A Study on the Preparation of Carbapenems

by

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ABSTRACT

The synthesis of a carbapenem nucleus by [2 + 2] cycloaddition of a ketene and an imine was investigarted. Reaction of pyrrole-2-carboxaldehyde with a base and subsequent reaction with either dichloroketene or azidoketene did not afford a carbapenem, however, 1-dichloroacetoxy-2,2-dichloro-3-oxo-pyrrolo{1,2-a}pyrrole (67) or the analogous azido derivative (75) was obtained. Reaction of 2,2,4-trimethyl-3,5-diphenyl-2H-pyrrole (84) with the same ketenes gave the corresponding carbapenems (85) and (87). Attempts to prepare an analogous beta-lactam (91) by a similar reaction with 2,2-dimethyl-4-ethyl-3-phenyl-2H-pyrrole (90) only afforded the N-acylated 5-hydroxypyrrole (92).

RESUME

On a étudié la synthèse de carbapénems par une cycloaddition [2+2] d'un cétène et d'une imine. La réaction de l'aldéhyde α-pyrrolique avec une base suivie d'une réaction avec le dichlorocétène ou l'azidocétène ne donne pas un carbapénem mais le dichloroacétoxy-1-dichloro-2,2-oxo-3-pyrrolo {1,2-a} pyrrole (67) ou le composé azido analogue (75). La réaction du triméthyl-2,2,4-diphényl-3,5- 2H- pyrrole (84) avec les mêmes cétènes donna les carbapénems correspondants (85) et (87). Des essais pour préparer le β-lactam analogue (91) par une réaction similaire avec la diméthyl-2,2-éthyl-4-phényl-3 2H pyrrole (90) ne donnèrent que l'hydroxy-5-pyrrole N-acylé (92).

To my loving husband, Richard who has always been there for support.

To my parents who have encouraged me to go on.

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Finally, I would like to express my sincere gratitude to Mrs. D. Lavoie for having typed this thesis and Dr. Jacques Banville for the translation of the abstract.

ABBREVIATIONS

Anal. calcd.	Analysis calculated
Bu	butyl
^{13}Cnmr	Carbon 13 Nuclear magnetic resonance
^{o}C	degrees in Centigrade
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMSO	Dimethyl sulfoxide
Et	ethyl
Fig.	figure
h	hours
Hz	Hertz
IR	infrared
LDA	Lithium diisopropylamine
M	Molecular ion
ml	milliliter
mmol	millimole
MS	Mass spectroscopy
NMR	Nuclear Magetic Resonance
Ph	phenyl
sat^{d}	saturated
sol^{n}	solution
TMSCl	Trimethylsilyl chloride
Ts	tosyl

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CHAPTER III Experimental Section

Chapter 1

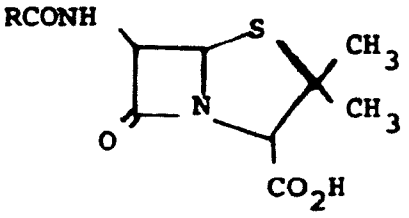
Introduction

1.1.0 History

Accounts of the history leading to the discovery of Thienamycin are taken from the following texts: 'Antibiotics of the Beta-Lactam Group' by D. Greenwood[1], 'Cephalosporins and Penicillins: Chemistry and Biology' by E.P. Abraham and P.B. Loder[2], 'Chemistry and Biology of β-Lactam Antibiotics' by R. Ratcliffe and G. Albers-Schonberg[3]. These texts are the sources of information referred for the following discussion, unless otherwise stated.

The events leading to the discovery of penicillin (1) (Fig 1) by Flemming in 1928 are legendary and probably have occurred purely by chance since Flemming himself could not reproduce the result under the same conditions. He later cultured this fungus from a mould broth filtrate. The work of Florey and co-workers at Oxford led to the concentration and partial purification of penicillin. In 1941, the first preparation of penicillin was tried on man with impressive results. However, soon thereafter in the early 1950's penicillin-resistant strains became prevalant and the search for other antibiotics was accelerated. By the late 1950's, the penicillin nucleus had been established as 6-aminopenicillanic acid (Fig. 1) and thus boosted the development of derivatives improving various properties of penicillins. In 1945, Giuseppe Brotzen, discovered a Cephalosporium fungus found in seawater near a sewage outlet which showed promising antibacterial activities in both Gram-negative and Gram-positive organisms. Mutants of this strain produced Cephalosporin C (Fig 1) which showed to be active against a broad spectrum of penicillin-resistant strains. Isolation of this new

antibiotic in quantity appeared to be an attractive prospect although the intrinsic activity is low. In 1961, the 7-aminocephalosporanic acid nucleus was first isolated and manifested a starting point for numerous semi-synthetic derivatives.



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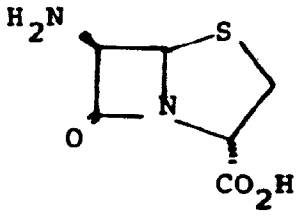

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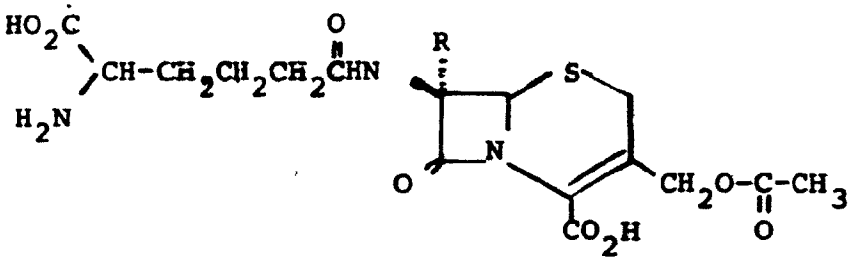

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Figure 1. Structures of penicillin 1, 6-aminopenicillanic acid 2, and Cephalosporin C 3.

In the next decade, various cephalosporins had taken their place in the therapeutic horizon. In 1976, three new naturally occurring β-lactams Norcardicin A (4), Clavulanic acid (5) and Thiemamycin (6) (Fig. 2) had

had been reported. Thienamycin was of particular interest since it demonstrated high activity over a broad spectrum of organisms and natural stability against β-lactamases. Due to the inherent instability of this highly strained β-lactam system, isolation of this antibiotic from broth for structure elucidation was a very difficult task. The details surrounding the events which led to the determination of the structure are somewhat lengthly and will not be discussed, however, x-ray analysis finally confirmed the structure.

Biologically active carbapenems containing an unsaturated carbapen-2-em carboxylic acid nucleus (6a) are depicted in Fig. 2. This numbering system has been generally accepted and will be referred to henceforth.

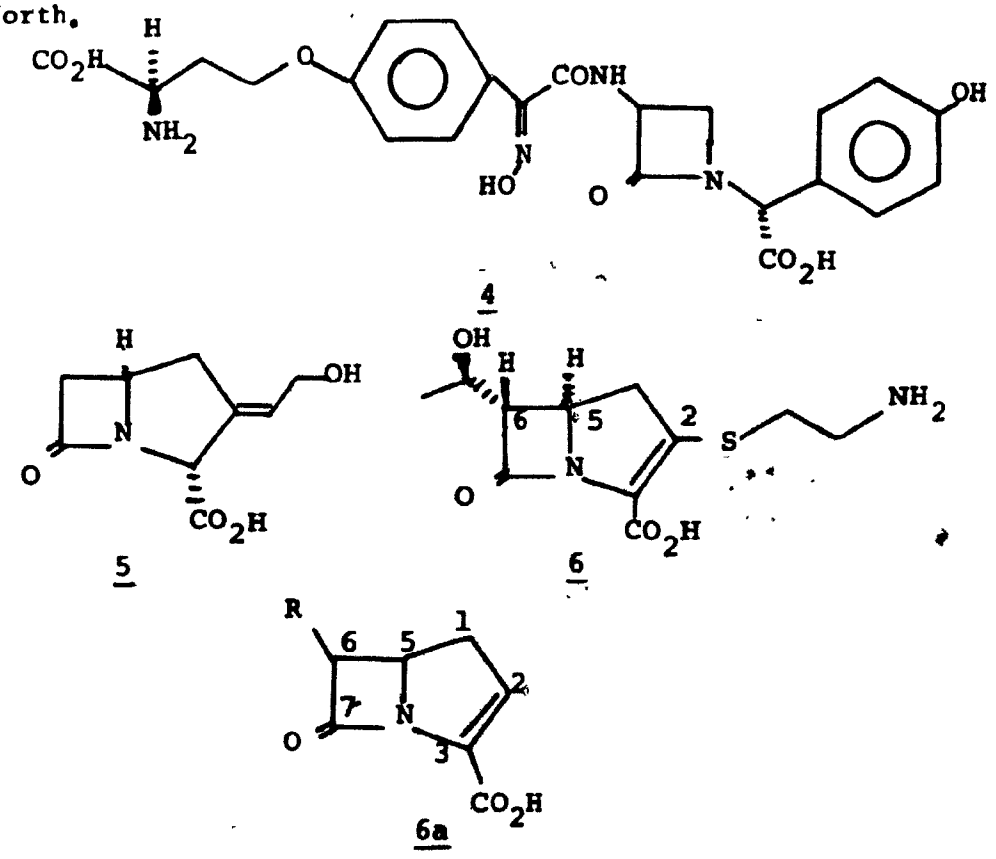

Figure 2. Structures of Norcardicin A (4), Clavulanic acid (5), Thienamycin (6), and the unsaturated carbapen-2-em carboxylic acid nucleus (6a).

Since all known carbapenem compounds have two or three chiral centers at C-5, C-6 and C-8, stereochemical considerations are important. The absolute configuration at C-5 of Thienamycin has been established as R, and is assumed that all biologically active carbapenems have this configuration since a mixture of synthetic (±) Thienamycin had shown to have half the potency of natural (+) Thienamycin. The trans-β-lactam configuration may have either 8R or 8S configuration; however, cis-β-lactam has found to have 8S configuration exclusively. To date, natural carbapenems with 5R, 6R, 8R configuration have not been reported. Finally, sulfate esters and sulfoxides of cis-β-lactam compounds have 8S configuration. In only one case, the sulfoxide chirality has been reported to be R.

Carbapenem compounds have obvious structural differences relative to the classical penicillins and cephalosporins. The pyrroline-azetidinone ring system is more strained due to the absence of the ring sulfur. The electron-withdrawing effect of the double bond also renders the amide bond more reactive. One of the major difference between natural carbapenem products and classical β-lactam antibiotics is the absence of a cis substituted 6(7)-amido group. Instead, these carbapenams all contain a 6-alkyl or substituted alkyl group either cis or trans relative to the azetidinone ring. The most common 6-substituted group being 1-hydroxyethyl or its sulfated analog having either R or S configuration at the hydroxy bearing carbon. Another structural difference is the aminoethylthio group at C-2. In contrast to classical antibiotics, carbapenems contain functional groups which can easily undergo chemical modification.

Considering the biological activities of carbapenem antibiotics, they possess high activity against both Gram-negative and Gram-positive

organisms as well as showing activity against β-lactamase strains such as the Pseudomonas species. Possibly the hydroxyl group binds to the same site normally bound by the 6β-amido group of classical β-lactam antibiotics during transpeptidization of the bacterial cell wall enzymes. Another important biological advantage of some carbapenems is β-lactamase inhibitory activity not observed in penicillins. Perhaps the 6α-substituent may mimic the 6α-methoxy group of the cephamycins (7) (Fig. 3) to provide lactamase resistance.

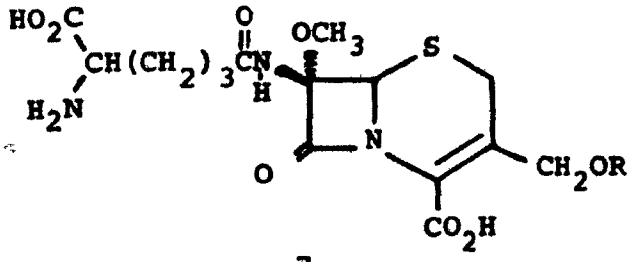

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Figure 3. The structure of cephamycins.

For all the aforementioned reasons, the thrust for finding analogues with broad-spectrum antibacterial activity and β-lactamase stability by synthetic means has been undertaken. The search for antibiotics with increased stability and having oral activity is currently a major goal in the development of derivatives.

1.2.0. Structure Activity Relationship

The antibiotic activity of a bicyclic β-lactam is based on its ability to interfere with the terminal step of bacterial cell wall biosynthesis. The labile β-lactam bond acylates the transpeptidase

enzymes which mediates the cross-linking of linear peptidoglycan strands that are responsible for the strengthening of the mucopeptide layer of the bacterial cell wall.

There are several theories which attempt to relate structural features with the effectiveness of this class of antibiotics.[4] A factor which may influence its activity is that of molecular geometry such that the antibiotics must be erroneously recognized as a normal substrate by the transpeptidase enzyme. Such an antibiotic would form an acyl-enzyme complex which can subsequently lead to a stable inactive enzyme.

Another consideration relating to geometry is the deviation of the β-lactam nitrogen from coplanarity relative to C-3, C-5 and C-7 as a base(Fig.4).

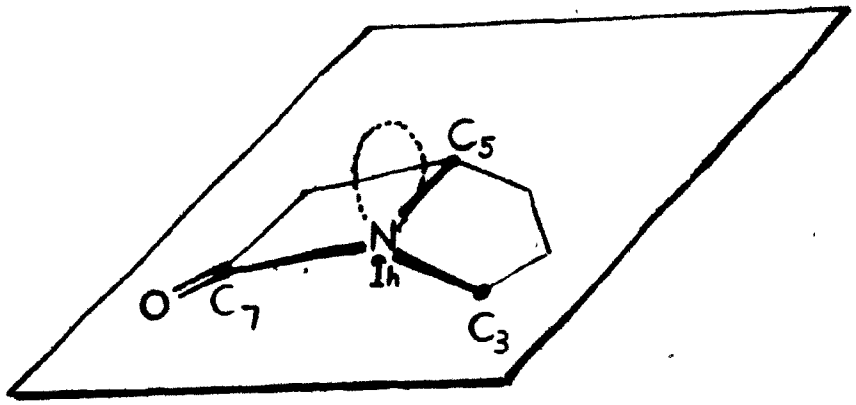


Figure 4 Depicts the deviation of nitrogen from coplanarity relative to C-3, C-5 and C-7 as a base.

It was postulated that as the altitude (h) of the pyramidal nitrogen increased, the ability to delocalize the unshared pair of electrons of nitrogen involved in π-bonding with the adjacent carbonyl carbon atom decreased. This inherently reduces normal amide resonance character.

(Fig. 5).

Figure 5. Amide resonance character.

In consequence, the amide bond can be readily cleaved and can account for rápid acylation by the enzyme.

A second consideration which was postulated for antibacterial activity is enamine resonance whereby the unshared nitrogen electrons can delocalize into the adjacent olefinic π-orbital system (Fig. 6).

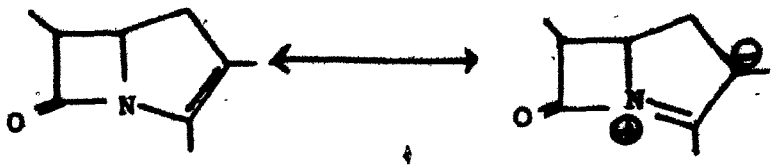


Figure 6. Enamine resonance character.

This suggests that if the unshared electron pair of nitrogen are involved in this type of resonance, then the ability for amide resonance to occur is significantly hindered.

These theories suggest that the ease of base hydrolysis of the

amide bond is the foundation for antibacterial activity. However, they do not explain anomalities observed for Δ^1-carbapenems which although have many of the aforementioned properties have found to be inactive. This leads to a third requirement which has been recently discussed by Cohen.[5] The pseudorotating movements of the penam nucleus are believed to be responsible for antibacterial activity. A molecule that is flexible in conforming with the geometrical requirements of an enzyme will posses activity, whereas, a rigid system (i.e. Δ^1-carbapenems) will be inactive. He also concluded that the requisite carboxyl group's at C-3 proximity to the β-lactam amide function enhances activity. For example, compounds having a distance of 3.0 - 3.9 A separating the carboxylic group from the amide oxygen were found to be active, whereas, the Δ^1-carbapenem had a distance greater than 4.1 A. This argument offered an explanation for inactivity of Δ^1-carbapenems.

The ability to acylate the transpeptidase enzyme is not the only sufficient prerequisite for a successful antibiotic. The substrate must also have the capability to permeate the active site as well as interact with the enzyme with the correct geometry as discussed earlier. There is no one definitive answer to biological action, however, contribution from all the aforementioned parameters provides a reasonable basis for predicting antibacterial activity.

1.3.0. Total Synthesis

A relatively recent field of carbapenam (or carbapenem) synthesis has emerged from the discovery of a naturally occurring, broad spectrum antibiotic, Thienamycin[6] [7] (Fig. 7).

Since its discovery, numerous methodologies leading to the 1-carbapen-2-em ring system (8) (Fig. 8) have been reported[8] and some of

which merit special attention.

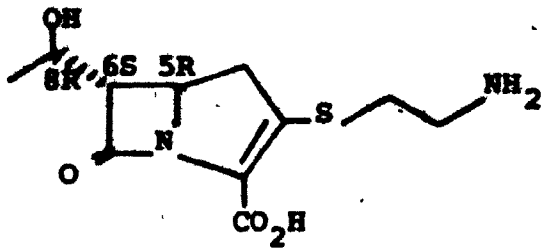
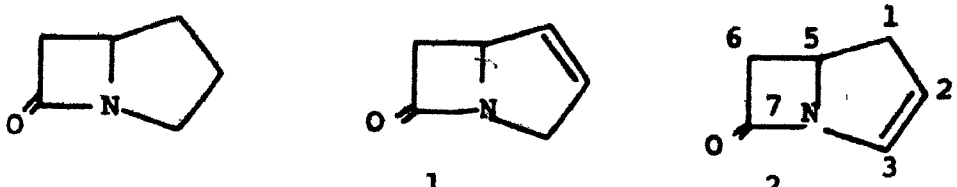


Figure 7. The structure of Thienamycin having 5R, 6S, 8R geometry.



carbapenam skeleton

Δ^1- carbapenem

Δ^2- carbapenem or 1-carbapen-2-em

8

Figure 8. The carbapenam (em) skeleton and numbering system.

Total sythesis of β-lactam anitbiotic and modified analogues have been widely researched by various chemists in the past decade. The works of Bose, Woodward and Sheehan, to name a few, have dramatically set the impetus for research in synthetic strategies to produce diverse analogs which are non-attainable by natural product modification.

The two principal difficulties involved in carbapenem synthesis are: 1) the construction of the bicyclic nucleus and 2) introduction of side chains at the 2- and 6-positions. Generally, the carbapenem is constructed by C-2 - C-3 or C-3 - N-4 bond formation fusing the pyrroline moiety to the azetidinone ring (Fig. 9). The required side chains at C-6 and sometimes at C-2 are attached to the precusor prior to cyclization. This avoids undue manipulation of the highly strained, labile bicyclic system. Some examples of this strategy will be discussed.

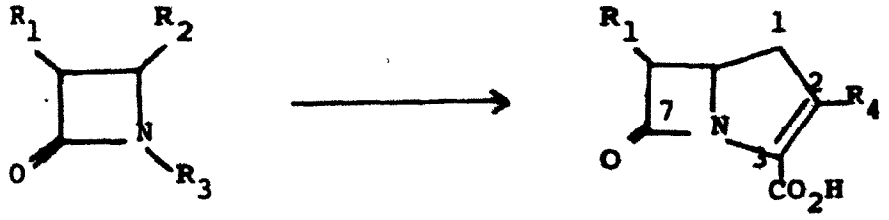


Figure 9. Construction of carbapenems by C-2 - C-3 or C-3 - N-4 formation.

1.3.1. Intramolecular Carbene Insertion

An approach developed by Merck chemists involves a carbene insertion reaction forming the C-3 - N-4 bond.[9] Recently Reider and Grabowski[10] have reported the preparation of carbapenems starting from aspartic acid employing this methodology (Fig. 10). The azetidinone 12 was prepared from L-aspartic acid (11) as described by Salzmann et al.[11] via a Grignard-mediated cyclization of a N-silylated aspartate ester. In this case, the benzyl ester was used. The nitrogen compound 12 was protected

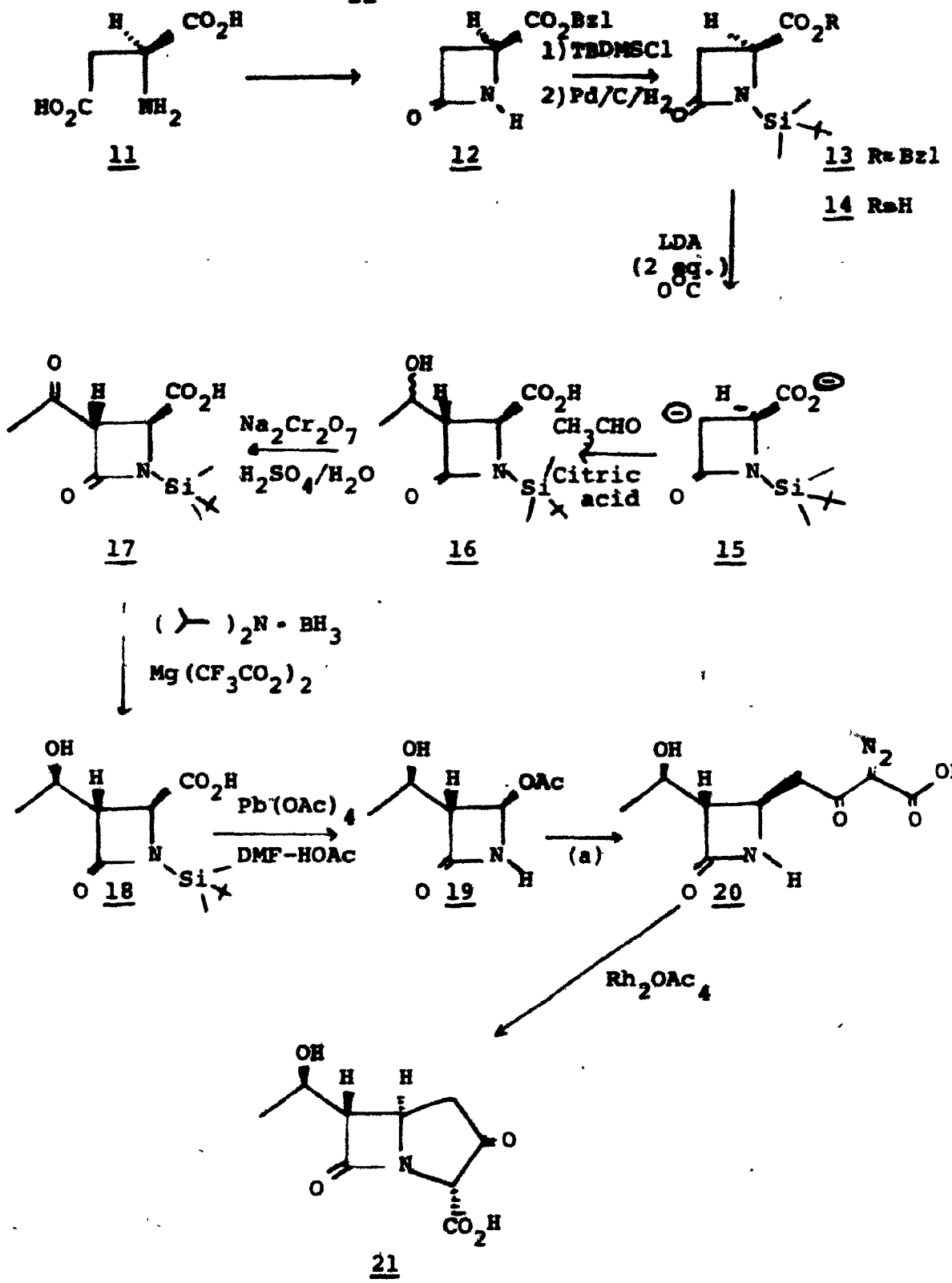
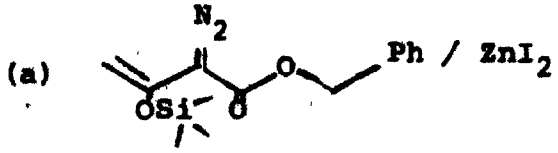


Figure 10. Preparation of a carbapenam by a carbene insertion reaction forming the C-3 - N-4 bond.



by silylation with tert-butyldimethylsilylchloride (98%) in the presence of triethylamine to give compound 13 which underwent debenzylation by hydrogenolysis to afford 14 (92%). The dianion 15 was generated with lithium diisopropylamide and subsequently was alkylated with acetaldehyde which upon acidic work-up afforded an epimeric mixture of hydroxy acids 16. Oxidation with sodium dichromate gave the keto-acid 17 which underwent stereospecific reduction with diisopropylamine borane in the presence of magnesium trifluoroacetate to give the desired 5S, 6S, 8R - hydroxy acid 18. Conversion of the carboxyl group to a suitable leaving group was affected by oxidative decarboxylation with lead tetraacetate to give 19 (82%). Reaction of the acetate 19 with silyl enol ether of benzyldiazoacetoacetate provided the 5R, 6S, 8R-diazohydroxyketoester 20. Ring closure via carbenoid insertion in the presence of rhodium II acetate afforded the bicyclic keto ester 21.

This reaction is strategically favourable in that the functional groups are introduced with the correct stereochemistry prior to cyclization.

1.3.2. Wittig Reaction

Another approach that is worthy of special mention is that of the intramolecular Wittig route based on the work of Woodward and co-workers[12 13] on penems and developed for carbapenems by Johnston and co-workers[14]. This method involves a C-2 - C-3 ring closure by heating azetidinonyl-phosphoranes.

The azetidinone 24 (Fig. II) was prepared by a $_{2}\pi_{s} + _{2}\pi_{a}$ cycloaddition of chlorosulfonyl isocynate (23) and 1- acetoxybutadiene (22). This compound upon reductive hydrolysis afforded the acetoxyvinylazetidinone 25. Catalytic hydrogenation followed by deacetylation in the presence of sodium methoxide in methanol gave the alcohol 26 which was converted to

the acetonide 27 by reaction with 2,2-dimethoxypropane and boron trifluoride etherate complex. The anion was generated with lithium diisopropylamide followed by addition of acetaldehyde to give an epimeric mixture of the trans-hydroxyethyl derivatives 28 and 29 in a ratio of 2:3. The mixture was converted to the O-para-nitrobenzyl ester 30 at which point the isomers were separable by crystallization. The acetonide was subsequently removed by hydrolysis to afford the alcohol 31. Various routes leading to the preparation of carbapenems by the Wittig reaction originate from this alcohol. An example using this intermediate is described by Kametani[8]. The alcohol 31 was condensed with glyoxalate followed by tert-butyldimethylsilyl group to give 32. Conversion into an ylide, deblocking and oxidation of the alcohol 33 gave the carbapenem 34. Photolytic removal of the ester afforded (±) - descysteaminylthienamycin 35. This route proved to be advantageous in that the bicyclic nucleus was formed under mild conditions having the concomitant double bond at the desired position. Another advantage of this strategy is the accessibility to C-2 substitution.

The Wittig reaction and the carbene insertion route are the two most prominent synthetic methods towards the preparation of carbapenems. These approaches are currently the most widely used processes in industry since the starting material is reasonably inexpensive and readily available.

So far, the preparation of carbapenems starting from azetidinones has been discussed. However, another strategy which should be noted is the cyclization to the β-lactam bicyclic system starting form the larger ring synthon. To date, only a few methodologies have been reported in the literature and will be dicussed in the following.

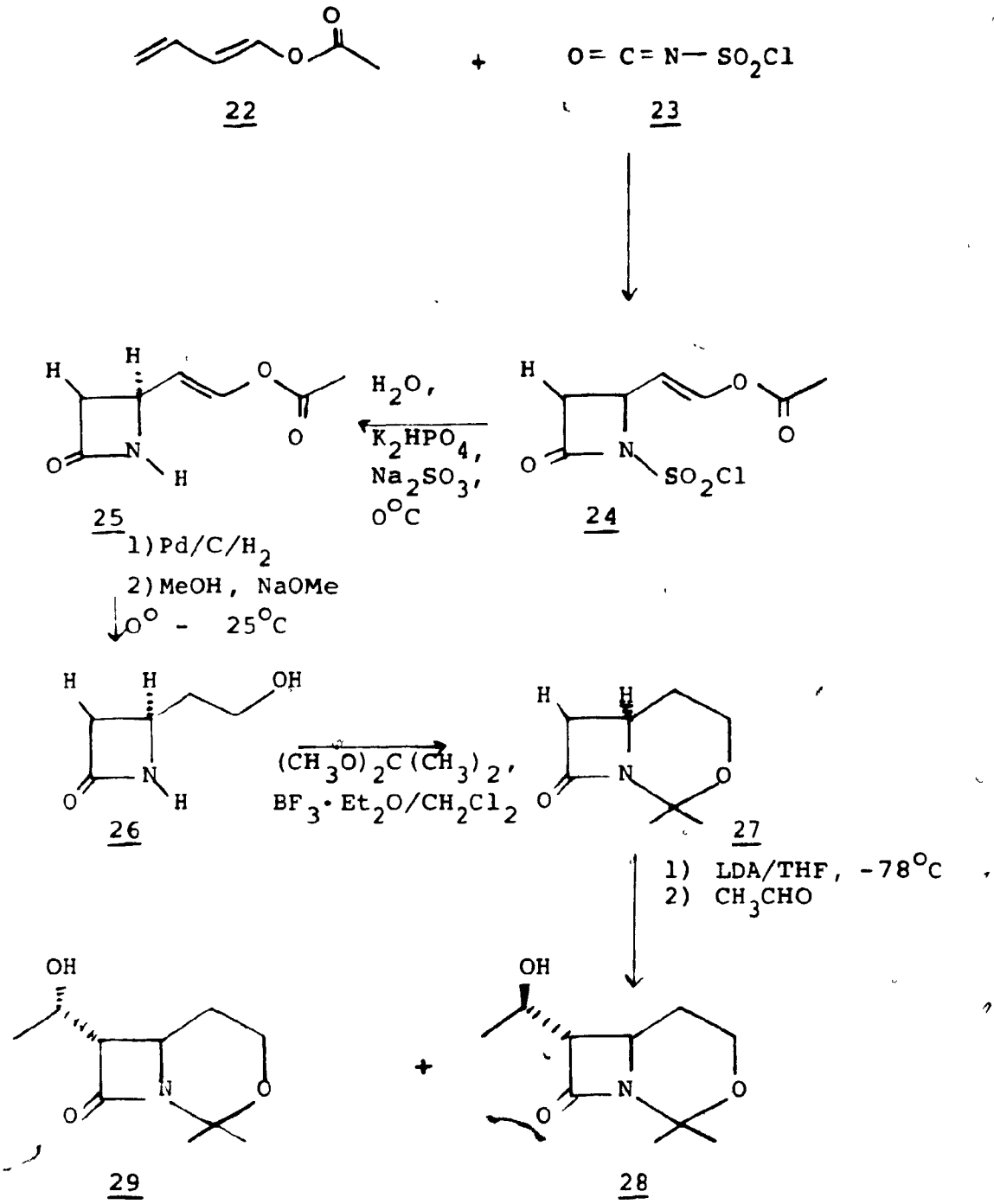
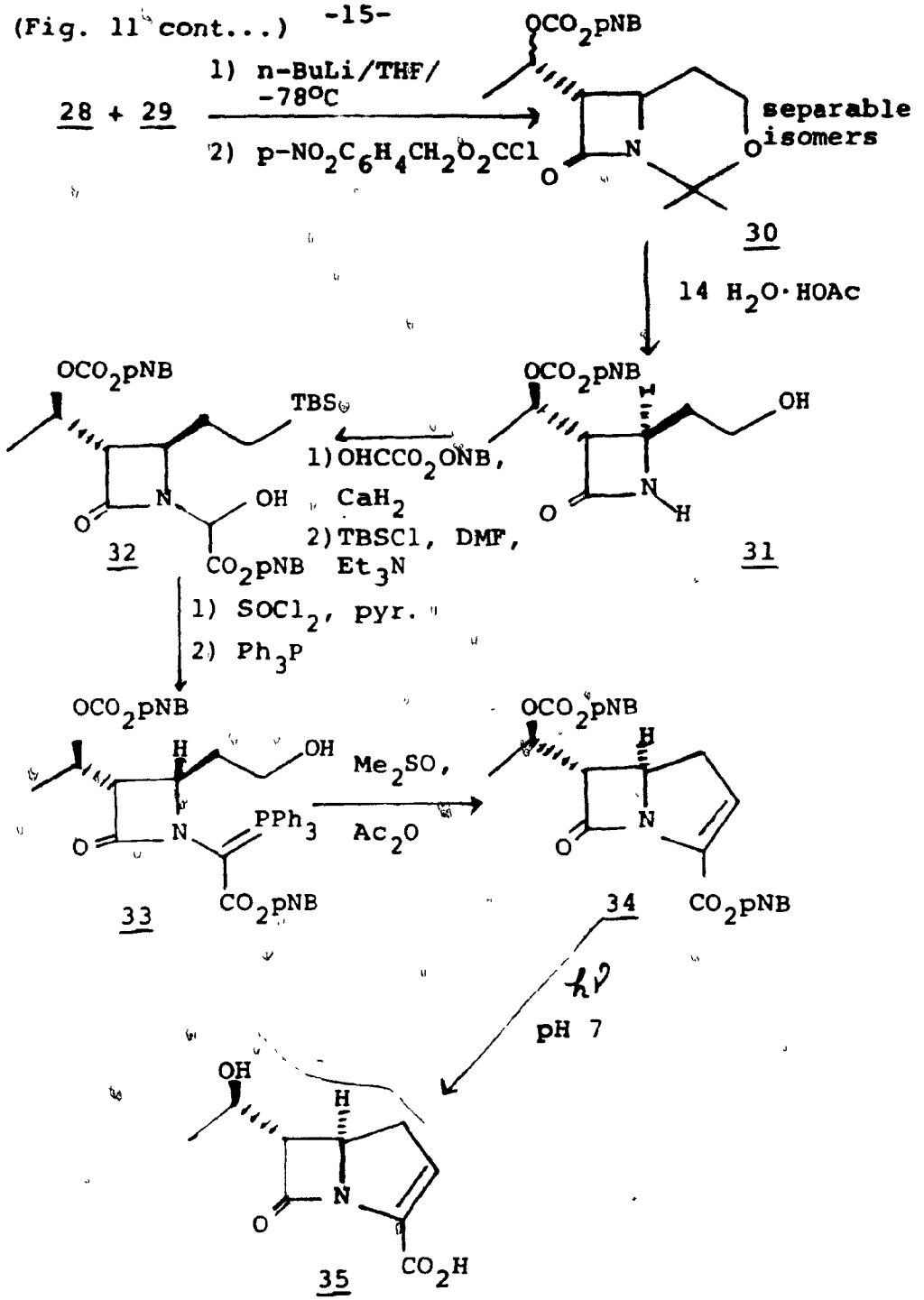


Figure 11. The Wittig route to the preparation of carbapenems.

(Fig. 11 cont...)


28 + 29
1) n-BuLi/THF/ -78°C
2) p-NO2C6H4CH2O2CCl
OCO2pNB
separable isomers
30
14 H2O·HOAc
OCO2pNB
OH
31
1) OHCCO2ONB, CaH2
2) TBSCl, DMF, Et3N
OCO2pNB
TBS
OH
CO2pNB
32
1) SOCl2, pyr.
2) Ph3P
OCO2pNB
OH
PPh3
CO2pNB
33
Me2SO, Ac2O
OCO2pNB
34
CO2pNB
hν
pH 7
OH
CO2H
35

1.3.3. Photolysis

Lowe and co-workers[15] have prepared nuclear analogues of penicillin-cephalosporin antibiotics by photolysis of the α-diazo amides 36 (Fig. 12).

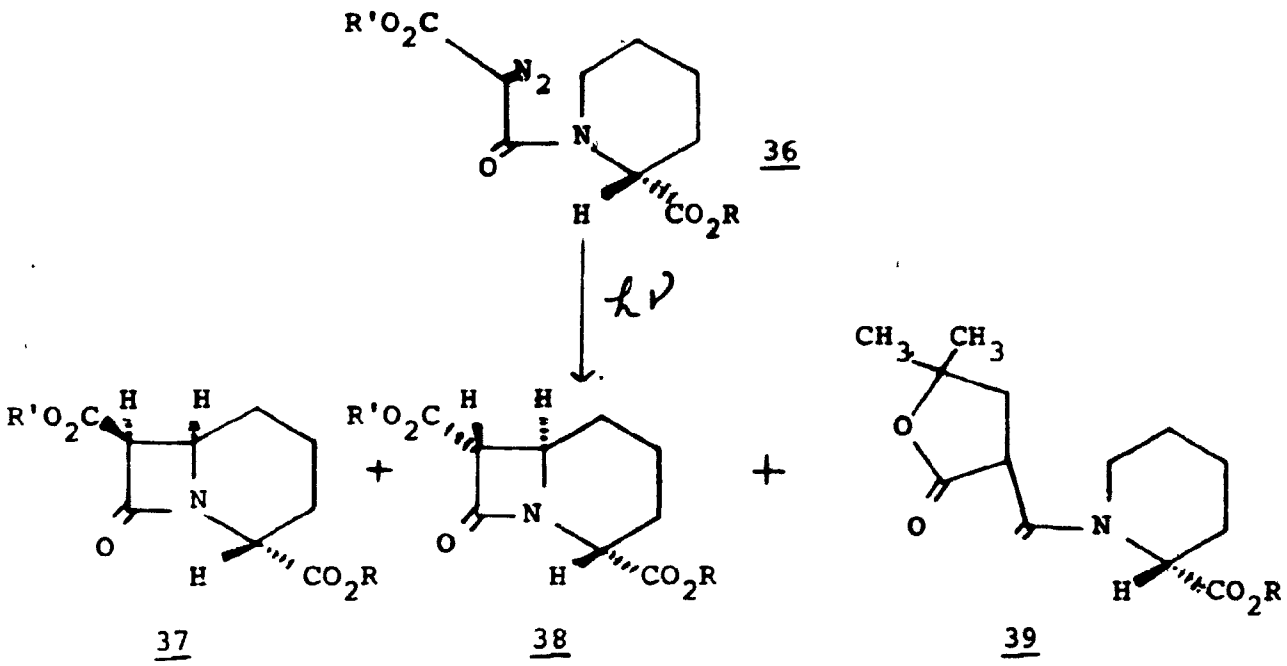


Figure 12 Photolysis of the diazo compound 36 in CCl_4. (R= Bzl, R'= ^tBu)

Introduction of a chiral substituent at C-2 directed the transient carbene intermediate stereoselectively to favor the desirable trans-2,6- steric relationship 37 and 38 in the fused β-lactam bicyclic system in a ratio of 1 : 2. One of the by-products of this reaction was a γ-lactone 39.

In a publication that followed two years later, Lowe[16] reported the synthesis of the highly unstable 7-oxo-1-azabicyclo{3.2.0.} heptane system 43 by photolytic Wolff rearrangement (Fig. 13).

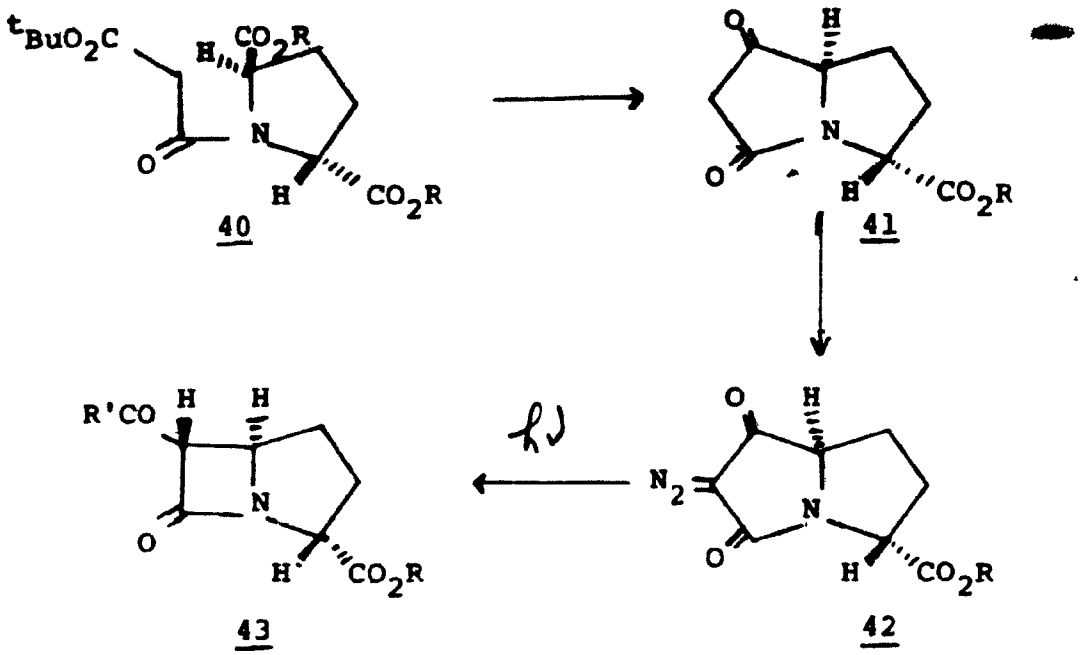


Figure 13 Photolytic Wolff rearrangement generating a highly strained 7-oxo-1-azabicyclo (3.2.0.) heptane system. (R = Et, R' = $PhCMe_2O_2CNHNH$)

The pyrrolizidinedione 41 was obtained by reaction of the diazo pyrrolidine derivative 40 with sodium hydride and heating. Diazo exchange of this compound afforded the diazodioxohexahydropyrrolizine carboxylate 42 which subsequently underwent photolytic Wolff rearrangement upon irradiation to afford the bicyclic compound 43. Due to the unstable nature of this compound, the product could not be isolated and consequently synthetic manipulation to obtain penicillin analogues could not be accomplished.

1.3.4. Cycloaddition

A number of key synthetic strategies have been already mentioned towards total synthesis of bicyclic β-lactam systems. It is appropriate

at this time to discuss cycloaddition reaction since the first β-lactam was prepared by a ketene-imine interaction.[17]

The reaction of ketenes with carbon-carbon double bonds is well documented.[18] This reaction has been described in terms of frontier molecular orbital interactions using the reaction of an olefin with a ketene as an example (Fig. 14).[19]

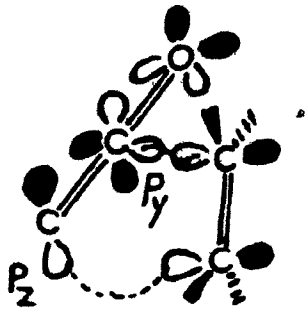


Figure 14 Overlap in a cycloaddition of an olefin to a ketene.

In this case, a concerted mechanism has been proposed on the basis of π-bond overlap of the olefin with the p_z orbital at the terminal carbon atom of the ketene, while the other end of th π-bond of the olefin overlaps with the p_y orbital of the central carbon atom of the ketene. The pathway is therefore a $({}_2\pi_s + {}_2\pi_a)$ process and regioselectivity is determined by the overlap of the large lobe of the HOMO of the olefin with the large lobe of the LUMO of the ketene which is located at the central carbon atom.

Generally, ketenes are generated <u>in situ</u> by treatment of an appropriate acetylchloride with a tertiary base. Ketenes react with imines also to give a (2 + 2) cycloadditon products depending on the structure

of the imine.[20] For example, Staudinger[17] reported the formation of a β-lactam by reaction of diphenyl ketene with cinnamylidene anil. In contrast, Pfleger[21] claimed to obtain dihydropyridones (Fig. 15).

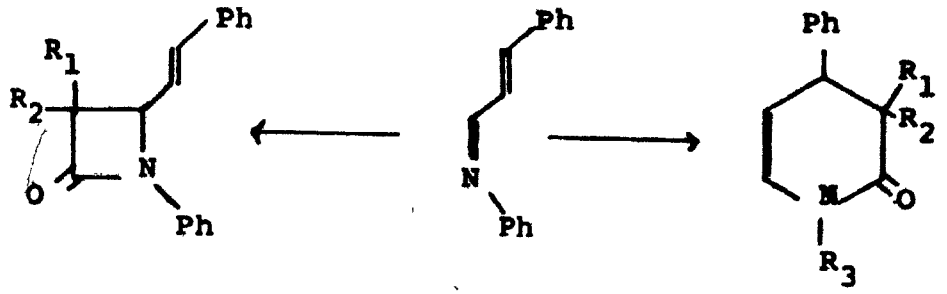


Figure 15 Reaction of diphenyl ketene with cinnamylidene anil.

The mechanism for the imine-ketene cycloaddition has been generally accepted to occur via a zwitterionic intermediate[22] which is stabilized by ring closure (Fig. 16).

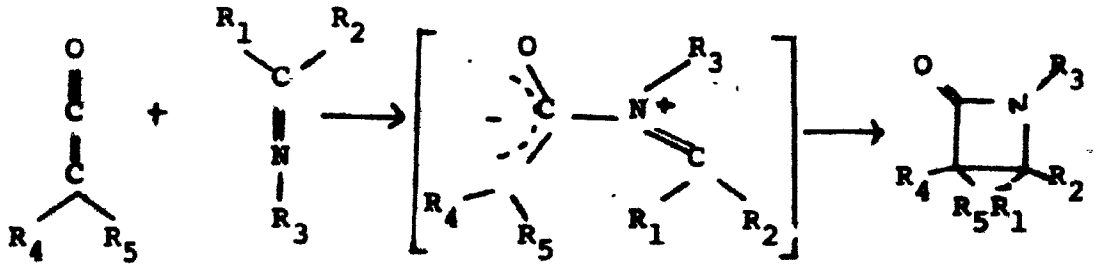


Figure 16 The mechanism for the imine-ketene cycloaddition.

Evidence of such a mechanism has been offered by Pacansky[22]. The thermal reaction of ketenes with imidazoles was followed by infrared spectroscopy. The formation and disappearance of a zwitterionic species was

observed to give a β-lactam.

This mechanism has also been postulated by Bose and co-workers[23a,b]. An α-atom with an unshared pair of electrons is capable of stabilizing transition states through a donor-acceptor complex as shown below[24](Fig. 17).

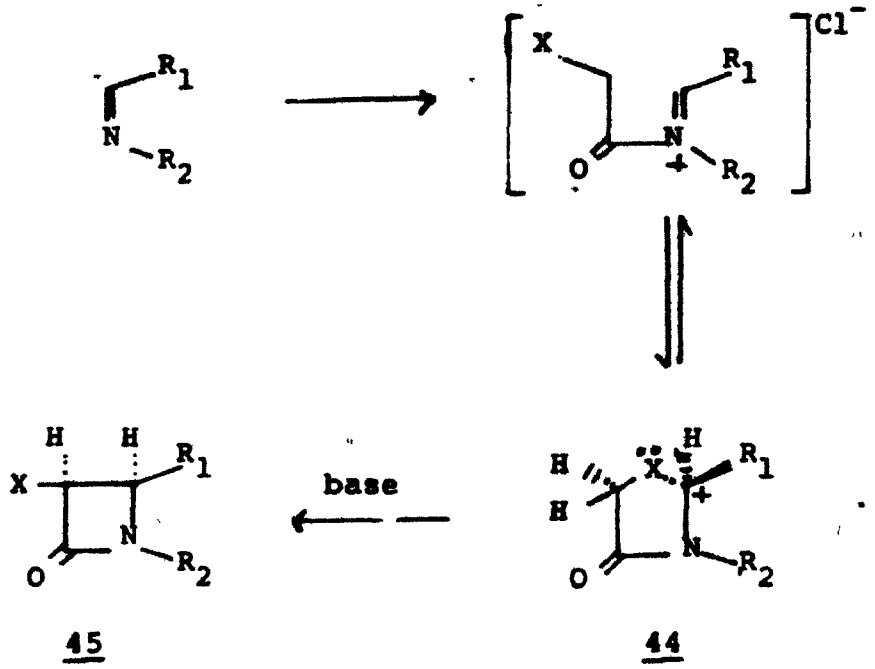


Figure 17 Stabilization of transition states via donor-acceptor complex.

Subsequent elimination of a proton would lead to compound 45 by cyclization of the two closest carbon atoms, C_3 and C_4 in this case. A consequence of this mechanism is that it should give rise to a β-lactam of cis stereochemistry. The work of Doyle and co-workers[24] have shown that systems which can potentially extend conjugation to enhance the transition state 44 promotes stereoselectivity of the reaction to afford a cis addition product. Doyle accounts for this high selectivity on the basis of the orientation of the C_3 - H bond axis of the deprotonated specie.

Either through inversion or rotation, alignment of the anionic orbital with the cationic p-orbital of the C_4-atom leads to the preferred stereoselectivity(Fig, 18).

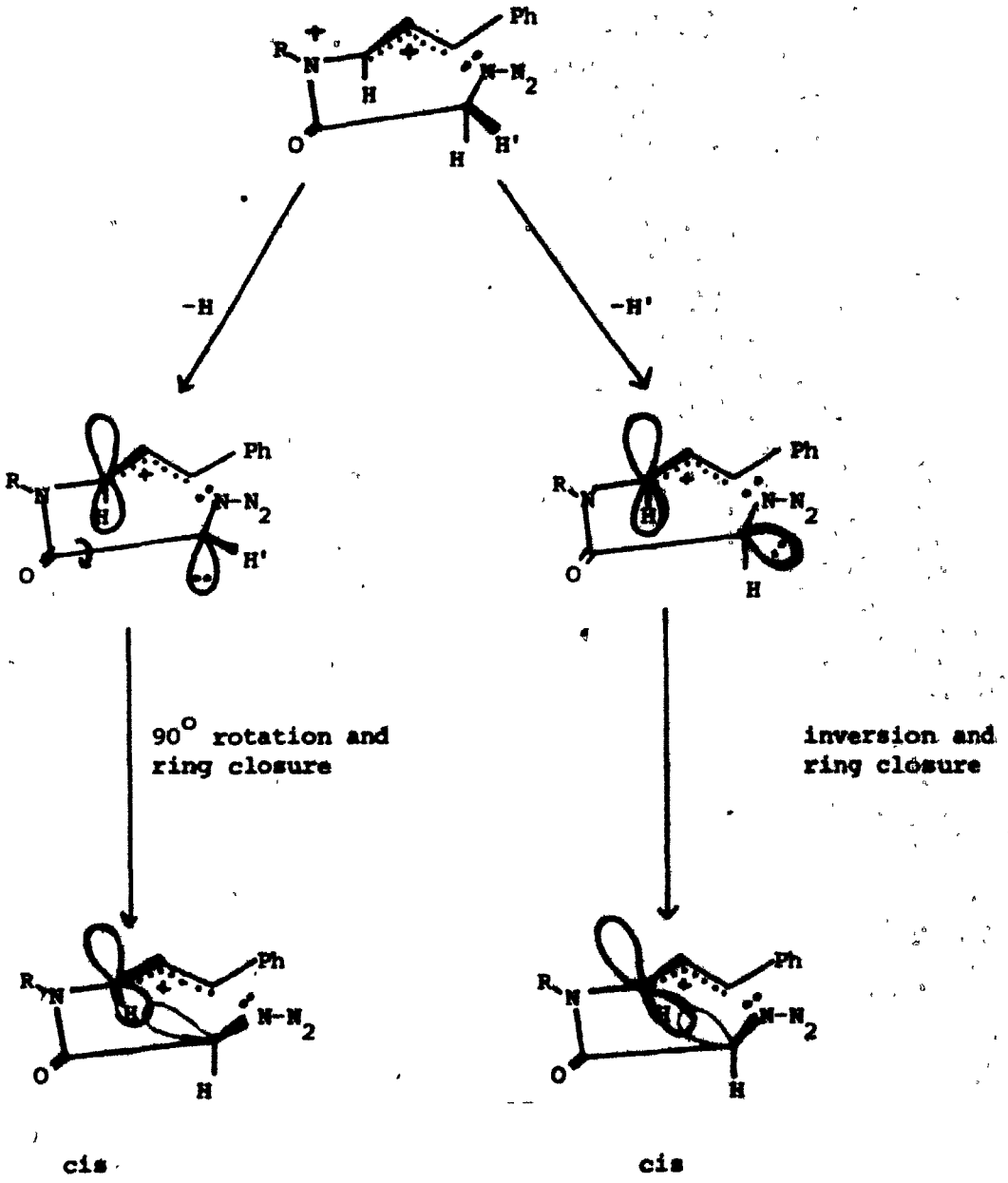


Figure 18 Stereoselectivity based on allignment of the orbitals.

The ketene-imine reactions discussed so far generally give cis products. However, not all reactions of this type are so highly stereospecific. For example, the stereochemistry of a resulting β-lactam may vary depending on the order in which the reagents are added. Bose[23b] has demonstrated that additions of acid chlorides to Schiff's bases generally afford products of trans geometry. For example, when azidoacetyl chloride was added to benzal aniline followed by addition of triethylamine, the resulting cis to trans ration was 1:3. However, when the order of addition was reversed the ratio of cis to trans was 3:1 (Fig 19). An explanation for this phenomena has been offered by Doyle[24]. When an acid chloride is added to the imine, a rapid and reversible formation of the immonium ion A occurs followed by a slower formation of the chloro compound B ($k_1 \gg k_2$). If the acid chloride contains α-substituent with a free pair of electrons, then one of the conformers of the acyl immonium ion is stablilized as C. The rate of formation of B verses C is dependant on the substituents of the Schiff base as well as the acid chloride. For example, if R_1 = simple alkyl, the rate of formation of B is enhanced, however, if R_1 = aromatic, the formation of B is repressed. Bose[23b] has shown that in the absence of triethylamine, the concentration of B is high. In the presence of triethylamine, proton abstraction from B to give D would lead to a mixture of cis and trans adducts E. However, if the acyl immonium ion A were formed in the presence of triethylamine, then proton abstraction from C would exclusively give the cis lactam E.

Dichloroketene generated from trichloroacetylchloride and activated zinc has been reported by Krepski and Hassner[25] and have been found to react readily with silyl enol ethers 46 (Fig 20.) to afford substituted

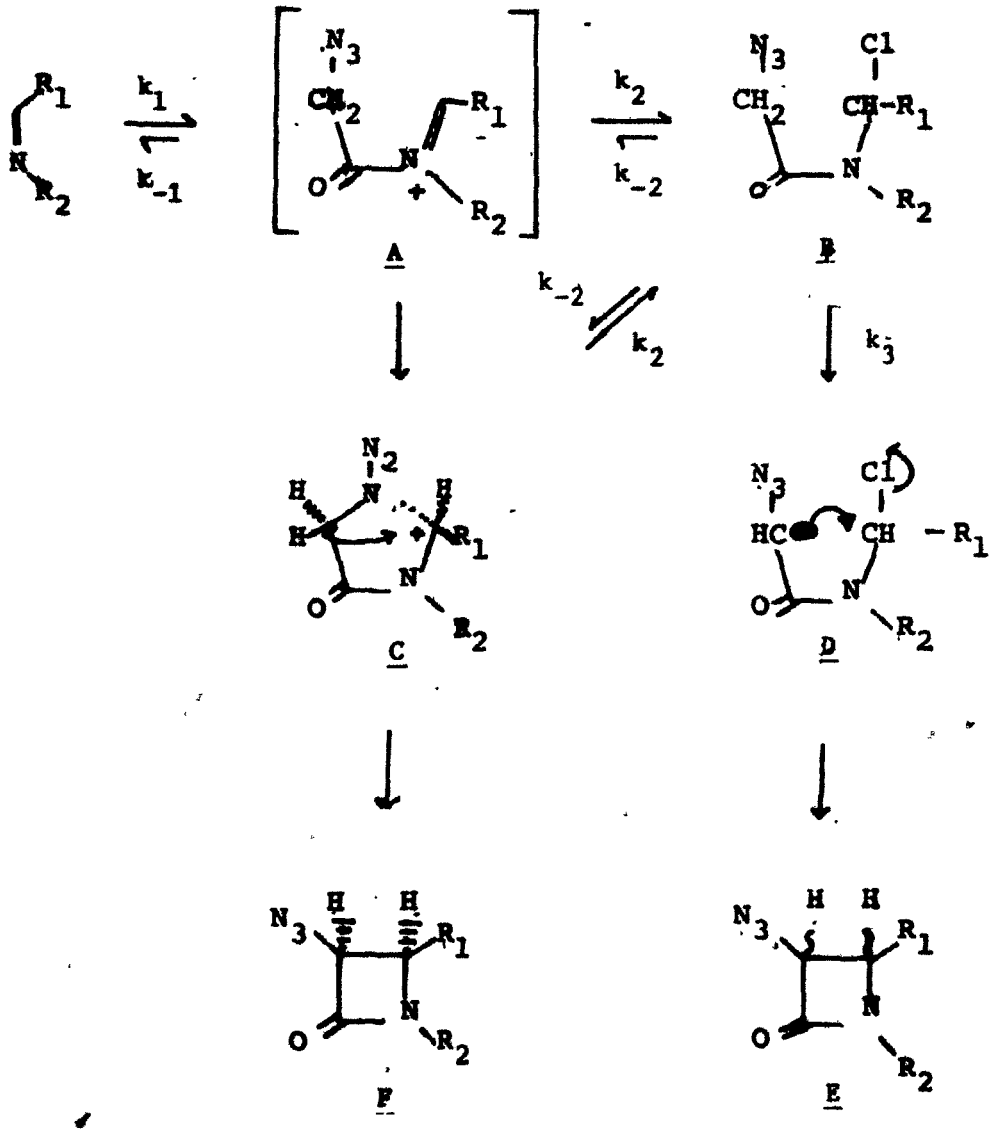
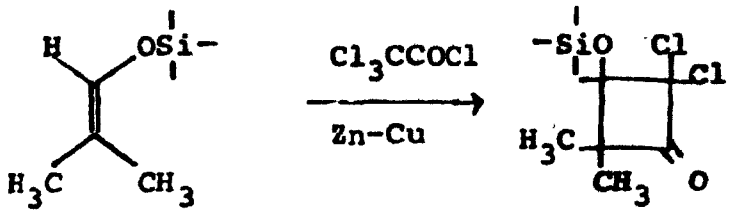


Figure 19 Reaction of azidoacetylchloride and benzal aniline in the presence and absence of triethylamine.

cyclobutanones 47.



46 47

Figure 20 Reaction of dichloroketene generated from trichloroacetylchloride and activated zinc with an enol silyl ether.

When dichloroketene was generated by triethylamine dehydrohalogenation of dichloroacetylchloride, no cycloadducts were observed with silyl enol ethers.

So far, carbapenems have been prepared by fusing the five membered ring onto a preformed monocyclic β-lactam. There are no account in the literature whereby a carbapenem is prepared starting from the pyrrolidine moiety. It is on this basis that our work had led us to embark on an extensive study on the synthesis of the carbapenem (carbapenam) nucleus employing this strategy.

Chapter 2

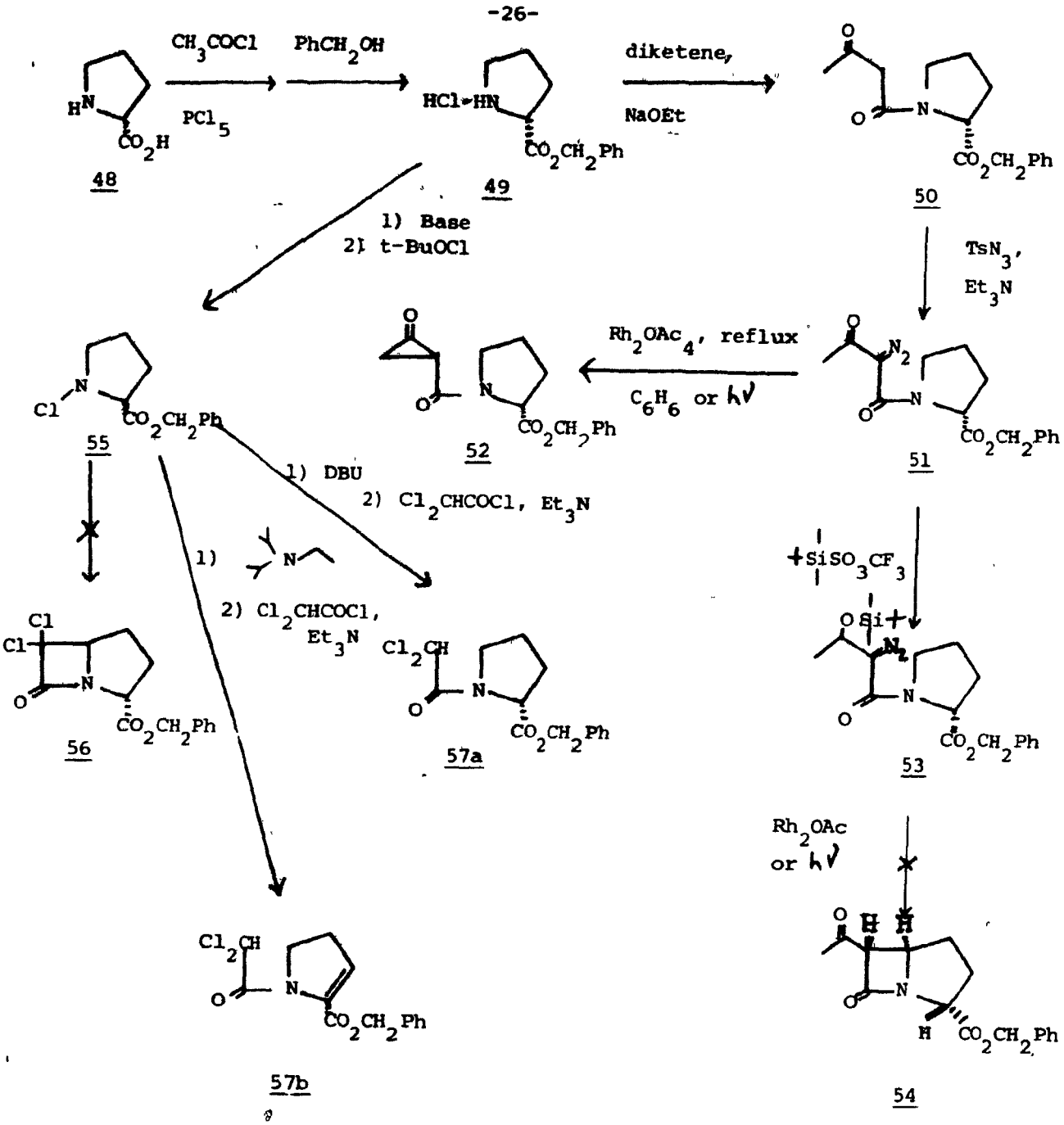
Results and Discussion

2.1.0 Carbene Insertion Route

The synthesis of bicyclic β-lactams via intramolecular C-H insertion by diazo ketones is well documented.[15,16] However, the synthesis of carbapenams employing this methodology has not been extensively studied. It was with this objective that we initially directed our study towards the synthesis of carbapenams.

Based on the work of Lowe and co-workers,[15,16] attempts to cyclize α-diazo-1-acetoacetyl proline benzyl ester (51) (Scheme I) under photolytic and catalytic conditions to give the corresponding β-lactam was undertaken. S-Proline (48) had been selected as the starting material. It is expected that the carboxyl group may direct the transient carbene intermediate to regioselectively insert into the least hindered C-H bond and stereoselectively to give the desired 3,5-trans stereochemistry (using carbapenam numbering) in the fused β-lactam.

It was first necessary to convert the carboxylic acid to an ester. The benzyl ester was selected on the basis of its crystalline property, its solubility in most organic solvents, and the possibility that it can be easily purified. Thus, starting from S-proline (48) (Scheme I), the benzyl ester 49 was obtained via the acid chloride.[26] The ester 49 showed an optical rotation $[\alpha]_D^{20°C} = -117.5°$. Evidence of the ester was ascertained by infrared spectroscopy which showed a $\nu_{C=O(ester)}$ at 1740 cm^{-1}. Also, due to the presence of the benzyl group, ^{1}Hnmr spectrum showed two new peaks at δ 7.32ppm (singlet, phenyl). Acylation of the aminobenzyl ester 49 with diketene[27] afforded the N-acetoacetylamino ester 50 under mild conditions. Compound 50 showed an optical rotation


CH3COCl
PCl5
PhCH2OH
diketene,
NaOEt
48
49
50
1) Base
2) t-BuOCl
TsN3,
Et3N
Rh2OAc4, reflux
C6H6 or hν
52
51
55
1) DBU
2) Cl2CHCOCl, Et3N
1)
2) Cl2CHCOCl, Et3N
56
57a
53
Rh2OAc
or hν
57b
54

SCHEME I

of $\alpha_D^{20°C}$ =-70.3°. Evidence of the structure is based on ir and ^{1}Hnmr spectroscopy and composition was confirmed by microanalysis. Two bands, one at 1640 cm^{-1} for $\nu_{C=O(acyl)}$ and the other at 1740 cm^{-1} for $\nu_{C=O(ester)}$ were observed in the infrared spectrum. In ^{1}Hnmr the acetyl methyl protons appeared as a singlet at δ 2.13 ppm and the acetoacetyl methylene protons were present as a singlet at δ 3.56 ppm. A possible mechanism for N-acylation is shown in Fig. 21.

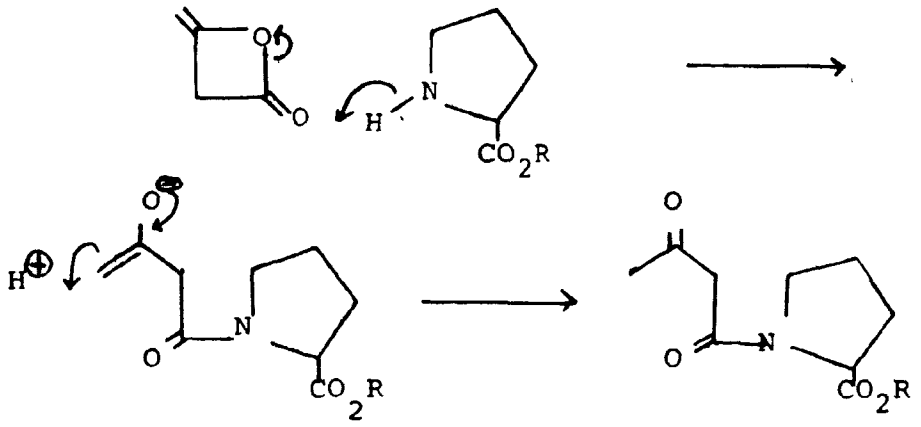


Fig. 21

The acetoacetamide 50 subsequently underwent diazo exchange with tosylazide[26] to give the diazo compound 51. The structure was evidenced by infrared spectroscopy showing an intense band at 2100 cm^{-1} for $\nu_{C=N=N}$. In its ^{1}Hnmr spectrum the methylene protons originally present in 50 at δ3.56 ppm were now absent. The diazo transfer reaction was carried out in the presence of a base. The mechanism of the reaction is assumed to involve the triazine intermediate which decomposes via proton transfer to the diazo structure (Fig. 22).[28]

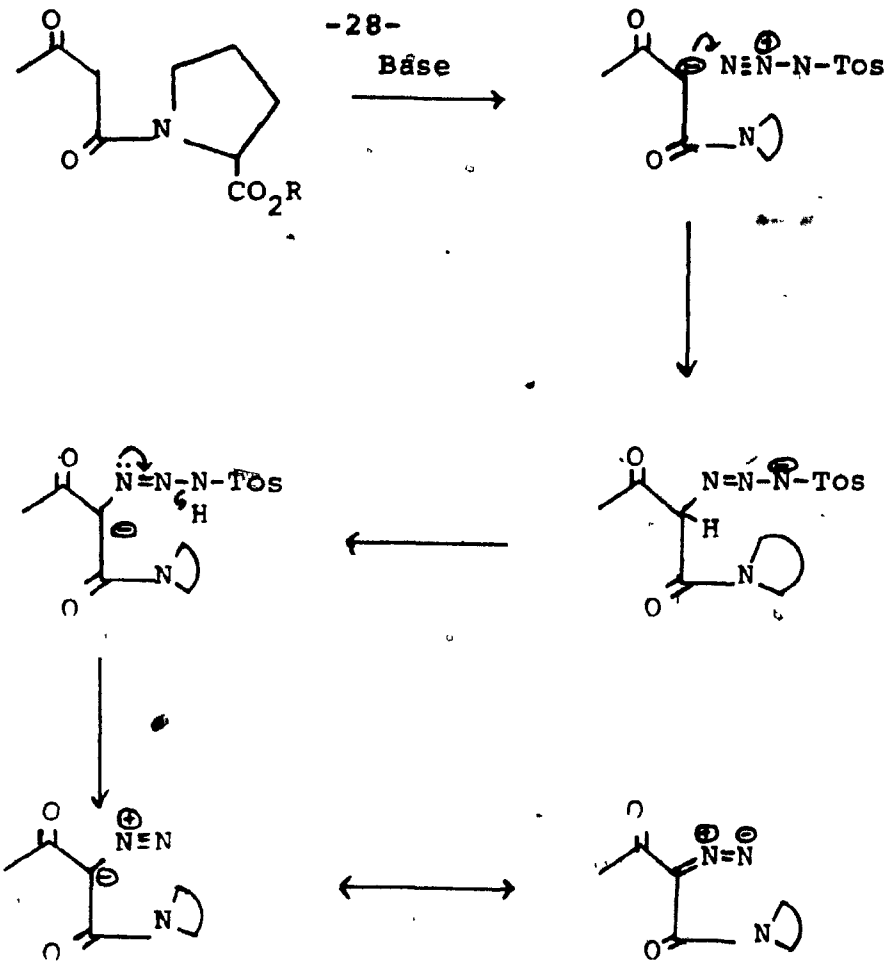


Figure 22

We had attempted to cyclize the α-diazoacetoacetamide 51 under several conditions. The use of rhodium (II) acetate as a catalyst for diazo decomposition for carbene insertion is well known.[29] Although the mechanism has not yet been fully understood, the transition metal probably forms an initial diazo compound-metal complex leading to the evolution of nitrogen resulting in the formation of a metal-carbene complex which inserts into the nearest labile bond, in this case, the α'C-H bond. Table I lists the various conditions and results obtained for the reaction of 51 with $Rh_2(OAc)_4$.

TABLE I: CONDITIONS FOR REACTION OF DIAZO COMPOUND - AND RHODIUM II ACETATE

Diazo compound, (mmoles)	Solvent (ml)	Rh_2OAc_4, (mg)	Temp °C	Reaction Time, (h)	Product(s) and Comments
0.30	C_6H_6, 5	1	60	2	Starting material
1.10	C_6H_6, 25	3.5	60	4	Decomposition
0.16	CH_2Cl_2, 5	1	25	18	Starting material
0.16	CH_2Cl_2, 5	1	60	72	Starting material
0.35	C_6H_6, 10	2	25	24	Starting material
0.35	C_6H_6, 10	20	25	72	Unidentified, however not β-lactam
0.40	C_6H_6, 12	25	45	2	Product with IR band at 1820 cm^{-1}
0.60	C_6H_6, 20	50	42	2.5	Quenched with MeOH, many products

In most cases, starting material was recovered. In some instances, starting material was consumed as evidenced by the disappearance of the 2100cm^{-1} band for $\nu_{C=N=N}$ in the infrared spectrum, however, no β-lactam band was observed (~1760cm^{-1}). A complex mixture of unidentified products were obtained. In one of the experiments, the formation of a cyclopropanone derivative 52 was suspected since a characteristic band[30] at 1820 cm^{-1} in the infrared spectrum was observed. Due to the unstable nature of this compound, isolation of this product was not possible.

Attempts to quench the reaction mixture with methanol to obtain the cyclopropanone acetal or hemiacetal was also unsuccessful. It seemed likely from the above observation that the acetyl part of 51 may have been involved in the reaction. To circumvent this, the ketone was transformed to the corresponding silyl enol ether 53 by reaction with tert-butyldimethylsilyl triflate in the presence of a base. The structure of 53 was confirmed by the observation of $CH_2{=}COSi\ (CH_3)_2C(CH_3)_3$ protons as two doublets at $\sim \delta$ 4.5 ppm in the ^{1}Hnmr spectrum. However, attempts to cyclize compound 53 with $Rh_2(OAc)_4$ only gave starting material (see Table II.

TABLE II: CONDITIONS FOR ATTEMPTS TO CYCLIZE ENOL SILYL ETHER

AMOUNT OF (mmol)	SOLVENT, (ml)	TEMPERATURE, C°	TIME h	CONDITION OF REACTION	RESULTS
.02	C_6H_6, 2	60	.5	Rh_2AOc_4 catalysis (2 mg)	No reaction
.10	CCl_4, 10	25	5	Photolytic	No reaction

Attempts to cyclize 51 or 53 photochemically using a Raynonet photo-chemical reactor was also investigated. The conditions and results are outlined in Table II and Table III. In every case only starting material was recovered.

TABLE III: CONDITIONS FOR PHOTOCHEMICAL REACTION OF DIAZOCOMPOUND

AMOUNT OF DIAZO CMPD (mmol)	SOLVENT, (ml)	TEMP °C	TIME OF EXPOSURE, h	RESULTS
0.16	CCl_4,25	25°C	2	No reaction
0.72	C_6H_6,25	25°C	2	No reaction
0.38	CCl_4,10	25°C	24	No β-lactam, weak IR band at 1820 cm^{-1}.

That we were unsuccessful in cyclizing the diazo ketone to the carbapenam 54 may stem from two possible explanations. Firstly, although no β-lactam was detected by ir spectroscopy, its formation and subsequent decomposition may have occurred. Based on the work of Lowe,[15,16] he observed the formation of a carbapenam by a phhotolytic Wolff rearrangement (see Chapter I, p.17, Fig. 13) in the presence of a trapping group such as β-methylphenethyl carbazate at -70°C to give the corresponding 7-oxo-1-azabicyclo (3.2.0) heptane derivative. However, this compound was found to be very unstable and could not be purified.

Secondly, it is likely that under certain conditions, the transient carbene has been formed as evidenced by the disappearance of $\nu_{C=N=N}$ band in the infrared spectrum, however, insertion into the proline nucleus is not favorable due to the formation of a highly strained bicyclic system.

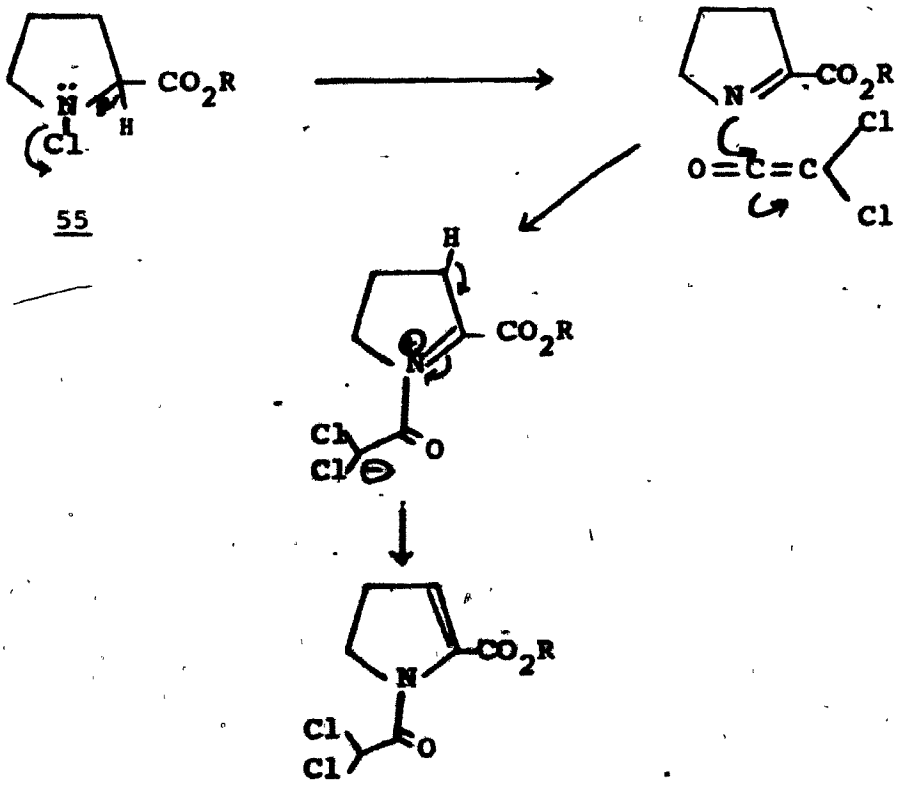
For whichever reason, the carbapenam was not formed. This approach does not appear to be a viable route. We therefore searched for alternate methodologies.

2.2.0 The Δ^1-Pyrrolidine Approach

A second approach utilizing the proline moiety was undertaken. It is well known that imines react with ketenes to give (2+2) cycloadducts[20, 31] and have been widely used for the synthesis of β-lactams.[32] The reaction of the imine generated from dehydrohalogenation of a N-chloro derivative of proline benzyl ester with a ketene generated from dichloroacetyl chloride in the presence of a base was therefore examined.

Benzyl N-chloropyrrolidine-2-carboxylate (55) (Scheme I) was prepared by reation of tert-butylhypochloride[40] with the benzyl ester of proline (49).[33] In the ^{1}Hnmr spectrum, the methine ring proton underwent an upfield shift to δ 3.2 ppm (previously observed at δ 4.6 ppm). The formation of N-Cl bond is evident from the ir spectrum by the absence of N-H stretching at 3450cm^{-1} and also the absence of the N-H proton in ^{1}Hnmr. Dehydrohalogenation of 55 in the presence of diisopropylethylamine and further reaction with dichloroacetyl chloride in the presence of triethylamine did not afford the desired β-lactam 56. Instead, the N-acylated pyrroline 57b was obtained as the product. Evidence of the structure of 57b was supported by spectroscopy. The ir spectrum showed a $\nu_{C=N}$ at 1665 cm^{-1} and also $\nu_{C=O(ester)}$ at 1730 cm^{-1}. In the ^{1}Hnmr

spectrum, the position of the double bond was ascertained by the absence of the $\underline{CH}CO_2R$ proton, also the C-3 proton appeared as a triplet centered at δ 6.24 ppm (J=3.1 Hz). The C-4 protons appeared as a doublet of triplets centered at δ 2.75 ppm (J=8.4 Hz and 3.1 Hz). The C-5 protons were observed as a triplet centered at δ 4.23 ppm. Evidence of the acyl moiety was supported by the dichloromethine peak at δ 6.34 ppm. Two other peaks were observed, one at δ 5.28 ppm and the other at δ 7.37 ppm for benzylic and the phenyl protons, respectively. The elemental composition was confirmed by microanalysis. A possible mechanism to account for the formation of 57b is shown below. (Fig. 23)



This reaction probably proceeds with an initial formation of the immonium intermediate which subsequently undergoes double bond migration instead of cycloaddition.

This result is consistent with a study by Moll and Wieland[34] whereby N-acyl-Δ^2-pyrrolines were obtained by reaction of 2-phenyl-Δ^1 pyrroline with diketene (Fig. 24).

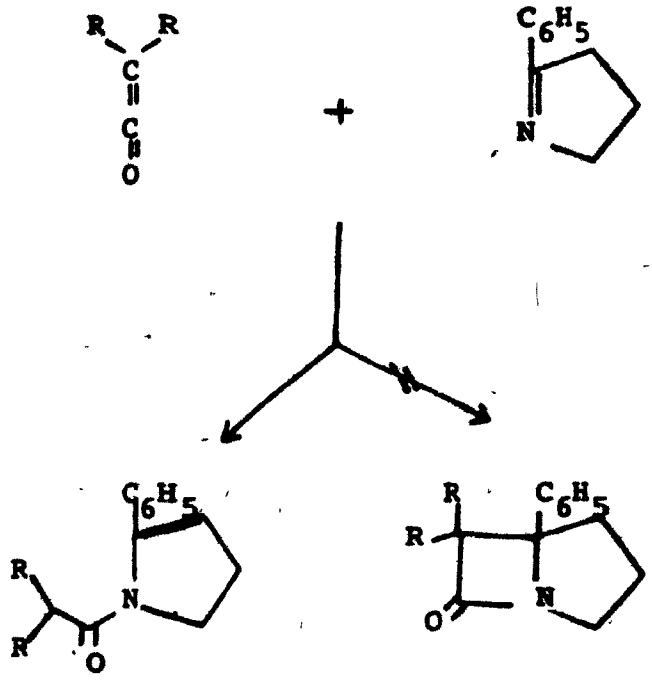


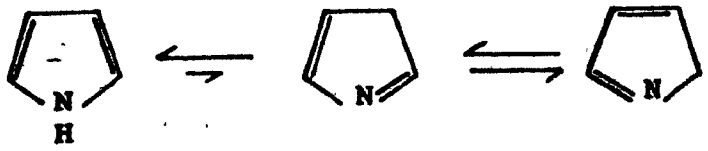
Figure 24

In view of the above results, that the rate of N-acylation and double bond migration is favored over cycloaddition reaction, a possible strategy is to eliminate the possibility of double bond migration. Our subsequent studies are therefore aimed at those approaches.

2.3.0 The Azafulvene Approach

A third approach which was investigated was the reaction of a ketene with an azafulvene.

Pyrrolenine forms (58b and 58c) of pyrrole (58a) and of simple derivatives are highly destabilized and consequently the tautomeric equilibrium is displaced in favor of pyrrole (58a) (Fig. 25).[35]



58a 58b 58c

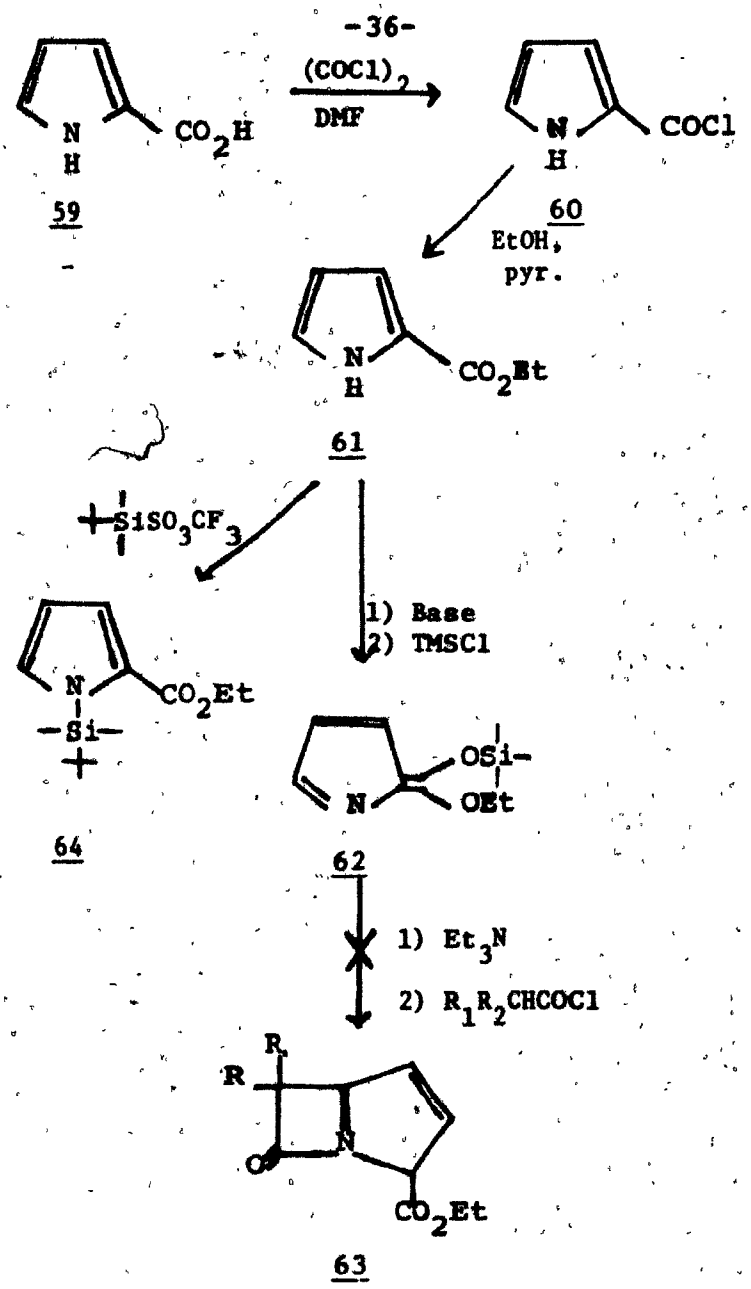
Figure 25

To date there are no reported cases whereby a stable pyrrolenine tautomeric form is known.[36] However, participation of substituents can give additional stabilization and can perhaps shift the tautomeric equilibrium to favor the pyrrolenine form. With this concept in mind, an extensive study on the preparation of azafulvenes, a type of pyrrolenine, was undertaken.

The reaction of ketenes with imines is well documented and yield (2+2) cycloaddition products.[20] Since an azafulvene is an imine, its reaction with a ketene was investigated as to whether a carbapenem would be obtained.

2.3.1 Generation of an Azafulvene from Ethyl Pyrrole-2-carboxylate (61)

The ethyl ester 61 was prepared via its acid chloride 60 starting from pyrrole-2-carboxylic acid (59) (Scheme II).[37] Evidence of the structure was determined spectroscopically. The infrared spectrum showed a characteristic $\nu_{C=O\ (ester)}$ at 1670 cm^{-1}. The methyl protons of the ethyl group were observed as a triplet centered at δ 1.35 ppm coupling (J=7.1 Hz) with the methylene protons which were positioned at δ 4.32 ppm as a quartet in the nmr spectrum. The ring protons appeared as two sets



59 60 61 64 62 63

SCHEME II

of multiplets having chemical shifts of δ 6.26 ppm and δ 6.92 ppm. Generation of the anion using an appropriate base and subsequent trapping of the enolate ion with TMSCl could give the azafulvene intermediate 62. However, isolation of this compound was not possible. This intermediate was, therefore, allowed to react in situ with an acid chloride/base (ketene generation) to see if any carbapenem 63 could be formed.

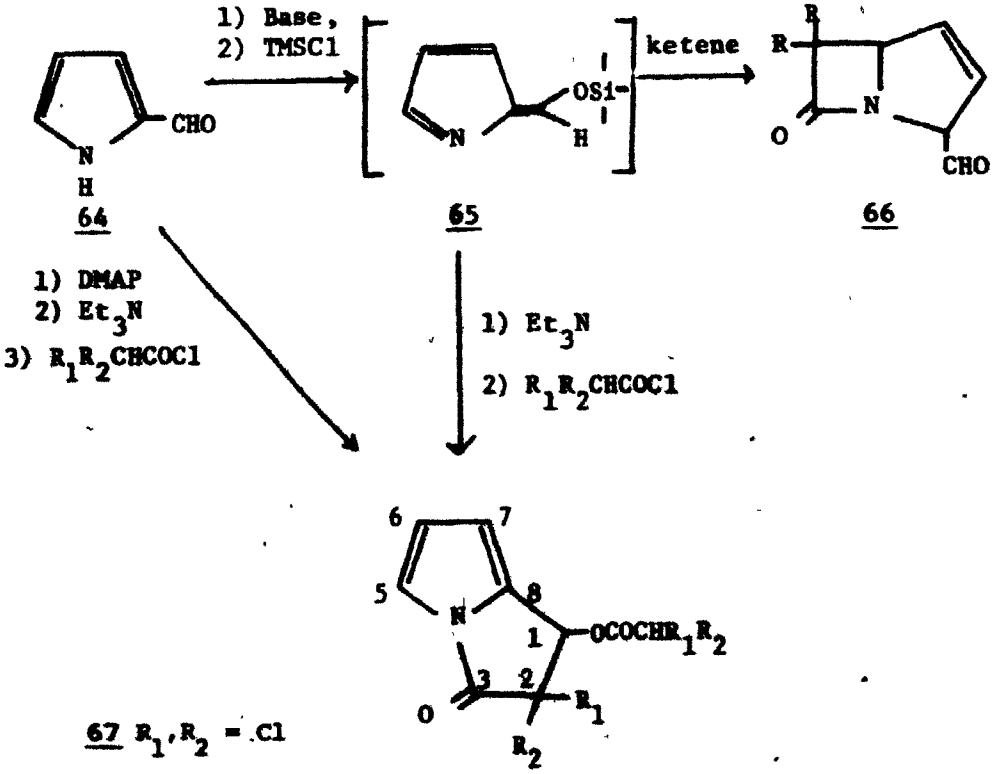
Some of the bases tried for the formation of the enolate anion of 61 were BuLi, KH, HMDSi, LDA and DMAP. In same cases, the base interfered in the reaction. For example, when LDA was used, problems arose when azidoacetyl chloride was added to the reaction mixture. Instead of forming azidoketene or cycloadducts thereof, the formation of N,N-diisopropylazidoacetamide resulted and the compound was isolated. The structure was supported by ir and nmr spectroscopy. A $\nu_{C=O(amide)}$ band was observed at 1650 cm^{-1} and $\nu_{C=N=N(azide)}$ at 2100 cm^{-1} in the ir spectrum. Proton nmr showed a multiplet at δ 1.25 - 1.54 ppm for the methyls of the diisopropyl group, a broad signal at δ 3.60 ppm for the methine hydrogen and a singlet at δ 3.86 ppm for the methylene protons. When butyllithium was used, and tert-butyldimethylsilyl triflate was employed as the anion trapping agent, the nmr spectrum of the product obtained after addition of azidoketene was found to have structure 64. It showed an upfield shift for all the ring and ester protons. Two additional singlets were observed at δ 0.92 ppm and δ 0.52 ppm and are assigned to the tert-butylsilyl protons and the dimethylsilyl protons, respectively. Also, the NH proton had disappeared. Furthermore, the 1770 cm^{-1} ester band in the infrared spectrum was unchanged, however, the NH absorption at ~3320 cm^{-1} disappeared. The mass spectrum did not show any molecular ion. When dimethylamino pyridine or potassium hydride were used

as the base, no reaction occurred and only starting material was recovered. Lithium hexamethyldisilazide gave a mixture of many products none of which were identified as a β-lactam.

It appears apparent from the above results that the preparation of an azafulvene starting from the pyrrole ester 61 is not feasible under these conditions probably due to difficulties encountered in trapping the anion as the O-silyl azafulvene. This led to the investigation of another pyrrole derivative.

2.3.2. Generation of an Azafulvene from Pyrrole-2-carboxaldehyde and Subsequent Reaction with a Ketene

The azafulvene approach to carbapenems was extended to the use of pyrrole-2-carboxaldehyde (64) (Scheme III) which could perhaps more readily form the azafulvene O-silyl compound 65. Various bases such as



67 R_1, R_2 = Cl

75 R_1=H, R_2=[illegible]

SCHEME III

LDA, KH and DMAP were examined as potential reagents for anion formation. The anion, once formed, could theoretically be trapped as a silyl ether or a borate ester to give the azafulvene 65. Isolation of this intermediate was again unsuccessful. The infrared spectrum still showed a carbonyl band at 1660 cm^{-1} after non-aqueous work-up. Subsequent reaction of the product obtained, presumably 65, with either dichloro or azido ketene generated in situ in the presence of triethylamine gave a compound with a C=O stretching frequency of 1770 cm^{-1} in the infrared spectrum. Two possible structures were proposed for this product, one being the carbapenem 66 and the other is the bicyclic amide 67. It was necessary to elucidate the structure chemically. Our preliminary studies led us to investigate how this compound was affected by acid. It is known that carbapenems are generally not stable in acid. Thus, when this compound was treated with 2N HCl no reaction occurred, the starting material was recovered. This led us to favor structure 67 as the product, however, more proof was necessary. The same product could also be obtained when TMSCl was omitted and supports the assumption that the azafulvene 65 is not essential for the formation of 67. Based on the assumption that the product has the structure 67, a possible mechanism for this reaction is shown in Fig. 27.

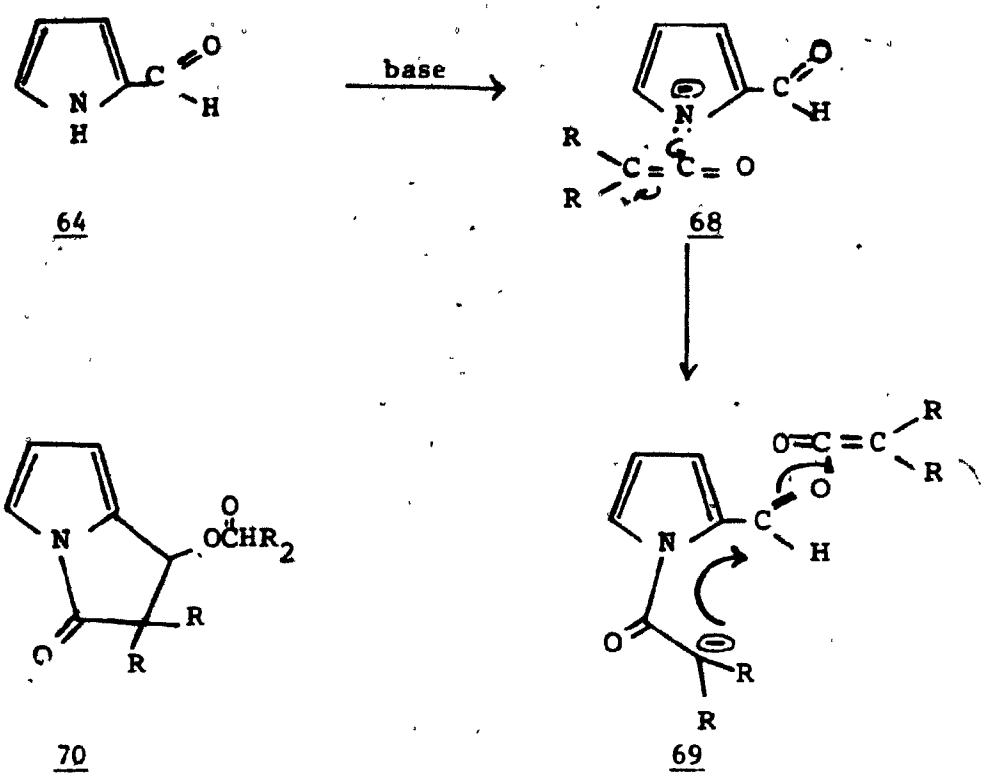
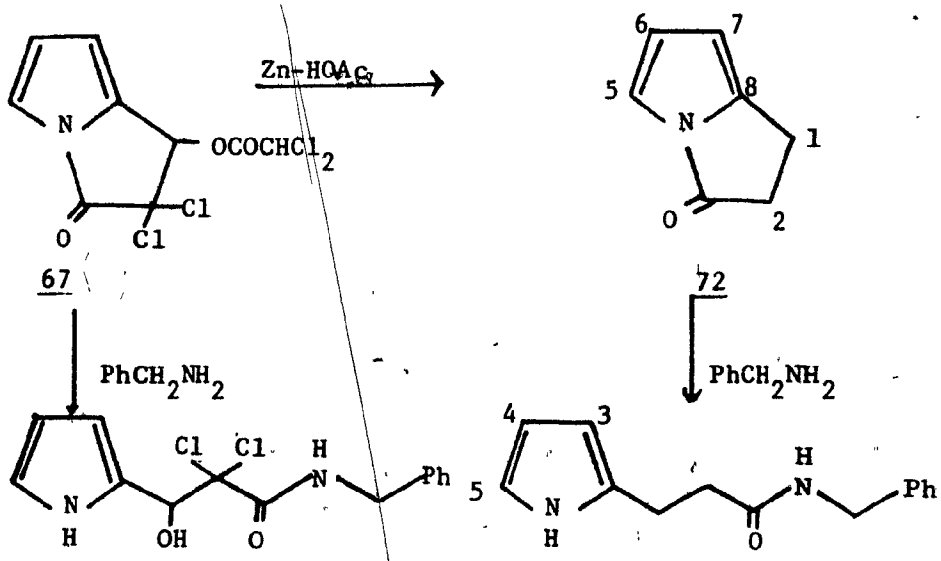


Figure 27

Initially, a proton is abstracted from the amine 64 by a base to generate the anion 68. Reaction of 68 in the ketene gives the N-acylated product 69 which undergoes an Aldol-type addition and subsequently reacts with a second equivalent of ketene to give 70. The composition of 67 was confirmed by elemental analysis and the structure was partially elucidated by spectrosocpy. The nmr spectrum showed a singlet at δ 6.02 ppm for the methine proton of the acetyl group, and a broad singlet at δ 6.42 ppm for H-1. The pyrrole ring protons were observed at δ 6.40 ppm. 6.67 ppm and δ 7.22 ppm each having a coupling constant of 3.2 Hz and are assigned to H-5, H-6 and H-7 respectively. The infrared spectrum showed a $\nu_{C=O(amide)}$ at 1770 cm^{-1} and $\nu_{C=O(ester)}$ at 1750 cm^{-1}. The high frequency of the

amide band supported the assumption that the structure was bicyclic with the pyrrole structure inhibiting the amide resonance as well as the presence of the electronegative chloride adjacent to the carbonyl group.* The mass spectrum did not show any molecular ion, however, a cluster of peaks at m/z = 318, 316 and 314 were observed and can be attributed to the isotope peaks of the ($M^{+\cdot}$-H) peak observed at m/z = 314 due to the presence of chlorine atoms in the molecule. The principal fragment that is observed is the loss of the dichloroacetoxy group giving a peak at m/z = 188 followed by the loss of a chlorine giving a major peak at 153.

Further proof of the structure of 67 was adduced by chemical evidence. When 1-dichloroacetoxy-2,2-dichloro-3-oxo pyrrolo {1,2-a} pyrrole (67) was subjected to reaction with benzylamine, ring opening occurred to afford the unstable pyrrole 71 (Scheme IV).



SCHEME IV

*The effect of chlorine adjacent to an amide carbonyl has been shown by Kellie.[59] The infrared spectrum of oxindole has a maximum carbonyl absorption at 1708 cm^{-1} and 1725 cm^{-1} in chloroform. The corresponding 3,3-dichloro analog has a maximum absorption at 1758 cm^{-1}.

The infrared spectrum of 71 showed a ν_{OH} band at 3400 cm^{-1} and the ν_{CON} band had now shifted to 1670 cm^{-1}. Proton nmr had shown an upfield shift for the pyrrole ring protons by approximately 0.2 ppm. The CHOH proton was observed as a singlet at δ 5.54 ppm. The presence of the benzyl group was confirmed by a peak observed at δ 4.50 ppm corresponding to the benzyl protons and a set of peaks centered at δ 7.27 ppm due to the aromatic protons of the phenyl group. Since this product was unstable, more proof of the structure assigned to 67 was required.

Reduction of 67 with zinc-acetic acid afforded 1,2-dihydro-3-oxo-pyrrolo[1,2-a]pyrrole (72) (Scheme IV). Due to the loss of the α-chlorines, the amide band was shifted to lower frequency (1720 cm^{-1}) in the infrared spectrum. The mass spectrum of this product (72) showed a molecular ion at m/z = 121 as the base peak followed by a peak due to the loss of 28 at m/z = 93.

Further evidence of structure 72 was confirmed by proton nmr. The C-1 and C-2 protons were observed as a singlet at δ 3.02 ppm and the pyrrole ring protons appeared at δ 5.95 (H-5), 6.45 (H-6) and 7.06 ppm (H-7). To ascertain whether C-1 and C-2 were adjacent, a ^{13}Cnmr spectrum was obtained. Two sets of triplets were observed, one at δ 34.8 ppm (C-1) and another at δ 19.3 (C-2) ppm having a coupling constant of J_{C-H} = 135 Hz. Final proof of structure (72) was supported by the stable product (73) obtained upon aminolysis with benzylamine (Scheme IV). This pyrrole (73) showed an amide band at 1615 cm^{-1} in the infrared spectrum. Nuclear magnetic resonance spectroscopy gave more evidence of the structure 73. The H-3 and H-4 pyrrole protons had underwent an upfield shift and were observed at δ 6.07 and δ 5.90 ppm, respectively. However, the H-5 proton had experienced a downfield shift relative to the bicyclic analog 72 and

appeared at δ 6.64 ppm. Other peaks were at δ 2.52 ppm (CH_2-C), 2.85 ppm (CH_2CO), 4.4 ppm ($\underline{CH_2}Ph$) and 7.76 ppm (phenyl). The mass spectrum showed a molecular ion peak at m/z = 228 as the base peak.

Preparation of 67 was best accomplished when 2,2-dimethylaminopyridine[38,39] was used as the base and two equivalents of dichloroacetyl chloride were added giving a yield of 52%. When LDA was used as the base to generate the anion, diisopropylamine participated in the reaction to give the bicyclic amide 74. The formation of 74 could be suppressed if diisopropylamine was removed by filtration. The mechanism by which this may occur is shown in Fig. 28.

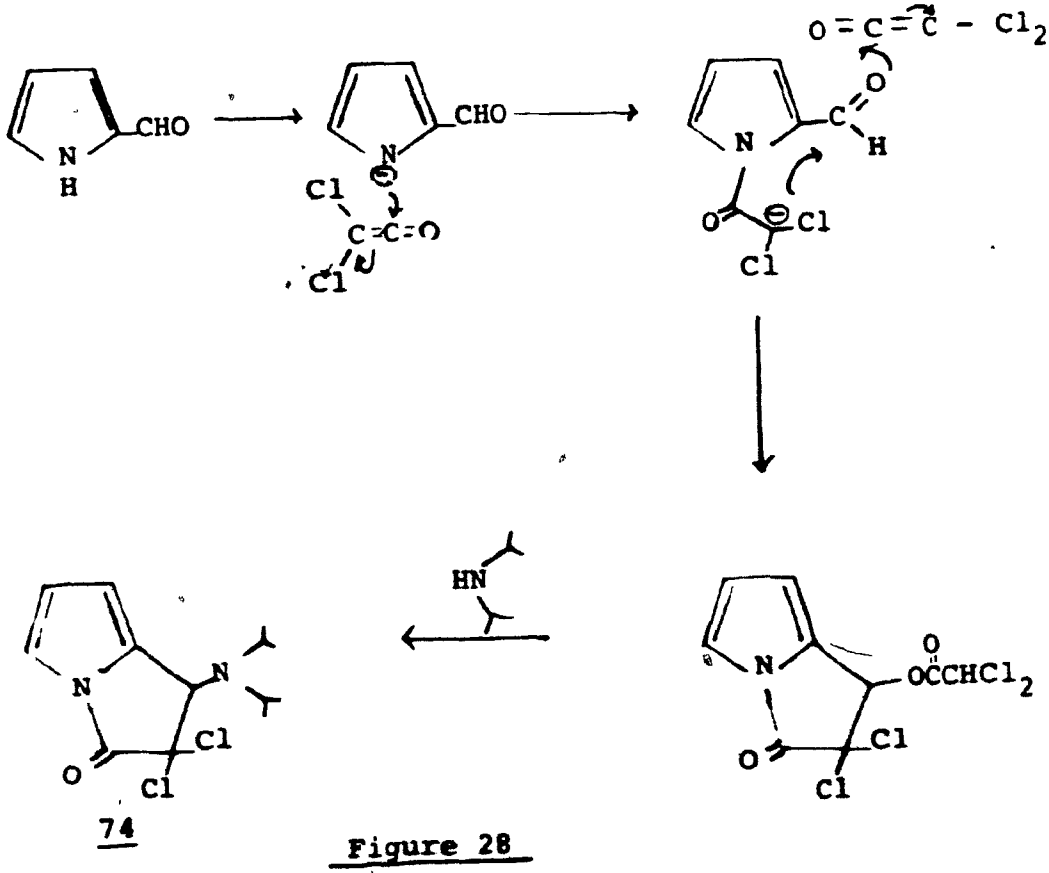
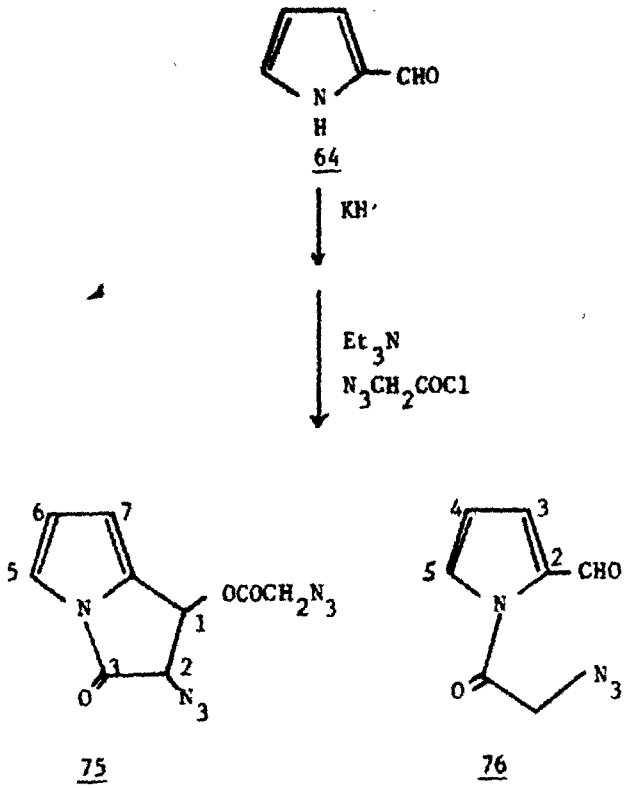


Figure 28

The mass spectrum of compound 74 showed a molecular ion at m/z = 288 (33%) plus an (M + 2) at m/z 290 (8%). The infrared spectrum gave an amide band at 1770 cm^{-1}. Evidence of the diisopropylamine group was ascertained by the nmr spectrum which showed a multiplet with an integrated area for twelve protons being assigned to the methyls at δ 1.12 ppm. A multiplet at δ 3.02 ppm with an integrated area for two protons is assigned to $\underline{CH}(CH_3)_2$. The nmr of the crude reaction product showed that the yield of 74 was greater than 50%, however, after purification by column chromatography, the actual yield was ∿3% due to partial decomposition of the product on silica gel.

Preparation of the corresponding azido analog 75 (Scheme V) by using dimethylaminopyridine as the base, gave a complicated mixture of many products which was not identified. Preparation of 1-azidoacetoxy-2-azido-3-oxo-pyrrolo{1,2-a}pyrrole (75) was achieved by using potassium hydride as the base to generate the anion. Other bases such as BuLi and LDA were also investigated without success. Only trace amounts of the bicyclic azido product 75 could be isolated, and the major product was the N-acylated pyrrole 76 along with starting material 64. The structure of the bicyclic product 75 was supported by spectroscopic data. The exocyclic methylene was observed at δ 3.96 ppm as a singlet. Two doublets at δ 4.74 ppm and another appearing at δ 5.80 ppm are assigned to $\underline{CH}N_3$ and $\underline{CH}CO_2R$ of the pyrroline ring, respectively. The pyrrole ring protons appeared at δ 6.35 ppm (H-5), 6.58 ppm (H-6) and 7.14 ppm (H-7) each being coupled to one another (J=3.2 Hz). The infrared spectrum showed a distinctive high frequency amide band at 1760 cm^{-1} indicative of a cyclic system similar to the dichloro compound 67. Due to the unstable nature of compound 75, elemental analysis was not possible.

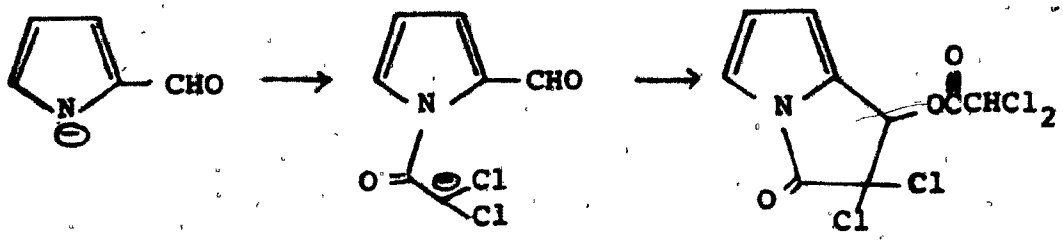

CHO
N
H
64
KH
Et_3N
N_3CH_2COCl
6
7
5
N
$OCOCH_2N_3$
1
3
2
O
N_3
4
3
5
2
CHO
N
O
N_3
75
76

SCHEME V

The mass spectrum did not show a molecular ion peak and, therefore, the molecular weight could not be ascertained. However, a major peak at m/z = 149 may be assigned to an ion resulting from the loss of azido ketene and a second azido group from the ester. Another major peak at m/z = 119 may be due to the loss of the acetyl moiety and a second molecule of azide from the molecular ion. The structure of 75 is supported by the good agreement in comparison of the spectroscopic data obtained relative to the spectroscopic properties of 1-dichloroacetoxy-2,2-dichloro-3-oxo-pyrrolo {1,2-a} pyrrole (67). Elucidation of the N-acylated structure 76 was also confirmed by spectroscopy. Although no molecular ion was observed in the mass spectrum, a major peak at m/z = 95 is probably due to the loss of the azidoacetoxy group. The ir spectrum showed an ν_{CON} at 1720 cm^{-1} and $\nu_{C=O(aldehyde)}$ at 1660 cm^{-1} also a $\nu_{N=N=N}$ at 2100 cm^{-1}. Evidence of the 2-formyl group was ascertained by the nmr spectrum whereby a singlet at δ 10.05 ppm was observed. Other peaks present were δ 4.59 ppm (singlet, CH_2N_3), 6.43 ppm (triplet, H-4), 7.25 ppm (d, H-5) and at 7.44 ppm (d, H-3). All the ring protons gave coupling constants of J=3.3, Hz.

In conclusion, the reaction of pyrrole-2-carboxaldehyde with a base and subsequent reaction with a ketene does not afford the corresponding carbapenem for two possible reasons. Firstly, the azafulvene perhaps is never formed and, therefore, only N-acylation occurs upon reaction of the anion with ketene according to path A (Fig. 29). Secondly, perhaps the azafulvene is formed, however, the [2+6] type addition of the zwitterion competes with [2+2] cycloaddition on the imine.

Path A



Path B

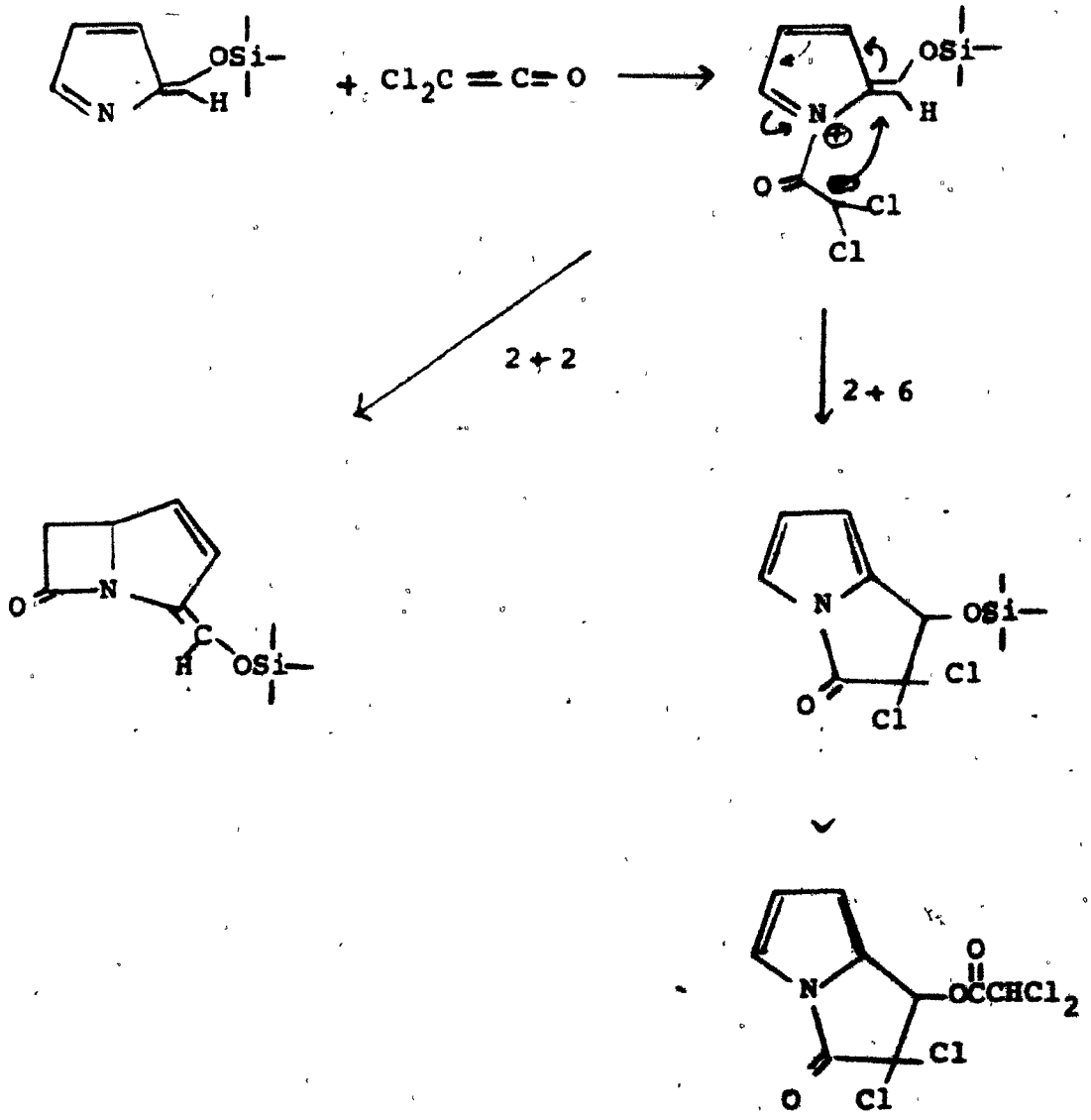


Figure 29

Although a carbapenem could not be synthesized by this method, 1,2-dihydro-3-oxo-pyrrolo[1,2-a] pyrrole (72) may offer an interesting route to pyrrolizidine-type alkaloids such as retronecine (Fig.30) which is a bicyclic tertiary amine with one double bond and two alcohol functions.[42]

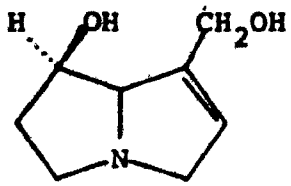
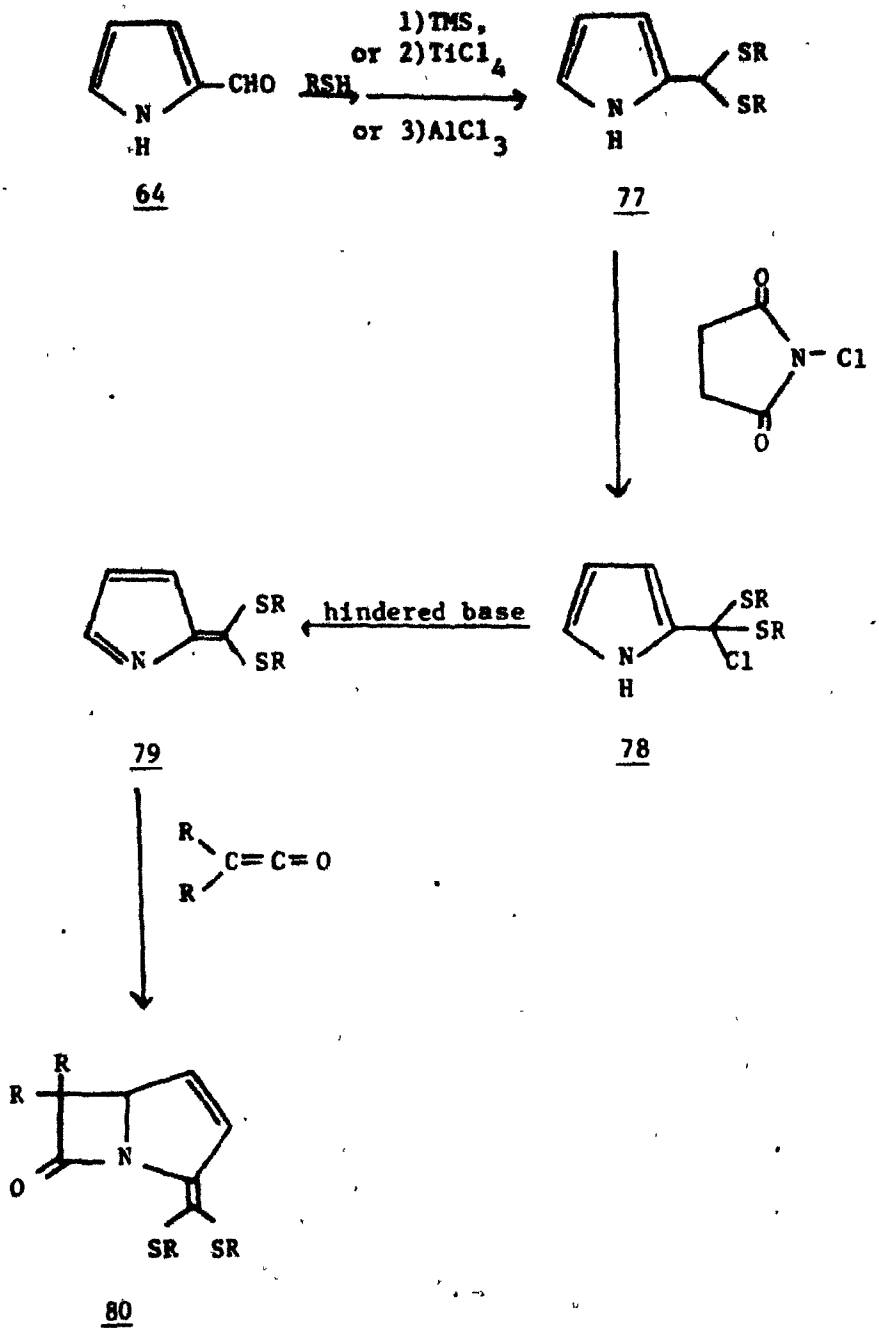


Figure 30

2.3.3. Preparation of Azafulvenes via Dithioacetals and Subsequent Reaction with a Ketene

It is well known that dithioacetals undergo α-chlorination[46] and thus can introduce a good leaving group at this position. A possible approach to a 'stable' azafulvene is outlined in Scheme VI.


CHO
RSH
1) TMS,
or 2) TiCl4
or 3) AlCl3
SR
SR
N
H
64
77
N- Cl
O
O
hindered base
SR
SR
Cl
79
78
R
R
C= C= O
R
R
O
N
SR SR
80

SCHEME VI

Azadithiafulvene analogues have been previously prepared by Nakayama and co-workers[56]. For example, 5-aza-1,4-dithiafulvalene was prepared by reaction of pyrrole with 2-methylthio-1,3-dithiolylium iodide at room temperature to afford the 2-(2-pyrrolyl)-1,3-dithiolylium iodide which was subsequently treated with DBU (Figure 31).

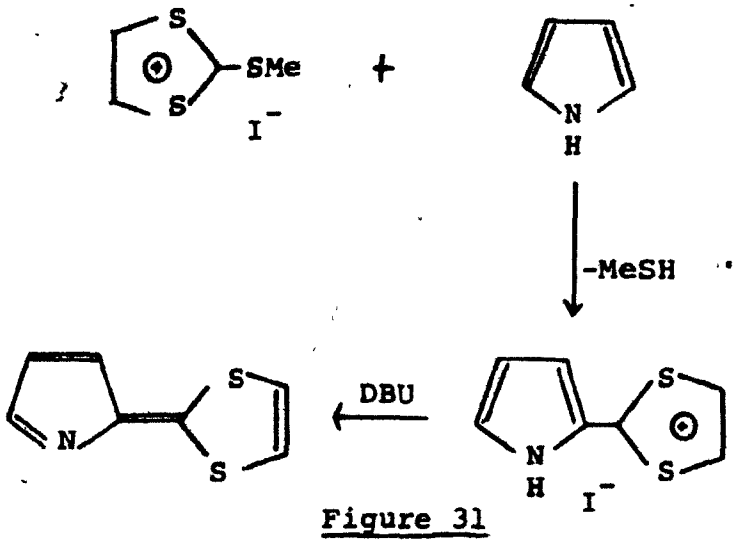


Figure 31

Preparation of 2-methylthio-1,3-dithiolylium iodide is a lengthly process and, therefore, it was hoped that Scheme VI may offer a simpler approach. The preparation of dithioacetals from carbonyl compounds is well documented and can be accomplished by reaction of the carbonyl compound with two equivalents of a thiol in the presence of reagents such as trimethylsilyl chloride[43], titanium tetrachloride[44], or aluminium trichloride[45]. The preparation of a 2-dithioacetal pyrrole, 77, by reaction of pyrrole 2-carboxaldehyde (64) with thiophenol using the above mentioned reagents (i.e., $TiCl_4$, TMSCl) was, therefore, investigated. Unfortunately, the preparation of the dithioacetal 77 was unsuccessful. In all cases, only black tar-like products were obtained probably due to

self condensation of the aldehyde 64 in acidic conditions to give a polymer (Fig. 32)[47]. After many unfruitful attempts, this method to

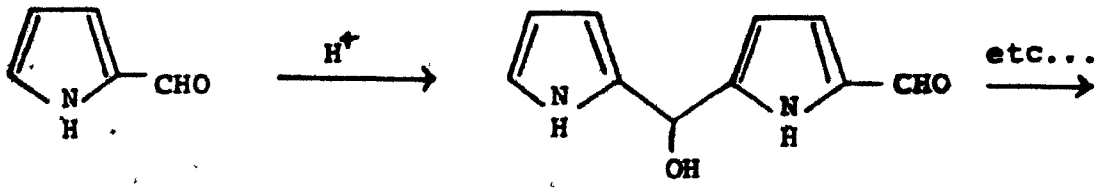
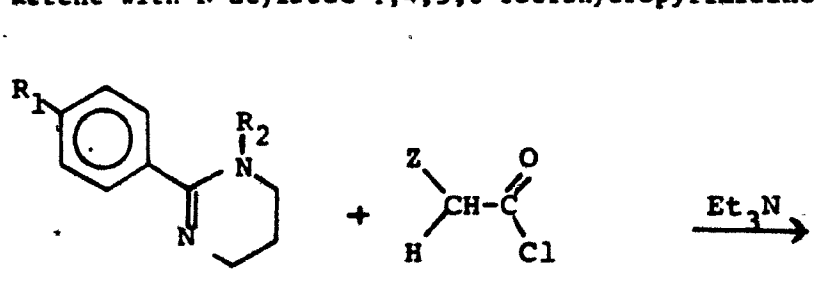


Figure 32

obtain an azafulvene was no longer pursued.

2.4.0. The Substituted Pyrrolinine Approach

Precedence for the preparation of β-lactams by reaction of ketenes with cyclic imine systems has appeared in the literature.[51, 52] Bose has reported the preparation of various azacepham analogs by reaction of a ketene with N-acylated 1,4,5,6-tetrahydropyrimidines [52](Fig. 33).



R_1	R_2	Z= OPh, N_3
H	H	
H	$p\text{-}SO_2C_6H_4CH_3$	
CO_2Et	$COCH_2Ph$	

Z	R_1	R_2
OPh	H	$COCH_2OPh$
N_3	H	$COCH_2N_3$
OPh	H	$p\text{-}SO_2C_6H_4CH$
OPh	CO_2Et	$COCH_2Ph$

Figure 33

Reaction of a lower homolog such as 2-phenyl-imidazoline with a ketene also afforded the corresponding β-lactam as confirmed by spectroscopic evidence (ie., ir, nmr) (Fig. 34). However, this bicyclic system was found to be unstable and decomposed upon purification.

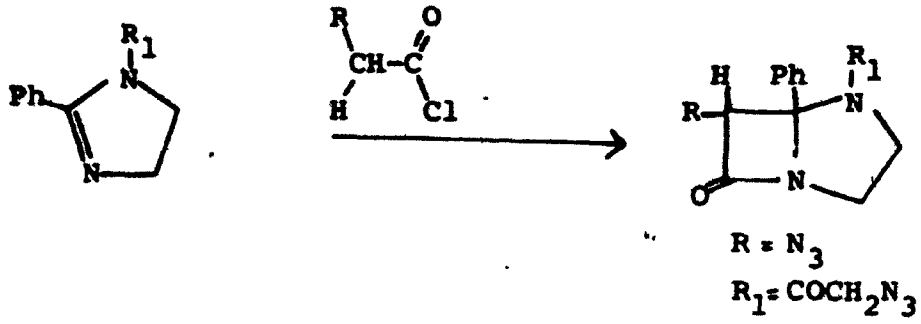


Figure 34

A second example appeared in the literature whereby Bose[51] reported the preparation of an exocyclic thio analog of the penicillin system by a ketene-cyclic imine reaction. Reaction of a thioimidate as shown in Fig. 35 with an acid chloride in the presence of triethylamine afforded the corresponding β-lactam. At first, this system was studied without the

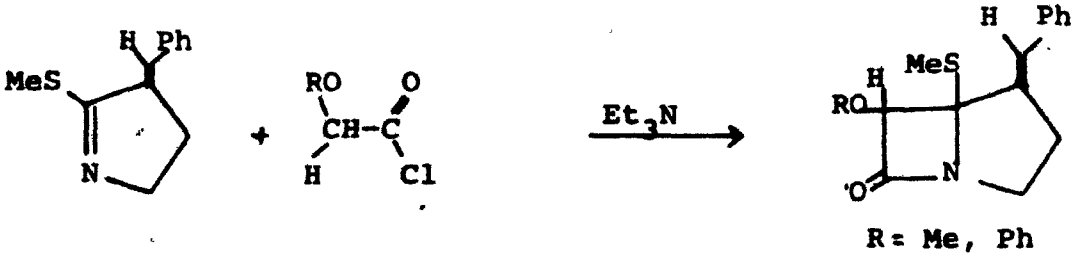


Figure 35

exocyclic benzylidene group, however, isomerization of the double bond occurred affording the N-acylated-Δ^2-pyrroline (Figure 36).

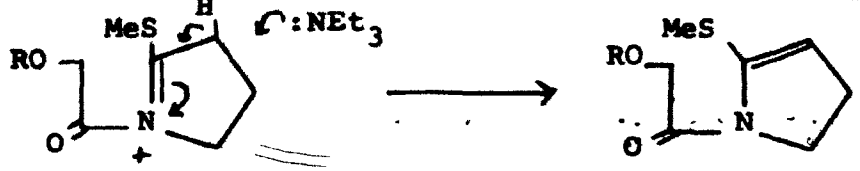
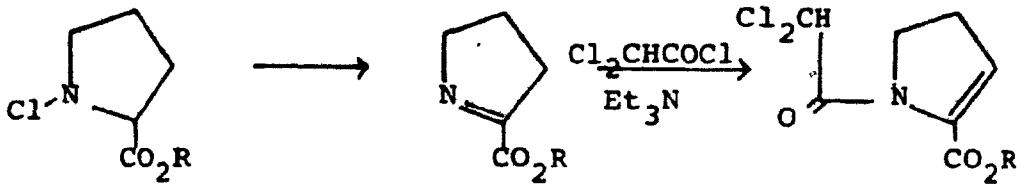


Figure 36

Introduction of the benzylidene group ruled out the possibility of this isomerization.

This is in accord with our observation that the imine 55b generated *in situ* from the N-chloro precursor 55a reacted with dichloroacetyl chloride/triethylamine to give the N-acylated pyrrolenine 57b with double bond isomerization (Fig. 37).



55a 55b 57b

Figure 37

Since the attempt to arrest the double bond isomerization by the azafulvene approach has failed, the remaining alternative appears to have a di-substituted pyrrolenine where migration of double bond is ruled out. This is illustrated in Figure 38. We undertook to examine this approach.

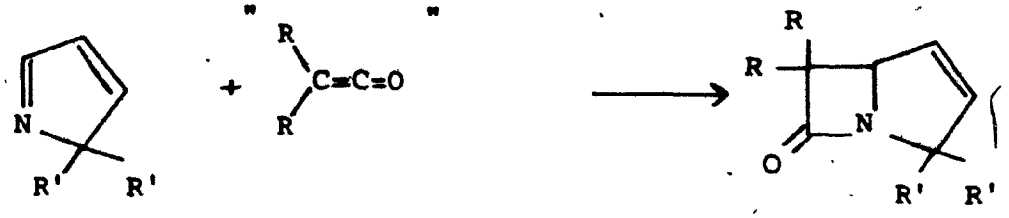
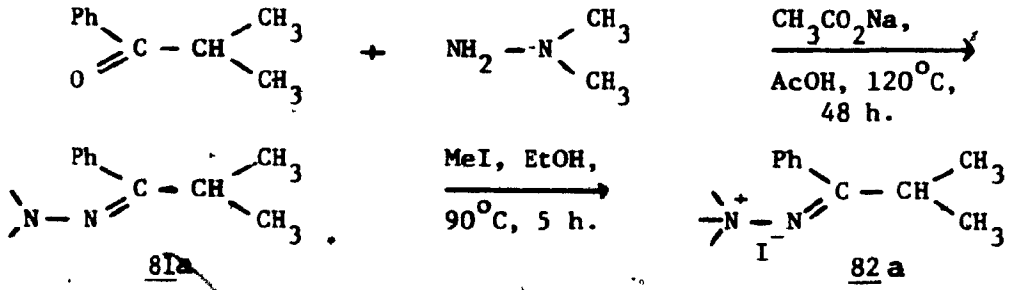


Figure 38

2.4.1. Preparation of the Substituted Pyrrolenines

Recently, Laurent[49,50,53] has described the preparation of Δ^1-pyrroles by reaction of carbanions of ketones or aldehydes with an azirine or its precursor, a dimethyl hydrazone methiodide in basic conditions. There are two other general methods which have been reported for the preparation of α-pyrrolenines. One of these methods described[54] is via alkylation of 2,5-disubstituted pyrrole Grignard derivatives. Another general preparation is reported by Friedrich and co-workers[55] whereby a photochemical addition of a vinyl sulfone or a vinyl-phosphonium salt on an azirine can give α-pyrrolenines. To date, the method described by Laurent seems to be the most convenient route.

METHOD A

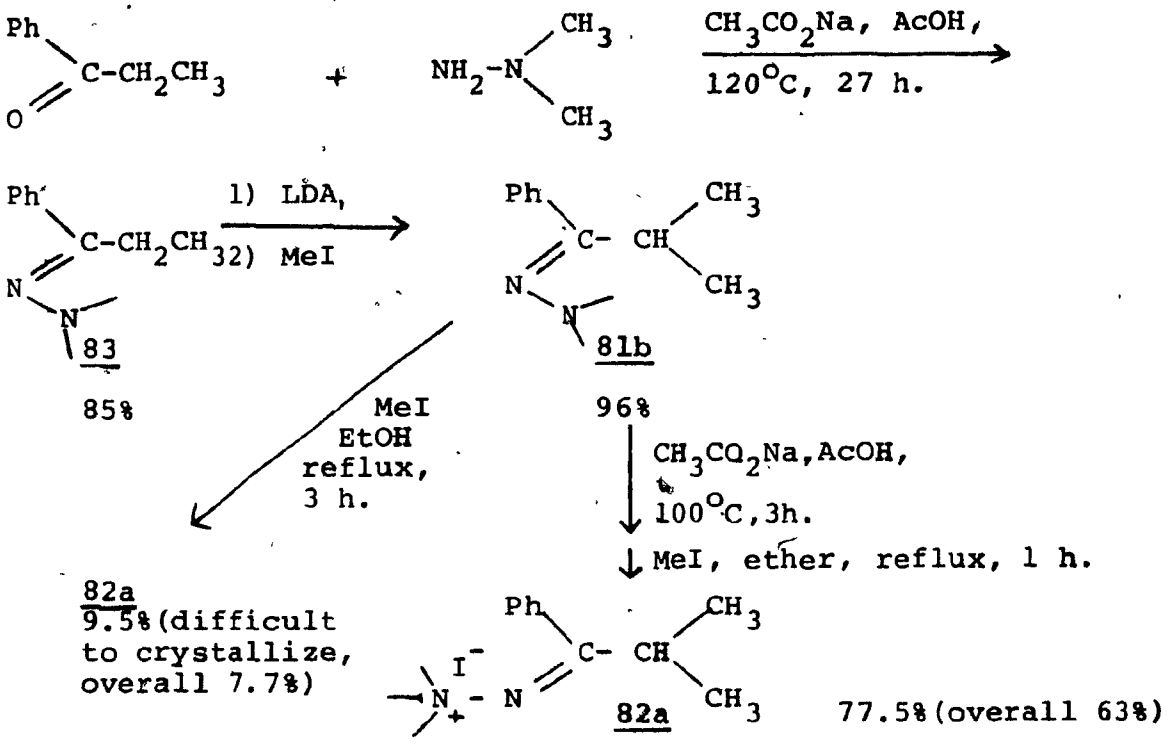


8.3% (based on isobutyrophenone)

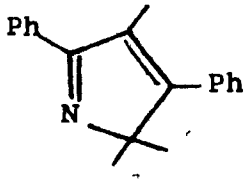
SCHEME VII

METHOD B

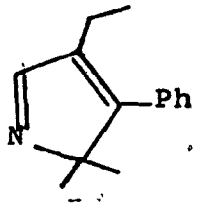
SCHEME VII (cont...)



We have chosen for this study the preparation of two pyrrolenines, 84 and 90 (Fig. 39), because both have been described in the literature. As it turned out, some modification of the literature procedure (Method A, Scheme VII) became necessary. The literature procedure, as cited in Laurent's publication[49], for the preparation of hydrazone methiodide 82 was based on previous work by Sato[47]. Thus, reaction of isobutyrophenone



84



90

Figure 39

with N,N-dimethyl hydrazine in a Paar pressure bomb and heating at 120°C for 48 hours afforded isobutyrophenone dimethyl hydrazone (81a). The ^{1}Hnmr spectrum of the distilled reaction product indicated that the reaction was only approximately 20% complete. The extent of the reaction was ascertained by the integrated area of the N-dimethyl peak observed at δ 2.54 ppm relative to the C-dimethyl peak at δ 1.14 ppm. Also the ir spectrum still showed the carbonyl band of isobutyrophenone at 1680 cm^{-1}. The mixture was then reacted with methyl iodide without further purification since the quaternized product 82a should crystallize as a salt out of the crude reaction mixture. Indeed, this reaction afforded 8.3% of isobutyrophenone dimethylhydrazone methiodide (82a) as a solid based on the starting quantity of isobutyrophenone. Isobutyrophenone was the only other product present. This method was unsatisfactory and since this product was a key starting material, investigation to improve the yield was undertaken.

The probable mechanism for this reaction is nucleophilic attack of the nitrogen of the hydrazine on the carbonyl compound as shown in Figure 40 followed by protonation of carbonyl oxygen and subsequent elimination of water.

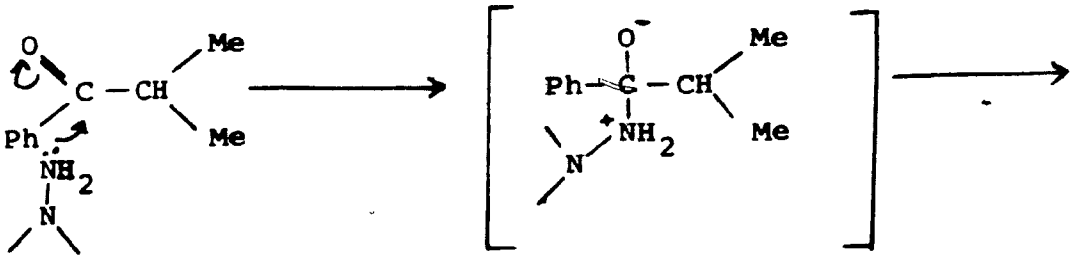
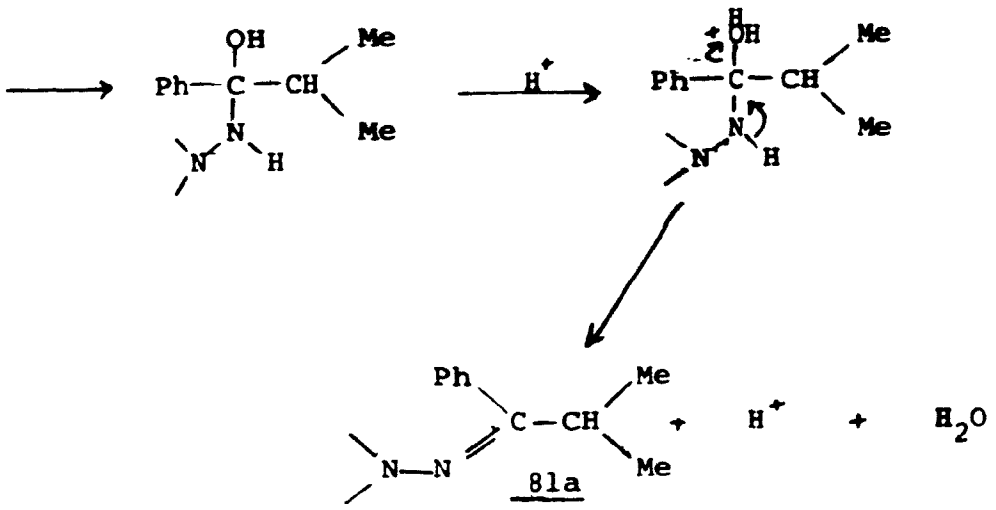


Figure 40

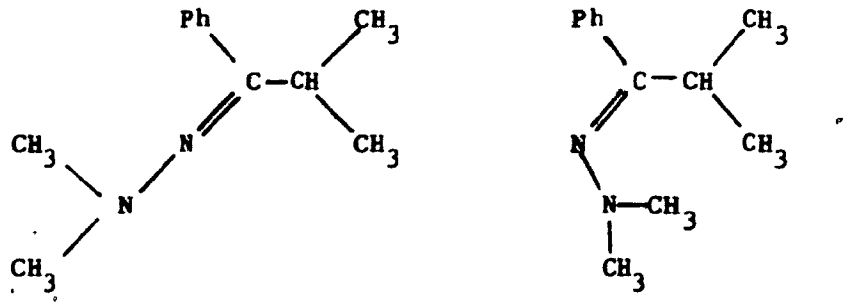
Figure 40 (cont...)



81a

There are two possible geometrical isomers for 81a, the N-dimethyl group may be syn or anti to the phenyl group. In this case, the syn isomer is the likely structure due to steric interaction of the C-dimethyl group and the N-dimethyl group. In Method A (Scheme VII), a probable reason for the poor yield obtained for 82a can be attributed to the difficulty in forming the hydrazone 81a due to this steric hinderance. This reasoning was confirmed when the same reaction was performed on the less sterically hindered homolog, propiophenone (Scheme VII) (Method B). Reaction of propiophenone with dimethyl hydrazine afforded the hydrazone 83 in good yield (85%). The structure was supported by spectroscopy. The ^{1}Hnmr spectrum showed a triplet at δ 1.07 ppm corresponding to the methyl protons of the ethyl and was coupled (J=7.7 Hz) with the methylene protons which appeared as a quartet at δ 2.91 ppm. The N-dimethyl protons appeared as a singlet at δ 2.57 ppm and the phenyl protons appeared as a multiplet at δ 7.31 to 7.72 ppm. The infrared spectrum showed a distinctive $\nu_{C=N}$ at 1601 cm^{-1}. This product (83) was then alkylated[48] by reaction with LDA and methyl iodide giving the desired isobutyrophenone dimethylhydrazone (81b) in good yield (96%). Elucidation of the structure was confirmed by the ^{1}Hnmr spectrum whereby the C-dimethyl protons

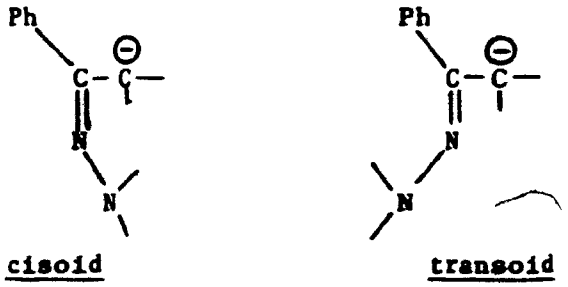
appeared as a doublet at δ 1.14 ppm which was coupled (J=7.1 Hz) with the methine proton observed as a septet centered at δ 3.86 ppm. The phenyl protons now appeared as a singlet at δ 7.33 ppm and the N-dimethyl protons now appeared as a singlet at δ 2.54 ppm. It is interesting to note that 81b is, in fact, different from 81a in both spectroscopic and chemical properties. For example, the N-dimethyl protons of 81a appeared at higher field than those of 81b and were observed at δ 2.40 ppm, also as a singlet. Therefore, they are geometrical isomers, with 81b having the anti structure (Figure 41). The structure 81b is also in line with the



81a 81b

Figure 41

observation by Fraser[38] that the α-carbanion of hydrazone has the cisoid structure in preference over the transoid structure (Figure 42).



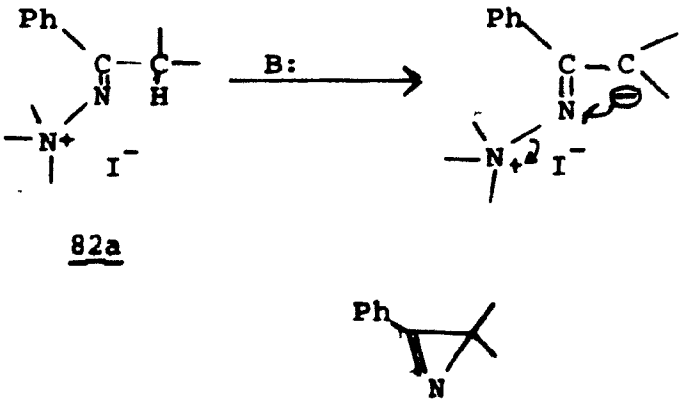
cisoid transoid

Figure 42

Methylation of the cisoid carbanion should give the anti compound 81b. Attempts to quaternize this product (81b) with methyl iodide in refluxing

ethanol gave a product which was difficult to crystallize and afforded only 9.5% of isobutyrophenone dimethylhydrazone methiodide (82a) as a solid. The difficulty encountered in obtaining a good yield of 82a may be due to the difficulty in isomerization of 81b to 81a under these conditions. Isomerization was, therefore, induced by heating the product (81b) obtained by Method B at 100°C for 3 hours with sodium acetate and acetic acid. Subsequent quaternization with methyliodide, indeed, gave a crystalline product 82a in good yield (77%). The structure of 82a was established on the basis of its ^{1}Hnmr spectrum. The C-dimethyl protons were observed as doublets at δ 1.10 ppm coupling (J=6.7 Hz) with the methine proton which appeared as a septet at δ 2.90 ppm. The N-trimethyl protons were observed as a singlet at δ 3.27 ppm and the phenyl protons appeared as a multiplet at δ 7.39-7.64 ppm.

The assumption that the quaternized hydrazone 82 has syn-stereochemistry can be supported by subsequent azirine formation. For example, if the mechanism for azirine formation is considered (Fig. 43), it can be assumed that the stereochemistry of the trimethylamino group should be anti to the attacking nucleophile.



82a

Figure 43

Azirine 89 was prepared according to a procedure outlined by Laurent[49]. Thus the hydrazone 82 was reacted with dimsyl sodium at room temperature to give 2,2-dimethyl-3-phenyl azirine 89. The structure was confirmed by spectroscopy. The ^{1}Hnmr spectrum showed a singlet at δ 1.42 ppm for the C-dimethyl protons plus a multiplet at δ 7.49-7.87 ppm for the aromatic protons. The $\nu_{C=N}$ band was observed at 1720 cm^{-1} in the infrared spectrum and the molecular ion m/z = 145 was observed in the mass spectrum. When this azirine 89 was reacted with the carbanion of butyraldehyde generated with potassium hydride, the corresponding 2H-pyrrole, 90 resulted[50]. The likely mechanism of this reaction is shown in Figure 44. Evidence of the structure was ascertained by spectroscopic methods.

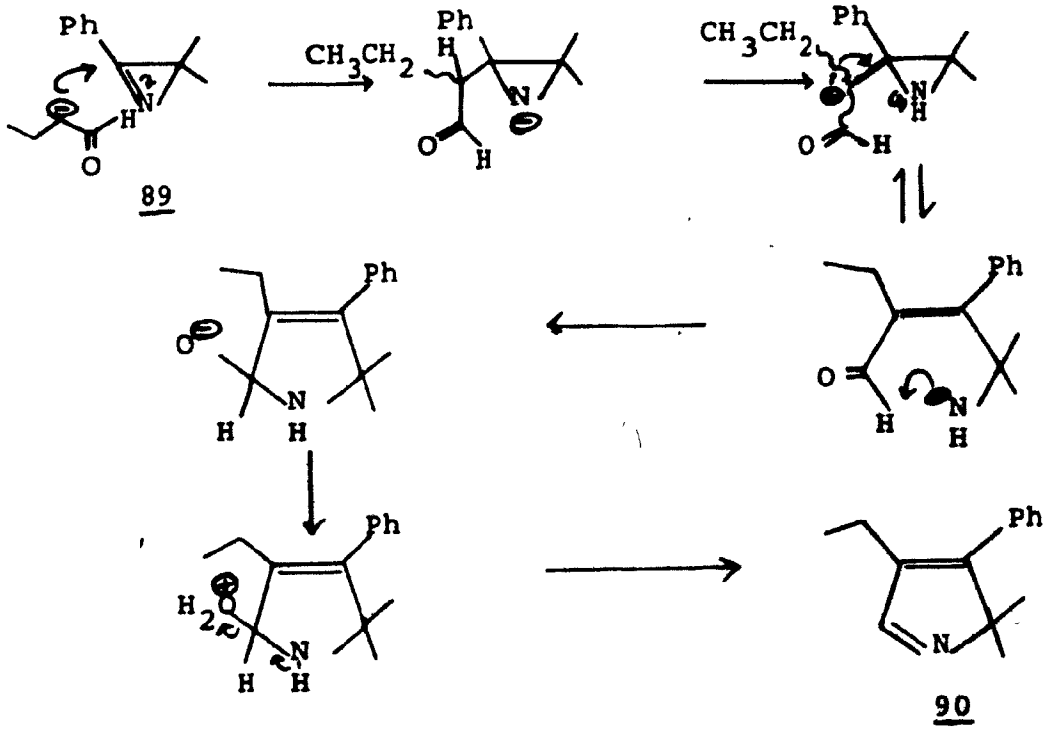


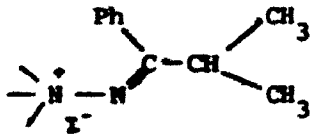
Figure 44

The methyl of the ethyl group was observed as a triplet at δ 1.07 ppm coupling (J=7.6 Hz) with the methylene protons appearing as a quartet at δ 2.22 ppm in the ^{1}Hnmr spectrum. The dimethyl protons appeared as a singlet at δ 1.32 ppm and the aromatic protons were observed as a multiplet at 7.04-7.42 ppm. The characteristic H-2 was observed as a singlet at δ 8.02. The mass spectrum gave the molecular ion at m/z = 199 as the base peak. The ir spectrum corresponded to the literature values.[50]

Unlike 2H-pyrrolenines, 2-substituted pyrrolenines may be prepared directly from the hydrazonium salt 82 whereby the azirine (89) is generated in situ. In this case, a ketone instead of an aldehyde is added to the reaction mixture and for this reason strong bases, such as dimsyl sodium, can be used without the problem of self-condensation expected in the aldehyde case. Hence, 2,2,4-trimethyl-3,5-diphenyl pyrrole (84) (Scheme VIII) was prepared according to the procedure outlined by Laurent[49] by reaction of the carbanion of propiophenone generated by dimsyl sodium with the azirine (89) formed in situ from the hydrazonium salt 82. The mass spectrum of 89 showed a characteristic molecular ion at m/z = 261 as the base peak. The nmr, ir and melting point corresponded to the literature values.[49]

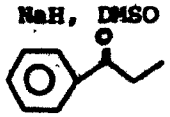
2.4.2. Results of the Reaction of Pyrrolenine Derivatives with Dichloroketene and Azidoketene

The reaction of 2,2,4-trimethyl-3,5-diphenyl-2H-pyrrole (84), an imine, with a ketene, such as dichloro or azido, was examined as to whether [2+2] cycloaddition products would result. Thus, when dichloroacetyl chloride was added to the pyrrolenine 84 (Scheme VIII) in the presence of triethylamine, the major product obtained was the β-lactam 85. The structure of this product was supported by its spectroscopic

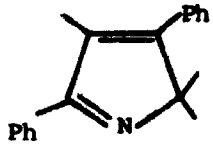


82

NaH, DMSO



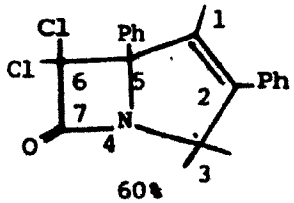
48%



84

$Cl_2CHCOCl$, Et_3N

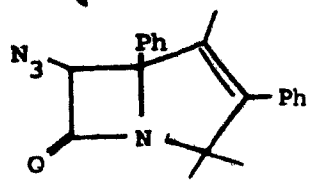
N_3CH_2COCl, Et_3N



60%

85

+



17%

87

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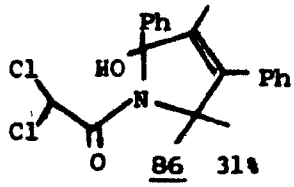
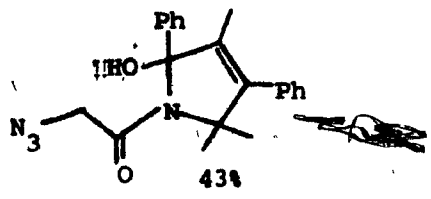


86 31%



43%

88

SCHEME VIII

properties. The high frequency β-lactam band was observed at 1780 cm^{-1} in the infrared spectrum. All protons in the ^{1}Hnmr spectrum had been shifted to higher field relative to the pyrrolenine 84. The gem-dimethyl protons now appeared as two singlets at δ 1.37 and δ 1.39 ppm and the allylic methyl protons were observed at δ 1.83 ppm as a singlet. The aromatic protons appeared as a multiplet at δ 6.97-7.96 ppm. The ^{13}C nmr spectrum showed peaks for seventeen carbons. Three distinctive methyl peaks were observed at 15.00, 25.25 and 28.61 ppm. The mass spectrum (E.I.) showed a very weak molecular ion peak at m/z = 371 with a relative intensity of 4%. The major fragmentation is due to the loss of ketene at m/z = 261 ($M-Cl_2C_2O$) which was observed as the base peak. A possible mechanism for the mass spectral fragmentation is shown in Figure 45. The E.I. mass spectrum also showed a molecular ion cluster at m/z = 370, 371, 372, 373, 374. The M+2 and M+4 peaks have intensities concurrent for the presence of two chlorines. Elemental analysis indicated that the product crystallized with chloroform.

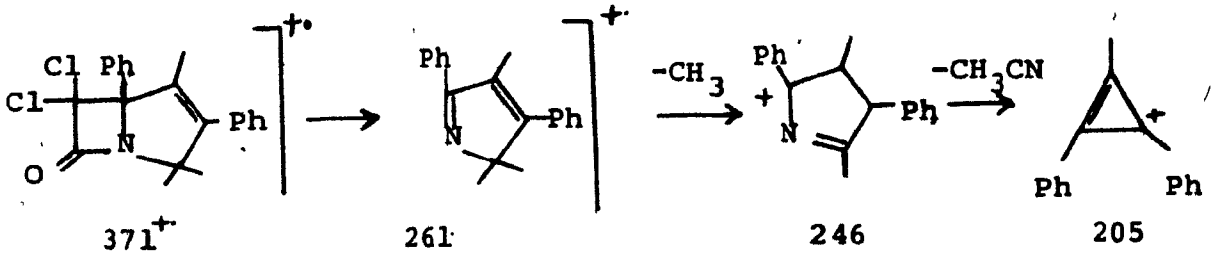


Figure 45

A by-product of the reaction was the uncyclized 2,2,4-trimethyl-3,5-diphenyl-5-hydroxy-1-dichloroacetoxy pyrrole (86) (Scheme VIII). The fact that this product was isolated indicates that the reaction mechanism for the formation of the β-lactam proceeds via a zwitterionic intermediate (see Fig. 46) which undergoes hydrations in the presence of water. The origin of the water may be due to moisture present in the solvent even after distillation and storage over molecular sieves. The structure of 86 was

determined by spectroscopic evidence. The infrared spectrum showed a broad hydroxyl band at 3350 cm^{-1} and an amide band at 1650 cm^{-1}. The ^{1}Hnmr spectrum showed a characteristic singlet at δ 6.22 ppm for the

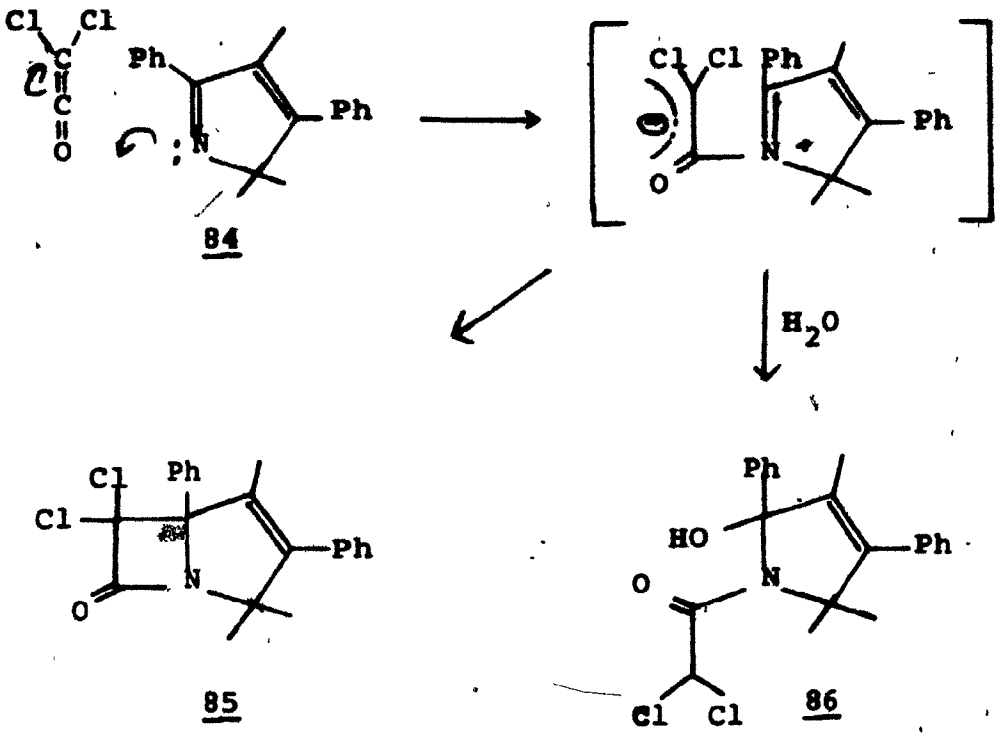


Figure 46

dichloromethyl proton, also a D_2O exchangeable OH proton was observed as a singlet at δ 2.79 ppm. The C-methyl protons were observed at δ 1.75 ppm. The C-dimethyl protons were shifted to lower field compared to 85 and appeared as two singlets at δ 1.29 and δ 1.72 ppm. The aromatic protons were observed as a multiplet at δ 7.14-7.59 ppm. Elemental analysis confirmed the composition of 86. The mass spectrum showed a molecular ion at m/z = 389 of moderate, relative intensity (24%). A possible fragmentation mechanism for 86 is shown in Figure 47.

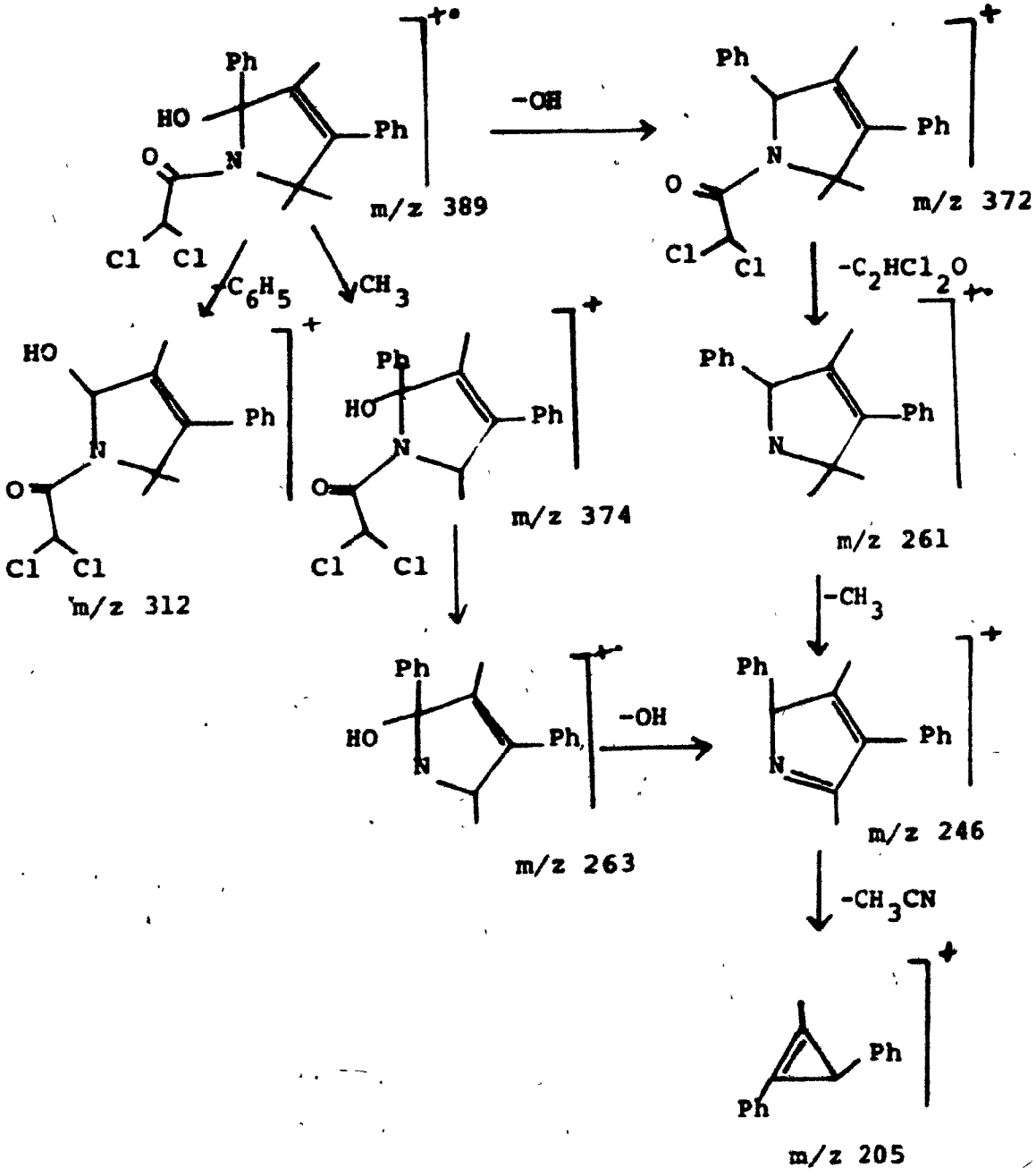

m/z 389
-OH
m/z 372
-C2HCl2O
m/z 261
-CH3
m/z 246
-CH3CN
m/z 205
-C6H5
-CH3
m/z 312
m/z 374
-OH
m/z 263

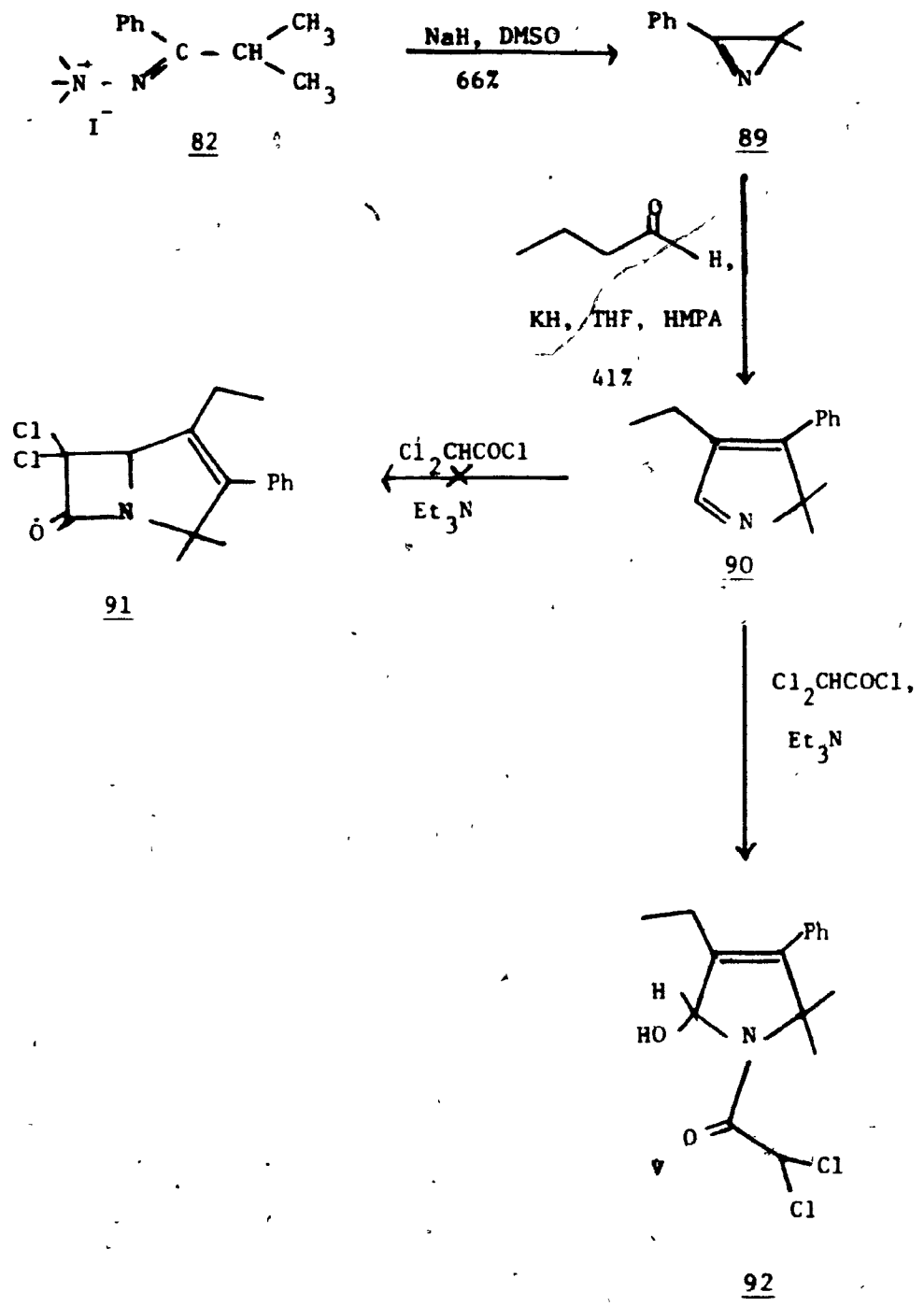
Figure 47

The corresponding azido analog 87 (Scheme VIII) was also prepared under similar conditions. In this case, a lower yield of the β-lactam compound 87 was obtained. The corresponding N-acylated compound 88 was the major product. Difficulty was encountered in the purification of the β-lactam product and perhaps the low yield can be accounted for by its partial decomposition on silica gel. The structures of the products are supported by spectroscopy based on similar properties observed for the dichloro analogs 85 and 86. The ir spectrum of the azido-β-lactam 87 showed a characteristic β-lactam band at 1765 cm^{-1} and $\nu_{N\equiv N}$ at 2100 cm^{-1}. The β-lactam carbonyl band is at lower frequency as compared to the dichloro analog and may be accounted for by the inductive effect of the chlorines. The pattern observed in the ^{1}Hnmr spectrum of the azido analog 87 was similar to that of the dichloro compound 85 except for a slight difference in chemical shift. For example, the gem-dimethyl protons were observed at lower field as two singlets at δ 1.42 and δ 1.55 ppm. The C-methyl proton appeared as a singlet at δ 1.77 ppm. The C-6 methine proton was observed as a singlet at δ 4.87 ppm. Although no molecular ion was observed in the mass spectrum, basically the same fragmentation pattern observed for the dichloro β-lactam 85 was recorded. The fragmentation also follows the same pathway starting by cleavage of azido ketene affording the m/z = 261 peak.

The second product isolated is 2,2,4-trimethyl-3,5-diphenyl-5-hydroxy-1-azidoacetoxypyrrole(88). Elucidation of the structure of 88 was based on the similarity of its ^{1}Hnmr and ir spectra with that of 86. The infrared spectrum showed a ν_{OH} at 3380 cm^{-1}, $\nu_{N\equiv N}$ at 2100 cm^{-1} and ν_{CON} at 1645 cm^{-1}. The ^{1}Hnmr spectrum showed a singlet at δ 1.71 ppm for the C-methyl protons, and two singlets at δ 1.24 and δ 1.71 ppm for the

gem-dimethyl protons. A D_2O exchangeable singlet at δ 2.93 ppm was observed for the hydroxy proton and the azido-methylene protons were observed as an AB quartet centered at δ 3.60 ppm. The aromatic protons appeared as a multiplet at δ 7.07-7.56 ppm.

Attempts to prepare an analogous β-lactam 91 by the reaction of 2,2-dimethyl-4-ethyl-3-phenyl-2H-pyrrole (90) (Scheme IX) with dichloroketene was unsuccessful. The major product of the reaction isolated was 1-dichloroacetoxy-2,2-dimethyl-3-phenyl-4-ethyl-5-hydroxypyrrole (92). The structure of 92 was determined on the basis of its spectroscopic properties. The infrared spectrum showed a broad hydroxyl band at 3390 and an amide band at 1690 cm^{-1}. Proton nmr showed a triplet (J=7.4 Hz) centered at δ 1.27 ppm for the methyl of the ethyl group. The methylene protons of the ethyl group appeared as a quartet centered at δ 2.02 ppm. The hydroxyl proton was observed as a doublet (J=12.2 Hz) which exchanged with D_2O. The adjacent methine proton appeared as a doublet at δ 5.94 ppm which collapsed to a singlet after D_2O exchange of the neighbouring hydroxyl group. The gem-dimethyl protons appeared as two singlets at δ 1.47 and δ 1.59 ppm. The dichloromethine proton was observed at δ 6.77 ppm as a singlet. The aromatic protons appeared as multiplet at δ 7.04-7.46 ppm. The composition of 92 was confirmed by elemental analysis. The mass spectrum did not show any molecular ion, however, the major fragmentation pathway is proposed in Figure 48 to account for the ions observed. The only other material resulting from the reaction of 90 with dichloroketene was a polar product(s) which remained at the origin on thin layer chromatographic plate which could not be eluted even with ethyl acetate. This product is undoubtably not the β-lactam 91 and was not identified. Attempts to change the reaction conditions (longer reaction


Ph
C – CH
CH3
CH3
N – N
I⁻
82
NaH, DMSO
66%
Ph
N
89
O
H,
KH, THF, HMPA
41%
Ph
N
90
Cl2CHCOCl
Et3N
Cl
Cl
Ph
O
N
91
Cl2CHCOCl,
Et3N
Ph
H
HO
N
O
Cl
Cl
92

SCHEME IX

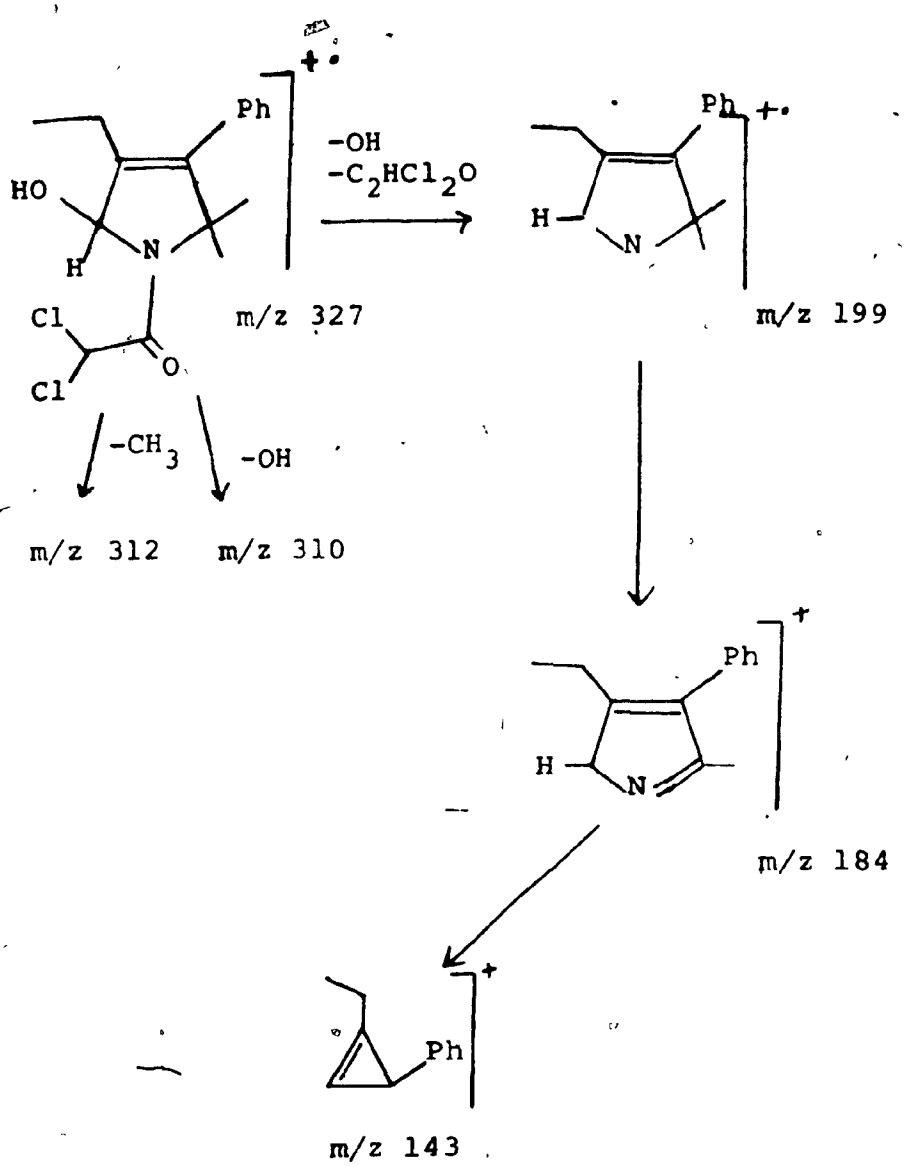


Figure 48

time, higher temp., etc...) to yield the desired β-lactam were unsuccessful. Table IV summarizes the various conditions tried for this reaction. It appears from run no. 1 that short reaction times and the addition of only one equivalent of base and acid chloride favor the formation of the N-acylated product 92.

TABLE IV: Conditions and Results for the Reaction of 2,2-Dimethyl-4-ethyl-3-phenyl-2H-pyrrole (90) with Dichloroacetyl Chloride in the Presence of Triethylamine

RUN No	CONCENTRATION of 90, molar	EQUIVALENTS OF $Cl_2CHCOCl$	EQUIVALENTS OF Et_3N	REACTION TIME, HOURS	TEMP., °C	RESULTS, % OF 92
1	0.15	1	1.2	0.6	-15	52
2	0.19	1.05	1.2	0.5, 8, 48	-15, 25, -20	17
3	0.15	1.3	1.5	0.5, 20	-15, 25	25
4	0.16	1.5	1.8	0.5, 18	-15, 25	29

Since we were unable to prepare the β-lactam 91 under these conditions, an alternative method to generate dichloroketene was investigated. According to work done by Krepski and Hassner[25], dichloroketene can be prepared by reaction of trichloroacetyl chloride and a freshly prepared zinc-copper complex. The ketene is formed from the acid chloride together with zinc chloride as a by-product. A trial run on the 3,5-diphenyl analog 84 was performed in order to establish the conditions required. The β-lactam 85 was obtained with a 34% yield and the structure was confirmed by spectroscopic comparison with previous results. Although no starting material was present in the reaction

mixture as evidenced by tlc (ether), 31% had been recovered after work-up and purification. A possible explanation is that some of the starting material may complex with zinc chloride which may give rise to a spot on the origin on tlc. The intensity of this spot was difficult to assess and, therefore, completion of the reaction was difficult to determine. When 2,2-dimethyl-4-ethyl-3-phenyl-2H-pyrrole (90) (Scheme IX) was reacted with the ketene generated from trichloroacetyl chloride and the zinc-copper complex, no β-lactam 91 was obtained. Instead, the N-acylated-5-hydroxy pyrrole 93 was the only identifiable product. The yield (11%) was low and tlc showed many other components, none of which were identified to be a β-lactam. Evidence of the structure of 93 was based on spectroscopic data and by comparison of these results to those properties of the dichloroanalog 92. Although no molecular ion was observed in the mass spectrum, the fragmentation pattern resembled 92 as shown in Figure 49.

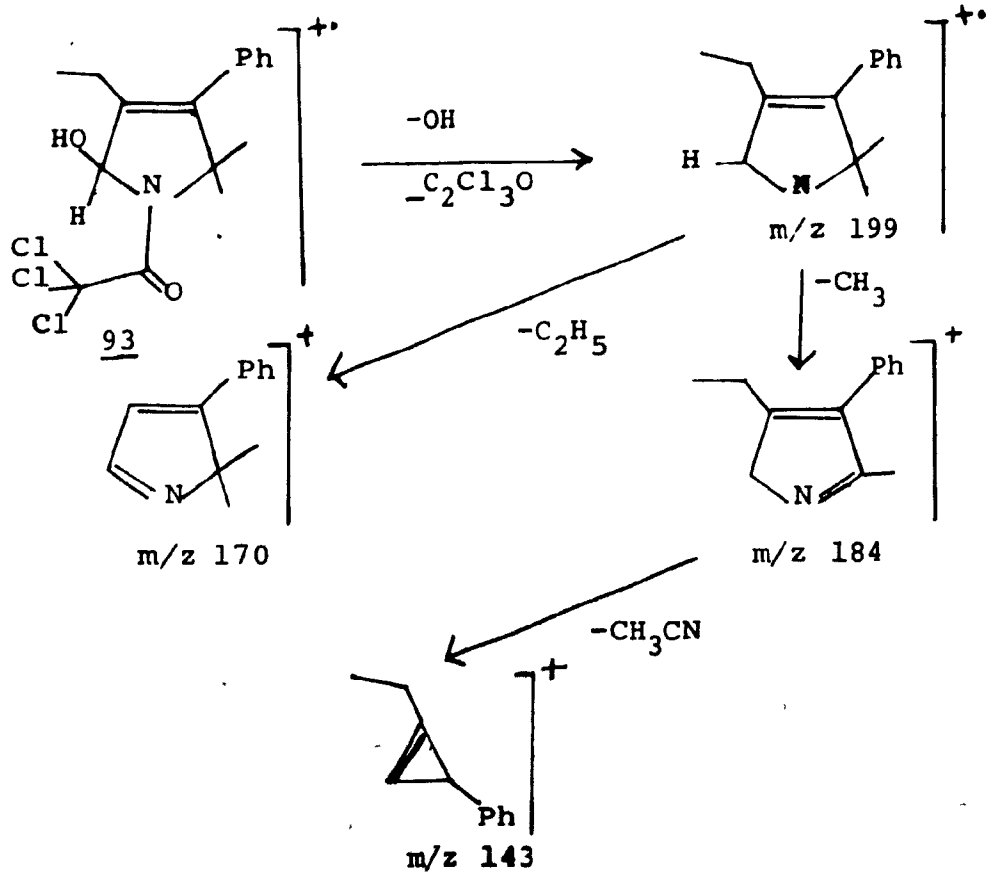


Figure 49

In the infrared spectrum, a band at 1690 cm^{-1} for $\nu_{C=O(amide)}$ and a broad band at 3360 cm^{-1} for ν_{OH} were observed. The ^{1}Hnmr showed two doublets one at δ 3.12 ppm and the other at δ 6.53 ppm which were coupled (J=6.0 Hz) and are attributed to the C-OH and C-H protons, respectively. The C-H proton collapsed to a singlet at δ 6.52 ppm when the C-OH proton peak was exchanged with D_2O. A triplet at δ 0.99 ppm coupled with a quartet centered at δ 2.02 ppm were observed for the ethyl group. The dimethyl group appeared as two singlets at δ 1.47 and δ 1.59 ppm and the phenyl protons were observed as a multiplet from δ 7.08 to 7.47 ppm. It appears that both routes in forming dichloroketene did not favor the formation of the β-lactam 91.

To summarize, we were able to prepare a carbapenem starting from 2,2,4-trimethyl-3,5-diphenylpyrrole (84) by reaction with either azidoketene or dichloroketene generated from the corresponding acid chloride and triethylamine. Also, we were able to prepare the dichloro carbapenem 85 by reaction with dichloroketene which was generated by dehalogenation of trichloroacetyl chloride by a zinc-copper complex. An explanation as to why cyclization only occurred with the diphenyl pyrrole 84 may be due to the electronic effect of the C-5 phenyl group. It is possible that the acylimmonium ion intermediate shown in Figure 50 is stabilized by extended conjugation. Based on studies by Bose and coworkers, Doyle[24] has postulated that the rate of formation of an acylimmonium ion is enhanced when the C-5 position has an aromatic function due to stabilization of the carbonium ion (see Introduction, page 20). Further study in this area is required to offer any definitive explanation.

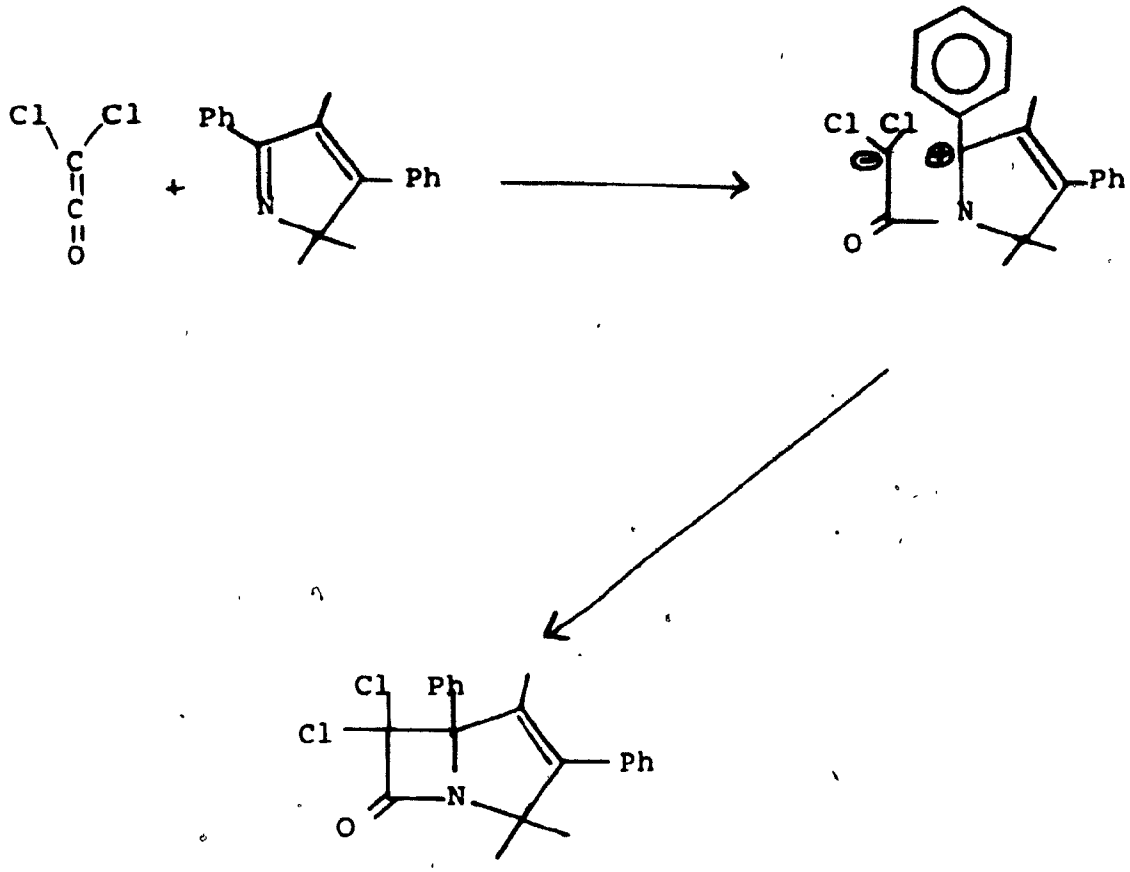


Figure 50

Chapter 3

Experimental Section

The infrared spectra were recorded on a Perkin-Elmer grating spectrophotometer model 267.

The mass spectra were measured on a Dupont 492B spectrometer using a direct insertion probe with an ionization potential of 70 eV unless stated otherwise.

The ultraviolet spectra were recorded on Unicam SP8-100 spectrophotometer.

Melting points were uncorrected and were obtained by an Electrothermal Melting Point Apparatus.

All proton nuclear magnetic resonance spectra were recorded on a 80-MHz Varian CFT-20 NMR Spectrometer. Tetramethylsilane was generally used as either an internal or exernal standard.

Optical rotation measurements were recorded on a Perkin-Elmer 141 Polarimeter at 20°C with a sodium D line using chloroform as the solvent.

Solvents and reagents used were reagent grade and were distilled where mentioned.

Chromatography was performed on Kieselgel 60 (70 - 230 mesh ASTM) and flash chromatography was performed on Kieselgel 60 (230 - 400 mesh ASTM) provided by Merck.

Carbon-13 spectra were recorded on a Bruker WH-90 spectrometer using deutrochloroform as internal reference unless otherwise stated.

Preparation of Proline Benzyl Ester Hydrochloride (49)

To a cooled suspension of S-proline (20g, 17 mmole) in acetylchloride (100 ml) was added phosphorous pentachloride (44 g) at 0° C with vigorous magnetic stirring under nitrogen atmosphere. After one hour, the solution was triturated with cold petroleum ether (37° - 65° C) (100 ml) to yield a precipitate which was collected by filtration and washed with pet. ether. The product was dried under high vaccuum to yield the acid chloride . The acid chloride was dissolved with cooling (0° C) in benzyl alcohol (50 ml) and stirred in the cold for 5 minutes longer. The solution was triturated with ether (50 ml) to give a precipitate which was collected and washed with ether to give 15.6 g (42%) of 49. It had a melting point: 135° - 138° C; $[\alpha]_D^{20}$ (chloroform)= -117.5° (1 g / 100 ml); Anal. calcd. for $C_{12}H_{15}NO_2 \cdot HCl \cdot 1/2\ H_2O$: C 57.48, H 6.63, N 5.59, Cl 14.14; Found : C 58.10, H 6.69, N 5.45, Cl 14.35; $IR_{(chloroform)}$: 1740 cm^{-1}; $NMR_{(chloroform-d)}$ δ: 1.98 - 2.37 (m, 4H, CH_2CH_2), 3.42 - 3.55 (m, 2H, CH-N), 4.41 - 4.66 (m, 1H, C-H), 5.18 (s, 2H, CH_2Ph), 7.32 (s, 5H, ArH).

Preparation of Benzyl N-Acetoacetyl Pyrrolidine-2-Carboxylate (50)[27]

To a suspension of S-proline benzyl ester hydrochloride 49 (15 g, 62 mmole) in absolute ethanol (150 ml) was added sodium ethoxide (4.2 g, 62 mmole) at 0° C with stirring. After 10 minutes, diketene (5.36 g, 64 mmole) was added and the solution stirred at 0° C for 4 hours. The solution was then diluted with ethyl acetate (400 ml) and washed successively with water, 2% HCl, 1% $NaHCO_3$, water and then dried over Na_2SO_4. The solvent was removed in vacuo to give an oil. The product was purified by chromatography on a silica gel column using 7% ethyl acetate - methylene chloride , then 10% ethyl acetate - methylene chloride. The product was crystallized from ethanol-hexane in the cold to

give 6.5 g (36%) of 50. It had a melting point : 68° - 71° C; $[\alpha]_D^{20°c}$ (chloroform) = -70.30° (1g/100 ml); $IR_{(chloroform)}$: 1740, 1640 cm^{-1}; Anal. calcd. for $C_{16}H_{19}NO_4.1/4H_2O$: C 65.40, H 6.69, N 4.76. Found: C 65.15, H 6.66, N 4.40; $NMR_{(DMSO-d_6)}$ δ: 1.80- 2.08 (m, 4H, CH_2CH_2), 2.13 (s, 3H, CH_3), 3.30 - 3.51 (m, 2H, CH_2N), 3.56 (s, 2H, $CH_2C=O$), 4.30 - 4.46 (m, 1H, CH), 5.12 (s, 2H, CH_2Ph), 7.36 (s, 5H, ArH); Mass spectrum m/z: M 289(3%), 155(9), 114(6), 112(9), 108(27), 91(47), 86(4), 85(7), 84(6), 79(22), 77(29), 74(32), 71(25), 70(100), 69(14), 68(27), 65(31), 59(25), 57(21), 51(29), 45(33); Exact mass: Calcd: 289.1314; Found: 289.1236.

Preparation of Benzyl N-(3'-oxo-2'-diazo-butanoyl)-pyrrolidine-2-carboxylate (51)[28]

To a solution of the compound 50 (2.0 g, 6.9 mmole) in dry acetonitrile (20 ml) was added triethylamine (720 mg, 7.2 mmole) and tosylazide (1.4 g, 6.6 mmole) at room temperature. The solution was stirred for 24 hours (overnight). The volatiles were removed in vacuo giving an oil which was dissolved in methylene chloride (50 ml) and washed with 0.005 M KOH (16 ml), then brine. The organic solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give an oil. The product was purified by flash chromatography on silica gel (mesh 230-400) using ether as the eluent giving 1.92 (87%) of the azido product 51. $NMR_{(chloroform-d)}$ δ: 1.99 - 2.32 (m, 4H, CH_2CH_2), 2.34 (s, 3H, CH_3), 3.48 - 3.64 (m, 2H, CH_2-N), 4.60- 4.62 (m, 1H, CH), 5.17 (d, 2H, CH_2Ph), 7.33 (s, 5H, ArH); $IR_{(chloroform)}$: 2100, 1740, 1640 cm^{-1}.

General Procedure for the Attempted Cyclization of the Diazo Compound 51 with Rhodium (II) Acetate

A solution of the diazo compound in benzene (10 mg/ml) is deoxygenated by bubbling nitrogen through the solution for fifteen

under reflux. After a period of time, the solution is then filtered and the solvent is removed in vacuo. The product is then analyzed in the usual way (IR, NMR, MS, elemental analysis, melting point).

Preparation of the Enol Silyl Ether of Compound 52.

To a solution of the azido compound 51 (300 mg, .95 mmole) in dry CH_2Cl_2 (2 ml) was added triethylamine (103 mg, 1.0 mmole) at 0° C under nitrogen atmosphere followed by tert-butyldimethylsilyl triflate (251 mg, .95 mmole). After 1.5 hours, the solution was neutralized with triethylamine (0.1 ml) and then diluted with CH_2Cl_2 (10 ml) and washed successively with water and then brine. The solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give 252 mg (64%) of the enol silyl ether of 52 as a liquid. The spectral data for 52 are: $IR_{(chloroform)}$: 2080, 1740, 1630 cm^{-1}; $NMR_{(chloroform-d)}$ δ: 0.0 (d, 6H, $SiMe_2$), 0.9 (d, 9H, tert-butyl), 1.7 - 2.22 (m, 4H, $-CH_2CH_2-$), 3.2 - 3.7 (m, 2H, CH_2N), 4.3 - 4.7 (m, 1H, CH), 4.5 (dd, 2H, $CH_2=C$), 5.10(s, 2H, CH_2Ph), 7.3 (s, 5H, ArH).

Preparation of Benzyl N-dichloroacetylpyrrolidine-2-carboxylate (57a) and Benzyl N-dichloroacetyl-Δ^2-pyrrole (57b)[33]

To a suspension of S-proline benzyl ester hydrochloride 49 (500 mg, 2.07 mmole) in ether (5 ml) was added anhydrous sodium carbonate (219 mg, 2.07 mmole) to generate the free base in situ. The solution was cooled to 0° C and a solution of tert-butyl hypochloride[40] (225 mg, 2.07 mmole) in dry ether (5 ml) was added dropwise over a period of 5 minutes. After stirring for 30 minutes longer, the mixture was cooled to -15° C and DBU (315 mg, 2.07 mmole)[a] was added followed by triethylamine (251 mg, 2.48 mmole). A solution of dichloroacetyl chloride (320 mg, 2.17 mmole) in methylene chloride (2 ml) was added dropwise over a period of 20 minutes

at -15°C. The solution was stirred for 45 minutes longer at this temperature. The mixture was diluted with ether and washed with pH 7 phosphate buffer (0.2M solution) (3 x 50 ml). The solution was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a pale yellow syrup. The product was purified by flash chromatography on silica gel (mesh 230-400) using methylene chloride as the eluent to afford 274 mg (42%) of 57a. The product crystallized on standing at room temperature. It had a melting point: 67-69°C; $IR_{(chloroform)}$: 1740, 1670 cm^{-1}; $NMR_{(chloroform-d)}$ δ:2.04 - 2.30 (m, 4H, CH_2CH_2), 3.74 - 3.91 (m, 2H, CH_2-N), 4.54 - 4.67 (m, 1H, CH-N), 5.17 (s, 2H, CH_2Ph), 6.12 (s, 1H, $CHCl_2$), 7.34 (s, 5H, ArH); Anal. Calcd. for $C_{14}H_{15}Cl_2NO_3$: C 53.18, H 4.78, N 4.43, Cl 22.43; Found: C 52.75, H 4.83, N 4.43, Cl 22.91; Mass spectrum m/z: M 315(2%), 182(46), 180(85), 108(74), 107(55), 100(38), 91(84), 86(68), 85(13), 84(97), 83(32), 79(80), 77(39), 72(40), 71(10), 70(75), 69(11), 58(13), 57(26), 55(11), 52(14), 51(100), 50(62), 49(98), 48(34).

[a] In a similar reaction using diisopropylethylamine as the base to generate the imine, the Δ^2-compound 57b was obtained in 22% yield. The spectral data for 57b are: $IR_{(chloroform)}$: 1730, 1665 cm^{-1}; $NMR_{(chloroform-d)}$ δ: 2.75 (dt, 2H, H-4 $J_{3,4}$=3.1 Hz, $J_{4,5}$=8.4 Hz), 4.23 (t, 2H, H-5, $J_{4,5}$=8.4 Hz), 5.28 (s, 2H, C-CH_2), 6.24 (t, 1H, H-3, $J_{3,4}$=3.1 Hz), 6.34 (s, 1H, $CHCl_2$), 7.37 (s, 5H, ArH); Anal. calcd. for $C_{14}H_{13}Cl_2NO_3$: C 53.52, H 4.17, N 4.46, Cl 22.57. Found: C 52.70, H 4.22, N 4.35, Cl 22.78; Mass spectrum m/z: M 313(1%), 184(22), 182(61), 181(20), 180(78), 131(25), 109(51), 108(47), 105(11), 103(13), 100(25), 92(25), 91(100), 85(14), 84(13), 83(40), 79(46), 77(26), 72(33), 71(12), 70(75), 69(27), 65(31), 58(28), 57(15), 55(10), 51(28), 50(10), 49(10), 48(10), 44(65), 41(50).

Preparation of Ethyl Pyrrole-2-carboxylate (61).[37]

A solution of pyrrole-2-carboxylic acid (10 g, 9 mmole), oxalyl chloride (50 ml) and dimethylformamide (5 drops) was stirred at 0° C for 4 hours and then at room temperature for 1 hour longer. The volatiles were removed under reduced pressure to give the acid chloride which was subsequently dissolved in a mixture of absolute ethanol (10 ml), pyridine (20 ml) and methylene chloride (20 ml) at 0° C. After stirring for 15 minutes at this temperature, the volatiles were removed in vacuo and the residue was dissolved in ethyl acetate (100 ml). The solution was washed successively with brine, sat^{d}. sodium bicarbonate sol^{n}, brine, 5% hydrochloric acid and finally with brine. The solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product was purified by flash chromatography on silica gel (mesh 230-400) using methylene chloride as the eluent. Fractions containing the product were combined and the solvent was removed under reduced pressure to give a dark syrup which was distilled at 110° C at 0.1mm Hg to give a colorless liquid which crystallized on standing at room temperature to give 10.6 g (85%) of 61 with spectral data: $NMR_{(chloroform-d)}$ δ: 1.35 (t, 3H, CH_3, J = 7.1), 4.32 (q, 2H, CH_2, J = 7.1 Hz), 6.26 (m, 1H, H-5), 6.92 (m, 2H, H-4 and H-3); $IR_{(chloroform)}$: 1670 cm^{-1}.

Preparation of 1-Diisopropylamino-2,2-dichloro-3-oxo-pyrrolo-{1,2-a}-pyrrole (74).

To a solution of pyrrole-2-carboxaldehyde (2.0 g, 21 mmole) in dry THF (10 ml) was added lithium diisopropylamide (1.5 equivalents) (prepared from diisopropylamine (3.19 g, 31.5 mmole) and n-butyllithium (1.55M in hexane) (2.02 g, 31.5 mmole) at -20° C. After 30 minutes, the solution was cooled to -78° C and trimethylsilylchloride (3.42 g, 31.5 mmole) was

added and continued to stir for 30 minutes. The solution was concentrated at 0° C under high vacuum and the residue was diluted with anhydrous ether (60 ml) to precipitate diisopropylamine hydrochloride which was removed by filtration through a celite pad under nitrogen. The filtrate was concentrated under high vaccuum at 0° C to approximately 5 ml. The dark residue was dissolved in methylene chloride (10 ml) and cooled to -15° C. Triethylamine (2.76 g, 27.3 mmole) was added followed by a dropwise addition of a solution of dichloroacetyl chloride (3.71 g, 25.2 mmole) in methylene chloride (20 ml). The addition took 2 hours and the solution continued to stir at -15° C for 30 minutes longer. The solution was diluted with methylene chloride and washed successively with brine, 5% hydrochloric acid, brine, saturated sodium bicarbonate solution and brine.[b] The solution was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The product was purified by chromatography on a silica gel column (mesh 70-230) using 5% ethyl acetate-hexane as the eluent to yield 140 mg (2.3%)[c] of 74 as a liquid. The spectral data for 74 are: $NMR_{(chloroform-d)}$ δ: 1.12 (m, 12H, $CH(CH_3)_2$), 3.02 (m, 2H, $C\underline{H}Me_2$), 4.98 (d, 1H, H-1, J = 1.1 Hz), 6.15 (dd, 1H, H-7, J = 1.1, J = 3.2 Hz), 6.58 (t, 1H, H-6, J = 3.2 Hz), 7.15 (d, 1H, H-5, J = 3.2 Hz); $IR_{(neat)}$: 1770 cm^{-1}; Mass spectrum m/z :(M+4) 292(2%), (M+2) 290(8%), M288(33%), 256(6), 254(25), 245(33), 247(9), 211(33), 205(13), 203(25), 190(22), 188(31), 169(35), 156(22), 155(20), 154(34), 153(42), 121(12), 120(10), 119(38), 118(27), 95(11), 94(33), 91(27), 86(45), 85(11), 84(44), 83(10), 71(24), 70(12), 69(22), 64(22), 63(10), 57(26), 55(23).[b] In a similar reaction, initial precipitation of diisopropylamine hydrochloride by dilution of the crude reaction mixture with ether and subsequent filtration and purification of an aliquot by flash chromatography afforded

1-dichloroacetoxy-2,2-dichloro-3-oxo-pyrrolo{1,2-a} pyrrole 67 in 3.2% yield.

[c] NMR of the crude reaction mixture after work-up indicated that compound 74 had been the major product and decomposition presumably occurred on the silica gel column during the purification process.

Preparation of 1-Dichloroacetoxy-2,2-dichloro-3-oxo-pyrrolo{1,2-a}pyrrole (67)[38, 39]

To a solution of pyrrole-2-carboxaldehyde (5.0 g, 52.6 mmole) and p-dimethylaminopyridine (640 g, 5.3 mmole) in methylene chloride (50 ml) was added triethylamine (11.56 g, 114.3 mmole) at room temperature and over nitrogen atmosphere. The solution of freshly distilled dichloroacetyl chloride (15.50 g, 105.2 mmole) in dry methylene chloride (125 ml) was added dropwise over a period of 5.5 hours. The solution was stirred for 30 minutes longer. The solution was diluted with ether and filtered to remove triethylamine hydrochloride. The filtrate was concentrated in vacuo and again triturated with ether and filtered. The filtrate was washed successively with brine, 5% hydrochloric acid, brine, saturated sodium bicarbonate solution and finally with brine. The solution was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The product was purified by flash chromatography on silica gel (mesh 230-400) using a mixture of methylene chloride-hexane (1:1) as the eluent to give 8.67 g (52%) of 67. The product was crystallized from ether-hexane. It had a melting point : 80 - 81° C; Anal. calcd. for $C_9H_5NCl_4O_3$: C 34.10, H 1.59, N 4.42, Cl 44.74. Found : C 34.19, H 1.65, N 4.42, Cl 44.23; $IR_{(KBr)}$: 1770, 1750 cm^{-1}; $UV_{(EtOH)}$: 210 nm, ε = 5634. $NMR_{(chloroform-d)}$ δ: 6.02 (s, 1H, $CHCl_2$), 6.40 (d, 1H, H-5, J = 3.2 Hz), 6.42 (bs, 1H, H-1), 6.67 (t, 1H, H-6, J = 3.2), 7.22

(dd, 1H, H-7, J = 3.2 Hz, J = 0.7 Hz); Mass spectrum m/z: 318(5%), 316(22), (M-H) 314(9), 280(39), 278(17), 190(33), 188(33), 155(26), 153(90), 125(34), 99(41), 94(27), 90(45), 85(37), 83(40), 64(12), 63(52), 62(68).

Reaction of Ethyl Pyrrole-2-carboxylate with an Acid Chloride in the Presence of a Base.

To a solution of ethyl pyrrole-2-carboxylate in THF (2 ml/mmole) at -78° C under nitrogen atmosphere was added the base[d] (1.05 to 1.10 equivalents). After 10 to 15 minutes, trimethylsilyl chloride (1.05 equivalents) was added and the solution was stirred for 30 minutes at -78° C. The solution was then warmed to -15° C and triethylamine (1.05 equivalents) was added, followed by a dropwise addition of a solution of the acid chloride (1.05 equivalents) in methylene chloride (100 mg/ml). After all the acid chloride was added, the solution was stirred at -15° C for 1 hour longer. The solution was then washed successively with brine, 5% hydrochloric acid, brine, saturated sodium bicarbonate solution and brine. The solution was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The product was purified by flash chromatography.

[d] Some of the bases tried were BuLi, LDA, KH, HMDSi, DMAP.

Preparation of 1- Dichloroacetoxy-2,2-dichloro-3-oxo-pyrrolo[1,2-a]pyrrole (67) using Dibutylboron Triflate.

To a suspension of potassium hydride (232 mg, 5.78 mmole) in dry THF (5 ml) over nitrogen atmosphere was added pyrrole-2-carboxaldehyde (500 mg, 5.26 mmole) in dry THF (5 ml) at room temperature. After 30 minutes, the white reaction mixture was cooled to -78° C and a solution of dibutylboron triflate[41] (1.513 g, 5.52 mmole) in THF (3 ml) was added to give a mustard yellow heavy suspension which was agitated at -78° C for 30

minutes. The reaction mixture was then warmed to -15° C to which was added dichloroacetyl chloride (814 mg, 5.52 mmole) in dry methylene chloride (5 ml) dropwise over a period of 45 minutes. The solution was stirred at -15° C for 30 minutes longer. The solution was cautiously poured into a stirring bath of saturated ammonium chloride solution and then extracted with methylene chloride (3 X 100 ml). The extracts were combined and washed successively with brine, 5% hydrochloric acid, brine, saturated sodium bicarbonate solution and finally with brine. The solution was dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The product was purified by flash chromatography using methylene chloride as the eluent to give 68 mg (4.1%) of 67 with a nmr and ir identical to the product obtained in a previous preparation using TMSCl as the enol trapping group.

Preparation of Dibutylboron Triflate[41]

In a flame dried flask over nitrogen atmosphere was placed tributylborane (4.55 g, 25 mmole) and trifluoromethanesulfonic acid (3.75 g, 25 mmole). The reaction was exothermic. The syrupy solution was stirred at room temperature for 3.5 hours. The product was purified by distillation at 42° C at 0.2 mm Hg to give 5.2 g (76%) of dibutylboron triflate.

Preparation of 1-Azidoacetoxy-2-azido-3-oxo-pyrrolo{1,2-a} pyrrole (75)

To a solution of pyrrole-2-carboxaldehyde (500 mg, 5.26 mmole) in freshly distilled THF (10 ml) under nitrogen was added a suspension of KH (232 mg, 5.78 mmole) (22.5% oil dispersion previously washed with hexane) in hexane (3 ml) at room temperature. After 15 minutes, the solution was cooled to -78° C and trimethylsilyl chloride (635 mg, 5.84 mmole) was added and the mixture was stirred for 30 minutes. The mixture was warmed

to -15° C and triethylamine (1.27 g, 12.6 mmole) was added followed by a dropwise additon of a solution of azidoacetyl chloride (1.38 g, 11.6 mmole) in methylene chloride (25 ml) over a period of 2 hours. The solution was stirred at -15° C for 1.5 hours longer. The resulting dark solution was cautiously poured into a stirring bath of saturated ammonium chloride solution. The organic phase was separated and diluted with ether to precipitate triethylamine hydrochloride. The mixture was filtered and the filtrate was washed successively with 5% hydrochloric acid, brine, saturated sodium bicarbonate solution and then brine. The solution was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product was purified by flash chromatography using methylene chloride as the eluent to yield 18 mg (3%) of 75, 157 mg (17%) of 76 and 194 mg (39%) of the starting material. The spectral data for compound 75 are: $NMR_{(chloroform-d)}$ δ: 3.96 (s, 2H, CH_2), 4.74 (d, 1H, CHN_3, J = 2.6 Hz), 5.80 (d, 1H, $\underline{CH}CO_2R$, J = 2.6 Hz), 6.35 (unresolved d, 1H, H-5, J = 3.2 Hz), 6.58 (t, 1H, H-6, J = 3.2 Hz), 7.14 (d, 1H, H-7, J = 3.1 Hz); $IR_{(neat)}$: 2105, 1760 cm^{-1}; Mass spectrum m/z: 150(17%), 149(84), 134(35), 120(26), 119(46), 106(26), 105(34), 104(18), 95(43), 94(36), 93(20), 92(29), 91(18), 83(20), 79(19), 77(18), 71(22), 69(13), 66(33), 65(21), 64(31), 57(32), 56(28), 55(27), 52(29), 51(17), 44(45) 43(56). Spectral data for 76 are: $NMR_{(chloroform-d)}$ δ: 4.59 (s, 2H, CH_2), 6.43 (t, 1H, H-4, J = 3.3 Hz), 7.25 (dd, 1H, H-5, J=3.3, J = 1.6 Hz), 7.44 (dd, 1H, H-3, J = 3.3, J = 1.6 Hz), 10.05 (s, 1H, CHO); $IR_{(neat)}$: 2100, 1720, 1660 cm^{-1}; Mass spectrum m/z : 96(18%), 95(97), 94(83), 67(27), 66(64), 44(43), 41(23), 40(25), 39(52), 38(16), 37(14), 29(14), 28(100).

Preparation of Azidoacetyl Chloride

A mixture of azidoacetic acid (10 g, 0.1 mmole) and thionyl chloride (0.2 mmole) was heated under reflux in a water bath at 60° C. After 2 hours, HCl gas evolution ceased and the excess thionyl chloride was removed by distillation. The product was distilled at 54 - 55° C at 25 mm Hg to give azidoacetyl chloride, 6.07 g (51%), as a colorless liquid with the following spectral data: $IR_{(neat)}$: 2090, 1780 cm^{-1}.

Reaction of 1-Dichloroacetoxy-2,2-dichloro-3-oxo-pyrrolo{1,2-a}pyrrole (67) with Benzylamine.

To a solution of 67 (500 mg, 1.59 mmole) in dry THF (5 ml) was added benzyl amine (340 mg, 3.17 mmole) at room temperature. The solution was stirred for 24 hours (overnight) and then was diluted with methylene chloride and washed with brine. The solution was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give a dark syrup. The product was purified by flash chromatography using mixtures of ethyl acetate-methylene chloride (1%, 2% and 5% respectively) as the eluent to afford 409 mg (81%) of compound 71 which was crystallized from ether-pet. ether to give an unstable off-white crystalline product. The spectral data for 71 are: $NMR_{(chloroform-d)}$ δ: 3.90(bs, 1H, CHOH), 4.50 (d, 2H, CH_2Ph, J = 5.8 Hz), 5.54 (s, 1H, CHOH), 6.19 (m, 1H, H-4), 6.27 (m, 1H, H-3), 6.77 (m, 1H, H-5), 7.27 (m, 5H, ArH); $IR_{(neat)}$: 3400, 1670 cm^{-1}; Mass spectrum m/z : 314(15), 312(19), 199(19), 184(26), 143(23), 86(16), 71(59), 70(20), 69(23), 57(100), 56(45), 55(21).

Preparation of 1,2-Dihydro-3-oxo-pyrrolo{1,2-a}pyrrole (72).

A mixture of 67 (1.5 g, 4.7 mmole) and zinc dust (1.57 g, 24 mmole) in acetic acid (40 ml) was stirred at 0° C for 1 hour. The mixture was diluted with methylene chloride and filtered. The filtrate was washed

successively with water, saturated bicarbonate solution and water. The solution was dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The product was purified by flash chromatography on silica gel (mesh 230-400) first eluting with methylene chloride, then with 5% ethyl acetate-methylene chloride to give 380 mg (66%) of 72. It had a melting point : 70 - 72° C; $NMR_{(chloroform-d)}$ δ: 3.02 (s, 4H, CH_2CH_2), 5.95 (d, 1H, H-5, J = 3 Hz), 6.45 (t, 1H, H-6, J = 3 Hz), 7.06 (d, 1H, H-7, J = 3 Hz); $^{13}Cnmr_{(chloroform-d)}$ (coupled) δ: 172.0 (s, C-3), 139.6 (s, C-8), 119.0 (d, C-6, ^1J = 171.2 Hz), 111.0 (d, C-5, ^1J = 190.3 Hz), 104.5 (d, C-7, ^1J = 170.1 Hz), 34.8 (t, C-1, ^1J = 134.1 Hz), 19.3 (t, C-2, ^1J = 136.7 Hz); $UV_{(EtOH)}$: 230 nm, ε = 9200; Mass spectrum m/z : M 121 (100%), 93(50), 92(40), 80(63), 79(19), 67(50), 66(40), 65(52), 64(27), 63(24), 62(14), 53(25), 52(37), 51(26). $IR_{(KBr)}$: 1720 cm^{-1}; Exact mass: Calcd: 121.0527; Found: 121.0539.

Reaction of 1,2-Dihydro-3-oxo-pyrrolo[1,2-a]pyrrole (72) with Benzylamine.

To a solution of 72 (145 mg, 1.2 mmole) in dry THF (2 ml) was added benzylamine (257 mg, 2.4 mmole) at room temperature with stirring. After 24 hours (overnight), the solution was diluted with methylene chloride, washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the product was purified by flash chromatography on silica gel (mesh 230-400) using 10% ethyl acetate-methylene chloride as the eluent to give 208 mg (76%) of 73 as a white solid. The product was recrystallized from methylene chloride-pet. ether. It had a melting point : 99 - 100°C; $NMR_{(chloroform-d)}$ δ: 1.61 (br, 1H, NH), 2.52, (m, 2H, CH_2C), 2.85 (m, 2H, CH_2CO), 4.4 (d, 2H, CH_2Ph, J = 4.4 Hz), 5.90 (bs, 1H, H-4), 6.07 (bs, 1H, H-3), 6.64 (bs, 1H, H-5), 7.76 (m, 5H, ArH); $IR_{(KBr)}$: 1615 cm^{-1}; $UV_{(EtOH)}$: $\lambda_{max=203nm}$, ε = 29678;

Mass Spectrum m/z : M 288(100%), 148(13), 121(63), 120(26), 107(22), 106(47), 105(10), 104(9), 95(39), 94(89), 93(63), 92(33), 91(64), 81(25), 80(87), 77(32), 67(31), 65(37), 53(39), 51(20), 41(21), 39(28); Exact mass: Cal^{c}d: 228.1262; Found: 228.1189.

Reaction of Pyrrole-2-carboxaldehyde with Thiophenol in the Presence of Trimethylsilylchloride[43]

To a solution of pyrrole-2-carboxaldehyde (1.0 g, 10.5 mmole) in dry methylene chloride was added thiophenol (2.32 g, 21 mmole) at room temperature and over nitrogen atmosphere. A solution of trimethylsilyl chloride (1.63 g, 15 mmole) in dry methylene chloride (3 ml) was added dropwise over a period of 15 minutes to give a dark solution. After 1 hour, the reaction mixture was washed with 5% sodium bicarbonate solution, saturated carbonate solution and brine. The solution was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The product was purified by flash chromatography using methylene chloride as the eluent. The resulting product was a tar-like syrup and this reaction failed to give the desired pyrrole-2-carboxaldehyde thioacetal.

Reaction of Pyrrole-2-carboxaldehyde with Thiophenol in the Presence of Titanium Tetrachloride[44]

A solution of pyrrole-2-carboxaldehyde (1.0g, 10.5 mmole) and thiophenol (2.89 g, 26.25 mmole) in chloroform (5 ml) was cooled to -20° C. Titanium tetrachloride (0.25 g, 1.3 mmole) was added to the above stirring solution over nitrogen atmosphere. The solution gradually warmed to room temperature. After 1 hour, water (5 ml) was added. The dark solution was extracted with chloroform and the insoluable material present in the extract was removed by filtration. The solution was dried over sodium sulfate and the solvent was removed under reduced pressure. The black syrup was purified by flash chromatography on silica gel (mesh

230-400) using 50% methylene chloride-hexane as the eluent. The resulting product was a tar-like syrup and failed to afford the desired thioacetal.

Preparation of Isobutyrophenone Dimethylhydrazone Methyliodide (82) Directly from Isobutyrophenone[47] (Method A).

A mixture of isobutyrophenone (7.51 g, 90 mmole), sodium acetate (820 mg, 10 mmole), acetic acid (2 drops) and dimethylhydrazine (7.51 g, 125 mmole) was heated in a sealed 45 ml Paar pressure bomb at 120° C for 16 hours. The resulting two phase system was separated and the aqueous phase was extracted with ether and combined with the organic phase which was subsequently washed with water, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the product was purified by distillation at 48° C at 0.5 mm Hg to afford 11.25 g of a mixture of starting material and isobutyrophenone dimethylhydrazone. The reaction was approximately 20% complete as evidenced by NMR. The product was used as such in the quaternization step.

All of the above product (81) was dissolved in absolute ethanol (10 ml) and methyl iodide (31.8 g, 2.24 mmole) was added. The solution was heated under reflux for 2 hours. The solvent was removed by distillation under reduced pressure and the product crystallized from ethanol-ether to give 1.34 g, (a second crop afforded 1.15 g) of the title compound 82 (8.3% yield based on isobutyrophenone). The spectral data obtained is: $NMR_{(D_2O)}$ δ: 1.10 (d, 6H, $CH(CH_3)_2$, J = 6.8 Hz), 2.89 (septet, 1H, CH, J = 6.8 Hz), 3.27 (s, 9H, $N(CH_3)_3$), 7.39 - 7.62 (m, 5H, ArH). For complete characterization of this compound, see later paragraphs.

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yellow syrup. The product was purified by distillation at 54° C at 0.1 mm Hg to give 15.5 g (96%) of isobutyrophenone dimethylhydrazone (81). The spectral data for 81 is: NMR$_{(chloroform-d)}$ δ: 1.14 (d, 6H, CH($\underline{CH_3}$)$_2$, J = 7.1 Hz), 2.54 (d, 6H, N(CH_3)$_2$), 3.86 (septet, 1H, CH, J = 7.1 Hz), 7.33 (s, 5H, ArH).

Preparation of Isobutyrophenone Dimethylhydrazone Methiodide (82)

A soltuion of isobutyrophenone dimethylhydrazone (6.85 g, 36 mmole) was heated in the presence of acetic acid (1 drop) and anhydrous sodium acetate (10 mg) in an oil bath at 100° C over nitrogen atmosphere for 3 hours. Once cooled, anhydrous ether (10 ml) was added followed by methyl iodide (20.44 g, 144 mmole). The mixture was heated under reflux and over nitrogen atmosphere. After 1 hour of heating the product began to crystallize and heating continued for 2 hours longer. The solution was cooled and the product was collected by filtration. The product was dried under high vaccuum to give 9.24 g (77.5%) of isobutyrophenone dimethylhydrazone methyliodide (82). NMR$_{(D_2O)}$ δ: 1.10 (d, 6H, CH($\underline{CH_3}$)$_2$, J = 6.8 Hz), 2.90 (septet, 1H, CH, J = 6.8 Hz), 3.27 (s, 9H, N(CH_3)$_3$), 7.39 - 7.64 (m, 5H, ArH).

Preparation of 2,2-Dimethyl-3-phenylazirine (89)[49]

To a suspension of sodium hydride (160 mg, 6.7 mmole) (50% oil dispersion previously washed with pet. ether (3 X 10 ml)) in dry DMSO (7 ml) at room temperature and over nitrogen atmosphere was added a solution of isobutyrophenone dimethylhydrazone methyliodide (2.222 g, 6.7 mmole) in dry DMSO (7 ml). After 3 hours, the reaction mixture was poured over crushed ice (10 g) and extracted with pet. ether (4 X 25 ml). The extracts were combined and washed with water (50 ml), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product

was purified by distillation at 55° C at 0.1 mm Hg giving 690 mg (66%) of 2,2-dimethyl-3-phenylazirine as a colorless liquid. The spectral data for 89 are: NMR (chloroform-d) δ : 1.42 (s, 6H, $C(CH_3)_2$), 7.49 - 7.87 (m, 5H, ArH); IR (neat) : 1720 cm^{-1}; Mass spectrum m/z : M 145 (77%), 144(88), 117(48), 115(21), 105(68), 104(91), 103(50), 77(99), 76(34).

Preparation of 2,2-Dimethyl-4-ethyl-3-phenyl-2H-pyrrole(90)[50]

In a dry 2-necked flask purged with nitrogen was placed potassium hydride (195 mg, 4.87 mmole) (22.5% oil dispersion previously washed with pet. ether (3 X 5 ml)) and freshly distilled dry THF (5 ml). The mixture was cooled to 0° C and distilled butyraldehyde (193 mg, 2.68 mmole) in dry THF (0.5 ml) was added dropwise over a period of 10 minutes. The solution was warmed to room temperature and carbanion formation took 1.5 hours monitored by the evolution of hydrogen. The solution was cooled to 0° C and HMPA (872 mg, 4.87 mmole) was added followed by a dropwise additon of 2,2-dimethyl-3-phenylazirine (390 mg, 2.68 mmole) in dry THF (1.5 ml) over a period of 30 minutes. The solution was warmed to room temperature and was stirred for 40 hours. The reaction mixture was poured into ice-water (20 ml) and extracted with ether (4 X 50 ml). The extracts were combined and dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product was purified by flash chromatography on silica gel (mesh 230-400) first eluting with methylene chloride, then ether to afford 184 mg (34.5%) of 2,2-dimethyl-4-ethyl-3-phenyl-2H-pyrrole as a liquid having an NMR (chloroform-d) δ : 1.07 (t, 3H, CH_2CH_3, J = 7.5 Hz), 1.32 (s, 6H, $C(CH_3)_2$), 2.22 (q, 2H, CH_2, J = 7.5 Hz), 7.04 - 7.42 (m, 5H, ArH), 8.02 (s, 1H, H-2); IR (neat) : 2850, 1600, 1535, 1490, 1460, 1360 cm^{-1}; Mass spectrum m/z : M 199(100%), 198(31), 185(23), 184(84), 171(27), 170(41), 144(34), 143(69), 142(21), 141(24), 129(42), 128(46), 127(11),

115(43), 105(22), 103(26), 91(24), 85(11), 77(31), 73(27), 71(12), 69(79), 57(31), 56(57), 55(43), 51(22).

Preparation of 2,2,4-Trimethyl-3,5-diphenyl-2H-pyrrole (84)[49]

To a suspension of sodium hydride (101 mg, 4.22 mmole) (50% oil dispersion previously washed with pet. ether) in dry DMSO (4 ml) over nitrogen atmosphere was added a solution of propiophenone (566 mg, 4.22 mmole) in dry DMSO (2 ml). The carbanion formation took 45 minutes. Then, a solution of isobutyrophenone dimethylhydrazone methyliodide (684 mg, 2.06 mmole) in dry DMSO (4 ml) was added dropwise over a period of 1 hour. The solution continued to stir for 48 hours at room temperature and over nitrogen. The mixture was poured into ice-water (20 ml) and extracted with ether (5 X 30 ml). The extracts were combined and washed with brine (3 X 40 ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified by flash chromatography on a silica gel column using ether-pet. ether (1:1) as the eluent. Fractions containing the product were combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a syrup which crystallized from pet. ether to afford 220 mg, and a second crop gave 41 mg (48.5%). It had a melting point: 58-60° C (lit. 59-61° C); $NMR_{(chloroform)}$ δ: 1.49 (s, 6H, $C(CH_3)_2$), 1.98 (s, 3H, $C-CH_3$), 7.13-7.87 (m, 10H, ArH); $IR_{(neat)}$: 1640, 1600, 1565, 1540, 1345 cm^{-1}; Mass spectrum m/z : M 261(100%), 260(70), 246(93), 219(39), 206(24), 205(60), 204(42), 203(22), 202(20), 184(19), 145(39), 143(20), 128(35), 116(11), 115(29), 104(51), 103(33), 102(11), 77(23), 51(18).

Reaction of 2,2,4-Trimethyl-3,5-diphenyl-2H-pyrrole (84) with Dichloroacetyl Chloride in the Presence of Triethylamine.

To a solution of 2,2,4-trimethyl-3,5-diphenyl-2H-pyrrole (92 mg, 0.35 mmole) in CH_2Cl_2 (1 ml) cooled to -15°C and over nitrogen atmosphere was added dry Et_3N (42 mg, 0.42 mmole). A solution of dichloroacetyl chloride (54 mg, 0.37 mmole) in CH_2Cl_2 (1 ml) was added dropwise over a period of 10 minutes. After 30 minutes, the solution was diluted with ether and the $Et_3N \cdot HCl$ precipitate was removed by filtration. The filtrate was washed successively with water (3 X 20 ml), then saturated solution of ammonium chloride (3 X 20 ml), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product was purified by flash chromatography on silica gel (mesh 230-400) using ether- pet. ether (1:1) as the eluent. The β-lactam was eluted first giving 78 mg (60%) of 85. The spectral data for 85 are: $NMR_{(chloroform-d)}$ δ: 1.37 (s, 3H, CH_3CN), 1.39 (s, 3H, CH_3CN), 1.83 (s, 3H, CH_3), 6.97 - 7.96 (m, 10H, ArH); Melting point $_{(CHCl_3\text{-ether-pet.ether})}$: 155-157° C; $IR_{(neat)}$: 1780 cm^{-1}. $^{13}Cnmr_{(chloroform-d)}$ δ: 15.00, 25.25, 28.61, 75.08, 77.22, 84.32, 111.56, 127.91, 127.98, 128.04, 128.40, 128.48, 129.03, 131.54, 134.53, 138.47, 142.25, 149.76, 160.84; Anal. calcd. for $C_{21}H_{19}NCl_2O$: C 67.75, H 5.14, N 3.76; Anal. calcd. for $C_{21}H_{19}NCl_2O \cdot 3/4CHCl_3$: C 56.56, H 4.31, N 3.03; Found: C 56.89, H 4.09, N 2.76; Mass Spectrum (C.I. ionization) m/z: 371(M ; 24%), 373(M + 2, 15), 375 (M + 4, 3), 339(10), 338(42), 337(32), 336(100), 335(12), 334(4), 261(7), 260(16); Mass spectrum (E.I. ionization) m/z: M 371(4%), (M + 2) 373(3), 338(5), 336(14), 262(20), 261(100%), 260(30), 247(10), 246(47), 205(44), 204(13), 149(13), 145(11), 128(10), 112(16), 110(23), 104(30), 103(10), 84(21), 82(73), 77(12). A

second product ascribed as the 2,2,4-trimethyl-3,5-diphenyl-5-hydroxy-1-dichloroacetoxy-2,5-dihydro-pyrrole (86) was eluted from the column to give 44 mg (31%) of material. It had a melting point: 148-150°C; NMR (chloroform-d) δ: 1.29 (s, 3H, CH_3), 1.72(s, 3H, CH_3CN), 1.75(s, 3H, CH_3CN), 2.79 (s, 1H, OH, exchangeable), 6.22 (s, 1H, $CHCl_2$), 7.14 - 7.59 (m, 10H, ArH); $IR_{(neat)}$: 3350, 1650 cm^{-1}; Mass spectrum m/z: M 389(24%), (M + 2) 391(28), (M + 4) 393(3), 378(10), 377(26), 376(65), 375(53), 374(81), 373(10), 372(38), 314(52), 312(85), 263(48), 262(47), 261(57), 260(26), 248(30), 247(67), 246(29), 220(12), 219(25), 205(35), 204(12), 202(15), 186(28), 185(13), 175(11), 157(28), 145(10), 143(11), 129(10), 128(13), 118(33), 117(10), 116(12), 115(40), 105(100%), 104(34), 103(13), 91(55), 83(10), 77(65), 74(12), 59(30). Anal calcd for $C_{21}H_{21}NCl_2O_2$: C 64.62, H 5.42, N 3.59. Found: C 64.21, H 5.54, N 3.40.

Reaction of 2,2,4-Trimethyl-3,5-diphenyl-2H-Pyrrole (84) with Azidoacetyl Chloride in the Presence of Triethylamine.

To a solution of 2,2,4-trimethyl-3,5-diphenyl-2H-pyrrole (84) (50 mg, 0.19 mmole), in anhydrous ether (1 ml) over nitrogen atmosphere and at -15° C was added triethylamine (39 mg, 0.38 mmole) followed by a dropwise addition of a solution of azidoacetyl chloride (27 mg, 0.23 mmole) in anhydrous ether (1 ml) over a period of 20 minutes. The solution gradually warmed to room temperature and continued to stir for a total of 2 hours. The triethylamine hydrochloride precipitate was removed by filtration and the filtrate was diluted with ether (10 ml) and was washed with saturated NH_4Cl solution. The solution was dried over $MgSO_4$, filtered and the solvent was removed in vacuo. The product was purified by flash chromatography on a silica gel column (mesh 230-400) using ether-pet. ether (1:1) as the eluent to give 45 mg of impure 87 and 30 mg (43%)

of pure 88. The impure fraction containing 87 was purified further by preparative thin layer chromatography on two pre-coated silica gel (mesh 70-230) plates (20X20 in.) using 75% methylene chloride-hexane as the eluent to afford 12 mg (18.5%) of the β-lactam 87 as a liquid. $NMR_{(acetone-d)}$ δ: 1.42 (s, 3H, CH_3CN), 1.55 (s, 3H, CH_3CN), 1.77 (s, 3H, $CH_3C{=}C$), 4.87 (s, 1H, CHN_3), 7.06 - 7.69 (m,10H, ArH). $IR_{(neat)}$: 2100, 1765 cm^{-1}; Mass spectrum m/z: 301(5%), 261(49), 246(24), 205(27), 149(85), 111(28), 109(13), 105(27), 104(12), 99(15), 97(36), 96(12), 95(42), 91(38), 85(80), 84(14), 83(55), 82(22), 81(39), 79(19), 77(26), 71(72), 70(29), 69(51), 67(15), 59(13), 58(25), 57(100%), 56(37), 55(61). Compound 88 melts at 90-92° C; $NMR_{(chloroform-d)}$ δ: 1.24 (s, 3H, CH_3), 1.71 (s, 6H, $2XCH_3$), 2.93 (s, 1H, OH, exchangeable), 3.60 (AB quartet, 2H,CH_2N_3), 7.07 - 7.56 (m, 10H, ArH); $IR_{(neat)}$: 3380, 2100, 1645 cm^{-1}.

Reaction of 2,2-Dimethyl-4-ethyl-3-phenyl-2H-pyrrole (90) with Dichloroacetyl Chloride in the Presence of Triethylamine.

To a cooled solution of 2,2-dimethyl-4-ethyl-3-phenyl-2H-pyrrole (90) (60 mg, 0.30 mmole) in CH_2Cl_2 (1 ml) at -15° C and over nitrogen atmosphere was added Et_3N (36 mg, 0.36 mmole) followed by a dropwise addition of a solution of dichloroacetyl chloride (45 mg, 0.30 mmole) in CH_2Cl_2 (1 ml) over a period of 10 minutes. After 30 minutes, the solution was diluted with ether and $Et_3N.HCl$ was removed by filtration. The filtrate was washed with water, then saturated NH_4Cl solution, dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the product was purified by flash chromatography on a silica gel column (mesh 230-400) using ether- pet. ether (1:1) as the eluent to give 51 mg (52%) of 92 as an amorphous solid. Crystallization from ether-pet. ether afforded an analytical sample. It had a melting point : 126-127° C and spectral data

are: $NMR_{(chloroform-d)}$ δ: 1.27 (t, 3H, CH_3CH_2, J = 7.4 Hz), 1.47 (s, 3H, CH_3CN), 1.59 (s, 3H, CH_3CN), 2.02 (q, 2H, CH_2CH_3, J = 7.4 Hz), 2.34 (d, 1H, OH, J = 12.2 Hz), 5.94 (d, 1H, CHOH, J = 12.2 Hz), 6.77 (s, 1H, $CHCl_2$), 7.04 - 7.46 (m, 5H, ArH); $IR_{(chloroform)}$: 3390, 2960, 1690 cm^{-1}; Anal. calcd. for $C_{16}H_{19}NCl_2O_2$: C 58.55, H 5.83, N 4.27. Found: C 58.63, H 6.06, N 4.09; Mass spectrum m/z: 314(15%), 312(20), 310(2), 199(19), 184(26), 143(23), 86(16), 71(59), 70(20), 69(23), 57(100), 56(45), 55(21).

Reaction of 2,2,4-Trimethyl-3,5-diphenyl-2H-pyrrole (84) with Trichloroacetyl Chloride in the Presence of a Zinc-Copper Complex.[25]

To a solution of 84 (54 mg, 0.21 mmole) in anhydrous ether (2 ml) was added a zinc-copper[25] complex (41 mg, 0.32 mmole) under N_2 atmosphere. The solution was cooled to -15°C and a solution of trichloroacetyl chloride (50 mg, 0.27 mmole) in dry ether (1 ml) was added dropwise over a period of 20 minutes. Once the addition was completed, the solution was gradually warmed to room temperature and was stirred for another 24 hrs (overnight). The mixture was diluted with ether (5 ml), filtered and washed with pH 7 phosphate buffer solution (0.2 M) (Fieser & Fieser, Vol. I) (2 x 10 ml). The solution was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product was purified by flash chromatography on silica gel (mesh 230-400) using 30% ether-pet. ether as the eluent to afford 18 mg (34%) of the β-lactam 85 whose spectroscopic properties were identical to the product (85) obtained by reaction of 84 with dichloroacetyl chloride and triethylamine. The starting material 84 was also recovered, 17 mg (31%).

Reaction of 2,2-Dimethyl-4-ethyl-3-phenyl-2H-pyrrole (90) with Trichloroacetyl Chloride in the Presence of a Zinc-Copper Complex[25]

A solution of 90 (43 mg, 0.22 mmole) in anhydrous ether (1 ml) was cooled to -15°C over nitrogen atmosphere. A zinc-copper complex[25] (0.43 mg, 0.33 mmole) was added followed by a dropwise addition of a solution of trichloroacetyl chloride (48 mg, 0.26 mmole) in anhydrous ether (1 ml) over a perios of 20 minutes. After 24 hours at room temperature, tlc (ether) indicated that the reaction was incomplete and the major component was the starting material (90). A second equivalent, as described above, of the zinc-copper complex followed by trichloroacetyl chloride was added in the same manner. After 15 minutes, no starting material was evident by tlc. The solution was diluted with ether (5 ml), filtered and the filtrate was washed with pH7 phosphate buffer solution (0.2M) (Fieser & Fieser, Vol. I) (2 x 20 ml). The solution was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product was purified by flash chromatography using 30% ether-pet. ether as the eluent giving 11 mg (14%) of 1-trichloroacetoxy-2,2-dimethyl-4-ethyl-3-phenyl-5-hydroxy-2H-pyrrole. $IR_{(neat)}$ 3360 cm^{-1}; 1690 cm^{-1}. $^1Hnmr_{(chloroform-d)}$ δ: 0.99 (t, 3H, $\underline{CH_3}CH_2$, J=7.4Hz), 1.47 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.02 (q, 2H, CH_2, J=7.4 Hz), 3.12 (d, 1H, OH, J=6.0 Hz, D_2O exchangeable), 6.53 (d, 1H, CH, J=6.0 Hz), 7.08-7.47 (m, 5H, phenyl). Mass spectrum m/z: 200(36%), 199(97), 198(19), 185(59), 184(100%), 171(20), 170(62), 149(51), 144(12), 143(87), 142(10), 141(14), 135(14), 129(64), 128(29), 127(14), 115(42), 111(12), 105(62), 98(13), 97(16), 95(13), 91(39), 85(35), 84(16), 83(36), 82(14), 81(17), 78(11), 77(44), 73(19), 71(48), 69(84), 68(14), 67(12), 65(11), 63(10), 58(11), 57(50), 57(47), 55(57), 53(10).

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