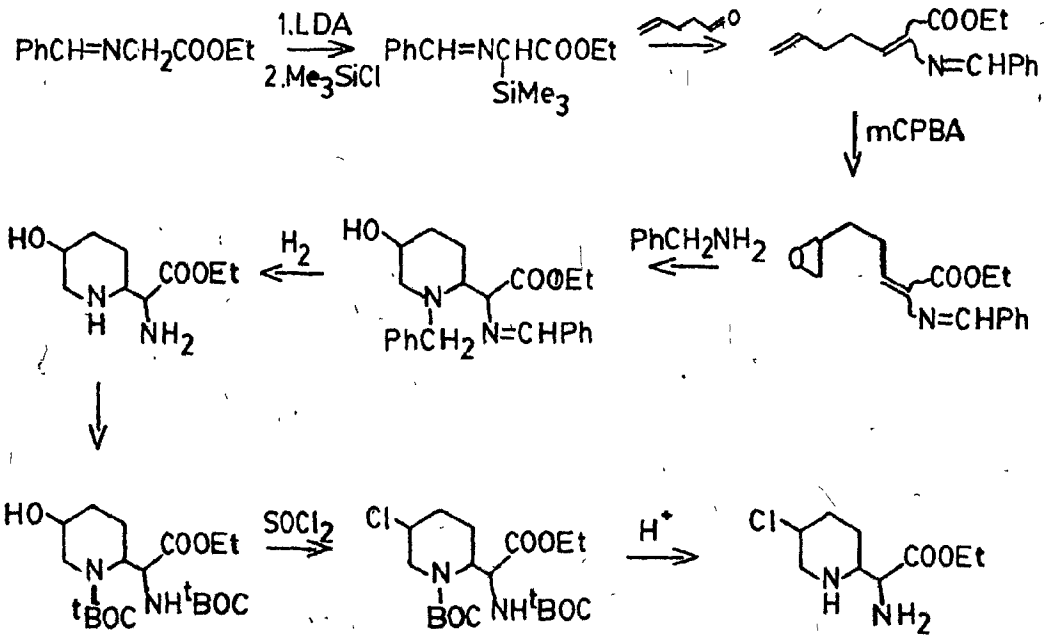
A preparation of amino acids similar to these methods is the alkylation of a formamidine derivative of an amino acid methyl ester.[99] The amino acid derivatives were formed by refluxing the free amino acid with dimethyl formamide dimethyl acetal, forming the ester and amidate at the same time.



(24)

The alkylation of these compounds occurred just as with the Schiff base derivatives. They also gave a Michael addition reaction similar to that reported by Stork, and reacted sluggishly with benzaldehyde and not at all with ketones.

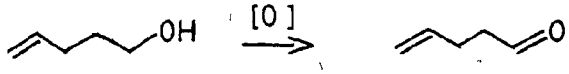
The ease of the alkylation reaction with benzylidene glycine ethyl ester made it seem a useful starting material for the silylation and olefination reactions which would produce an α,β-unsaturated amino acid derivative. With this as a starting point, then, a possible scheme for the synthesis of (5-chloro-2-piperidyl) glycine was outlined.



Scheme 2

4-Pentenal

The carbonyl compound chosen for the olefination reaction was 4-pentenal since its terminal double bond would provide a handle for introduction of the chlorine and formation of the piperidine ring. A seemingly straightforward means of preparing this aldehyde was the oxidation of 4-penten-1-ol.



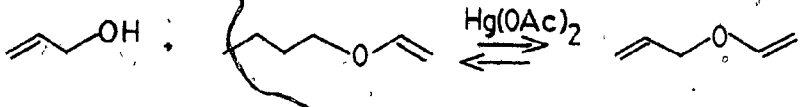
(25)

The oxidation occurr smoothly with Collins reagent[100] (CrO_3-pyridine complex in methylene chloride) indicated by the appearance of a signal at δ9.7 in the nmr of the reaction mixture. However, isolation of the volatile aldehyde from the large amount of solvent needed in this reaction proved very difficult.

The use of polymer supported reagents in many reactions has made work-up and isolation of the product much easier than with one-phase reactions. A polymer supported chromic acid reagent has been reported[101] to oxidize alcohols to aldehydes and ketones. The reagent is formed by treatment of an anion exchange resin with an aqueous solution of chromium trioxide. The alcohol is then stirred with a slurry of the resin in an appropriate solvent at reflux. Hexane, benzene, chloroform, and tetrahydrofuran were reported to be suitable solvents.

When 4-penten-1-ol was stirred with the CrO_3-resin in refluxing hexane, the oxidation was complete after three hours (GLC showed disappearance of starting material and nmr showed a singlet at δ9.1). The resin was filtered off and the hexane solution was carefully distilled. NMR of the distillate showed that the aldehyde had been carried over with the hexane (peak at δ9.1). When the oxidation was repeated in ether, the reaction was not complete after 48 hours and the resin beads had broken up. The use of triglyme as solvent with heating at 80° also gave a very slow reaction.

The 4-pentenal was, finally, prepared by the thermal Claisen rearrangement of allyl vinyl ether.[102] Allyl vinyl ether was prepared by mercuric acetate catalyzed vinyl transetherification of n-butyl vinyl ether and allyl alcohol.[103]



(26)

The allyl vinyl ether (b.p. 68°) was continuously distilled out of the reaction mixture.

The allyl vinyl ether was then heated in 1-methyl naphthalene and rearranged to 4-pentenal by a 3,3-sigmatropic shift process.

(27)

The nmr of the product showed the presence of the aldehyde (a one-proton triplet at δ9.7) and the terminal double bond (a one-proton multiplet at δ5.8 and a two-proton multiplet at δ5.1), and the IR showed a strong carbonyl absorption at 1720 cm^{-1} and a weak C=C absorption at 1640 cm^{-1}.

Silylation of Glycine Derivatives

Having prepared the aldehyde needed for the olefination reaction, the silyl glycine had to be prepared. Glycine ethyl ester was condensed with benzaldehyde to form the benzylidene derivative.[96]

$$EtOOCCH_2NH_2 \cdot HCl + PhCHO \xrightarrow[MgSO_4,\ CH_2Cl_2]{Et_3N} EtOOCCH_2N{=}CHPh \qquad (28)$$

The benzylidene glycine ethyl ester was treated with one equivalent of lithium diisopropylamide in tetrahydrofuran at -78° and, after stirring 1/2 hour, one equivalent of trimethylchlorosilane was added. The mixture was allowed to warm to room temperature before work-up with saturated ammonium chloride and ether. Solvent removal lead to recovery of the starting benzylidene glycine ethyl ester.

The formation of the anion was confirmed by adding n-butyl bromide to the benzylidene glycine ethyl ester-lithium diisopropylamide mixture at -78°. Work-up of this reaction gave the alkylated product as indicated by the appearance in the nmr of a multiplet at δ1.6-δ0.9 and disappearance of the singlet of the glycine methylene group at δ4.3.

$$PhCH{=}NCH_2COOEt \xrightarrow[2.nBuBr]{1.LDA} PhCH{=}NCH(CH_2CH_2CH_2CH_3)COOEt \qquad (29)$$

Since it seems unlikely that trimethylchlorosilane would not have reacted with the anion, it must be that the product formed was not stable to the conditions used for work-up. Carbon-trimethylsilyl bonds are generally stable to these conditions, but oxygen-trimethylsilyl bonds are not. The most likely product to have been formed in this reaction, then, is the O-silylated product, a ketene acetal.

$$PhCH{=}NCH{-}C(=O)OEt + Me_3SiCl \longrightarrow PhCH{=}NCH{=}C(OSiMe_3)OEt + Cl^{\ominus} \qquad (30)$$

On work-up this product would be hydrolyzed back to the starting material. That this conclusion is reasonable may be seen by comparison with results in related systems.

N,N-bis(trimethylsilyl)glycine esters have been reported[104] to be alkylated at the carbon by treatment with base and an alkyl halide or an aldehyde. However, when the anion reacted with trimethylchlorosilane, O-silylation took place.

$$(Me_3Si)_2NCH_2COOEt \xrightarrow{base} \begin{cases} \xrightarrow{RX} (Me_3Si)_2NCH(R)COOEt \\ \xrightarrow{RCHO} (Me_3Si)_2NCH(CHR{-}OH)COOEt \\ \xrightarrow[Me_3SiCl]{} (Me_3Si)_2NCH{=}C(OEt)OSiMe_3 \end{cases} \qquad (31)$$

Similar results were reported by Rathke and Sullivan on the silylation of lithium ester enolates.[105] Silylation of methyl or ethyl acetate gave predominantly O-silylation and ethyl esters of higher acids gave almost exclusively O-silylation. Tert-butyl esters gave better yields of the C-silylated products. t-butylacetate gave essentially only C-silylation and t-butyl butanoate gave 60% C-silylation.

$$RCH_2COOR' \xrightarrow[2.Me_3SiCl]{1.LDA} \underset{\displaystyle SiMe_3}{\underset{|}{RCH}}COOR' + RCH=C\begin{matrix}OSiMe_3\\ OR'\end{matrix} \qquad (32)$$

It appears, then, that substitution in the alcohol part of the ester (e.g. R'=t-butyl) favors C-silylation and substitution at the -carbon (R≠H) favors O-silylation.

Since a t-butyl ester would be more likely than an ethyl ester to give C-silylation, benzylidene glycine t-butyl ester was prepared. Unfortunately, this ester did not give C-silylation either, even when hexamethylphosphoramide was used as a cosolvent; only the starting material was recovered.

$$PhCH=NCH_2COO^tBu \xrightarrow[2.Me_3SiCl]{1.LDA} \not\rightarrow \quad PhCH=N\underset{\displaystyle SiMe_3}{\underset{|}{C}}HCOO^tBu \qquad (33)$$

α,β-unsaturated-α-silyl Esters

One result which contradicts the trend set by the others is Rathke's report[106] that t-butyl trimethylsilyl acetate could be silylated on the carbon a second time, giving t-butyl bis(trimethylsilyl) acetate. The reaction gave 70% of the C-silylated product and 30% of the O-silylated product.

$$Me_3SiCH_2COO^tBu \xrightarrow[2.\ Me_3SiCl]{1.\ LDA} \underset{70\%}{(Me_3Si)_2CHCOO^tBu} + \underset{30\%}{Me_3SiCH{=}C(OSiMe_3)(O^tBu)} \qquad (34)$$

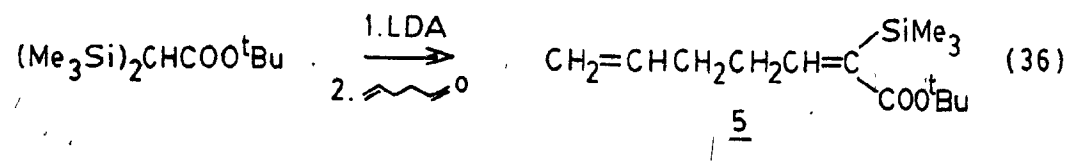
Tert-butyl bis(trimethylsilyl) acetate has been used to prepare α,β-unsaturated-α-silyl esters.[106]

$$(Me_3Si)_2CHCOO^tBu \xrightarrow[2.\ RR'CO]{1.\ LDA} RR'C{=}C(SiMe_3)(COO^tBu) \qquad (35)$$

Vinyl silanes readily undergo electrophilic substitution resulting in replacement of the silyl group by the electrophile.[107] Halogens are among the electrophiles which readily displace a vinyl silyl group, so an α,β-unsaturated-α-silyl ester should be readily converted to an α,β-unsaturated-α-halo ester. The α-halogen would allow introduction of the α-amino group of the target compound by nucleophilic substitution later in the synthesis.

Tert-butyl bis(trimethylsilyl) acetate was prepared and treated at -78° with lithium diisopropylamide, then 4-pentenal was added. The reaction was worked up and the product was

purified by distillation (b.p. 52°, 0.05 mm).

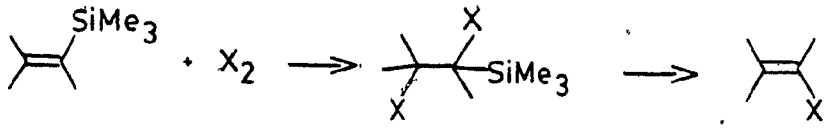


(36)

5

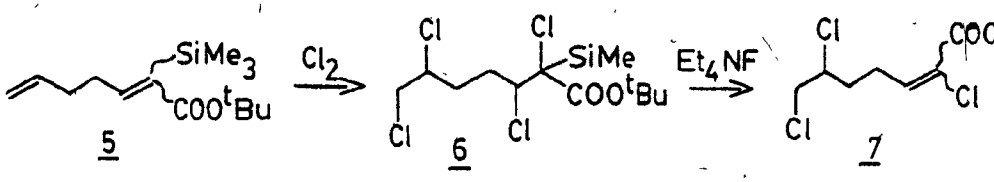
IR of the product shows the ester (1700 cm^{-1}) and two carbon-carbon double bonds (1640 cm^{-1} and 1605 cm^{-1}). GLC and nmr show the presence of the two different geometrical isomers at the 2,3-double bond. In the nmr there are two triplets (δ7.0 and δ6.1) for the vinyl proton at C-3 and two singlets each for the t-butyl (δ1.6 and δ1.55) and trimethylsilyl (δ0.2 and δ0.3) groups. The product, then, is an almost equal mixture of E and Z t-butyl 2-trimethylsilyl-2,6-heptadienoate.

The electrophilic substitution of a vinyl silyl group by chlorine or bromine occurs by addition of the halogen to the double bond, followed by desilicohalogenation. With alkenylsilanes the reaction with bromine occurs with inversion of stereochemistry at the double bond,[108-110] presumably due to anti-addition of bromine across the double bond, followed by anti-elimination of bromosilane. The elimination step may be spontaneous,[110] but often the dihalo compound can be isolated, and elimination occurs on stirring in a polar solvent, such as acetonitrile[110] of dimethylsulfoxide,[111] or by treatment with base[108] or fluoride ion.



(37)

When t-butyl 2-trimethylsilyl-2,6-heptadienoate was treated with chlorine, the tetrachloro adduct was formed. Elimination occurred on treatment with tetraethylammonium fluoride.

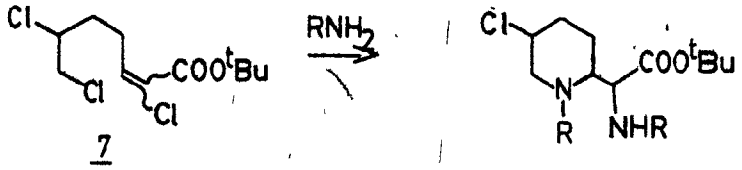


5 6 7

(38)

The tetrachloro compound (6) was not purified, but nmr of the crude product of the chlorination showed the presence of the trimethylsilyl group (δ0.1, singlet) and the absence of vinyl protons. After desilicohalogenation the trimethylsilyl peak in the nmr had disappeared, and the triplets for the vinyl proton at C-3 had reappeared at δ6.9 and δ6.3. A three proton multiplet at δ3.7 indicated the protons on C-6 and C-7 where chlorine had also added. The IR showed the presence of the ester (1720 cm^{-1}) and one carbon-carbon double bond (1615 cm^{-1}).

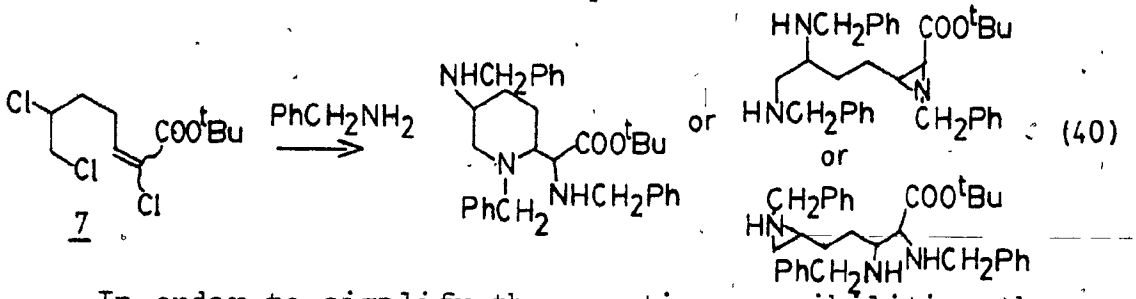
This trichloro compound 7 could, perhaps, react with ammonia or a primary amine to give both the piperidine ring and the α-amino group.



7

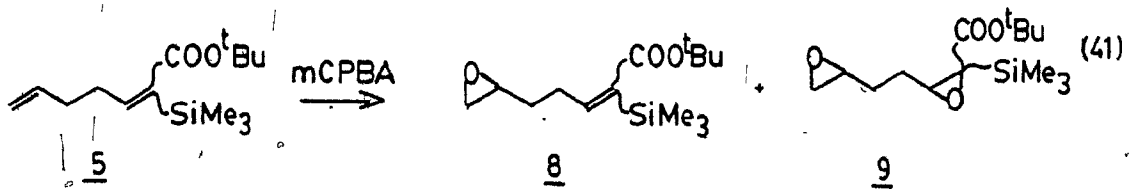
(39)

The reaction of the trichloride 7 with ammonia was very sluggish, so benzylamine was used. A solution of 7 and two equivalents of benzylamine in toluene was refluxed for 24 hours, at which time glc showed no benzylamine, but still some 7 as well as a new peak. When an excess of benzylamine was used, all the 7 reacted and the same product peak appeared in the glc. NMR of the product indicates the presence of three benzyl groups (a fifteen proton singlet at δ7.3 and a six proton broad singlet at δ3.8), and no vinyl proton. The IR absorption for the carbon-carbon double bond at 1615 cm^{-1} had also disappeared. The product was not fully characterized, but there are several possibilities.



(40)

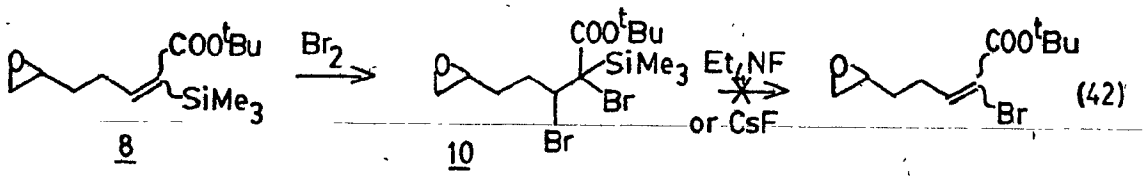
In order to simplify the reaction possibilities the terminal double bond of the vinylsilane 5 was epoxidized before halogenation, as had been planned in the original synthetic plan (Scheme 2).



(41)

The reaction of compound 5 with meta-chloroperbenzoic acid gave mostly the desired terminal epoxide. The nmr signals at δ5.8 and δ5.0 in 5 were not present in the spectrum of 8, and the absorption at 1605 cm^{-1} did not appear in the IR. A small amount of the diepoxide 9 was also formed. It showed no vinyl protons in the nmr and no carbon-carbon double bonds in the IR, the carbonyl absorption shifted to 1750 cm^{-1}.

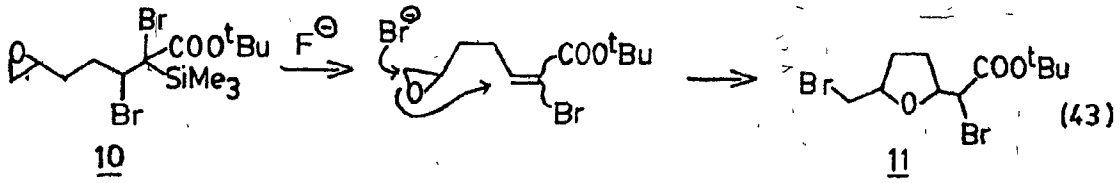
The epoxide 8 was then brominated with the expectation that debromosilylation would give the α-bromo-α,β-unsaturated ester. The dibromo adduct was obtained easily, but treatment with either tetraethylammonium fluoride or cesium fluoride led to loss of the trimethylsilyl group, but not regeneration of the double bond.



8 10 (42)

The nmr of the product showed no trimethylsilyl group and no vinyl proton; IR showed the ester carbonyl (1750 cm^{-1}), but no carbon-carbon double bond and no hydroxyl group. The highest peak in the mass spectrum was a cluster at 300, 302 and 304 indicating the presence of two bromine atoms. Since t-butyl esters rarely give a molecular ion, but lose isobutylene in a McLafferty rearrangement, it is assumed that the molecular weight of the product is 356. This would correspond to the trimethylsilyl group's being lost and a

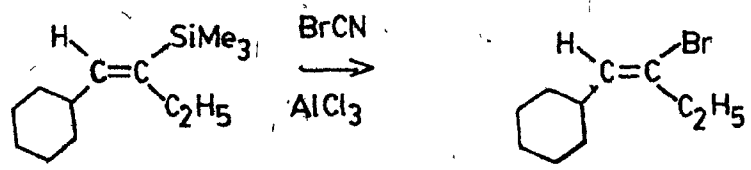
hydrogen added. The presence of the t-butyl group is evident from the nmr; singlets at δ1.55 and δ1.5. In the mass spectrum there are peaks of equal intensity at m/e 207 and 209, indicating the presence of one bromine. This fragment can result from loss of isobutylene and $-CH_2Br$, implying the presence of a bromomethyl group in the molecule. Probably the normal loss of bromide ion occurred, but it then attacked the epoxide, opening the ring. The oxygen gave a Michael addition to the double bond producing a tetrahydrofuran structure (11).



10 11 (43)

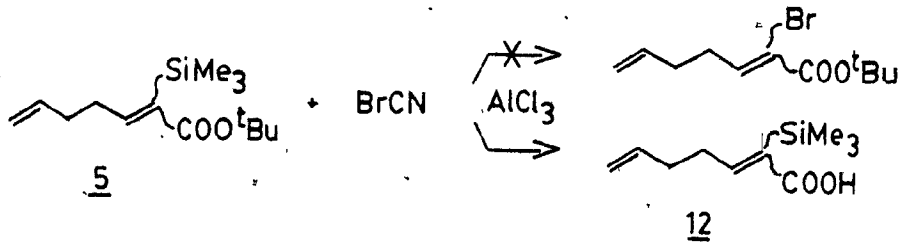
Although vinyl silanes have been reported[108,110] to react with iodine to give the corresponding vinyl iodides with retention of configuration, when compound 8 was treated with iodine, no reaction occurred.

The reaction of vinyl silanes with cyanogen bromide in the presence of aluminum trichloride has been reported[110] to give substitution of bromine for the silyl group with retention of configuration.



(44)

When compound 5 was treated with cyanogen bromide and aluminum trichloride, the trimethylsilyl group was not displaced, but the t-butyl ester was hydrolyzed.



5 12 (45)

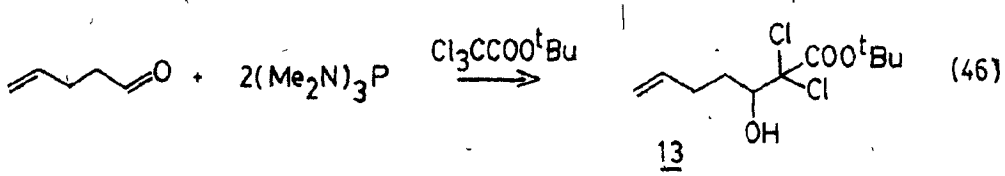
In the nmr of the product the peaks for the t-butyl group were not seen, but there was a peak at δ0.1 for the trimethylsilyl group and a broad singlet at δ11.2 for the carboxylic acid proton. The carbonyl absorption in the IR had shifted to 1680 cm^{-1}.

α,β-unsaturated-α-halo Esters

Since the electrophilic substitution of the vinyl silane did not give the desired α,β-unsaturated-α-halo ester, other methods for the formation of this system were tried. The two methods which used a trichloroester and a phosphine, either triphenylphosphine or tris(dimethylamino)phosphine, in reaction with an aldehyde were appealing for their simplicity.

The method[86] using tris(dimethylamino)phosphine was tried first. To a mixture of 4-pentenal and two equivalents of tris(dimethylamino)phosphine in tetrahydrofuran at -20° was added one equivalent of t-butyl trichloroacetate. Following the reaction by glc showed disappearance of both the ester and the aldehyde. The product isolated, however, was not the desired α-chloro-α,β-unsaturated ester. The

expected vinyl proton triplet did not appear in the nmr and the IR indicated a hydroxyl group (3470 cm^{-1}).

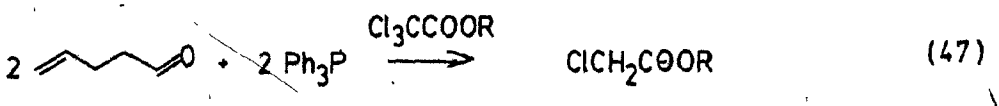


(46)

13

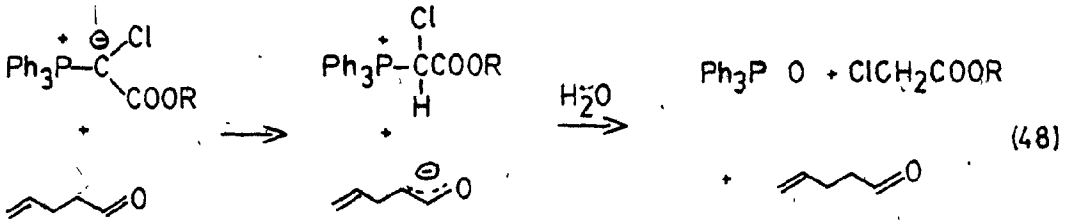
Apparently the intermediate alkoxide ion was not deoxygenated despite the presence of a second equivalent of phosphine, nor did it cyclize to the epoxide. The structure of this product was deduced from its nmr and IR spectra, but it was not fully characterized. The terminal double bond appears in the IR at 1645 cm^{-1} and the vinyl protons are seen in the nmr. The ester carbonyl absorbs at 1750 cm^{-1}. When the reaction was repeated at room temperature and at -40°, the same product was obtained.

The triphenylphosphine method[84] was also applied to 4-pentenal. To a solution of two equivalents each of 4-pentenal and triphenylphosphine in methylene chloride or tetrahydrofuran was added one equivalent of either benzyl or t-butyl trichloroacetate. Following the reaction by glc showed disappearance of the acetate. When no acetate remained, the reaction was worked up, but the only product recovered was benzyl or t-butyl chloroacetate.



(47)

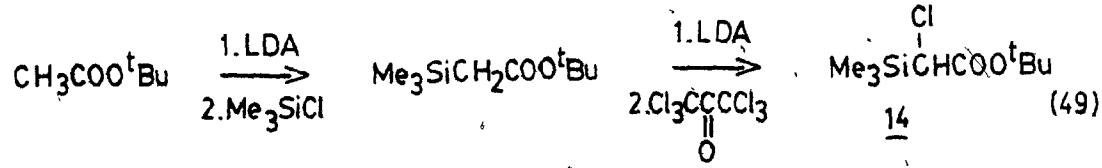
Any aldehyde present in the crude product would have been lost when the solvent was evaporated. The most likely explanation of these results is that the ylid formed preferred proton exchange with the enolizable aldehyde to nucleophilic attack on the carbonyl.



(48)

Since these methods using organophosphorus reagents were unsuccessful in forming the desired α,β-unsaturated-α-chloro ester, the possibilities of the silicon olefination reaction were further considered. If an α-chloro-α-trimethylsilyl acetate were prepared its anion should react with 4-pentenal to give the desired compound. Two possibilities for preparing t-butyl α-chloro-α-trimethylsilyl acetate were the chlorination of t-butyl trimethylsilyl acetate or the silylation of t-butyl chloroacetate.

Tert-butyl trimethylsilylacetate was chlorinated, in about 60% yield, by reaction of its anion with hexachloroacetone.[112]



(49)

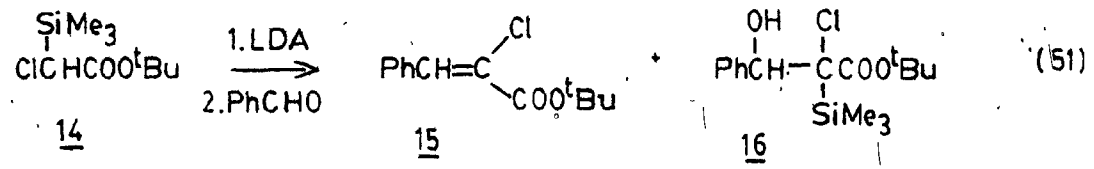
Despite the difficulties encountered in the silylation of the glycine derivatives, the C-silylation of t-butyl chloroacetate was successful.

$$ClCH_2COO^tBu \xrightarrow[2.\,Me_3SiCl]{1.\,LDA} \underset{\underline{14}}{ClCHCOO^tBu} \quad (SiMe_3) \qquad (50)$$

Distillation of the crude product gave a 50% yield of t-butyl trimethylsilyl-α-chloroacetate, and recovery of 30% of the t-butyl chloroacetate. Thus, both C-silylation and O-silylation must have occurred, but a reasonable yield of the C-silylated product was obtained and the t-butyl chloroacetate recovered could be recycled. This method of preparing compound 14 was preferred since it required only one step rather than the two steps involved in the preparation and chlorination of the silylacetate.

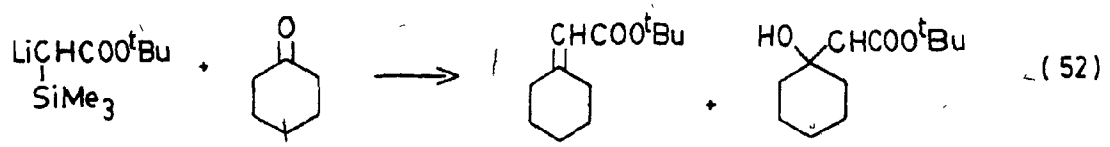
The olefination reaction of t-butyl trimethylsilylchloroacetate was first investigated using benzaldehyde. The acetate was added to a solution of lithium diisopropylamide in tetrahydrofuran at -78°, and, after 1/2 hour, one equivalent of benzaldehyde was added. After the reaction mixture warmed to room temperature it was worked up (saturated ammonium chloride solution/pentane). NMR (Figure 6) of the crude product showed a singlet at δ0.1 indicating that the elimination of the trimethylsilyl group was not complete, but singlets at δ7.0 and δ7.7 indicated that some of the desired

product had been formed. The IR of the crude product showed the presence of an -OH group (3380 cm^{-1}), also indicating that elimination was not complete.



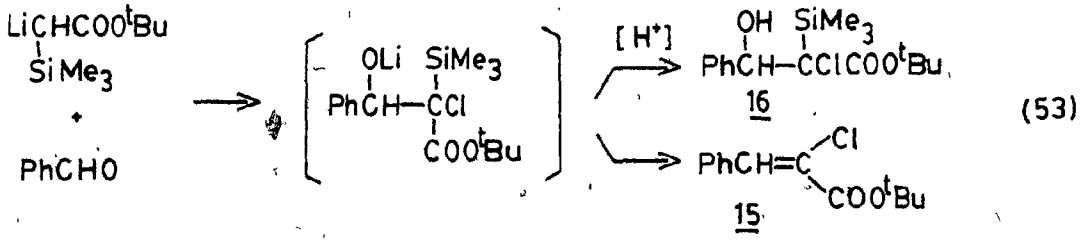
14 15 16 (51)

Rathke reported[94a] a similar result when the reaction between lithio-t-butyl trimethylsilylacetate and cyclohexanone was quenched at -78°.



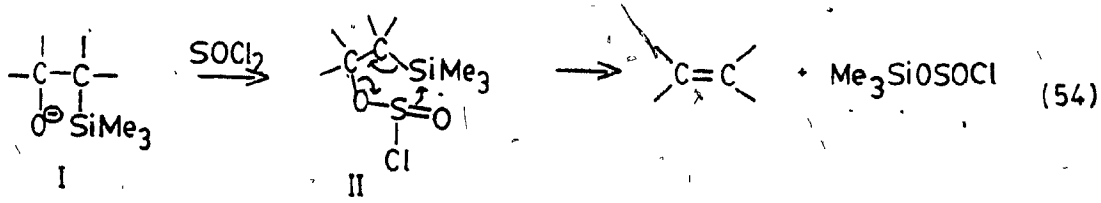
(52)

The hydroxysilane was formed by protonation of the intermediate adduct, and the vinyl ester by elimination of Me_3SiOLi.



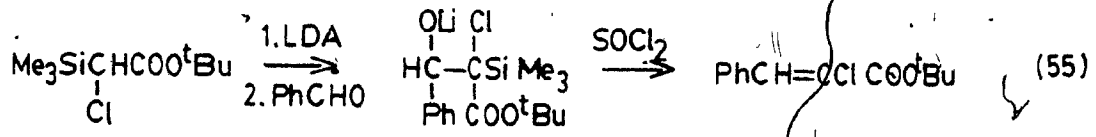
16 15 (53)

In the preparation of terminal alkenes from trimethylsilylmethyllithium and a carbonyl compound the elimination was not spontaneous and the β-hydroxysilane was isolated.[93] Elimination in this case could be brought about by treatment of the adduct *in situ* with thionyl chloride or acetyl chloride. It is assumed that thionyl chloride reacts with the adduct I forming intermediate II, which then undergoes elimination.



I II (54)

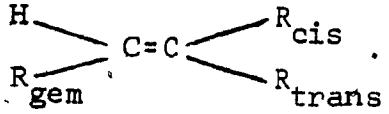
The reaction between lithio-t-butyl trimethylsilyl-chloroacetate and benzaldehyde was repeated, but after the mixture was stirred at -78° for 1/2 hour, it was warmed to 0° and two equivalents of thionyl chloride were added. The reaction was maintained at 0° for 1/2 hour and at room temperature for one hour, then worked up. NMR (Figure 7) of the crude product showed no trimethylsilyl peak. The product was purified by thin layer chromatography.



14 15 (55)

The nmr showed two different vinyl proton singlets (δ7.0 and δ7.8) and two different t-butyl singlets (δ1.4 and δ1.6), and glc showed two peaks of almost equal size. This indicates that both the E and Z isomers were formed.

The chemical shift of an olefinic proton can be estimated[113] by the equation $\delta = 5.25 + Z_{gem} + Z_{cis} + Z_{trans}$ where the Z factors are shielding values for the substituents



. Using this equation the vinyl protons

of compound 15 are calculated to have chemical shifts of δ7.94 for the Z isomer and δ7.36 for the E isomer. Although these values are not exactly those observed it may be assumed that the lower field signal is indeed that of the Z isomer. Measurement of the relative amounts of the isomers from the glc or nmr gave a Z:E ratio of 56%:44%.

This olefination reaction was applied to a variety of aldehydes and ketones (Table 1), most of which gave good yields of the α-chloro-α,β-unsaturated esters. Most of the reactions showed little stereoselectivity, giving almost equal amounts of the Z and E isomers. The greater stereoselectivity was seen with those carbonyl compounds in which one substituent was considerably bulkier than the other; the Z alkene predominated in the product. The predominance of the Z isomers is confirmed by nmr in the reactions with aldehydes by the relative intensities of the vinyl proton signals, but is assumed for the ketones on the basis of steric preference.

With the exception of t-butyl 2-chloro-3-phenylacrylate none of these compounds gave a molecular ion in the mass spectrum, the highest mass ion being $[M^{+\cdot} - 56]$ from the McLafferty rearrangement of the t-butyl ester. The molecular ions at m/e 238 and 240 of t-butyl 2-chloro-3-phenyl-acrylate did appear. The base peak in all cases was either $[M - 56]^{+\cdot}$ or m/e 57.

The reaction with 4-pentenal gave the desired t-butyl 2-chloro-2,6-heptadienoate in 49% yield. (b.p. 68-70°, 1.0 mm).

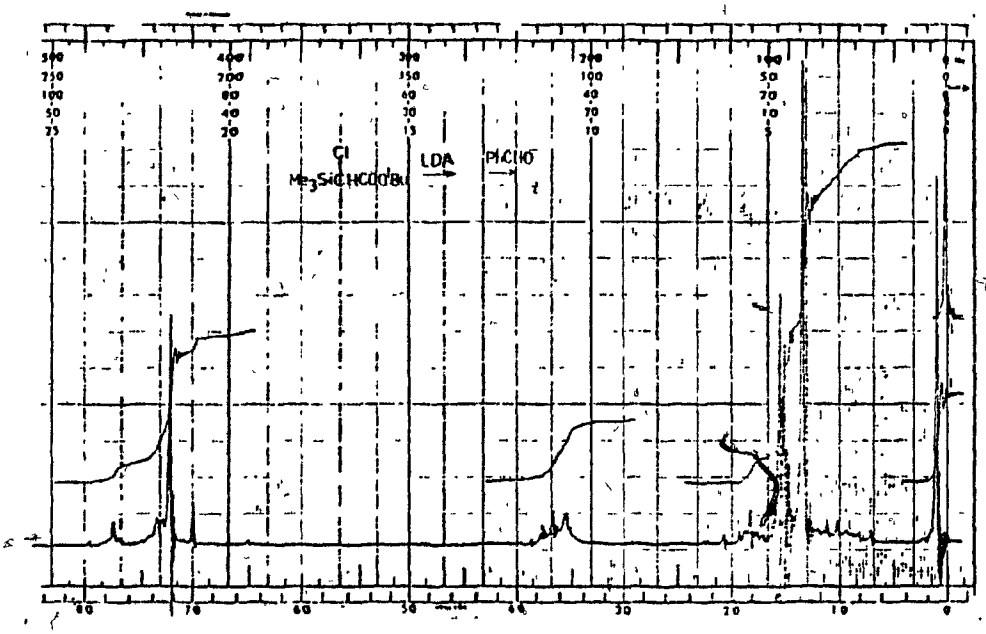


Figure 6.

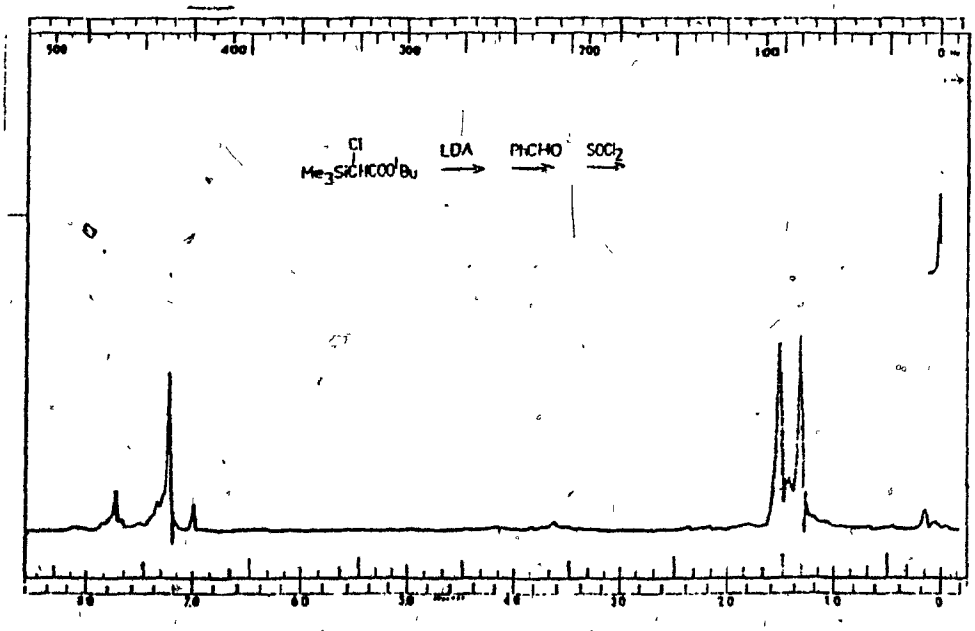
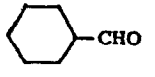
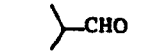
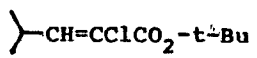
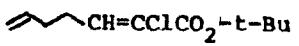
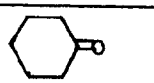
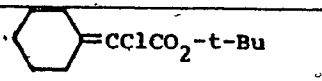
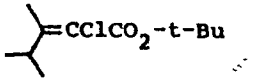
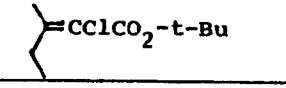
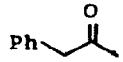
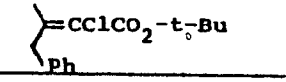
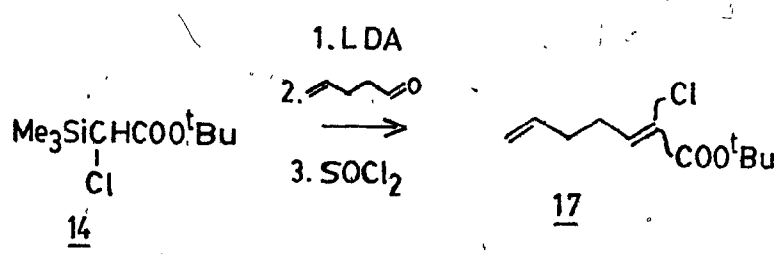


Figure 7.

TABLE I. Synthesis of α-chloro-α,β-unsaturated esters.

Carbonyl Compound	Product	Isolated yield (%)[a]	Ratio of isomers[b] (Z:E)	^{1}H nmr and ir data[d,e]
C_6H_5CHO	$C_6H_5CH{=}CClCO_2$-t-Bu	55	54:46	1.4 and 1.6(s,9H), 7.1 and 7.8(s,1H), 7.3(s,5H); 1720
		44	56:44	1.6(s,9H), 1.3-1.8(b,11H), 6.1 and 6.8(d,1H); 1715, 1725
		25	64:36	1.00 and 1.05(d,6H); 1.5 (s,9H), 2.9(m,1H), 6.0 and 6.7(d,1H); 1720, 1730
		49	66:34	1.6(s,9H), 2.4(m,4H), 5.1 (m,2H), 5.8(m,1H), 6.3 and 6.9(t,1H); 1715, 1722
		44	-	1.5(s,9H), 1.6(b,6H), 2.5 (m,4H); 1720
		17	82:18	1.05(d,6H), 1.5(s,9H),1.8 (s,3H), 3.3(m,1H); 1715, 1730
		55	51:49	1.0(m,3H); 1.5(s,9H),1.9 and 2.1(s,3H), 2.3(m,2H); 1715
		40	77:23	1.5(s,9H), 1.8 and 1.95 (s,3H), 3.8(s,2H), 7.2 (s,5H); 1715

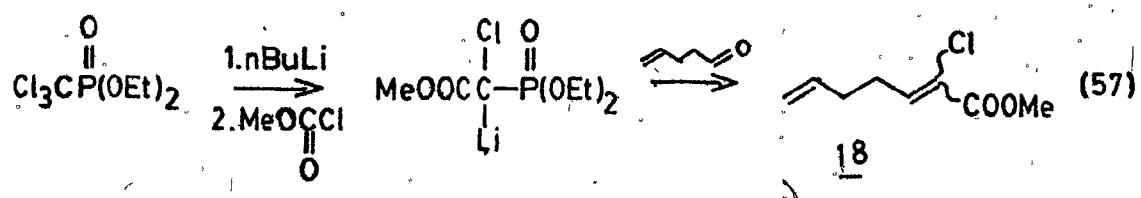
(a) Isolated yield of the pure product by distillation or thin layer chromatography.
(b) Ratio of isomers estimated by GLC.
(d) ^{1}H nmr are reported in δ ppm in CCl_4 solution; IR spectra are reported in cm^{-1} as neat.
(e) The purity and molecular weight of each compound has been ascertained by GC-MS.



14 17 (56)

The nmr indicated the presence of both isomers of the α,β-unsaturated ester (triplets at δ6.3 and δ6.9). The terminal double bond gave signals at δ5.8 and δ5.1 and the t-butyl ester appeared as a singlet at δ1.6. In the IR there were carbonyl peaks at 1715 cm^{-1} and 1722 cm^{-1} and carbon-carbon double bond peaks at 1630 cm^{-1} and 1640 cm^{-1}. The base peak in the mass spectrum was m/e 57, and the highest mass peak was m/e 160 with the chlorine isotope peak at m/e 162, this peak was loss of isobutylene from the molecular ion.

The report of the preparation of α,β-unsaturated-α-chloroesters using diethyltrichloromethanephosphonate appeared after this work had been completed. Applying this method to 4-pentenal gave the methyl analogue of compound 17, methyl 2-chloro-2,6-heptadienoate.



18 (57)

As with the silicon method, both isomers were formed as indicated by two peaks of almost equal size in the glc and

two triplets for the proton at C-3 in the nmr (δ6.3 and δ6.9). This method offered no advantage over the silicon method, and would not be applicable to preparation of the readily cleaved t-butyl ester since t-butyl chloroformate is not stable.

The preparation of compound 17 provided a useful intermediate for the synthesis, however, its use would require the replacement of the chlorine by an amino group later in the synthesis. A similar compound with a nitrogen functionality instead of the chlorine would perhaps be a more convenient intermediate. The preparation of t-butyl azidoacetate, then, was investigated. First, t-butyl azidoacetate was prepared by the reaction of t-butyl chloroacetate with sodium azide.[114]

$$ClCH_2COO^tBu + NaN_3 \xrightarrow[H_2O]{\text{acetone}} N_3CH_2COO^tBu \qquad (58)$$

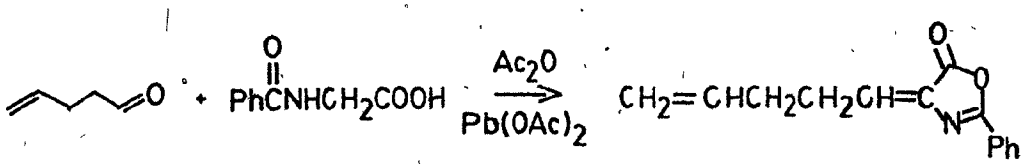
Silylation of t-butyl azidoacetate under the same conditions used for t-butyl chloroacetate was not successful. When the azidoacetate was added to the lithium diisopropylamide solution, a deep purple color formed which persisted after the addition of trimethylchlorosilane. After work-up the crude product would not distill and nmr showed only a signal for the t-butyl group (δ1.4). The IR spectrum showed the azido group (2110 cm^{-1}) and ester group (1735 cm^{-1}) to be present.

$$N_3CH_2COO^tBu \xrightarrow[2.\ Me_3SiCl]{1.\ LDA} N_3CH(SiMe_3)COO^tBu \qquad (59)$$

Since the anion appeared to be polymerizing despite the low temperature of the reaction mixture, the azidoacetate and trimethylchlorosilane were mixed together and the mixture added dropwise to the LDA solution so the silylchloride could react with the anion as soon as it was formed. However, the same purple color appeared as before and none of the desired product was formed. The result was the same when the reaction was run at -100°.

The two direct methods of formation of α,β-unsaturated-α-amino acid derivatives, the Erlenmeyer azlactone synthesis[75,76] and the reaction of a carbonyl compound with an isocyanoacetate,[77] were also carried out with 4-pentenal.

Robertson's modification[76] of the Erlenmeyer azlactone synthesis was used. A mixture of hippuric acid, 4-pentenal, acetic anhydride, and lead acetate reacted in refluxing tetrahydrofuran. The disappearance of the aldehyde was monitored by nmr.

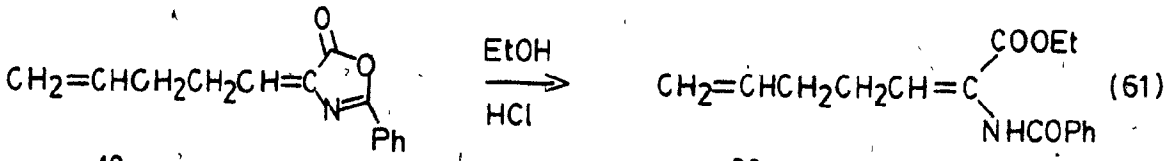


(60)

19

The product, after chromatography on a silica gel column, was a colorless oil and gave one peak on glc. Only one triplet (δ6.5) for the vinyl proton of the conjugated double bond appeared in the nmr. The IR spectrum showed the carbonyl at 1800 cm^{-1} and the C=N at 1670 cm^{-1}.

The azlactone 19 could be converted to the N-benzoyl ethyl ester by solvolysis in ethanol.



19 20 (61)

In following this reaction by glc the single product of the starting material disappeared and two new peaks appeared, but, on further refluxing, one of the new peaks decreased and the other increased. The reaction was worked up when glc showed only one peak. The crude product was chromatographed on silica gel and recrystallized from chloroform/hexane to give colorless crystals, m.p. 99-100°. The nmr showed one triplet (δ6.7) for the vinyl proton of the α,β-unsaturated ester. The IR indicated the N-H (3310 cm^{-1}), ester carbonyl (1720 cm^{-1}), and amide carbonyl (1650 cm^{-1}).

The condensation of 4-pentenal with ethyl isocyanoacetate[77] was also investigated. First, N-formyl glycine ethyl ester[115] was prepared from ethyl glycinate and triethyl orthoformate, then dehydrated[116] with phosgene to give ethyl isocyanoacetate, b.p. 53-55°, 2 mm.

$$HClH_2NCH_2COOEt + HC(OEt)_3 \longrightarrow EtOOCCH_2NHCHO \xrightarrow[Et_3N]{Cl_2CO} EtOOCCH_2N{=}C \quad (62)$$

Reaction of ethyl isocyanoacetate with butyllithium and 4-pentenal gave, after work-up with aqueous acetic acid/ether and chromatography, a colorless oil.

$$C{=}NCH_2COOEt \xrightarrow[2.\ \text{O}]{1.\ n\text{BuLi}} \xrightarrow[H_2O]{\text{HOAc}} CH_2CHCH_2CH_2CH{=}C\begin{matrix}\diagup COOEt \\ \diagdown NHCHO\end{matrix} \quad (63)$$

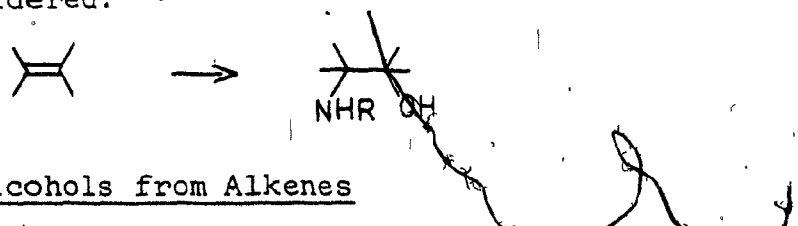
21

The product gave only one peak on glc, but nmr showed the presence of both isomers in approximately equal amounts. There were two triplets (δ7.0 and δ6.4) for the vinyl proton of the α,β-unsaturated ester and the ethyl group appeared as two overlapping quartets (centered at δ4.5 and δ4.1) and two overlapping triplets (centered at δ1.3 and δ1.25). The IR spectrum showed the N-H (3300 cm^{-1}), ester carbonyl (1710 cm^{-1}), and amide carbonyl (1685 cm^{-1}).

CHAPTER IV

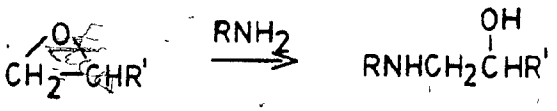
SYNTHESIS OF β-AMINO ALCOHOLS AND FORMATION OF THE PIPERIDINE RING

The synthesis of the α-substituted-α,β-unsaturated esters (compounds 17, 19, 20, and 21) provided intermediates containing all the carbon atoms of the target compound, (5-chloro-2-piperidyl)glycine. The next consideration was functionalization of the terminal double bond to allow introduction of the chloro substituent and formation of the piperidine ring. In view of the problems encountered with the reaction of t-butyl 2,6,7-trichloro-2-heptenoate (compound 7) with benzylamine, it seemed that it would be better to introduce the chlorine after the piperidine ring had been formed. Since alcohols are readily converted to chlorides, methods of forming β-amino alcohols from alkenes were considered.

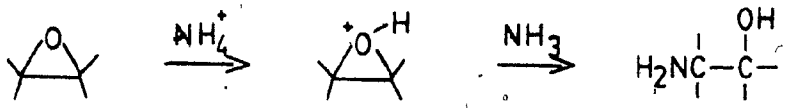


β-amino Alcohols from Alkenes

A common synthesis of β-amino alcohols from alkenes is the epoxidation of the double bond followed by ring opening with ammonia or an amine.[117] With unsymmetrical epoxides the amine attacks predominantly, sometimes exclusively, at the less substituted carbon; thus, terminal epoxides give the 1-amino-2-hydroxy compound.

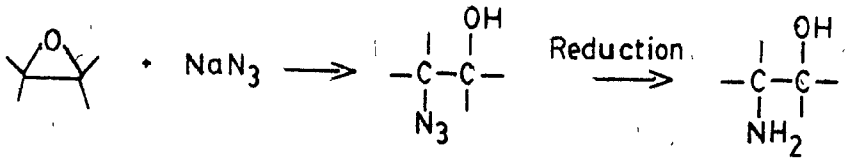


Anhydrous ammonia reacts very poorly with epoxides, but the presence of one equivalent of water greatly enhances the reaction.[118] This suggests that ammonia is not sufficiently nucleophilic to open an unprotonated epoxide, but reacts only after the epoxide has been protonated (presumably by ammonium ion).



These reactions between epoxides and amines are generally carried out at elevated temperatures and/or for long periods of time, so side reactions and decomposition are sometimes a problem. It has been reported[119] that the reaction occurs much more readily in the presence of neutral alumina. In this procedure the amine is first adsorbed on the alumina as a slurry in ether, then the epoxide is added and the reaction occurs at the alumina surface. As in the uncatalyzed reaction, attack on unsymmetrical epoxides is primarily at the less substituted carbon.

A less direct synthesis of β-amino alcohols is the reaction of epoxides with sodium azide and subsequent reduction of the azido alcohol, usually by catalytic hydrogenation or lithium aluminum hydride.[120,121]



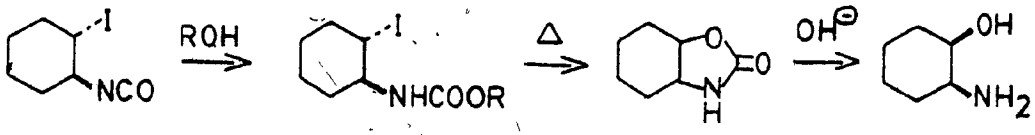
The regioselectivity is the same as in the reaction with amines: azide attacks the less substituted carbon of unsymmetrical epoxides. This method, although it requires the extra reduction step, offers the advantages that sodium azide is easier to handle and more nucleophilic than ammonia. The reaction has been carried out in refluxing aqueous dioxane[120] and at room temperature under phase transfer conditions using either tetrabutyl ammonium bromide or 18-Crown-6.[121]

Other methods for the oxyamination of alkenes do not involve intermediate epoxides. One method starts with the addition of iodine isocyanate to a double bond;[122] the iodine isocyanate is generated in the presence of the alkene from iodine and silver isocyanate.

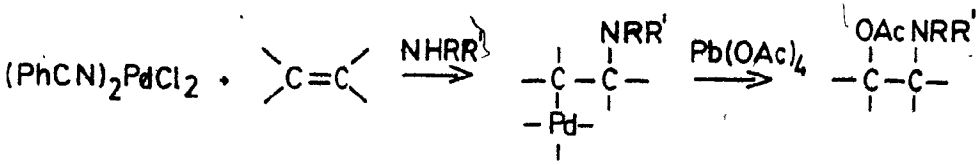
Electron deficient alkenes, such as α,β-unsaturated carbonyl compounds, do not react with this reagent. The reaction is regioselective with the iodine adding to the less substituted carbon of unsymmetrical alkenes. Thus, when 1-hexene reacted with iodine isocyanate a mixture of regioisomers was formed, but 1-iodo-2-isocyanohexane was the major product.

$$CH_2{=}CH(CH_2)_3CH_3 \xrightarrow{INCO} \underset{\text{major}}{ICH_2{-}\overset{NCO}{\overset{|}{C}}H(CH_2)_3CH_3} + \underset{\text{minor}}{OCNCH_2{-}\overset{I}{\overset{|}{C}}H(CH_2)_3CH_3}$$

The β-iodo isocyanate can then be transformed into the corresponding β-hydroxy amine.

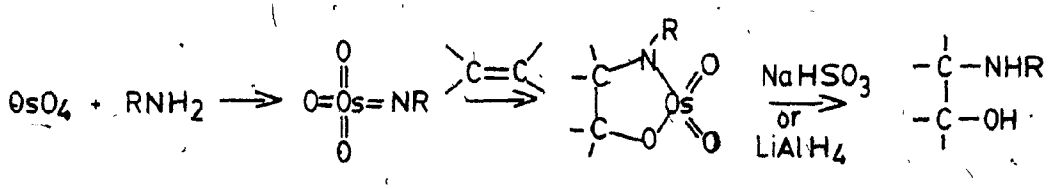


An alkene can be activated to direct amination by formation of a pallidium π-complex.[123] After amination the organopalladium intermediate can be oxidized with lead tetraacetate to a β-amino acetate.[124]

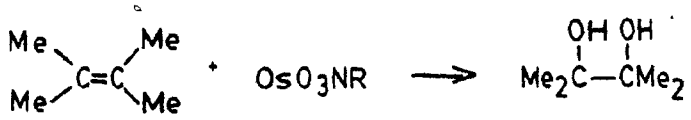


Regioselectivity of the reaction depends upon the amine used. With terminal alkenes dimethylamine, methyl amine, and ammonia add exclusively to C-2, diethyl amine adds equally to C-1 and C-2, and diisopropyl amine adds exclusively to C-1. The yields with methyl amine and ammonia were significantly lower than with the dialkyl amines.

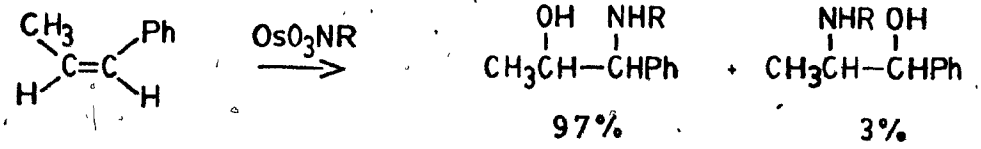
The oxidation of alkenes to diols by osmium tetroxide, used in either stoichiometric or catalytic amounts, is a well known reaction. In 1975 Sharpless reported[125] that osmium tetroxide would react with some primary amines to give imido derivatives, and that these osmium imido compounds react with alkenes to form β-amino alcohols.



The alkyl group of the amine had to be tertiary (t-butyl or t-amyl), and the osmium reagent was used in a stoichiometric amount. The reaction with monosubstituted, gem-disubstituted, and trisubstituted alkenes was regiospecific with the nitrogen adding to the less substituted carbon. Some trisubstituted alkenes gave significant amounts of diol in addition to the amino alcohol, and tetramethylethylene gave only diol.

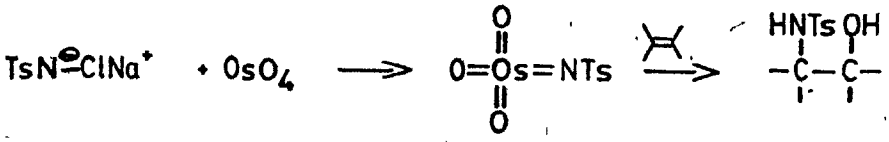


Cis and trans disubstituted alkenes gave mixtures of regioisomers, the ratio dependent upon the alkene. If one carbon has an aryl substituent the nitrogen tends to add to that carbon predominantly.



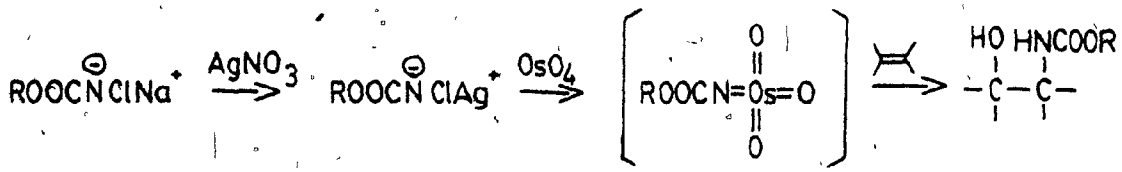
As with trisubstituted alkenes, these disubstituted alkenes also give some diol, with the cis alkenes having a greater tendency to form diol than the trans alkenes.

In 1976 a modification of this procedure was reported[126] which used Chloramine-T ($CH_3-C_6H_4-SO_2-N^{-}-Cl\,Na^{+}$) and a catalytic amount of osmium tetroxide. It is assumed that the reaction involves a sulfonyl-imido osmium intermediate which is regenerated under the reaction conditions.



This method has the advantages of using only a catalytic amount of osmium tetroxide and of introducing the nitrogen bearing a group which can be subsequently removed. Monosubstituted alkenes react quickly and give predominantly the regioisomer with the nitrogen on the less substituted carbon. Gem-disubstituted alkenes react more slowly, but with similar regioselectivity; cis and trans disubstituted alkenes are less regioselective. Trisubstituted alkenes react slowly, if at all, and give lower yields. Neither tetramethylethylene nor dimethyl fumarate reacts with the reagent.

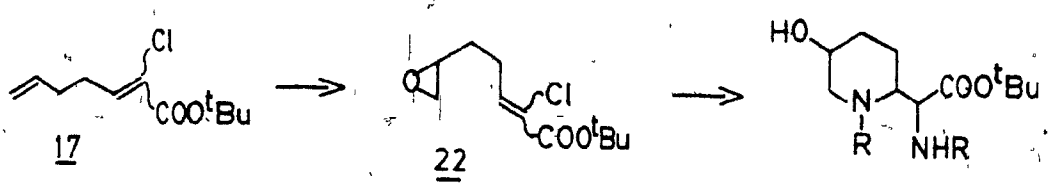
Another variation of the oxyamination reaction[127] used N-chlorosodiocarbamates instead of Chloramine-T, thus allowing preparation of compounds with a more easily removed group on the nitrogen. In this procedure the active reagent in forming the osmium compound is actually an N-chloro-N-argentocarbamate which is generated *in situ* by reaction of the N-chlorosodiocarbamate with silver nitrate.



This reagent gives better regioselectivity with terminal alkenes (nitrogen attack at the less substituted carbon) than does the Chloramine-T reagent. It reacts more effectively with trisubstituted alkenes.

The regiochemistry of the β-amino alcohols formed by the methods discussed should be summarized with respect to terminal (monosubstituted) alkenes. The nitrogen adds to the less substituted carbon in the nucleophilic opening of epoxides, whether by amines or azide ion, and in the osmium tetroxide mediated oxyaminations. The nitrogen adds to the more substituted carbon in the addition of iodine isocyanate to alkenes. The regioselectivity of the addition of amines to alkene-palladium complexes depends upon the amine used.

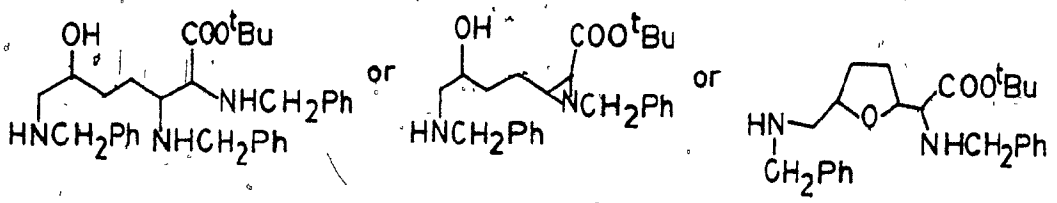
The epoxide opening by ammonia or an amine appeared to be the simplest, most direct method to use, and its use had been planned when the difficulties with the desilicohalogenation reaction occurred. The epoxidation of the terminal double bond of t-butyl 2-chloro-2,6-heptadienoate and subsequent reaction with an amine could give the piperidyl amino ester.



17 22

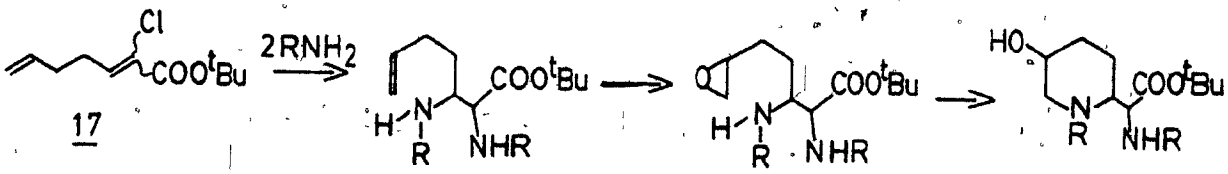
Compound 17 was epoxidized with m-chloroperbenzoic acid giving cleanly the terminal epoxide with no reaction at the α,β-unsaturated ester. The signals in the nmr for the vinyl protons of the terminal double bond (δ5.1 and δ5.8) disappeared, but the other vinyl proton signals remained (δ6.3 and δ6.9).

When the epoxide 22 was reacted with benzylamine in refluxing toluene, a complex mixture of products was obtained. The result was essentially the same whether one equivalent, two equivalents, or an excess of benzylamine was used, except that with one equivalent some starting material remained unreacted. There are three sites in the molecule which can react with a nucleophile, and in addition to the benzylamine another nucleophile is created when the epoxide opens. Several products other than the one desired are possible.

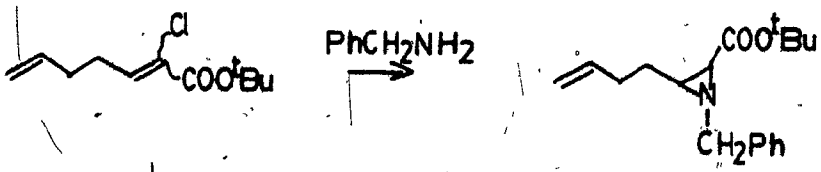


Aziridine Formation

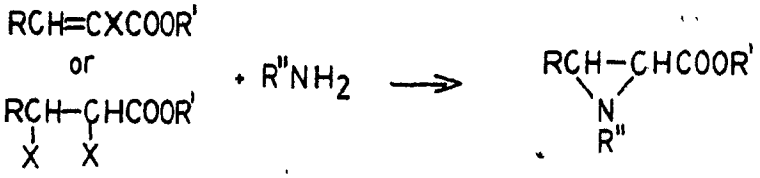
The complications in this reaction did not invalidate the use of nucleophilic opening of an epoxide by an amine for functionalization of the terminal double bond, but did call for some change in strategy. The reaction might be simplified by reacting benzylamine with the diene 17 and then forming the epoxide at the terminal double bond.



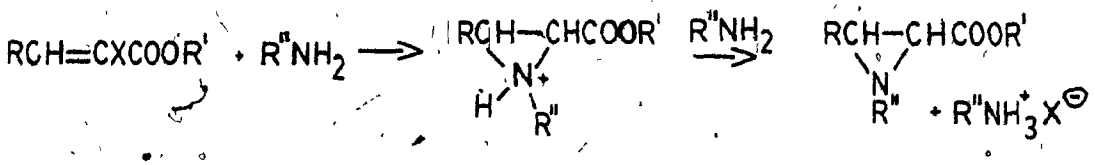
When the diene 17 was reacted with benzylamine in refluxing toluene, the product formed had incorporated only one benzylamine group. NMR of the crude product showed peaks at δ7.2 (s,5H) and δ4.6 (br.s.,2H) for the benzyl group and δ1.5 (s,9H) for the t-butyl group; and IR showed no N-H absorption. This result was obtained using either two equivalents or an excess of benzylamine. The product was not fully characterized, but a search of the literature made it clear that the reaction was forming an aziridine, and that it was unlikely that this could be avoided.



Several groups[128-133] have studied the formation of aziridines by the reaction of primary amines with either α,β-unsaturated-α-halo esters or α,β-dihalo esters.

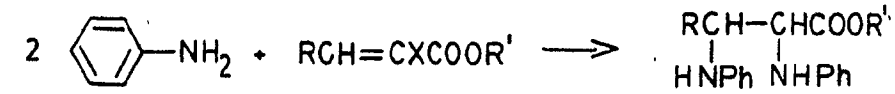


When equimolar amounts of amine and ester are used, the product[132] is a mixture of equal amounts of aziridine ester and the starting α-halo-α,β-unsaturated ester. If two or more equivalents of amine are used the aziridine is the sole product. Thus, it is assumed that the reaction goes through an intermediate aziridinium ion.



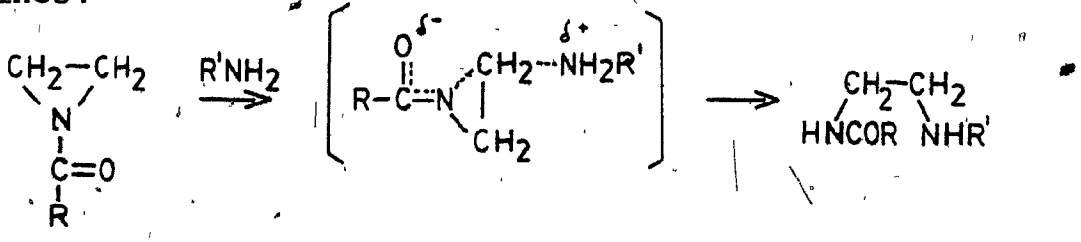
This is supported by the fact that if only one equivalent of primary amine reacts in the presence of triethylamine, the result is the same as when two equivalents of primary amine are used; no starting material is recovered.[128] The tertiary amine takes the place of a second mole of primary amine in converting the aziridinium ion to the free aziridine.

The anomalous behavior of aniline[129] also supports this mechanism. Aniline reacts with α,β-unsaturated-α-halo esters to give α,β-diamino esters rather than aziridines.

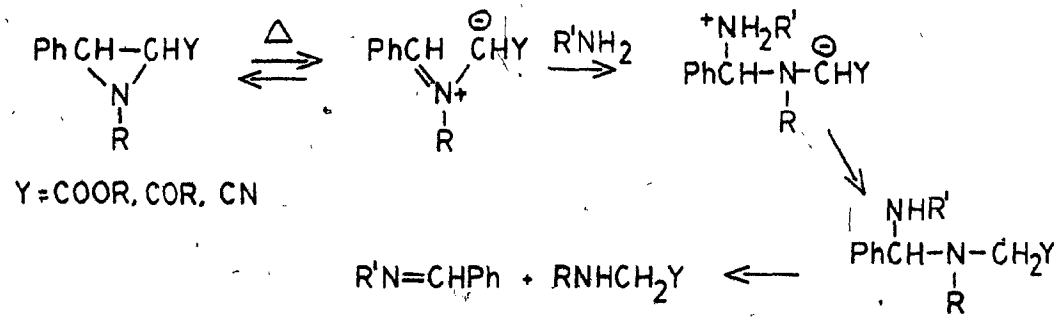


The lower bacisity of aniline (pK 4.58) compared to other primary amines (pK > 9) means that it is not sufficiently basic to remove a proton from the aziridinium ion, but instead acts as a nucleophile opening the aziridinium ring.

The use of ammonia or a primary amine in this reaction will always give an aziridine rather than a diamine, but aziridines can be opened to form diamines. However, unless an activating group is present on the aziridine nitrogen, acid catalysis is required.[134] Activating substituents are those which can stabilize the developing negative charge in the transition state of ring opening. Therefore, N-acetyl aziridines and N,N-ethyleneurethanes react readily with amines.[135]

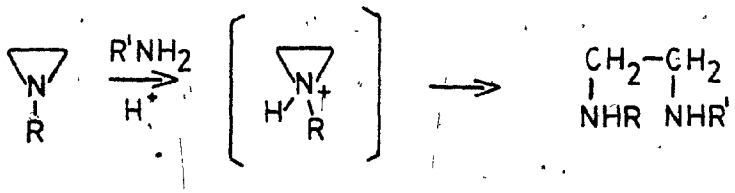


Aziridines with an ester, ketone, or cyano group on one carbon and a phenyl group on the other are cleaved to an imine and an amine on heating with an amine in toluene.[136] These aziridines are opened at the carbon-carbon bond on heating at moderate temperatures.

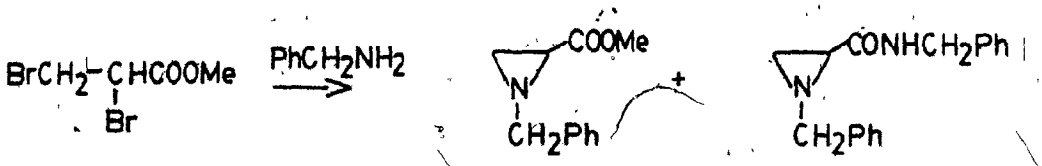


Without the phenyl group present this reaction does not occur: aziridines of the type  do not react with amines in refluxing toluene.

Aziridines other than these two particular cases react with amines only in the presence of proton[134] or Lewis[137] acids.

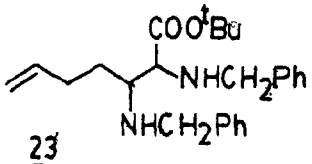


This reaction has not been reported with aziridinyl esters, but it is likely that, under the conditions necessary for ring opening, the ester would be converted to an amide. In at least one case,[128] during the formation of an aziridine from an α,β-dibromoester, some of the ester was converted to the amide.



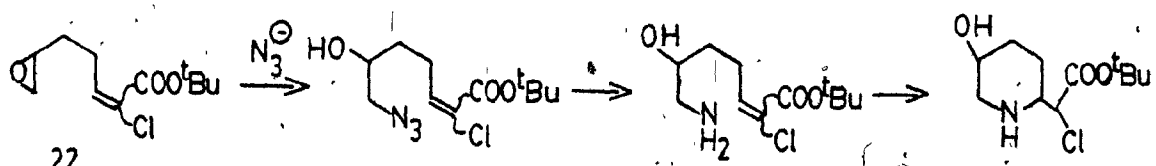
This reaction would be expected to increase in the presence of an acid catalyst.

It did not seem likely that the diamine 23 could be formed from the diene 17.



23

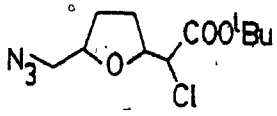
The problem of aziridine formation could, perhaps, be avoided if epoxide 22 were opened with azide ion.



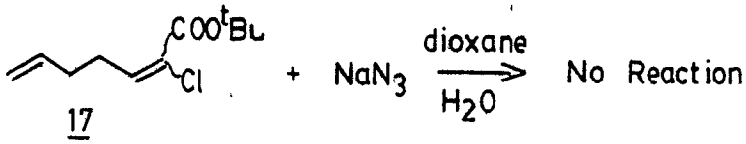
22

The epoxide 22 was treated with sodium azide in refluxing aqueous dioxane. Following the reaction by glc showed the two peaks of the starting material disappear and one new peak appear. The IR of the product shows a peak for the azide at 2100 cm^{-1}, but the peak for the carbon-carbon double bond (at 1630 cm^{-1} in the epoxide) had disappeared and the ester carbonyl absorption (at 1720 cm^{-1} in the epoxide) had moved to 1735 cm^{-1}. The nmr shows no vinyl protons. The base peak in the chemical ionization mass spectrum is at m/e 163 with the chlorine isotope peak at 165, and the highest mass peak is at m/e 248 and 250. If it is assumed that the addition of N_3^- and H^+ has occurred in the reaction then the molecular weight of the product would be 275. The peak at m/e 248 would result from loss of N_2, and the peak at m/e 163 from loss of the t-butyl group (57) and CH_2N_3 (56).

The product, then is probably a tetrahydrofuran structure resulting from attack by the oxygen on the double bond after the opening of the epoxide.

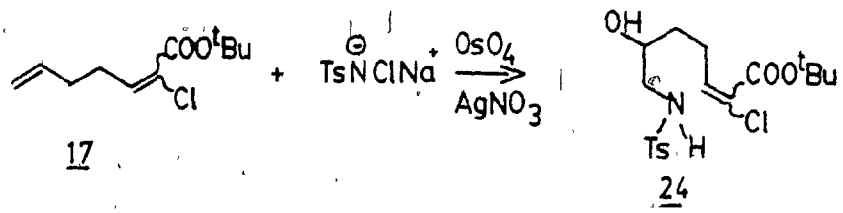


This structure for the product is supported by the fact that when the diene 17 was subjected to the same reaction conditions, no reaction occurred.



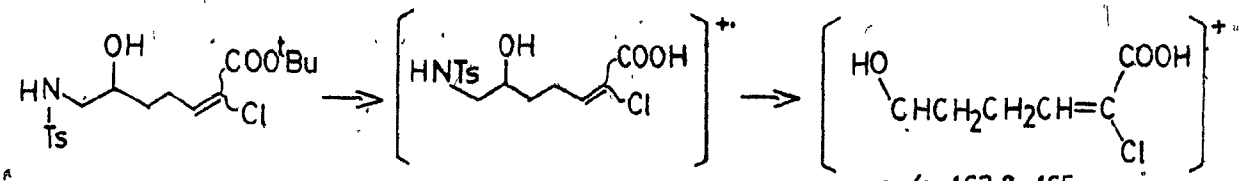
Thus, it is unlikely that the azide ion added to the double bond of the epoxide. The Michael addition of azide ion to the α,β-unsaturated ester was also tried in dimethylformamide, dimethylsulfoxide, and hexamethylphosphoramide, but no reaction occurred in any of these solvents.

The problems of aziridine and tetrahydrofuran formation led to the investigation of methods other than epoxide opening for the oxyamination of the terminal double bond of compound 17. The Chloramine-T and osmium tetroxide method should produce predominantly the regioisomer with the nitrogen on the terminal carbon which is the one needed in this case. It is less clear whether the reaction would occur selectively at the terminal double bond, but the general tendency of the reagent to react more rapidly with monosubstituted than with trisubstituted alkenes or with electron-deficient alkenes makes this selectivity seem probable.

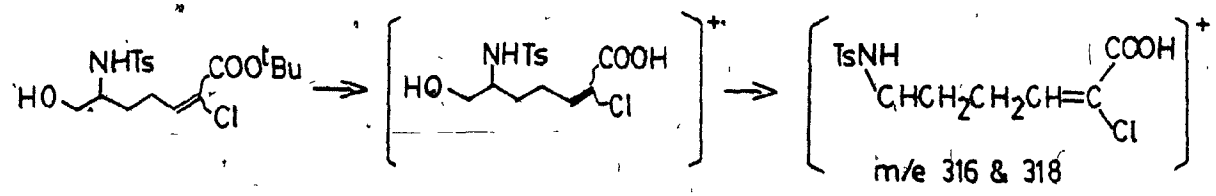


17 24

Compound 17 was stirred with 1.25 equivalents of Chloramine-T, 0.01 equivalent of osmium tetroxide, and 1.25 equivalents of silver nitrate (to precipitate the chloride ion formed) in t-butanol at 60°. The reaction was followed by glc and was complete after four hours. NMR confirmed that the reaction had occurred at the terminal double bond (the signals at δ5.1 and δ5.8 were not present in the product) and that the α,β-unsaturated ester was not affected (vinyl proton triplet at δ6.9). The tosyl group appeared as a quartet (4H) at δ7.5 and a singlet (3H) at δ2.4. The IR of the product showed O-H (3505 cm^{-1}) N-H (3290 cm^{-1}), ester carbonyl (1720 cm^{-1}), C=C(1630 cm^{-1}), and the aromatic ring (1600 cm^{-1}). It was not apparent from the nmr whether one or both regioisomers had been formed; the mass spectrum indicated the presence of both with peaks at m/e 163 and 165 and m/e 316 and 318. The molecular ion did not appear in the mass spectrum, the highest mass peaks were m/e 347 and 349 with electron impact and m/e 348 and 350 with chemical ionization.



$M^{+\cdot}$ = 403 & 405 m/e 347 & 349 m/e 163 & 165



m/e 316 & 318

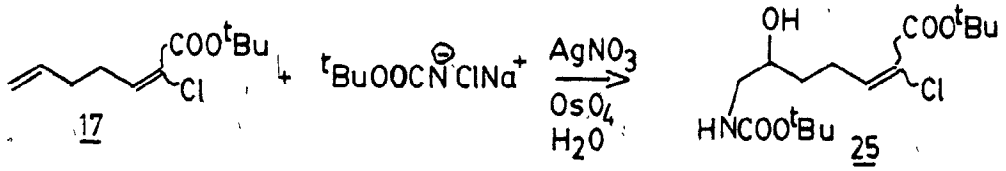
Thin layer chromatography of the product gave only one spot in several solvent systems, so the ratio of regio-isomers was not determined. The yield of the mixture of isomers was 93%.

The variation of this reaction using N-chlorosodio t-butyl carbamate was also applied to compound 17 and gave oxyamination of the terminal double bond. First the N-chloro-N-sodio carbamate was prepared by treatment of t-butyl carbamate with t-butyl hypochlorite and sodium hydroxide.

$$^{t}BuOOCNH_2 \xrightarrow[2.\,NaOH]{1.\,^{t}BuOCl} {}^{t}BuOOCN^{\ominus}ClNa^{+}$$

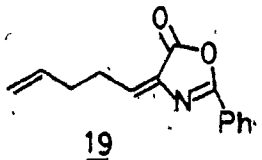
N-chlorosodio t-butyl carbamate was stirred with silver nitrate in acetonitrile, then water, osmium tetroxide, and compound 17 were added. Following the reaction by glc showed it to be essentially complete after nine hours.

Preparative tlc of the crude product gave primarily the oxyamination product with small amounts of starting material and t-butyl carbamate.



As before, the peaks for the vinyl protons at δ5.1 and δ5.8 were not seen in the nmr of the product, but there were triplets at δ6.9 and δ6.3 for the remaining vinyl proton. The IR showed a very broad peak at 3380 cm^{-1} for the O-H and N-H and a broad carbonyl peak at 1710 cm^{-1}. The mass spectrum indicated greater regioselectivity than in the Chloramine-T reaction. The highest mass peak was at m/e 237 and 239 which resulted from the loss of two molecules of isobutylene from the molecular ion (349 and 351). There was a large peak at m/e 163 and 165 which could result from the loss of $CH_2NHCOOH$ along with the two isobutylenes. If there were a terminal hydroxyl group a peak for the loss of CH_2OH would be expected, as was seen in the product of the Chloramine-T reaction. However, there was only a very small peak at m/e 206 and 208, indicating that little of the undesired isomer was formed. The base peak in the spectrum was m/e 75 which could be $[CH_2NHC(OH)_2]^+$, also indicating that the nitrogen had added to the terminal carbon.

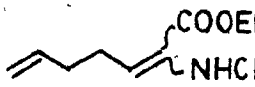
Since this method of oxyamination was successful with the α-chloro-α,β-unsaturated ester compound 17, it was also tried on the α,β-unsaturated esters with α-nitrogen substituents. When the oxazolidine compound 19, was treated with Chloramine-T, osmium tetroxide, and silver nitrate, only the starting material and p-toluene sulfonamide were recovered.



19

OsO_4, Chloramine-T → No Reaction

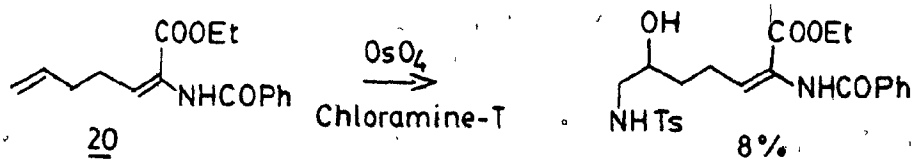
There was also no reaction with the α-formamino-α,β-unsaturated ester compound 21.



21

OsO_4, Chloramine-T → No Reaction

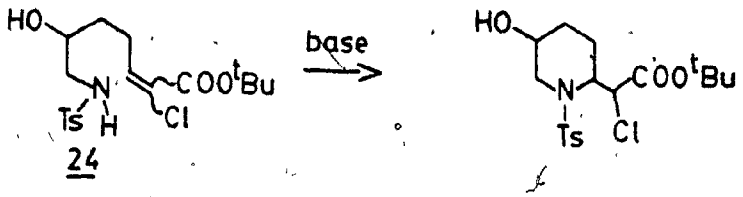
The oxyamination reaction was also tried with the N-benzoyl ethyl ester derived from the oxazolidine, compound 20. When this reaction was carried out, as with the other compounds, for twenty-four hours using 0.01 equivalent of osmium tetroxide, only starting material was recovered. The reaction was repeated using 0.03 equivalent of osmium tetroxide and heating to 60° for three days. TLC of the crude product gave mostly starting material and a small amount of a more polar compound. The nmr showed only one vinyl proton (triplet δ6.6) and the presence of the tosyl group (aromatic protons at δ7.5 and a three proton triplet at δ2.4). This seemed to be the desired product, but the yield was only about 8%.



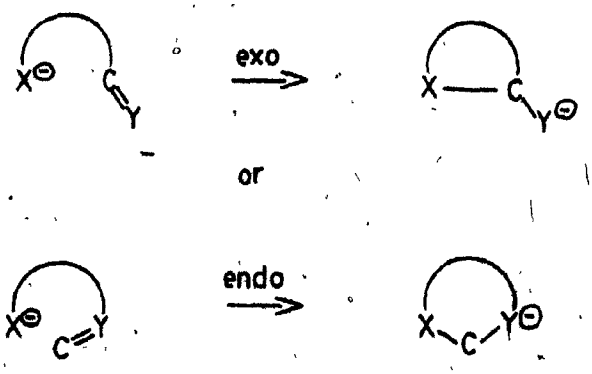
Since it seemed that only greatly increasing the amount of osmium tetroxide would increase the yield, this reaction was not pursued further.

Ring Closure

The oxyamination of t-butyl 2-chloro-2,6-heptadienoate provided compound 24 from which the piperidine ring could be formed by an intramolecular Michael-type reaction.



The relative facility of ring closures have been discussed and a set of rules was formulated.[138] The factors considered in the rules were whether the bond broken in the reaction is exocyclic or endocyclic to the ring formed, the size of the ring formed, and the hybridization of the carbon atom undergoing the cyclization reaction.



The rules were classified by hybridization of the carbon atom involved.

Rule 1. Tetrahedral systems:

a) 3 to 7-exo-tet are all favored,

b) 5 and 6 endo-tet are disfavored.

Rule 2. Trigonal systems:

a) 3 to 7-exo-trig are all favored,

b) 3 to 5-endo-trig are disfavored,
6 and 7 -endo-trig are favored.

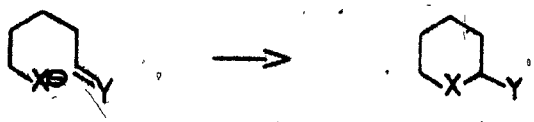
Rule 3. Digonal systems:

a) 3 and 4-exo-dig are disfavored,
5 to 7-exo-dig are favored,

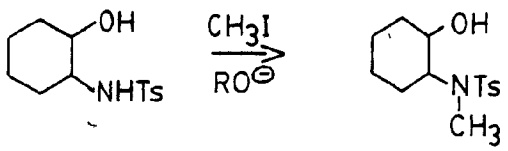
b) 3 to 7-endo-dig are favored.

These rules are an expression of the stereochemical requirements of the transition states for the reactions. In the favored ring closures the chain linking the two reacting groups allows them to assume the required transition state geometry. In the disfavored cases severe distortions of bond angles or lengths would be required for ring closure to occur.

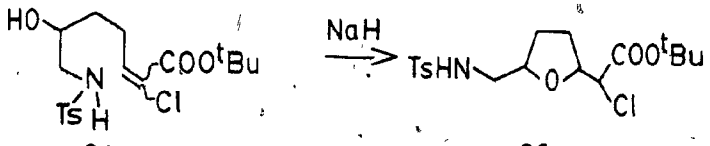
By these rules the proposed ring closure in compound 24 would be classified as 6-exo-trig, which is a favored closure.



In the first report of the Chloramine-T oxyamination reaction[126] several transformations of the oxyamination product of cyclohexene were presented. Notably, it was reported that the acidity of the sulfonamide hydrogen was sufficient to allow selective derivatization of the nitrogen.

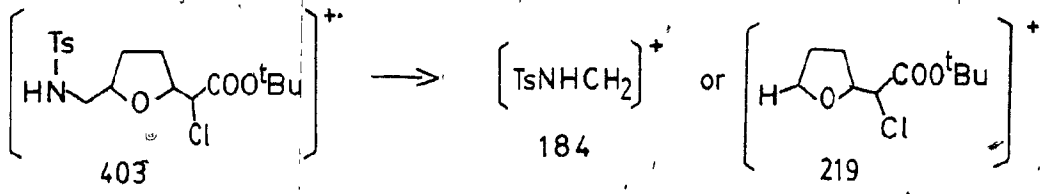


Thus, it seemed reasonable to expect that treatment of compound 24 with base would give the piperidine ring. The product from the Chloramine-T oxyamination of compound 17, a mixture of 24 with the other regioisomer, was treated with one equivalent of sodium hydride in tetrahydrofuran. NMR of the product showed that cyclization had occurred: the vinyl proton had disappeared. IR, however, suggested that the cyclization had occurred through the oxygen rather than the nitrogen. This cyclization would be classified as 5-exo-trig in Baldwin's system,[138] which is a favored process. The peak at 3505 cm^{-1} in the IR of the starting material was not present in the product, but the peak at 3290 cm^{-1} remained. The ester carbonyl peak shifted to 1740 cm^{-1} because of loss of conjugation. The product, then, was probably the tetrahydrofuran 26.



24 26

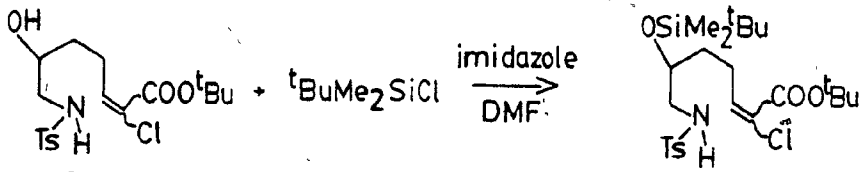
This structure is supported by the mass spectrum. The molecular ion (403) does not appear, but there is a large peak at m/e 184 which could be $[CH_2NHTs]^+$.



403 184 219

There is also a smaller peak at m/e 219 with the chlorine isotope peak at 221.

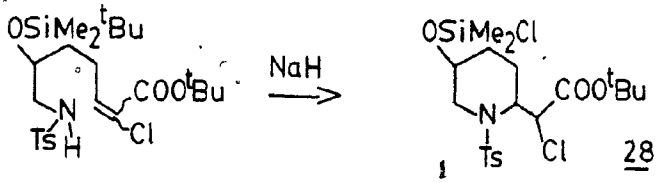
In order to prevent formation of the tetrahydrofuran the hydroxyl group was protected as its t-butyldimethylsilyl ether. Compound 24 was reacted with one equivalent of t-butyldimethylsilyl chloride and two equivalents of imidazole in dimethylformamide.[139]



24 27

NMR of the product showed the presence of the t-butyldimethylsilyl group, a nine proton singlet at δ0.9 and a six proton singlet at δ0.0. In the IR the peak at 3505 cm^{-1} (O-H) had disappeared, but the peak at 3290 cm^{-1} (N-H) was still present. The yield was 80%.

Compound 27 was then treated with one equivalent of sodium hydride in tetrahydrofuran. The crude product, a yellow oil, formed crystals on standing. The crystals were recrystallized from hexane to give colorless crystals, m.p. 147-150°. NMR showed disappearance of the vinyl proton. IR showed disappearance of the N-H peak and the carbon-carbon double bond (3290 cm^{-1} and 1630 cm^{-1} in 27) and shift of the ester carbonyl peak to 1730 cm^{-1}.



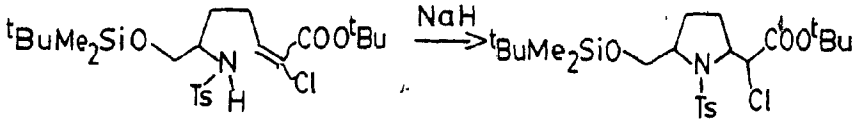
27 28

The mass spectrum showed an extremely weak molecular ion (m/e 517 and 519); the largest high mass peaks were those from loss of isobutylene from the ester (m/e 461 and 463), loss of the t-butyl group from the silicon (m/e 460 and 462), and loss of both these groups (m/e 404 and 406).

When the mother liquor from the first crop of crystals was triturated with hexane and cooled, more crystals formed. This crop, after recrystallization from hexane, melted at 106-108°. The nmr, IR, and mass spectrum of this product, however, were identical to those of the higher melting compound, so they may just be different diastereomers. The yield of the crystalline products was 53%.

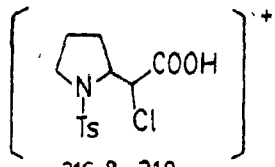
The oil residue, which could not be induced to form more crystals, gave almost identical nmr and IR spectra to the crystalline product. The mass spectrum indicates

that this oil contains the pyrrolidine formed from the other regioisomer of the oxyamination product.



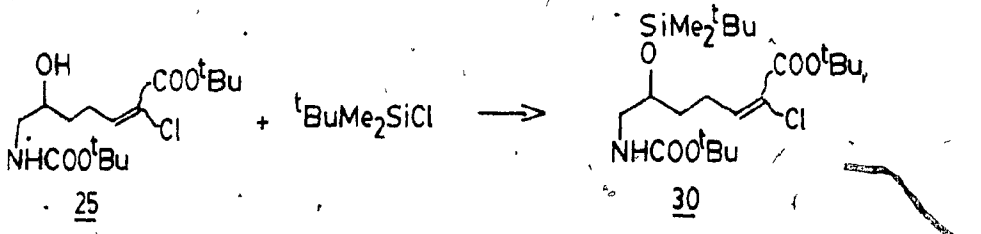
29

The mass spectrum of this compound is quite similar to that of compound 28, but has peaks at m/e 316 and 318 which are not present in the spectrum of the crystalline compound.



316 & 318

The silylation and cyclization reactions were also carried out with the t-butyl carbamate oxyamination product, compound 25. The silylation occurred just as with the N-tosyl compound.



25 30

The nmr showed incorporation of the t-butyldimethylsilyl group, a nine proton singlet at δ0.8 and a six proton singlet at δ0.0.

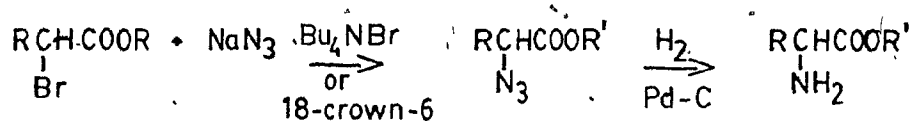
This compound was then treated with sodium hydride in THF, but, when the reaction was worked up, only starting material, compound 30, was recovered. The cyclization was also tried using lithium diisopropylamide as base, but the result was the same: compound 30 was recovered. This result demonstrates the lesser nucleophilicity of the urethane nitrogen compared to the sulfonamide nitrogen of compound 27.

CHAPTER V

AMINO ACID FORMATION AND DIMERIZATION

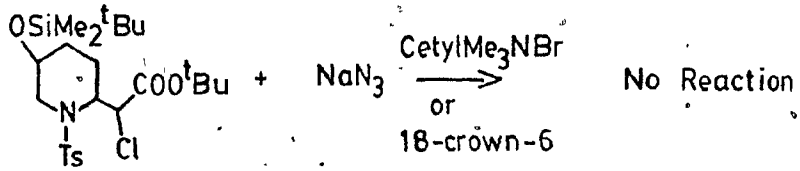
Replacement of Chlorine

The next problem after the successful formation of the piperidine ring was the replacement of the chlorine alpha to the ester with an amino group. The preparation of α-amino esters in good yields by reaction of α-bromo esters with sodium azide under phase transfer conditions and subsequent reduction of the azide was recently reported.[140]



Glycine methyl ester, alanine ethyl ester, and ethyl α-amino butyrate were synthesized by this method.

Compound 28 was dissolved in chloroform and an excess of sodium azide in water and 5 mole % of cetyl trimethyl ammonium bromide were added. The mixture was stirred at room temperature for twenty-four hours, but no reaction occurred; the starting material was recovered. The reaction was repeated using acetonitrile and 18-crown-6, but still no reaction occurred.



28

Various other solvents (aqueous dioxane, dimethylformamide, dimethylsulfoxide, and hexamethylphosphoramide) were tried without phase transfer catalysts, both at room temperature and at 60°, but no reaction occurred. When the reaction temperature was raised to 90° with HMPA the starting material decomposed.

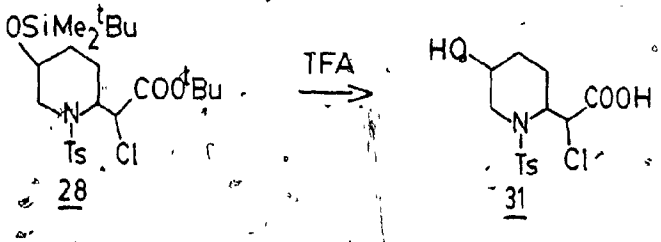
This reaction would be expected to occur by an S_N2 mechanism since the electronic effect of the ester group would make loss of the chlorine to form a carbonium ion unfavorable. The S_N2 path is not particularly favorable in this case, however, since the secondary carbon at which the reaction would occur is sterically hindered. Also, the report of this reaction described the use of α-bromo esters and an α-chloro ester would be less reactive.

A classical method for the synthesis of α-amino acids is the reaction of the α-halo acid with aqueous ammonia. This reaction is more successful with acids than with esters. An acid can aid the reaction by neighboring group participation, forming an α-lactone.

$$\mathrm{RCHCOOH}\ (\mathrm{X}) + \mathrm{NH_3/H_2O} \longrightarrow \left[\mathrm{RCH}\!-\!\mathrm{C}(=\mathrm{O})\!-\!\mathrm{O}\right] \longrightarrow \mathrm{RCHCOOH}\ (\mathrm{NH_2})$$

The reaction is still slow, even with acids. For example, in the synthesis of phenylalanine, α-bromo-β-phenyl propionic acid was treated with aqueous ammonia at room temperature for seven days.[141] Compound 28 was treated with trifluoroacetic acid to cleave the ester. The ester was cleaved,

but the silyl ether was also cleaved.



28 31

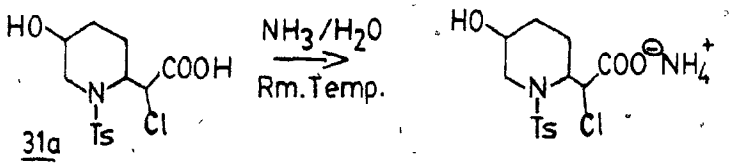
The nmr of the product lacked the peaks for the t-butyl ester group (δ1.5) and the t-butyldimethylsilyl group (δ0.9 and δ0.0). The IR showed peaks at 3440 cm^{-1} and 1740 cm^{-1}.

In an effort to hydrolyze the ester without cleaving the silyl ether compound 28 was treated with glacial acetic acid. Even after heating at 65° overnight, the starting material was recovered. Since acetic acid (pK 4.76) was not strong enough, formic acid (pK 3.77) was tried. This had the same result as trifluroacetic acid, both the ester and silyl ether were cleaved.

The two different batches of Compound 28 with different melting points were hydrolyzed separately, each giving a colorless crystalline product which had identical spectra. The acid (compound 31a) from the ester of melting point 147-150° had a melting point of 175-177°, and the acid (compound 31b) from the ester of melting point 106-108° had a melting point of 196-198°.

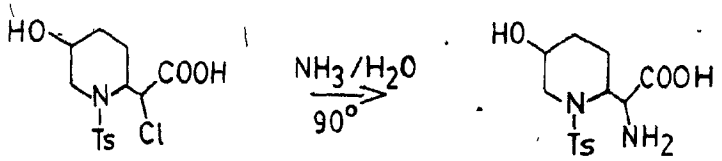
Compound 31a was stirred with a large excess of aqueous ammonia at room temperature for four days. The ammonia and water were removed giving a glassy solid whose IR showed a very broad peak at 3200 cm^{-1} and a peak

at 1600 cm^{-1}. The product was dissolved in water and acidified with 10% HCl. On acidification a precipitate formed which gave nmr and IR identical to compound 31. The amino acid had not been formed.



31a

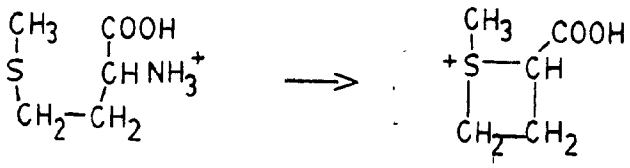
Compound 31a was again dissolved in aqueous ammonia and the solution was sealed in a thick-walled Pyrex tube and heated to 90°. After four days the ammonia and water were evaporated to give a white solid. The nmr and IR spectra were similar, but not identical, to those of the product of the room temperature reaction. When this product was dissolved in water and acidified, it remained in solution. The IR of the acidified product was distinctly different from that of the acidified product of the room temperature reaction. In addition to the peaks at 3420 cm^{-1} and 1740 cm^{-1}, there are peaks at 3150 cm^{-1} and 1410 cm^{-1} which did not appear in the IR of compound 31.



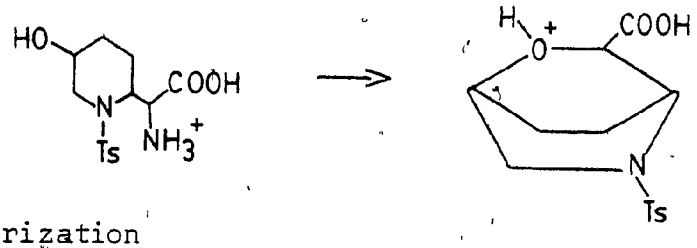
31a 32

The product gave only one spot on thin layer chromatography (butanol:acetic acid:water or chloroform:methanol: aqueous ammonia) and was ninhydrin positive. It did not

melt but decomposed at about 180°. The chemical ionization mass spectrum showed a small $[M+1]^{+\cdot}$ peak at 329 and a large peak at 312 for loss of ammonia. The loss of ammonia is often seen in the chemical ionization mass spectra of amino acids.[142] This fragmentation is favored when a particularly stable ion is formed, as with methionine.

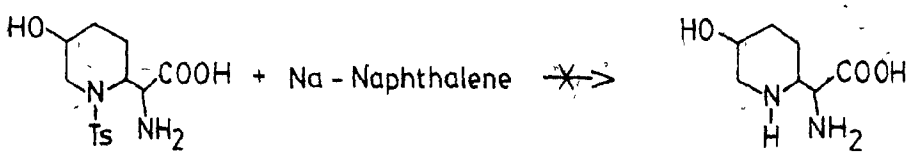


The hydroxyl group of compound 32 could participate in an analogous way.



Dimerization

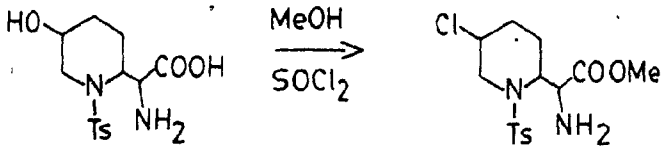
With the amino acid formed the sulfonamide protecting group on the piperidine nitrogen could be removed. Since alkyl halides are not stable to the reductive methods for cleavage of sulfonamides, this had to be done before the hydroxyl group was replaced by chlorine. The most convenient method of reductive cleavage of sulfonamides uses sodium naphthalene in 1,2-dimethoxyethane.[143] Compound 32 was added to a solution of twenty equivalents of sodium naphthalene in 1,2-dimethoxyethane. When the reaction mixture was worked up after 1.5 hours, the starting material was recovered.



32

The removal of the sulfonyl group was not pursued further at this point, but formation of the piperazinedione was considered.

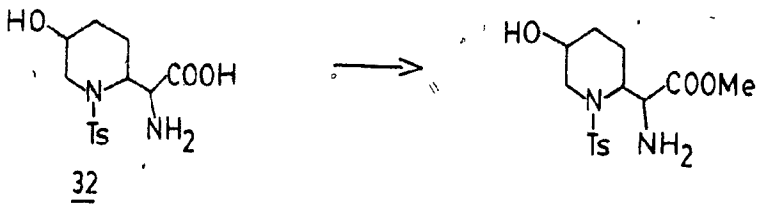
As discussed in Chapter II, amino acid esters readily dimerize in solution, this being the usual method of preparing symmetrical piperazinediones.[36] The preparation of the methyl ester of compound 32 was considered. The esterification reagents used were methanol-anhydrous HCl, methanol-thionyl chloride, and 2,2-dimethoxypropane-aqueous HCl.[144] The thionyl chloride-methanol reaction would be expected to cause replacement of the hydroxyl group by chlorine as well as esterification.



32

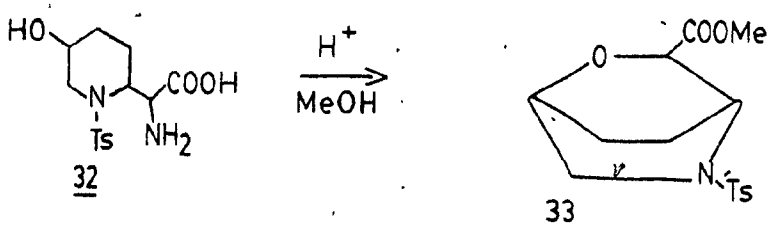
However, this reaction gave a mixture of products which were not identified.

The methanol-HCl and 2,2-dimethoxypropane-HCl reactions should give only esterification.



32

Application of either of these methods to compound 32 gave the same product. NMR confirmed the presence of a methyl ester, a singlet at δ3.8. IR showed the ester carbonyl at 1755 cm^{-1}, but no O-H or N-H absorption appeared. This colorless crystalline product was soluble in chloroform and melted at 149-151°. The highest mass peak in the mass spectrum was m/e 325 and the next highest was m/e 266. This product has probably been formed by nucleophilic displacement of ammonia by the hydroxyl oxygen.



32 33

Thus, the amino ester must be unstable to the acid conditions of the esterification reaction and the cyclic ether 33 formed.

The formation of the cyclic ether indicates that the substituents on the piperidine ring are cis. There are four possible pairs of enantiomers of compound 32, two with cis ring substitution and two with trans substitution (Figure 8). The trans diequatorial would be expected to be

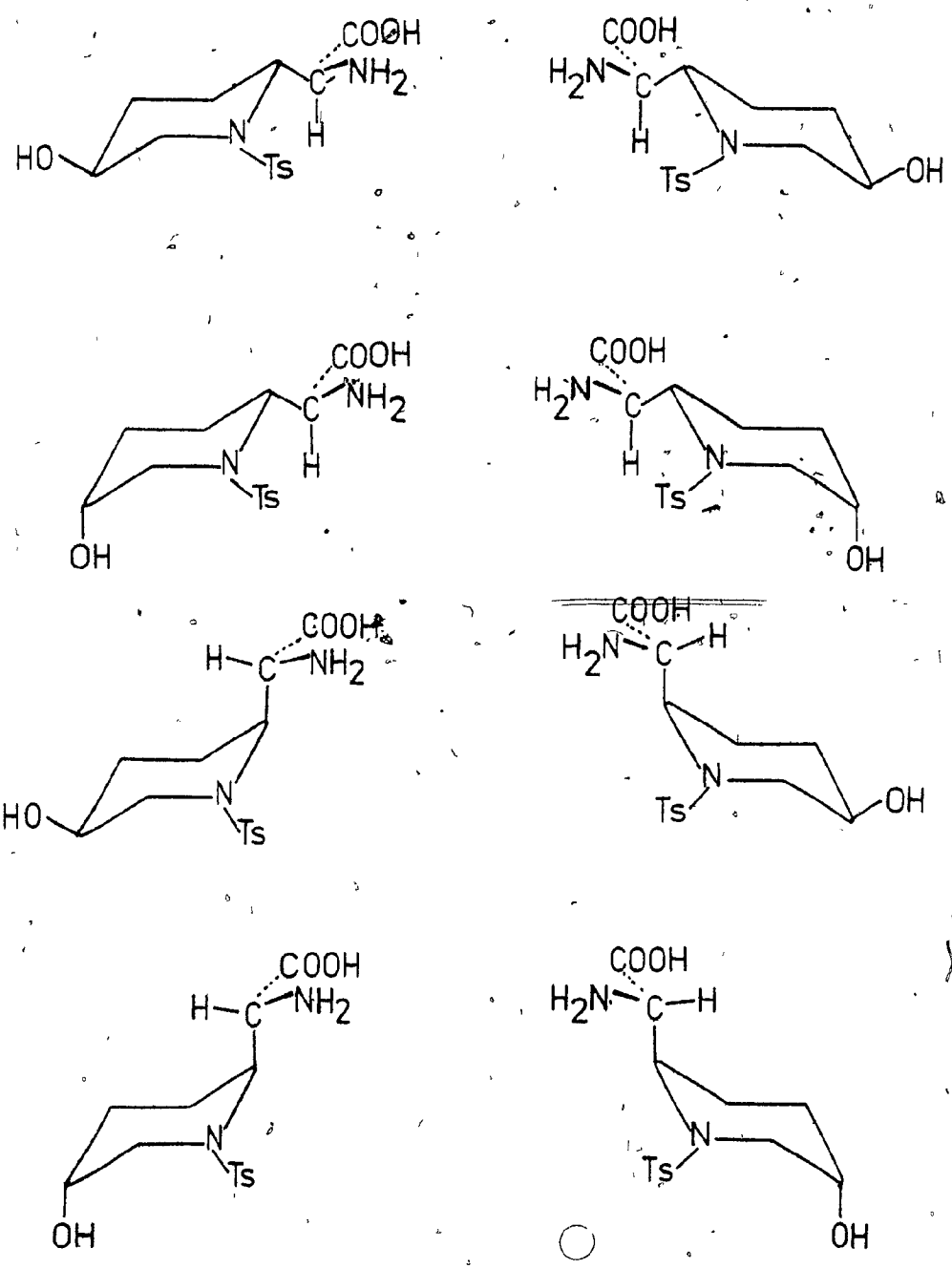
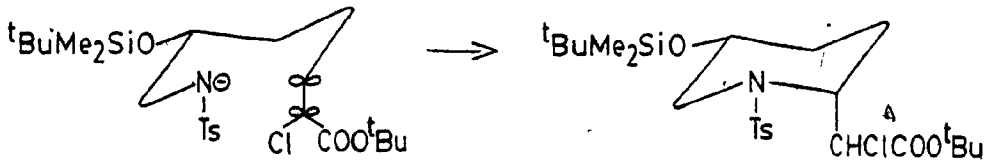


Figure 8. Isomers of (1-tosyl-5-hydroxy-2-piperidyl) glycine.

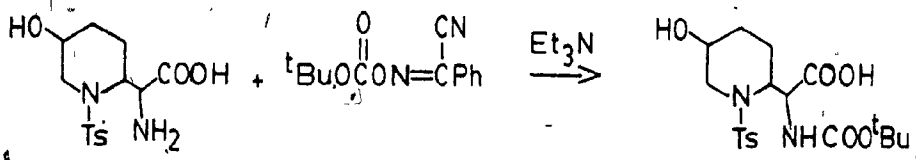
the most stable. The stability of the cis isomer with the hydroxyl in the axial position would be increased by hydrogen bonding with the ring nitrogen. However the geometry of the ring substituents was determined in the cyclization reaction when the hydroxyl group was protected as its t-butyldimethylsilyl ether, so no hydrogen bonding could occur. The geometry of the ring substituents is determined by the geometry of the transition state of the cyclization reaction. In the Michael reaction the nucleophile prefers to approach the carbon-carbon double bond perpendicularly for maximum orbital overlap.[150]



This transition state geometry forces the formation of a ring with the C-2 substituent in the axial position. The C-5 substituent, however, is free to adopt the less crowded equatorial configuration. Therefore, a cis (axial-equatorial) 2,5-disubstituted piperidine ring is preferentially formed.

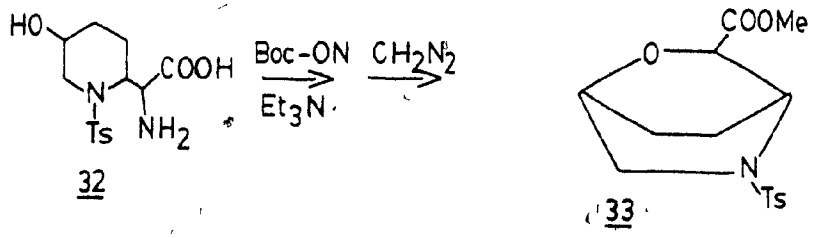
Because of the formation of the cyclic ether 33 in the acidic esterification reactions, the use of diazomethane for esterification was considered. Since diazomethane would be unlikely to react with the zwitterion form of the

amino acid, protection of the amine with the t-butyloxycarbonyl group was first carried out. Compound 32 reacted with 2-t-butoxycarbonyloxyimino-2-phenylacetonitrile[145] in the presence of triethylamine.



32

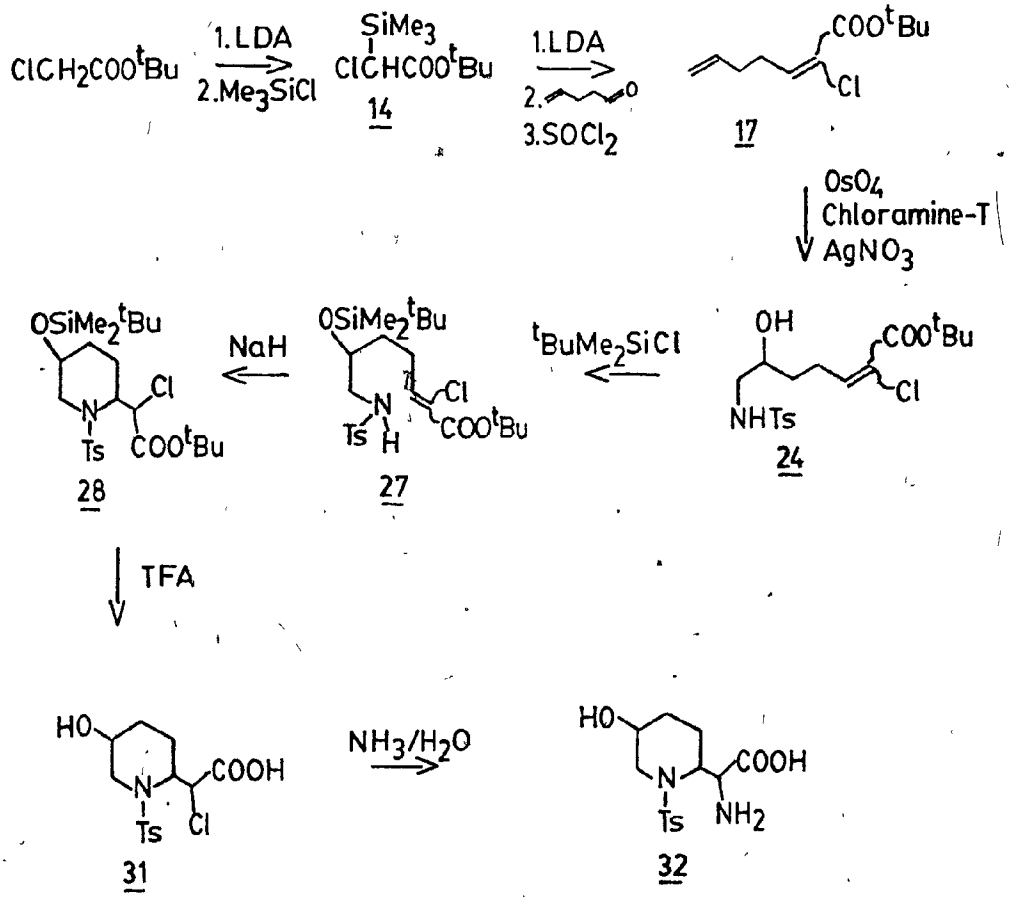
NMR of the product showed the presence of a t-butyl group, a singlet at δ1.4. This product was not purified, but was treated with an excess of diazomethane. The product of the methylation reaction showed no t-butyl group in the nmr. Its nmr, IR, and mass spectra were essentially identical to the cyclic ether, compound 33.



32 33

It is not clear exactly when the cyclization occurred. It may have been during the acid work-up of the t-butyloxycarbonylation reaction, and the t-butyl peak in the nmr was an impurity rather than being from the presence of compound 34. This amine-protection and esterification sequence was not studied further, since the t-butyloxycarbonyl group is removed by acid. Even if a milder work-up gave compound 34 and the methylation were successful, the acidic conditions which would then be used to unblock the amine would probably lead to the formation of compound 33 again.

This work terminates with the synthesis of (1-p-toluenesulfonyl-5-hydroxy-2-piperidyl)glycine and the observation of its instability to acidic esterification conditions. It is presumed that this final product, which was formed in 10.5% overall yield from t-butyl chloroacetate, has the substituents on the piperidine ring in the cis geometry. The synthetic sequence which lead to (1-p-toluenesulfonyl-5-hydroxy-2-piperidyl)glycine is shown in Scheme 3.



Scheme 3.

CHAPTER VI

SUGGESTIONS FOR FURTHER WORK

The use of (1-p-toluenesulfonyl-5-hydroxy-2-piperidyl) glycine as a precursor of 3,6-bis(5-chloro-2-piperidyl)-2,5-piperazinedione is a possibility if the problems of the cyclic ether formation and removal of the tosyl protecting group can be solved.

An answer to the problem of cleavage of the sulfonamide may be found in the recent observation that some sulfonamides can be cleaved photolytically.[146] Benzylsulfonamides and benzenesulfonamides were cleaved by photolysis in methanol or isopropanol to give good yields of the free amines.

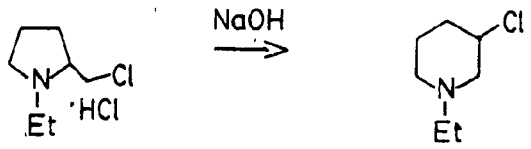
$$\begin{matrix} PhCH_2SO_2NHR \\ \text{or} \\ PhSO_2NHR \end{matrix} \xrightarrow{h\nu} H_2NR$$

Para-toluenesulfonamides were not discussed, but would be expected to behave similarly. If the tosyl group did give problems in the photolysis it should be possible to use a benzenesulfonyl group instead. It has been reported that Chloramine-B ($PhSO_2NClNa$) can replace Chloramine-T in the osmium tetroxide catalyzed oxyamination reaction.[147] The photolytic method of deprotection of the piperidine nitrogen could be used after the chlorine had been introduced at the 5-position.

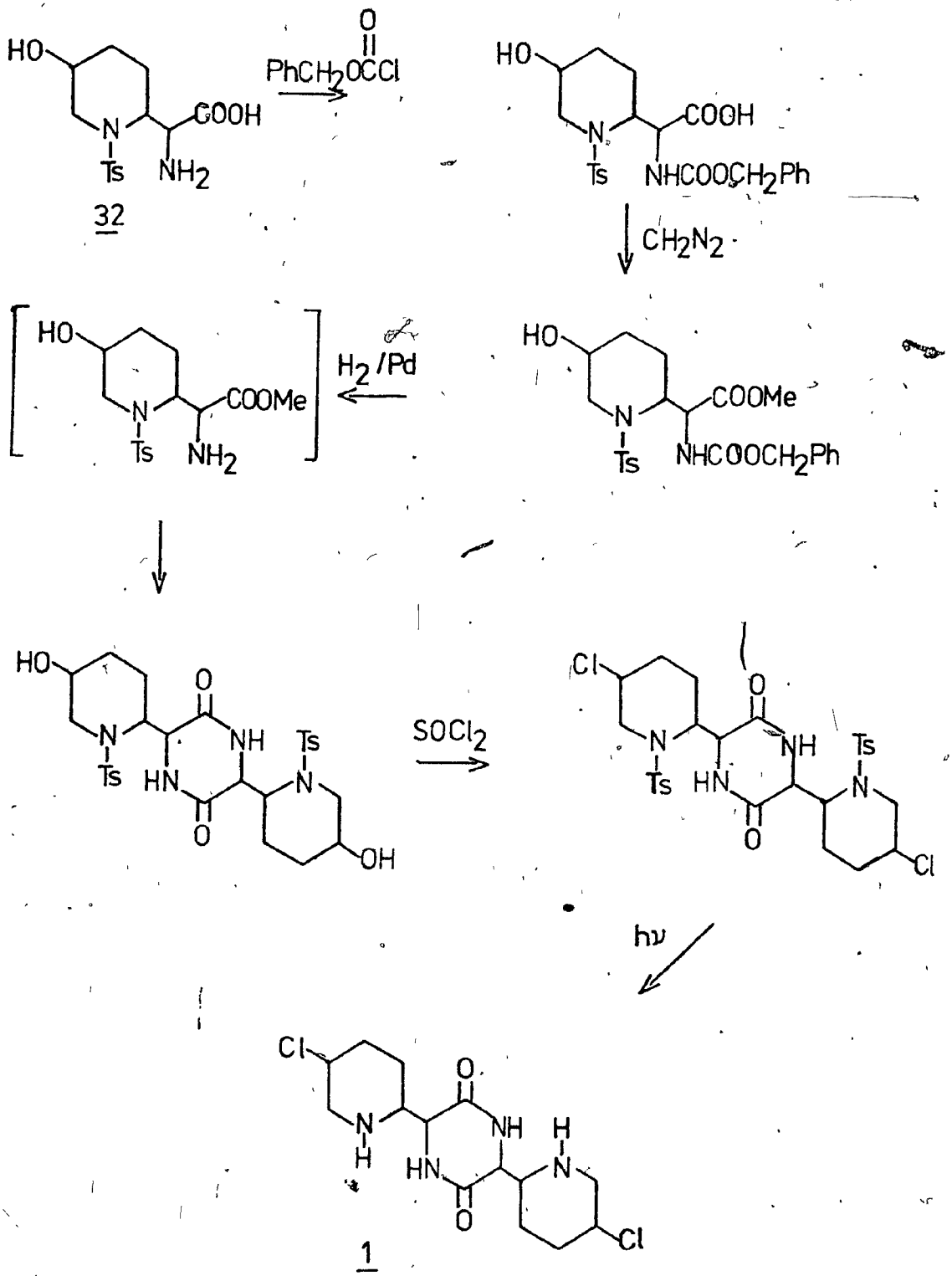
The cyclic ether formation could be prevented by avoiding acidic conditions until after the piperazinedione has been formed. A possible reaction sequence leading to 3,6-bis(5-chloro-2-piperidyl)-2,5-piperazinedione is shown in Scheme 4.

A drawback of the synthesis developed for compound 32 is the oxyamination reaction which is regioselective, but not regiospecific, thus lowering the overall yield. It might be possible, however, that the regioisomer with the terminal hydroxyl could also be used as an intermediate in the synthesis of 3,6-bis(5-chloro-2-piperidyl)-2,5-piperazinedione.

When 1-ethyl-2-chloromethyl pyrrolidine hydrochloride is neutralized with base to form the free amine, it spontaneously rearranges,[148] through a bicyclic aziridinium ion,[149] to 1-ethyl-3-chloropiperidine.



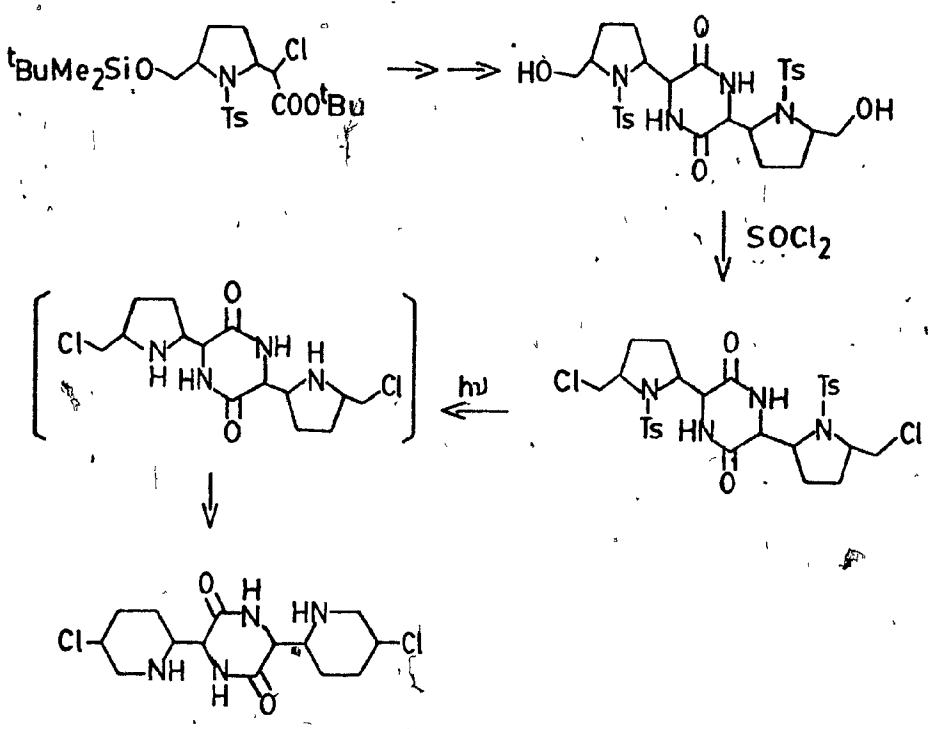
If the pyrrolidine compound 29 were carried through the synthetic sequence this ring enlargement would probably occur when the chlorine was introduced and the sulfonamide cleaved.



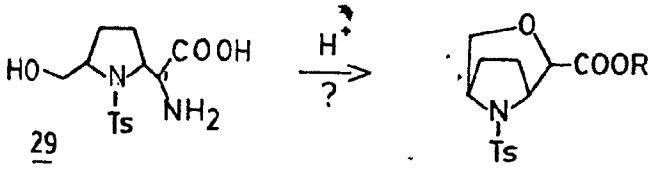
32

1

Scheme 4. Possible Route to Compound 1.



The pyrrolidine compound 29 has not been carried through the reaction sequence to give the amino acid analogous to compound 32, so its sensitivity to acid is not known.



29

Further work may lead to the synthesis of 3,6-bis(5-chloro-2-piperidyl)-2,5-piperazinedione starting with the synthesis of (1-p-toluenesulfonyl-5-hydroxy-2-piperidyl) glycine developed in this work.

CHAPTER VII

EXPERIMENTAL

Common chemicals were obtained from commercial sources and were purified as necessary. Melting points were obtained on a Gallenkamp melting point apparatus and were not corrected.

Nuclear magnetic resonance spectra (NMR) were recorded on Varian Associates T-60 or T-60A spectrometers.

Infrared spectra (IR) were recorded on Perkin-Elmer Model 257 or Model 297 grating infrared spectrometers. Spectra were calibrated with the 1602 cm^{-1} band of polystyrene film.

Mass spectra were recorded on a HP 5984A or LKB 9000 mass spectrometer. GC-MS used a 2m column of 5% OV-101 on chromosorb 750. Ion source energy was 70 ev. Chemical ionization used iso-butylene or methane as ionizing gas.

Gas chromatograms were performed on a F & M Model 5715A Research Chromatograph. Two 6ft by 1/8 in stainless steel columns were used: 5% OV-101 on chromosorb 750, or 10% SE-30 ultraphase on chromosorb W.

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee or Guelph Chemical Laboratories Ltd., Guelph, Ontario.

Allyl Vinyl Ether

A solution of 5 g mercuric acetate in 130 ml (100 g, 1 mole) n-butyl vinyl ether and 70 ml (60 g, 1.04 mole) allyl alcohol in a 300 ml round-bottomed flask fitted for fractional distillation was slowly heated until allyl vinyl ether began to distil out of the reaction mixture (65-70°). Slow distillation was continued for 24 hours. The crude product was redistilled from sodium hydride, b.p. 67-68°. Yield: 58 g (69%). NMR: δ6.3 (d of d,1H), δ5.8(m,1H), δ5.2(m,2H), δ4.0(m,4H). Lit.[103] b.p.66-67°.

4-Pentenal

In a 3-neck 100 ml flask fitted with a reflux condenser, thermometer, and dropping funnel 50 ml 1-methyl naphthalene was heated to 140°, 20 g allyl vinyl ether was added with stirring over 30 min. After addition the temperature was 110°. The solution was refluxed overnight and the temperature rose to 130°. The mixture was distilled rapidly with distillate up to 200° collected. The product was redistilled to give 16 g 4-pentenal, b.p. 101-103°. Yield: 16 g (80%). NMR: δ9.7 (t,1H), δ5.8 (m,1H), δ5.1 (m,2H), δ2.4 (m,4H) IR: 1720 cm^{-1} (S), 1640 cm^{-1} (W). Lit.[102] b.p. 102°.

Benzylidene Glycine Ethyl Ester

In a 250 ml flask were placed 10.1 g (0.0725 mole) glycine ethyl ester hydrochloride, 20 ml (0.145 mole) triethyl amine, 6 g magnesium sulfate, and 150 ml methylene chloride. The suspension was stirred at room temperature while 7.7 g (0.0725 mole) benzaldehyde was added dropwise.

The residue was taken up in ether and the solution washed with saturated salt solution. The organic phase was dried and concentrated to give a slightly yellow oil, benzylidene glycine ethyl ester. Yield: 9.6 g (70%). NMR: 8.0 (S,1H), 7.3 (m,5H), 4.25 (S,2H), 4.1(q,2H), 1.2 (t,3H). IR: 1740 cm^{-1} (S), 1650 cm^{-1} (m).

t-butyl Azidoacetate

In a 300 ml flask with a reflux condenser were placed 30 g (0.2 mole) t-butyl chloroacetate, 24 g (0.37 mole) sodium azide, and 90 ml of 60% (V/V) acetone-water. The mixture was refluxed on a steam bath for 18 hrs., then the acetone was evaporated off and 15 ml water added. The layers were separated and the aqueous layer extracted twice with ether. The ether extracts were added to the original organic layer and the solution was dried. After evaporation of the ether the product was distilled, giving t-butyl azidoacetate, b.p. 42-44° (1.7 mm). Yield: 23 g (73%). NMR: δ3.6 (S,2H), δ1.5 (S,9H). IR: 2110 cm^{-1} (S), 1740 cm^{-1} (S). Lit.[114] b.p.33-41° (1 mm)

Glycine t-butyl Ester, Phosphite Salt

A solution of 19.4 g (0.12 mole) t-butyl azidoacetate in 100 ml methanol was placed in a 300 ml flask and 0.5 g 5% palladium on carbon was added. The solution was stirred under a hydrogen atmosphere for 10 hrs., then the catalyst was filtered off. To the filtrate was added 10 g phosphorous acid, and the mixture warmed to dissolve the acid. After

cooling to room temperature 100 ml ether was added and the precipitated glycine t-butyl ester phosphite was filtered off. M.P. 148-150[b] (dec.) Yield: 13.2 g (52%). Lit.[114] m.p. 144-147[c].

Benzylidene Glycine t-butyl Ester

This reaction was carried out just as for the ethyl ester, using 4.26 g (0.02 mole) glycine t-butyl ester phosphite. Benzylidene glycine t-butyl ester Yield: 3.5 g (80%) NMR: δ8.0 (t,1H), δ7.4 (m,5H), δ4.1 (d,2H), δ1.4 (s,9H). IR: 1740 cm^{-1} (s), 1645 cm^{-1} (m).

Attempted Silylation of Benzylidene glycine Esters

In a 50 ml three-necked flask under nitrogen lithium diisopropylamide was formed by adding 0.625 ml of 2.4 M n-butyl lithium in hexane (1.5 mmole) to a solution of 0.152 g (1.5 mmole) diisopropyl amine in 25 ml THF at 0°. The mixture was then cooled to -78° and 0.5 ml HMPA was added. Benzylidene glycine ethyl ester, 0.286 g (1.5 mmole), was added dropwise and the mixture stirred at -78° for 1/2 hr. Chlorotrimethylsilane, 0.163 g (1.5 mmole) was added, then the mixture was allowed to warm to room temperature and stirred for 1 hr. The mixture was poured into saturated aqueous ammonium chloride and extracted with ether. The organic extract was dried and the ether removed to give 0.21 g of a yellow oil shown by nmr to be benzylidene glycine ethyl ester. The same procedure was used with the t-butyl ester which was also recovered unchanged.

Ethyl α-Benzylimino Hexanoate

As in the previous experiment benzylidene glycine ethyl ester was added to lithium diisopropylamide at 078°. Then 0.205 g (1.5 mmole) 1-bromo-butane was added and the mixture allowed to warm to room temperature. The same work-up gave a yellow oil. Yield: 0.31 g (84%). Ethyl α-benzylamino hexanoate. NMR: δ8.0 (s,1H); δ7.3 (m,5H), δ4.2 (t,1H), δ4.1 (q,2H), δ1.6-0.9 (m,12H).

t-Butyl Trimethylsilyl Acetate

A 300 ml three-necked flask, flushed with nitrogen and cooled in an ice bath, was charged with 41.6 ml (100 mmole) of 2.4 M n-BuLi in hexane. Then 14.0 ml (100 mmole) diisopropylamine was added dropwise with stirring. When addition was complete, the hexane was removed under reduced pressure, and the lithium diisopropylamide was dissolved in 100 ml THF. The solution was cooled to -78° and 13.5 ml (100 mmole) t-butyl acetate was added dropwise and the mixture was stirred for 1/2 hr. Then 10.8 g (100 mmole) chlorotrimethylsilane was added dropwise, and the mixture was allowed to warm to room temperature. The reaction mixture was poured into saturated aqueous ammonium chloride and extracted with ether. The organic layer was washed with water and saturated salt solution and dried. Removal of the ether gave t-butyl trimethylsilyl acetate, 16.7 g (89%). NMR: δ1.7 (s,2H), δ1.4 (s,9H), δ0.1 (s,9H). IR: 1710 cm^{-1} (s). Lit.[105] b.p. 67° (13 mm).

t-Butyl Bis(Trimethylsilyl) Acetate

The second silylation was carried out just as the first using 18.8 g (100 mmole) of t-butyl trimethylsilylacetate. The product was distilled to give t-butyl bis(trimethylsilyl)-acetate, b.p. 57-59° (0.3 mm). Yield 10.3 g (40%). Lit[106] bp. 61° (.4mm NMR: δ1.5 (s,1H), δ1.4 (s,9H), δ0.1 (s,18H). IR: 1710 cm^{-1}.

t-Butyl-2-trimethylsilyl-2,6-heptadienoate (5)

Lithium diisopropylamide (25 mmole), prepared as above, was dissolved in 25 ml THF and cooled to -78° under nitrogen. Then 6.25 g (25 mmole) $(Me_3Si)_2CHCOOt\text{-}Bu$ was added dropwise and the solution stirred at -78° for 1 hr. before 2.1 g (25 mmole) of 4-pentenal was added. The mixture was allowed to warm to room temperature, then poured into saturated aqueous ammonium chloride and extracted with pentane. The organic extract was dried over anhydrous potassium carbonate and the solvent removed. The product was distilled giving t-butyl-2-trimethylsilyl-2,6-heptadienoate, b.p. 52-55° (0.05 mm). Yield 3.8 g (60%). NMR: δ7.0 (t) + δ6.1 (t) (1H), δ5.8 (m,1H), δ5.0 (m,2H), δ2.3 (m,4H), δ1.6 (s) + δ1.55 (s)(9H), δ0.3 (s) + δ0.2 (s)(9H). IR: 1700 cm^{-1} (s), 1640 cm^{-1} (w), 1605 cm^{-1} (w).

t-Butyl-2,6,7-trichloro-2-heptenoate (7)

In a 25 ml three-necked flask 2.54 g (10 mmole) of 5 was dissolved in 10 ml chloroform. The flask was cooled in an ice bath and chlorine was bubbled into the solution for 1 1/2 hrs. The chloroform was evaporated and the

residue was dissolved in 35 ml acetonitrile. To the acetonitrile solution was added 1.49 g (10 mmole) tetraethylammonium fluoride and the mixture stirred at room temperature for 2 hrs. The reaction mixture was partitioned between ether and water, the ether layer dried and concentrated. The crude product was chromatographed on a column of 30 g silica gel using chloroform. The purified product was a pale yellow oil, t-butyl-2,6,7-trichloro-2-heptenoate. Yield 2.1 g (73%). NMR: δ6.9 (t) + δ6.3 (t) (1H), δ3.7 (m,3H), δ2.3 (m,4H), δ1.6 (s) + δ1.5 (s)(9H). IR: 1720 cm^{-1} (s), 1615 cm^{-1} (w).

Reaction of 7 with Benzylamine

In a 25 ml flask were placed 0.7 g (2.5 mmole) compound 7, 0.6 ml (5 mmole) benzylamine, and 10 ml toluene, and the solution was refluxed for 24 hrs. The solvent was evaporated and the crude product was purified by column chromatography on silica gel using chloroform as eluent. Some compound 7 (0.2 g) was recovered as well as the product (0.75 g) which had incorporated three benzyl groups. NMR: δ7.3 (s,15H), δ4.8 (d,1H), δ3.8 (br,6H), δ2.4 (br,4H), δ1.7 (br,4H), δ1.45 (s) + δ1.4 (s) + δ1.35 (s) (9h). IR: 3290 cm^{-1} (br), 1715 cm^{-1} (s).

t-Butyl-6,7-epoxy-2-trimethylsilyl-2-heptenoate (8)

In a 25 ml flask were placed 2.0 g (7.9 mmole) t-butyl-2-trimethylsilyl-2,6-heptadienoate, 1.9 g (9.3 mmole) of 85% m-chloroperbenzoic acid, and 15 ml methylene chloride, and the solution was stirred at room temperature overnight. The white precipitate which formed was filtered off and the

filtrate washed with 5% sodium sulfite and 5% sodium carbonate. The organic solution was dried and evaporated. The crude product was purified by preparative tlc using toluene to give t-butyl-6,7-epoxy-2-trimethylsilyl-2-heptenoate. Yield: 1.8 g (86%). NMR δ6.9 (t) + δ6.1 (t) (1H), δ2.5 (m,5H), δ1.7 (m,2H), δ1.4 (s) + δ1.45 (s) (9H), δ0.2 (s) + δ0.1 (s) (9H). IR: 1720 cm^{-1} (s), 1620 cm^{-1} (w).

t-Butyl α-bromo-α-(5-bromomethyl-2-tetrahydrofuranyl)acetate (11)

In a 25 ml flask 0.27 g (1 mmole) compound 8 was dissolved in 5 ml methylene chloride and 0.16 g (1 mmole) bromine in 5 ml methylene chloride was added dropwise with stirring. After stirring 1 1/2 hr at room temperature the color of the bromine had disappeared and the solvent was evaporated. The residue was dissolved in 10 ml acetonitrile and 0.15 g (1 mmole) tetraethylammonium fluoride was added. The mixture was stirred for 1 hr. then partitioned between ether and water. The organic layer was dried and concentrated, and the crude product was purified by preparative tlc using toluene to give t-butyl α-bromo-α-(5-bromomethyl-2-tetrahydrofuranyl)-acetate. Yield 0.25 g (70%). NMR: δ4.2-3.3 (m,5H), δ2.2-2.0 (m,4H), δ1.55 (s) + δ1.5 (s) (9H). IR: 1750 cm^{-1} (s).

2-Trimethylsilyl-2,6-heptadienoic Acid (12)

In a 25 ml flask 0.106 g (1 mmole) cyanogen bromide and 0.134 g (1 mmole) freshly sublimed aluminum trichloride were dissolved in 9 ml methylene chloride and cooled to 0°. A solution of t-butyl-2-trimethylsilyl-2,6-heptadienoate

(0.254 g, 1 mmole) in 1 ml methylene chloride was added dropwise and the mixture stirred at 0° for 1 hr. The reaction mixture was poured into water and extracted with ether, and the organic extract was dried and evaporated, giving 2-trimethylsilyl-2,6-heptadienoic acid. Yield 0.19 g (96%). NMR: 11.2 (br,1H), δ7.1 (t) + δ6.1 (t) (1H), δ5.5 (m,1H), δ4.8 (m,2H), δ2.4-1.9 (m,4H), δ0.1 (s,9H). IR: 1680 cm^{-1} (s), 1640 cm^{-1} (w), 1605 cm^{-1} (w).

t-Butyl-2,2-dichloro-3-hydroxy-6-heptenoate (13)

In a 25 ml three-necked flask 0.084 g (1 mmole) 4-pentenal was dissolved in 4 ml THF and cooled to -20° under nitrogen, then 0.326 g (2 mmole) tris(dimethylamino) phosphine in 3 ml THF was added. After 10 min. 0.22 g (1 mmole) t-butyl trichloroacetate in 3 ml THF was added, and the mixture stirred at -20° for 1/2 hr., then allowed to warm to room temperature. The reaction mixture was poured into water and extracted with ether. The organic extract was dried and evaporated and the crude product was purified by preparative tlc using hexane-chloroform (4:1), giving t-butyl-2,2-dichloro-3-hydroxy-6-heptenoate. Yield 0.12 g (45%). NMR: δ5.9(m,1H), δ5.2(m,2H), δ2.1(m,6H), δ1.6(s,9H). IR: 3470 cm^{-1} (br), 1750 cm^{-1} (s), 1645 cm^{-1} (w).

Attempted Reaction of 4-Pentenal, t-Butyl Trichloroacetate and Triphenylphosphine.

In a 25 ml three-necked flask flushed with nitrogen 0.168 g (2 mmole) 4-pentenal and 0.524 g (2 mmole) triphenylphosphine were dissolved in 5 ml THF and 0.22 g (1 mmole)

t-butyl trichloroacetate in 5 ml THF was added dropwise. The mixture refluxed for two days, then the THF was evaporated off. The residue was extracted with hexane, and, after removal of the solvent, gave t-butyl chloroacetate. Yield 0.11 g (73%). NMR: δ3.8 (s,2H), δ1.4 (s,9H). IR: 1760 cm^{-1} (s).

t-Butyl-α-chloro-α-trimethylsilylacetate (14)

a) In a 50 ml three necked flask flushed with nitrogen 20 mmole of lithium diisopropylamide was prepared from 2.82 ml diisopropylamine and 9.1 ml of 2.2 M n-butyl lithium. After removal of the hexane the base was dissolved in 20 ml THF and the solution cooled to -78°. Then 3.76 g (20 mmole) of t-butyl trimethylsilylacetate was added, followed after 1/2 hr by 5.28 g (20 mmole) hexachloroacetone. After the mixture warmed to room temperature it was poured into saturated aqueous ammonium chloride and extracted with ether. The ether extract was dried and concentrated. The crude product was distilled giving t-butyl-α-chloro-α-trimethylsilyl acetate, b.p. 48-50° (0.8 mm). Yield 2.71 g (61%) NMR: δ3.6 (s,1H), δ1.5 (s,9H), δ0.1 (s,9H). IR: 1745 cm^{-1} (s).

b) The same product could be obtained by a similar reaction using 3.0 g t-butyl chloroacetate and 2.56 ml trimethylchlorosilane. Distillation gave t-butyl-α-chloro-α-trimethylsilylacetate. Yield 2.2 g (50%).

t-Butyl-2-chloro-2,6-heptadienoate (17)

In a 100 ml three-necked flask flushed with nitrogen 20 mmole lithium diisopropylamide was prepared and dissolved in 20 ml THF. The solution was cooled to -78° and 4.46 g (20 mmole) t-butyl-α-chloro-α-trimethylsilyl acetate was added dropwise. After 15 min 1.68 g (20 mmole) 4-pentenal was added. The mixture was stirred at -78° for 1/2 hour, then allowed to warm to 0°, and 3.0 ml (40 mmole) thionyl chloride was added. The reaction mixture was stirred at 0° for 1/2 hr., then warmed to room temperature, poured into water, and extracted with pentane. Distillation of the organic phase gave t-butyl-2-chloro-2,6-heptadienoate, b.p. 68-70° (1.0 mm). Yield 2.1 g (49%) NMR: δ6.9 (t) + δ6.3 (t) (1H), δ5.8 (m,1H), δ5.1 (m,2H), δ2.4 (m, 4H), δ1.6 (s,9H). IR: 1722 cm^{-1} (s), 1715 cm^{-1} (s).

The same reaction was carried out on a 1 mmole scale with other carbonyl compounds, and the products purified by tlc using hexane-chloroform (4:1).

From 0.112 g cyclohexylaldehyde, t-butyl-2-chloro-3-cyclohexyl propenoate (0.106 g, 44%). NMR: δ6.8 (d) + δ6.1 (d) (1H), δ1.3-1.8 (br,11H), δ1.6 (s,9H). IR: 1725 cm^{-1} (s), 1715 cm^{-1} (s).

From 0.106 g benzaldehyde, t-butyl-2-chloro-3-phenyl propenoate (0.131 g, 55%). NMR: δ7.3 (s,5H), δ7.8 (s) + δ7.1 (s) (1H), δ1.6 (s) + δ1.4 (s) (9H), IR: 1720 cm^{-1} (s).

From 0.072 g isobutyraldehyde, t-butyl-2-chloro-4-methyl-2-pentenoate (0.05 g, 25%). NMR: δ6.7 (d) + δ6.0 (d) (1H), δ2.9 (m,1H), δ1.5 (s,9H), δ1.05 (d) + δ1.00 (d) (6H). IR: 1730 cm^{-1} (s), 1720 cm^{-1} (s).

From 0.098 g cyclohexanone, 1-chloro-1-carboxy t-butyl methylenecyclohexane (0.10 g, 44%). NMR: δ2.5 (m,4H), δ1.6 (br,6H), δ1.5 (s,9H). IR: 1720 cm^{-1} (s).

From 0.086 g methyl isobutyl ketone, t-butyl-2-chloro-3,4-dimethyl-2-pentenoate (0.037 g, 17%). NMR: δ3.3 (m,1H), δ1.8 (s,3H), δ1.5 (s,9H), δ1.05 (d,6H). IR: 1730 cm^{-1} (s), 1715 cm^{-1} (s).

From 0.072 g methyl ethyl ketone, t-butyl-2-chloro-3-methyl-2-pentenoate (0.111 g, 55%). NMR: δ2.3 (m,2H), δ1.9 (s) + δ2.1 (s) (3H), δ1.5 (s,9H), δ1.0 (m,3H). IR: 1715 cm^{-1} (s).

From 0.134 g phenylacetone, t-butyl-2-chloro-3-methyl-4-phenyl-2-butenoate (0.105 g, 40%). NMR: δ7.2 (s,5H), δ3.8 (s,2H), δ1.95 (s) + δ1.8 (s) (3H), 1.5 (s,9H). IR: 1715 cm^{-1} (s).

Methyl-2-chloro-2,6-heptadienoate (18)

In a 300 ml three-necked flask flushed with nitrogen were placed 20 ml THF, 25 ml ether, and 6.4 g (25 mmole) diethyl-trichloromethane phosphonate, and the flask was cooled to -105°. Then 50 mmole of n-butyl lithium (1.6 M in hexane) was added dropwise. During this addition the temperature of the reaction mixture rose to -85° and was held at this temperature for 15 min., then cooled to -120°. During

dropwise addition of 2.36 g (25 mmole) methyl chloroformate in 10 ml ether the temperature rose to -100°. The mixture was warmed to -60° and 2.1 g (25 mmole) 4-pentenal in 10 ml ether was added. The reaction mixture was stirred at room temperature for 1 hr., then cooled to -20° and hydrolyzed with 25 ml 2N sulfuric acid. The mixture was extracted with ether, and the organic extract was washed with saturated salt solution and dried. Distillation gave methyl-2-chloro-2,6-heptadienoate, b.p. 55-58° (0.08 mm). Yield 1.8 g (41%). NMR: δ6.9 (t) + δ6.3 (t) (1H), δ5.7 (m,1H), δ5.0 (m,2H), δ3.7 (s,3H), δ2.3 (m,4H). IR: 1740 cm^{-1} (s), 1725 cm^{-1} (s).

Attempted Silylation of t-butyl Azidoacetate

In a 50 ml three-necked flask flushed with nitrogen 20 mmole lithium diisopropylamide was prepared and dissolved in 20 ml THF. The solution was cooled to -78° (or -100°), a mixture of 3.14 g (20 mmole) t-butyl azidoacetate and 2.6 ml (20 mmole) trimethylchlorosilane was added and stirred for 1 1/2 hr, then warmed to room temperature. The reaction was worked up with ammonium chloride solution and ether, and the organic layer was dried. The product, a dark red oil, could not be distilled. NMR: δ1.4 (s). IR: 2110 cm^{-1} (m), 1735 cm^{-1} (s).

2-Phenyl-4(4-pentenal)-5-oxazolone (19)

A mixture of 1.79 g (10 mmole) hippuric acid, 1.01 g (12 mmole) 4-pentenal, 1.39 ml (30 mmole) acetic anhydride, and 1.6 g (5 mmole) lead acetate in 20 ml THF was refluxed for 3 hr. The reaction mixture was taken up in ether and

washed with 10% sodium carbonate solution. The organic layer was dried and the solvent evaporated. Purification of the crude product by chromatography on a silica gel column using hexane-chloroform (2:1) gave: Yield 1.8 g (79%). NMR: δ7.6 (m,5H), δ6.5 (t,1H), δ5.8 (m,1H), δ5.0 (m,2H), δ2.5 (m,4H). IR: 1800 cm^{-1} (s), 1670 cm^{-1} (m), 1640 cm^{-1} (w).

Ethyl 2-Benzoylamino-2,6-heptadienoate (20)

To a solution of 0.10 g (0.44 mmole) compound 19 in 10 ml absolute ethanol was added 8 drops concentrated hydrochloric acid, and the mixture was refluxed for 18 hrs. The ethanol was evaporated and the residue was taken up in ether and washed with 5% aqueous sodium bicarbonate. The ether solution was dried and the solvent evaporated. The crude product crystallized on standing and was recrystallized from carbon tetrachloride to give ethyl-2-benzoylamino-2,6-heptadienoate, m.p. 99-100°. Yield 0.078 g (65%). NMR: δ7.6 (m,6H), δ6.7 (t,1H), δ5.7 (m,1H), δ5.0 (m,2H), δ4.1 (q,2H), δ2.3 (m,4H), δ1.3 (t,3H). IR: 3310 cm^{-1} (br), 1720 cm^{-1} (s), 1650 cm^{-1} (s), 1600 cm^{-1} (w).

Ethyl Isocyanoacetate

A solution of 6.4 g (64 mmole) phosgene in 55 ml methylene chloride was added dropwise to a refluxing solution of 7.94 g (60 mmole) N-formyl glycine ethyl ester in 19.4 ml triethylamine and 30 ml methylene chloride. When the addition was complete, the reaction mixture was concentrated under reduced pressure and 15 ml benzene was

added. The mixture was filtered and the precipitate washed with benzene. The filtrate was distilled giving ethyl isocyanoacetate, b.p. 53-55°. Yield: 4.6 g (68%). NMR: δ4.2 (s,2H), δ4.2 (q,2H), δ1.3 (t,3H). IR: 2150 cm^{-1} (m), 1740 cm^{-1} (s). Lit.[116] b.p. 53-55°.

Ethyl-2-formylamino-2,6-heptadienoate (21)

To a solution of 1.13 g (10 mmole) ethyl isocyanoacetate in 10 ml THF cooled to -78° under nitrogen was added 6.5 ml (10 mmole) 1.6 M n-butyl lithium in hexane. Then a solution of 0.84 g (10 mmole) 4-pentenal in 5 ml THF was added, and the reaction mixture allowed to warm to room temperature. The THF was removed under reduced pressure and the residue treated with 15 ml of 1 M acetic acid. The acid solution was extracted with ether, and the organic extract dried and the solvent evaporated. Column chromatography on silica gel with ether gave ethyl-2-formylamino-2,6-heptadienoate. Yield: 1.2 g (61%). NMR: δ8.0 (d,1H), δ7.0 (t) + δ6.4 (t) (1H), δ5.7 (m,1H), δ4.9 (m,2H), δ4.15 (q) + δ4.1 (q) (2H), δ2.2 (m,4H), δ1.3 (t) + δ1.25 (t) (3H). IR: 3300 cm^{-1} (br), 1710 cm^{-1} (s), 1685 cm^{-1} (s).

t-Butyl-6,7-epoxy-2-chloro-2-heptenoate (22)

To a solution of 2.1 g (10 mmole) t-butyl-2-chloro-2,6-heptadienoate in 20 ml methylene chloride was added 2.3 g (11 mmole) 85% m-chloroperbenzoic acid. The mixture was stirred for 14 hr. at room temperature and then filtered. The filtrate was washed with 5% aqueous sodium sulfite and 5% aqueous sodium carbonate, then dried and evaporated to

give t-butyl-6,7-epoxy-2-chloro-2-heptenoate. Yield 1.8 g (78%). NMR: δ6.8 (t) + δ6.2 (t) (1H), δ2.4 (m,7H), δ1.3 (s,9H). IR: 1720 cm^{-1} (s), 1630 cm^{-1} (w).

Reaction of t-Butyl-2-chloro-2,6-heptadienoate with Benzylamine

A solution of 0.22 g (1 mmole) t-butyl-2-chloro-2,6-heptadienoate and 0.21 g (2 mmole) benzylamine in 10 ml toluene was refluxed for 18 hr. The reaction mixture was taken up in ether and washed with water. The organic layer was dried and evaporated to give, probably, t-butyl-2,3-(N-benzylaziridinyl)-6-heptenoate. Yield 0.23 g (80%). NMR: δ7.2 (s,5H), δ5.6 (m,1H), δ5.0 (m,2H), δ4.6 (s,2H), δ3.5 (br,2H), δ2.3 (m,4H), δ1.5 (s,9H). IR: 1720 cm^{-1} (s).

t-Butyl-α-chloro-α(5-azidomethyl-2-tetrahydrofuranyl) Acetate

In a 10 ml flask 0.27 g (1.2 mmole) t-butyl-2-chloro-6,7-epoxy-2-heptenoate was dissolved in 5 ml dioxane. The solution was heated to reflux and 0.13 g (2 mmole) sodium azide was added dropwise. The mixture was refluxed for 9 hr., at this time two layers had formed in the reaction mixture. The layers were separated and the aqueous layer was extracted with ether. The ether extracts were combined with the original organic layer, dried, and concentrated. The product was a slightly yellow oil, t-butyl-α-chloro-α(5-azidomethyl-2-tetrahydrofuranyl) acetate. Yield 0.24 g (87%). NMR: δ4.3 (m,3H), δ3.3 (br d,2H), δ2.0 (m,4H), δ1.5 (s,9H). IR: 2100 cm^{-1} (s), 1735 cm^{-1} (s).

t-Butyl-2-chloro-6-hydroxy-7-tosylamino-2-heptenoate (24)

In a 100 ml flask 1.08 g (5 mmole) t-butyl-2-chloro-2,6-heptadienoate was dissolved in 50 ml t-butyl alcohol, and 1.76 g (6.25 mmole) Chloramine-T trihydrate, 13 mg osmium tetroxide, and 1.06 g (6.25 mmole) silver nitrate were added. The reaction mixture was stirred and heated at 60° for 4 hr. Then 20 ml of 2.5% aqueous sodium bisulfite was added and the mixture was refluxed for 1 hr. The silver chloride was filtered off and the butanol evaporated. The residue was taken up in methylene chloride and washed with 1% sodium hydroxide in saturated salt solution and with water. The organic layer was dried and evaporated to give t-butyl-2-chloro-6-hydroxy-7-tosylamino-2-heptenoate. Yield: 1.86 g (93%). NMR: δ7.5 (q,4H), δ6.9 (t,1H), δ3.6 (m,2H), δ2.9 (m,3H), δ2.4 (s,3H), δ2.3 (br,1H), δ1.6 (br,2H), δ1.5 (s,9H). IR: 3505 cm^{-1} (br), 3290 cm^{-1} (br), 1720 cm^{-1} (s), 1630 cm^{-1} (w), 1600 cm^{-1} (w).

t-Butyl-2-chloro-6-hydroxy-7-t-butoxycarbonylamino-2-heptenoate (25)

In a 250 ml flask 2.59 g (15 mmole) N-chlorosodio t-butyl carbamate and 5.1 g (30 mmole) silver nitrate were dissolved in 100 ml acetonitrile and after about 10 min a yellow suspension developed. To this suspension was added 0.81 ml (45 mmole) water, 2.17 g t-butyl-2-chloro-2,6-heptadienoate, and 25 mg (0.1 mmole) osmium tetroxide, and the mixture was stirred at room temperature for 14 hr.

Then 2.5 ml saturated sodium chloride solution was added and the precipitated silver chloride was filtered off. The filtrate was refluxed with 40 ml of 2.5% aqueous sodium bisulfite for 1 hr. The mixture was concentrated and the aqueous residue was extracted with methylene chloride. The organic extract was dried and evaporated and the crude product was chromatographed on a silica gel column using chloroform to give t-butyl-2-chloro-6-hydroxy-7-t-butoxycarbonylamino-2-heptenoate. Yield 2.8 g (80%). NMR: δ6.9 (t) + δ6.3 (t) (1H), δ5.1 (br,1H), δ3.3 (m,4H), δ2.5 (m,4H), δ1.5 (s,9H), δ1.4 (s,9H). IR: 3380 cm^{-1} (br), 1710 cm^{-1} (s), 1630 cm^{-1} (w).

t-Butyl-α-chloro-α(5-tosylaminomethyl-2-tetrahydrofuranyl) Acetate (26)

To a solution of 0.08 g (0.2 mmole) compound 24 in 10 ml THF was added 8.6 mg (0.2 mmole) of 56% sodium hydride. The mixture was stirred at room temperature under nitrogen for 3.5 hr. The reaction mixture was taken up in ether and washed with water. The organic phase was dried and evaporated to give t-butyl-α-chloro-α(5-tosylaminomethyl-2-tetrahydrofuranyl) acetate. Yield 75 mg (94%). NMR: δ7.5 (q,4H), δ4.2 (m,4H), δ3.1 (m,1H), δ2.5 (s,3H), δ2.0 (m,4H), δ1.5 (s,9H). IR: 3290 cm^{-1} (br), 1740 cm^{-1} (s), 1600 cm^{-1} (w).

t-Butyl 2-Chloro-6-(t-butyldimethylsilyloxy)-7-tosylamino-2-heptenoate (27)

A solution of 2.7 g (6.7 mmole) compound 24, 1.0 g (6.7 mmole) t-butyldimethylsilyl chloride, and 0.91 g (13.4 mmole) imidazole in 10 ml dimethylformamide was stirred

at 50° for 21 hr. The reaction mixture was taken up in ether and washed with water. The organic phase was dried and evaporated. The crude product was chromatographed on a silica gel column using chloroform to give compound 27. Yield 2.8 g (80%). NMR: δ7.45 (q,4H), δ6.8 (t) + δ5.3 (t) (1H), δ3.6 (m,2H), δ2.8 (m,2H), δ2.4 (s,3H), δ2.2 (m,1H0, δ1.7 (m,2H), δ1.5 (s,9H), δ0.9 (s,9H), δ0.0 (s,6H). IR: 3290 cm^{-1} (br), 1720 cm^{-1} (s), 1630 cm^{-1} (w), 1600 cm^{-1} (w).

t-Butyl α-Chloro-α-(5-t-butyldimethylsilyloxy-1-tosyl-2-piperidyl) Acetate (28)

To a solution of 5.2 g (10 mmole) compound 27 in 100 ml THF was added 0.41 g (10 mmole) of 56% sodium hydride and the mixture was stirred at room temperature for 3 hr. The reaction mixture was partitioned between ether and water, and the organic layer was dried and evaporated. The crude product formed crystals on standing which were recrystallized from hexane giving compound 28, m.p. 148-150°. Yield: 2.1 g (40%). When the mother liquor was concentrated and allowed to stand in the cold with a small amount of hexane added, more crystals formed, also compound 28, but m.p. 106-108°. Yield 0.7 g (13%). Total yield 2.8 g (53%). NMR: δ7.6 (q,4H), δ4.4 (br s,1H), δ3.8-2.8 (m,4H), δ2.5 (s,3H0, δ2.3-1.7 (m,4H), δ1.5 (s,9H), δ0.9 (s,9H), δ0.0 (s,6H). IR: 1730 cm^{-1} (s), 1600 cm^{-1} (w). For $C_{24}H_{40}O_5ClNSiS$ Calculated: C,55.62; H,7.80; N,2.70. Found C, 55.93; H, 8.07; N, 2.61.

Attempted Reaction of Compound 28 with Sodium Azide

a) A solution of 0.1 g (0.2 mmole) compound 28 in 5 ml chloroform and a solution of 0.065 g (1 mmole) sodium azide in 2 ml water were stirred with 5 mg cetyl trimethyl ammonium bromide at room temperature overnight. The reaction mixture was extracted three times with ether. Drying and evaporation of the organic layer gave compound 28.

b) A mixture of 0.065 g sodium azide and 10 mg 18-crown-6 in 10 ml acetonitrile was stirred for 1/2 hr then 0.1 g compound 28 was added. The mixture was refluxed overnight, then the acetonitrile was evaporated. The residue was taken up in ether and washed with water. Drying and evaporation of the organic layer gave compound 28.

α-Chloro-α(1-tosyl-5-hydroxy-2-piperidyl) Acetic Acid (31)

A solution of 1.5 g (2.9 mmole) compound 28 (m.p. 147-150°) in 3 ml trifluoroacetic acid was stirred at room temperature for 45 min. The excess trifluoroacetic acid was evaporated under reduced pressure, and the residue was taken up in ether and washed with water. Drying and evaporation of the ether layer and recrystallization of the crude product from chloroform-hexane gave α-chloro-α(1-tosyl-5-hydroxy-2-piperidyl) acetic acid, m.p. 175-177°., Yield 0.98 g (98%).

When compound 28 (m.p. 106-108°) was hydrolyzed in the same way the product had m.p. 196-198°. NMR: δ7.6 (q,4H),

δ4.6 (s,1H), δ4.5 (br,1H), δ4.0-2.7 (m,4H), δ2.5 (s,3H), δ1.8 (m,4H). IR: 3440 cm^{-1} (br), 1740 cm^{-1} (s), 1600 cm^{-1} (w). For $C_{14}H_{18}O_5NSCl$ Calculated: C, 48.34; H, 5.22; N, 4.03. Found: C, 48.56; H, 5.40; N, 3.98.

(1-Tosyl-5-hydroxy-2-piperidyl) Glycine (32).

A solution of 1.05 g (3 mmole) compound 31 in 15 ml 30% aqueous ammonia was sealed in a thick walled Pyrex tube and heated at 90° for four days. The tube was opened and the excess ammonia and water were evaporated. The crude product was recrystallized from methanol giving (1-tosyl-5-hydroxy-2-piperidyl) glycine, m.p. 180° (d). Yield 0.89 g (90%). NMR: δ7.6 (q,4H), δ4.6 (br,2H), δ4.0-3.0 (m,4H), δ2.5 (s,3H), δ1.7 (m,4H). IR: 3000 cm^{-1} (very br), 1590 cm^{-1} (s,br).

After acidification: 3420 cm^{-1} (br), 3150 cm^{-1} (br), 1740 cm^{-1} (s).

For $C_{14}H_{20}N_2O_5S$ Calculated: C, 51.20; H, 6.15; N, 8.53. Found: C, 50.47; H, 6.25; N, 8.80.

Attempted Reaction of Compound 32 with Sodium Naphthalene

In a 25 ml three-necked flask flushed with nitrogen 0.25 g (2 mmole) naphthalene and 50 mg (2 mmole) sodium in 5 ml 1,2-dimethoxyethane were stirred at room temperature for 1 1/2 hr until a dark green color developed. Then 40 mg (0.12 mmole) compound 32 was added and the mixture stirred for 2 hr. The reaction mixture was poured into water and extracted with pentane. The aqueous phase was neutralized with 10% HCl and evaporated. The residue was recrystallized from water giving compound 32.

(2-Tosyl-8-carboxymethyl)-2-aza-7-oxabicyclo-(2,2,2)octane (33)

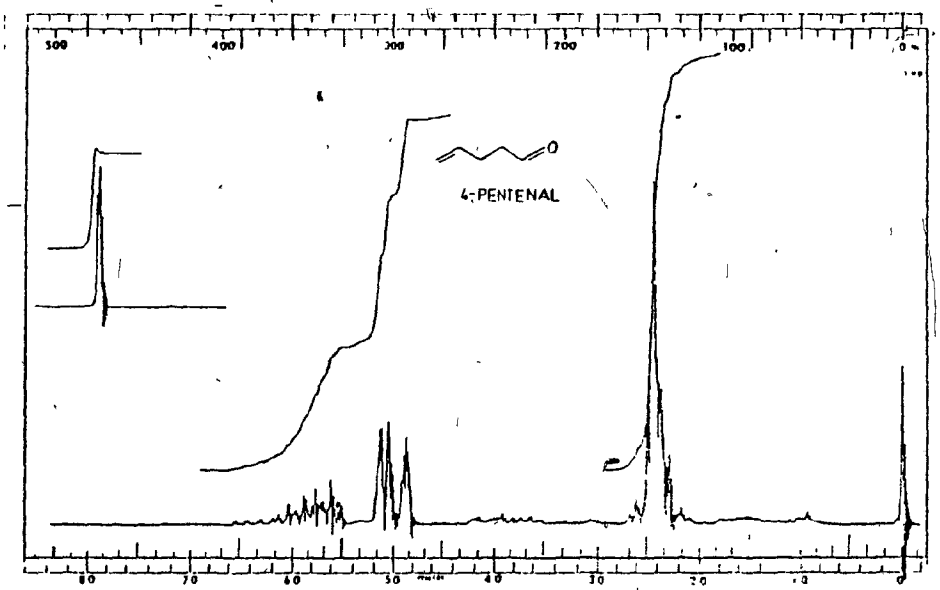
a) To 10 ml methanol saturated with anhydrous HCL was added 50 mg (1-tosyl-5-hydroxy-2-piperidyl) glycine and the solution refluxed for 14 hr. The methanol was evaporated and the residue was partitioned between ether and water. The ether layer was dried and evaporated giving compound 33, m.p. 149-151°. Yield 45 mg (90%).

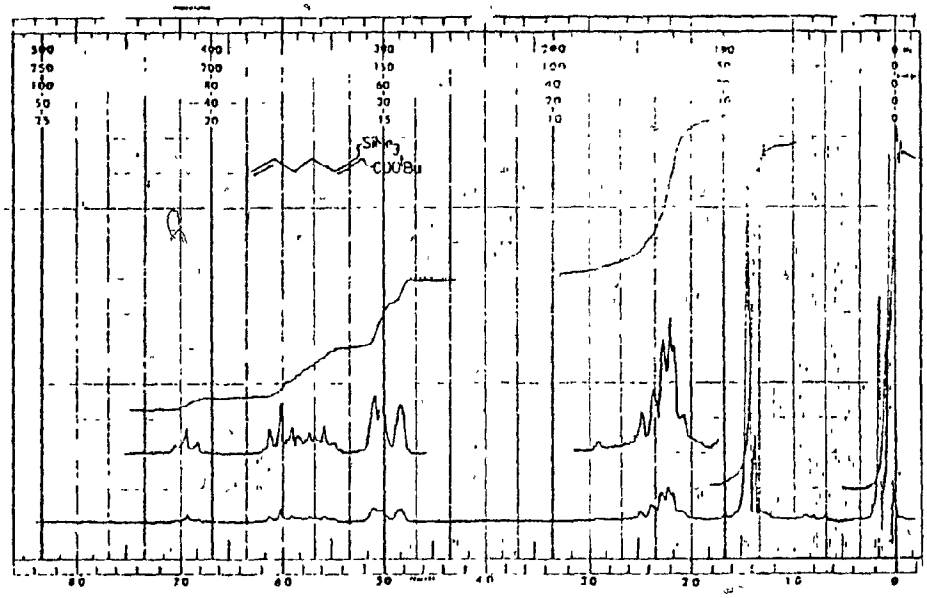
b) A mixture of 50 mg compound 32, 4 ml 2,2-dimethoxypropane, 4 ml methanol, and 5 drops concentrated HCl was refluxed for 1/2 hr, then stirred at room temperature for 8 hr. The solvents were evaporated and the residue taken up in water and neutralized with sodium bicarbonate. The neutral mixture was extracted with chloroform giving compound 33, m.p. 149-151°. Yield 42 mg (84%).
NMR: δ7.5 (q,4h), δ4.2 (br,2H), δ4.1 (m,1H), δ3.8 (s,3H), δ3.5 (m,2H), δ2.5 (s,3H), δ1.8 (m,4H). IR: 1755 cm^{-1} (s), 1600 cm^{-1} (w).

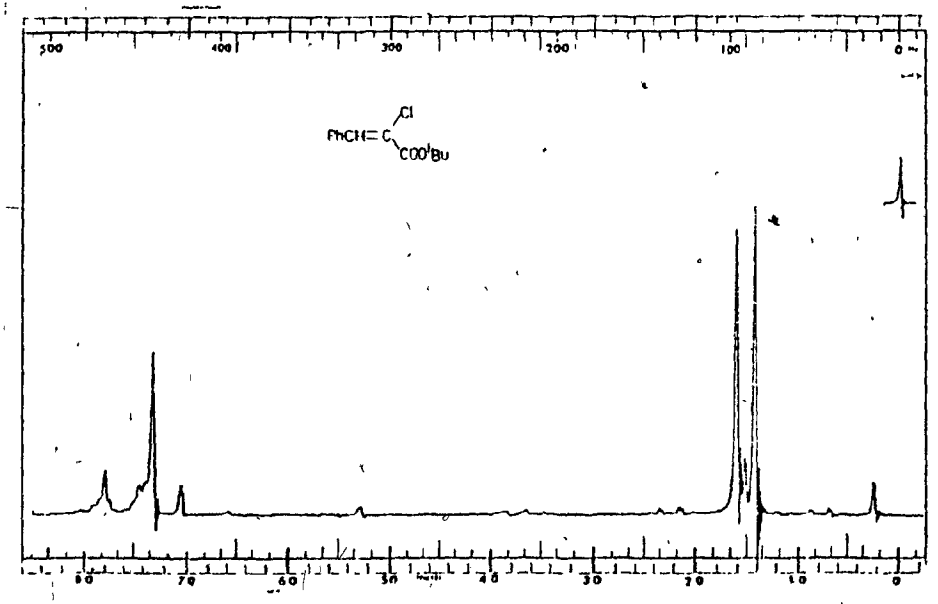
Reaction of Compound 32 with 2-t-Butyloxycarbonyloxyimino-2-phenylacetonitrile and Diazomethane

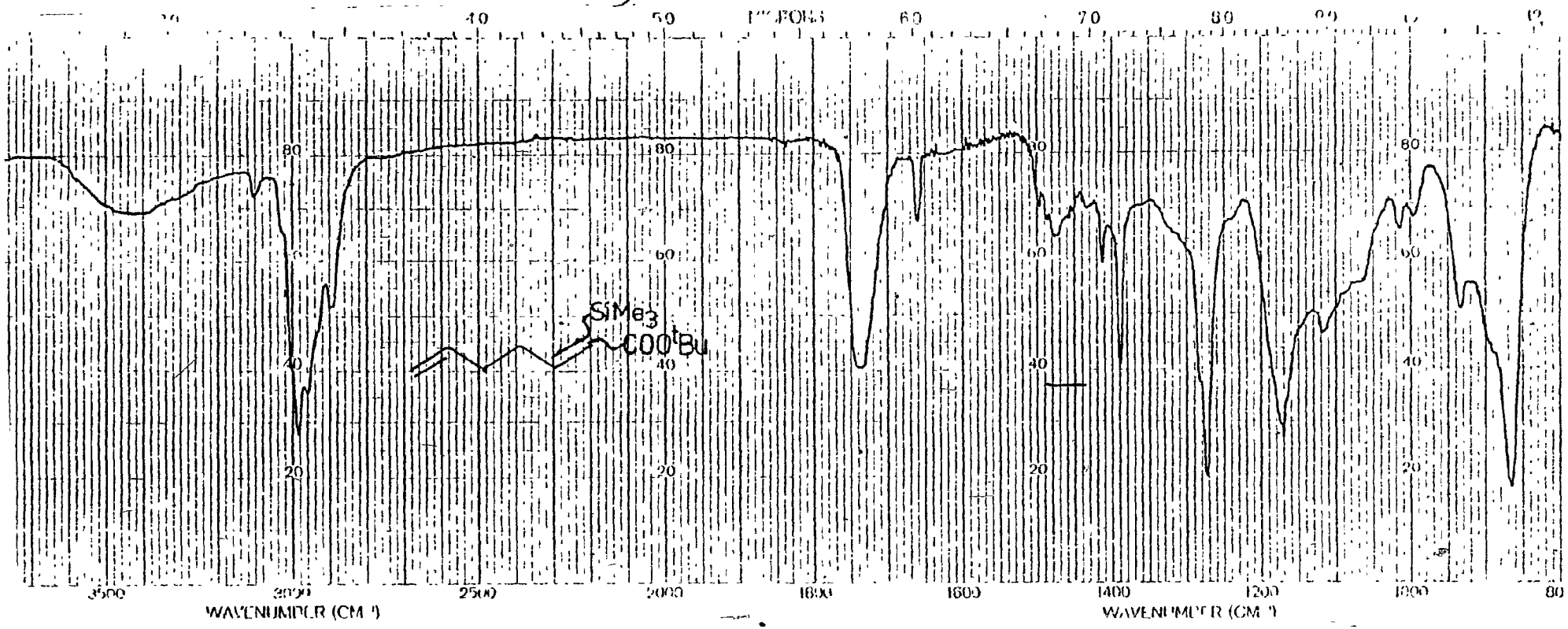
To a solution of 0.164 g (0.5 mmole) compound 32 and 0.105 ml (0.75 mmole) triethylamine in 3 ml water was added 0.14 g (0.55 mmole) 2-t-butyloxycarbonyloxyimino-2-phenylacetonitrile in 2 ml dioxane. The mixture became homogeneous in 2 hr and was stirred for 8 hr. After addition of water and ethyl acetate, the aqueous layer was separated, washed with ethyl acetate. The extract was dried and evaporated and

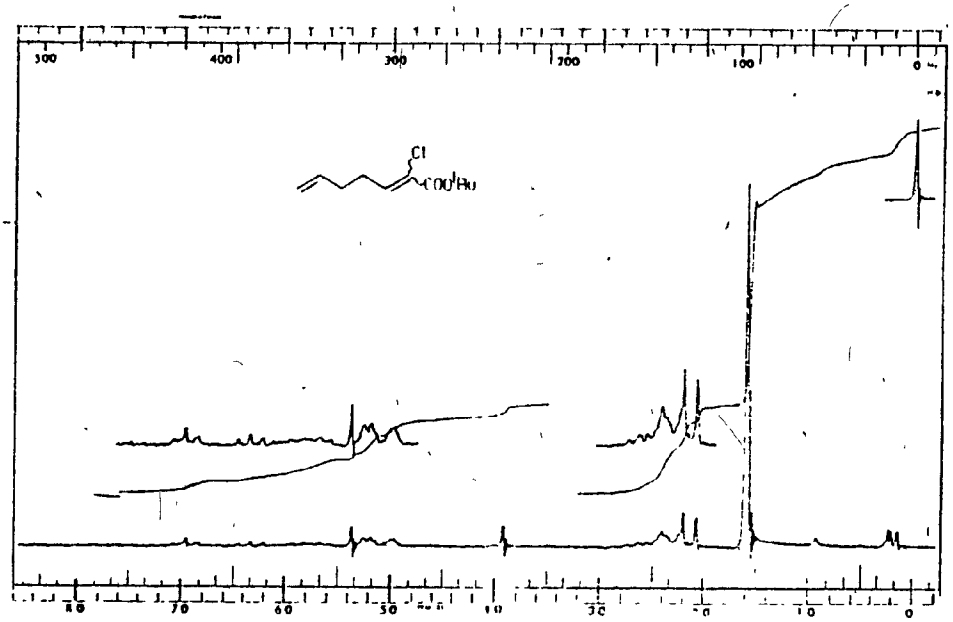
the residue was dissolved in ether. The ether solution was added to a solution of 0.2 g (5 mmole) diazomethane in ether at 0°. The solution was stirred at 0° for 1 hr. The excess diazomethane was destroyed by addition of acetic acid just until the color was discharged. Evaporation of the solvents gave compound 33.

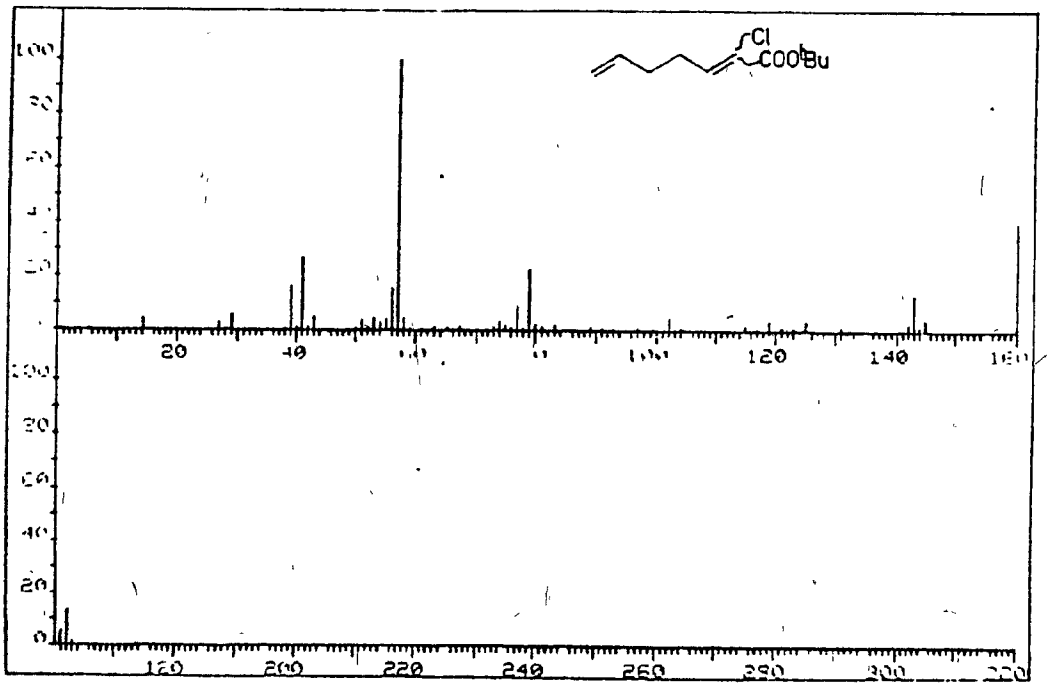

4-PENTENAL

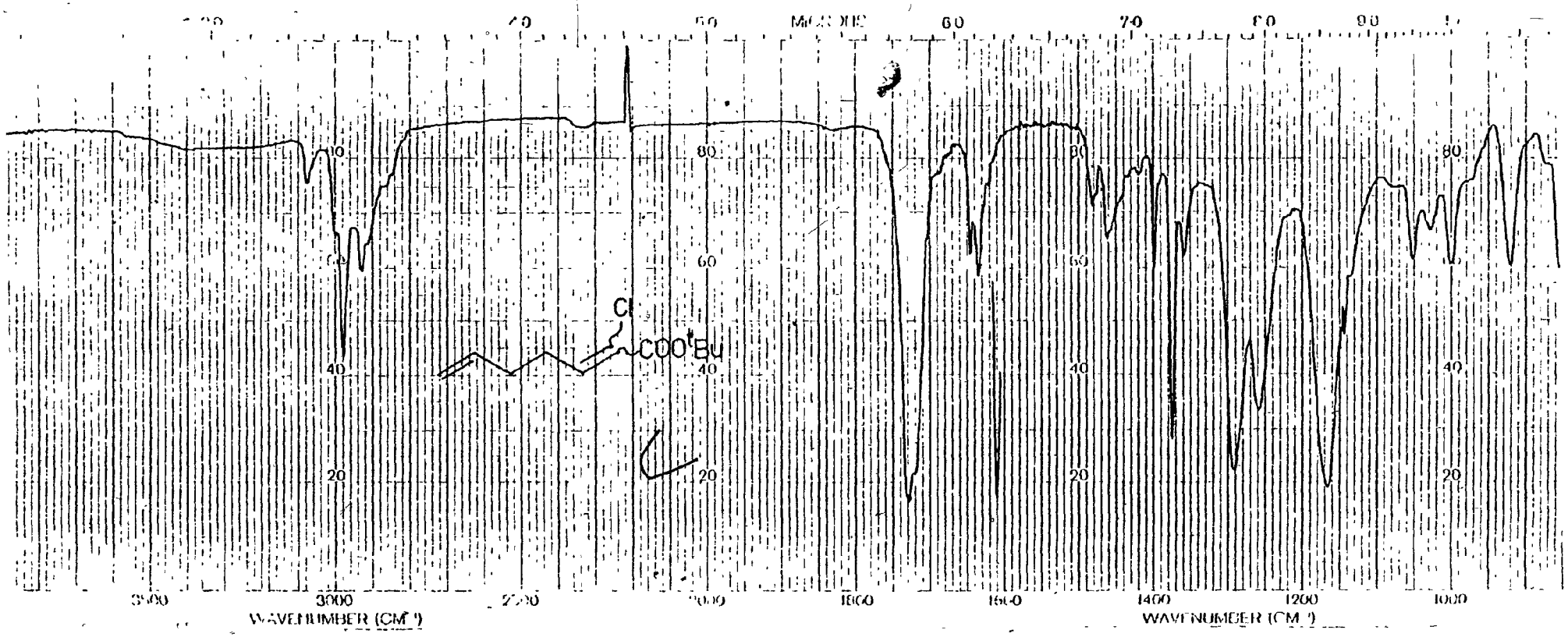

SiMe3
COO'Bu

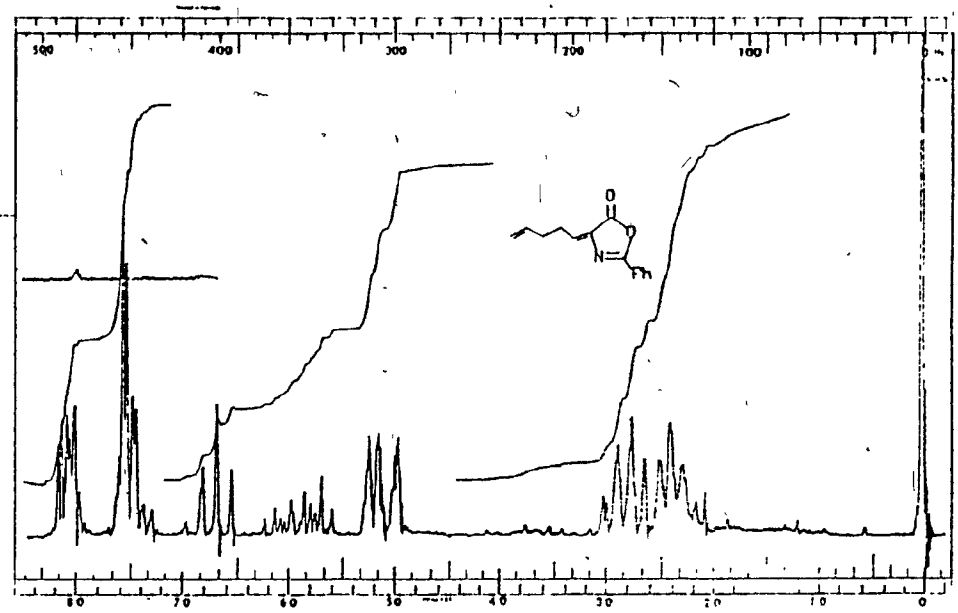

Cl
PhCH=C
COO'Bu

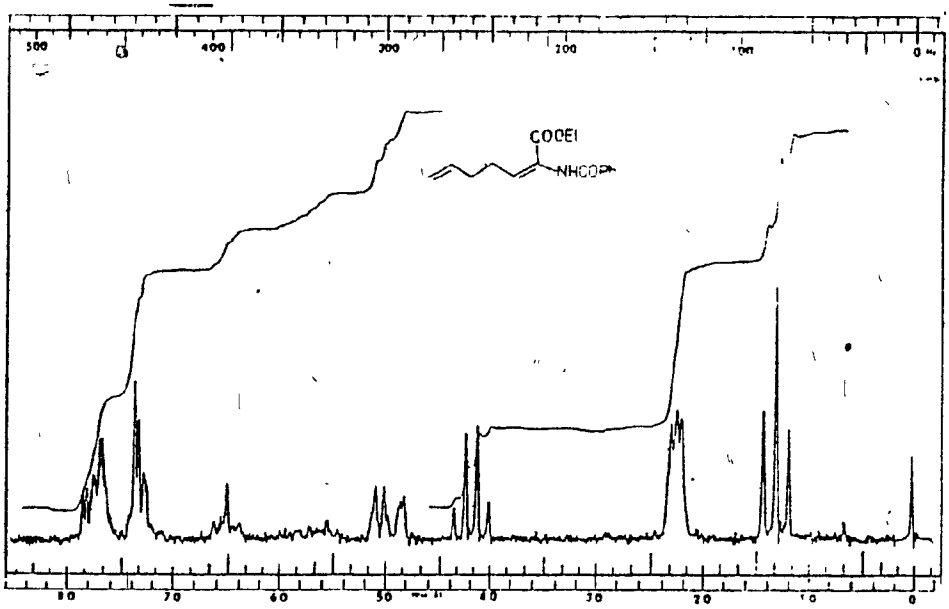

SiMe3
COO^{t}Bu
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)

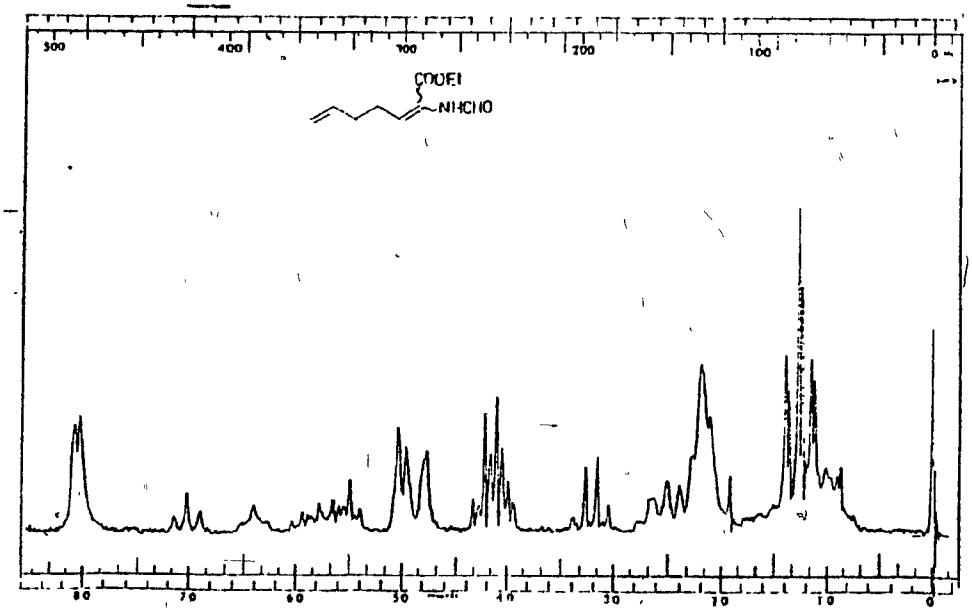

Cl
COOtBu

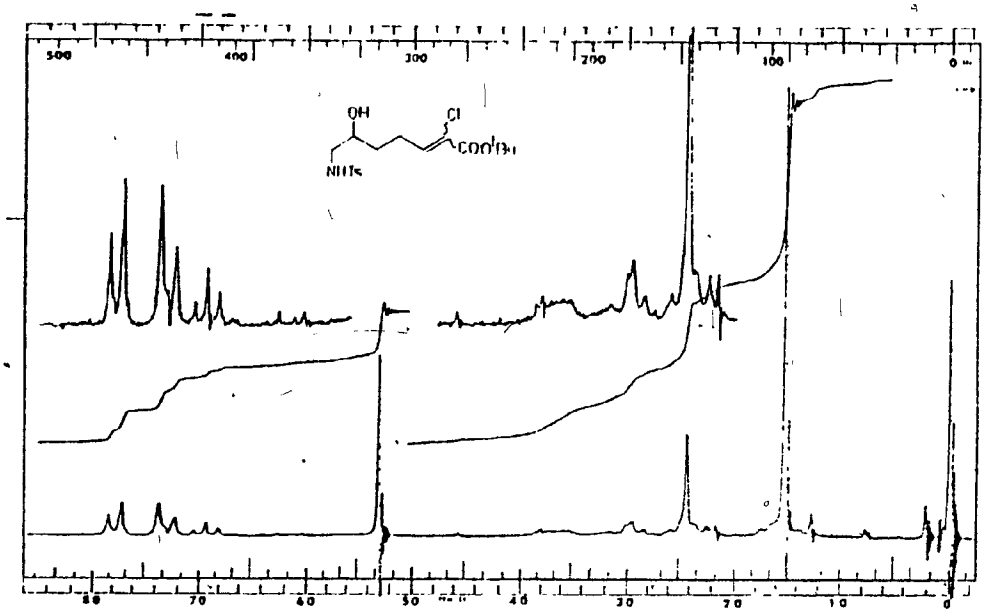

Cl
COOtBu

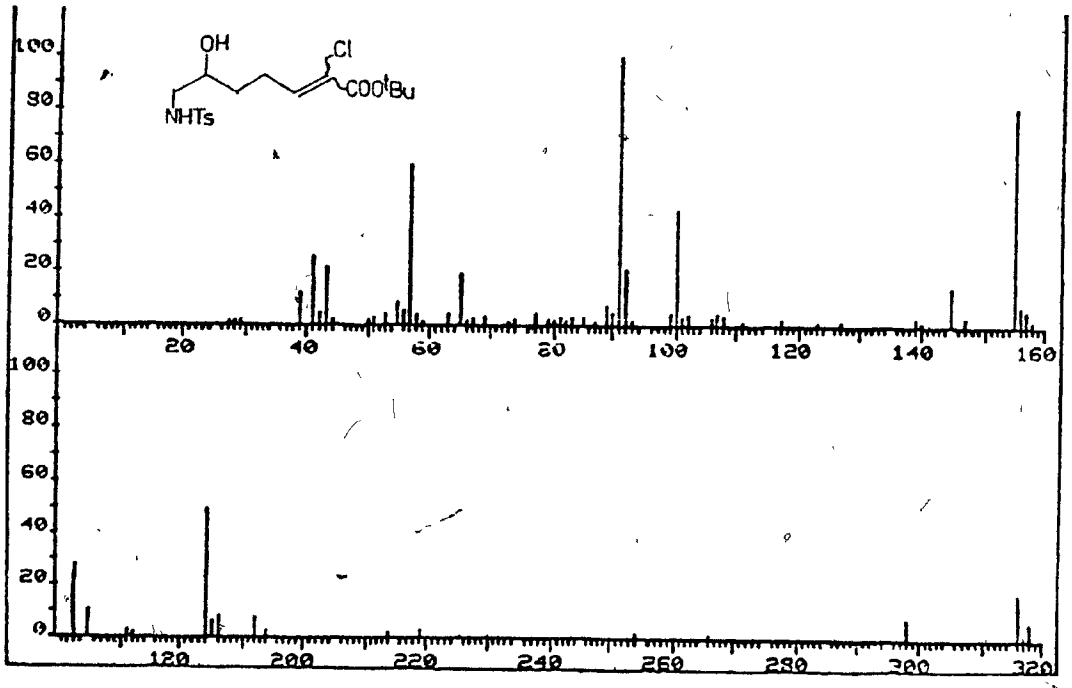

WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)
Cl
COO'Bu

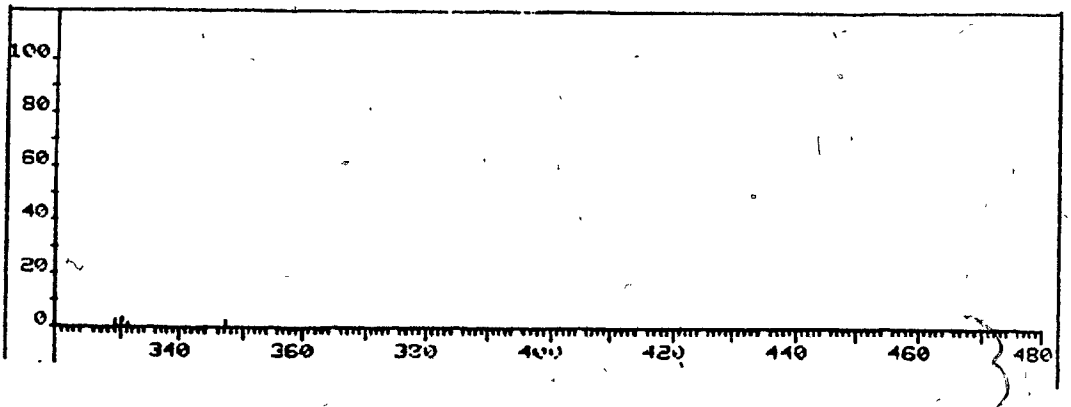


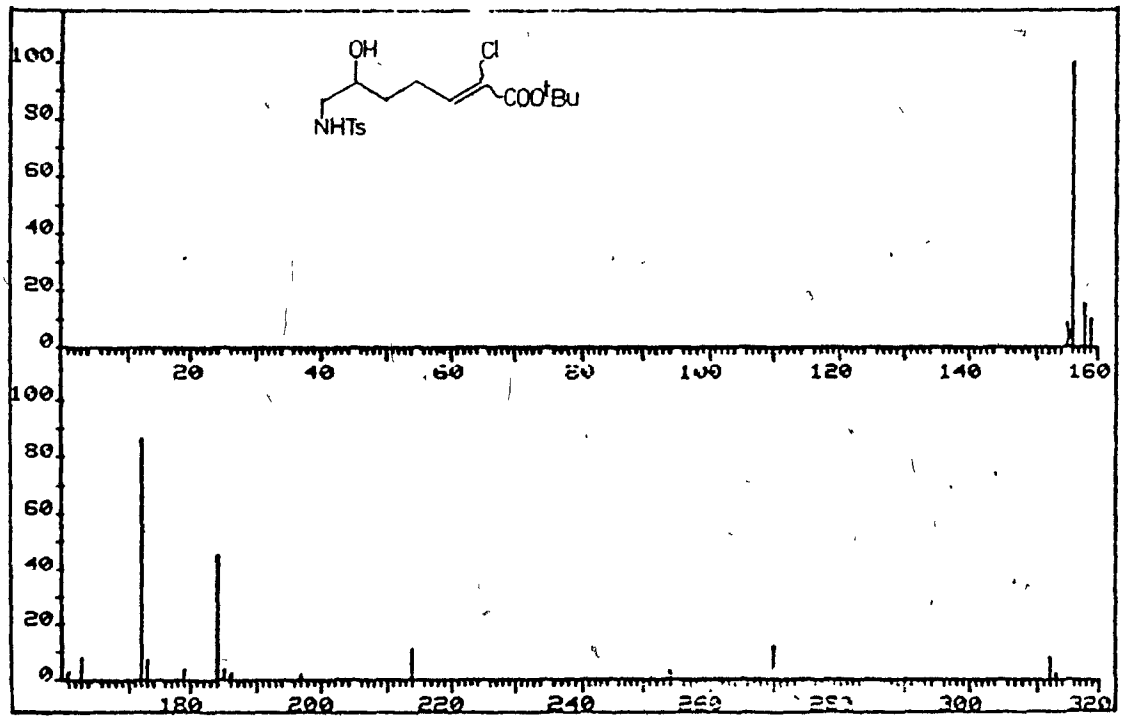

COOEt
NHCOPh

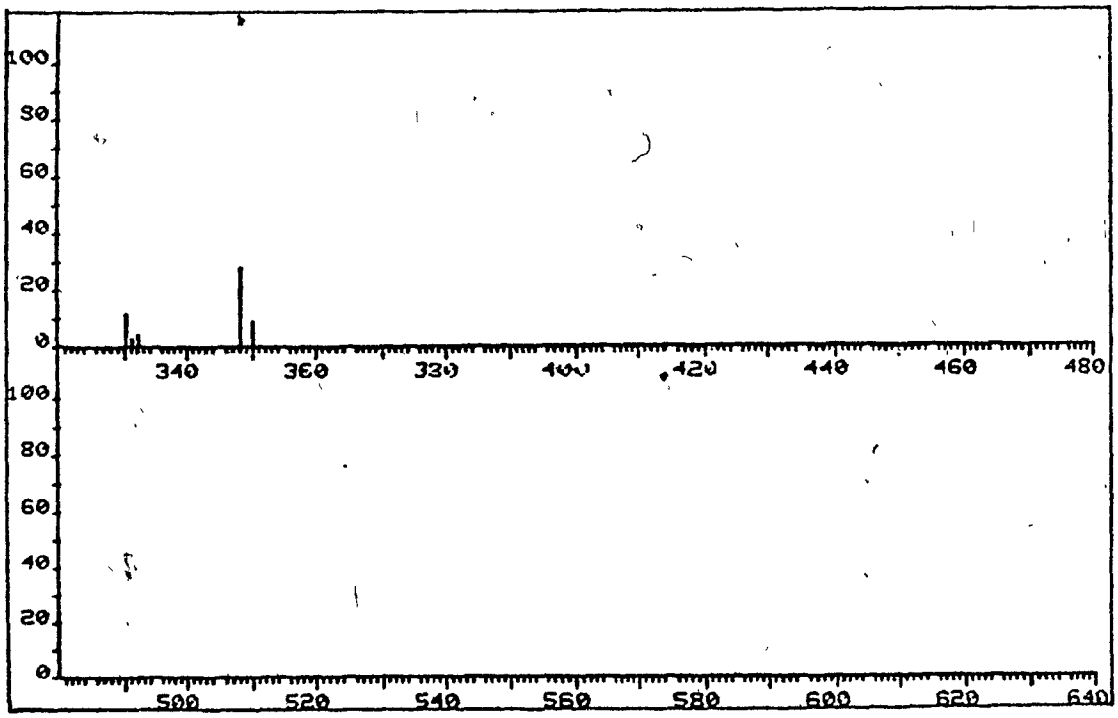

COOEt
NHCHO

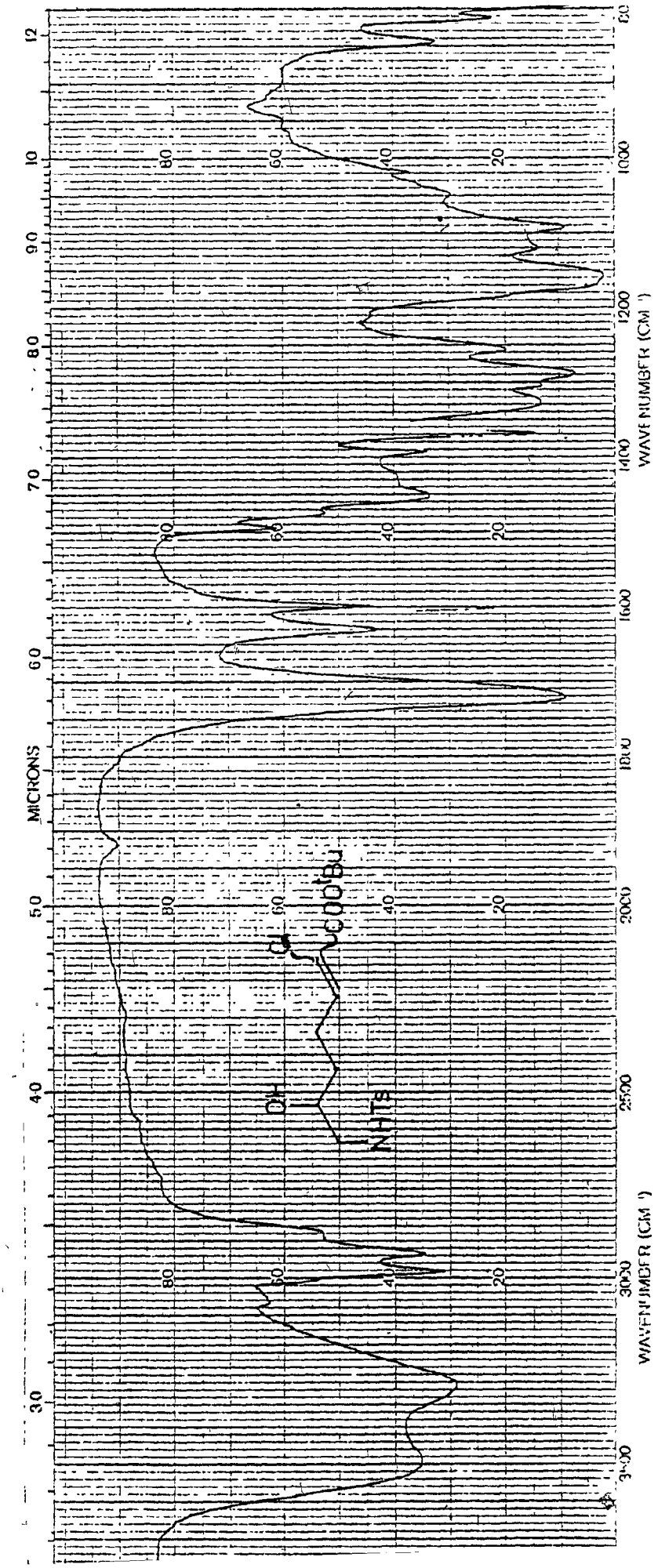

OH
Cl
NHTs
COOtBu

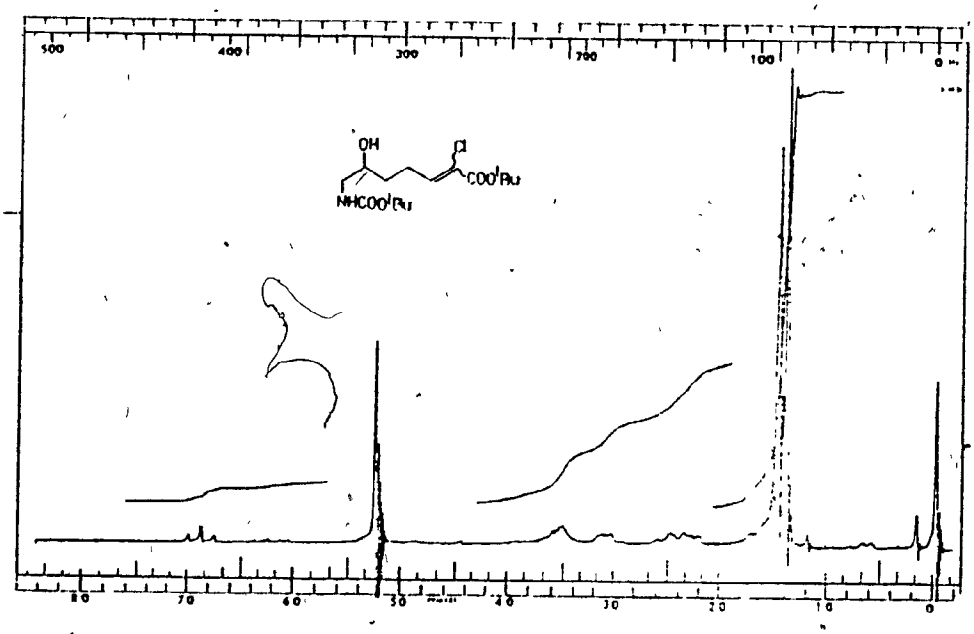

OH
Cl
NHTs
COOtBu

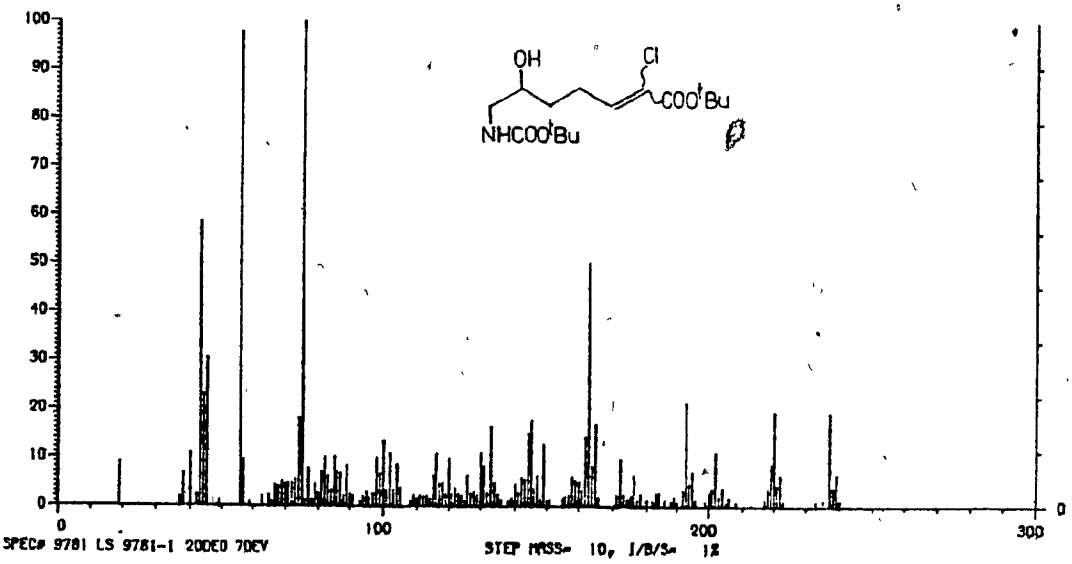


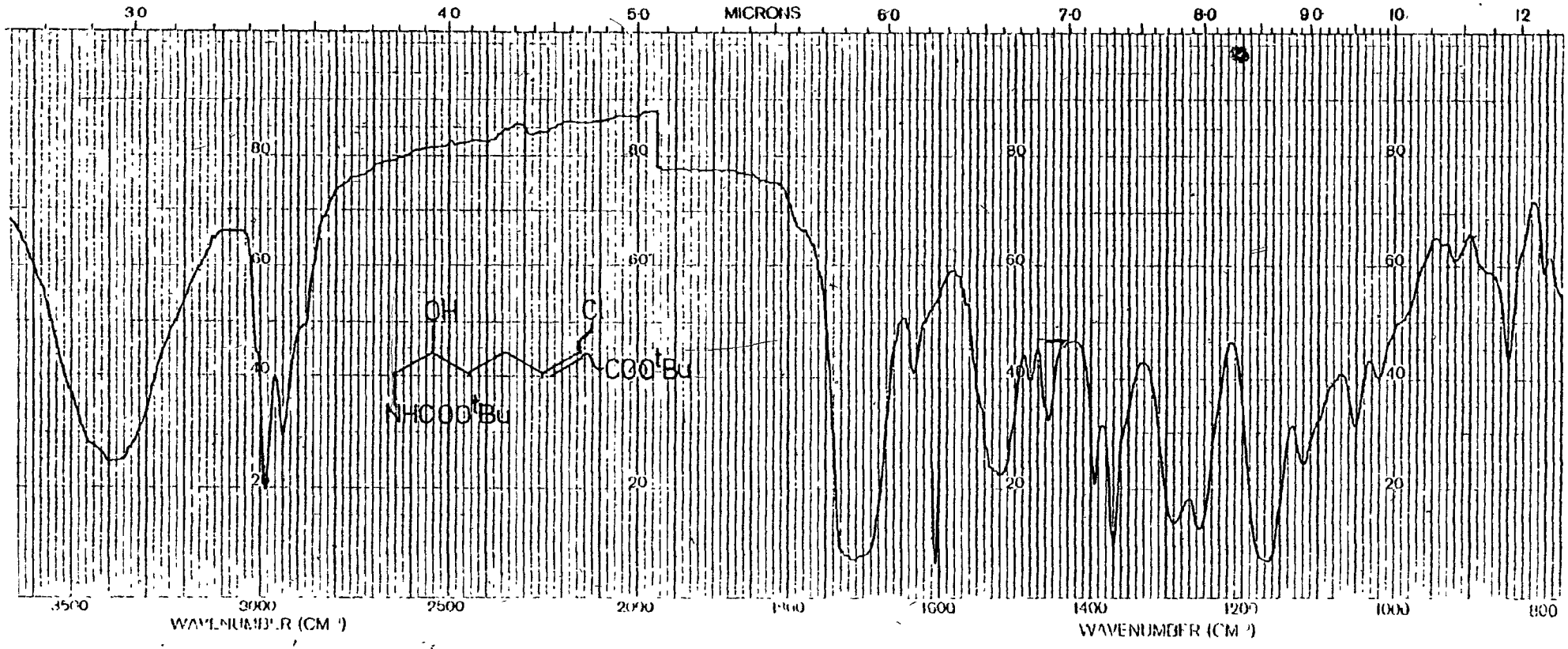

OH
Cl
COO^{t}Bu
NHTs
100
80
60
40
20
0
20
40
60
80
100
120
140
160
100
80
60
40
20
0
180
200
220
240
260
280
300
320

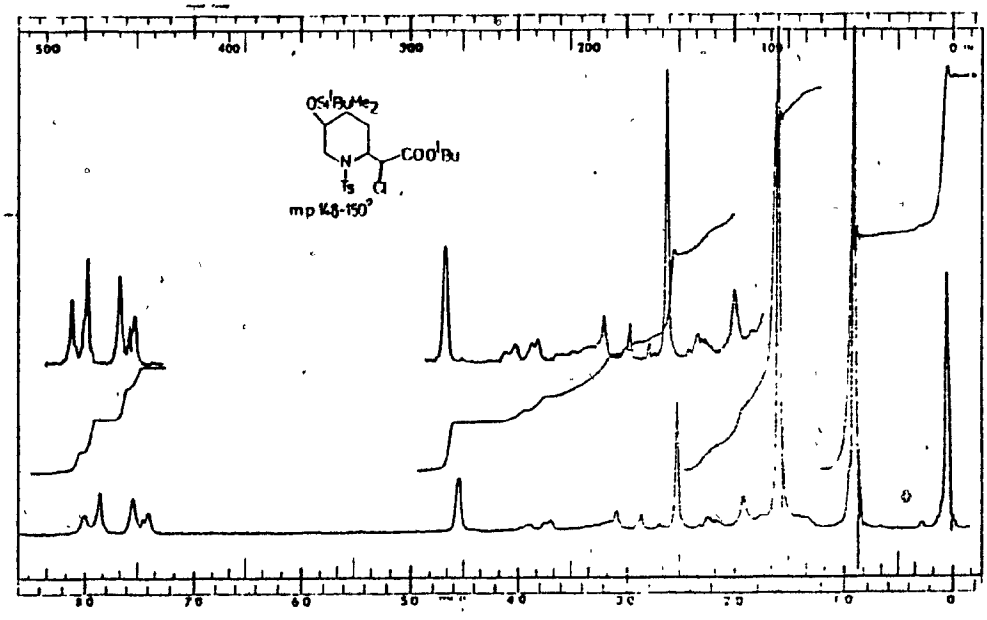

100
80
60
40
20
0
340
360
380
400
420
440
460
480
100
80
60
40
20
0
500
520
540
560
580
600
620
640

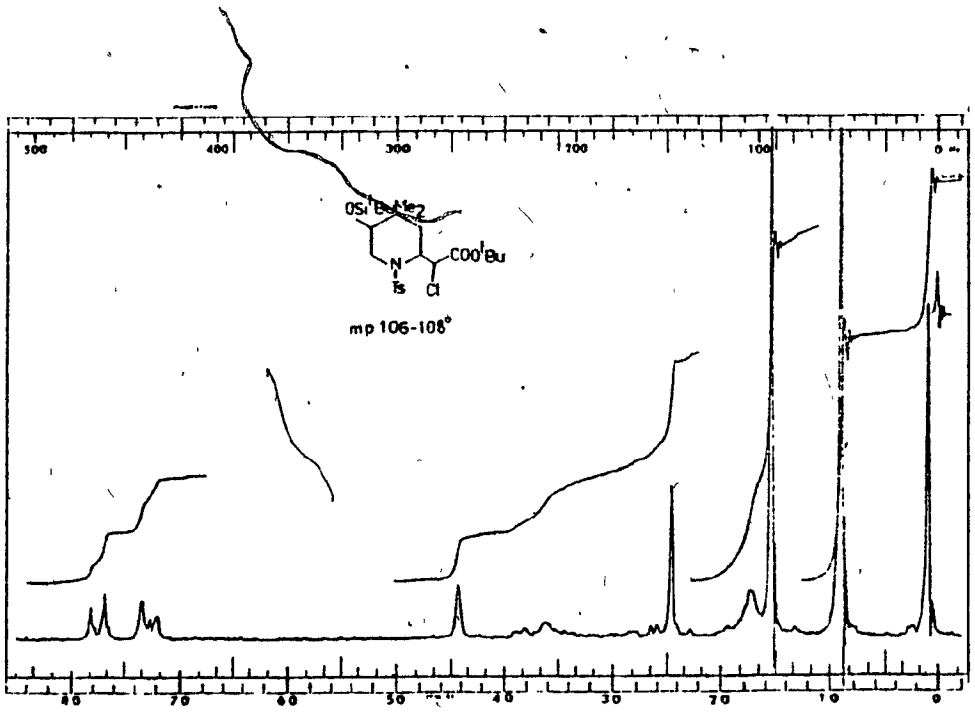

MICRONS
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)
OH
NHTs
OtBu

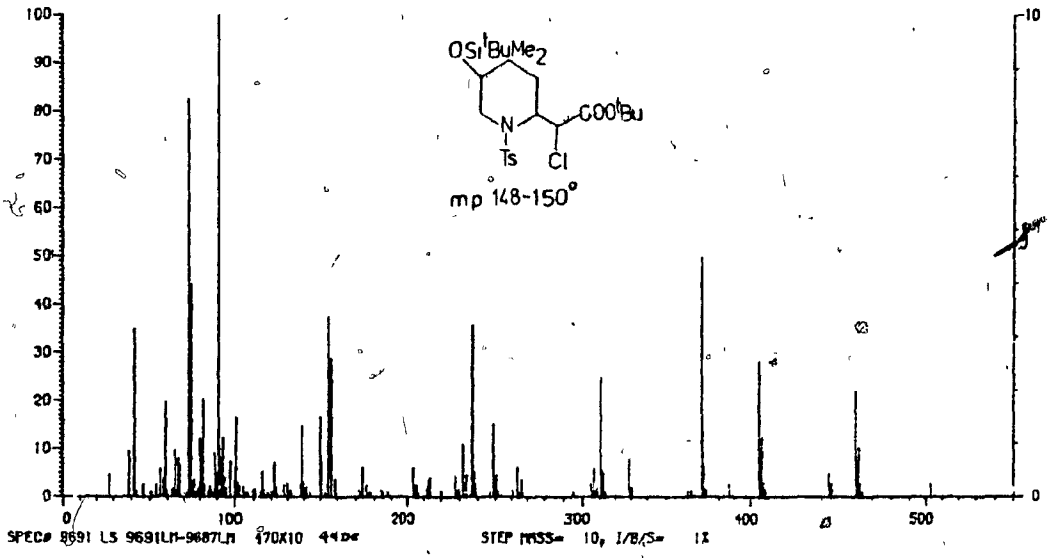

OH
Cl
COO^{t}Bu
NHCOO^{t}Bu

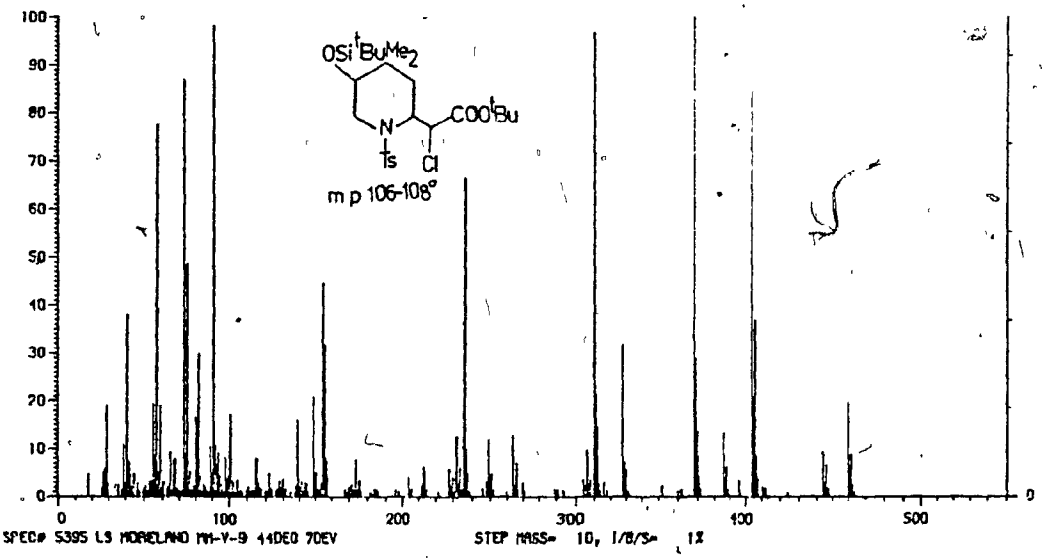

OH
Cl
COO^{t}Bu
NHCOO^{t}Bu
SPEC# 9781 LS 9781-1 20DE0 70EV
STEP MASS= 10, I/B/S= 1%

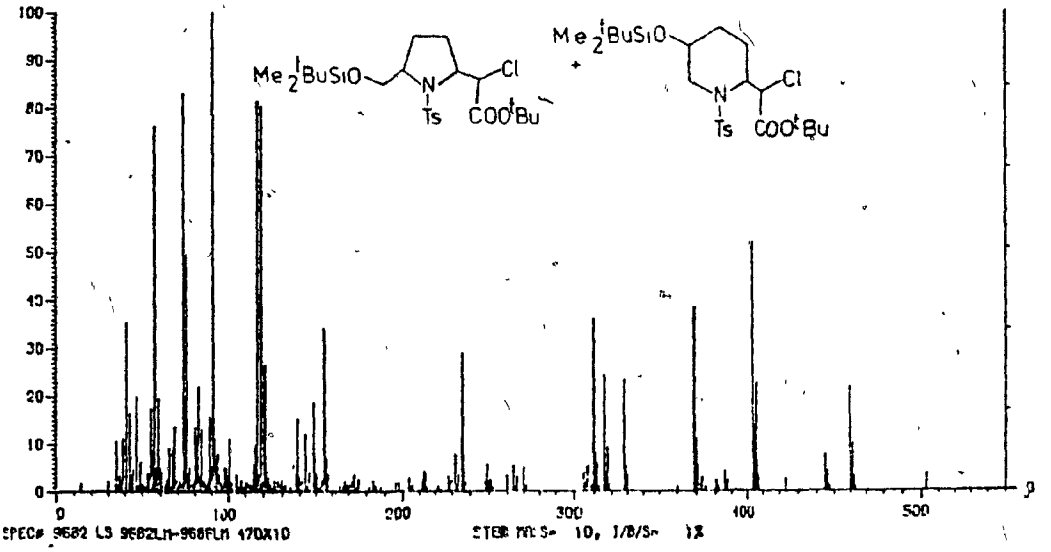

3.0
4.0
5.0
MICRONS
6.0
7.0
8.0
9.0
10.
12
80
60
40
20
OH
C
COO^{t}Bu
NHCOO^{t}Bu
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
WAVENUMBER (CM^{-1})
WAVENUMBER (CM^{-1})

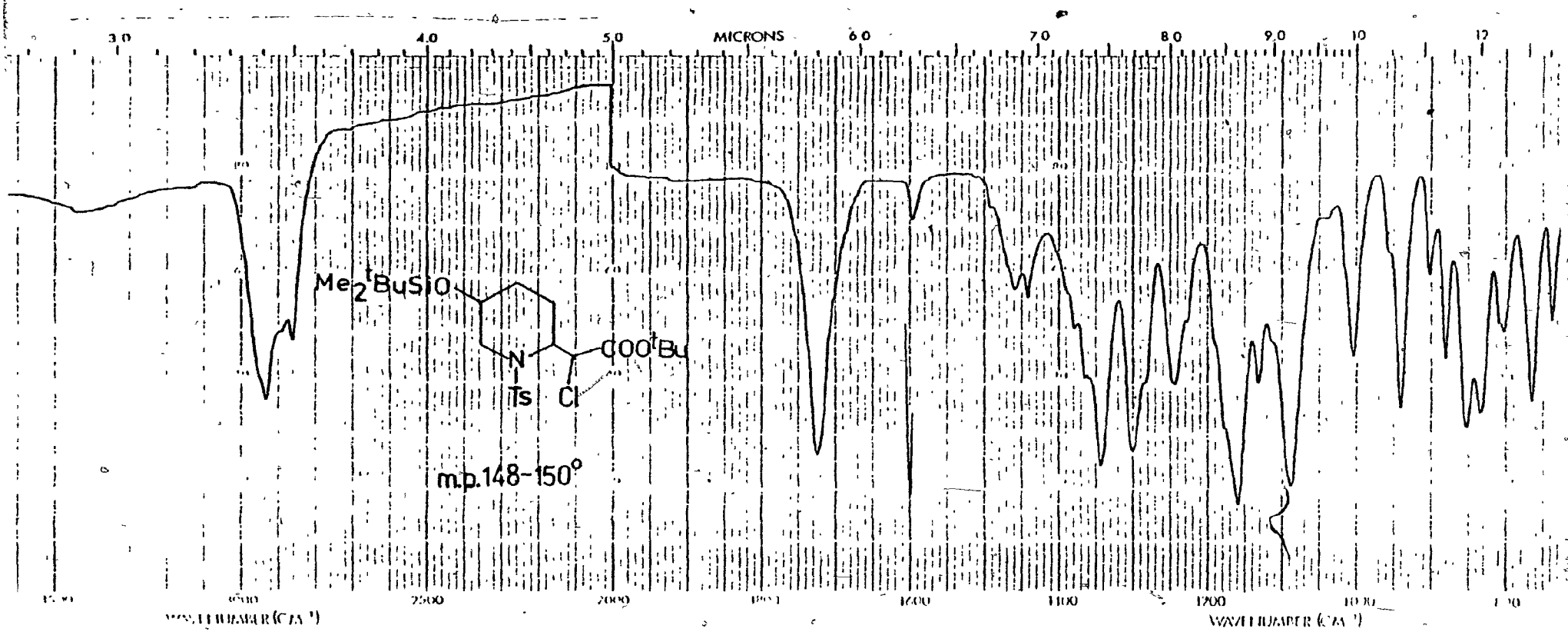

OSi^{t}BuMe$_2$
COO^{t}Bu
Ts
Cl
mp 148-150°

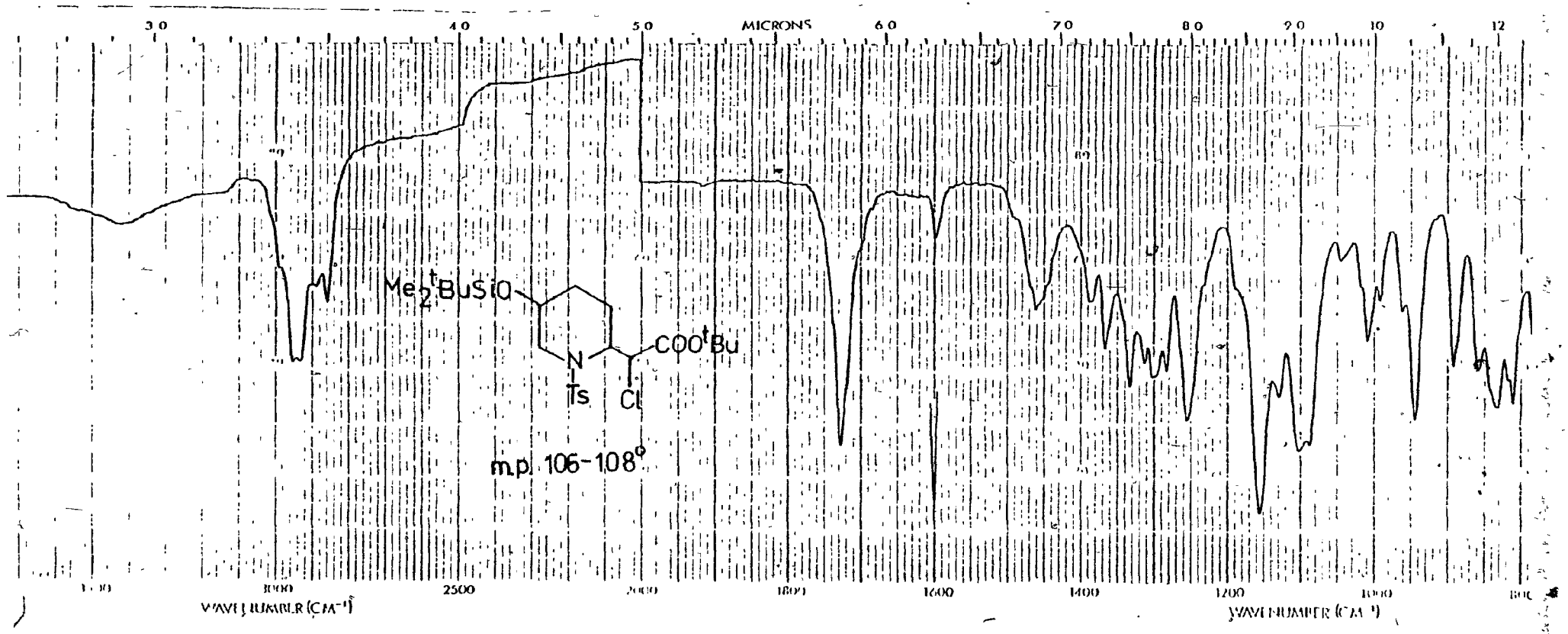

OSi^{t}BuMe$_2$
COO^{t}Bu
Ts
Cl
mp 106-108°

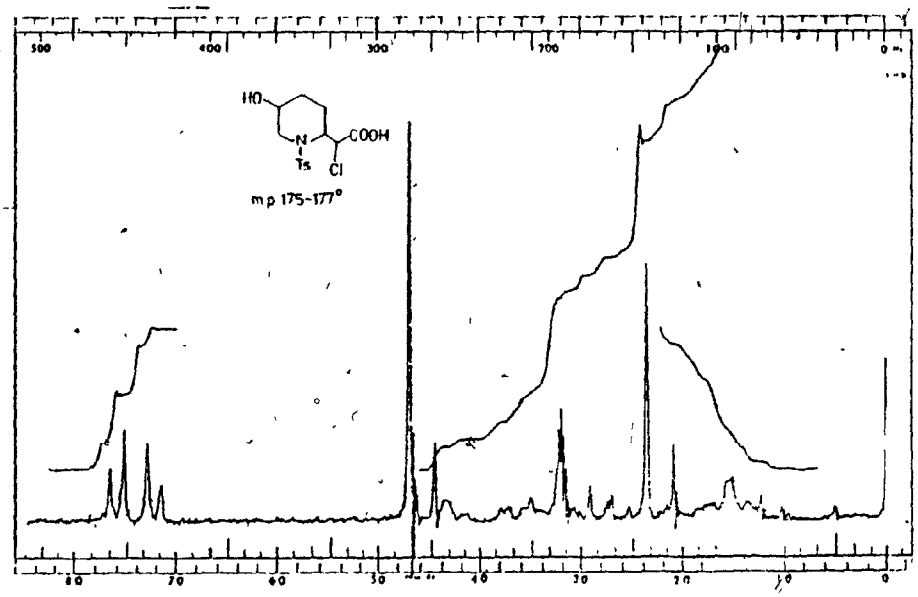

OSi^{t}BuMe$_2$
COO^{t}Bu
N
Ts
Cl
mp 148-150°
SPEC# 8691 LS 9691LM-9687LM 470X10 44DE
STEP MASS= 10, I/B/S= 1%

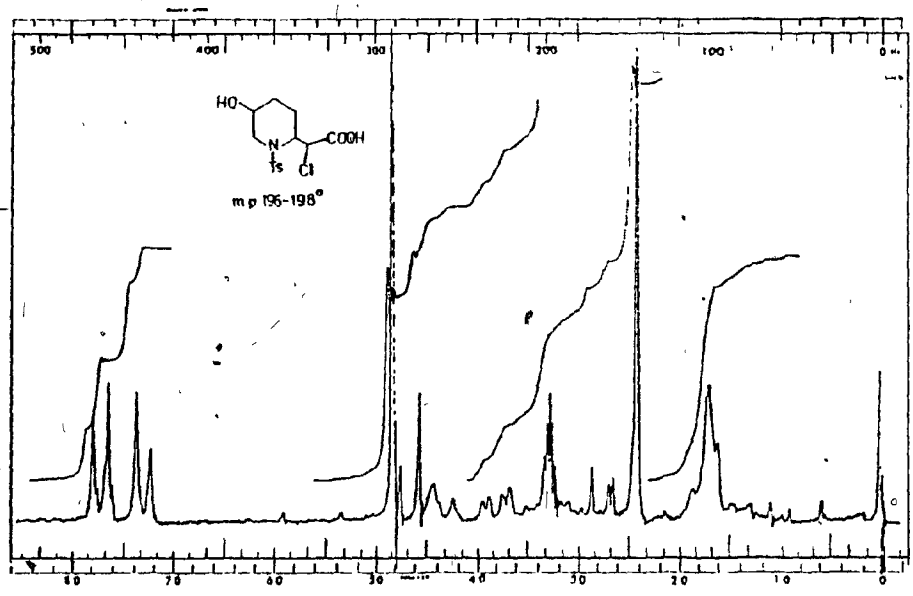

OSi^{t}BuMe$_2$
COO^{t}Bu
N
Ts
Cl
mp 106-108°
SPEC# 5395 LS MORELAND MM-V-9 44DEG 70EV
STEP MASS= 10, I/B/S= 1%

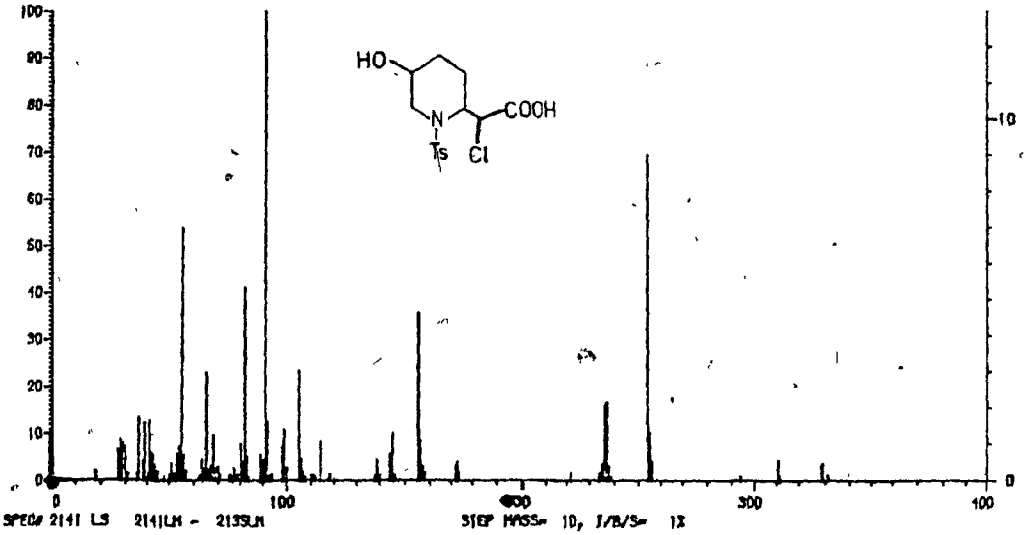

Me$_2$^{t}BuSiO
Cl
N
Ts
COO^{t}Bu
Me$_2$^{t}BuSiO
Cl
N
Ts
COO^{t}Bu
SPEC# 9682 LS 9682LM-9686LM 470X10
STEP MASS= 10, I/B/S= 1%

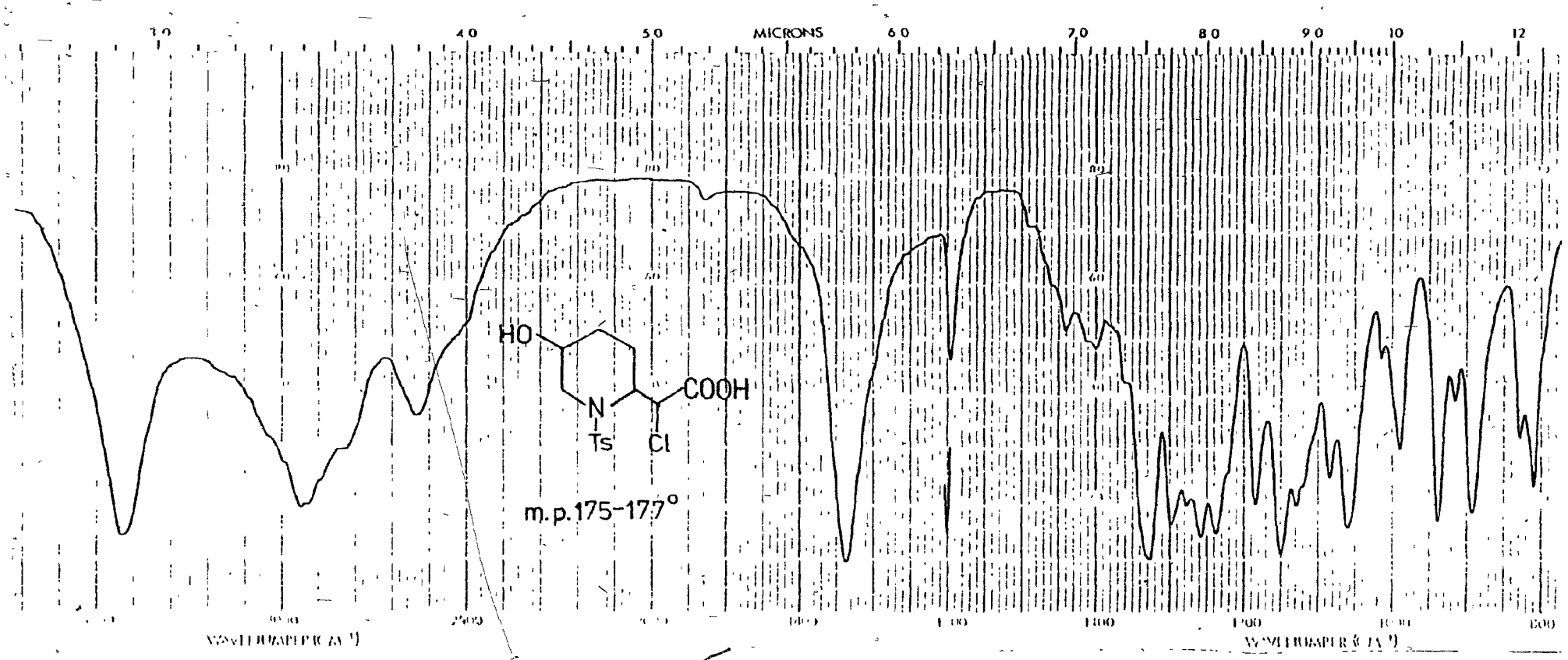

MICRONS
Me2tBuSiO
N
Ts
Cl
COOtBu
m.p.148-150°

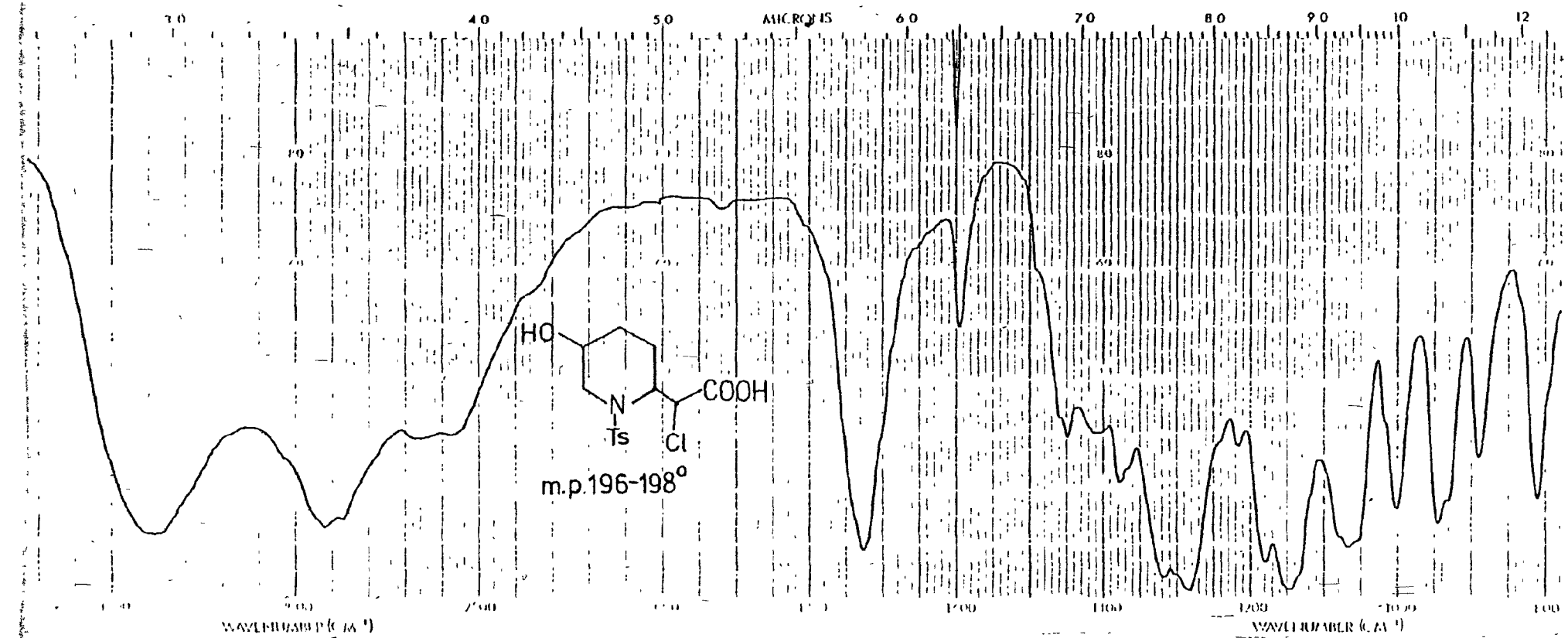

MICRONS
Me2tBuSiO
N
Ts
Cl
COOtBu
m.p. 106-108°
WAVENUMBER (CM-1)
WAVENUMBER (CM-1)

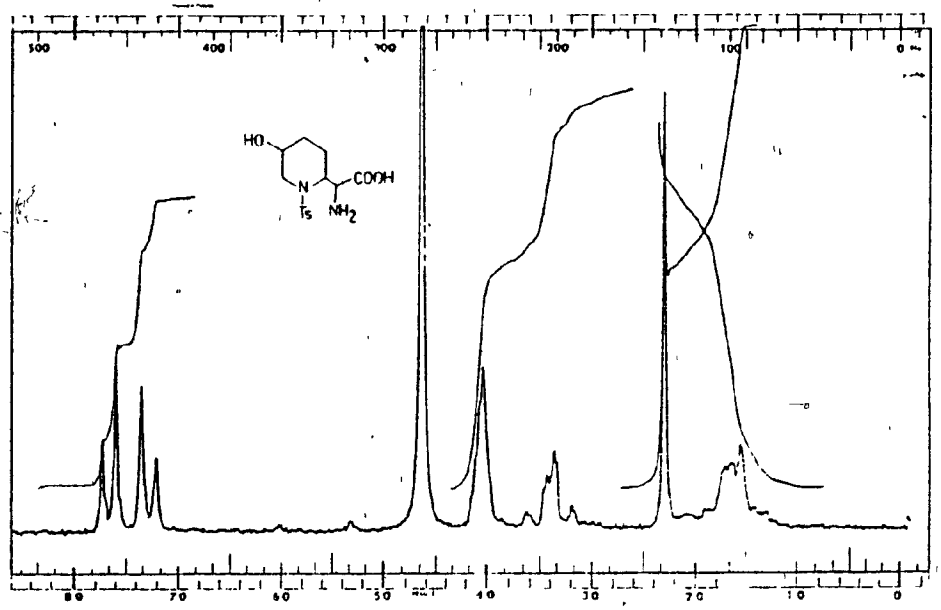

HO
COOH
N
Ts
Cl
mp 175-177°

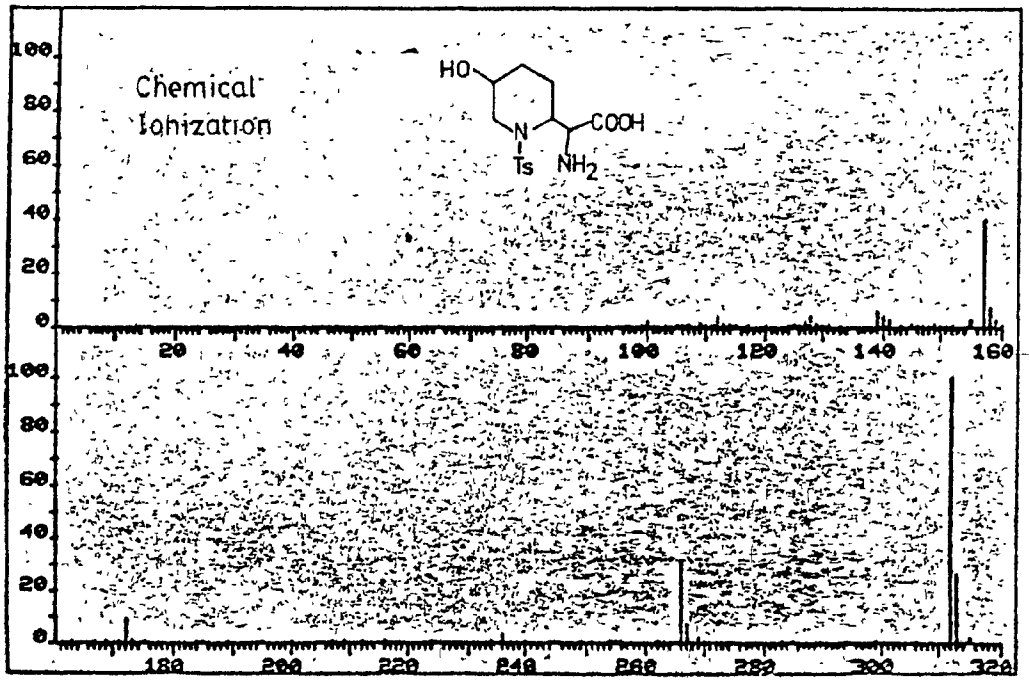

HO
COOH
N
Ts
Cl
mp 196-198°

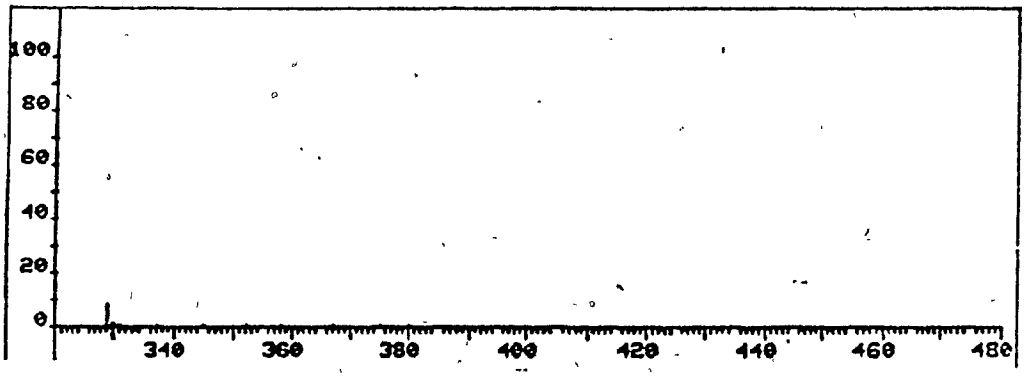

HO
COOH
N
Ts
Cl

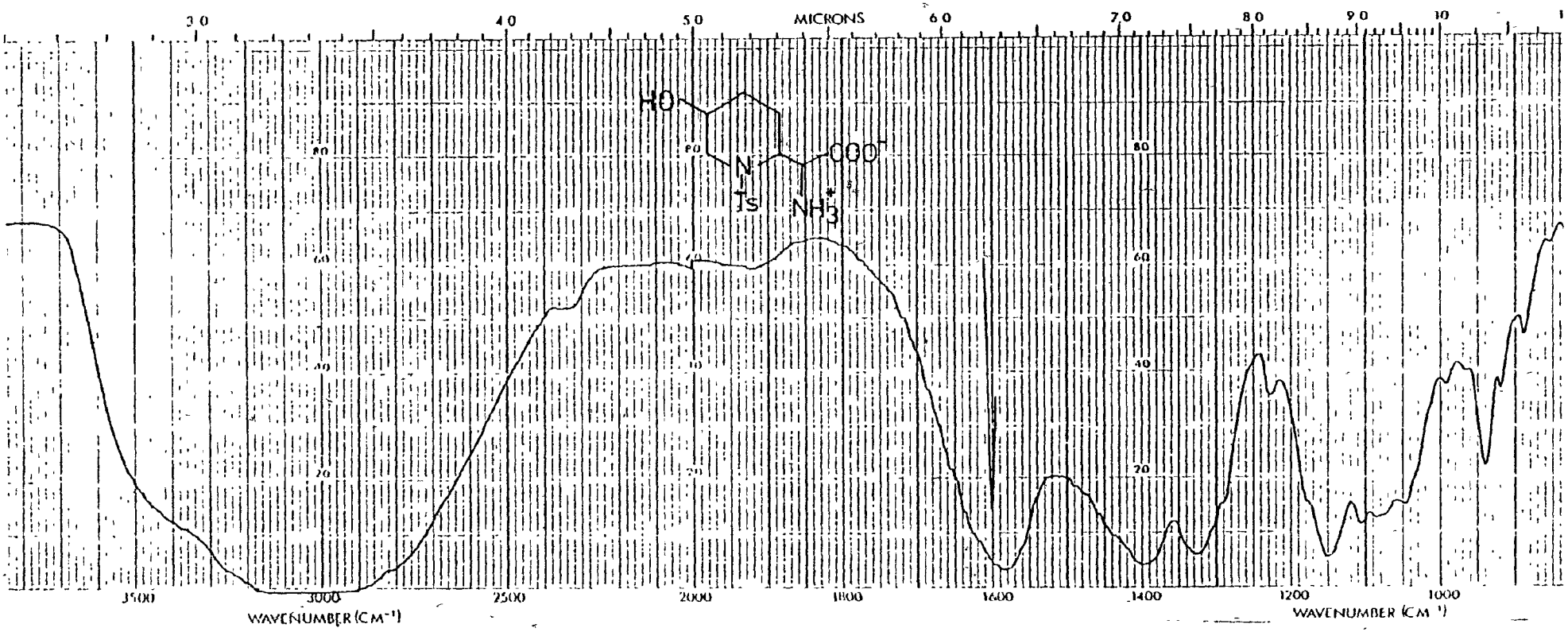

MICRONS
HO
COOH
N
Ts
Cl
m.p.175-177°

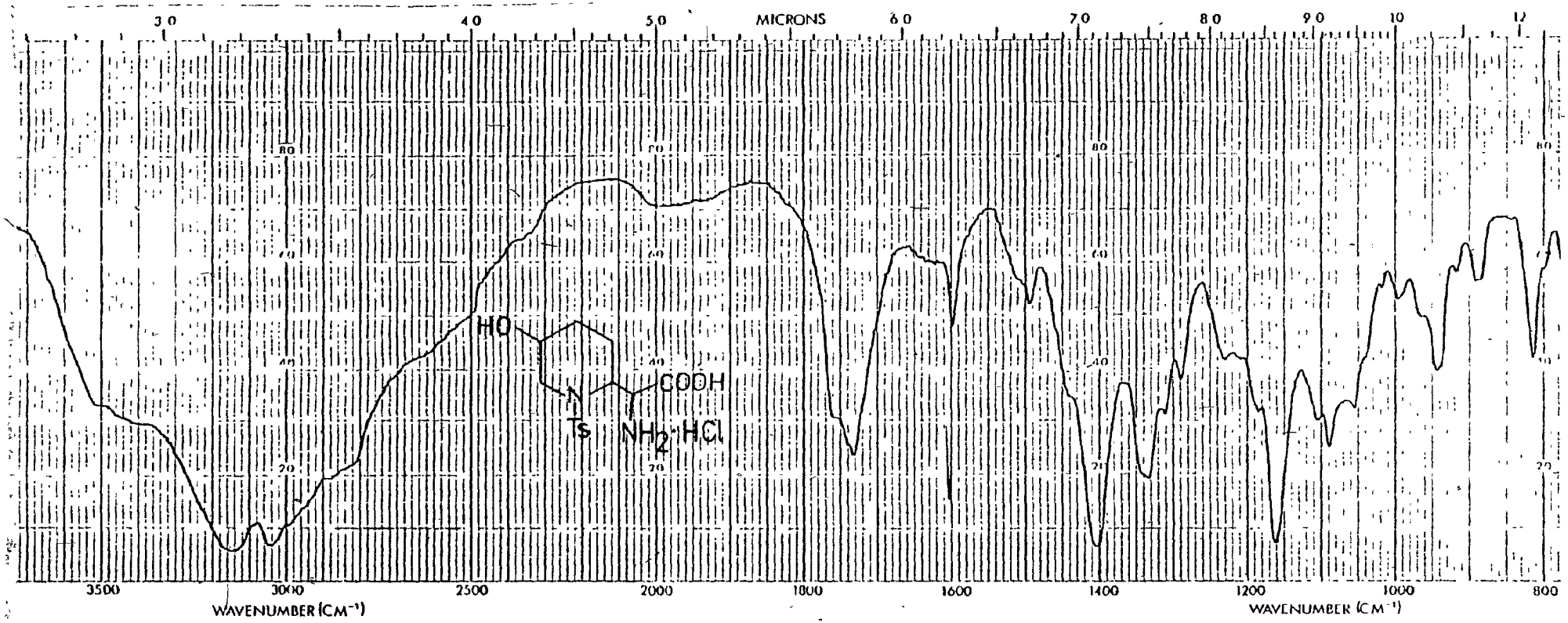

MICRONS
WAVENUMBER (CM⁻¹)
HO
N
Ts
Cl
COOH
m.p.196-198°

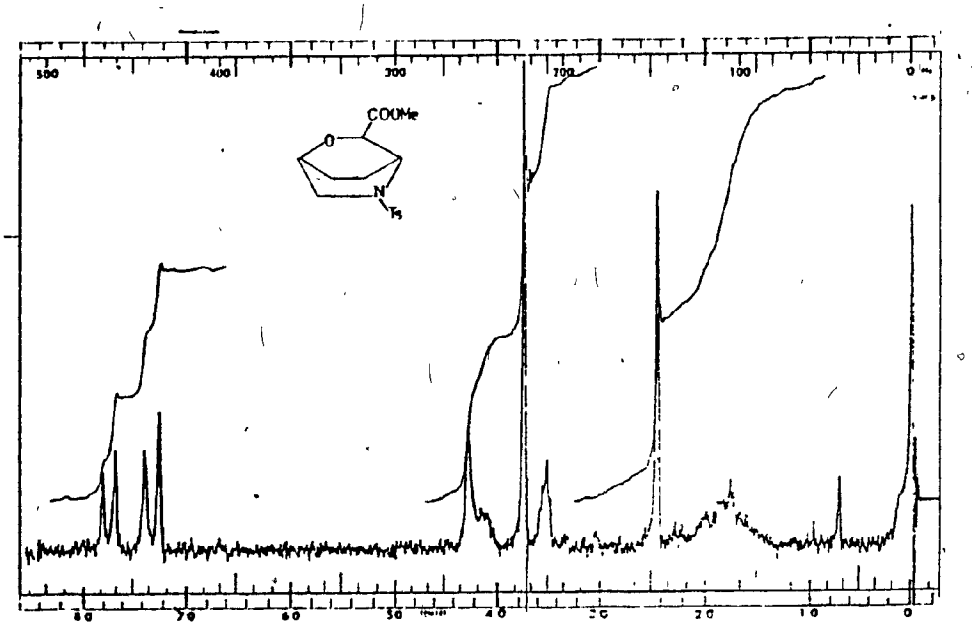

HO
COOH
N
Ts
NH2

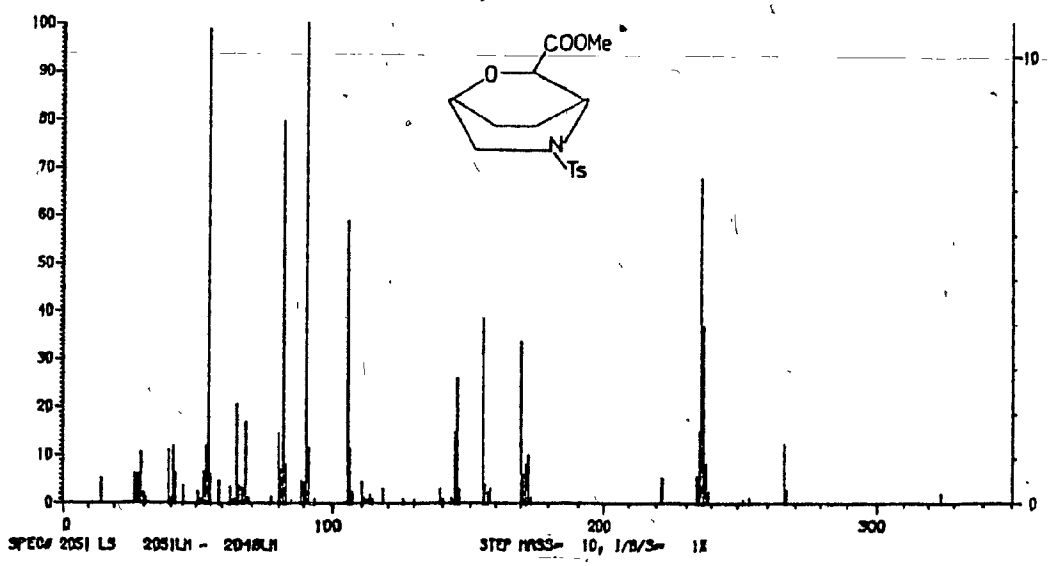

Chemical Ionization
HO
COOH
N
Ts
NH2

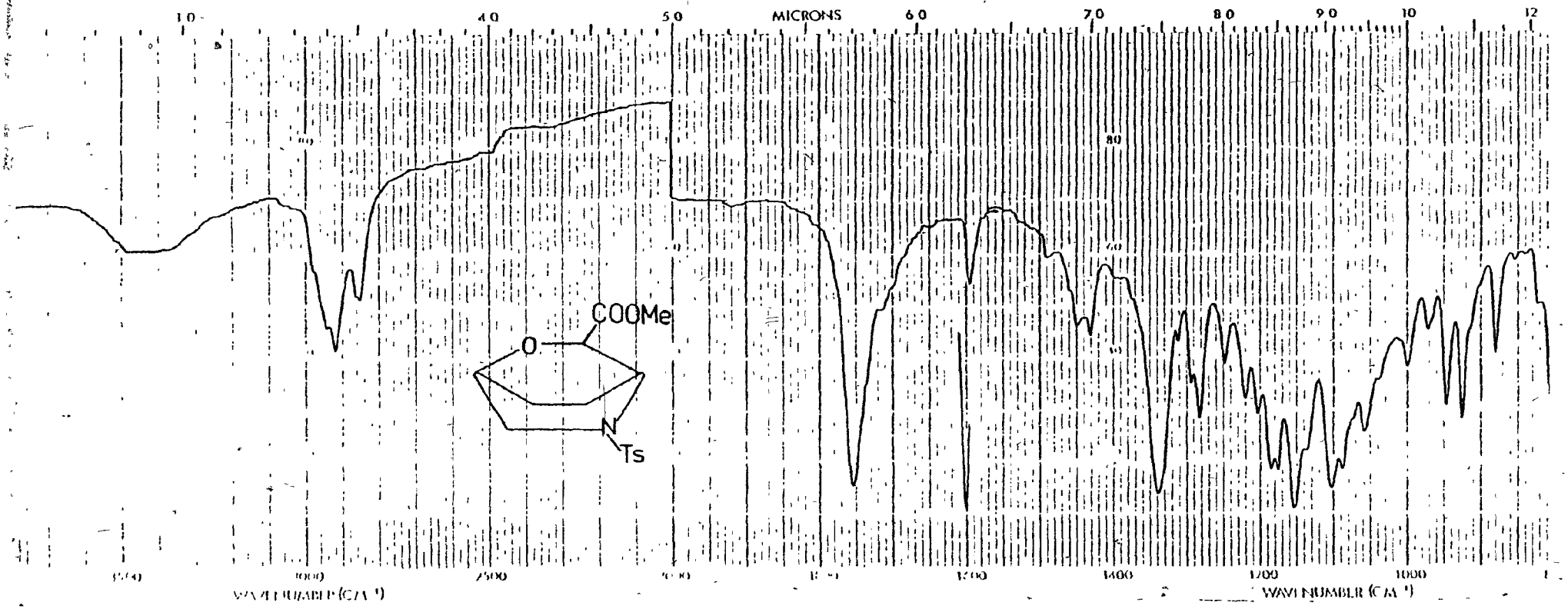


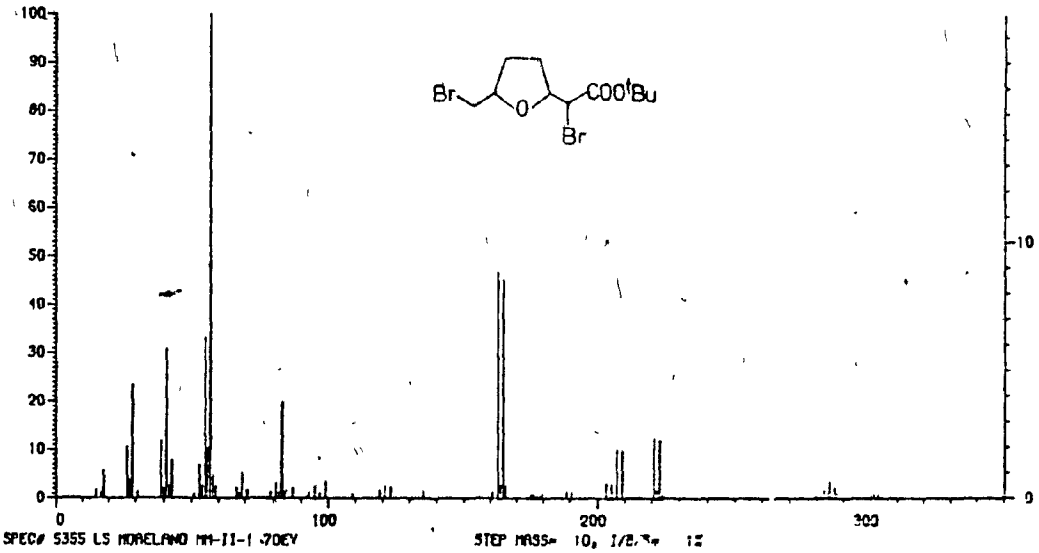

3.0
4.0
5.0
MICRONS
6.0
7.0
8.0
9.0
10
HO
N
S
COO⁻
NH3⁺
100
80
60
40
20
3500
3000
2500
2000
1800
1600
1400
1200
1000
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)

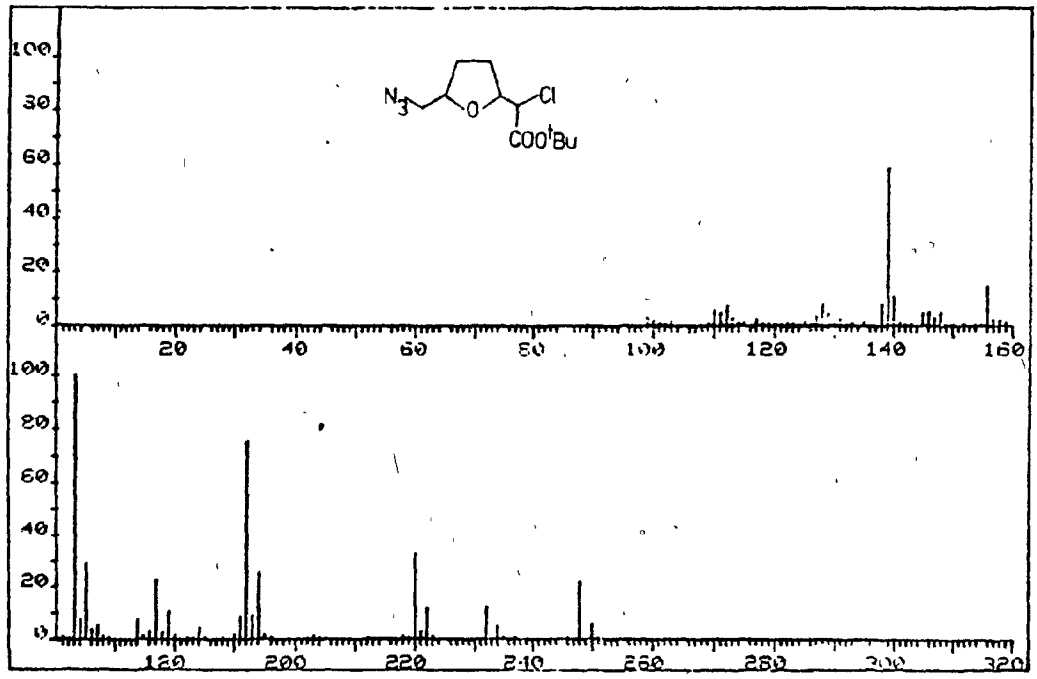

3.0
4.0
5.0
MICRONS
6.0
7.0
8.0
9.0
10
12
HO
COOH
Ts
NH2·HCl
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)

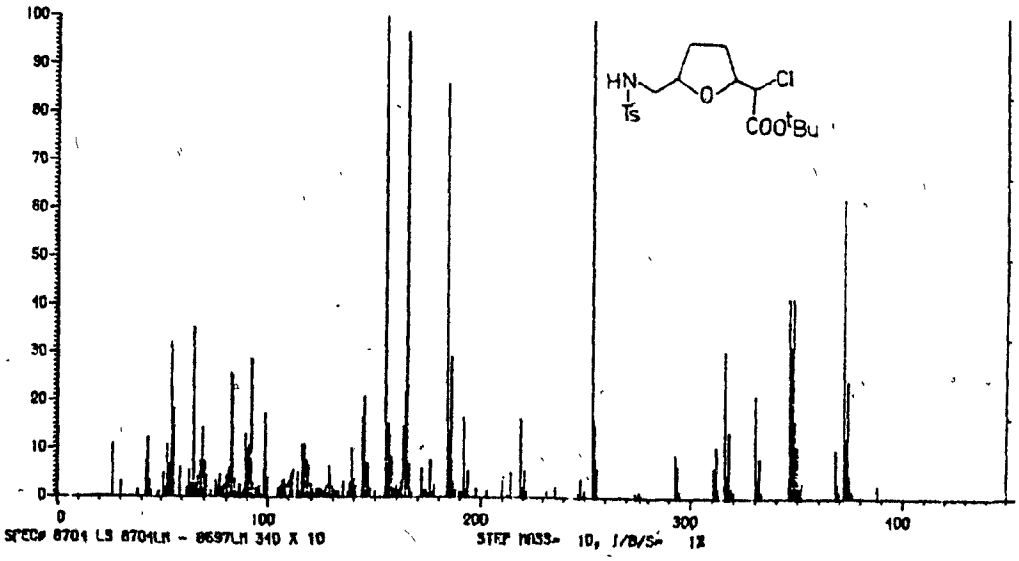

COOMe
O
N
Ts


COOMe
O
N
Ts
100
90
80
70
60
50
40
30
20
10
0
0
100
200
300
10
0


MICRONS
COOMe
O
N
Ts
WAVENUMBER (CM⁻¹)


Br
O
COO^{t}Bu
Br
SPEC# 5355 LS MORELAND MM-II-1 70EV
STEP MASS= 10, I/B/S= 1%


N$_3$
O
Cl
COO^{t}Bu


HN
Ts
O
Cl
COO^{t}Bu
SPEC# 8701 LS 8701LR - 8697LR 340 X 10
STEP MASS= 10, I/B/S= 1%

STATEMENT OF ORIGINAL CONTRIBUTIONS TO KNOWLEDGE

A new synthesis of α-chloro-α,β-unsaturated esters from carbonyl compounds and t-butyl α-chloro-α-trimethylsilyl acetate was developed. This method was shown to be applicable to a variety of carbonyl compounds.

The osmium tetroxide catalyzed reactions with Chloramine-T and N-chlorosodio t-butyl carbamate were used to selectively oxyaminate one double bond of a diene.

Several new compounds were synthesized and characterized, including (1-tosyl-5-hydroxy-2-piperidyl-glycine and (2-tosyl-8-carboxymethyl)-2-aza-7-oxabicyclo-(2,2,2)-octane.

Part of this work has been published:

"The Synthesis of Alkenes from Carbonyl Compounds and Carbanions alpha to Silicon. VII. A Synthesis of α-chloro-α,β-unsaturated Esters."

T.H. Chan and M. Moreland. Tetrahedron Letters, 515 (1978).

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