THE SYNTHESIS

OF

AN OXACEPHAM DERIVATIVE

A THESIS

BY

BONG YOUNG CHUNG

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Bong Young Chung

Department of Chemistry

McGill University

Montreal, Quebec, Canada

Abstract

The total synthesis of an oxacepham derivative starting from D-mannitol was accomplished. During the course of the synthesis, an improved procedure for the preparation of oxazolidine mesylate was developed. Also, a new aldehyde protecting group was developed which was stable to nucleophilic attack by oxygen anions and was easily removed with mercuric chloride or with m-chloroperbenzoic acid. Several attempts using different acid protecting groups for the synthesis of the oxacepham derivatives were investigated in detail and the resulting products were characterized. In addition, many new compounds were prepared and characterized.

La Synthèse d'un Dérivé Oxacépham

Bong Young Chung

Department of Chemistry

McGill University

Montreal, Quebec, Canada

Résumé

La synthèse totale d'un dérivé oxacépham à partir du D-mannitol a été effectuée. Durant ce travail, une procédure améliorée pour la préparation du mésylate de l'oxazolidine a été développée. De plus, un nouveau groupe protecteur d'aldéhydes a été utilisé, lequel a été stable à l'attaque nucléophile par des anions oxygénés et a été facilement enlevé avec le chlorure mercurique ou l'acide m-chloroperbenzoïque. Plusieurs tentatives utilisant différents groupes protecteurs d'acides pour la synthèse de dérivés oxacéphams ont été étudiées en détail et les produits obtenus ont été caractérisés. Plusieurs nouveaux composés ont aussi été préparés et caractérisés.

To Whom I Owe

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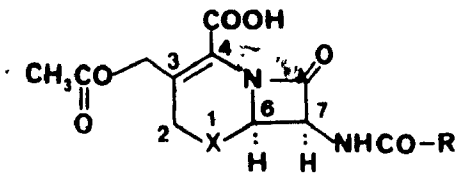
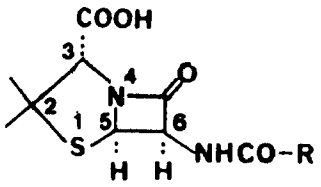
INTRODUCTION

Cephalosporins or cephems are β-lactam containing heterocyclic compounds of the type (1) which are closely related to penicillins (2), in terms of their structures and various antibiotic and chemical properties. If the sulfur atom of cephalosporins is replaced by oxygen, the resulting compounds are oxadethiacephalosporins (3), which will be referred to as oxacephems.



(1) X = S
(3) X = O



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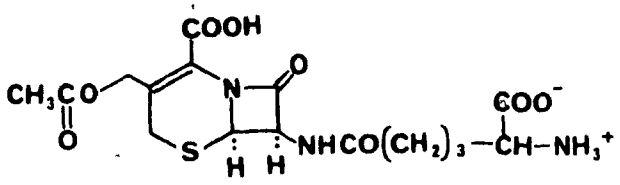
Since these oxacephems are not naturally occurring and their chemical synthesis has never been attempted until quite recently, their chemical and biological properties were entirely unknown. Hence, it is worthwhile to describe the backgrounds of cephalosporins first, and then the anticipated properties of the oxacephem derivatives.

1. Cephalosporin C and the related antibiotics.

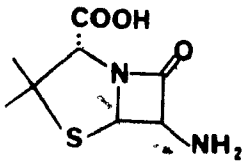
During the search for antibiotic-producing organisms, Brotzu[1] in 1945 discovered a new fungus near a sewage outlet in the sea off Sardinia, which he concluded was similar to Cephalosporium acremonium. Because of the inadequate facilities in Sardinia, a culture of the Cephalosporium species was sent to Sir Howard Flory at Oxford University who had been very active in penicillin research.



(4)

A detailed examination of all the antibiotics produced by this Cephalosporium species was carried out by Abraham and Newton[2], also at Oxford University. In 1955 they isolated from its cultures a new antibiotic substance, Cephalosporin C (4), whose structure was determined by the same authors[3] and confirmed by Hodgkin and Maslen[4] by means of single crystal X-ray diffraction studies in 1961.

A variety of derivatives of 6-aminopenicillanic acid (5) can be easily biosynthesized through appropriate modification of the culture medium. Thus any multistep chemical synthesis of penicillins can hardly be expected to be of immediate practical importance. This is not true, however, for the cephalosporin series of β-lactam antibiotics. While a strain of Cephalosporium species,



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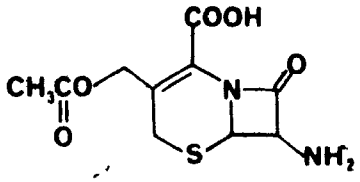
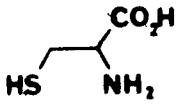


(6)

mutant 8650, which produced much more cephalosporin C than the wild strain, was discovered by the Antibiotics Research Station of the Medical Research Council[5], attempts to induce the biosynthesis of cephalosporin analogs during fermentation have not been successful, because the key intermediate, 7-aminocephalosporanic acid (6), is not easily biosynthesized. Hence, many attempts to synthesize cephalosporin derivatives have been made, but without much success.

The most successful stereospecific total synthesis of cephalosporin C and cephalothin was announced by Woodward[6] in his Nobel lecture in 1965. By using natural L-cysteine (7) as a starting material, no resolution step was necessary, and by protecting the various functional groups of this amino acid in cyclic intermediate (8), complete stereochemical control in the introduction of the new asymmetric center, namely the 7-position of cephalosporin C, was achieved.



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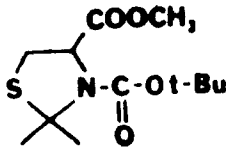
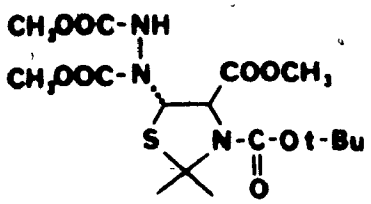


(8)

L-Cysteine (7) was protected with an acetonide function and then treated with t-butoxycarbonyl chloride to give an acid which was esterified with diazomethane to give (8). This intermediate (8) was reacted with dimethyl azodicarboxylate to afford (9) which was oxidized with lead tetraacetate and then treated with sodium acetate in methanol to give the trans hydroxy compound (10). Treatment of a derivative of (10) with azide followed by reduction with aluminum amalgam in methanol gave the desired cis amino ester (11), which was transformed to the β-lactam (12) using triisobutyl aluminum.



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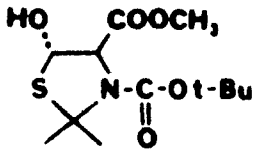

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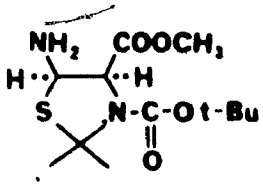

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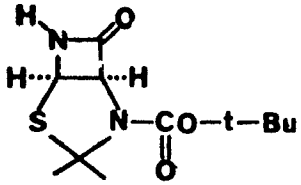
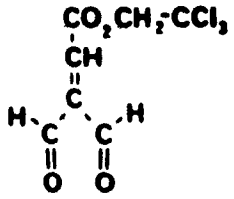


(12)

This β-lactam was condensed with the preformed dialdehyde (13) to afford (14), whose N-and S-protecting groups were removed by trifluoroacetic acid to give the amino aldehyde (15). The 7-amino group of (15) was then acylated with thienylacetyl chloride or protected D-α-aminoadipic acid and the aldehyde group was reduced with diborane. Then, acetylation of the resulting hydroxy group, isomerization of the double bond in pyridine and reductive cleavage of the trichloroethyl ester group with zinc in 90 % aqueous acetic acid gave cephalosporin C (4) and cephalothin (16).



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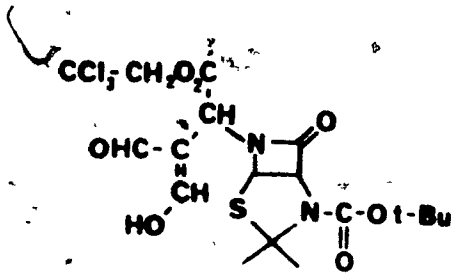

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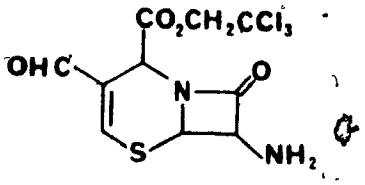

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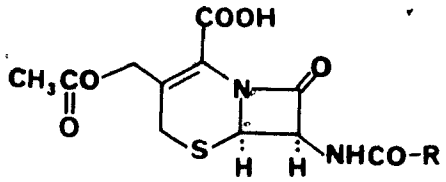


(4) $R = (CH_2)_3CH(COO^-)-NH_3^+$

(16) $R = CH_2$-(2-thienyl)

The other total synthesis of a cephalosporin derivative has been reported by Heymès, Amiard and Nominé[7], and Christensen[8] recently published a practical approach to cephalosporin derivatives. A number of review articles and monographs[9-17] have dealt with other synthetic approaches and with the chemistry and biological activity of the cephalosporin antibiotics.

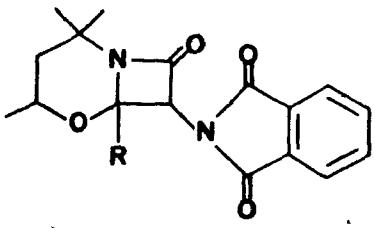
Cephalosporins and penicillins seem to have similar modes of action, interfering with bacterial cell wall

synthesis[18-21]. However, cephalosporins have some characteristics that in some cases make them more useful than penicillins. They are, like penicillins, non-toxic, but they are more acid stable than penicillins and more chemical variations are possible. They are active against penicillin resistant staphylococci, and have good gram-positive and some gram-negative antibacterial activity. Perhaps, the greatest advantage of cephalosporins over penicillins is that they are less susceptible to cause allergic reactions. The most important disadvantage, however, is that they are much more expensive than penicillins.

Cephalosporins as well as penicillins are not effective against all infectious diseases. Certain kinds of diseases, however, can easily be cured by these compounds. Respiratory diseases, such as pneumonia, scarlet fever, sore throat, and ear infections all respond to cephalosporin treatment. Many infections of the urinary tract, infections of wounds, boils, gas gangrene, and abscesses, tetanus and meningitis can be controlled. Also, syphilis and gonorrhea can be cured with cephalosporins.

2. Oxygen analogs of cephalosporin antibiotics

In 1968, Sheehan[22] reported the synthesis of a new series of oxygen analogs of the cepham ring system (17). This was the only example of the oxacepham ring system in the literature when we started our research in 1973.



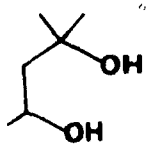
R = C_6H_5

$CH_2-C_6H_5$

C_6H_4-m-NO_2

(17)

He prepared the 2-aryl-5,6-dihydro-1,3-oxazine (18) by condensation of a nitrile (19) with 2-methyl-2,4-pentanediol (20) in the presence of sulfuric acid, a reaction which was originally described by Tillmanns and Ritter[23]. The reaction of these oxazines (18) with phthaloylglycyl chloride (21) and triethylamine in refluxing benzene gave the β-lactam, 2,4,4-trimethyl-6-aryl-7-phthalimidooxacepham (17).



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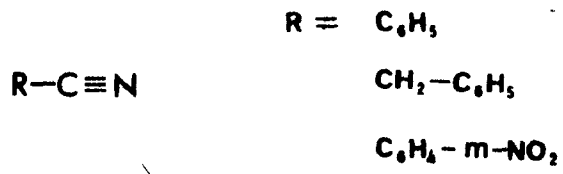

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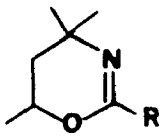

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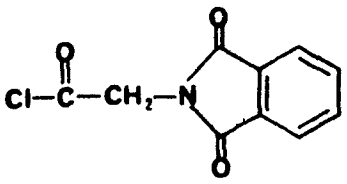
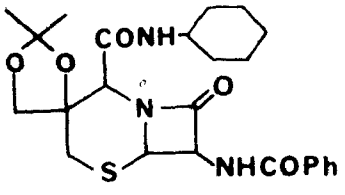


(21)

The β-lactam carbonyl absorption frequency of these oxacepham derivatives in the infrared appeared at 1760 cm^{-1}. This frequency is nearly 20 cm^{-1} higher than that (1740 cm^{-1}) of the cepham derivative (22) which was synthesized by Rossy[24] and by Rosebery[25]. Both of these β-lactam carbonyl absorption frequencies should increase when the double bond is introduced in the 3-position, because the β-lactam nitrogen planarity is decreased. This is true for the cephems (1), for which the β-lactam absorption frequency appears at 1785 - 1790 cm^{-1}. Thus we would expect that the β-lactam carbonyl absorption frequency of the oxacephem derivatives (3) would appear around 1800 - 1810 cm^{-1}.



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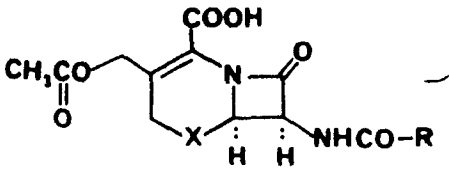
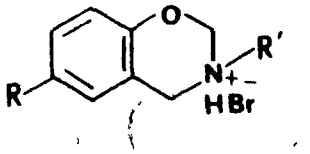


(1) X = S
(3) X = O

Concerning the β-lactam carbonyl absorption frequency of cephems or penicillins, a relationship has been established between their absorption frequency and biological activity. Morin[26] has shown that, provided that a direct correlation exists between β-lactam carbonyl absorption frequency and acylation ability (i.e. the higher the frequency, the higher the acylation ability), a rough but positive relationship between acylation ability and biological activity can be inferred from their infrared data. This relationship has been further verified by Sweet and Dahl[19] who, on the basis of X-ray structure data on the various cephems and penicillins, suggested that, as the biological activity increases, the β-lactam nitrogen planarity decreases, and the ease of basic hydrolysis of the β-lactam amide bond increases.

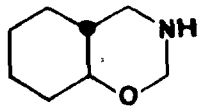
From the above relationships, we would expect that oxacephems (3) might well have higher biological activity than the corresponding cephems (1), if the two hydrogens attached to the β-lactam ring have the correct stereochemistry and all of the attached functional groups are the same.



R = Br, C_6H_5

R' = CH_2 C_6H_5, C_6H_{11}

(23)



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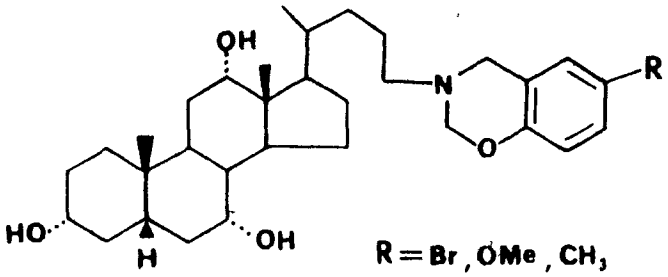


R = Br, OMe, CH_3

(25)

Furthermore, certain kinds of compounds having a 1,3-oxazine ring fused to aromatic, heterocyclic or alicyclic nuclei have been reported to have considerable antibacterial, antifungal or cancerostatic activities. For example, the dihydrobenzoxazine derivatives (23) showed a

strong cancerostatic activity in mice[27], the alicyclic perhydro-1,3-oxazine compound (24) antitumor activity[28] and the steroidal derivatives (25) antibacterial and antifungal activities[29].

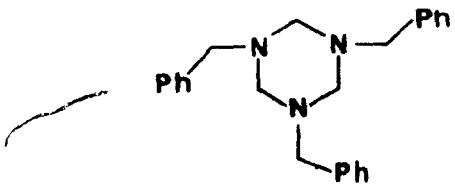
In addition to these various antibacterial activities of the dihydro-1,3-oxazine derivatives, the anticipated higher β-lactam carbonyl absorption frequency of the oxacephem derivatives in the infrared could promise that the unnatural oxacephem derivatives, available only by chemical synthesis, would have more effective biological activities than the corresponding cephems. It is partially upon these anticipated biological activities that the work in the following chapters was undertaken.

During the course of our studies, Christensen and Cama[30] reported a total synthesis of an oxacephem derivative, oxacephalothin.

The starting point of their synthesis was 1,3,5-tribenzyl-hexahydro-s-triazine (26), prepared from benzylamine and formaldehyde. Treatment of (26) with diethyl phosphite and hydrogen chloride gave N-benzylaminomethyldiethylphosphonate hydrochloride salt (27) and its hydrogenolytic debenzylation and neutralization gave aminomethyldiethylphosphonate (28). The amino group was then protected with benzaldehyde and the carboxylic

function was inserted with phenyl lithium and benzyl chloroformate to give the acylated Schiff base (29).

The benzylidene group was then removed by exchange with p-toluenesulfonic acid and by neutralization of the resulting sulfonate with potassium hydrogen phosphate to give benzyl α-aminodiethylphosphonoacetate, which was thioformylated with ethyl thionoformate to produce benzyl α-thioformamidodiethylphosphonoacetate (30).



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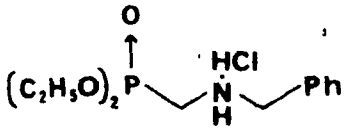

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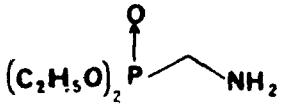

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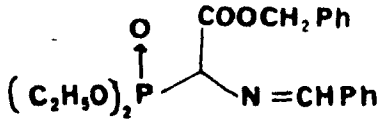

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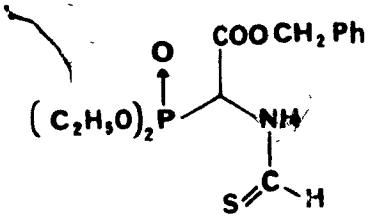

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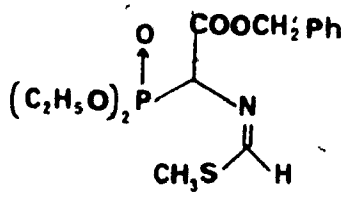
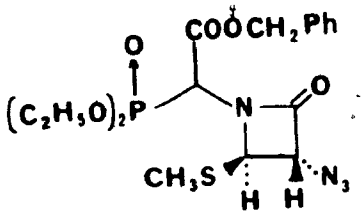
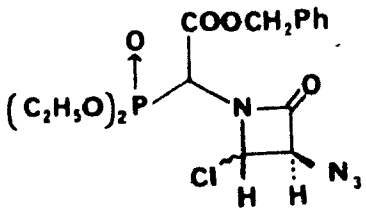


(31)

Treatment of (30) with methyl iodide in the presence of potassium carbonate gave the Schiff base (31), which was condensed with azidoacetyl chloride. The resulting thiomethoxy β-lactam (32) was then reacted with chlorine to give the isomeric chloro compound (33). Treatment of (33) with 3-hydroxy-2-oxo-n-propyl acetate and separation of the resulting isomers gave (34) in 23 % yield, which was cyclized to (35) in 28 % yield by means of a Wittig reaction.



(32)



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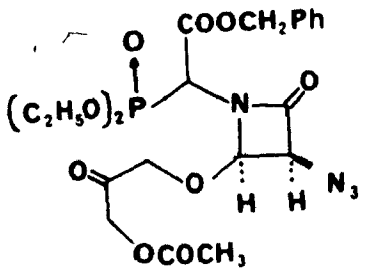

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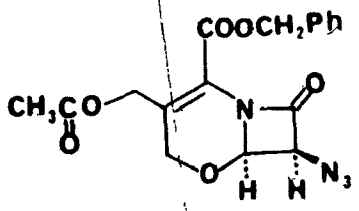
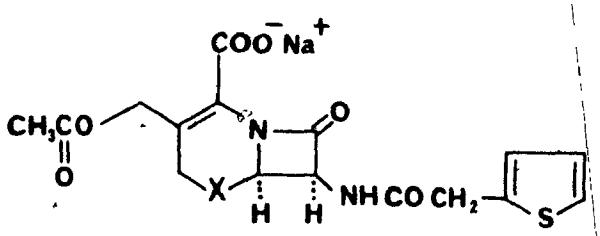


(35)

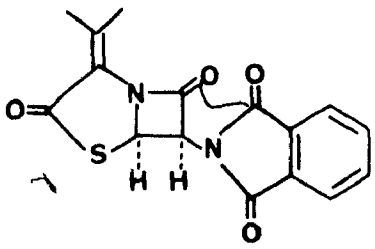
Reduction of the azide function with platinum oxide, followed by acylation of the resulting amino group with thienylacetyl chloride, and hydrogenolysis of the benzyl ester on palladium on charcoal gave the desired oxacephalothin (36), which appeared to be the first total synthesis of an oxacephem derivative.



(36) X = O

(16) X = S

A partial synthesis of the oxacephem derivative (38) from anhydro-6-phthalimidopenicillin (37) was also reported in December, 1974 by S. Wolfe[31].



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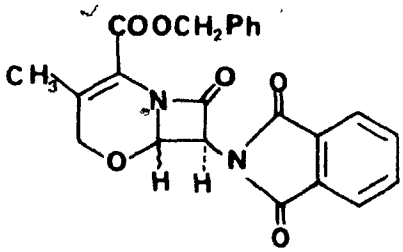
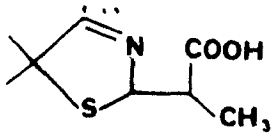


(38)

In the lecture concerning the synthesis of oxacephalothin (36), Christensen[32] showed that the β-lactam carbonyl absorption frequency of oxacephalothin in the infrared appeared at 1802 cm^{-1}, which is 20 cm^{-1} higher than that of cephalothin itself. He also showed that the gram-positive antibacterial activity of oxacephalothin is exactly the same as that of cephalothin, but its gram-negative activity is doubled. These results indicated that the assumptions upon which the following work was undertaken were correct.

3. Outline of the project

In 1962 Ugi[33] reported a new method to synthesize a penicillin analog (43) by treatment of the imine acid (39) with an isonitrile (41) in a two phase mixture of water and petroleum ether. He explained that in aqueous media, the imine acid is in equilibrium with the zwitterion (40), which reacts with an isonitrile to form the bicyclic adduct (42), and that this adduct is converted to the penicillin analog (43) by means of the trans-annular acyl migration (Ugi reaction).



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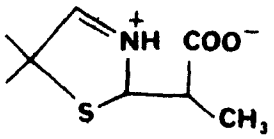
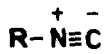


(40)



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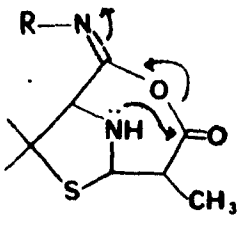

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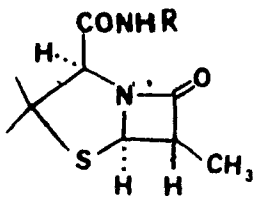
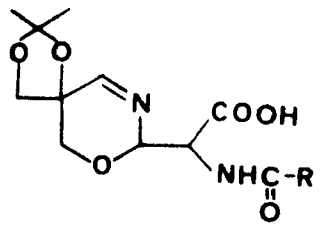
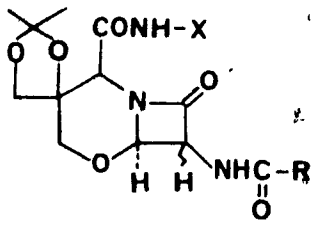


(43)

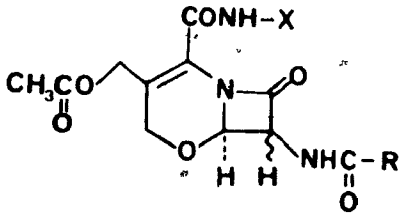
This reaction suggested an approach to synthesize a new class of antibiotics, the oxacepham derivatives (45). If we prepared the desired imine acids (44), we could synthesize the oxacepham derivatives (45) by means of an Ugi reaction. These oxacepham derivatives would then be transformed to the oxacephem derivatives (46) and after resolution, the two amide groups would be removed by phosphorus pentachloride[34] to produce 7-aminooxacephalosporanic acid (47).



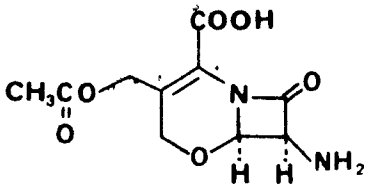
(44)



(45)



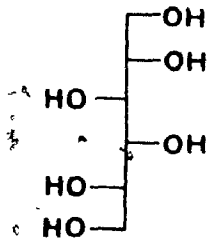
(46)



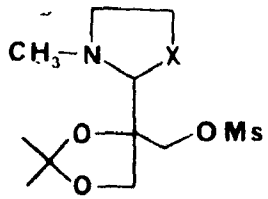
(47)

The objective in this work was to devise a novel and adaptable scheme for the synthesis of the oxacepham derivatives (45) using readily available starting materials.

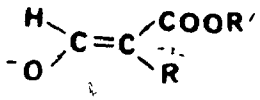
The starting point of the synthesis was D-mannitol (48), from which the mesylates (49) and (50) were prepared. Treatment of these mesylates with the enolic salts of the type (51) produced the condensation products (52). From these products, attempts were made to synthesize the oxacepham derivatives (45).



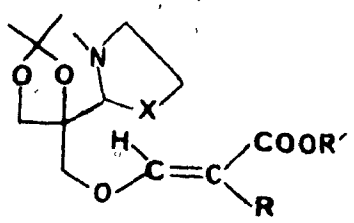
(48)



(49) X = O
(50) X = S

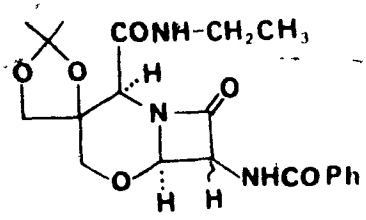


(51)



(52)

Chapter I deals with the preparation of the mesylates (49) and (50) starting from D-mannitol (48). Using these mesylates, we attempted to prepare the imine acids (44) by introducing methyl esters (chapter II), 2-benzyl-5-oxazolones (chapter III) and benzyl esters (chapter IV) as acid protecting or acid producing groups, but without much success. However, we achieved the synthesis of the oxacepham derivative (53) using β,β,β-trichloroethyl esters as an acid protecting group. This synthesis is described in chapter V.

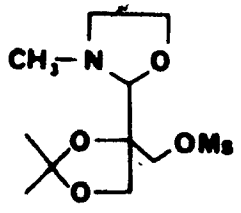


(53)

CHAPTER I

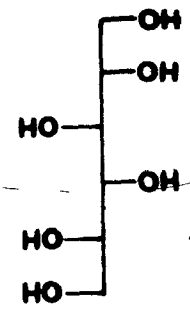
SYNTHESIS OF OXAZOLIDINE AND THIAZOLIDINE MESYLATES

The synthesis of the oxazolidine mesylate (49), developed by Rossy[35] and Rosebery[25] in this laboratory, suffered from the fact that several steps were laborious and proceeded in relatively low yield, and that the final product was contaminated with variable amounts of a side product (10-50 %), the presence of which had not been recognized.



(49)

The starting point of their synthesis was D-mannitol (48), from which the diacetonide (54) was prepared by the Baer and Fischer method[36]. Cleavage of the vicinal diol with lead tetraacetate in benzene and the quick distillation gave glyceraldehyde acetonide (55) in variable yield[36].



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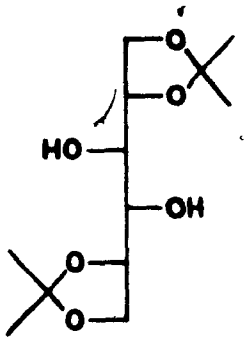
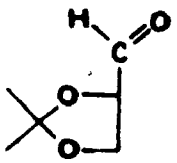


(54)

Because of the easy polymerization of this aldehyde on standing, freshly distilled glyceraldehyde acetonide (55) was immediately treated with formaldehyde and potassium carbonate in aqueous methanol. After removal of the methanol in vacuo below 40°C using a rotary evaporator, extraction of the remaining aqueous solution with methylene chloride and evaporation gave a sticky dioxan (56).



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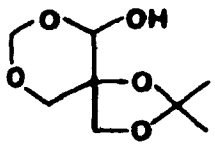
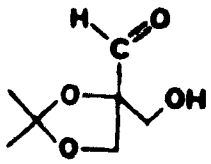
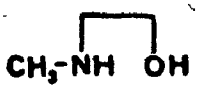


(56)

Pyrolysis of a small amount of the dioxan under high vacuum and the quick distillation of the product gave a 50 % yield of the hydroxy aldehyde (57), which was immediately treated with N-methylethanolamine (58) to produce the oxazolidine alcohol (59).

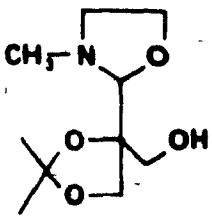


(57)

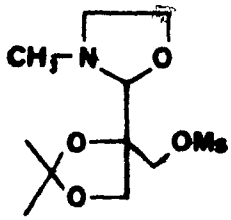


(58)

In Rosebery's synthesis, the sticky dioxan (56) was directly treated with N-methylethanolamine in refluxing benzene and the produced oxazolidine alcohol (59) distilled under high vacuum. The oxazolidine alcohol was then mesylated with methanesulfonyl chloride, yielding "a quantitative yield of the pure oxazolidine mesylate (49)".

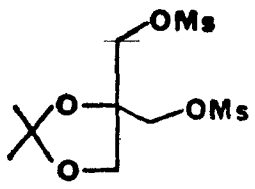


(59)



(49)

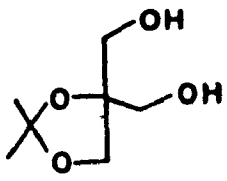
Although their work was successful in the preparation of the oxazolidine mesylate (49), we found, repeating the whole reaction sequence, that the oxazolidine mesylate was contaminated with the dimesylate (61).



(61)

When all of these reactions were repeated and attempts to recrystallize the mesylation product from petroleum ether (60-80°C) were made, less than half of the expected product was obtained as the pure oxazolidine mesylate (49). The residue was then passed through an alumina (Act. I, neutral) column using a mixture of methylene chloride-ethyl ether (1:1) as an eluent and the solvent evaporated. Recrystallization of the resulting solid from methylene chloride-petroleum ether (60-80°C) (1:1) gave varying amounts (10-50 % of the mesylation product) of the side product as white needles. It was assigned the dimesylate structure (61) on the basis of its microanalysis and nmr spectrum[37].

Since the dimesylate (61) must be derived from the diol (60), we concluded that the diol had been formed by a Cannizzaro reaction occurring during the work-up of the dioxan (56), which had involved removal of methanol in the presence of potassium carbonate and formaldehyde, and that the diol accompanied the oxazolidine alcohol (59) as a contaminant. Indeed, Rossy reported that g.l.c. of the oxazolidine alcohol showed varying amounts of a side product that he had removed by filtration through an alumina column.



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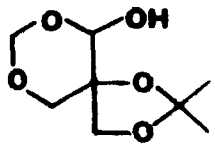
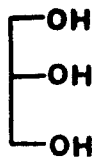


(56)

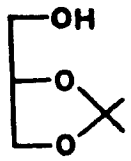
In order to proceed with the synthesis, it was imperative to eliminate this side product during the reaction sequence, to simplify some key steps, and to increase the overall yield of the oxazolidine mesylate.

Although D-mannitol (48) was converted into mannitol diacetonide (54) in up to 50 % yield by the procedure of Baer and Fischer[36], and the diacetonide (54) was cleaved

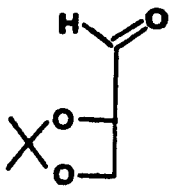
with lead tetraacetate into glyceraldehyde acetonide (55), it was difficult to scale up, because of the extremely large amounts of reagents employed. Instead of following this procedure, attempts to transform the simple glycerol (62) into glyceraldehyde acetonide (55) were made.



(62)



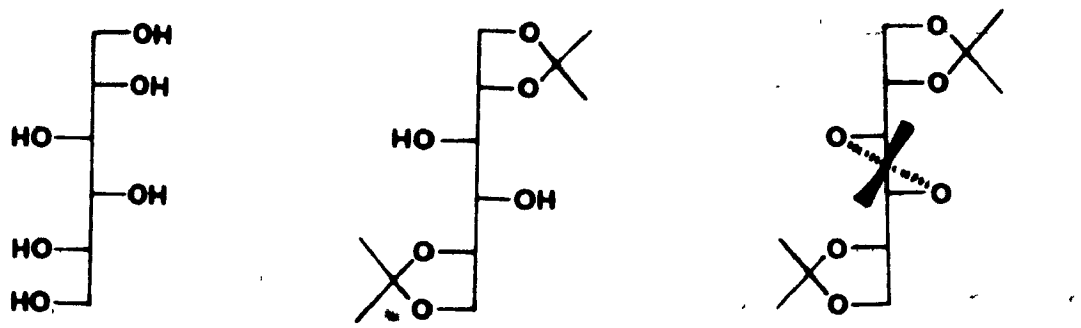
(63)



(55)

Treatment of glycerol (62) with dimethoxypropane and acetone in the presence of catalytic amounts of p-toluenesulfonic acid afforded a 90 % yield of glycerol acetonide (63)[38]. However, several attempts to oxidize glycerol acetonide to glyceraldehyde acetonide (55) using chromium trioxide-pyridine complex in methylene chloride[39], seloxcette[40], or Corey's chromium trioxide-3,5-dimethylpyrazole complex in methylene chloride[41] were unsuccessful, probably because of the further oxidation or the polymerization of the generated product during the reaction or the purification periods. Thus the transformation of glycerol to glyceraldehyde acetonide could not be achieved.

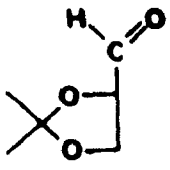
Therefore, we followed Kohan's modified method[42] for the preparation of mannitol diacetonide (54) from D-mannitol (48). A suspension of D-mannitol was stirred in a mixture of dimethoxypropane and acetone with a catalytic amount of p-toluenesulfonic acid at room temperature. Removal of the unreacted D-mannitol and neutralization with potassium carbonate gave a mixture of diacetonide (54) and triacetonide (64). Two recrystallizations of the crude mixture from petroleum ether



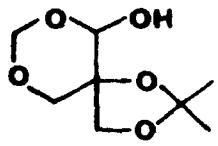
(48) (54) (64)

(60-80°C) afforded the pure mannitol diacetonide (54) in 30 % yield. Although the yield of this method was lower than that of the Baer and Fischer method, the shortness of the reaction time, and the fewer reagents required, as well as the simple work-up, made this procedure more suitable for the preparation of large quantities of mannitol diacetonide (54).

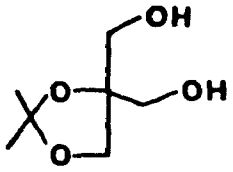
The problem was the transformation of the mannitol diacetonide (54) to glyceraldehyde acetonide (55) and the subsequent formation of the dioxan (56). Although the glyceraldehyde acetonide was prepared by the cleavage of vicinal diol with lead tetraacetate in benzene[36], large amounts of benzene had to be used and the yield was quite variable since the product co-distilled with benzene and rapidly polymerized on standing. Furthermore, when the dioxan (56) was prepared by the treatment of the freshly distilled glyceraldehyde acetonide (55) with formaldehyde and potassium carbonate in aqueous methanol, it was found to be contaminated with the diol (60).



(55)



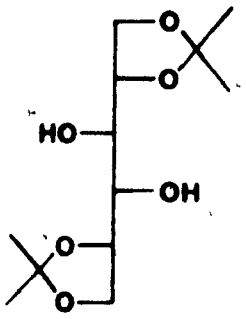
(56)



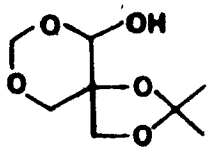
(60)

Ideally, the two reactions should be combined in a one-pot procedure using water as a solvent and thus obviating the necessity to remove the methanol. Several attempts by Rosebery (unpublished results) to cleave mannitol diacetonide (54) with periodate gave glycer-

aldehyde acetonide (55) in less than 20 % yield. Re-examination of the reaction showed that, using distilled water as a solvent, the reaction was complete after less than five minutes, and that the pH of the reaction mixture dropped rapidly to three. We therefore decided to study the periodate cleavage reaction under buffered conditions[43].



(54)

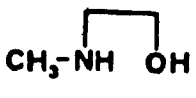


(56)

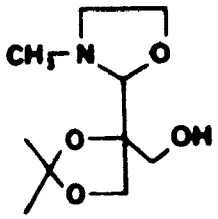
Mannitol diacetonide (54) was dissolved in a pH 5 buffer solution and 1.1 equivalents of sodium periodate added with vigorous stirring. A careful study indicated that the starting material had completely disappeared within five minutes, and that the produced glyceraldehyde acetonide (55) started decomposing very rapidly due to the slightly acidic condition. When the periodate reaction was carried out in pH 6 buffer solution, the reaction was complete after 30 minutes with little degradation of glyceraldehyde acetonide (55). Hence, without isolation of the generated glyceraldehyde

acetonide, two equivalents of aqueous formaldehyde and potassium carbonate were added and the reaction mixture kept overnight. Extraction with methylene chloride and evaporation gave a 80 % yield of the pure, crystalline dioxan (56).

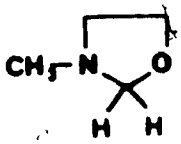
This new procedure had the advantage that the whole sequence was carried out in water without isolating glyceraldehyde acetonide (55), and that the pure dioxan (56) was obtained by one single extraction procedure.



(58)



(59)

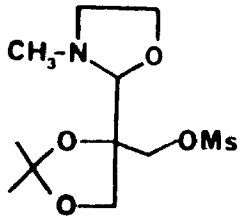


(65)

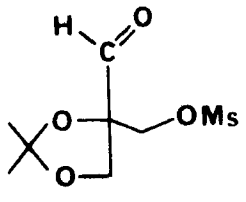
Since the pure dioxan (56) was obtained in a high yield, we followed the Rosebery's method to prepare the oxazolidine alcohol (59). The pure dioxan was directly treated with N-methylethanolamine in refluxing benzene, which rapidly produced the oxazolidine alcohol (59) and N-methyloxazolidine (65). Water was removed from the reaction mixture by azeotropic distillation and, on evaporation of the remaining solvent, N-methyloxazoli-

dine (65) co-evaporated. The residue was then vacuum distilled to give a 90 % yield of the pure oxazolidine alcohol (59).

There was no difficulty in the preparation of the oxazolidine mesylate (49) from the pure oxazolidine alcohol (59). Slow addition of methanesulfonyl chloride to the mixture of the oxazolidine alcohol (59) and triethylamine in methylene chloride at low temperature (-30°~-60°C) gave a quantitative yield of the crystalline oxazolidine mesylate (49).



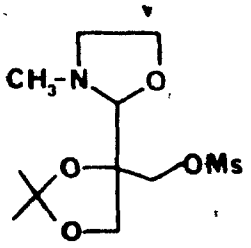
(49)



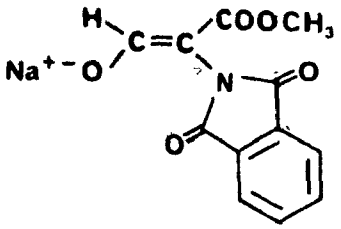
(66)

The hydrolysis of the oxazolidine group of the oxazolidine mesylate (49) to the corresponding aldehyde mesylate (66) was also easily accomplished in high yield with 50 % aqueous acetic acid within two hours.

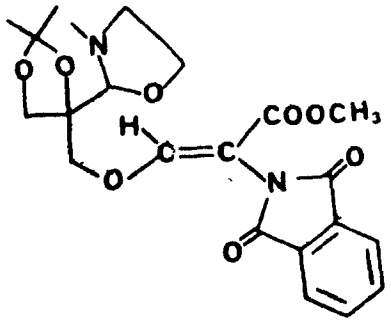
Although the yield and purity of the oxazolidine mesylate (49) was improved, it was discovered to be very difficult to carry out the next reaction with this mesylate, because the oxazolidine group was not stable enough to the nucleophilic attack by an oxygen anion. When the oxazolidine mesylate (49) was treated with the sodium salt of methyl ester (67b) in 2-butanone, a 1:1 mixture of the products, the desired oxazolidine methyl ester (68) and a rearranged perhydrooxazepine derivative (69), was obtained (see Chapter II).



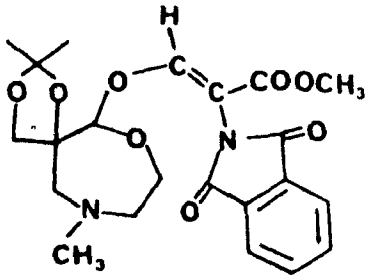
(49)



(67b)

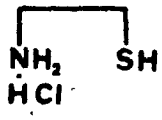


(68)

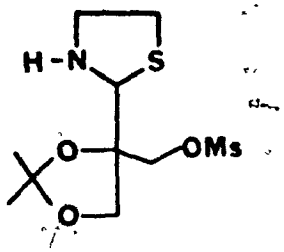


(69)

Since the laboriously prepared oxazolidine mesylate (49) afforded such a mixture in the next reaction, and the resulting mixture appeared to be very difficult to separate by usual methods, it was decided to introduce a more stable and easily removable aldehyde protecting group, namely a thiazolidine.



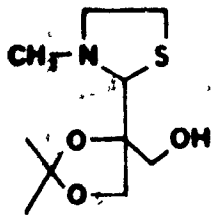
(70)



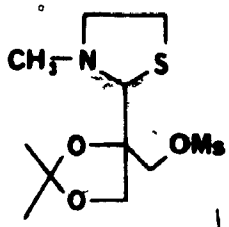
(71)

In a first experiment, we tried to exchange the easily hydrolyzable oxazolidine group with a thiazolidine moiety. Treatment of the oxazolidine mesylate (49) with commercially available aminoethanethiol hydrochloride (70) in refluxing methanol, ethyl ether or benzene, however, did not give the pure thiazolidine mesylate (71), probably due to the cleavage of the acetonide function or the formation of the hemiacetal or thioacetals. Reaction of the oxazolidine mesylate (49) with N-methylaminoethanethiol hydrobromide was also unsuccessful.

Since this transacetalization was unsuccessful, it was decided to prepare the thiazolidine alcohol (72) first, and then to mesylate to the corresponding thiazolidine mesylate (50). It was anticipated that N-methylaminoethanethiol (73) would undergo a reaction similar to that described for N-methylethanolamine (58) and the dioxan (56) to give the alcohol (72), thus necessitating few changes in the reaction sequence described.

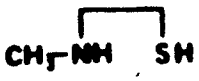


(72)



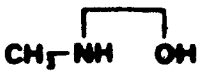
(50)

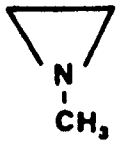
In a first attempt to prepare N-methylaminoethanethiol (73), ethylene sulfide (74) was treated with aqueous methylamine in the presence of silver nitrate, a modification of the method developed by Meneghini[44]. However, it did not give the thiol (73), because of the highly hygroscopic property of the thiol which was later discovered. Therefore, we decided to follow the classical but lengthy method to prepare N-methylaminoethanethiol.

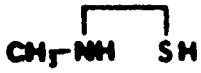


(73) (74)

N-methylethanolamine (58) was treated with sulfuric acid followed by sodium hydroxide, to give N-methylaziridine (75)[45], which was then reacted with methanolic hydrogen sulfide[46]. Evaporation of the methanol gave a white crystalline N-methylaminoethanethiol (73) in an overall yield of 30 %.

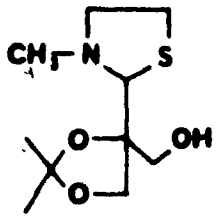




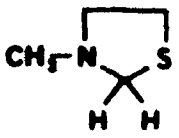


(58) (75) (73)

Preparation of the thiazolidine alcohol (72) was then the same as that of the oxazolidine alcohol (59). Treatment of the pure dioxan (56) with N-methylaminoethanethiol (73) in refluxing benzene and vacumm distillation gave N-methylthiazolidine (76) (b.p. 55°C/20mmHg) and the thiazolidine alcohol (72) (b.p. 127°-130°C/0.2 mmHg)



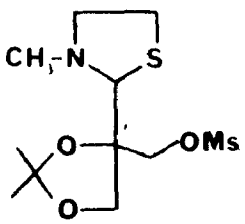
(72)



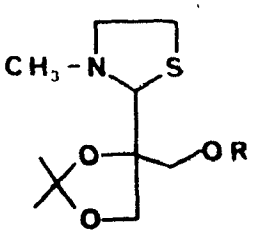
(76)

in more than 90 % yield. Its nmr spectrum indicated that (72) consisted of the two possible epimers in a 1:1 ratio. No attempt was made to separate these epimers.

Alcohol (72) was then mesylated quantitatively with methanesulfonyl chloride in the presence of triethylamine to give the crystalline thiazolidine mesylate (50). Alcohol (72) also gave a trifluoroacetate (77), but the formation of the reactive trifluoromethanesulfonate (78) using trifluoromethanesulfonyl chloride or anhydride was unsuccessful, because the generated triflate was hydrolyzed during the purification step. Only the starting material was recovered.



(50)

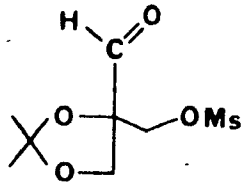


(77) $R = \overset{O}{\overset{\|}{C}}CF_3$

(78) $R = \overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}CF_3$

(77, 78)

The hydrolysis of the thiazolidine function to the aldehyde was satisfactory. When the thiazolidine mesylate (50) was treated with mercuric chloride[47] in aqueous acetonitrile or tetrahydrofuran, it gave the aldehyde mesylate (66) in as high a purity and yield as the one from the acidic hydrolysis of the oxazolidine mesylate (49). Surprisingly, this thiazolidine group was also cleaved to the aldehyde in good yield within 2 minutes when (50) was treated with m-chloroperbenzoic acid in methylene chloride at 0°C. As expected, the thiazolidine ring was resistant to the nucleophilic attack by oxygen anion and stable to the mild reducing reagents (i.e. hydrogenation on Pd/C).



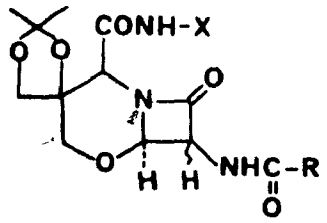
(66)

Having now achieved a short, high yield and simple synthesis of oxazolidine and thiazolidine mesylates (49) and (50), their condensation with various enolic salts and subsequent reactions towards the synthesis of the oxacepham derivatives were studied next. These studies will be discussed in the following chapters.

CHAPTER II

PRELIMINARY STUDIES TOWARDS THE SYNTHESIS OF THE KEY INTERMEDIATE, IMINE ACID, USING METHYL ESTER AS AN ACID BLOCKING GROUP

The first approach towards the synthesis of the oxacepham derivative (45) involved the condensation of the sodium or thallium salts of the methyl ester (67b, 67c) with oxazolidine mesylate (49).

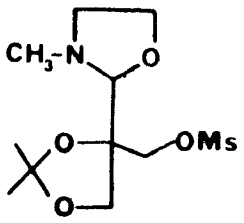


(45)

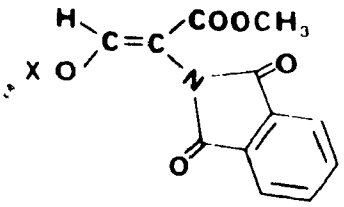
Phthaloylglycine was transformed to the corresponding methyl ester and the methyl ester formylated with methyl formate to methyl 2-phthalimido-3-hydroxyacrylate (67a) by the known method[48]. The thallium[49] and sodium salts (67b, 67c) were then prepared by treatment of this hydroxy compound with thallium ethoxide in benzene or sodium ethoxide in ethanol.

The sodium or thallium salt was suspended in a solution of the oxazolidine mesylate (49) in 2-butanone and the mixture heated to reflux to obtain the oxazolidine ester (68). Thin layer chromatography showed that after 6 hours, the starting material had completely reacted, but that two new spots appeared. Filtration, evaporation and purification through an alumina column gave a white foam.

Microanalysis and mass spectrum of this crude product showed that the 1:1 condensation reaction had occurred, but the nmr spectrum clearly showed a new peak at δ =5.14 ppm, which could not be explained without considering the cleavage and rearrangement of the oxazolidine group.

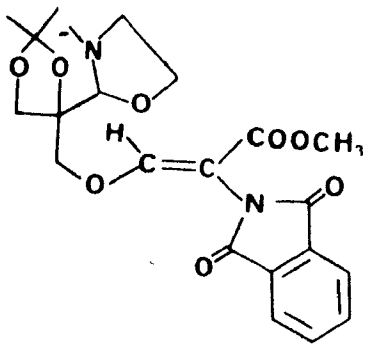


(49)



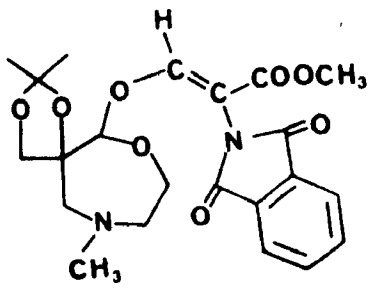
(a) X = H
(b) X = Na
(c) X = Tl

(67)

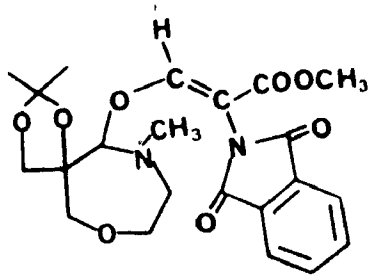


(68)

Attempts to separate these two products using column chromatography or thin layer chromatography failed, because the two products had nearly the same R_f values and the oxazolidine group was not stable to silica. After much experimentation, it was found that, when the crude product was dissolved in a minimum amount of ethyl ether and kept overnight in the refrigerator, the perhydrooxazepine derivative (69) crystallized out. Microanalysis and the mass spectrum of this product showed it to be an isomer of the desired product (68). Evaporation of the remaining solution then gave a 45 % yield of the desired oxazolidine ester (68), for which the infrared, nmr and mass spectral data were consistent with the proposed structure.



(69)



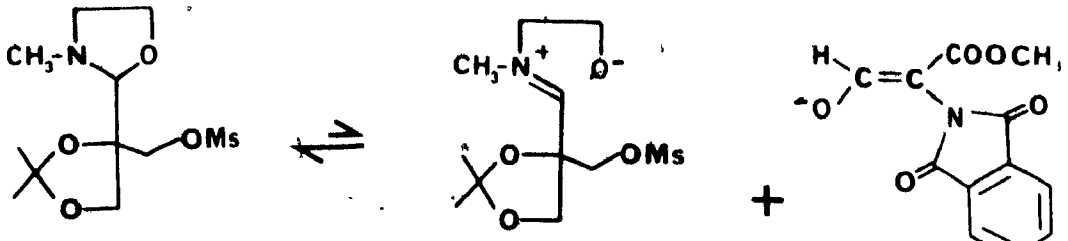
(79)

There are two possible structures, (69) or (79), for the isomeric product. Since it is known[50] that oxazolidines containing a secondary amine function exist in part as the tautomeric Schiff base, it could be assumed that oxazolidine

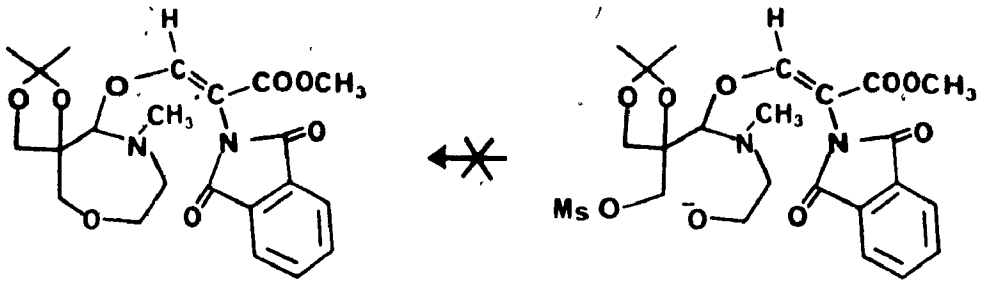
mesylate (49) may exist to a small extent as the imminium ion (80). Reaction of the imminium ion with the nucleophile (67b, 67c) may then give the intermediate (81a), which may be expected to cyclize to give (79). However, the nmr data of the isomeric product did not fit this structure. One would also anticipate that (79) would not be stable to 50 % aqueous acetic acid, but the isomeric product was stable to this condition.

Therefore, we proposed that the reaction took place through the sequence, (81a)→(81b)→(69), to give the rearranged product (69) (see the diagram on the following page). The nmr spectrum of the isomeric product is then consistent with the proposed structure (69), in which the singlet at δ=5.14 ppm came from a proton of O-CH-O, and the multiplet at δ=2.4-2.7 ppm from four protons of CH_2-N-CH_2 (compare the two spectra of (68) and (69)).

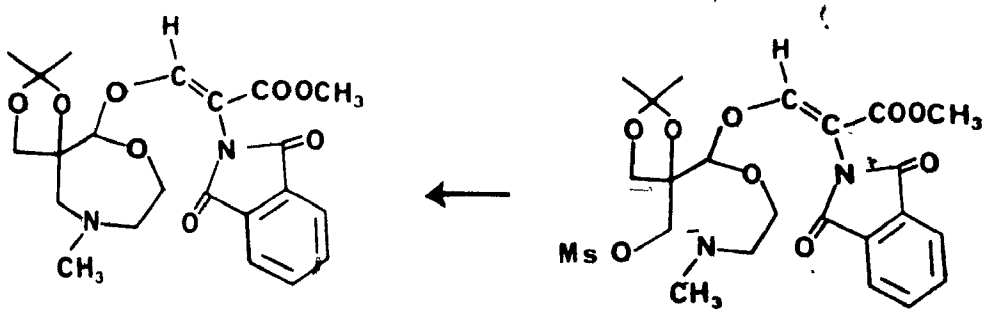
Other possible structures were also eliminated because of the presence of the ester function, double bond, phthalimido group and the acetonide function in the infrared spectrum of the isomeric product.



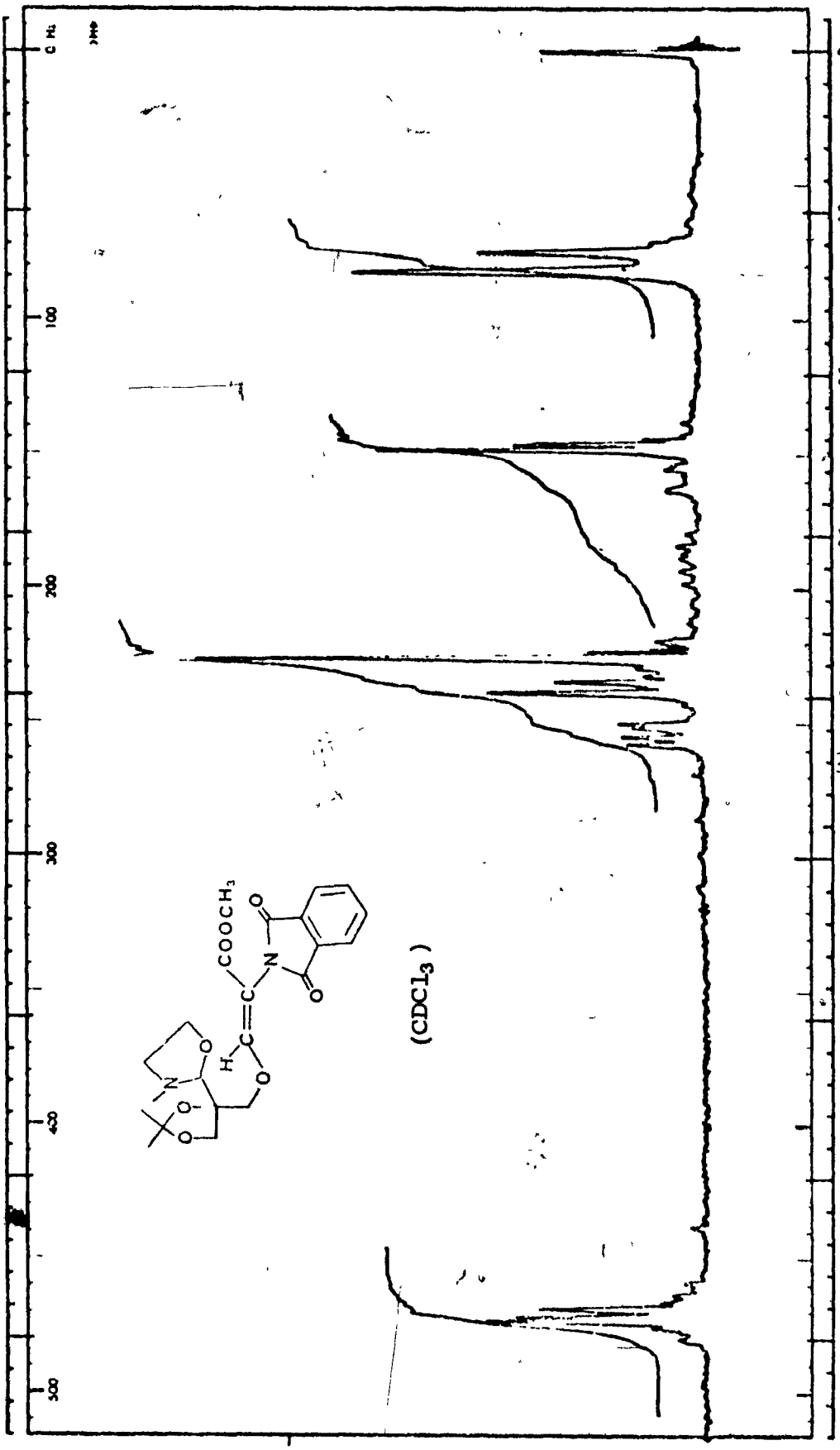
(49) (80) (67)

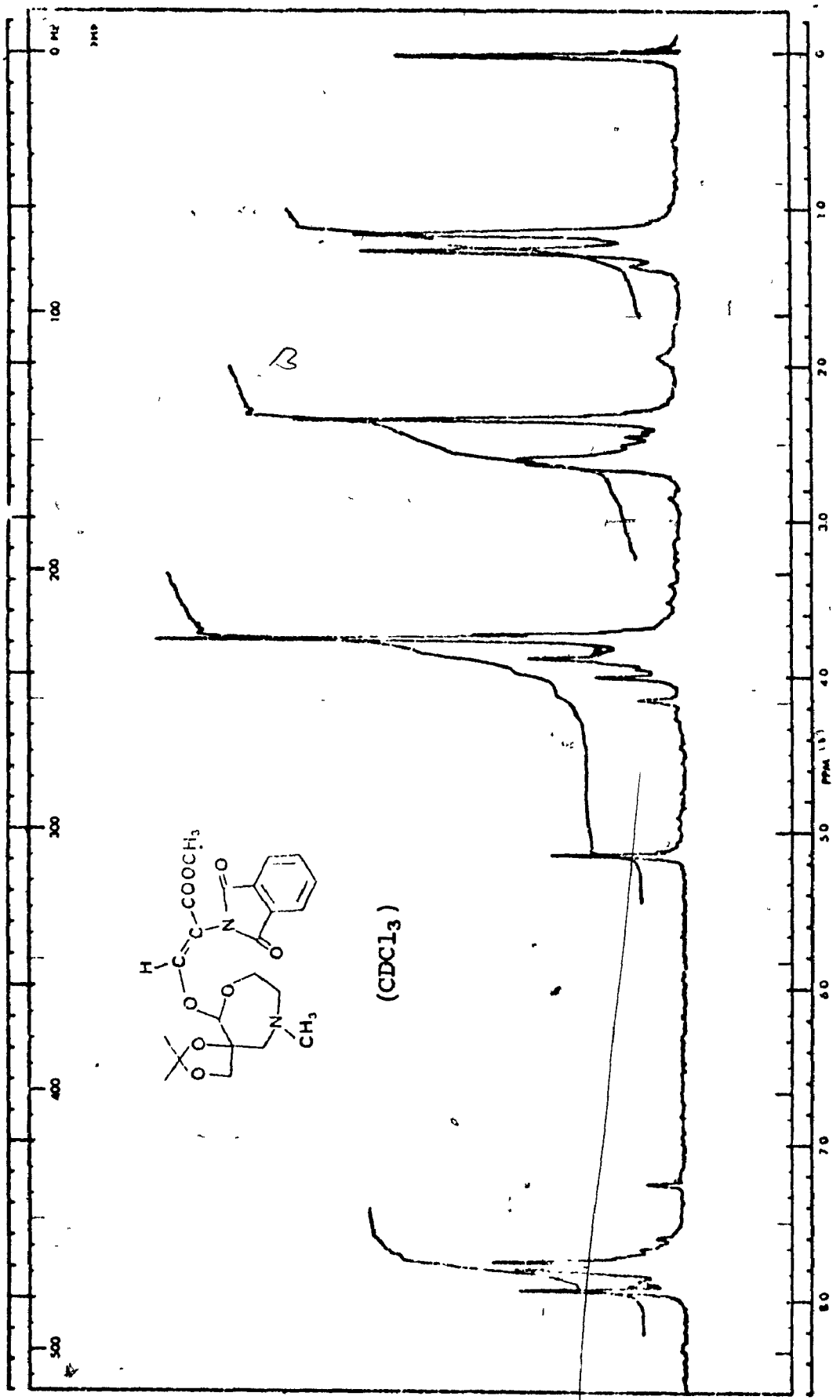


(79) (81a)

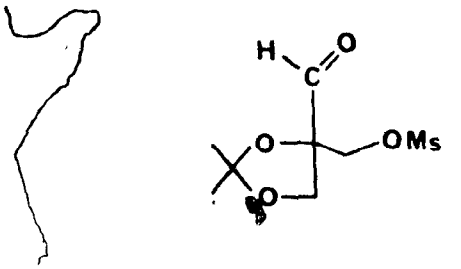


(69) (81b)

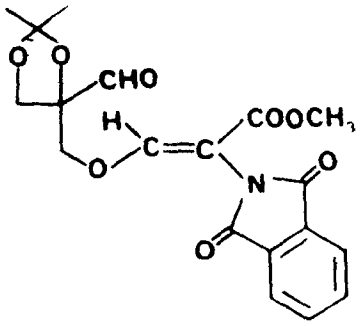

COOCH3
(CDCl3)
PPM (δ)


0 Hz
100
200
300
400
500
10
20
30
40
50
60
70
80
PPM (δ)
B
(CDCl3)
COOCH3
CH3

Because of the instability of the oxazolidine group to oxygen nucleophiles, the aldehyde mesylate (66) was directly treated with the sodium salt (67b) to prepare the aldehyde methyl ester (82), and the reaction followed by nmr spectroscopy. Prolonged heating of the solution of the aldehyde mesylate (66) and 1.1 equivalents of the salt (67b) in deutero-dimethylsulfoxide, however, did not show the displacement of the mesylate. 2 Equivalents of the sodium salt also gave the same result.

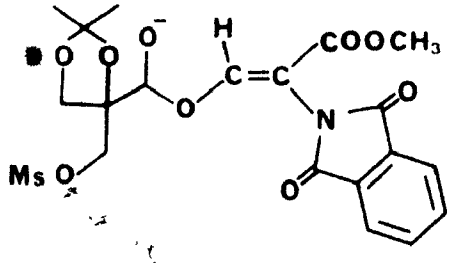


(66)



(82)

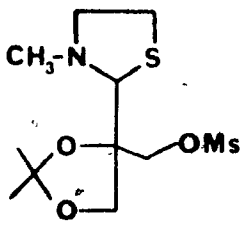
We thus concluded that the formation of the hemiacetal (83) had first taken place, and that the mesylate group in this intermediate was too unreactive to undergo displacement, even with excess amount of the sodium salt, probably due to steric hindrance and/or the anionic property of the hemiacetal (83).



(83)

Since this direct condensation reaction did not proceed and the oxazolidine mesylate (49) gave a mixture which was very difficult to separate, it was decided to use the thiazolidine mesylate (50).

Treatment of the thiazolidine mesylate (50) with 1.3 equivalents of the sodium salt of the methyl ester (67b or 84b) in refluxing 2-butanone gave a quantitative yield of the thiazolidine methyl ester (85 or 86) as an amorphous solid. No trace of cleavage products could be detected in this reaction.



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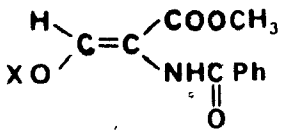
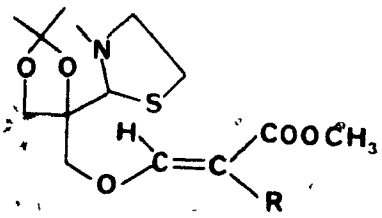


(a) X = H

(b) X = Na

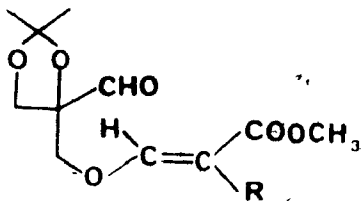
(84)



(85) R = Phthalimido

(86) R = NHC(=O)Ph

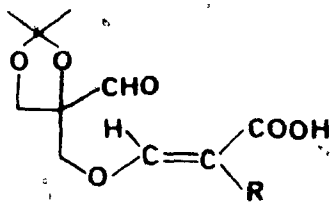
Hydrolysis of the thiazolidine function of the thiazolidine methyl esters (85 and 86) to the corresponding aldehyde methyl esters (82 and 87) was carried out by treatment of (85) and (86) with mercuric chloride in a mixture of tetrahydrofuran and water (5:1). Evaporation and extraction with benzene afforded a crystalline aldehyde methyl ester (82) and (87) respectively in up to 95 % yield. Hydrolysis of the oxazolidine methyl ester (68) with 50 % aqueous acetic acid also gave a quantitative yield of the aldehyde (82) as a crystalline compound.



(82) R = Phthalimido

(87) R = NHC(=O)Ph

Attempts to convert this aldehyde methyl ester (82 or 87) to the aldehyde acid (88 or 89) were unsuccessful. Treatment of the aldehyde methyl esters with 1 equivalent or an excess amount of sodium hydroxide in aqueous tetrahydrofuran, dioxane or methanol, and with barium hydroxide in absolute methanol[51] led to the disappearance of starting material according to thin layer chromatography, but the desired aldehyde acid (88 or 89) could not be detected and no product could be isolated.

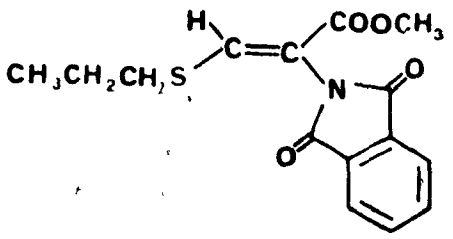


(88) R = Phthalimido

(89) R = NHC Ph
‖
O

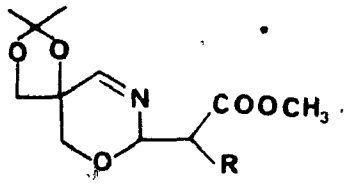
Attempts were then made to remove the methyl ester function under the mildest hydrolytic conditions possible. However, after prolonged stirring of the aldehyde methyl esters in aqueous tetrahydrofuran, dioxane or dimethoxyethane solutions of bicarbonate, only starting material was recovered. Attempts to generate the aldehyde acid (88 or 89) using anhydrous lithium iodide in pyridine[52], lithium iodide in dimethylformamide[53], lithium iodide and

sodium cyanide mixture in dimethylformamide[54] or potassium t-butoxide in dimethylsulfoxide[55] only led to black tars. Also, an attempt to remove the methyl ester function of the aldehyde ester (82) using lithium n-propylmercaptide in hexamethylphosphotriamide[56] gave a complex mixture, from which a small amount of the n-propylthiomethylene compound (90) was isolated. Similar results were obtained using the oxazolidine methyl ester (68) or the thiazolidine methyl esters (85 and 86).



(90)

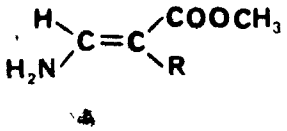
Since the aldehyde esters had a weak enol ether bond, one would anticipate that this ether bond would be cleaved by the above nucleophiles (as in case of mercaptide) and that the aldehyde function might have a role in giving a complex mixture. We thought that if the enol ether bond and the aldehyde function could be suitably modified, the resulting molecule would be more stable to the reaction conditions of the ester hydrolysis. We thus tried to transform the aldehyde esters (82, 87) to the imine esters (91, 92), which are intermediates in the synthetic sequence.



(91) R = Phthalimido

(92) R = NHC(=O)Ph

The aldehyde methyl ester (82 or 87) was dissolved in a number of solvents such as ethanol, tetrahydrofuran or methylene chloride and the solution was saturated with ammonia at 0°C and then allowed to stand at room temperature. Thin layer chromatography showed that after 4 hours, the starting material had completely reacted, but several new spots appeared. The mass spectrum of the crude mixture indicated that the correct product (91 or 92) was formed but the aminomethylene compound (93) was also obtained.

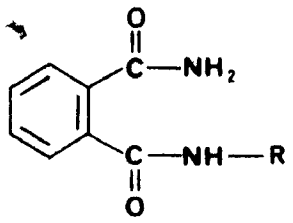


R = Phthalimido,

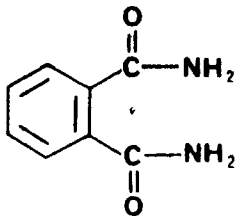
NHC(=O)Ph

(93)

In particular, when the phthalimido compound (82) was reacted, the cleavage of the phthalimido group also occurred. The phthalimido group is known to be cleaved by amines or hydrazines[57], thus the treatment of (82) with excess ammonia would have given the mixture of (94) and (95), along with the other products.

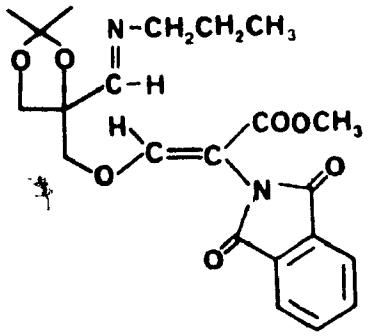


(94)



(95)

Since these cleavage reactions of the phthalimido group and of the enol ether bond had occurred with excess ammonia, it was decided to use exactly one equivalent of ammonia. As a prelimiary reaction, the aldehyde ester (82) was treated with 1 equivalent of n-propylamine in methylene chloride for 6 hours at room temperature. Evaporation of the solvent, and purification through a silica gel column

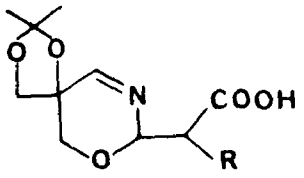


(96)

gave only the Schiff base (96) without affecting the phthalimido group or enol ether bond, showing that the aldehyde function was the most reactive electrophile in (82).

Therefore, the aldehyde methyl ester (82 or 97) was dissolved in a minimum amount of tetrahydrofuran and 1.1 equivalents of ammonia in tetrahydrofuran was added. The mixture was tightly covered and kept overnight at room temperature. Drying, evaporation and passage through a silica gel column gave more than 90 % yield of the pure imine methyl ester (91 or 92) as an amorphous solid.

Attempts to hydrolyze the methyl ester function of these imine methyl esters (91 and 92) to the imine acids (97 and 98) were also unsuccessful. Similar results were obtained as in the attempted hydrolysis of the aldehyde esters (82 and 87).



(97) R = Phthalimido

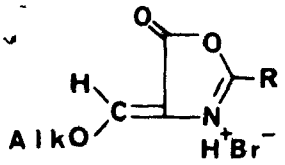
(98) R = NHC Ph
‖
O

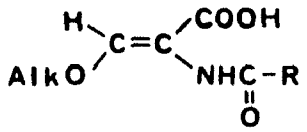
Since the methyl esters were used to determine the best reaction conditions of each step, and these esters could not be hydrolyzed without destruction of the whole molecule, it was decided to introduce other esters that would be removed either by extremely mild hydrolytic conditions or by non-hydrolytic methods.

CHAPTER III

BRIEF STUDIES OF 2-BENZYL-5-OXAZOLONE DERIVATIVES AND THEIR APPLICATION TO THE SYNTHESIS OF THE KEY INTERMEDIATE

Whilst the methyl esters did not afford the key intermediate, we found that hydrobromides of 4-alkoxy-methylene-2-alkyl or 2-benzyl-5-oxazolone (99) would give the corresponding free acids (100) by simple treatment with water [58]. We attempted to apply this reaction method to the synthesis of the imine acid (101).

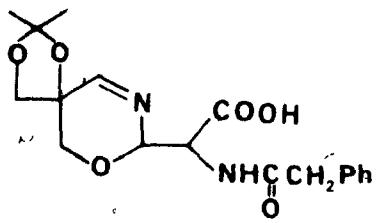




Alk = Me, Et

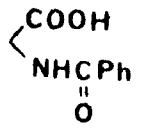
R = Benzyl, Amyl, Heptyl

(99) (100)

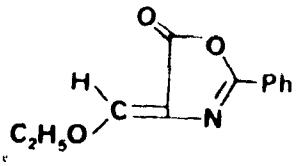


(101)

In a first attempt, we tried to hydrolyze the easily available but conjugated 4-ethoxymethylene-2-phenyl-5-oxazolone (103). Treatment of the 2-phenyl-5-oxazolone (103) with acid or base gave the hydroxymethylene oxazolone (104)[60]. The hydrobromide salt (105), which was prepared by passing hydrogen bromide gas to the ethereal solution of (103), also did not give the acid (106) when it was treated with water. It was thus concluded that the conjugation of the Δ^2 double bond with its 2-substituent, a phenyl group, stabilized the oxazolone ring system and protected the oxazolone from the hydrolysis.



(102)



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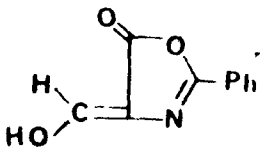

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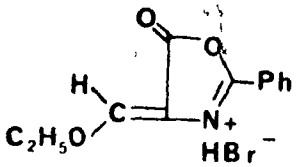

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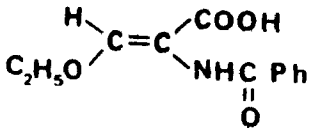
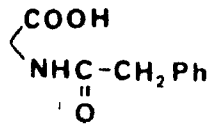
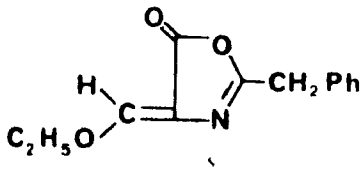


(106)

This result led us to prepare one of the non-conjugated oxazolones, 4-ethoxymethylene-2-benzyl-5-oxazolone (107), and to examine the ring opening reaction.



(108)

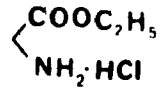


(107)

The 2-phenyl derivative (103) was easily prepared from the reaction of hippuric acid (102) and triethyl orthoformate in refluxing acetic anhydride[59]. However, the 2-benzyl derivative (107) could not be prepared by the same reaction using phenylacetylglycine (108). G.l.c. showed that a complex mixture containing more than 10 components was obtained. Hence, we used the following method to prepare (107) although it was more complicated.

Glycine ethyl ester hydrochloride (109) was converted in 90 % yield to N-formylglycine ethyl ester (110)[61], which was formylated with ethyl formate and sodium ethoxide to the enolic sodium salt (111). Without purification, the sodium salt was treated with ethanolic hydrogen chloride, followed by sodium bicarbonate, and the resulting liquid

distilled to give β,β-diethoxyalanine ethyl ester (112) in 48 % yield[62]. The amino group of (112) was protected with phenylacetyl chloride and the ester function was hydrolyzed to give 2-phenylacetamido-3,3-diethoxypropionic acid (113) in more than 90 % yield.[62]



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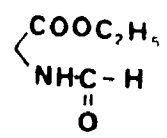

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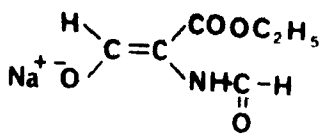

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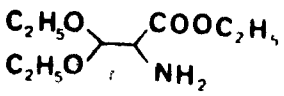

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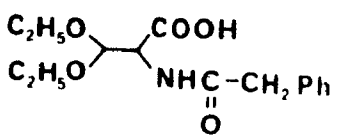
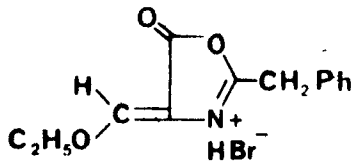


(113)

Treatment of the propionic acid (113) with warm acetic anhydride and evaporation of the solvent afforded a quantitative yield of 2-benzyl-4-ethoxymethylene-5-oxazolone (107)[63] as a pale yellow oil.

The hydrobromide salt (114) was then prepared from the reaction of this oxazolone (107) with hydrogen bromide gas in ethyl ether, or directly from the reaction of the propionic acid (113) and phosphorus tribromide[63]. When this salt (114) was treated with water, an oil

rapidly separated and solidified. The nmr, infrared and uv spectra of this product showed that 3-ethoxy-2-phenyl-acetamidoacrylic acid (115) was obtained.



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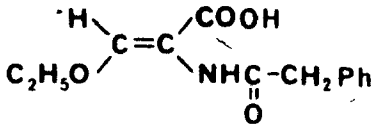
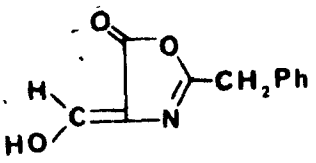


(115)

Since we confirmed that the hydrobromide salt of the 2-benzyl-5-oxazolone (114) gave the free acid (115) by simple treatment with water, we attempted to apply this reaction method to our reaction sequence.

2-Phenylacetamido-3,3-diethoxypropionic acid (113) was transformed to 4-ethoxymethylene-2-benzyl-5-oxazolone (107) and the oxazolone was reacted with sodium hydroxide. Acidification of the aqueous solution gave a 86 % yield of 4-hydroxymethylene-2-benzyl-5-oxazolone (116)[63]. The thallium salt (117) was then prepared by the reaction of (116) with thallium ethoxide in dioxane.

Treatment of the thiazolidine mesylate (50) with an excess amount of the thallium salt (117) in refluxing dry 2-butanone gave a 94 % yield of the thiazolidine oxazolone (118) as a pale yellow oil.



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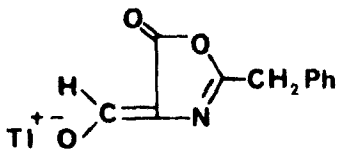

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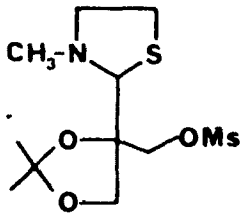

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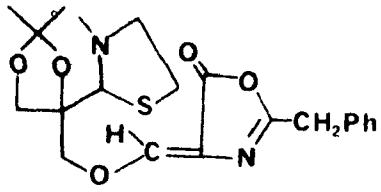
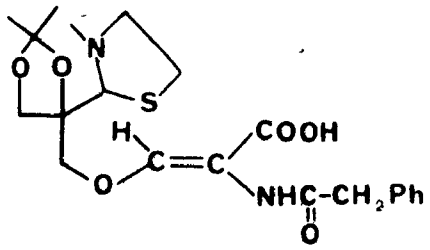
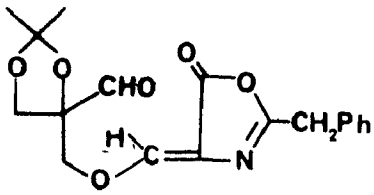


(118)

Attempts to generate the thiazolidine acid (119) from the thiazolidine oxazolone (118) gave a complex mixture. When the oxazolone (118) was treated with hydrogen bromide in ethyl ether and the resulting salt was treated with water, the infrared and uv spectra of the product showed a substantial amount of the unreacted oxazolone (118) was still present. Since (118) has two amino groups, we thought that these amino groups competitively reacted with hydrogen bromide. The resulting mixture of the hydrobromide salts may have given a mixture of products when the salts were treated with water. Since no pure product could be obtained, this particular approach to prepare the thiazolidine acid (119) had to be abandoned.

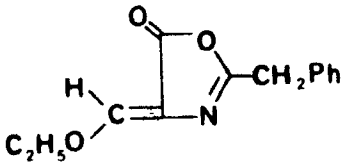


(119)

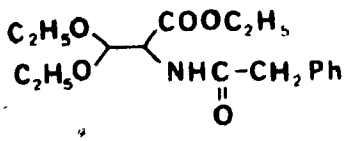


(120)

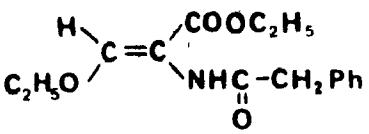
In a next attempt, we tried to remove the thiazolidine group of the thiazolidine oxazolone (118) to prepare the aldehyde oxazolone (120) using mercuric chloride in aqueous acetonitrile or tetrahydrofuran. This reaction also gave a mixture of the products, from which only 45 % yield of a reasonably pure aldehyde oxazolone (120) was isolated by means of preparative thin layer chromatography.



(107)

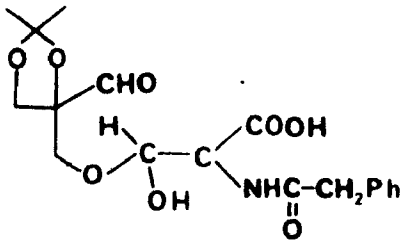


(121)

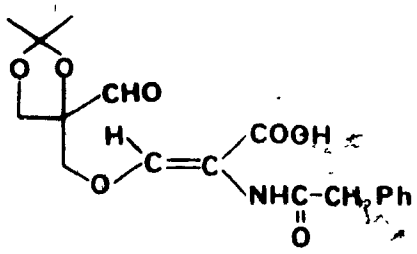


(122)

Since it is known that[58] the ethanolysis of 2-benzyl-4-ethoxymethylene-5-oxazolone (107) gives a mixture of the acetal ester (121) and the acrylic ester (122) within a few minutes, one would anticipate that the generated aldehyde oxazolone (120) may react further with water to give a mixture of (123) and the aldehyde acid (124) along with the desired aldehyde oxazolone (120).

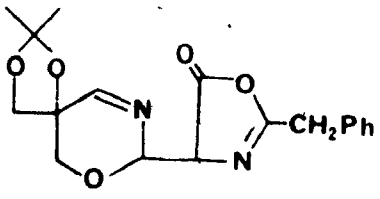


(123)

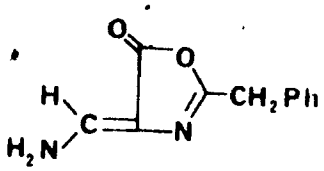


(124)

Using this reasonably pure aldehyde oxazolone (120), attempts to prepare the imine oxazolone (125) were made. However, when the aldehyde oxazolone was treated with one equivalent of ammonia in tetrahydrofuran, only the aminomethylene oxazolone (126) was obtained within a few seconds.

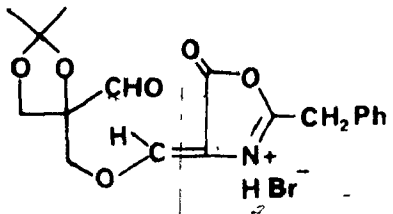


(125)

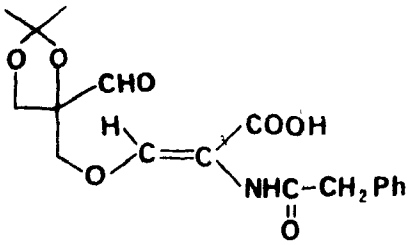


(126)

Since it was impossible to obtain the thiazolidine acid (119) or the imine oxazolone (125), we attempted to prepare the aldehyde acid (124). The aldehyde oxazolone (120) was treated with hydrogen bromide and the precipitated salt (127) was immediately treated with water or sodium acetate solution. Although the uv spectrum of the product showed that the oxazolone moiety was no longer present, and the infrared spectrum showed the broad peaks at 2500-3300 cm^{-1} corresponding to acids, the nmr spectrum indicated that the acetonide function was substantially cleaved and the acidic proton could not be detected.

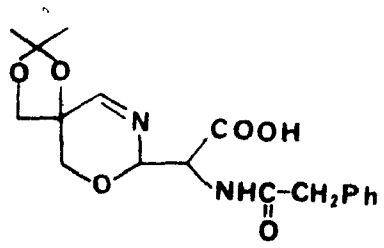


(127)



(124)

We thus concluded that, as the highly anhydrous reaction conditions could not be maintained during the passing of hydrogen bromide gas into the ethereal solution of the aldehyde oxazolone (120), strong hydrolytic conditions resulted and thus the acetonide function did not survive and a mixture of products was obtained.

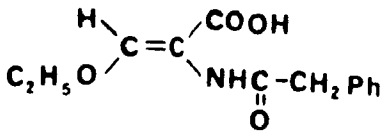


(101)

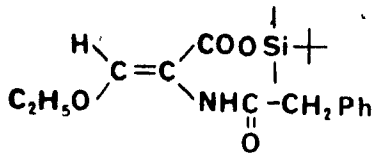
Since we could not prepare the imine oxazolone (125) or the aldehyde acid (124), it was impossible to synthesize the key intermediate, the imine acid (101), and thus we gave up this approach.

Although we failed to prepare the imine acid (101), 3-ethoxy-2-phenylacetamidoacrylic acid (115), which was derived from 4-ethoxymethylene-2-benzyl-5-oxazolone hydrobromide salt (114), had a similar molecular structure as those of the intermediates in our reaction sequence. From this acid, we made some easily hydrolyzable esters which might be applied to our reaction sequence as acid blocking groups, and examined their hydrolysis conditions and applicabilities to the reaction sequence.

The first approach dealt with the silyl ester (128). Treatment of the acid (115) with t-butyldimethylsilyl chloride and imidazole in dimethylformamide[64] gave a 68 % yield of the silyl ester (128). This ester was easily hydrolyzed by tetraethylammonium fluoride in tetrahydrofuran[65] or potassium fluoride in acetonitrile[66] within a few minutes. It was also stable to the saturated ammonia solution in methylene chloride for 24 hours. However, it was found that the silyl ester was unstable to the condition in which the thiazolidine group was cleaved with mercuric chloride in our reaction sequence, being easily solvolyzed to the free acid (115) in aqueous acetonitrile or tetrahydrofuran within 40 minutes.



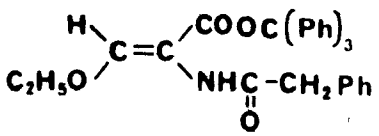
(115)



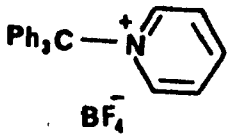
(128)

The next approach involved the trityl ester (129). Trityl esters are known to be easily cleaved by weak acid[67]. Although the trityl ester (129) was easily prepared from the acid (115) and trityl pyridinium fluoroborate complex[68]

(130) in methylene chloride, it also appeared to be solvolyzed to the free acid (115) in aqueous acetonitrile or tetrahydrofuran within two hours.

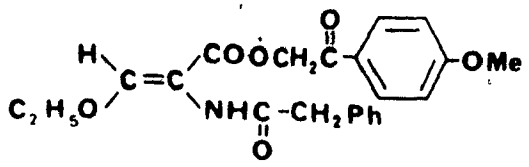


(129)

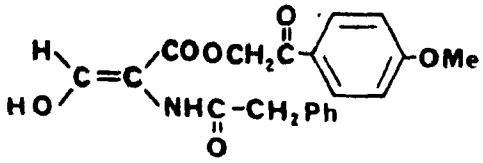


(130)

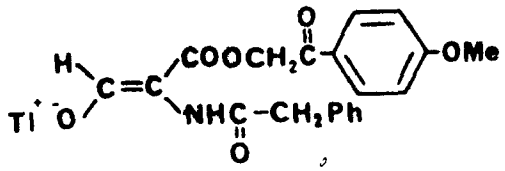
The other approach utilized the p-methoxyphenacyl ester (131). These esters are known to give the free acids by photolysis[69]. Treatment of the acid (115) with p-methoxyphenacyl bromide and triethylamine in dimethylformamide gave a quantitative yield of the ester (131). However, an attempt to cleave the ethoxy group with sodium hydroxide gave only the free acid (115), rather than the hydroxy ester (132), from which the sodium salt (133) would have to be prepared for condensation with the thiazolidine mesylate (50) to give the thiazolidine ester (134).



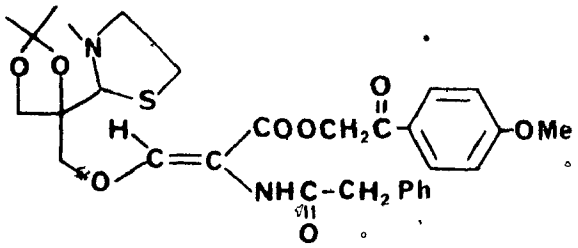
(131)



(132)



(133)



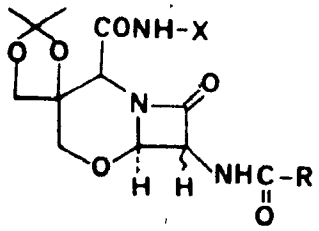
(134)

Having failed to prepare the imine acid (101), using 2-benzyl-5-oxazolone derivatives, we gave up this approach and attempted to use the benzyl esters which would be hydrogenolyzed to the free acid. This will be discussed in the next chapter.

CHAPTER IV

SYNTHETIC STUDIES TOWARDS THE PREPARATION OF THE OXACEPHAM DERIVATIVE USING BENZYL AND p-NITROBENZYL ESTERS AS ACID PROTECTING GROUPS

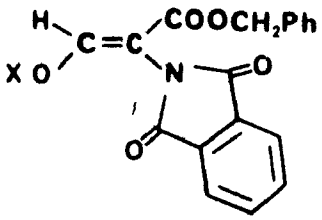
Benzyl esters are known to be easily hydrogenolyzed to the corresponding acids under neutral conditions[70] and p-nitrobenzyl esters are hydrogenolyzed even faster than benzyl esters under the same reaction conditions[71]. We attempted to use these benzyl esters as acid protecting groups in our reaction sequence to synthesize the oxacepham derivatives (45)



(45)

Phthaloylglycine benzyl ester was formylated with benzyl formate and sodium hydride to benzyl 2-phthalimido-3-hydroxyacrylate (135a)[48], and its thallium salt (135b) was prepared by treatment of (135a) with thallium ethoxide. 2-Benzamido-3-hydroxyacrylic acid benzyl ester (136a)[72] and the corresponding p-nitrobenzyl ester (137a) were also

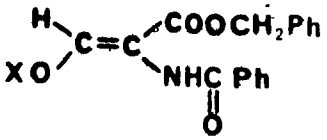
prepared from the reaction of 4-hydroxymethylene-2-phenyl-5-oxazolone (104) with benzyl alcohol or p-nitrobenzyl alcohol respectively, and their sodium salts (136b, 137b) were prepared from the reaction of the hydroxy compounds with sodium ethoxide in ethanol.



(a) X = H

(b) X = Tl

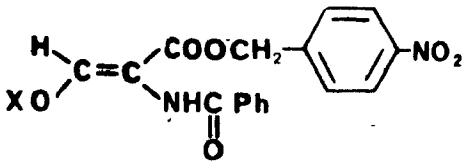
(135)



(a) X = H

(b) X = Na

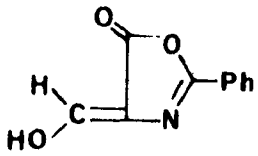
(136)



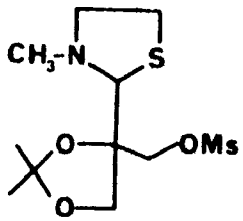
(a) X = H

(b) X = Na

(137)

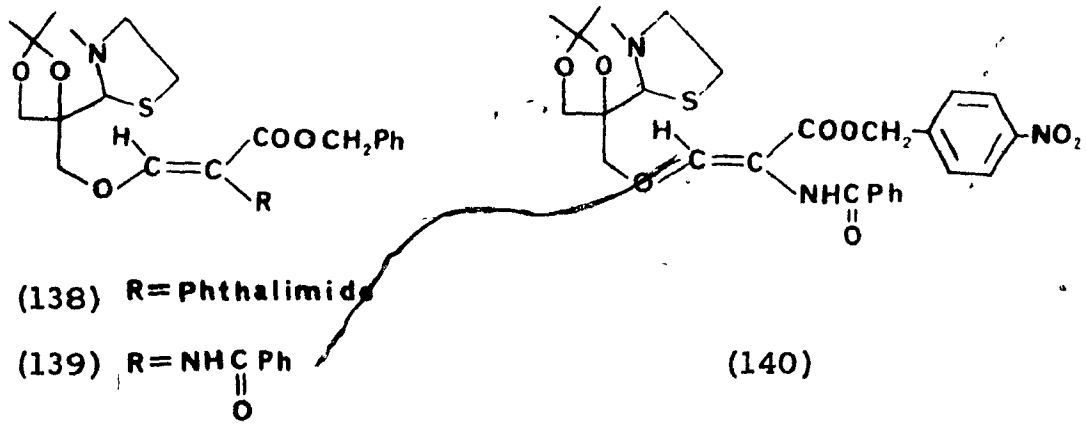


(104)



(50)

Condensation of the thiazolidine mesylate (50) with the salts (135b, 136b or 137b) in refluxing 2-butanone gave a quantitative yield of the thiazolidine esters (138, 139 and 140).

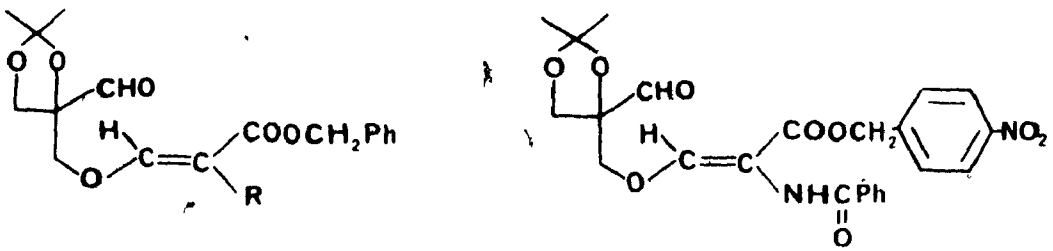


(138) R=Phthalimido

(139) R=NHC(=O)Ph

(140)

Hydrolysis of the thiazolidine group of the thiazolidine esters to the corresponding aldehydes (141, 142 and 143) was also carried out using mercuric chloride in aqueous tetrahydrofuran, in which the phthalimido aldehyde ester (141) was obtained in a quantitative yield, but the other aldehyde esters (142, 143) in only 75% yield.

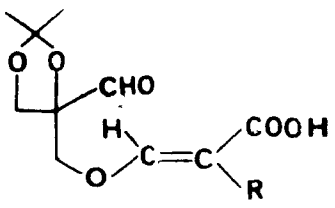


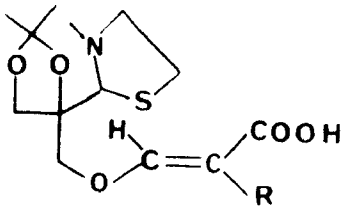
(141) R=Phthalimido

(142) R=NHC(=O)Ph

(143)

Attempts to convert these aldehyde esters to the aldehyde acids (88, 89) by hydrogenolysis using palladium on charcoal in ethanol or ethyl acetate were unsuccessful. Although the ester function completely disappeared within 2 hours, the infrared and nmr spectra of the product indicated that the aldehyde group was no longer present. This was confirmed by the hydrazone formation[73], which did not take place when 2,4-dinitrophenylhydrazine was added to the methanolic solution of the product. Attempts to hydrogenolyze the thiazolidine esters (138, 139 and 140) to the thiazolidine acids (144, 145) were also unsuccessful. Only starting materials were recovered after 24 hours.





(88) R = Phthalimido

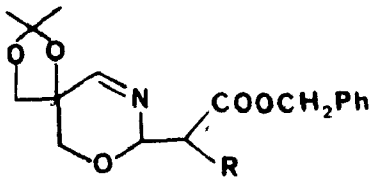
(89) R = NHC Ph (O)

(144) R = Phthalimido

(145) R = NHC Ph (O)

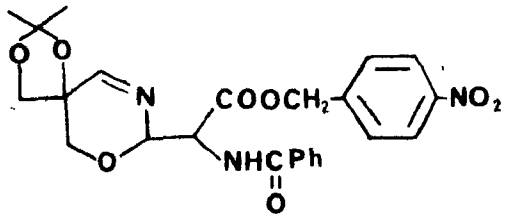
Since the aldehyde acids or the thiazolidine acids could not be produced, the imine esters (146, 147 and 148) were prepared by treatment of the aldehyde esters (141, 142 and 143) with 1.1 equivalents of ammonia in tetrahydrofuran.

In general, it is known that imines are more stable to hydrogenolysis than aldehydes.



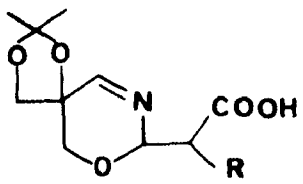
(146) R= Phthalimido

(147) R= NHC Ph (O)



(148)

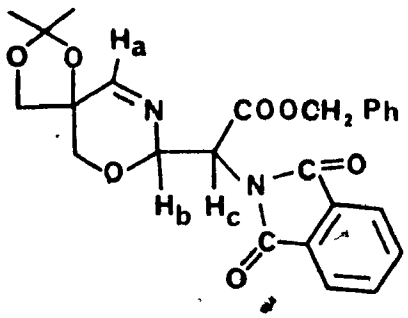
We then attempted to hydrogenolyze the benzyl ester function of the imine esters to prepare the imine acids (97, 98). When the hydrogenolysis of (146) was performed using palladium on charcoal in ethanol or ethyl acetate at 1 atm, a product was obtained within 2 hours, in which the infrared spectrum showed the disappearance of the ester peak at 1760 cm^{-1}.



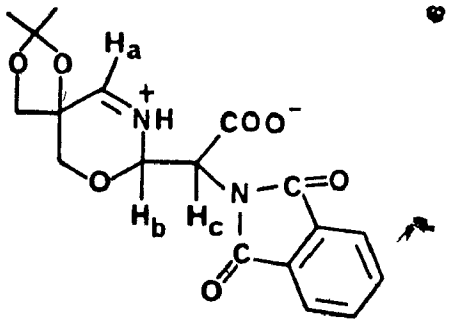
(97) R= Phthalimido

(98) R= NHC Ph (O)

This product, however, was not extractable with sodium bicarbonate or sodium hydroxide, and its nmr and mass spectra were quite different from the expected ones. Although the benzyl group was no longer present in the nmr spectrum, the expected acidic proton of the imine acid (97) or the proton on the imminium nitrogen of the zwitterion (149) was not observed. Furthermore, the two protons, H_a and H_b, which had appeared at δ=7.82 ppm and δ=5.74-5.98 ppm respectively in the imine ester (146), disappeared. Eight protons appeared as broad multiplets at δ=2.94-4.03 ppm. Five of these protons, H_c and four protons adjacent to oxygen, corresponded to the five protons which had appeared in this region in (146). No change was observed for the absorptions of the phthalimido and acetonide functions.



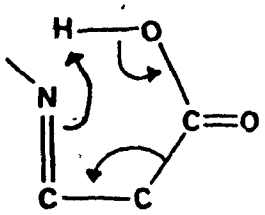
(146)



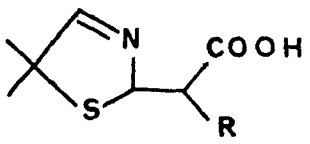
(149)

The mass spectrum of the product did not show the molecular ion (M^+=374) of the imine acid (97), but a strong peak appeared at m/e=330 which was the parent peak of the decarboxylated product of the imine acid (97) (molecular weight of the decarboxylated compound is 330). This product also did not undergo the Ugi reaction when it was treated with ethyl[74], isopropyl[75], or cyclohexyl[76] isonitrile in a two phase mixture of water and petroleum ether.

Similar results were obtained when the other imine esters (147, 148) were submitted to the hydrogenolysis-Ugi reaction sequence.



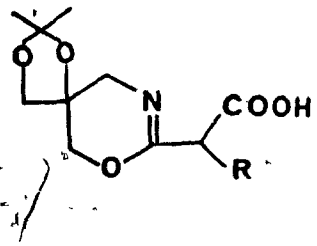
(150)



(151)

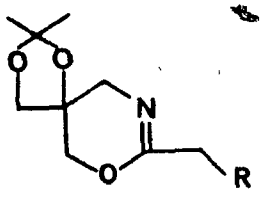
It is known[77] that the β-imino acids of the type (150) are easily decarboxylated by the mechanism shown in (150), and there is also some old experimental evidence[33,78] that the imine acids of the type (151) were decarboxylated even on standing at room temperature. Therefore we concluded that, on the basis of the infrared

and nmr spectral data of the product, the hydrogenolysis of the imine esters (146, 147, 148) produced the desired imine acids (97, 98), but that it was rapidly isomerized to (152), which then lost carbon dioxide and isomerized to give the decarboxylated product (153). The nmr spectral data were then consistent with this structure (153), in which the broad multiplets of eight protons at δ = 2.94–4.03 ppm consisted of four protons adjacent to oxygen and the other four protons adjacent to nitrogen.



R = Phthalimido, NHCPh (O)

(152)



R = Phthalimido, NHCPh (O)

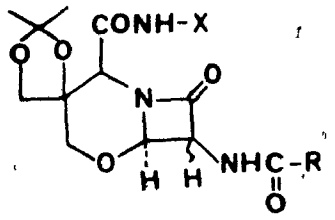
(153)

Having failed to synthesize the oxacepham derivatives using benzyl and p-nitrobenzyl esters, we attempted to use β,β,β-trichloroethyl esters as acid protecting groups and this is discussed in the next chapter.

CHAPTER V

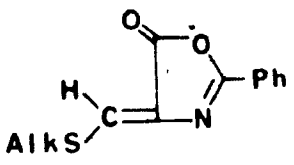
SYNTHESIS OF AN OXACEPHAM DERIVATIVE

β,β,β-Trichloroethyl esters are known to be cleaved to the corresponding acids by zinc-acetic acid[6,79], activated zinc-tetrahydrofuran[80] or potentiostatic electrolysis[81]. Therefore we attempted to use these esters as acid protecting groups in our reaction sequence for the synthesis of the oxacepham derivatives (45).

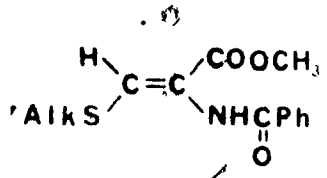


(45)

In the course of the attempted synthesis of the cepham derivative (22), Rosebery[25] found that the methanolysis of the 2-phenyl-4-thioalkoxymethylene-5-oxazolones (154) gave the methyl esters (155) in the presence of triethylamine.

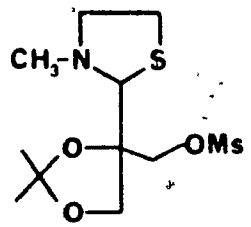


(154)

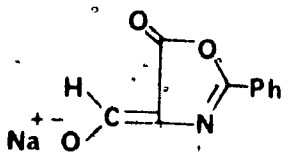


(155)

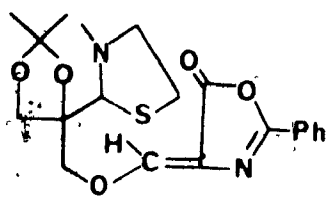
In a first attempt to prepare the β,β,β -trichloroethyl esters, we tried to apply this reaction. 4-Hydroxymethylene-2-phenyl-5-oxazolone sodium salt (156) was condensed with the thiazolidine mesylate (50) in



(50)

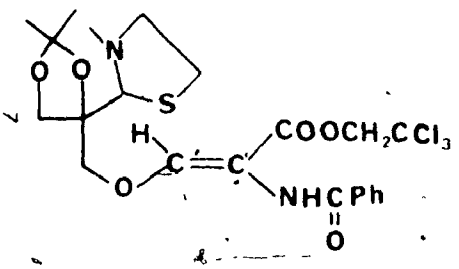


(156)

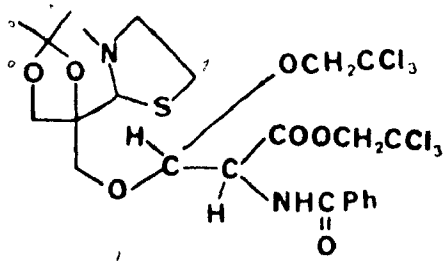


(157)

refluxing 2-butanone and the resulting thiazolidine oxazolone (157) was treated with β,β,β-trichloroethanol in the presence or absence of triethylamine. However, this alcoholysis did not give the pure thiazolidine ester (158). The nmr, infrared and mass spectral data of the product showed that it consisted of a mixture of about equal amounts of the desired thiazolidine ester (158) and the acetal ester (159).



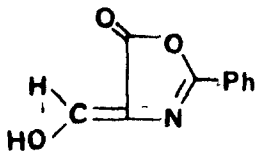
(158)



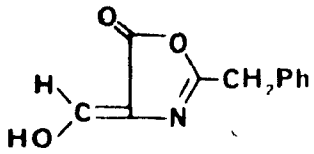
(159)

While the ring opening reaction of the thiazolidine oxazolone (157) did not give the pure ester (158), we noticed that, during the study of 2-benzyl-5-oxazolones, the alcoholysis of the 4-hydroxymethylene-5-oxazolones (104, 116) would give the 3-hydroxy acrylates in an acceptable yield[82].

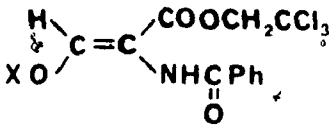
Treatment of the 4-hydroxymethylene-5-oxazolones (104, 116) with 1 equivalent of β,β,β-trichloroethanol in refluxing benzene and subsequent recrystallization



(104)

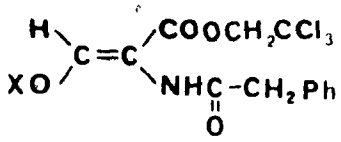


(116)



(a) X = H
(b) X = Na

(160)



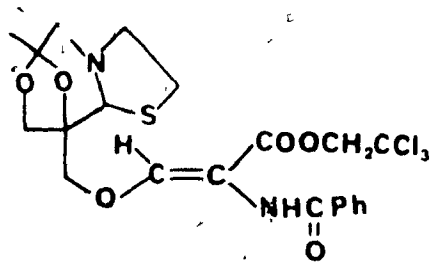
(a) X = H
(b) X = Na

(161)

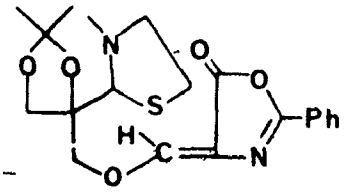
afforded a 70-75 % yield of the hydroxy acrylates (160a, 161a). The sodium salts (160b, 161b) were then prepared in 94 % yield from the hydroxy acrylates and sodium ethoxide in ethanol.

Condensation of the thiazolidine mesylate (50) with the sodium salt of the benzamido acrylate (160b) in refluxing 2-butanone gave the thiazolidine ester (158), which was contaminated with variable amounts of the oxazolone (157). A careful study showed that the amount of the contaminated oxazolone (157) increased with temperature and reaction time. When the bath temperature

was kept at 110°C for 24 hours, the amount of the contaminating oxazolone was nearly 10 % of the product. However, when the reaction was performed at 80°C for 6 hours, the infrared and uv spectra of the product showed that no oxazolone was present.

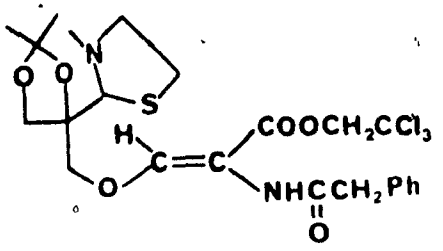


(158)

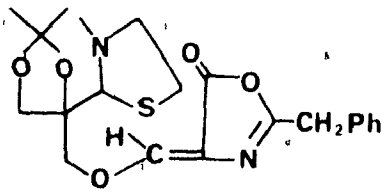


(157)

The sodium salt of the phenylacetamido acrylate (161b) was also condensed with the thiazolidine mesylate (50), and the resulting phenylacetamidothiazolidine ester (162) was not contaminated with the corresponding oxazolone (118), even if the bath temperature was raised to 110°C.

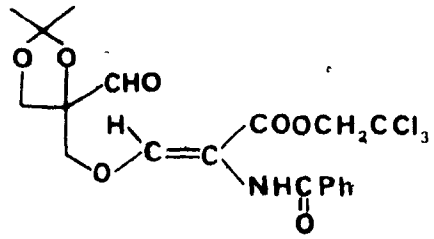


(162)

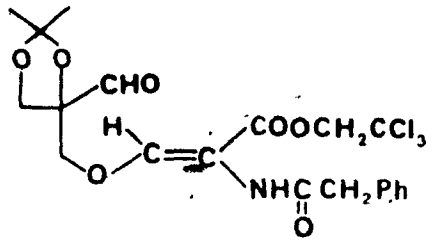


(118)

This result was expected, since phenylacetylglycine (108) did not cyclize to give the oxazolone derivative (107) when it was treated with triethyl orthoformate in the presence of acetic anhydride (see chapter III).



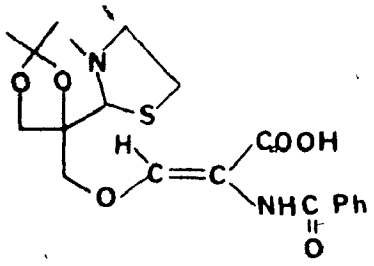
(163)



(164)

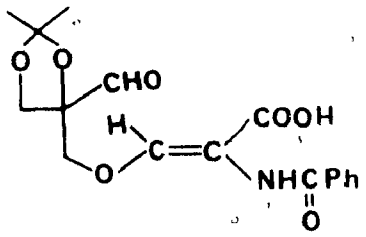
The aldehyde esters (163, 164) were then prepared in 75-85 % yield by treatment of the thiazolidine esters (158, 162) with mercuric chloride in aqueous acetonitrile.

Treatment of the thiazolidine ester (158) with zinc dust in 90 % aqueous acetic acid also afforded the thiazolidine acid (145) in 70 % yield.



(145)

Attempts to prepare the aldehyde acid (89), however were unsuccessful. Treatment of the aldehyde ester (163) with zinc dust in 90 % aqueous acetic acid, and the treatment of the thiazolidine acid (145) with mercuric chloride in aqueous acetonitrile did not give the pure aldehyde acid (89). The product was extractable with sodium bicarbonate and its infrared spectrum showed the

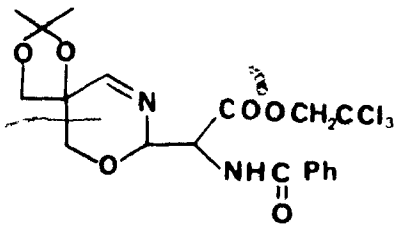


(89)

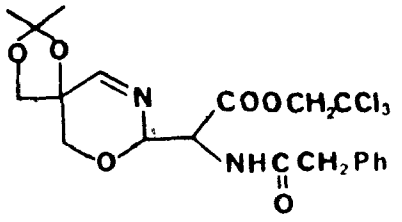
broad peaks at 2500-3300 cm^{-1} corresponding to an acid. The correct microanalysis was also obtained. However, the broad nmr spectrum and the complicated mass spectrum of this product made a proper interpretation impossible.

Since the expected aldehyde acid (89) had double bond, aldehyde and acid functions, it might be anticipated that the product might be hydrated and cyclized, and/or the partial formation of the anhydride might have taken place to give the complicated nmr spectrum.

Treatment of the aldehyde ester (163) with activated zinc in refluxing tetrahydrofuran[80] gave only the starting material. Potentiostatic electrolysis[81] of the aldehyde ester (163) was attempted using a mercury pool electrode as the cathode and lithium perchlorate in dry methanol as an electrolyte. At a potential difference of -1.65 V, a complex mixture was obtained, in which the trichloroethyl group was not cleaved. Therefore we gave up this particular approach to prepare the aldehyde acid (89).



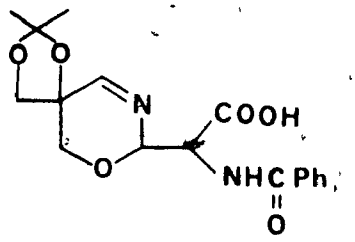
(165)



(166)

Since the synthesis of the aldehyde acid (89) appeared to be quite difficult, the imine esters (165, 166) were prepared by treatment of the aldehyde esters (163, 164) with 1.1 equivalents of ammonia in tetrahydrofuran. It should be noted that when the aldehyde ester (163) was treated with excess ammonia, the trichloroethyl group also reacted along with the aldehyde function.

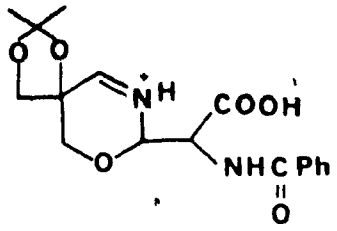
The next step was the preparation of the imine acid (98). Attempts to remove the trichloroethyl group of the imine ester (165) using activated zinc[83] in refluxing tetrahydrofuran[80] or controlled potential electrolysis[81] failed. Accordingly, we attempted to cleave the trichloroethyl group using zinc-acetic acid. When the imine ester (165) was treated with zinc dust in 90 % aqueous acetic acid at 0°C, thin layer chromatography showed that the starting material had completely disappeared within 2 hours.



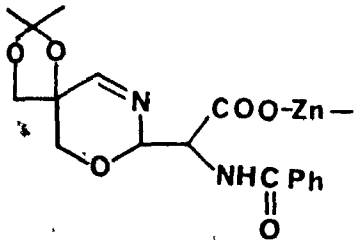
(98)

However, it appeared to be very difficult to purify the generated imine acid (98) because of the following reasons: i) The imine acid was so easily decarboxylated (mentioned in chapter IV) that we had to keep the reaction and purification periods as short as possible. ii) The isoelectric point of the neutral amino acids is generally pH 5-6. Since the reaction was performed in 90 % aqueous

acetic acid (pH=2.5), the generated imine acid (98) may exist as the protonated form (167). This protonated product may then be removed by washing with water during the purification step. iii) The generated imine acid formed the zinc salt (168), which was usually cleaved with hydrochloric acid. However, in our reaction, hydrochloric acid could not be used because the imine acid had an active imminium nitrogen, which may form a hydrochloride salt. This salt may also be removed during the purification step.



(167)

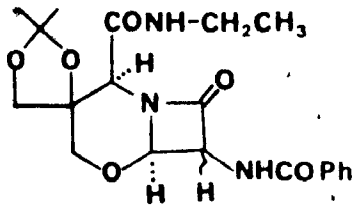


(168)

Because of the above reasons, we planned to perform the cleavage reaction and the subsequent Ugi reaction without isolating the pure imine acid (98).

The imine ester (165) was stirred vigorously with an excess amount of fresh zinc dust in 90 % aqueous acetic acid at 0°C for 2 hours. The unreacted zinc was then filtered off and the filtrate quickly evaporated under

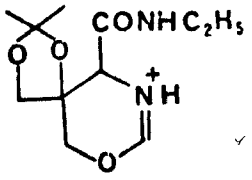
high vacumm. The resulting white solid was dissolved in a minimum of methylene chloride and hydrogen sulfide was passed into the solution to cleave the zinc salt. Zinc sulfide was filtered off and the filtrate diluted with petroleum ether. Phosphate buffer (pH 6) and ethyl isonitrile were added and the two phase mixture was vigorously stirred for 12 hours at room temperature. The crude product was observed to contain the β-lactam (53) as evidenced by its infrared absorption. The crude mixture was purified by means of thin layer chromatography.



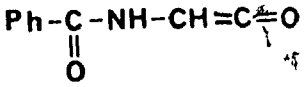
(53)

Although the yield of this reaction was only 5 %, the infrared spectrum of the oily product showed the β-lactam carbonyl absorption at 1750 cm^{-1} and its nmr spectrum was consistent with the oxacepham derivative (53) (see pages 89 and 90 for the nmr and infrared spectrum).

The mass spectrum of (53) showed m/e = 403 (M^+) and the characteristic fragmentations of the β-lactam ring[84]; m/e = 243 (M^+) for the ion (169) and m/e = 161 (M^+) for the ion (170).



(169)

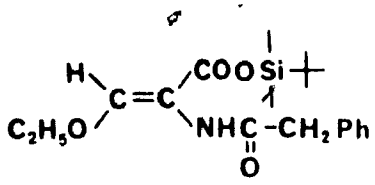


(170)

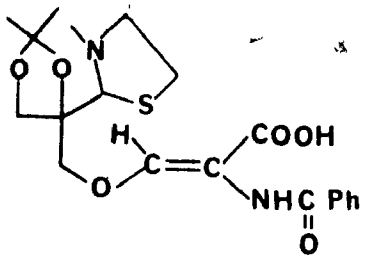
This reaction was repeated several times but the yield of the oxacepham derivative (53) could not be improved. We felt that this low yield was due to the decarboxylation of the imine acid (98) as it was produced during the hydrolysis of the imine ester (165). The mass spectrum of the crude product showed a parent peak (m/e = 304) corresponding to this decarboxylated product. Because of this easy decarboxylation of the imine acid, we felt that an acid protecting group which can be hydrolyzed quickly under mild condition should be introduced. The most suitable one would be t-butyldimethylsilyl ester.

During the course of our study, we found that the silyl ester (128) was stable to ammonia in methylene chloride for 24 hours but solvolyzed within 40 minutes in aqueous acetonitrile or tetrahydrofuran (see p. 64). This would rule out the possibility of cleaving the

thiazolidine group in the presence of the silyl ester with mercuric chloride in aqueous tetrahydrofuran. However, the alternative method to cleave the thiazolidine group using m-chloroperbenzoic acid in methylene chloride could be safely used without solvolysis of the silyl ester (see p. 37). Furthermore, the thiazolidine acid (145) which can be used to prepare the thiazolidine silyl ester (171) was readily obtained from the trichloroethyl ester in good yield (see p. 80).



(128)

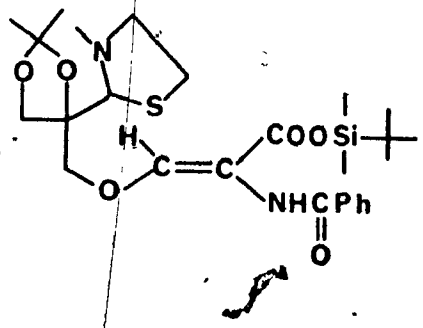


(145)

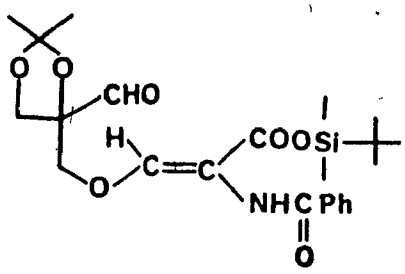
On the basis of the above information, we prepared the thiazolidine silyl ester (171) from t-butyldimethylchlorosilane and thiazolidine acid (145) in 80 % yield. The thiazolidine group of (171) was then cleaved with 2.1 equivalents of m-chloroperbenzoic acid in methylene chloride to give the aldehyde silyl ester (172) in more than 75 % yield.

The aldehyde silyl ester (172) would in principle be transformed to the imine ester (173) by treatment with 1 equivalent of ammonia. This imine ester can then be

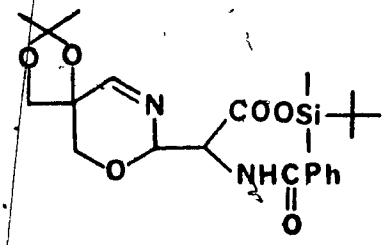
solvolyzed with aqueous tetrahydrofuran or cleaved with tetraethylammonium fluoride to give the imine acid (98) within a few minutes. Without isolation of this intermediate, the Ugi reaction can be done in situ to prepare the oxacepham derivative (53). These remaining reactions will be carried out by Karl Grozinger.



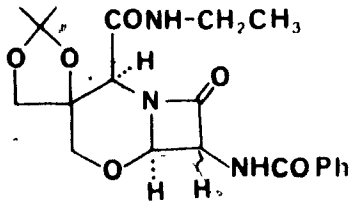
(171)



(172)

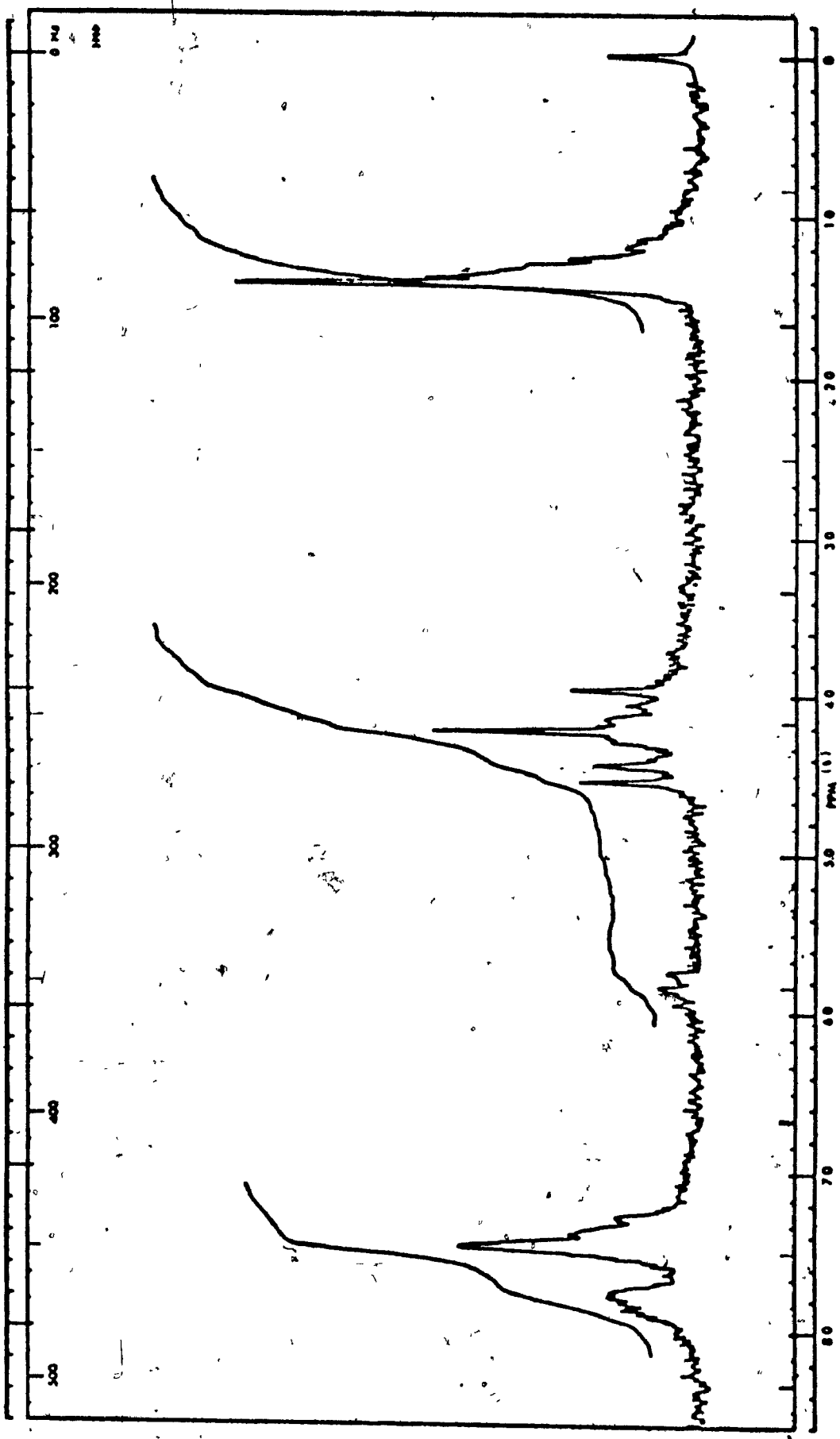


(173)

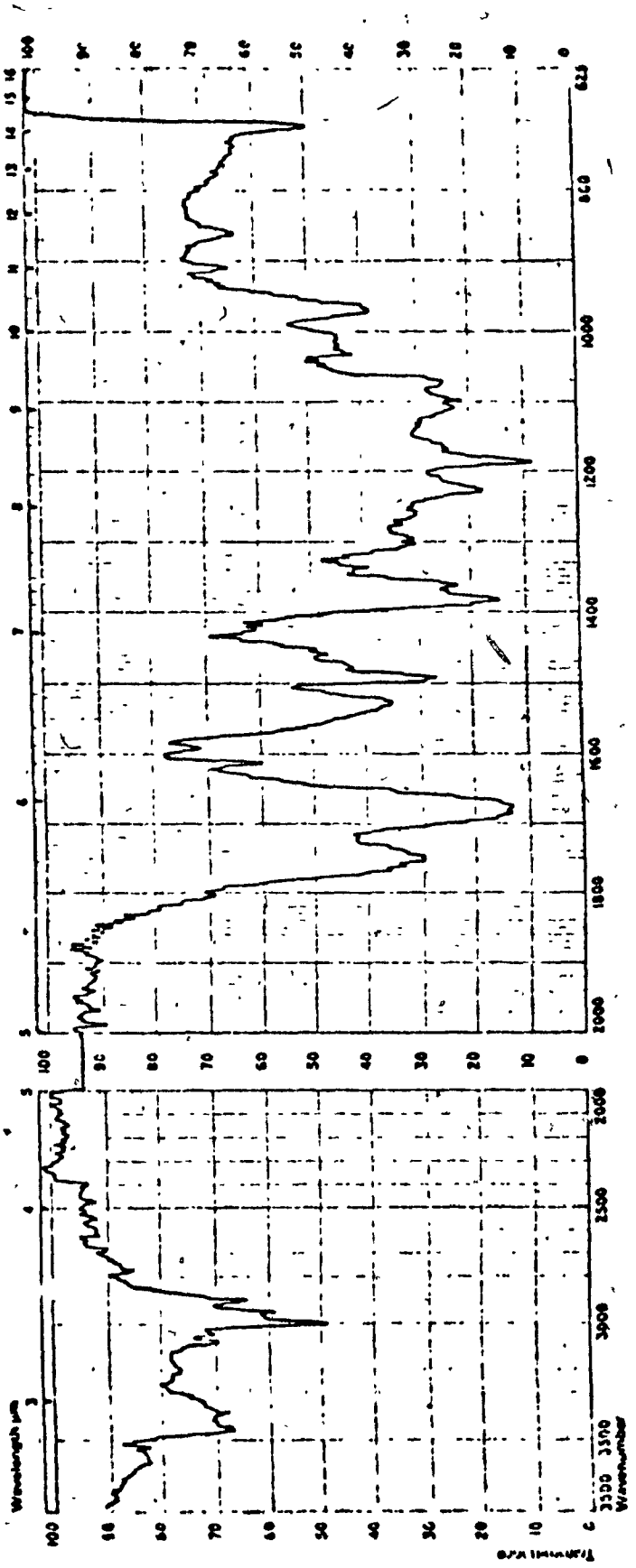


(53)

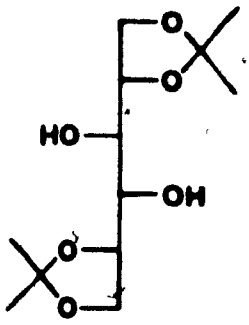
Because of the large number of compounds mentioned in connection with the synthesis of the oxacepham derivative (53), the complete synthetic sequence is summarized on pages 91 and 92.



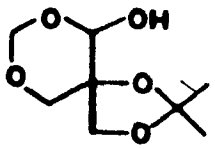
Nmr spectrum of (53) ($CDCl_3$)



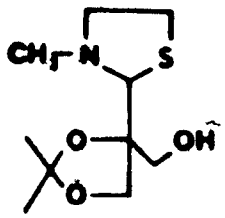
Ir spectrum of (53) ($CHCl_3$)



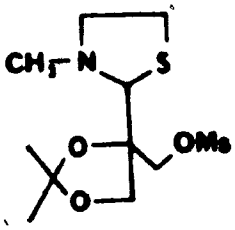
81 %



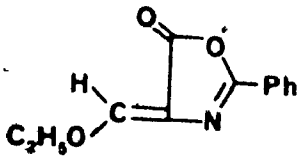
90 %



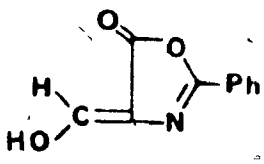
100 %



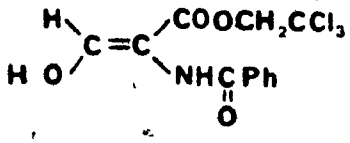
94 %



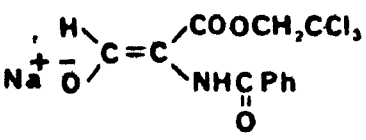
85 %

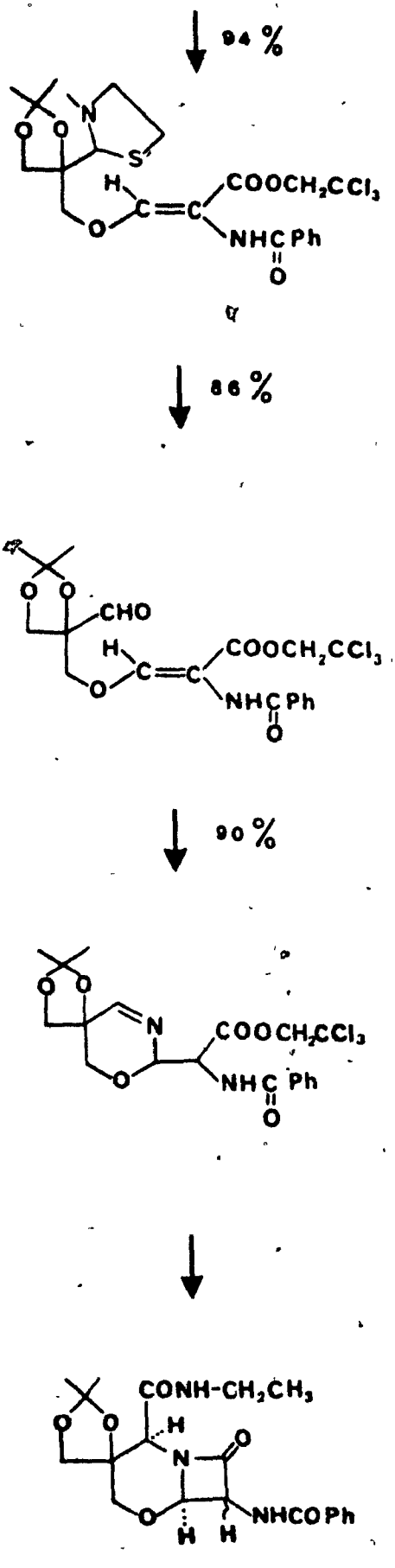


81 %



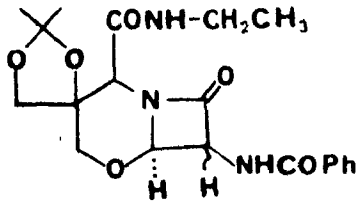
95 %



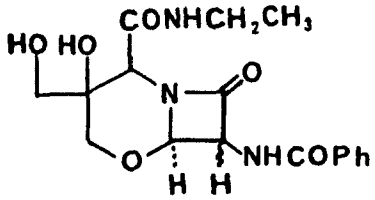

94 %
COOCH2CCl3
NHCPh
86 %
CHO
90 %
CONH-CH2CH3
NHCOPh

PROPOSALS FOR FURTHER STUDY

The work that has been discussed in the preceding chapters is a series of studies aimed at synthesis of oxacepham derivatives. As discussed in the last chapter, further studies to improve the yield of the oxacepham derivative (53) using the t-butyldimethylsilyl protecting group will be undertaken by a co-worker in our laboratory.



(53)

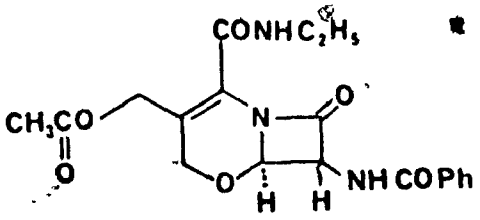


(174)

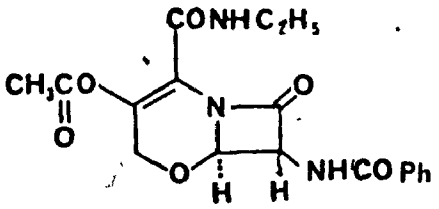
With a reasonable yield of (53), the following work should be undertaken to prepare oxacephem derivatives. The hydrolysis of the acetonide function of (53) using trifluoroacetic acid will give the diol (174). From this diol, two possible oxacephem derivatives (47) and (177) can be prepared.

For the preparation of (47), selective protection of the primary alcohol of (174) with acetic anhydride in pyridine and elimination of the tertiary alcohol possibly with methanesulfonyl chloride in triethylamine will give

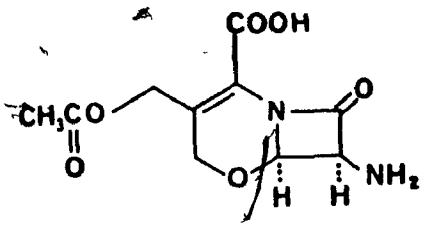
(175). Hydrolysis of the two amide groups of (175) with phosphorus pentachloride in methylene chloride and separation of the two possible stereoisomers by physical methods will give 7-aminooxacephalosporanic acid (47).



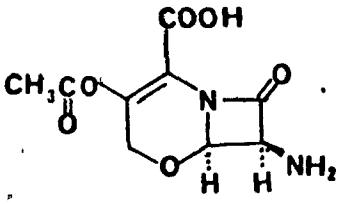
(175)



(176)



(47)



(177)

For the preparation of (177), the diol (174) can be cleaved with sodium metaperiodate and the resulting enol can be protected with acetyl chloride in pyridine to give (176). Hydrolysis of the two amide groups of (176) and separation of the two isomers will give (177). This compound can lead to a new series of oxacephalosporins.

CONTRIBUTIONS TO KNOWLEDGE

A total synthesis of an oxacepham derivative starting from D-mannitol was accomplished.

An improved procedure for the preparation of oxazolidine mesylate starting from D-mannitol was developed.

A new aldehyde protecting group, N-methylthiazolidine, was developed. It is stable to acids, hydrogenolysis, acylating agents and nucleophilic attack by oxygen anions, but can be easily removed with mecuric chloride or with m-chloroperbenzoic acid.

Many new compounds were prepared and characterized.

EXPERIMENTAL

Melting points were determined on a Gallenkamp block and are uncorrected.

Mass spectra were obtained on an AEI-MS-902 mass spectrometer at 70eV using a direct insertion probe. Nmr spectra were recorded on Varian T-60 and HA-100 spectrometers using tetramethylsilane as an internal standard. Doublets, triplets, and quartets in the nmr spectral data were recorded as the center of the peaks and multiplets as their range of absorption. Ir spectra were obtained on a Unicam SP-1000 and Perkin-Elmer PE-257 infrared spectrophotometers. Uv spectra were recorded using a Unicam SP-800 spectrophotometer.

Analytical thin layer chromatography was performed on silica gel coated plastic plates (Eastman Kodak) and on a preparative scale on silica gel (Merck $UV_{254,366}$) coated glass plates. Woelm alumina (neutral, Act. I) and silica gel (Act. III) were used for column chromatography.

Microanalyses were carried out by C. Daessle, Montreal. All chemicals are "Reagent Grade" unless otherwise specified.

EXPERIMENTAL - CHAPTER I

Preparation of mannitol diacetonide (54)

D-Mannitol (182 g) was suspended in a mixture of acetone (1500 ml) and dimethoxypropane (180 g). p-Toluenesulfonic acid (1 g) was added and the suspension was stirred at room temperature for one hour. Unreacted mannitol (90 - 100 g) was filtered off and the filtrate shaken with anhydrous potassium carbonate (50 g) until it was colorless. Potassium carbonate was filtered off and the filtrate evaporated to dryness in vacuo. The semi-solid residue was transferred to an Erlenmeyer flask containing petroleum ether (60 - 80°C) (3500 ml) and heated to boiling with good stirring until almost all the solid had been dissolved. The undissolved material was immediately filtered and the filtrate heated to boiling. The solution was cooled and the product collected by filtration, washed with cold petroleum ether and allowed to dry.

Yield: 30 g, mp : 119 - 121°C (lit.[36] 119°C)

Nmr ($CDCl_3$): δ 1.37, 1.42, (each s, 6H, acetonide), 2.70 (broad s, 2H, OH), 3.6 -4.25 ppm (m, 8H)

Ir (KBr): 3400, 3280, 3000, 2946, 2900, 1427, 1396, 1385, 1374, 1169, 1135, 1078, 1050 cm^{-1}

Preparation of glycerol acetonide (63)

The procedure of Renoll and Newman[38] was followed and the fraction boiling at 89-92°C/17-18 mmHg (lit.[38] 80-81°C/11 mmHg) was collected.

Yield: 91 %

Nmr ($CDCl_3$): δ 1.37, 1.42 (each s, 6H, acetonide), 3.5-4.3 ppm (m, 6H)

Ir (CCl_4): 3490, 3000-2905, 1470, 1392, 1378, 1221, 1167, 1040, 1080 cm^{-1}

Preparation of glyceraldehyde acetonide (55)

The procedure of Baer and Fischer[36] was followed. The product was a colorless oil and distilled at 55-58°C/22 mmHg (lit.[36] 35-42°C/8-11 mmHg).

Yield: 75 %

Nmr ($CDCl_3$): δ 1.43, 1.49 (each s, 6H, acetonide), 3.8-4.33 (m, 3H, OCH_2 and OCH), 9.7 ppm (d, J=4Hz, 1H, aldehyde)

Ir (neat): 3450, 1725 (aldehyde), 1260, 1220, 1080 cm^{-1}

Preparation of the dioxan (56) from (55)

The procedure of Rossy[35] was followed using glyceraldehyde acetonide (55), formaldehyde and potassium

carbonate in aqueous methanol. We found, however, this product was contaminated with an impurity.

Direct preparation of the dioxan (56) from (54)

Mannitol diacetonide (54) (24 g) was dissolved in a pH 6 buffer solution (400 ml) and sodium periodate (20.4 g) was added. After the mixture was stirred for 30 minutes, 40 % formaldehyde (74 ml) and a solution of potassium carbonate (23.1 g) in water (70 ml) were added. The mixture was stirred overnight at room temperature and extracted three times with methylene chloride. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The crystalline product was pure enough for further use.

Yield: 28.3 g (81 %), mp: 89-90°C

Nmr (Acetone-d_6): δ 1.49 (s, 6H, acetonide), 3.9 (ABq, J=10 Hz, 2H, OCH_2), 4.2 (ABq, J=10 Hz, 2H, OCH_2), 4.02-5.97 (broad, 1H, OH), 5.0 (ABq, J=7 Hz, 2H, O-CH_2-O), 5.12 ppm (s, 1H, O-CH-O)

Ir (KBr): 3405, 3100-2910, 1470, 1396, 1384, 1220, 1162, 1090, 1080 cm^{-1}

Preparation of the oxazolidine alcohol (59)

The dioxan (56) (25 g), prepared directly from mannitol diacetonide, was dissolved in benzene (500 ml) and N-methylethanolamine (20.7 g=2.1 equivalents) was added. Slow distillation resulted in the removal of water. After 400 ml of benzene had been collected, the remaining benzene was evaporated in vacuo. The residue was distilled under high vacuum and the fraction boiling at 100-103°C/0.5 mmHg was collected.

Yield: 25.8 g (89 %)

Nmr ($CDCl_3$): δ 1.42 (s, 6H, acetonide), 2.60 (s, 3H, $N-CH_3$) 2.52-3.47 (m, 2H, $N-\underline{CH_2}-CH_2-O$), 3.50-4.20 (m, 7H, $N-CH_2-\underline{CH_2}-O$, N-CH-O, $\underline{CH_2}-OH$ and $\underline{CH_2}-OC$), 4.48 ppm (broad s, 1H, OH)

Ir (neat): 3600-3300 (OH), 2810 ($N-CH_3$), 1470, 1380, 1260, 1225, 1150, 1080, 1070, 1050 cm^{-1}

Preparation of the oxazolidine mesylate (49)

The pure oxazolidine alcohol (59) (27.6 g) was dissolved in a mixture of triethylamine (19.4g=1.5 equiv.) and methylene chloride (250 ml). The solution was cooled to -50°C in a dry ice-acetone bath and freshly distilled methanesulfonyl chloride (16.2 g) in methylene chloride (50 ml) was added dropwise over a period of 2 hours with

good stirring. The mixture was then poured into water (200 ml) in a separatory funnel and the organic layer was washed twice more with ice water. The methylene chloride solution was dried over anhydrous sodium sulfate and evaporated in vacuo. The oily residue which crystallized after treatment with ethyl ether and cooling to -20°C, was collected by filtration and dried in vacuo.

Yield: 37.6 g(100 %), mp: 83-84°C

Nmr ($CDCl_3$): δ 1.42 (s, 6H, acetonide), 2.47 (s, 3H, N-CH_3), 2.42-3.38 (m, 2H, N-$\underline{CH_2}$-CH_2-O), 3.03 (s, 3H, CH_3-SO_2), 3.67-4.30 ppm (m, 7H, O-$\underline{CH_2}$-CH_2-N, N-CH-O, SO_2-O-CH_2 and O-CH_2-C)

Ir (KBr): 2820, 1475, 1380, 122, 1180, 1080, 1010 cm^{-1}

Separation of the dimesylate (61) from the crude mesylation Product.

The dimesylate (61) was purified as follows.

After mesylation of the impure oxazolidine alcohol (59), prepared from the impure dioxan (56), the pure oxazolidine mesylate (49) was separated by recrystallization of the crude product from petroleum ether (60-80°C). The residue was then passed through an alumina column using a mixture of methylene chloride and ethyl ether (1:1) as eluent and the solvent evaporated. The resulting solid was recrystallized from petroleum ether (60-80°C)-methylene chloride (1:1).

mp: 67-68°C

Nmr ($CDCl_3$): δ 1.47 (s, 6H, acetonide), 3.08 (s, 6H, two SO_2-CH_3), 3.98 (s, 2H, OCH_2), 4.25 ppm (s, 4H, SO_2-O-CH_2)

Ir (KBr): 3500, 3008, 2958, 1495, 1470, 1430, 1396, 1385, 1355, 1290, 1270, 1224, 1188, 1128, 1050 cm^{-1}

Analysis: Calculated for $C_9H_{18}O_8S_2$: C, 34.28; H, 5.96; S, 20.23, Found: C, 34.11; H, 5.81; S, 20.34

Preparation of the aldehyde mesylate (66) from the oxazolidine mesylate (49)

The procedure of Rossy[35] was followed.

The oxazolidine mesylate (49) (590 mg) was dissolved in 50 % aqueous acetic acid (20 ml) and the mixture was stirred vigorously for 2 hours at room temperature. Water was added and the aqueous solution extracted three times with chloroform. Each extract was washed twice with cold water. The combined extracts were dried over anhydrous sodium sulfate and evaporated to dryness in vacuo, which gave a colorless oil.

Yield: 464 mg (97.5%)

Nmr ($CDCl_3$): δ 1.45, 1.50 (each s, 6H, acetonide), 3.09 (s, 3H, SO_2-CH_3), 4.07 (ABq, J=8 Hz, 2H, CH_2-O-C) 4.36 (s, 2H, SO_2-O-CH_2), 9.6 ppm (s, 1H, H-C=O)

Ir (neat): 3475, 2997, 2945, 2900, 1725 (aldehyde), 1448, 1328, 1247, 1210, 1165, 1050 cm^{-1}

Preparation of N-methylaziridine (75)

A mixture of N-methylethanolamine (58) (150 g) and concentrated sulfuric acid (210 g) was heated slowly to 130°C and water was slowly distilled off. When all the water had been removed, the temperature was raised to 250°C and the mixture cooled immediately. The black solid was dissolved in water (700 ml) and a sodium hydroxide solution (400 g in 500 ml of water) was added. The mixture was slowly distilled with vigorous stirring and 400 ml of distillate consisting of aziridine and water was collected in an ice bath. Potassium hydroxide (100 g) was added in portions to the distillate with cooling, and the separated organic layer collected and distilled. The fraction boiling at 27-31°C (lit.[45] 26-30°C) was collected.

Yield: 45.6 g (40 %)

Nmr ($CDCl_3$): δ 0.95 and 1.65 (each t, 4H, CH_2-CH_2), 2.27 ppm (s, 3H, N-CH_3)

Ir ($CHCl_3$): 3100-2800, 2500, 1670, 1470, 1309, 1100, 995 cm^{-1}

Preparation of N-methylaminoethanethiol (73)

Dry methanol (300 ml) was cooled in a dry ice-acetone

bath and saturated with hydrogen sulfide. A solution of N-methylaziridine (75) (36 g) in dry methanol (200 ml) was added dropwise to this mixture with slow bubbling of hydrogen sulfide for 2 hours. The mixture was then brought to room temperature and stirred overnight under dry nitrogen. The methanol was evaporated in vacuo and the resulting white solid was collected by filtration with the aid of cold pentane. This product was found to be very hygroscopic, and thus was kept in the refrigerator under nitrogen.

Yield: 41.5 g (72 %), mp: 50-53°C (lit.[46] 48-54°C)

Nmr ($CDCl_3$): δ 1.82 (s, 1H, SH), 2.23 (s, 1H, NH), 2.59 (s, 3H, CH_3), 2.46-2.78 ppm (m, 4H, $N-CH_2-CH_2-S$)

Ir ($CHCl_3$): 3340(NH), 3060-2800, 2520 (SH), 1680, 1485, 1120 cm^{-1}

Preparation of the thiazolidine alcohol (72)

The dioxan (56) (19 g) and N-methylaminoethanethiol (73) (19.1 g) were dissolved in dry benzene (500 ml) and the mixture heated until benzene distilled slowly. After 400 ml of benzene had been collected, the remaining benzene was evaporated in vacuo. The residue was distilled under high vacuum and the fraction boiling at 127-130°C/0.2 mmHg was collected.

Yield: 21.3 g (90 %)

Nmr ($CDCl_3$): δ 1.47 (s, 6H, acetonide), 2.50, 2.58 (each s,

3H, $N-CH_3$) 2.87-3.23 (m, 4H, $N-CH_2-CH_2-S$), 3.8 (q, J=5Hz, 2H, OCH_2-C), 3.93 (q, 2H, OCH_2), 4.1 (s, 1H, OH), 4.48, 5.57 ppm (each s, 1H, N-CH-S)

Ir (neat): 3460 (broad, OH), 3000-2800, 1470, 1390, 1379, 1300, 1216, 1071, 1000 cm^{-1}

Mass spectrum (70eV): m/e = 233 (M^+)

Analysis: Calculated for $C_{10}H_{19}NO_3S$: C, 51.49; H, 8.21; N, 6.01; S, 13.72, Found: C, 51.53, H, 8.17; N, 6.13; S, 13.63

Preparation of the thiazolidine mesylate (50)

A solution of the thiazolidine alcohol (72) (11.65 g) and triethylamine (7.6 g) in methylene chloride (200 ml) was cooled to -50°C in a dry ice-acetone bath and freshly distilled mesyl chloride (6.3 g = 1.1 equivalent) in methylene chloride (50 ml) was added dropwise over a period of 2 hours. The mixture was poured into water (300 ml) and the organic layer washed twice with cold water. The methylene chloride solution was dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The oily residue was dissolved in ethyl ether (10 ml) and kept overnight in the refrigerator. The white crystalline product was collected by filtration, washed with cold ethyl ether and dried in vacuo.

Yield: 15.5 g (100 %), mp: 65-66°C

Nmr ($CDCl_3$): δ 1.44 (s, 6H, acetonide), 2.37, 2.42 (each s, N-CH_3), 2.8-3.18 (m, 4H, N-CH_2-CH_2-S), 3.06 (s, 3H, SO_2-CH_3), 3.95 (q, 2H, CH_2-O), 4.20, 4.25 (each s, 1H, S-CH-N), 4.30 ppm (s, 2H, CH_2-OSO_2)

Ir (KBr): 3030-2810, 1455, 1391, 1380, 1361, 1339, 1300 1252, 1220, 1200, 1180 cm^{-1}

Analysis: Calculated for $C_{11}H_{21}NO_5S_2$: C, 42.45; H, 6.75 N, 4.50; S, 20.58, Found: C, 42.25; H, 6.59; N, 4.62; S, 20.32

Preparation of the thiazolidine trifluoroacetate (77)

A solution of trifluoroacetic anhydride (2.1 g) in methylene chloride (10 ml) was added dropwise to a mixture of the thiazolidine alcohol (72) (1.16 g) and triethylamine (0.98 g) in methylene chloride in a dry ice-acetone bath for two hours. The mixture was poured into water (50 ml) and the separated organic layer washed with water. Drying over anhydrous sodium sulfate, filtration and evaporation gave a pale yellow oil.

Yield: 1.53 g (98 %)

Nmr ($CDCl_3$): δ 1.44 (s, 6H, acetonide), 2.40; 2.50 (each s, 3H, N-CH_3), 2.8-3.4 (m, 4H, N-CH_2-CH_2-S), 3.9-4.65 ppm (m, 5H, OCH_2 and N-CH-S)

Ir (neat): 3010-2820, 1795 (ester), 1715, 1394, 1395, 1384 1228, 1175, 1160 cm^{-1}

Analysis: Calculated for $C_{12}H_{18}NO_4SF_3$: C, 43.76; H, 5.51; N, 4.25; S, 9.74; F, 17.31, Found: C, 43.49; H, 5.57; N, 4.11; S, 9.34; F, 17.74

Preparation of the aldehyde mesylate (66) from the thiazolidine mesylate (50) using mercuric chloride

The thiazolidine mesylate (50) (311 mg) was dissolved in 80 % aqueous acetonitrile or tetrahydrofuran (10 ml) and mercuric chloride (280 mg = 1.1 equiv.) was added. The white milky suspension was refluxed for 1 hour and then filtered. The filtrate was evaporated in vacuo and the residue extracted with methylene chloride. The methylene chloride solution was washed with dilute hydrochloric acid and water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness in vacuo, giving a white oil.
Yield: 248 mg (96 %)
The nmr and ir spectra were exactly the same as those of the product from the acidic hydrolysis of the oxazolidine mesylate (49).

Preparation of the aldehyde mesylate (66) from the thiazolidine mesylate (50) using m-chloroperbenzoic acid

Thiazolidine mesylate (50) (311 mg) was dissolved in methylene chloride (5 ml) and m-chloroperbenzoic acid

(344 mg=2 equivalents) was added at 0°C. The mixture was stirred for 5 minutes and washed with sodium bicarbonate solution. Drying over anhydrous sodium sulfate, evaporation, passing through a silica gel column using ethyl ether as eluent and evaporation gave a white oil.

Yield: 188 mg (72 %)

The nmr and ir spectra were the same as those of the prodcut from the acidic hydrolysis of the oxazolidine mesylate (49).

EXPERIMENTAL - CHAPTER II

Preparation of methyl 2-phthalimido-3-hydroxyacrylate (67a)

The procedure of Sheehan and Johnson[48] was followed. The crude product was recrystallized from benzene.

Yield: 40 %, mp: 137-139°C (lit.[48] 140.5-142°C)

Nmr (DMSO-d_6): δ 3.65 (s, 3H, CH_3), 7.83 (s, 4H, phthalimido), 8.0 (s, 1H, C=CH), 9.5 ppm (broad, 1H, OH)

Ir (KBr): 3500-3100, 1800/1730 (phthalimido), 1740 (ester), 1700 cm^{-1} (C=C)

Preparation of methyl 2-phthalimido-3-hydroxyacrylate thallium salt (67c)

Methyl 2-phthalimido-3-hydroxyacrylate (67a) (2.47 g) was dissolved in hot benzene (50 ml) and thallium ethoxide (2.74 g, Aldrich, 98 %) was added. The pale yellow powder which settled down immediately was collected by filtration and recrystallized from ethanol.

Yield: 4.5 g (100 %), mp: 245-247°C (decomp.)

Nmr (DMSO-d_6): δ 3.6 (s, 3H, CH_3), 7.9 (s, 4H, phthalimido), 8.98 ppm (s, 1H, C=CH)

Ir (KBr): 3600-3300 (salt), 1800/1730 (phthalimido), 1720 (ester), 1670 (C=C), 1578, 1450 cm^{-1}

Analysis: Calculated for $C_{12}H_8NO_5Tl$: C, 32.03; H, 2.04; N, 3.11 Found: C, 31.76; H, 2.01; N, 3.23

Preparation of methyl 2-phthalimido-3-hydroxyacrylate sodium salt (67b)

Methyl 2-phthalimido-3-hydroxyacrylate (67a) (13.4 g) was dissolved in benzene (100 ml) and an ethanolic solution of sodium ethoxide (1.28 g of sodium in 100 ml of ethanol) was added. The mixture was refluxed for one hour, cooled and the yellow precipitate was collected.

Yield: 13.7 g (98 %), mp: 270-272°C (decomp.)

Nmr (D_2O): δ 3.7 (s, 3H, CH_3), 7.95 (s, 4H, phthalimido), 8.95 ppm (s, 1H, C=CH)

Ir (KBr): 3400, 1800/1730 (phthalimido), 1720 (ester), 1690 (C=C), 1590, 1458, 1430 cm^{-1}

Preparation of methyl 2-phthalimido-3-(((2',2'-dimethyl-4'-(3"-methyloxazolidine-2"-yl)-1',3'-dioxolan-4'-yl) methyl)oxy)acrylate (68)

The thallium salt (67c) (3.375 g) was suspended in a solution of the oxazolidine mesylate (49) (1.475 g) in dry 2-butanone (50 ml). The mixture was refluxed for 6 hours, allowed to cool and filtered. The yellow filtrate was concentrated under reduced pressure. The resulting

foamy solid showed two spots in t.l.c. This crude product was passed through an alumina column using methylene chloride-ethyl ether (5:1) as eluent. A total of 100 ml of the eluant was collected and evaporated in vacuo. The white foamy solid was dissolved in ethyl ether (5 ml) and kept overnight in the refrigerator. The crystalline compound (the undesired perhydrooxazepine derivative) was filtered off and the filtrate was evaporated, giving a white solid.

Yield: 1.0 g (45 %), mp: 43-45°C

Nmr ($CDCl_3$): δ 1.27, 1.38 (each s, 6H, acetonide), 2.45, 2.50 (each s, 3H, $N-CH_3$), 2.4-2.7 and 3.0-3.3 (m, 2H, $N-\underline{CH_2}-CH_2-O$), 3.72 (s, 3H, $O-CH_3$), 3.6-4.02 (m, 2H, $N-CH_2-\underline{CH_2}-O$), 3.91 (s, 1H, N-CH-O), 4.0 (s, 2H, $O-CH_2$), 4.22 (q, 2H, OCH_2), 7.68-8.0 ppm (m, 5H, phthalimido and C=CH)

Ir ($CHCl_3$): 3050-2950, 1800/1740 (phthalimido), 1735 (ester), 1670 cm^{-1} (C=C)

Mass spectrum (70eV): m/e=446 (M^+)

Analysis: Calculated for $C_{22}H_{26}N_2O_8$: C, 59.18; H, 5.87; N, 6.28 Found: C, 58.93; H, 6.04; N, 6.42

<u>The perhydrooxazepine derivative (69) from the reaction of the mesylate (49) and the salt (67c)</u>

This crystalline compound was separated by the method

mentioned above.

Yield: 46 %, mp: 173-174°C

Nmr ($CDCl_3$): δ 1.15, 1.25 (each s, 6H, acetonide), 2.34 (3H, N-CH_3), 2.4-2.7 (m, 4H, CH_2-N-CH_2), 3.73 (s, 3H, OCH_3), 3.7-4.14 (m, 4H, OCH_2), 5.13 (s, 1H, O-CH-O), 7.63-7.94 (m, 4H, phthalimido) 7.92 ppm (s, 1H, C=CH)

Ir (KBr): 2990-2808, 1800/1740 (phthalimido), 1725 (ester), 1670 (C=C), 1480, 1390, 1380 cm^{-1}

Mass spectrum (70eV): m/e = 446 (M^+)

Analysis: Calculated for $C_{22}H_{26}N_2O_8$: C, 59.18; H, 5.87; N, 6.28 Found: C, 58.89; H, 6.01; N, 6.54

Preparation of methyl 2-phthalimido-3-(((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1',3'-dioxolan-4'-yl) methyl)oxy)acrylate (85)

The sodium salt (67b) (7 g) was suspended in a solution of the thiazolidine mesylate (50) (6.22 g) in dry 2-butanone (100 ml). The mixture was refluxed for 6 hours, cooled and filtered. Evaporation of the solvent gave a foam, which was passed through a silica gel column using methylene chloride-ethyl ether (1:1) as eluent. Evaporation of the solvent gave a white foamy solid.

Yield: 9.2 g (100 %)

Nmr ($CDCl_3$): δ 1.27, 1.37 (each s, 6H, acetonide), 2.28,

2.35 (each s, 3H, N-CH_3), 2.78-3.23 (m, 4H, N-CH_2-CH_2-S), 3.73 (s, 3H, OCH_3), 3.8-4.02 (m, 2H, OCH_2), 4.14-4.33 (m, 3H, $OCH_2$and N-CH-S), 7.7-8.02 ppm (m, 5H, phthalimido and C=CH)

Ir ($CHCl_3$): 2985, 1800/1735 (phthalimido), 1720 (ester), 1667 (C=C), 1428, 1395, 1380, 1100 cm^{-1}

Mass spectrum (70eV): m/e = 462 (M^+)

Analysis: Calculated for $C_{22}H_{26}N_2O_7S$: C, 57.14; H, 5.67; N, 6.04; S, 6.92 Found: C, 57.38; H, 6.02; N, 5.89; S, 6.62

Preparation of methyl 2-benzamido-3-hydroxyacrylate (84a)

This pale yellow oily compound was prepared in the same way as (67a) from methyl hippurate.

Yield: 36 %

Nmr (benzene-d_6): δ 3.42 (s, 3H, OCH_3), 6.9-7.82 (m, 6H, phenyl and C=CH), 7.43 (broad, 1H, NH), 8.4 ppm (broad, 1H, OH)

Ir (CCl_4): 3400 (OH), 1710 (ester), 1675 (amide and C=C), 1550, 1453, 1360, 1280, 1100 cm^{-1}

Preparation of methyl 2-benzamido-3-hydroxyacrylate sodium salt (84b)

This compound was prepared in the same way as (67b) from (84a).

Yield: 95 % based on sodium, mp: 204-205°C (decomp.)

Nmr (DMSO-d_6): δ 3.62 (s, 3H, $COOCH_3$), 7.4-7.98 (m, 5H, phenyl), 8.43 (s, 1H, NH), 8.78 ppm (s, 1H, C=CH)

Ir (KBr) : 3320 (salt), 3055-2858, 1660, 1625, 1590, 1540, 1455, 1380, 1328, 1200, 1110 cm^{-1}

Analysis: Calculated for $C_{11}H_{10}NO_4Na$: C, 54.32; H, 4.15; N, 5.76, Found: C, 54.41; H, 4.42; N, 5.67

Preparation of methyl 2-benzamido-3-(((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1',3'-dioxolan-4'-yl) methyl)oxy)acrylate (86)

This foamy compound was prepared in the same way as (85) from (50) and (84).

Yield: 97 %

Nmr ($CDCl_3$): δ 1.33-1.45 (m, 6H, acetonide), 2.33, 2.40 (each s, 3H, N-CH_3), 2.8-3.2 (m, 4H, N-$\underline{CH_2}$-$\underline{CH_2}$-S), 3.73 (s, 3H, $COOCH_3$), 3.7-4.32 (m, 4H, two OCH_2), 4.35, 4.46 (each s, 1H, N-CH-S), 7.2-7.98 ppm (m, 7H, phenyl, NH and C=CH)

Ir (CCl_4): 3440, 3010-1960, 1725 (ester), 1695 (C=C), 1665 (amide), 1517, 1490, 1390, 1378 cm^{-1}

Mass spectrum (70eV): m/e = 436 (M^+)

Analysis: Calculated for $C_{21}H_{28}N_2O_6S$: C, 57.79; H, 6.47; N, 6.42; S, 7.33, Found: C, 57.65; H, 6.75; N, 6.23; S, 7.11

Preparation of methyl 2-phthalimido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (82) from (85)

The thiazolidine methyl ester (85) (4.62 g) was dissolved in tetrahydrofuran-water (4:1) (50 ml) and mercuric chloride (3.0 g = 1.1 equiv.) was added. The immediately formed milky suspension was refluxed for 1 hour, cooled and filtered. The filtrate was concentrated under reduced pressure and the residue extracted three times with benzene. The combined extracts were washed with dilute hydrochloric acid and water, dried over anhydrous sodium sulfate and filtered. Evaporation of the solvent gave a white foamy solid.

Yield: 3.89 g (100 %)

Nmr ($CDCl_3$): δ 1.43 (s, 6H, acetonide), 3.72 (s, 3H, $COOCH_3$), 3.9-4.12 (m, 2H, OCH_2), 4.33 (s, 2H, OCH_2), 7.68-8.0 (m, 4H, phthalimido), 7.9 (s, 1H, C=CH), 9.8 ppm (s, 1H, aldehyde)

Ir (KBr): 3500 (hydrate form of aldehyde), 3050-2950, 1800/1735 (phthalimido), 1735 (ester), 1720 (aldehyde), 1670 cm^{-1} (C=C)

Mass spectrum (70eV): m/e = 389 (M^+)

Analysis: Calculated for $C_{19}H_{19}NO_8H_2O$: C, 56.02; H, 5.20; N, 3.44, Found: C, 56.29; H, 5.21; N, 3.89

Preparation of methyl 2-phthalimido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (82) from (68)

The oxazolidine methyl ester (68) (446 mg) was dissolved in 50 % aqueous acetic acid (10 ml) and the mixture stirred for 2 hours at room temperature. Water (20 ml) was added and the mixture extracted three times with chloroform. The extracts were back-washed twice with water, combined and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 380 mg (99 %) of a white foamy solid.

The nmr, ir and mass spectral data were the same as those of the product from the thiazolidine ester (85).

Preparation of methyl 2-benzamido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (87) from (86)

This white foamy compound was prepared in the same

way as (82) from (86), but it was further purified by passing it through a silica gel column using ethyl ether.

Yield: 70 %

Nmr ($CDCl_3$): δ 1.43 (s, 6H, acetonide), 3.7 (s, 3H, $COOCH_3$), 3.75-4.30 (m, 4H, two OCH_2), 7.25-8.0 (m, 7H, phenyl, NHC=O and C=CH), 9.67 ppm (s, 1H, aldehyde)

Ir ($CHCl_3$): 3440, 3000, 2960, 1730, (broad, ester and aldehyde) 1685 (C=C), 1660 (amide), 1495, 1452, 1395, 1385, 1150, 1100 cm^{-1}

Mass spectrum (70eV): m/e = 363 (M^+)

Analysis: Calculated for $C_{18}H_{21}NO_7$: C, 59.49; H, 5.83; N, 3.86, Found: C, 59.03; H, 5.96; N, 3.72

Preparation of the Schiff base (96) from (82)

The aldehyde ester (82) (97 mg) was dissolved in methylene chloride (10 ml) and n-propylamine (15 mg) in methylene chloride (5 ml) was added at 0°C. The mixture was stirred for 1 hour, dried over anhydrous sodium sulfate and filtered. Evaporation of the solvent gave a white oil.

Nmr ($CDCl_3$): δ 0.85 (t, 3H, $CH_2-\underline{CH_3}$), 1.4 (s, 6H, acetonide), 1.5-1.7 (m, 2H, $\underline{CH_2}-CH_3$), 3.39 (t, 2H, $N-CH_2$), 3.72 (s, 3H, OCH_3), 4.1 (s, 2H, OCH_2), 4.33 (s, 2H, OCH_2), 7.64-8.02 ppm (m, 6H, phthalimido, C=CH and N=CH)

Preparation of a standard ammonia solution in tetrahydrofuran

Dry tetrahydrofuran was saturated with ammonia and the excess ammonia was allowed to evaporate by stirring at room temperature for 2 hours. 10 ml of this solution was diluted with water (10ml) and 10 ml of a known normality of hydrochloric acid was added. A few drops of phenolphthalein were then added and the acidic solution titrated with a standard sodium hydroxide solution. From these data, the normality of the ammonia solution was calculated.

Preparation of α-phthalimido-2,2-dimethyl-1,3,7-trioxa-9-aza (spiro) [4,5] dec-9-ene-8-acetic acid methyl ester (91) from (82)

The aldehyde ester (82) (1 g) was dissolved in tetrahydrofuran (5 ml) and 0.12 N ammonia solution in dry tetrahydrofuran (23.2 ml = 1.1 equiv.) was added. The mixture was kept overnight at room temperature, dried over anhydrous sodium sulfate and evaporated. The foamy solid was passed through a silica gel column using methylene chloride-ethyl ether (5:1) as eluent. Evaporation of the solvent gave a white solid. Yield: 0.89 g (91 %), mp: 71-73°C

Nmr ($CDCl_3$): δ 1.42 (s, 6H, acetonide), 3.73 (s, 3H, $COOCH_3$), 3.90 (s, 2H, OCH_2), 3.59-4.02 (m, 2H, OCH_2), 4.8-5.1 (m, 1H, N-CH-COO), 5.72-5.9 (m, 1H, N-CH-O), 7.68-8.00 ppm (m, 5H, phthalimido and N=CH)

Ir (CCl_4): 3400, 3000-2900, 1800/1735 (phthalimido), 1750 (ester), 1670 cm^{-1} (broad, amide and C=N)

Mass spectrum (70eV): m/e = 388 (M^+)

Analysis: Calculated for $C_{19}H_{20}N_2O_7$: C, 58.76; H, 5.19; N, 7.21, Found: C, 58.31; H, 5.50; N, 7.33

Preparation of α-benzamido-2,2-dimethyl-1,3,7-trioxa-9-aza (spiro) [4,5] dec-9-ene-8-acetic acid methyl ester (92) from (87)

This white foamy compound was prepared in the same way as (91) from (87) in 93 % yield.

Nmr ($CDCl_3$): δ 1.56 (s, 6H, acetonide), 3.77 (s, 3H, OCH_3), 3.6-4.18 (m, 5H, two OCH_2 and N-CH-COO), 5.3-5.4 (m, 1H, N-CH-O), 6.9 (broad, 1H, NH), 7.25-8.0 ppm (m, 6H, phenyl and N=CH)

Ir ($CHCl_3$): 3450, 3000-2880, 1750 (ester), 1675 (broad, amide and C=N), 1530, 1500, 1396, 1385 cm^{-1}

Mass spectrum (70eV): m/e = 362 (M^+)

Analysis: Calculated for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12 N, 7.73, Found: C, 59.50; H, 6.17; N, 8.02

EXPERIMENTAL - CHAPTER III

Preparation of 4-ethoxymethylene-2-phenyl-5-oxazolone (103)

Hippuric acid (72 g) and triethyl orthoformate (60 g) were heated for 1 hour under reflux with acetic anhydride (80 g) (bath temp. = 140-150°C). Low boiling material was then removed by vacuum distillation. The dark red resudue solidified on cooling and triturating with cold ethanol. Treatment of the red solid with charcoal and recrystallization from petroleum ether (60-80°C) gave pink needles.

Yield: 35 g (53 %), mp: 97-98°C (lit.[59] 97-98°C)

Nmr ($CDCl_3$): δ 1.47 (t, J=7 Hz, 3H, CH_3), 4.35 (q, J=7 Hz, 2H, CH_2), 7.14(s, 1H, C=CH), 7.18-8.0 ppm (m, 5H, phenyl)

Ir (KBr): 1785 (C=O), 1673 cm^{-1} (C=N)

Preparation of 4-hydroxymethylene-2-phenyl-5-oxazolone (104)

4-Ethoxymethylene-2-phenyl-5-oxazolone (103) (10.85 g) was suspended in a 0.1 N sodium hydroxide solution (50 ml) and the mixture stirred vigorously until everything went into solution. The red solution was extracted with ethyl ether to remove any unreacted material and the aqueous solution acidified with cold dilute hydrochloric acid.

The precipitate was collected by filtration, washed several times with cold water and dried over NaOH in vacuo.

Yield: 8.07 g (85 %), mp: 150-151°C (lit.[60] 152°C)

Nmr (DMSO-d_6): δ 7.33-8.12 (m, 5H, phenyl), 7.7 (s, 1H, C=CH), 10.48 ppm (s, 1H, OH)

Ir (KBr): 3500 (broad), 1795 (oxazolone), 1613, 1585, 1500, 1380, 1300, 1118 cm^{-1}

Preparation of N-formylglycine ethyl ester (110)

The procedure of Jones[61] was followed exactly and the fraction boiling at 95°C/0.2 mmHg (lit.[61] 110°C/1 mmHg) was collected.

Yield: 90 %

Nmr ($CDCl_3$): δ 1.33 (t, J=7 Hz, 3H, CH_3), 4.12 (m, 2H, CH_2COO), 4.25 (q, J=7 Hz, 2H, $\underline{CH_2}-CH_3$), 7.35 (broad, 1H, NH), 8.3 ppm (s, 1H, CHO)

Ir (neat): 3300, 2980, 1740 (ester), 1660 (amide), 1525, 1376, 1200 cm^{-1}

Preparation of β,β-diethoxyalanine ethyl ester (112)

A suspension of sodium ethoxide (48.5 g = 0.71 mole) in dry zylene (150 ml) was added in small portions to a mixture of N-formylglycine ethyl ester (110) (91.7 g = 0.7 mole) and ethyl formate (222 g = 3 mole) over a

period of 1 hour at 0°C. The mixture was stirred vigorously for an additional hour and kept overnight in the refrigerator. Anhydrous ethyl ether (200 ml) was added and the solid collected by filtration, washed with ethyl ether and dried in vacuo. This sodium salt (111) was then added to the ethanolic hydrogen chloride solution (1000 ml, 15 % by weight) at 0°C and the mixture allowed to stand overnight at room temperature. This solution was concentrated to a heavy syrup under reduced pressure and treated with chloroform (900 ml). The solution was stirred vigorously for 4 hours while sodium bicarbonate (200 g) was added in portions. The suspension was filtered and the filtrate washed with 5 % bicarbonate solution and brine water, dried over anhydrous sodium sulfate and evaporated in vacuo. The pale red residue was distilled at 76 - 82°C (0.4 mmHg) and redistilled at 71 - 72°C (0.1 mmHg) (lit.[62] 71°C/0.1 mmHg).

Yield: 66 g (51 %)

Nmr ($CDCl_3$): δ 1.1-1.42 (m, 9H, three CH_3), 1.66 (s, 2H, NH_2), 3.61 (d, 1H, N-CH-COO), 3.4-3.92 (m, 4H, OCH_2), 4.22 (q, J=7 Hz, 2H, $COOCH_2$), 4.78 ppm (d, 1H, O-CH-O)

Ir (neat): 3365, 2960-2860, 1730 (ester), 1580, 1480, 1370, 1300, 1215, 1100, 1060, 1020 cm^{-1}

Preparation of 2-phenylacetamido-3,3-diethoxypropionic acid (113)

Phenylacetyl chloride (17 g) was added dropwise to a vigorously stirred mixture of β,β-diethoxyalanine ethyl ester (112) (22 g), sodium bicarbonate (22 g), chloroform (350 ml) and water (70 ml) for 1 hour. The mixture was stirred for an additional hour at room temperature and filtered. The filtrate was washed with water, dried over anhydrous sodium sulfate and evaporated. To this crude ester, ethanolic sodium hydroxide solution (4.3 g of NaOH in 250 ml of ethanol) was added and the solution stirred overnight at room temperature. Ethanol was evaporated and the residue dissolved in water (150 ml). Any free organic material was removed by extraction with ethyl ether and the aqueous solution acidified with 1 N hydrochloric acid. Extraction with ethyl acetate, drying and evaporation gave a white solid.

Yield: 29 g (90 %), mp: 110-111°C (lit.[62] 112-113°C)

Nmr ($CDCl_3$): δ 1.12 (t, J=7 Hz, 6H, two $CH_2-\underline{CH_3}$), 3.65 (s, 2H, $\underline{CH_2}-C_6H_5$), 3.57 (q, J=7 Hz, 4H, two $\underline{CH_2}-CH_3$), 4.7-4.93 (m, 2H, O-CH-CH-N), 6.5 (broad, 1H, NH), 7.33 (s, 5H, phenyl), 10.39 ppm (s, 1H, COOH)

Ir (KBr): 3340, 2965, 2870, 1710 (acid), 1620 (amide), 1550, 1490, 1432, 1355, 1337, 1230 cm^{-1}

Preparation of 2-benzyl-4-ethoxymethylene-5-oxazolone hydrobromide (114)

2-Phenylacetamido-3,3-diethoxypropionic acid (113) (2.95 g) was dissolved in dioxane (30 ml) and phosphorus tribromide (2.98 g) was added dropwise over a period of 30 minutes. Ethyl ether (50 ml) was added and the white precipitate collected by vacuum filtration.

Yield: 2.8 g (90 %), mp: 123-124°C (decomp.) (lit.[63] 90-115°C)

Nmr (methanol-d_4): δ 1.35 (t, J=7 Hz, 3H, CH_3), 4.24 (q, J=7 Hz, 2H, CH_2), 5.0 (s, 2H, $C\underline{H}_2$-C_6H_5), 7.35 (s, 5H, phenyl), 5.48 (broad, 1H, N^+H), 7.8 ppm (s, 1H, C=CH).

Ir (KBr): 2935 (broad), 2312 (N^+H), 1822 (oxazolone), 1642, 1530, 1490, 1448, 1303, 1218, 1110 cm^{-1}

Preparation of 3-ethoxy-2-phenylacetamidoacrylic acid (115)

2-Benzyl-4-ethoxymethylene-5-oxazolone hydrobromide (114) (1.3 g) was treated with water (10 ml). The salt immediately changed to the oil, which crystallized on standing. Extraction with ethyl acetate, drying and evaporation gave a white solid.

Yield: 940 mg (91 %), mp: 134-135°C (lit.[58] 134-135°C)

Nmr ($CDCl_3$): δ 1.26 (t, J=7 Hz, 3H, CH_3), 3.67 (s, 2H $C\underline{H}_2$-C_6H_5), 4.07 (q, J=7 Hz, 2H, OCH_2) 6.7 (broad, 1H, NH), 7.35 (s, 5H, phenyl),

7.42 (s, 1H, C=CH), 10.37 ppm (broad, 1H, COOH)

Ir (KBr): 3221 (acid), 1640 (amide), 1527, 1491, 1430, 1305, 1232, 1158, 1150, 1130, 1108, 1016 cm^{-1}

Preparation of 2-benzyl -4-hydroxymethylene-5-oxazolone (116)

A suspension of 2-phenylacetamido-3,3-diethoxypropionic acid (113) (17.7 g) in acetic anhydride (100 ml) was heated on a steam bath for 1 hour while a rapid stream of dry nitrogen was passed above the surface of the liquid. The acetic anhydride was distilled off under vacuum and the residue (2-benzyl-4-ethoxymethylene-5-oxazolone) shaken vigorously with 1/2 N sodium hydroxide solution (150 ml) until everything went into solution. Any free organic material was removed by extraction with ethyl ether (100 ml) and the aqueous solution acidified with dilute hydrochloric acid with cooling. The yellow solid was collected by filtration, washed with cold water and dried over NaOH in vacuo.

Yield: 11.8 g (84 %), mp: 130-131°C (decomp.) (lit.[63] 130-132°C)

Nmr (DMSO-d_6): δ 3.84 (s, 2H, CH_2), 7.32 (s, 5H, phenyl), 7.63 (s, 1H, C=CH), 9.98 ppm (broad, 1H, OH)

Ir (KBr): 3480, 2512 (broad), 1810 (oxazolone), 1683 1612, 1600, 1480, 1468, 1430, 1370, 1340, 1269, 1227, 1213, 1152 cm^{-1}

Preparation of 2-benzyl-4-hydroxymethylene-5-oxazolone thallium salt (117)

2-Benzyl-4-hydroxymethylene-5-oxazolone (116) (2.03 g) was dissolved in a mixture of dioxane and ethyl ether (1:1) and thallium ethoxide (2.50 g) was added. The mixture was vigorously stirred for 10 minutes. The pale yellow precipitate was collected by filtration, washed with same solvent and dried in vacuo.

Yield: 3.98 g (98 %), mp: 185-187°C

Nmr (DMSO-d_6): δ 3.76 (s, 2H, CH_2), 7.14 (s, 5H, phenyl), 8.73 ppm (s, 1H, C=CH)

Ir (KBr): 3450 (broad), 3080-2930, 1720, 1700, 1684, 1635, 1585, 1553, 1508, 1465, 1440, 1427, 1363, 1349, 1298, 1245 cm^{-1}

Analysis: Calculated for $C_{11}H_8NO_3Tl$: C, 32.47; H, 1.98; N, 3.45, Found: C, 32.27; H, 2.02; N, 3.66

Preparation of 4-((((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1',3'-dioxolan-4'-yl)methyl)oxy)methylene)-2-benzyl-5-oxazolone (118)

This oily compound was prepared in the same way as (85) from (50) and (117) under nitrogen.

Yield: 94 %

Nmr ($CDCl_3$): δ 1.26-1.58 (m, 6H, acetonide), 2.32, 2.44

(each s, 3H, N-CH_3), 2.71-3.5 (m, 4H, N-CH_2-CH_2-S), 3.81 (s, 2H, $C\underline{H}_2$-C_6H_5), 3.73-4.34 (m, 4H, two OCH_2), 4.35, 4.47 (each s, 1H, N-CH-S), 7.27 (s, 1H, C=CH), 7.31 ppm (s, 5H, phenyl)

Ir ($CHCl_3$): 3435, 3110-2987, 1785 (oxazolone), 1690 (C=C), 1472, 1395, 1384, 1323, 1170, 1085 cm^{-1}

Mass spectrum (70eV): m/e = 418 (M^+)

Analysis: Calculated for $C_{21}H_{26}N_2O_5S$: C, 60.28; H, 6.26; N, 6.70; S, 7.65, Found: C, 60.51; H, 6.43; N, 6.32; S, 7.52

Preparation of 2,2-dimethyl-4-((((5'-oxo-2'-benzyl-2'-oxazolidine-4'-ylidene)methyl)oxy)methyl)-1,3-dioxolane-4-carboxaldehyde (120) from (118)

This white foamy solid was prepared in the same way as (82) from (118) and mercuric chloride and further purified by preparative thin layer chromatography.

Yield: 45 %

Nmr ($CDCl_3$): δ 1.48 (s, 6H, acetonide), 3.86 (s, 2H, $C\underline{H}_2$-C_6H_5), 3.94-4.57 (m, 4H, two OCH_2), 7.3 (s, 1H, C=CH , 7.38 (s, 5H, phenyl), 9.72 ppm (s, 1H, CHO)

Ir ($CHCl_3$): 3430, 3028, 2980, 1795 (oxazolone), 1730 (aldehyde), 1690, (C=C), 1630, 1455, 1440, 1430, 1395, 1385, 1370, 1180, 1100 cm^{-1}

Mass spectrum (70eV) : m/e = 345 (M^+)

Preparation of t-butyldimethylsilyl 3-ethoxy-2-phenyl-acetamido acrylate (128)

A solution of 3-ethoxy-2-phenylacetamidoacrylic acid (115) (872 mg), t-butyldimethylchlorosilane (633 mg = 1.2 equivalents) and imidazole (581 mg = 2.5 equiv.) in dimethylformamide (2 ml) was stirred for 24 hours at room temperature. Chloroform (15 ml) was added and the solution washed several times with cold water, bicarbonate solution and water. The solution was dried over anhydrous sodium sulfate, filtered and evaporated. The oily residue was passed through a silica gel column using methylene chloride-ethyl ether (3:1) as eluent. Evaporation of the solvent and pumping overnight under high vacuum gave 730 mg (61 %) of a white oil.

Nmr (CCl_4) : δ 0.37 (s, 6H, CH_3-Si-CH_3), 1.05 (s, 9H, t-butyl), 1.42 (t, J=7 Hz, 3H, CH_2-$\underline{CH}_3$), 3.6 (s, 2H, $\underline{CH}_2$-C_6H_5), 4.09 (q, J=7 Hz, 2H, $\underline{CH}_2$-CH_3), 6.5 (broad, 1H, NH), 7.1 (s, 1H, C=CH), 7.27 ppm (s, 5H, phenyl)

Ir ($CHCl_3$): 3430, 3000, 1695 (ester and amide), 1521, 1370, 1320, 1140 cm^{-1}

Mass spectrum (70eV): m/e = 363 (M^+)

Analysis could not be performed because the chlorosilane was contaminated.

Preparation of trityl 3-ethoxy-2-phenylacetamidoacrylate (129)

3-Ethoxy-2-phenylacetamidoacrylic acid (115) (498 mg) was dissolved in dry methylene chloride (50 ml) at 0°C and trityl pyridinium fluoroborate (130)[68] (860 mg = 1.1 equiv.) was added with good stirring. The fluoroborate dissolved slowly and a white milky suspension appeared. Stirring was continued for 30 minutes at 0°C and the temperature brought to room temperature. The solution was washed with water and dilute sodium bicarbonate solution and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a white solid.

Yield: 860 mg (88 %), mp: 159°C

Nmr ($CDCl_3$): δ 1.18 (t, J=7 Hz, 3H, CH_3), 3.6 (s, 2H, $C\underline{H}_2$-C_6H_5), 3.98 (q, J=7 Hz, 2H, OCH_2), 6.4 (broad, 1H, NH), 7.23 ppm (m, 21H, C=CH and four phenyl)

Ir (KBr): 3270, 3065-2915, 1730 (ester), 1670/1660 (C=C and amide), 1525, 1460, 1363, 1300, 1230 cm^{-1}

Mass spectrum (70eV): m/e =491 (M^+)

Analysis: Calculated for $C_{32}H_{29}NO_4$: C, 78.18; H, 5.95; N, 2.85, Found: C, 78.26; H, 5.62; N, 3.04

Preparation of p-methoxyphenacyl 3-ethoxy-2-phenylacetamidoacrylate (131)

A solution of 3-ethoxy-2-phenylacetamidoacrylic acid

(115) (2.49 g), p-methoxyphenacyl bromide (2.19 g) and triethylamine (1.01 g) in dimethylformamide (20 ml) was kept in the refrigerator for 2 days. Ice water (150 ml) was added with vigorous stirring and the resulting precipitate collected by filtration and dried in vacuo. Recrystallization from ethanol gave white crystals.

Yield: 3.78 g (94 %), mp: 115-116°C

Nmr ($CDCl_3$): δ 1.3 (t, J=7 Hz, 3H, CH_3), 3.63 (s, 2H, $C\underline{H}_2$-C_6H_5), 3.84 (s, 3H, OCH_3), 4.05 (q, J=7 Hz, 2H, $C\underline{H}_2$-CH_3), 5.27 (s, 2H, $COOCH_2$), 6.63 (broad, 1H, NH), 7.25 (s, 5H, phenyl), 7.4 (s, 1H, C=CH), 6.77, 6.92, 7.72 and 7.87 ppm (each s, 4H, p-methoxyphenyl)

Ir (KBr): 3270, 3200, 3080-2948, 1725 (ketone), 1700 (ester), 1668 (amide and C=C), 1610, 1548, 1433, 1385, 1300, 1270, 1252, 1230 cm^{-1}

Analysis: Calculated for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52, Found: C, 66.89; H, 6.09; N, 3.74

EXPERIMENTAL - CHAPTER IV

Preparation of benzyl 2-phthalimido-3-hydroxyacrylate (135a)

The procedure of Sheehan and Johnson[48] was followed, and the pale yellow solid was recrystallized from ethanol-water (1:1).

Yield: 42 %, mp: 149-150°C (lit.[48] 153-154°C)

Nmr (DMSO-d_6): δ 5.1 (s, 2H, CH_2), 7.23 (s, 5H, phenyl), 7.77 (s, 4H, phthalimido), 7.9 (s, 1H, C=CH), 11.6 ppm (broad, 1H, OH)

Ir (KBr): 3240, 1800/1730 (phthalimido), 1730 (ester), 1680 (C=C), 1620, 1595, 1512, 1440 cm^{-1}.

Preparation of benzyl 2-benzamido-3-hydroxyacrylate (136a)

4-Hydroxymethylene-2-phenyl-5-oxazolone (104) (9.5 g) was suspended on dry benzene (200 ml) and benzyl alcohol (6 g = 1.1 equiv.) was added. The mixture was refluxed for 6 hours, cooled and the clear red solution evaporated. The residue was collected by filtration and recrystallized from petroleum ether (60-80°C). Treatment of the product with charcoal gave pale yellow crystals.

Yield: 10.7 g (72 %), mp: 112-113°C (lit.[72] 112-113°C)

Nmr ($CDCl_3$): δ 5.25 (s, 2H, CH_2), 7.4 (s, 5H, $CH_2-C_6H_5$), 7.35-8.0 (m, 6H, $O=C-C_6H_5$ and C=CH), 8.4 (broad,

1H, NH), 12.3 ppm (d, 1H, OH)

Ir (KBr): 3352 (OH), 1705 (ester), 1665 (amide and C=C) 1618, 1584, 1560, 1400, 1358, 1100 cm^{-1}

Preparation of p-nitrobenzyl 2-benzamido-3-hydroxyacrylate (137a)

This white crystalline compound was prepared in the same way as (136a) from (104) and p-nitrobenzyl alcohol, and recrystallized from benzene.

Yield: 82 %, mp: 150-151°C

Nmr (DMSO-d_6): δ 5.3 (s, 2H, CH_2), 7.25-8.34 (m, 11H, C_6H_5, C_6H_4, NH and C=CH), 9.1 ppm (s, 1H, OH)

Ir (KBr): 3385, 3105, 1715 (ester), 1670 (amide and C=C), 1618, 1544, 1453, 1392, 1350, 1108 cm^{-1}

Analysis: Calculated for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12; N, 8.18, Found: C, 59.64; H, 4.26; N, 8.31

Preparation of benzyl 2-phthalimido-3-hydroxyacrylate thallium salt (135b)

Benzyl 2-phthalimido-3-hydroxyacrylate(135a) (3.23 g) was dissolved in hot ethanol (100 ml) and thallium ethoxide (2.5 g) was added. The mixture was heated and then cooled to 0°C. The pale yellow crystals were collected by filtration and dried in vacuo.

Yield: 5 g (95 %), mp: 200-201°C (decomp.)

Nmr (DMSO-d_6): δ 5.1 (s, 2H, CH_2), 7.38 (s, 5H, phenyl), 7.94 (s, 4H, phthalimido), 9.2 ppm (s, 1H, C=CH)

Ir (KBr): 3470, 1790/1725 (phthalimido), 1725 (ester), 1662 (C=C), 1522, 1450, 1410, 1360, 1100 cm^{-1}

Analysis: Calculated for $C_{18}H_{22}NO_5Tl$: C, 41.01; H, 2.28; N, 2.66, Found: C, 40.98; H, 2.19; N, 2.67

Preparation of benzyl 2-benzamido-3-hydroxyacrylate sodium salt (136b)

Benzyl 2-benzamido-3-hydroxyacrylate (136a) (16.24 g) was suspended on ethanol (10 ml) and an ethanolic solution of sodium ethoxide (1.15 g of sodium) was added with vigorous stirring. The suspension dissolved immediately and the sodium salt precipitated. Ethyl ether (100 ml) was added and the white salt collected by filtration, washed with ethyl ether and dried in vacuo.

Yield: 14.66 g (91 %), mp: 213-215°C (decomp.)

Nmr (DMSO-d_6): δ 5.03 (s, 2H, CH_2), 7.3 (s, 5H, $CH_2C_6\underline{H}_5$) 7.25-8.0 (m, 5H, $O{=}C{-}C_6H_5$), 8.95 (s, 1H, NH), 9.22 ppm (s, 1H, C=CH)

Ir (KBr): 3450, 3220-3040, 1656, 1625, 1610, 1580, 1566, 1543, 1500, 1480, 1413, 1370, 1300, 1172, 1110 cm^{-1}

Analysis: Calculated for $C_{17}H_{14}NO_4Na$: C, 63.95; H, 4.39; N, 4.39, Found: C, 63.42; H, 4.15; N, 4.51

Preparaion of p-nitrobenzyl 2-benzamido-3-hydroxyacrylate sodium salt (137b)

This yellow powder was prepared in the same way as (136b) from (137a).

Yield: 94 %, mp: 206-208°C

Nmr (DMSO-d_6): δ 5.3 (s, 2H, CH_2), 7.46-8.47 (m, 9H, phenyl and p-nitrophenyl), 8.63 (broad, 1H, NH), 9.2 ppm (s, 1H, C=CH)

Ir (KBr): 3264 (salt), 1670, 1665, 1633, 1590, 1548, 1385, 1368, 1335, 1300, 1175, 1120 cm^{-1}

Analysis: Calculated for $C_{17}H_{13}N_2O_6Na$: C, 56.05; H, 3.57; N, 7.69, Found: C, 55.85; H, 3.74; N, 7.78

Preparation of benzyl 2-phthalimido-3-(((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1',3'-dioxolan-4'-yl)methyl) oxy)acrylate (138)

The thallium salt (135a) (8 g = 1.5 equiv.) was suspended in a solution of the thiazolidine mesylate (50) (3.11 g) in 2-butanone (100 ml) and the mixture refluxed for 6 hours. The salt was filtered off and the filtrate evaporated in vacuo. The residue was passed through a silica gel column

using methylene chloride-ethyl ether (5:1) as eluent. Evaporation of the solvent gave a white foamy solid.

Yield: 5.26 g (98 %), mp: 51-52°C

Nmr ($CDCl_3$): δ 1.28, 1.37 (each s, 6H, acetonide), 2.25, 2.35 (each s, 3H, N-CH_3), 2.8-3.12 (m, 4H, N-CH_2-CH_2-S), 3.6-4.37 (m, 5H, two OCH_2 and N-CH-S), 5.1 (s, 2H, CH_2), 7.23 (s, 5H, CH_2-C_6H_5), 7.52-8.0 ppm (m, 5H, phthalimido and C=CH)

Ir ($CHCl_3$):1800/1730 (phthalimido), 1730 (ester), 1665 (C=C), 1476, 1430, 1392, 1380, 1295, 1160, 1100 cm^{-1}

Mass spectrum (70eV): m/e = 538 (M^+)

Analysis: Calculated for $C_{28}H_{30}N_2O_7S$: C, 62.44; H, 5.62; N, 5.20; S, 5.94. Found: C, 62.59; H, 5.51; N, 5.40; S, 6.02

Preparation of benzyl 2-benzamido-3-(((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (139)

This white foamy compound was prepared in the same way as (138) from (136b) and (50).

Yield: 96 %

Nmr ($CDCl_3$): δ 1.28, 1.37 (each s, 6H, acetonide), 2.27, 2.35 (each s, 3H, N-CH_3), 2.8-3.8 (m, 4H, N-CH_2-CH_2-S), 3.69-4.52 (m, 5H, two OCH_2 and N-CH-S), 5.25 (s, 2H, CH_2-C_6H_5), 7.43 (s, 5H, CH_2-C_6H_5), 7.43-8.05 ppm (m, 7H,

O=C-C_6H_5, NH, and C=CH)

Ir ($CHCl_3$):3448, 3018-2820, 1722 (ester), 1690 (amide), 1675 (C=C), 1515, 1495, 1394, 1382, 1300 cm^{-1}

Mass spectrum (70eV): m/e = 512 (M^+)

Analysis: Calculated for $C_{27}H_{32}N_2O_8S$: C,63.27; H, 6.29; N, 5.47; S, 6.24, Found: C, 62.98; H, 6.33; N, 5.76; S, 6.45

Preparation of p-nitrobenzyl 2-benzamido-3-(((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1',3'-dioxolan-4'-yl)methyl) oxy)acrylate (140)

This pale yellow foamy compound was prepared in the same way as (138) from (137b) and (50).

Yield: 93 %, mp: 48-49°C

Nmr ($CDCl_3$): δ 1.33, 1.43 (each s, 6H, acetonide), 2.27, 2.35 (each s, 3H, N-CH_3), 2.76-3.1 (m, 4H, N-CH_2-CH_2-S), 3.67-4.42 (m, 5H, two OCH_2 and N-CH-S), 5.25 (s, 2H, CH_2-C_6H_4), 7.18-8.23 ppm (11H, phenyl, p-nitrophenyl, NH and C=CH)

Ir ($CHCl_3$):3440, 2960, 1725 (ester), 1685 (amide and C=C), 1615, 1590, 1541, 1493, 1390, 1380, 1300 cm^{-1}

Mass spectrum (70eV): m/e =557 (M^+)

Analysis: Calculated for $C_{27}H_{31}N_3O_8S$: C, 58.16; H, 5.60; N, 7.54; S, 5.74, Found: C, 57.81; H, 5.87; N, 7.43; S, 5.60

Preparation of benzyl 2-phthalimido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (141) from (138)

The thiazolidine ester (138) (2.15 g) was dissolved in tetrahydrofuran-water (4:1) (30 ml) and mercuric chloride (1.2 g) was added. The immediately formed milky suspension was brought to reflux and stirred for 1 hour. The fine suspension was filtered off and the filtrate evaporated. The residue was extracted three times with benzene and the combined extracts were washed with dilute hydrochloric acid and water, dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The crude product was passed through a silica gel column using methylene chloride-ethyl ether (5:1) as eluent. Evaporation of the solvent gave a white foamy solid.

Yield: 1.78 g (96 %), mp: 56-57°C

Nmr ($CDCl_3$): δ 1.43 (s, 6H, acetonide), 4.0 (ABq, 2H, J= 6 Hz, OCH_2), 4.22 (s, 2H, OCH_2), 5.18 (s, 2H, CH_2-C_6H_5), 7.27 (s, 5H, phenyl), 7.82 (s, 1H, C=CH), 7.64-8.0 (m, 4H, phthalimido), 9.73 ppm (s, 1H, CHO)

Ir (KBr): 3480, 3072-2900, 1800/1735 (phthalimido), 1735 (ester), 1720 (aldehyde), 1665 (amide and C=C), 1430, 1395, 1382, 1290, 1100 cm^{-1}

Mass spectrum (70eV): m/e = 465 (M^+)

Analysis: Calculated for $C_{25}H_{23}NO_8$: C, 64.51; H, 4.98; N, 3.01, Found: C, 64.34; H, 5.01, N, 3.25

Preparation of benzyl 2-benzamido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (142) from (139)

This white foamy compound was prepared in the same way as (141) from (139).

Yield: 75 %

Nmr ($CDCl_3$): δ 1.43 (s, 6H, acetonide), 4.0-4.34 (m, 4H, two OCH_2), 5.23 (s, 2H, $C\underline{H}_2-C_6H_5$), 7.34 (s, 5H, $CH_2-C_6\underline{H}_5$), 7.25-8.0 (m, 7H, $O=C-C_6H_5$, NH and C=CH), 9.72 ppm (s, 1H, CHO)

Ir ($CHCl_3$): 3425, 3000-2942, 1720 (broad, ester and CHO), 1680 (amide and C=C), 1510, 1495, 1395, 1382, 1300, 1150, 1100 cm^{-1}

Mass spectrum (70eV): m/e = 439 (M^+)

Preparation of p-nitrobenzyl 2-benzamido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (143) from (140)

This yellow foamy compound was prepared in the same way as (141) from (140).

Yield: 72 %, mp: 57-58 °C

Nmr ($CDCl_3$): δ 1.42 (s, 6H, acetonide), 3.83-4.3 (m, 4H, two OCH_2), 5.25 (s, 2H, $C\underline{H}_2$-C_6H_4), 7.18-8.13 (m, 11H, phenyl, p-nitrophenyl, NH and C=CH), 9.64 ppm (s, 1H, CHO)

Ir ($CHCl_3$): 3400, 1715 (ester), 1705 (aldehyde), 1660 (amide and C=C), 1600, 1464, 1370, 1343, 1280, 1140, 1085 cm^{-1}

Mass spectrum (70eV): m/e = 484 (M^+).

Analysis: Calculated for $C_{24}H_{24}N_2O_9$: C, 59.50; H, 4.99; N, 5.87, Found: C, 59.79; H, 4.79; N, 5.64

Preparation of α-phthalimido-2,2-dimethyl-1,3,7-trioxa-9-aza (spiro) [4,5] dec-9-ene-8-acetic acid benzyl ester (146) from (141)

The aldehyde ester (141) (1.16 g) was dissolved in dry tetrahydrofuran (5 ml) and 1.1 equivalents of ammonia solution in tetrahydrofuran was added. The mixture was kept overnight at room temperature, dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The residue was passed through a silica gel column using methylene chloride-ethyl ether (5:1) as eluent. Evaporation of the solvent gave a white solid.

Yield: 1.1 g (94 %), mp: 66-68 °C

Nmr ($CDCl_3$): δ 1.42 (s, 6H, acetonide), 3.77-4.13 (m, 4H, two OCH_2), 5.0 (d, 1H, N-CH-COO), 5.38

(s, 2H, $C\underline{H}_2-C_6H_5$), 5.74-5.98 (m, 1H, N-CH-O), 7.38 (s, 5H, phenyl), 7.82 (d, 1H, N=CH), 7.99 ppm (s, 4H, phthalimido)

Ir (KBr): 3500, 2995-2880, 1800/1730 (phthalimido), 1760 (ester), 1660 (amide and C=N), 1395, 1382, 1280, 1220, 1100 cm^{-1}

Mass spectrum (70eV): m/e = 464 (M^+)

Analysis: Calculated for $C_{25}H_{24}N_2O_7$: C, 64.65; H, 5.21; N, 6.03, Found: C, 64.43; H, 5.31; N, 6.18

Preparation of α-benzamido-2,2-dimethyl-1,3,7-trioxa-9-aza (spiro) [4,5] dec-9-ene-8-acetic acid benzyl ester (147) from (142)

This white foamy compound was prepared in the same way as (146) from (142).

Yield: 92 %

Nmr ($CDCl_3$): δ 1.38 (s, 6H, acetonide), 3.4-4.15 (m, 5H, two OCH_2 and N-CH-COO), 5.25 (s, 2H, $C\underline{H}_2-C_6H_5$), 5.43 (m, 1H, N-CH-O), 7.43 (s, 5H, $CH_2-C_6\underline{H}_5$), 7.33-7.98 ppm (m, 7H, NH, O=C-C_6H_5 and N=CH)

Ir ($CHCl_3$): 3450, 3000-2885, 1755 (ester), 1675 (amide and C=N), 1528, 1470, 1395, 1383, 1180 cm^{-1}

Mass spectrum (70eV): m/e = 438 (M^+)

Analysis: Calculated for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39, Found: C, 65.82; H, 6.04; H, 6.51

Preparation of α-benzamido-2,2-dimethyl-1,3,7-trioxa-9-aza (spiro) [4,5] dec-9-ene-8-acetic acid p-nitrobenzyl ester (148) from (143)

This pale yellow solid was prepared in the same way as (146) from (143).

Yield: 91 %, mp: 63-64°C

Nmr ($CDCl_3$): δ 1.33, 1.39 (each s, 6H, acetonide), 3.34-4.23 (m, 5H, two OCH_2 and N-CH-COO), 5.28 (s, 2H, $C\underline{H}_2-C_6H_4$), 5.34-5.45 (m, 1H, N-CH-O), 7.05 (broad , 1H, NH), 7.37-8.18 ppm (m, 10H, phenyl, p-nitrophenyl and N=CH)

Ir ($CHCl_3$):3460, 1750 (ester), 1695 (amide), 1630 (C=N), 1548, 1395, 1366, 1310, 1158, 1110 cm^{-1}

Mass spectrum (70eV): m/e = 483 (M^+)

Analysis: Calculated for $C_{24}H_{25}N_3O_8$: C, 59.62; H, 5.21; N, 8.69. Found: C, 59.26; H, 5.47; N, 8.90

The Hydrogenolysis product of the imine ester (146)

The imine ester (146) (464 mg) was dissolved in absolute ethanol (20 ml) and an excess amount of palladium on charcoal (10 %) was added. The hydrogenolysis was

performed under 1 atm at room temperature for 2 hours. The solid was filtered off and the filtrate evaporated to dryness in vacuo. The white solid was washed several times with benzene and dried in vacuo.

Yield: 300 mg (91 %), mp: 72-73°C

Nmr ($CDCl_3$): δ 1.32, 1.37 (each s, 6H, acetonide), 2.94-4.03 (broad m, 8H, two NCH_2, two OCH_2), 7.6 ppm (s, phthalimido)

Ir (KBr): 3450, 1795/1730 (phthalimido), 1650 (C=N), 1413, 1385, 1225, 1100, 1065 cm^{-1}

Mass spectrum (70eV): m/e=330 (M^+)

Preparation of ethyl isonitrile

The procedure of Jackson and McKusick[74] was followed and the fraction boiling at 76-79°C (lit.[74] 77-79°C) was collected.

Yield: 41 %

Nmr ($CDCl_3$): δ 1.2-1.53 (m, 3H, CH_3), 3.2-3.65 ppm (m, 2H, CH_2)

Ir (CCl_4): 3010, 2170 (N≡C), 1480, 1466, 1395, 1360, 1100 cm^{-1}

EXPERIMENTAL - CHAPTER V

Preparation of 4-hydroxymethylene-2-phenyl-5-oxazolone sodium salt (156)

This white powder was prepared in the same way as (136b) from (104) and sodium ethoxide, and recrystallized from ethanol-dioxane (1:3).

Yield: 92 %, mp: 298-300°C (decomp.)

Nmr (DMSO-d_6): δ 7.5-8.13 (m, 5H, phenyl),
9.07 ppm (s, 1H, C=CH)

Ir (KBr): 3460 (broad), 3070-2865, 1735, 1705, 1652, 1640, 1595, 1580, 1460, 1372, 1340, 1240 cm^{-1}

Analysis: Calculated for $C_{10}H_6NO_3Na$: C, 56.88; H, 2.86; N, 6.63. Found: C, 56.67; H, 3.11; N, 6.92

Preparation of 4-((((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1',3'-dioxolan-4'-yl)methyl)oxy)methylene)-2-phenyl-5-oxazolone (157)

The sodium salt (156) (3.17 g = 1.5 equiv.) was suspended in a solution of the thiazolidine mesylate (50) (3.11 g) in 2-butanone (100 ml) and refluxed for 8 hours at 100°C. The salt was filtered off and the filtrate evaporated. The residue was dissolved in ethyl ether (50 ml), treated with charcoal, filtered and the filtrate evaporated. The yellow residue was passed through a silica

gel column using methylene chloride-ethyl ether (1:1) as eluent. Evaporation of the solvent gave a pale yellow foam.

Yield: 3.80 g (94 %)

Nmr ($CDCl_3$): δ 1.48 (s, 6H, acetonide), 2.38, 2.52 (each s, 3H, $N-CH_3$), 2.8-3.32 (m, 4H, $N-CH_2-CH_2-S$), 3.9-4.65 (m, 5H, two OCH_2 and N-CH-S), 7.42-8.24 ppm (m, 6H, phenyl and C=CH)

Ir (CCl_4): 3010-2822, 1800 (oxazolone), 1680 (C=C), 1456, 1395, 1385, 1338, 1310, 1262, 1228 cm^{-1}

Mass spectrum (70eV): m/e = 404 (M^+)

Analysis: Calculated for $C_{20}H_{24}N_2O_5S$: C, 59.40; H, 5.98; N, 6.93; S, 7.91. Found: C, 59.12; H, 6.14; N, 6.90; S, 7.74

Preparation of β,β,β-trichloroethyl 2-benzamido-3-hydroxy-acrylate (160a)

4-Hydroxymethylene-2-phenyl-5-oxazolone (104) (9.45 g) was suspended on dry benzene (500 ml) and β,β,β-trichloroethanol (7.5 g) was added. The suspension was stirred under reflux for 6 hours and the clear solution evaporated. The oily residue was triturated with petroleum ether (30-60°C) and kept overnight in the refrigerator. The red solid was collected by filtration and recrystallized from petroleum ether (60-80°C). Treatment with charcoal gave white needles.

Yield: 13.7 g (81 %), mp: 97-98°C

Nmr ($CDCl_3$): δ 4.98 (s, 2H, CH_2-CCl_3), 7.57-8.15 (m, 6H, phenyl and C=CH), 8.6 (broad, 1H, NH), 12.7 ppm (broad, 1H, OH)

Ir (KBr): 3380, 1725 (ester), 1665 (amide and C=C), 1615, 1554, 1505, 1463, 1390, 1357, 1325, 1312, 1280, 1268, 1240, 1162, 1115 cm^{-1}

Analysis: Calculated for $C_{12}H_{10}NO_4Cl_3$: C, 42.57; H, 2.98; N, 4.14; Cl, 31.61. Found: C, 42.83; H, 2.74 N, 4.27; Cl, 31.29

Preparation of β,β,β-trichloroethyl 2-phenylacetamido-3-hydroxyacrylate (161a)

This pale yellow crystal was prepared in the same way as (160a) from (116) and β,β,β-trichloroethanol, and recrystallized from cyclohexane.

Yield: 75 %, mp: 74-75°C

Nmr ($CDCl_3$): δ 3.73 (s, 2H, $C\underline{H}_2$-C_6H_5), 4.74 (s, 2H, CH_2-CCl_3), 7.33 (s, 5H, phenyl), 7.37 (s, 1H, C=CH), 7.55 (broad, 1H, NH), 12.21 ppm (broad, 1H, OH)

Ir (KBr): 3300 (OH), 1730 (ester), 1670 (amide and C=C), 1572, 1341, 1290, 1231, 1125 cm^{-1}

Analysis: Calculated for $C_{13}H_{12}NO_4Cl_3$: C, 44.28; H, 3.43; N, 3.97; Cl, 30.16. Found: C, 44.49; H, 3.71 N, 4.17; Cl, 29.99

Preparation of β,β,β-trichloroethyl 2-benzamido-3-hydroxyacrylate sodium salt (160b) from (160a)

β,β,β-trichloroethyl 2-benzamido-3-hydroxyacrylate (160a) (4.06 g = 1.2 m mole) was suspended on absolute ethanol (5 ml) and an ethanolic solution of sodium ethoxide (230 mg of sodium in 10 ml of ethanol) was added. The mixture was shaken for 10 minutes and ethyl ether (50 ml) added. The precipitated sodium salt was collected by filtration, washed several times with ethyl ether and dried in vacuo.

Yield: 3.4 g (95 %), mp: 200-202°C (decomp.)

Nmr (DMSO-d_6): δ 4.74 (s, 2H, CH_2-CCl_3), 7.25-8.17 (m, 5H, phenyl), 8.27 (broad, 1H, NH), 9.12 ppm (s, 1H, C=CH)

Ir (KBr): 3300 (broad, salt), 3070, 2960, 1675, 1640, 1592, 1540, 1500, 1373, 1287, 1160 cm^{-1}

Analysis: Calculated for $C_{12}H_9NO_4Cl_3Na$: C, 39.87; H, 2.52; N, 3.89; Cl, 29.50, Found: C, 39.90 H, 2.63; N, 4.13; Cl, 29.74

Preparation of β,β,β-trichloroethyl 2-phenylacetamido-3-hydroxyacrylate sodium salt (161b) from (161a)

This white salt was prepared in the same way as (160b) from (161a) and sodium ethoxide.

Yield: 93 % based on sodium, mp: 92-93°C (decomp.)

Nmr (D_2O): δ 3.49 (s, 2H, $C\underline{H}_2$-C_6H_5, 4.43 (s, 2H, CH_2-CCl_3), 7.14 (s, 5H, phenyl), 8.58 ppm (s, 1H, C=CH), $\underline{NH}$ was exchanged with D_2O.

Ir (KBr):3405, 3300, 3048, 2983, 1678, 1652, 1570, 1418, 1376, 1290, 1125 cm^{-1}

Analysis:Calculated for $C_{13}H_{11}NO_4Cl_3Na$: C, 41.68; H, 2.96; N, 3.74;Cl, 28.39 Found: C, 41.74; H, 3.18; N, 3.42; Cl, 28.06

Preparation of β,β,β-trichloroethyl 2-benzamido-3-(((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (158)

The sodium salt (160b) (5.6 g = 1.5 equiv.) was suspended in a solution of the thiazolidine mesylate (50) (3.11 g) in dry 2-butanone (50 ml) and the mixture stirred at 80-85°C (bath temperature) for 12 hours. The salt was filtered off and the filtrate evaporated. The red residue was dissolved in ethyl ether (50 ml), treated with charcoal, filtered and evaporated. The yellow oil was further purified by passing through a silica gel column using methylene chloride-ethyl ether (1:1) as eluent. Evaporation of the solvent gave a pale yellow foam.

Yield: 5.21 g (94 %)

Nmr ($CDCl_3$): δ 1.33, 1.42 (each s, 6H, acetonide), 2.37 2.42 (each s, 3H, N-CH_3), 2.77-3.2 (m, 4H, N-

CH_2-CH_2-S), 3.84-4.54 (m, 5H, two OCH_2 and N-CH-S), 4.87 (s, 2H, CH_2-CCl_3), 7.33-8.0 ppm (m, 7H, phenyl, NH and C=CH)

Ir (CCl_4): 2990-2800, 1730 (ester), 1698 (amide), 1660 (C=C), 1503, 1480, 1381, 1369, 1210 cm^{-1}

Mass spectrum (70eV); m/e = 554 (M^+)

Analysis: Calculated for $C_{22}H_{27}N_2O_6SCl_3$: C, 47.71, H, 4.91; N, 5.06; S, 5.79; Cl, 19.20. Found: C, 47.99; H, 5.10; N, 5.26; S, 5.50; Cl, 19.41

Preparation of β,β,β-trichloroethyl 2-phenylacetamido-3-(((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (162)

This foamy compound was prepared in the same way as (158) from (50) and (161b).

Yield: 93 %

Nmr ($CDCl_3$): δ 1.27-1.50 (m, 6H, acetonide), 2.28, 2.35 (each s, 3H, NCH_3), 2.78-3.11 (m, 4H, $N-CH_2-CH_2-S$), 3.63 (s, 2H, $CH_2-C_6H_5$), 3.8-4.27 (m, 5H, two OCH_2 and N-CH-S), 4.75 (s, 2H, CH_2-CCl_3), 6.9 (broad, 1H, NH), 7.3 (s, 5H, Phenyl), 7.53 ppm (s, 1H, C=CH)

Ir (CCl_4): 3433, 3010-1200, 1735 (ester), 1700 (amide), 1664 (C=C), 1500, 1460, 1390, 1380, 1285 cm^{-1}

Mass spectrum (70eV): m/e = 568 (M^+)

Analysis: Calculated for $C_{23}H_{29}N_2O_6SCl_3$: C, 48.64; H, 5.15; N, 4.93; S, 5.63; Cl, 18.73. Found: C, 48.97; H, 5.32; N, 4.89; S, 5.89; Cl, 18.55

Preparation of β,β,β-trichloroethyl 2-benzamido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)oxy) acrylate (163) from (158)

A solution of the thiazolidine ester (158) (1.11 g) in acetonitrile-water (4:1) (20 ml) was added dropwise to a solution of mercuric chloride (0.6 g) in the same solvent (10 ml) under nitrogen and the milky suspension stirred at 50°C for 3 hours. The suspension was filtered and the filtrate evaporated. The residue was extracted three times with benzene and the combined extracts were washed with dilute hydrochloric acid and water, dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The residue was further purified by passing through a silica gel column using methylene chloride-ethyl ether (1:1) as eluent. Evaporation of the solvent gave a white foamy solid.

Yield: 0.83 g (86 %)

Nmr ($CDCl_3$): δ 1.39, 1.44 (each s, 6H, acetonide), 3.88-4.31 (m, 4H, two OCH_2), 4.83 (s, 2H, CH_2-CCl_3), 7.24-8.0 (m, 7H, phenyl, NH and C=CH), 9.72 ppm (s, 1H, CHO)

Ir (CCl_4): 3430, 2990-2790, 1730 (ester), 1710 (aldehyde), 1686 (amide), 1665 (C=C), 1480, 1381, 1372, 1285, 1230, 1100, 1061 cm^{-1}

Mass spectrum (70 eV): m/e = 481 (M^+)

Analysis: Calculated for $C_{19}H_{20}NO_7Cl_3$: C, 47.47; H, 4.19; N, 2.90; Cl, 22.12, Found: C, 47.20; H, 4.26; N, 3.15; Cl, 21.98

Preparation of β,β,β-trichloroethyl 2-phenylacetamido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (164) from (162)

This white foamy solid was prepared in the same way as (163) from (162).

Yield: 68 %

Nmr ($CDCl_3$): δ 1.47 (s, 6H, acetonide), 3.6 (s, 2H, $C\underline{H}_2$-C_6H_5), 3.78-4.21 (m, 4H, two OCH_2), 4.67 (s, 2H, CH_2-CCl_3), 7.18 (broad, 1H, NH), 7.23 (s, 5H, phenyl), 7.42 (s, 1H, C=CH), 9.67 ppm (s, 1H, CHO)

Ir (CCl_4): 3430, 3040-2960, 1740 (ester), 1700 (broad, aldehyde and amide), 1665 (C=C), 1501, 1386, 1378, 1285, 1225, 1165, 1118, 1060 cm^{-1}

Mass spectrum (70 eV): m/e = 494 (M^+)

Analysis: Calculated for $C_{20}H_{22}NO_7Cl_3$: C, 48.55; H, 4.48; N, 2.83. Found: C, 48.86; H, 4.78; N, 3.01

Preparation of 2-benzamido-3-(((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1',3'-dioxolan-4'-yl)methyl)oxy)acrylic acid (145) from (158)

The thiazolidine ester (158) (554 mg) was dissolved in 90 % aqueous acetic acid (10 ml) and an excess amount of zinc dust was added. The mixture was stirred for 2 hours at room temperature and filtered. The filtrate was poured into water (20 ml) and the aqueous solution extracted with ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The residue was passed through a silica gel column, first eluting with methylene chloride-ethyl ether (1:1) to remove any neutral compounds and then with methanol. The methanol solution was evaporated in vacuo and the residue was dissolved in ethyl ether and filtered. Evaporation of ethyl ether gave a white solid.

Yield: 295 mg (70%), mp: 67-69°C

Nmr ($CDCl_3$): δ 1.43 (s, 6H, acetonide), 2.23-2.49 (m, 3H, HN^+-CH_3), 2.68-3.17 (m, 4H, $N-CH_2-CH_2-S$), 3.67-4.48 (m, 5H, two OCH_2 and N-CH-S), 7.23-8.0 (m, 7H, phenyl, NH and C=CH), 8.5 ppm (broad, 1H, N^+H)

Ir (KBr): 3450 (broad), 3018-2780, 1720 (acid), 1678 (amide), 1646 (C=C), 1548, 1500, 1395, 1385, 1280, 1230, 1162, 1070 cm^{-1}

Mass spectrum (70 eV): m/e = 422 (M^+)

Analysis: Calculated for $C_{20}H_{26}N_2O_6S$: C, 56.86; H, 6.20; N, 6.63; S, 7.58. Found: C, 56.75; H, 6.42; N, 6.45; S, 7.79

Attempted preparation of 2-benzamido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)oxy)acrylic acid (89) from (163)

The aldehyde ester (163) (482 mg) and zinc dust were stirred in 90 % aqueous acetic acid (5 ml) for 2 hours at 0°C. Ethyl acetate (20 ml) was added and the solid filtered off. The filtrate was washed with dilute hydrochloric acid and water, dried over anhydrous sodium sulfate and filtered. Evaporation of the solvent gave a white solid.

Yield: 127 mg (36 %), mp: 106-109°C

Ir (KBr): 3360 (broad), 1720 (broad, acid and aldehyde), 1662 (amide and C=C), 1534, 1495, 1394, 1385, 1230, 1161, 1100 cm^{-1}

Analysis: Calculated for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01, Found: C, 57.99; H, 5.33; N, 3.94

The nmr and mass spectra could not be interpreted.

Preparation of α-benzamido-2,2-dimethyl-1,3,7-trioxa-9-aza (spiro) [4,5] dec-9-ene-8-acetic acid β,β,β-trichloroethyl ester (165) from (163)

A solution of the aldehyde ester (163) (0.4 g) in dry tetrahydrofuran (5 ml) was treated with 1.1 equivalents of ammonia in dry tetrahydrofuran and the mixture kept overnight at room temperature. Drying over anhydrous sodium sulfate, filtration and evaporation gave a foamy solid, which was further purified by passing it through a silica gel column using methylene chloride-ethyl ether (1:1) as eluent. Evaporation of the solvent gave a white foam.

Yield: 0.36 g (90 %)

Nmr ($CDCl_3$): δ 1.57 (s, 6H, acetonide), 3.68-4.39 (m, 3H, OCH_2 and N-CH-COO), 4.2 (s, 2H, OCH_2), 4.8-5.0 (m, 2H, CH_2-CCl_3), 5.49 (m, 1H, N-CH-O), 7.0 (broad, 1H, NH), 7.28-8.0 ppm (m, 6H, phenyl and N=CH)

Ir (CCl_4): 3018-2865, 1770 (ester), 1688 (amide), 1665 (C=N), 1520, 1490, 1390, 1378, 1226, 1162, 1100, 1063 cm^{-1}

Mass spectrum (70 eV): m/e = 480 (M^+)

Analysis: Calculated for $C_{19}H_{21}N_2O_6Cl_3$: C, 47.57; H, 4.41; N, 5.84; Cl, 22.17. Found: C, 47.46; H, 4.61; N, 6.02; Cl, 22.24

Preparation of α-phenylacetamido-2,2-dimethyl-1,3,7-trioxa-9-aza (spiro) [4,5] dec-9-ene-8-acetic acid β,β,β-trichloroethyl ester (166) from (164)

This yellow foamy compound was prepared in the same way as (165) from (164).

Yield: 91 %

Nmr ($CDCl_3$): δ 1.42 (s, 6H, acetonide), 3.69 (s, 2H, $C\underline{H}_2$-C_6H_5), 3.6-4.28 (m, 5H, two OCH_2 and N-CH-COO), 4.7-4.93 (m, 2H, CH_2-CCl_3), 5.43 (broad, 1H, N-CH-O), 6.25 (broad, 1H, NH), 7.33 ppm (6H, phenyl and N=CH)

Ir (CCl_4): 3465, 3005-2895, 1775 (ester), 1690 (amide and C=N), 1508, 1390, 1380, 1220, 1100 cm^{-1}

Mass spectrum (70 eV): m/e = 493 (M^+)

Analysis: Calculated for $C_{20}H_{23}N_2O_6Cl_3$: C, 48.65; H, 4.70; N, 5.47; Cl, 21.54; Found: C, 48.26; H, 4.83; N, 5.31; Cl, 21.61

Preparation of the oxacepham derivative (53)

The imine ester (165) (1.0 g) was dissolved in 90 % aqueous acetic acid (10 ml) and zinc dust (2.0 g) was added. The mixture was stirred for 2 hours at 0°C and the solid was filtered off. The filtrate was evaporated under high vacumm and the resulting solid was washed

several times with petroleum ether (60-80°C) and dissolved in chloroform (5 ml). Hydrogen sulfide was passed into the solution and the precipitated zinc sulfide was filtered off. To this filtrate, petroleum ether (60-80°C) (20 ml), pH 6 buffer solution (30 ml) and ethyl isonitrile (0.5 g) were added respectively and the two phase mixed with vigorous stirring for 12 hours. The two phases were then separated and the aqueous layer extracted twice with chloroform. The combined organic layers were washed with 0.1 N hydrochloric acid, sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and evaporated in vacuo. The crude product showed several spots in t.l.c. and thus purified by thin layer chromatography on silica gel plates (10 mm, dimethoxyethane/CCl_4 = 1/4, R_f = 0.5). Yield: 42 mg (5 %)

Nmr ($CDCl_3$): δ 1.2-1.53 (m, 9H, acetonide and CH_3), 3.74-4.62 (m, 8H, N-CH_2, two OCH_2 and two N-CH-C=O), 5.83 (broad q, J=6 Hz, 1H, N-CH-O), 7.2-8.0 ppm (m, 7H, two of NHC=O and phenyl)

Ir (CCl_4): 3460/3380 (NH), 3000/2960/2900 (CH), 1750 (lactam), 1685/1675 (amide), 1530, 1492, 1390, 1380, 1374, 1300, 1227, 1188 cm^{-1}

Mass spectrum (70eV): m/e=403 (M^+), 345 (403 - acetone), 303 (345 - N=C=O), 243 (for the ion (169)), 161 (for the ion (170))

Preparation of t-butyldimethylsilyl 2-benzamido-3-(((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (171)

The thiazolidine acid (145) (320 mg), t-butyldimethylchlorosilane (170 mg = 1.5 equivalents) and imidazole (127 mg = 2.5 equivalents) were dissolved in dry dimethylformamide (5 ml) and the mixture was stirred for 24 hours at room temperature. The mixture was poured into chloroform (50 ml) and the resulting solution was washed with brine, sodium bicarbonate solution and water. The chloroform solution was dried over anhydrous sodium sulfate, filtered and the solvent evaporated. The white foam was pumped overnight but the chlorosilane could not be completely removed.

Yield: 310 mg (80 %)

Nmr (CCl_4): δ 0.3 (s, 6H, CH_3-Si-CH_3), 0.97 (s, 9H, t-butyl), 1.23-1.47 (m, 6H, acetonide), 2.3, 2.35 (each s, NCH_3), 2.7-3.1 (m, 4H, N-CH_2-CH_2-S), 3.87-4.66 (m, 5H, two OCH_2 and N-CH-S), 7.18-7.86 ppm (m, 7H, phenyl, O=CNH and C=CH)

Ir (CCl_4): 3400, 3060-2800, 1730-1660 (intense broad peaks, ester, amide and C=C), 1518, 1486, 1385, 1370, 1310, 1226, 1145 cm^{-1}

Mass spectrum (70eV): m/e = 536 (M^+)

Preparation of t-butyldimethylsilyl 2-benzamido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)oxy) acrylate (172) from (171)

The thiazolidine silyl ester (171) (270 mg) was dissolved in methylene chloride (5 ml) and the solution cooled to 0° C. m-Chloroperbenzoic acid (220 mg = 2.1 equivalents, Aldrich, 85 %) was added to this solution and the mixture stirred for 5 minutes at this temperature. The resulting solution was diluted with methylene chloride (10 ml) and washed with sodium bicarbonate solution and water. Drying and evaporation gave a white foam.

Yield: 185 mg (79 %)

Nmr ($CDCl_3$): δ 0.3 (s, 6H, CH_3-Si-CH_3), 0.95 (s, 9H, t-butyl), 1.27-1.57 (m, 6H, acetonide), 3.43-4.5 (m, 4H, two OCH_2), 7.24-7.93 (m, 7H, phenyl, O=CNH and C=CH), 9.57 ppm (s, 1H, CHO)

Ir ($CHCl_3$): 3410, 2950/2850, 1730-1660 (intense broad peaks, ester, aldehyde, amide and C=C), 1520, 1490, 1485, 1385, 1375, 1318, 1155 cm^{-1}

Mass spectrum (70eV): m/e = 463 (M^+)

Microanalysis could not be performed because of the contamination with the chlorosilane.

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