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SYNTHETIC APPROACHES

TO

NUCLEAR ANALOGUES

OF

β-LACTAM ANTIBIOTICS

BY

MICHAEL D. HRYTSAK

A THESIS

SUBMITTED TO THE

SCHOOL OF GRADUATE STUDIES

UNIVERSITY OF OTTAWA

IN PARTIAL FULFILLMENT OF THE

MSc. DEGREE REQUIREMENTS

ABSTRACT

Several nuclear analogues of β-lactams in the 2-hetero-isocepham series were prepared. Condensation of a preformed β-lactam nucleus with nitro olefins, followed by reduction or oxidation of the nitro group and subsequent ring closure led to a variety of analogues.

The preparation of a new nitro olefin and a novel nitro to carbomethoxy conversion are described.

ACKNOWLEDGEMENTS

To my research supervisor, DR. T. Durst, I am grateful for his expert guidance, timeless patience and unending enthusiasm.

I would also like to thank my lab mates, Bevin, Margie and Eva for helpful discussions, DR. R. R. Fraser for interpreting spectra and R. Capoor and J. Krause for recording spectra.

It is these people that I will look back upon fondly when I recall my experience at U of O.

A special thanks goes to my wife Melanie for her encouragement.

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LIST OF ABBREVIATIONS

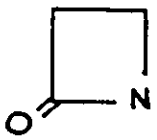
Ac	acetyl
Ac_2O	Acetic anhydride
7-ACA	7-aminocephalosporanic acid
6-APA	6-aminopenicillanic acid
:B	base
n-BuLi	n-Butyllithium
t-Bu	tert-butyl
Bu_4NF	Tetrabutylammonium fluoride
Bz	benzyl
DBN	1,5-Diazabicyclo (4.3.0) non-5-ene
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
Et	ethyl
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOH	Ethanol
HMPA	Hexamethylphosporamide
HPLC	High Performance Liquid Chromatography
L	leaving group
LDA	Lithium diisopropylamide
Me	methyl
MCPBA	m-Chloroperoxybenzoic acid
Me	methyl
MeOH	Methanol
MIC	Minimum Inhibitory concentration
Ms	mesyl
MsCl	Methanesulfonyl chloride
NaOAc	Sodium acetate
NaOMe	Sodium methoxide
NBS	N-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
PLC	Preparative Layer Chromatography
R	alkyl, aryl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
Ø	phenyl

INTRODUCTION

PREAMBLE

Historically, no other class of antibiotics has captured the imagination and held the continued interest of chemists as have the β-lactams. In fact, the development of the chemistry of these antibiotics has paralleled the growth of modern organic chemistry. From structure determination to total synthesis, new reagents and techniques have continually been developed and brought into use.

With the discovery of penicillin in 1929 by Fleming[1], the field of β-lactam antibiotics was born. A concentrated effort by British and American scientists during the second world war enabled penicillin to be produced industrially[2]. Around 1945 Brotzu[3] discovered, in the microbial flora of Mediterranean seawater near a sewage pipe, an organism which produced a substance which demonstrated antibiotic properties. The organism was of the Cephalosporium species, from which the antibiotic cephalosporin C was ultimately isolated in 1953[4], and its structure determined in 1961[5]. Both penicillins and cephalosporins were found to possess the β-lactam ring system 1 as their most striking structural feature. Penicillins 2 were found to be effective primarily against Gram positive bacteria, cephalosporins 3 against Gram positive as well as some Gram negative species. They are highly toxic to pathogens while being beneficial to the mammalian host. At the time of discovery, the β-lactam ring system was considered quite rare and difficult to construct. Following the discovery of penicillins and cephalosporins came other natural products featuring the β-lactam moiety, including pachystermines A and B 4[6], wildfire toxin 5[7], bleomycins 6[8] and nocardins 7[9]. All are monocyclic β-lactams. Recently, two promising β-lactams have been isolated from fermentation broths of Streptomyces species,



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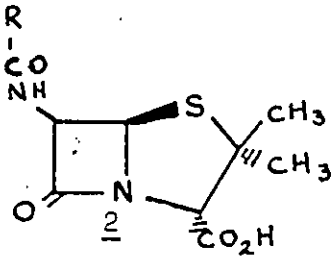
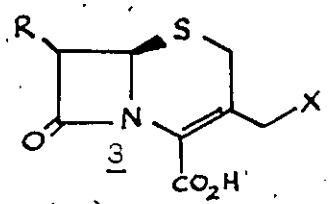


2

a) R= ϕCH_2- PEN G

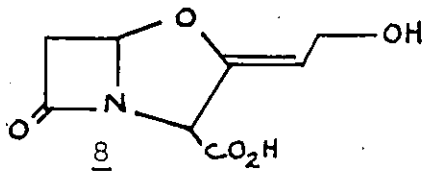
b) = ϕOCH_2- PEN V

c) = $\phi CH(NH_2)$- AMPICILLIN



3

a) X= $(CH_2)_3CH(NH_2)COOH$



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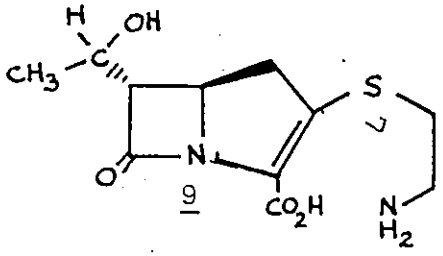

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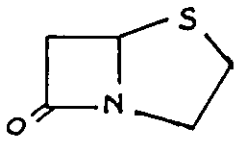

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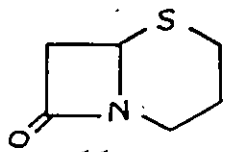

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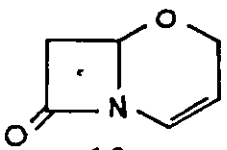

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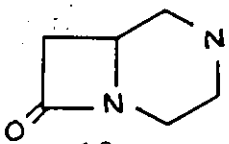

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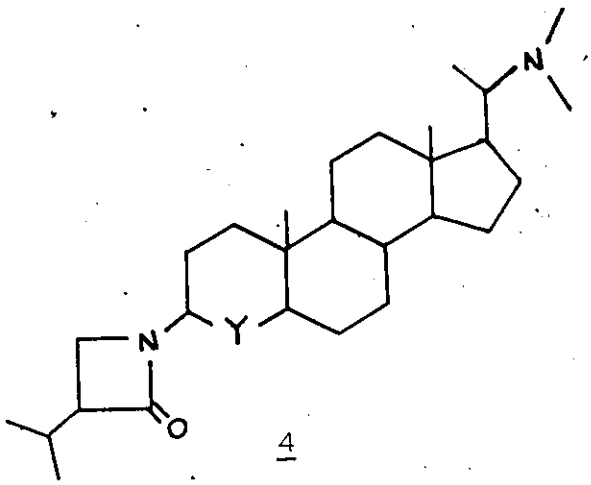
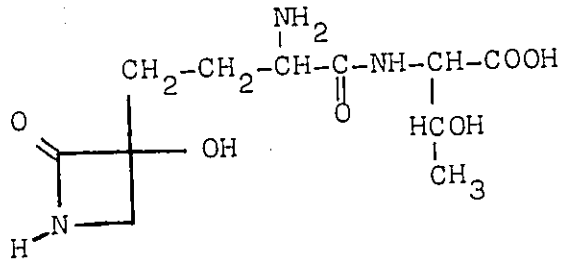


4

PACHYSTERMINE

A Y= C=O

B Y= CHOH



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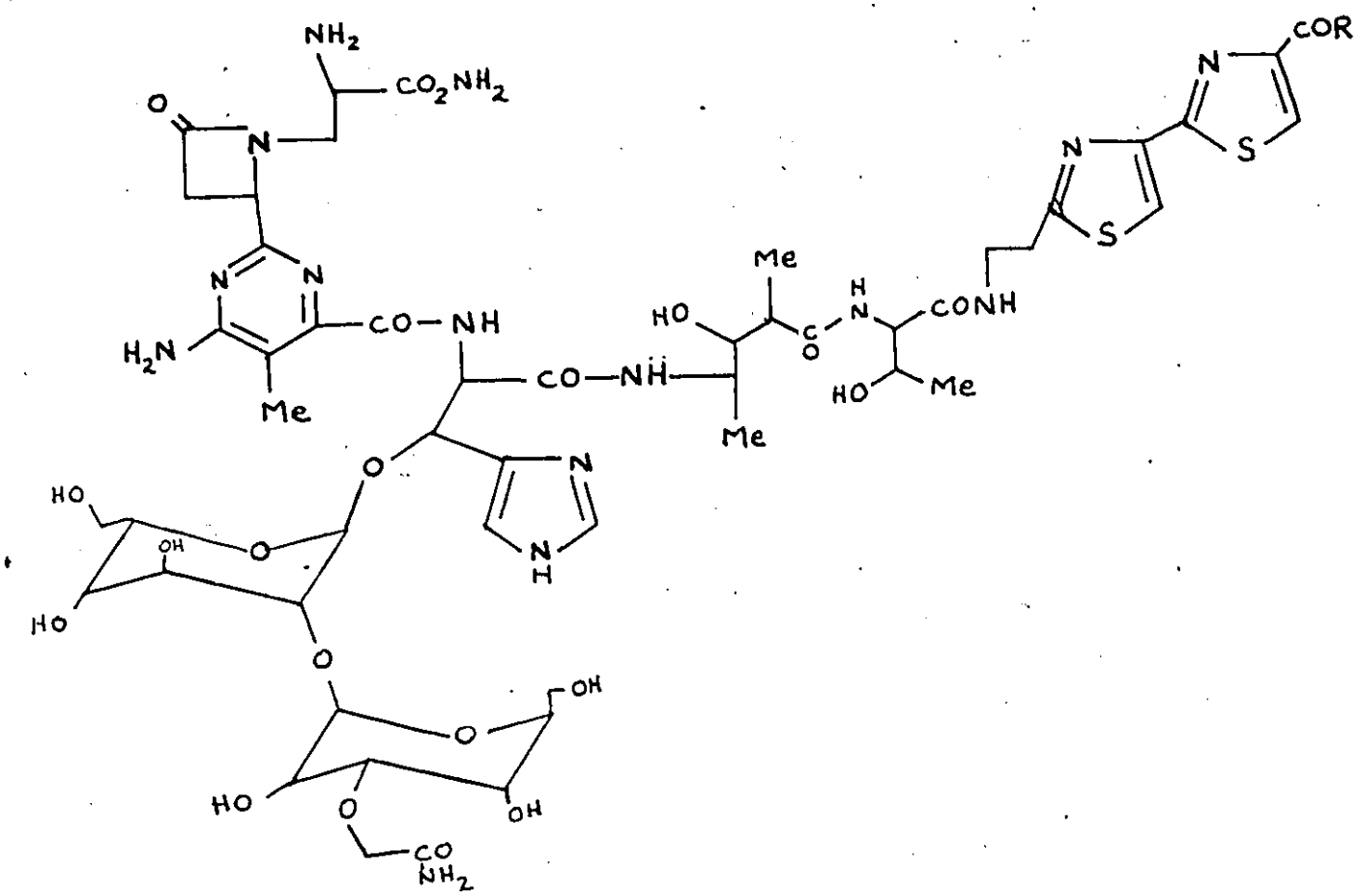
WILDFIRE TOXIN



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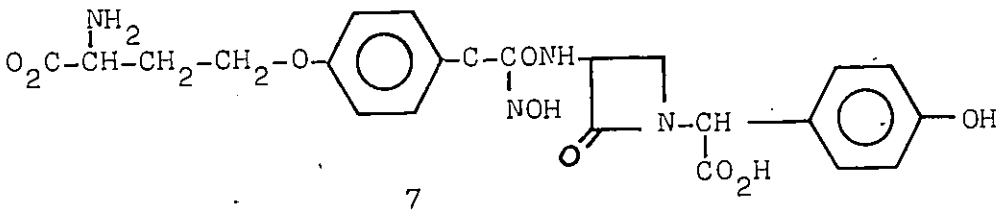
BLEOMYCIN



7
NOCARDIN

namely clavulanic acid 8[10] and thienamycin 9[11]. The former is not an antibiotic substance, rather it is an irreversible β-lactamase inhibitor. Thus the minimum inhibitory concentration (MIC) of amipicillin 2c (a semi-synthetic penicillin) in the presence of 8 against β-lactamase producing species is dramatically reduced. Thienamycin on the other hand shows excellent activity against Gram positive and negative bacteria and demonstrates better β-lactamase stability. Both are "non - classical" bicyclic β-lactams in that they do not possess either of the typical nuclei found in the penicillins (penam 10) or cephalosporins (cepham 11). It would seem that the β-lactam ring is not so rare in nature as it was once thought to be.

NOMENCLATURE

As a number of naturally occurring β-lactams were discovered, many varied systems of nomenclature evolved to describe the assorted bicyclic nuclei. The literature commonly refers to β-lactams as 2-azetidinones or azetidin-2-ones. This system is most often used to describe monocyclic structures. In the case of fused bicyclic systems, the two basic nuclei found in penicillins and cephalosporins are referred to as penam, 10 and cepham 11 respectively. If unsaturation is present, the roots are appropriately changed to penem and cephem.

If the sulfur atom is replaced by carbon, oxygen or nitrogen, or the position of the sulfur atom is changed, the convention used is to indicate the position of the heteroatom by a number (using the natural sulfur position as number one) followed by the chemical name or symbol of the heteroatom, this followed by the appropriate root. In cases where the heteroatom is not in the usual position, the prefix "iso" is inserted before the root. For example compound 12 is referred to as an 1-O-cephem (1-oxacephem), similarly compound 13 is a 2-N-isopenam (2-azaisopenam). This nomenclature has evolved primarily to describe the explosion of nuclear analogs in the literature. The recently discovered clavulanic acid 8 and thienamycin 9 could be described as having the 1-oxapenam and carbapenem skeletons respectively.

Throughout this thesis, the azetidinone nomenclature will be used to describe monocyclic β-lactams and the above convention for bicyclic structures.

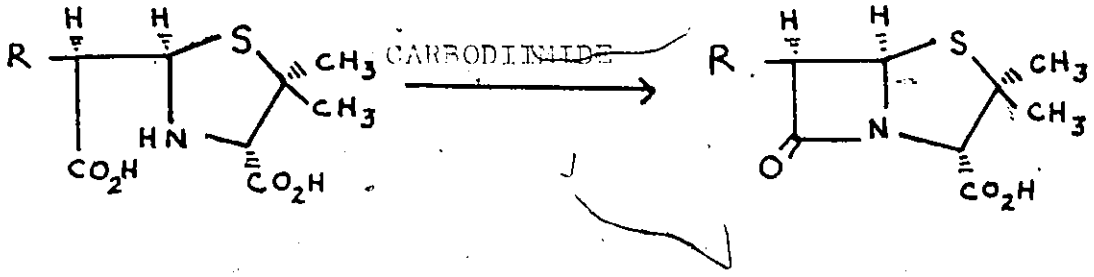
SYNTHESIS OF β-LACTAMS

The most efficient syntheses of β-lactam antibiotics are of course performed by microorganisms. Industrially, they are used to produce several thousand tons of penicillins annually. Given this situation, scientists are hardly in a position to compete with microbes for supremacy in the production of β-lactam antibiotics. This was never the intent, more importantly the objective (aside from academic interest) was to prepare antibiotics of varying structural feature hoping to gain insight into structure - activity relationships. Armed with this knowledge, scientists could then design and synthesize potentially more effective antibiotics. This objective became increasingly more important as the occurrence of bacterial species capable of resisting traditional drugs began to appear. Three main avenues were open to exploration, total synthesis, semi-synthesis and the synthesis of totally new structures, the nuclear analogs.

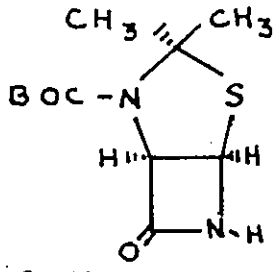
If one examines the structures of penicillins and cephalosporins, it may be noted that both are relatively simple molecules. Closer examination however, reveals considerable challenge to the synthetic organic chemist; firstly the ever present stereochemical considerations and secondly, but not so obvious, is the high degree of substitution of the carbon skeleton[12]. Only the methyl groups of penicillin and carbon 3 of cephalosporins are not attached to a heteroatom. This makes the molecule very susceptible to chemical attack, therefore any synthetic scheme would have to be designed with mild conditions in mind.

All of these challenges were met by Sheehan[13] who first synthesized phenoxymethyl penicillin. The key feature of Sheehan's synthesis was the last step, ring closure to the

β-lactam. Previous attempts at such closures had failed, however using carbodiimide, the closure was facilitated.



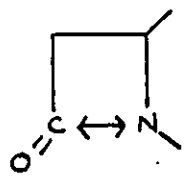
In view of this success, other groups designed their own syntheses of β-lactam antibiotics. Sheehan's method, although innovative, had the main drawback of lack of stereospecificity in some steps. Woodward's total synthesis of cephalosporins represented a major step towards more efficient synthesis[14]. The key intermediate in Woodward's synthesis was the fused thiazolidine 14. It was later discovered that 17 could be prepared from 6-aminopenicillanic acid (6-APA), making this synthesis even more attractive[15].

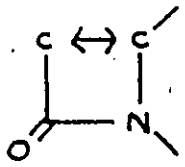


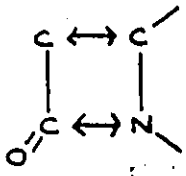
14

By inspection of the β-lactam ring system, one can contrive many different means of ring closure to the bicyclic structure, three of which are most conducive to a total synthetic scheme;

(i) C 2 to N
(ii) C 3 to C 4
(iii) simultaneous C 2 to N, C 3 to C 4


(i)

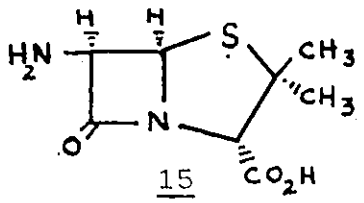

(ii)


(iii)

These three general strategies have been used in total synthetic schemes. We have already seen examples of method (i) in the Sheehan and Woodward syntheses. Approach (i) has also been used by Squibb[16] and Roussel[17] groups. Lowe[18] followed approach (ii), using a carbene insertion.

Approach (iii) has become a very popular method. It was first described by Bose[19], and further developed by groups at Merck[20] and Syntex[21]. This method is an outgrowth of Staudinger's original synthesis of β-lactams in 1907[22]. It involves a 2 + 2 cycloaddition reaction between a ketene (or ketene precursor) and an imine (Schiff base). Today, most total syntheses use the ketene-imine approach; mainly because mild, selective reagents and techniques have been developed to the extent that (unlike in early syntheses) the β-lactam ring can remain intact throughout the entire synthesis, therefore not restricting chemists to ring close at, or near the final step. Another advantage gained in using earlier formed β-lactams is that of versatility, allowing entry to numerous analogs from a common intermediate.

The area of semi-synthetic antibiotics began when, in 1953, Kato[23] isolated an unusual penicillin from the fermentation broth of Penicillium chrysogenum, which lacked an acylamino side chain at carbon 6; this substance was identified as 15.



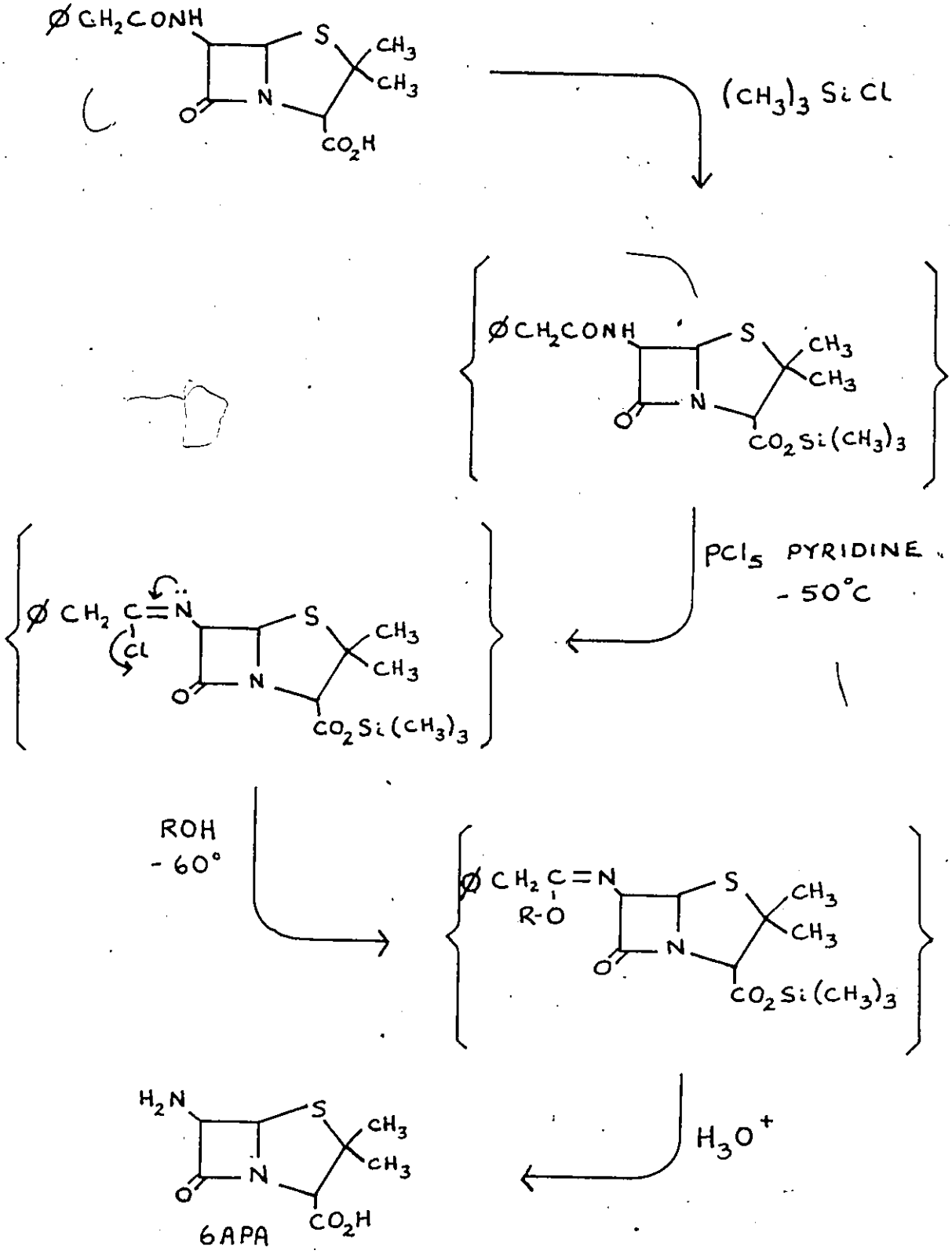
15

Perron (1960) reported the acylation of 6-APA with various acid chlorides. From these early acylations, thousands of new penicillins were synthesized, all varying in their acyl amino side chains - some were superior to the penicillins available from fermentation broths. Until this time, new penicillins could only be prepared by changing the fermentation broth composition. This method was limited, because the Penicillium fungus was selective as to the structures it would incorporate. Therefore the isolation and manipulation of 6-APA was a tremendously important event.

In 1967[25] a new chemical method evolved for the preparation of 6-APA. This involves cleavage of the C 6 amide function. The procedure involves initially silylating the C 3 carboxyl group, followed by addition of solid phosphorus pentachloride, thus forming an imino chloride. This chloride was converted to the imino ether and finally hydrolyzed to 6-APA. (SCHEME I).

The discovery of 7-aminocephalosporanic acid (7-ACA) occurred during the isolation of cephalosporin C. It, like 6-APA, could be used as a starting material for the preparation of thousands of new cephalosporins by simply acylating

IMINO CHLORIDE CLEAVAGE



SCHEME I

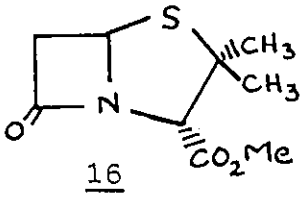
the free 7-amino group. Also, like 6-APA, it could be prepared via imino chloride cleavage of natural cephalosporins. However this approach is not industrially feasible because, unlike penicillins, the isolation of cephalosporins from culture media is very costly. As previously stated, world-wide production of penicillins reaches thousands of tons per year, hence they may be regarded as a "raw" material. The problem of cephalosporin isolation was sidestepped by Morin[26] and co-workers who developed a penam-cephem conversion. In this conversion the sulfoxide 17 (obtained from 16 and various oxidants) is treated with acetic anhydride forming the 3-β-acetoxy cepham 18 via a rearrangement.

Elimination of acetic acid from 18 gave the ceph-3-em 19 (SCHEME II). This ring expansion sequence is now the basis of the commercial route to cephalosporins[27].

With the preparation of totally and semi-synthetic β-lactam antibiotics under control, chemists turned their attention to "improving" upon nature by changing the very nucleus of the molecules themselves, entering the field of nuclear analogs.

It was anticipated that ring systems other than the penam or cepham would demonstrate antibiotic activity. If these could be prepared by total synthesis it would give tremendous insight into structure-activity relationships.

PENAM - CEPHAM CONVERSION



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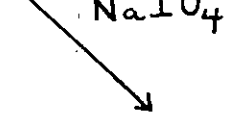

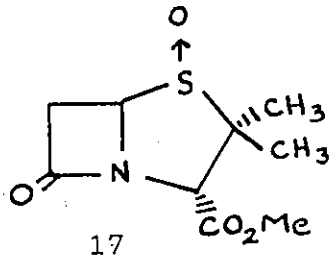

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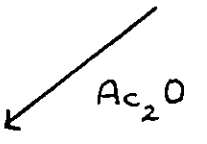

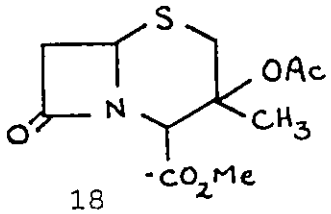

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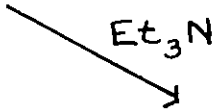

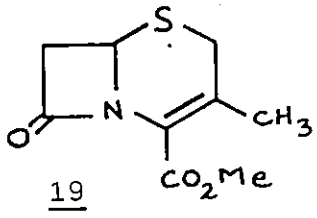

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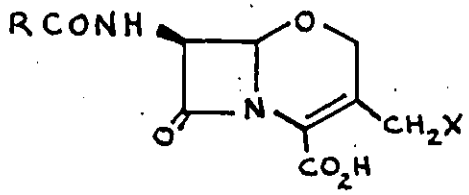
SCHEME II

1 - OXACEPHALOSPORINS

Perhaps the most promising of the nuclear analogs to be tested to date are of the 1-oxacephem 20 type.



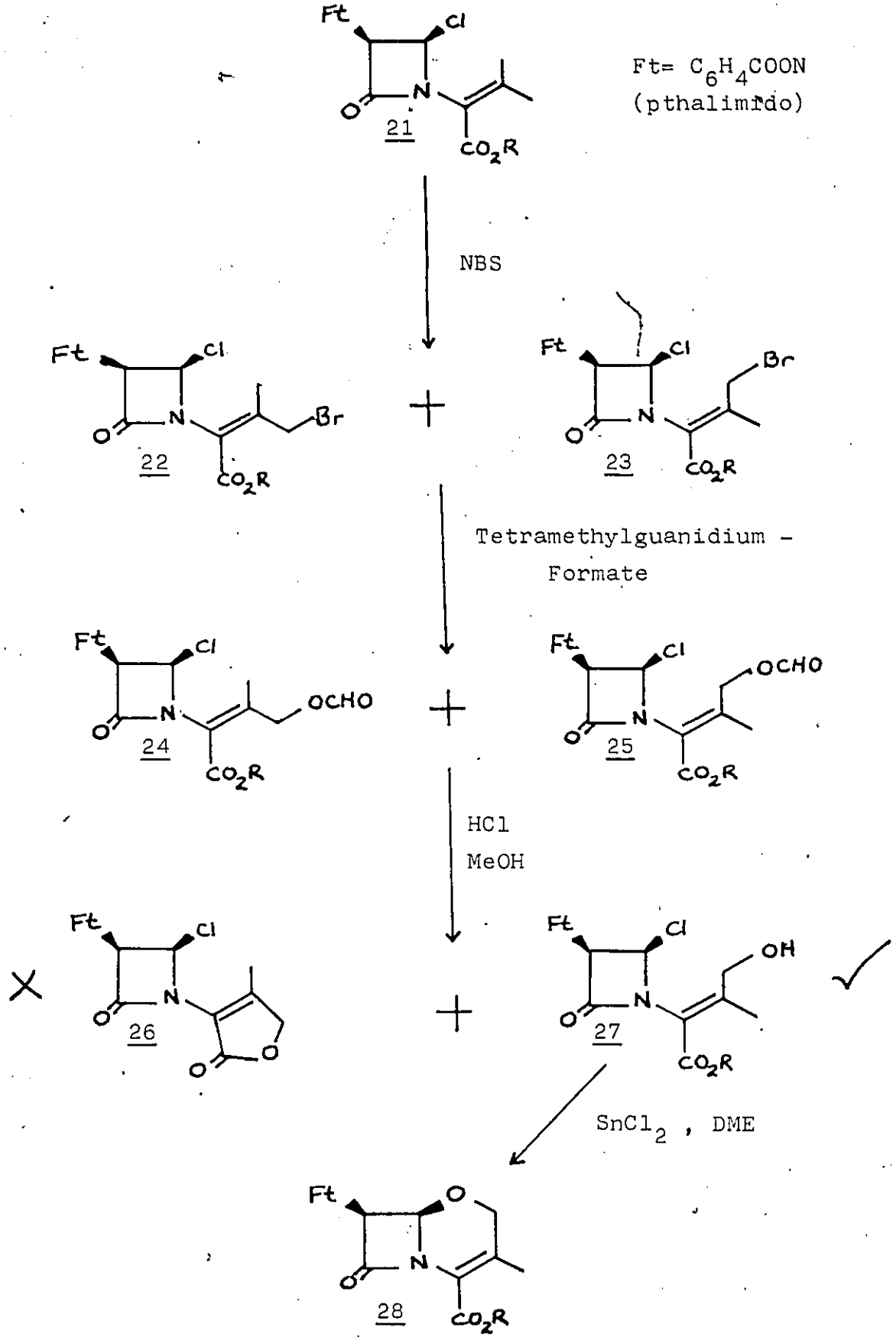
20

In 1974 Wolfe[28] described the synthesis of this novel bicyclic ring system. It had been postulated that the degree of strain of the bicyclic system of penicillins and cephalosporins was directly related to its antibiotic activity. Woodward[29] (1949) pointed out that in simple β-lactams, the carbonyl frequency in the infrared occurs at 1730 cm^{-1} but in penicillins this absorption is noted around 1775 cm^{-1}. This shift is indicative of an increase in ring strain. Bicyclic β-lactams should thus be more readily opened, hence better acylating agents. This irreversible acylation reaction[30], that interferes with the synthesis of bacterial cell walls, is the basis for the biological activity of β-lactams. In 1969 Morin[31] found a positive correlation between IR frequency and biological activity.

Replacement of the sulfur atom by a smaller heteroatom such as oxygen should increase the strain of the bicyclic system, give a corresponding increase in the frequency of carbonyl absorption, which would be reflected in higher activity.

Wolfe began his 1-oxacephem synthesis with the 4-chloroazetidinone 21 prepared from anhydro-6-phthalimidopenicillin. Allylic bromination with NBS gave a mixture of regioisomers 22 + 23 which was treated with tetramethylguanidium formate, yielding a mixture of isomeric formates

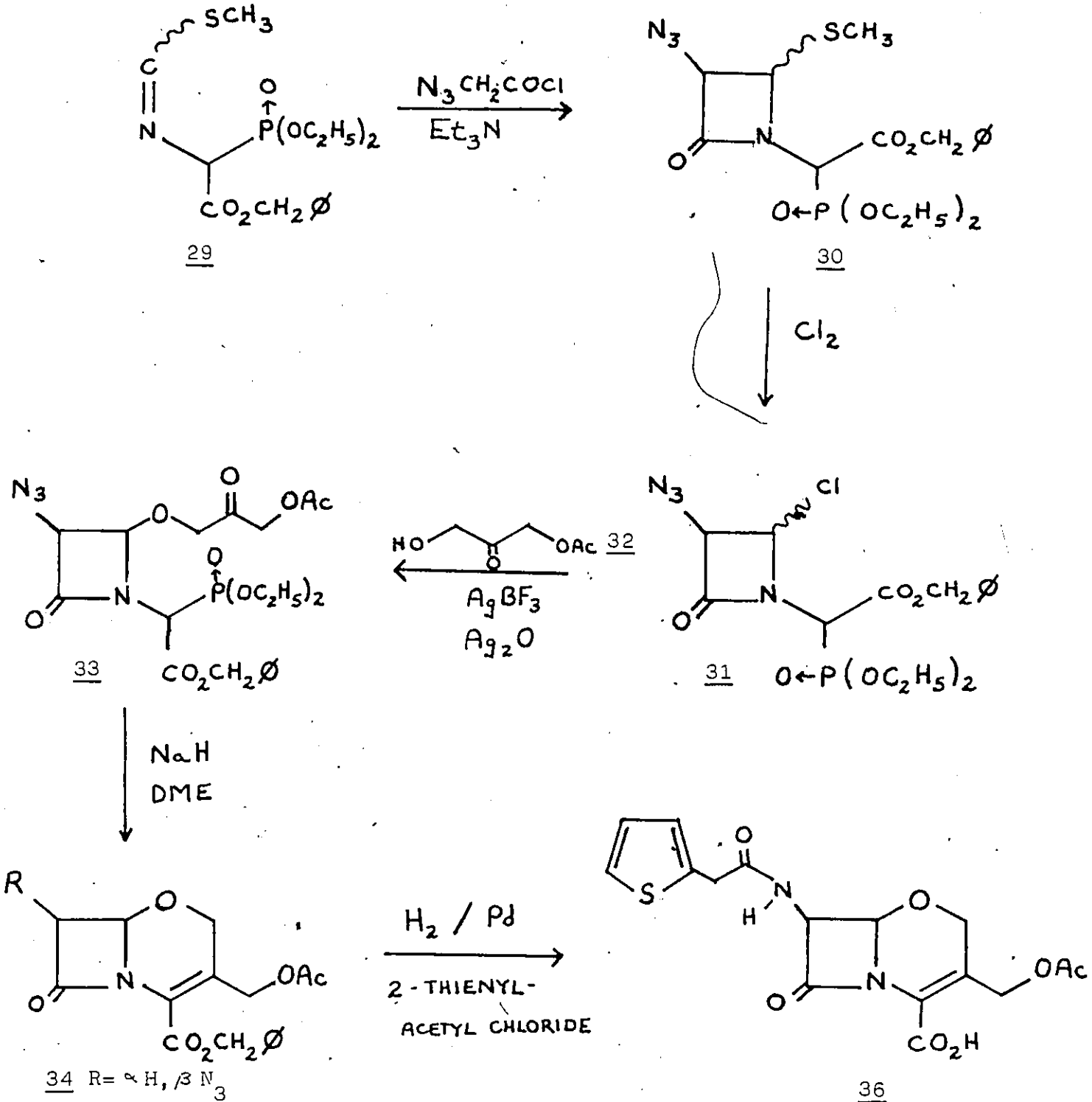
SCHEME III


Ft
Cl
N
O
21
CO_2R
Ft= C_6H_4COON
(pthalimido)
NBS
22
Br
23
Tetramethylguanidium -
Formate
24
OCHO
25
HCl
MeOH
26
O
27
OH
$SnCl_2$, DME
28

24 + 25. These were hydrolyzed to the corresponding alcohols, the "E" isomer 26 lactonizing. The isomeric alcohol 27 was cyclized to the 1-oxacephem 28 upon treatment with stannous chloride in dimethoxyethane or tetrahydrofuran. (SCHEME III).

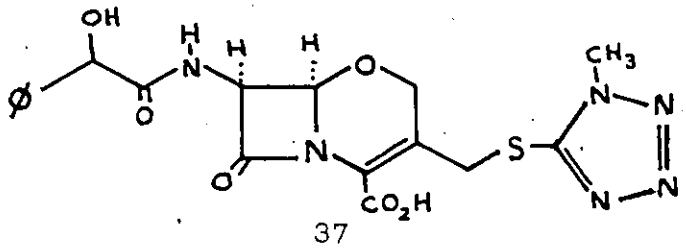
In 1974, Christensen[32] published a synthesis of 1-oxacephem 35 which is the 1-oxo analog of the widely used broad spectrum antibiotic cephalothin 36. In contrast to Wolfe's approach, this method did not begin with a pre-formed β-lactam. Christensen chose to generate the β-lactam in a later step *via* the ketene-imine cycloaddition route. Addition of azidoacetyl chloride to a mixture of 29 and triethylamine resulted in the formation of β-lactam 30. Replacement of the thiomethyl group by chlorine gave 31, a 4-chloroazetidinone. Christensen used 31 in an O-alkylation reaction to build the six-membered ring. Using 1-hydroxy-3-acetoxy-2-propanone 32 in the presence of silver, O-alkylation was achieved, giving 33. Ring closure occurred via an intramolecular Wittig reaction using sodium hydride in dimethoxyethane. The desired *cis* isomer 34 was separated from the *trans* 35. The azido group in 40 was reduced and then acylated with 2-thienylacetyl chloride, to afford (±)-1-oxacephalothin 36 (SCHEME IV). Biological screening indicated a two-fold increase in activity over cephalothin (by M I C), thus demonstrating that the sulfur atom of cephalosporins was *not* essential for activity.

In 1977 Christensen[33], using a similar approach, was successful in preparing the 1-oxo analog 37 of another cephalosporin, cefamondole 3[c]. It, too, demonstrated antibiotic activity comparable to its sulfur-bearing analog.



29 30 31 32 33 34 R= ∝H, β N_3 35 R= ∝ N_3, βH 36

SCHEME IV

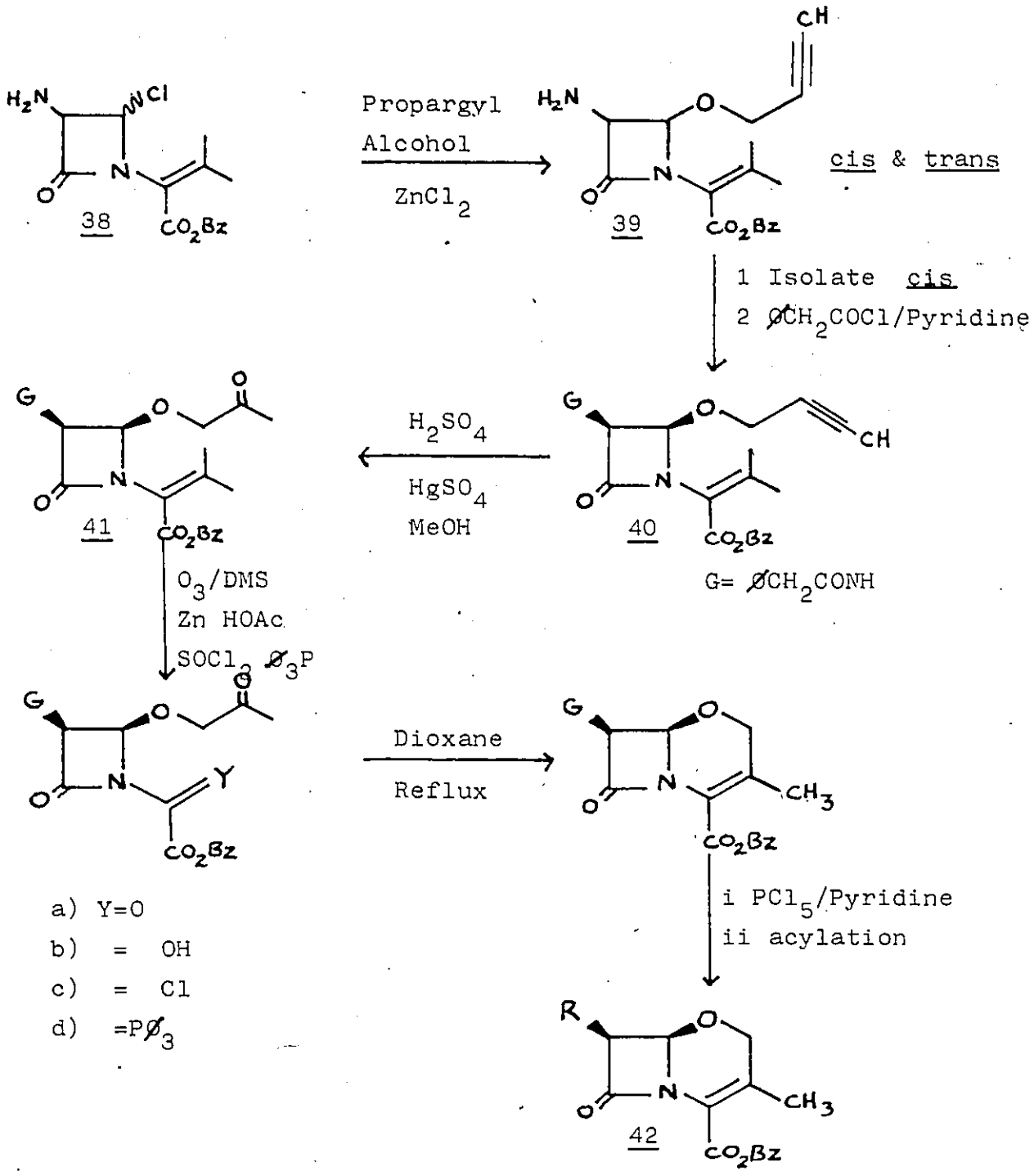


37

Until these encouraging results were published, most research was aimed at side chain variations at C 6 of penicillins and C 7 and C 3 of cephalosporins, the latter occurring via nucleophilic displacement of the natural acetoxy group.

Again in 1977, workers at Shionogi & Co. Ltd.[34] published their synthesis of 1-oxacephems. Their starting material, 4-chloroazetidinone 38, was derived from 6-APA and thus the final cis products would possess the natural chirality. Reaction of 38 with propargyl alcohol in the presence of zinc chloride gave 39 which was acylated to 40, then subjected to a mercuric sulfate-catalyzed hydration, thus generating the methyl ketone 41. The ketone 41 eventually takes part in an intramolecular Wittig reaction (following transformation of the isopropylidene moiety into phosphorane). The C 7 amino group was de-protected, several acylamino groups were introduced and the products 42 tested. Most compounds showed a four-to eight-fold increase in activity (by M I C) over the corresponding cephalosporins. The main disadvantage to this synthesis is that only compounds with a C 3 methyl group can be formed. (SCHEME V).

In 1979 Shionogi[35] workers published a more refined version of their 1-oxacephem synthesis. Rather than using the mercuric sulfate hydration step (which can lead only to C 3 methyl groups), they reduced the propargyl group of 43 to the vinyl group of 44. This was epoxidized with MCPBA to

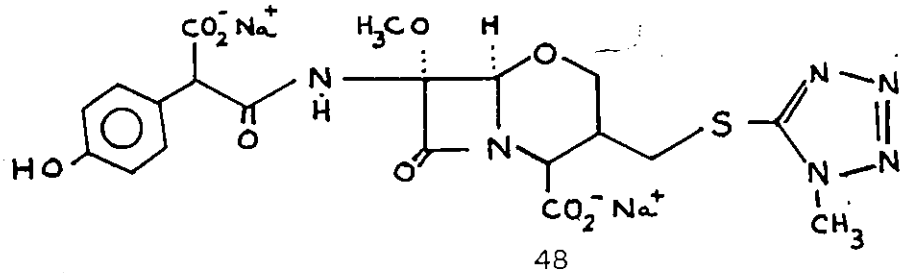

38
Propargyl Alcohol
ZnCl2
39
cis & trans
1 Isolate cis
2 ØCH2COCl/Pyridine
40
G= ØCH2CONH
H2SO4
HgSO4
MeOH
41
O3/DMS
Zn HOAc
SOCl2 Ø3P
a) Y=O
b) = OH
c) = Cl
d) =PØ3
Dioxane
Reflux
i PCl5/Pyridine
ii acylation
42

SCHEME V

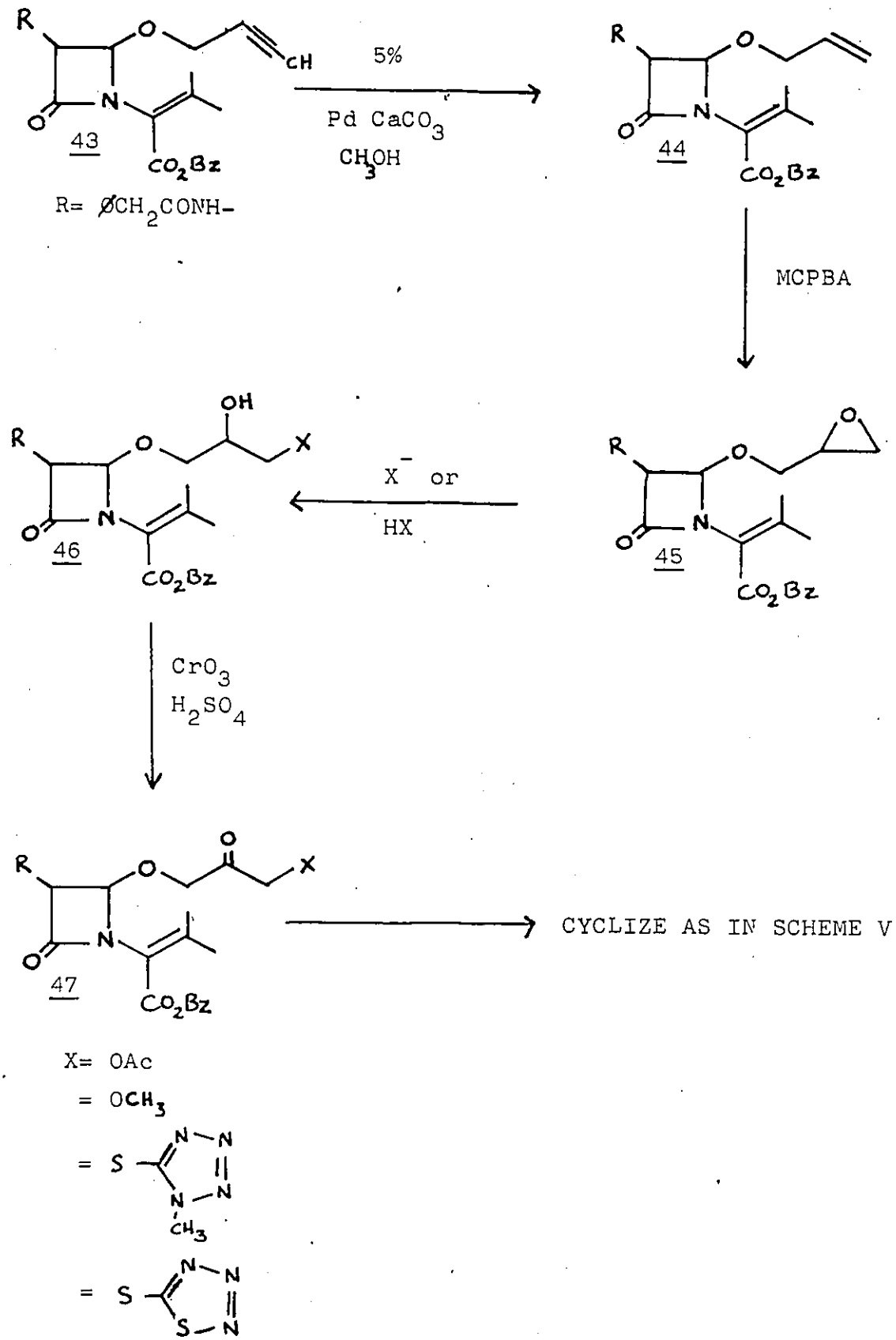
45. Any desired C 3 side chain could then be prepared by opening the epoxide with an appropriate nucleophile. The secondary alcohol 46 thus formed was oxidized to the ketone 47 and cyclized as before. (SCHEME VI).

It had been shown by this time that the presence of steric bulk at C 7 increased the β-lactamase resistance of cephalosporins. The naturally occurring cephamycin features a 7-alpha-methoxy group. Previous studies had indicated that the optimum size for the ether group at C 7 for biological activity with β-lactamase stability was the methoxy group[36]. With this in mind, the Shionogi workers prepared 48 following essentially the pathway described in SCHEME VI. This compound showed excellent activity against a widely expanded spectrum of Gram negative bacteria and a β-lactamase-producing strain of Klebsiella pneumoniae.

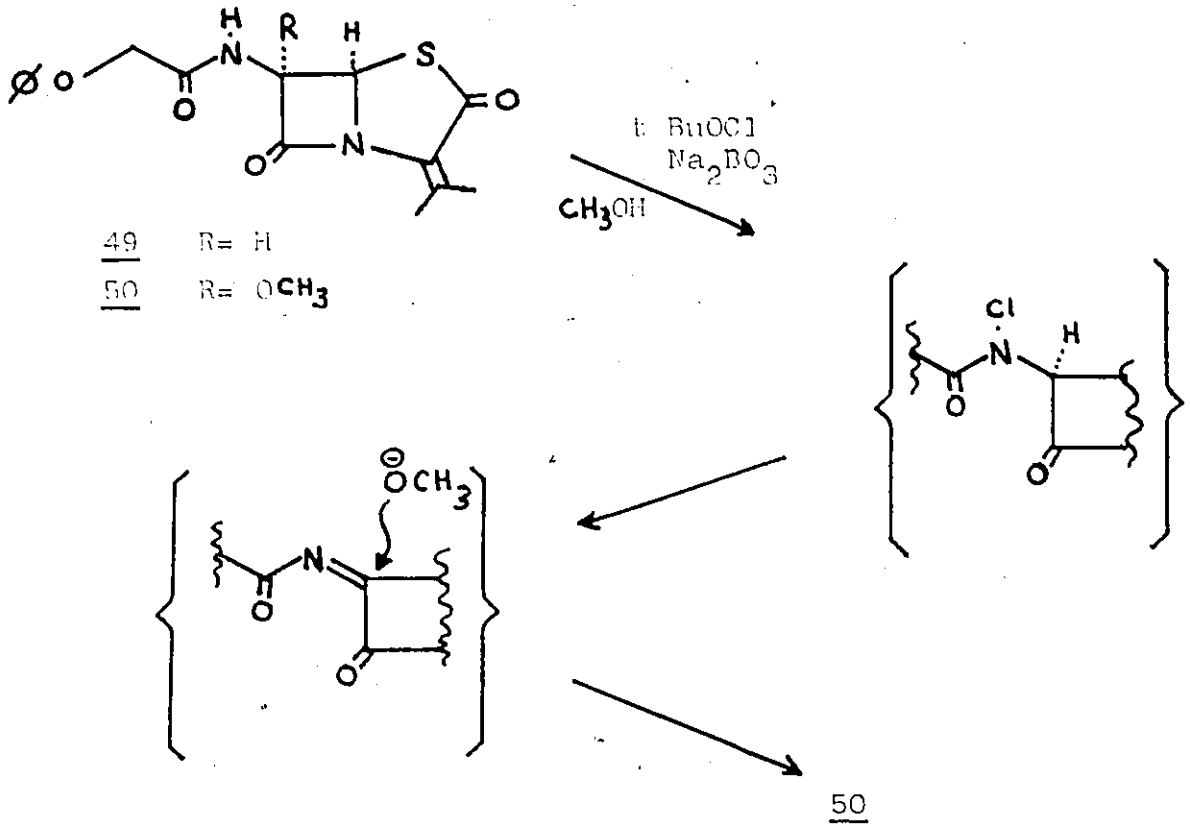
Introduction of the 7-alpha-methoxy group is accomplished by adding methanol to an acylimine function at C 7 of cephalosporins. Baldwin[37] performed this Michael addition on anhydro-penicillin V 49 by first halogenating the amide nitrogen with t-butyl hypochlorite. Dehydrohalogenation gave the acylimine. Stereoselective addition of methanol to the alpha face afforded 6-alpha-methoxy anhydropenicillin 50 in quantitative yield.



48


R
O
CH
5%
Pd CaCO3
CH3OH
43
CO2Bz
R= ØCH2CONH-
44
MCPBA
45
X⁻ or
HX
OH
X
46
CrO3
H2SO4
47
CYCLIZE AS IN SCHEME V
X= OAc
= OCH3
= S
N
CH3

SCHEME VI



Koppel[38] refined this method, utilizing methanolic lithium methoxide as base and t-BuOCl again as chlorinating agent at low temperature. Using this method various cephalosporins were etherified at C 7 stereoselectively in good yield ($>75\%$). Of course, in a total synthetic scheme, the chlorination step may not be necessary if the acylimino group has already been introduced at C 7 .

These results were so encouraging that shortly after Christensen's work was published, the search was on for other nuclear analogs where sulfur was not only replaced by oxygen but nitrogen, and at loci other than position one.

2-OXO AND 2-AZAISOCEPHEMS

We have already seen how substitution of sulfur by oxygen in the cephalosporins can result in a four to eight fold increase in antibiotic activity. The Bristol Laboratories group headed by Doyle and Belleau[39] embarked on an investigation of a number of 2-heterosubstituted cephalosporins. Their target molecules were designed on the following criteria, necessary for activity, established by inspection of known active compounds.

(i) presence of a β-lactam ring fused to a five membered ring or to a six-membered ring with double bond, imparting strain on the β-lactam.

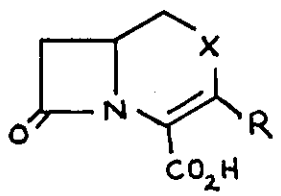
(ii) in saturated systems, the double bond be conjugated with the β-lactam nitrogen.

(iii) an acylamino function alpha to the β-lactam carbonyl.

(iv) "cis" stereochemistry of the β-lactam protons.

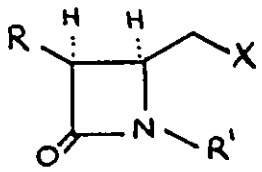
(v) a free carboxylic acid alpha to the β-lactam nitrogen in the five or six membered ring.

With these criteria in mind, they set out to synthesize compounds of the general structure:



X= O, N-R

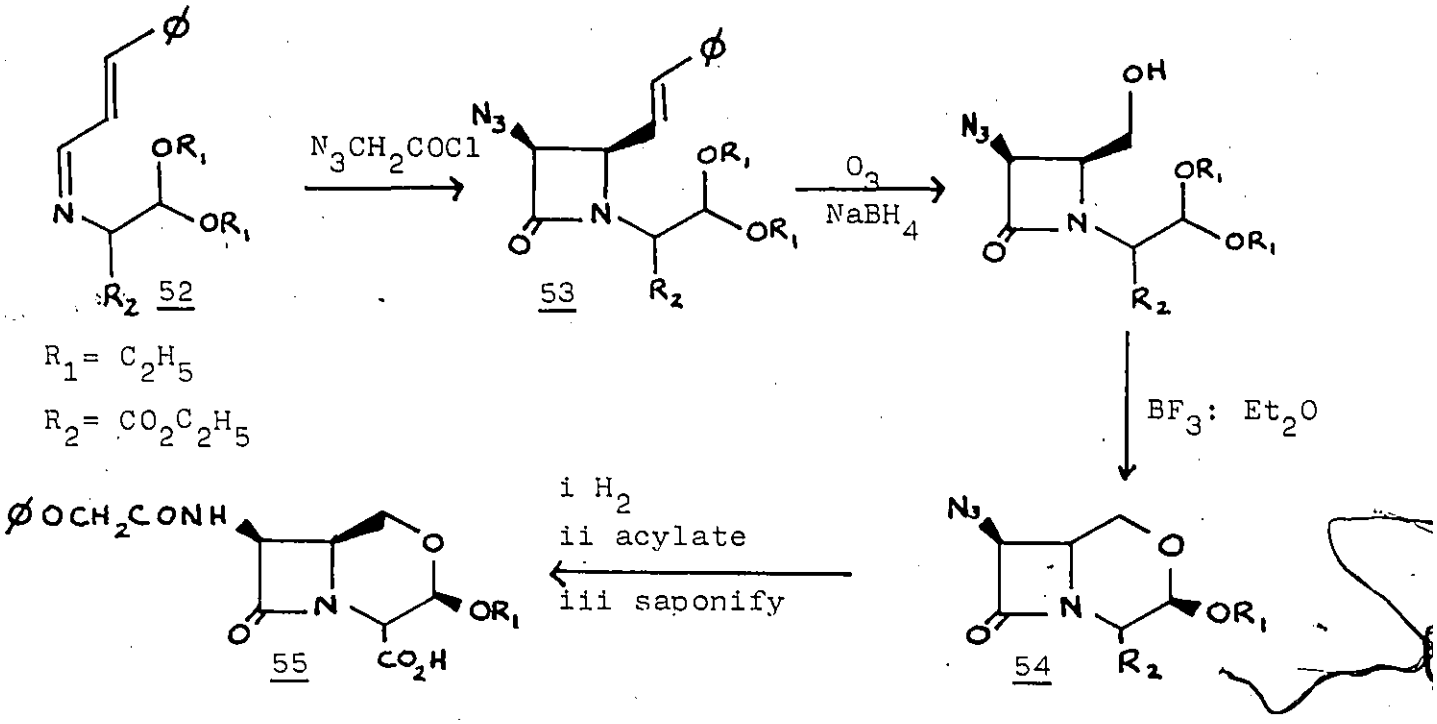
Earlier, 2-heteroatom type compounds had been synthesized by Lowe[40], however they failed to exhibit antibiotic activity because they did not satisfy the above structural prerequisites for activity. The β-lactam 51 was considered a suitable starting material, this structure allowed construction of the six membered ring with a 2-heteroatom.



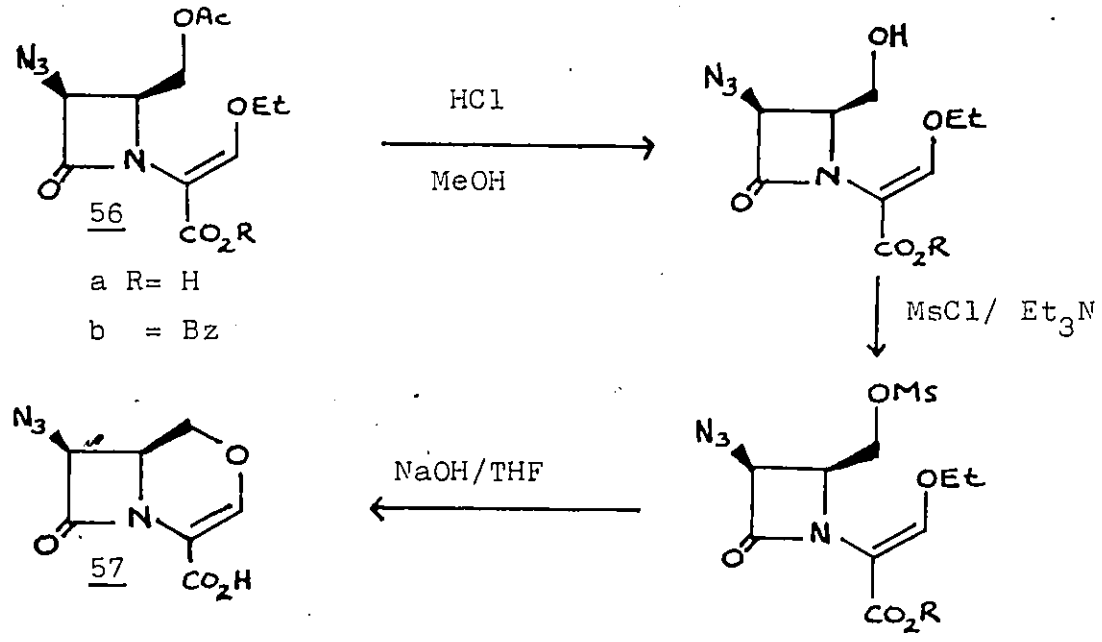
51

Rather than using a free aldehyde, a masked aldehyde in the form of a 4-styryl group was chosen, for ease of preparation and handling. The styryl group could be oxidatively degraded to the aldehyde with ozone.

Formation of the required β-lactam was accomplished by the familiar ketene-imine route, a key discovery being the exclusive formation of "cis" β-lactams by the addition of azidoacetyl chloride to the Schiff base in the presence of triethylamine rather than vice versa. Thus, azetidinone 53 was synthesized from azidoacetyl chloride and Schiff base 52. Following ozonolysis, reduction, and treatment with boron trifluoride etherate, the O-2-isocepham 54 was obtained in 50% yield. The synthesis was completed to 55. Not unexpectedly 54 exhibited only a very low level of activity. All efforts to convert 55 into the desired unsaturated counterpart through loss of ethanol failed.

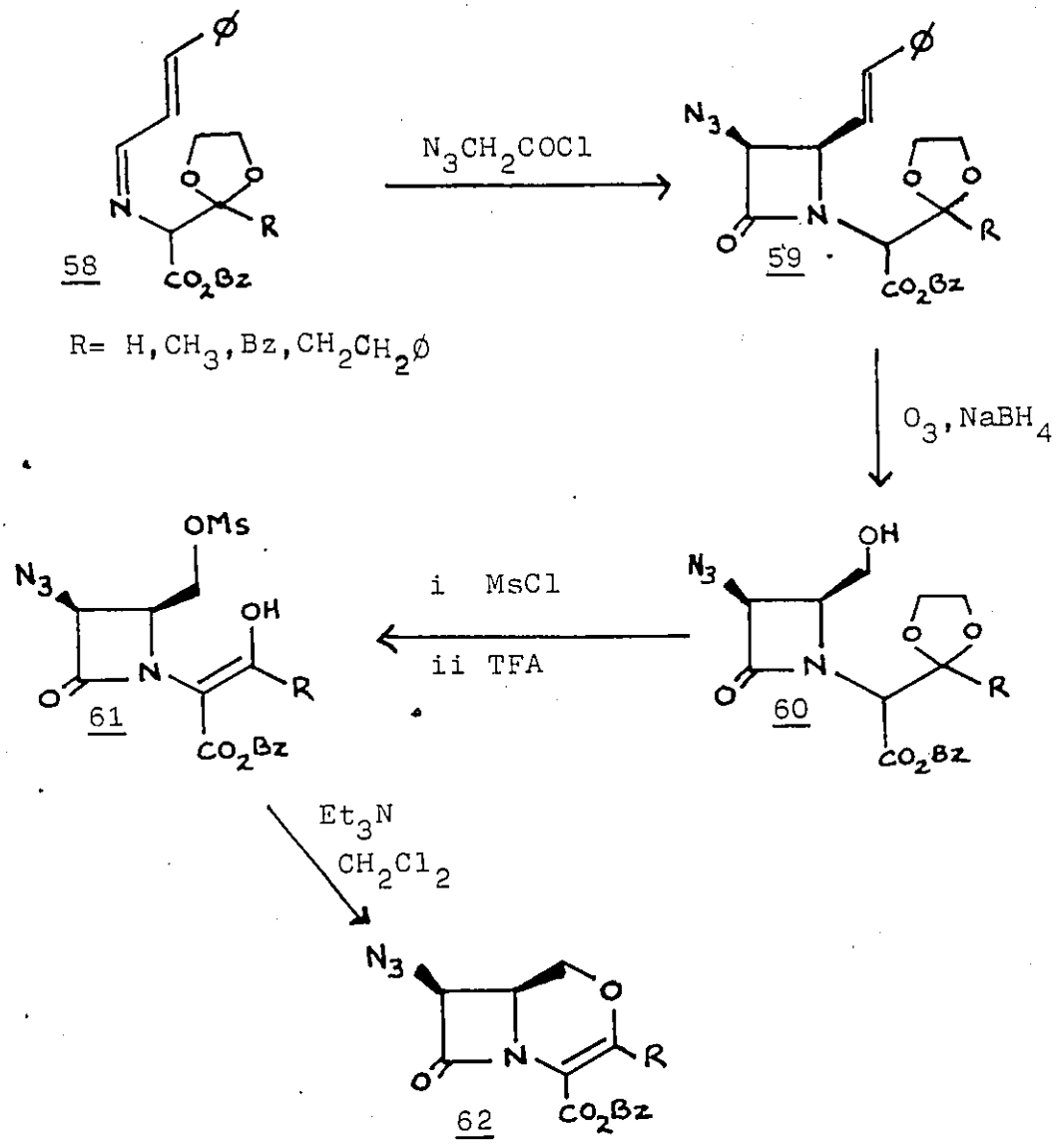


Therefore a new strategy had to be adopted. It was discovered that treatment of 55 with zinc chloride in acetic anhydride (in an effort to eliminate ethanol) gave azetidinone 56a. The benzyl ester 56b was hydrolyzed, mesylated and treated with NaOH/THF giving 7β-azido-2-O-isoceph-3-em-4-carboxylate 57 in 33 % yield.

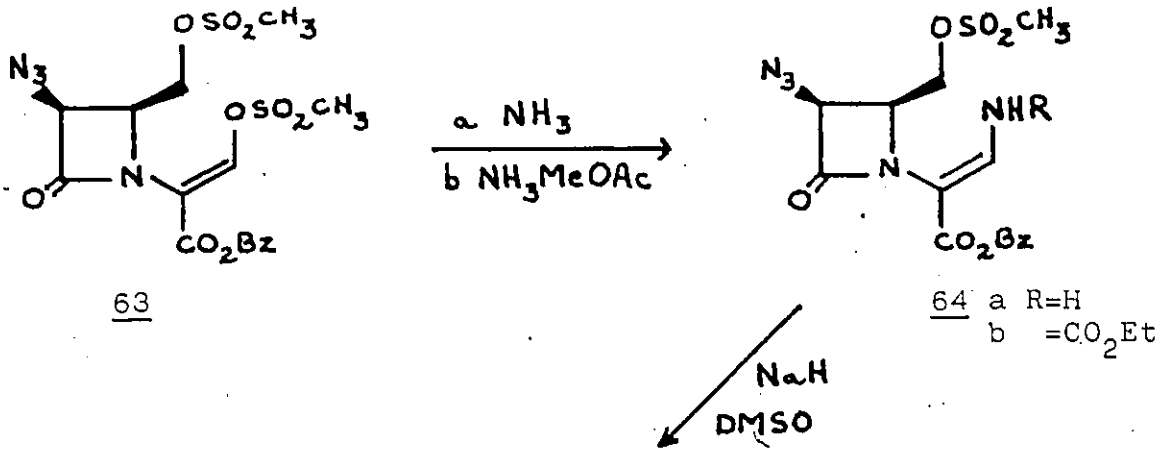


This sequence is applicable only to form C 3 unsubstituted O-2-isocephems.

In order to produce 2-O-isocephems having substitution at position 3, the sequence (58 → 62) was developed, incorporating a protected ketone rather than an aldehyde into the starting imine. The enol 61 cyclized in excellent yield to 62 upon refluxing in methylene chloride with triethylamine. In this way, Doyle and Belleau prepared several O-2-isocephems and tested their antibiotic qualities[41]. The O-2-isocephems were prepared with a wide variety of side chains at C 3 and C 7 ; most displayed biological activity comparable to cephalosporins.



The high degree of antibiotic activity in the O-2-isocephems prompted the investigation of the N-2-isocephem system. From earlier work, Doyle and Belleau[42] had available the bis mesylate 63. Treatment of this with either ammonia or monomethyl ammonium acetate gave amine 64.

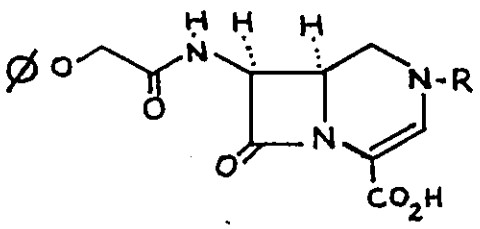


63

64 a R=H
b =CO_2Et

65 R=CO_2Et

Cyclization of 64b (but not 64a) could be achieved by treatment with sodium hydride, giving the 2-N-isocephem 65. In subsequent conversions, 64b was reduced, and acylated to the phenoxyactamide 66. Compound 66 was found to possess a low level of activity.



66 a R=CH_3

b =CO_2Et

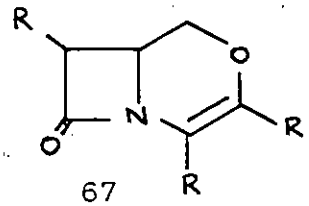
Since these earliest nuclear analogs, many others have been prepared, including 2-isocephems, 1-oxapenems, N-2-isopenems, carbapenems, 1-oxa-2-penems and recently 3-oxacephems and 2-penems. The 3-oxacephams are the first 4:6 bicyclic β-lactams lacking unsaturation in the six-membered ring to demonstrate antibacterial activity, and the 2-penem nucleus is the structurally simplest β-lactam showing activity. This is most likely due to the very highly strained ring system as indicated by the carbonyl absorption of about 1810 cm^{-1}. Many of these as well as a few other variations are discussed by Christensen in a recent review.[43]

From the activity demonstrated by many nuclear analogs it is clear that many of the criteria necessary for activity must be revised . We now realize that the sulfur atom may be replaced, a 7-alpha-methoxy group may be introduced, unsaturation omitted (3-oxacephams) and C6(7) amide side chain replaced by hydroxyethyl (thienamycin) or deleted altogether (2-penems) with considerable retention of activity and, in many cases, the added bonus of β-lactamase resistance. Therefore a new, wide open approach could be adopted, as it would seem the only structural feature, the only common denominator, essential for activity, is the β-lactam nucleus itself!

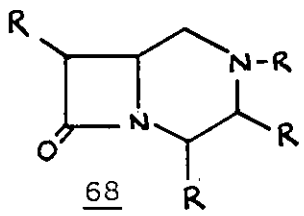
While examining the work of Doyle and Belleau, we had decided that a possibly more flexible approach to both the O-2-isocephem and 2-N-isocepham systems from a more common intermediate might be feasible.

On closer inspection of 67 and 68 we noted that both compounds could be retrosynthetically related to a nitro compound 69. If a nitro intermediate could be reduced to a amine, entry into the 2-azaisocephams might be possible. Similarly, oxidation of a nitronate intermediate to a carbonyl might allow entry into the more valuable 2-oxacephems.

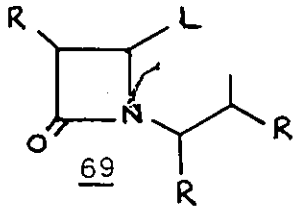
This thesis explores these possibilities.



67



68



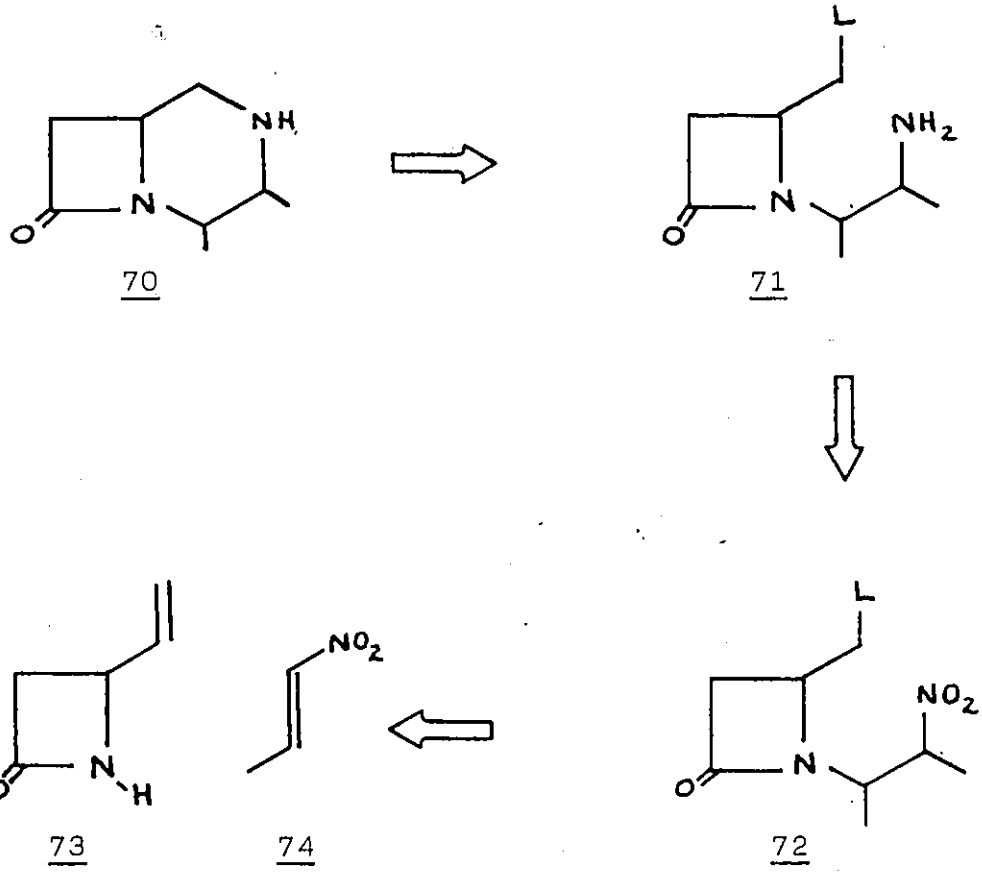
69

RESULTS AND DISCUSSION

DESCRIPTION OF THE PROJECT

The purpose of this work was to investigate the possibility of using nitro olefins in the preparation of two types of synthetic β-lactam nuclei, namely the 2-azacephems and the 2-oxacephems (the latter being a group that has attracted much attention recently[44]). If successful, this could prove to be a flexible approach to nuclear analogues of β-lactam antibiotics, since entry into both systems would be attained using a common intermediate. This would also add to the already long list of synthetic uses for nitro olefins[45], the synthesis of biologically active non-nitro compounds using nitro olefins as intermediates.

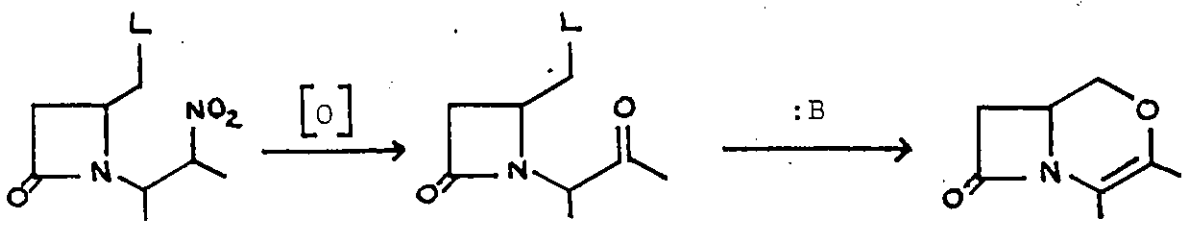
If a retrosynthetic analysis is applied to the target molecules, our purpose becomes more clear.



70 71 73 74 72

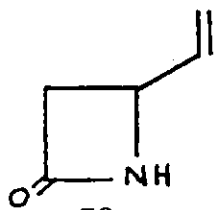
The rupturing of the C1-N bond in 70 generates intermediate 71, (L is a suitable leaving group). The amino function of 71 should be easily obtained by reduction of the corresponding NO_2 derivative 72 which in turn should be accessible by combining the two synthons 73 and 74 in a Michael addition reaction. The vinyl group in 73 serves as a latent leaving group.

The key intermediate 72 can also serve as an entry into the 2-oxacepham or cephem system since a nitro group is synthetically equivalent to a carbonyl function. These potential interconversions are shown below.



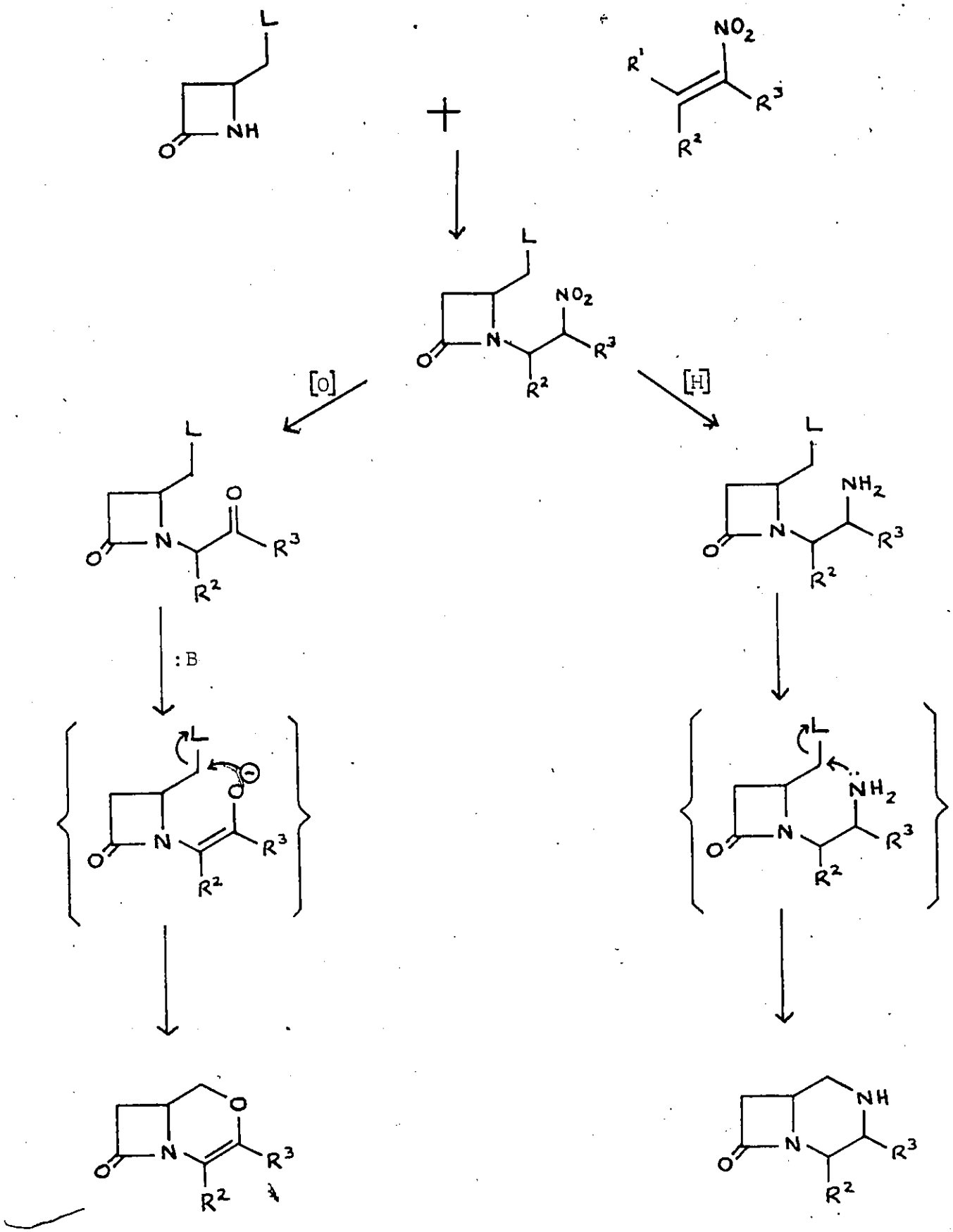
72

In order to test these proposed reaction sequences a suitable β-lactam had to be selected. The azetidinone chosen was 4-vinyl azetidinone 73.[66]



73

Its choice was due to its satisfying all reaction needs, in addition to its ease of preparation in relatively large scale (up to 40 g) via the 2 + 2 cycloaddition reaction between chlorosulfonyl isocyanate and 1, 3-butadiene. The 4-vinyl group can easily be transformed into a good



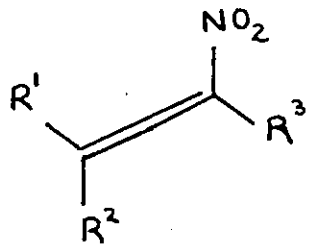
SCHEME VII

leaving group by ozonolysis, reduction, and mesylation of the resulting alcohol. Furthermore, Hamlet and Durst (unpublished observation) have shown that 73 can be alkylated at C3 under stereochemical control.

The nitroalkene 74 used in the Michael addition reaction should bear substituents which are either present or easily converted into those found in pharmacologically active bicyclic β-lactams. Thus, R^1 which becomes the 3-substituents in the cephams can be a variety of substituents, including alkyl, aryl, heteroalkyl or ester. Either R^2 or R^3 should be a carboxylate function or readily transformed into a carboxylate group, the remaining substituent being hydrogen. Benzyl 3-nitrobut-2-ene 81 should be an ideal substrate.

A literature search for nitro compounds turned up few compounds of this type, with β-nitroacrylate 78 being the only one incorporating most of the desired features. Thus, a synthesis of compounds such as 74 had to be designed.

While this work was in progress we decided to test the feasibility of the reactions outlined in Scheme VII utilizing the series of nitroolefins tabulated below. The main body of the discussion in this thesis concerns the results of these studies.



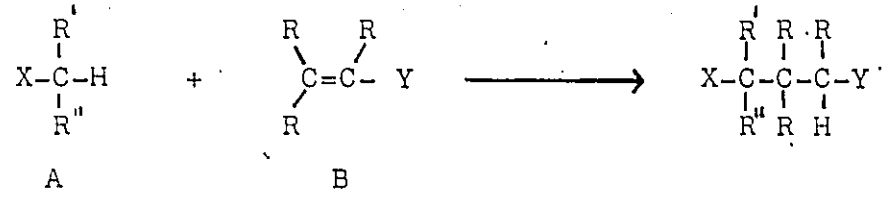
COMPOUND		R^1	R^2	R^3
β-nitrostyrene	75	H	Ø	H
1-phenyl-2-nitroprop-1-ene	76	H	Ø	CH_3
2-Nitrobut-2-ene	77	H	CH_3	CH_3
Ethyl 3-nitroacrylate	78	H	CO_2Et	H
Benzyl α-nitrocinnamate	79	H	Ø	CO_2Bz
Methyl α-nitrocinnamate	80	H	Ø	CO_2CH_3
Benzyl 3-nitrobut-2-enoate	81	H	CO_2Bz	CH_3

In presenting the results, it was decided to discuss the complete sequence of reactions, shown in Scheme VII, for each individual nitroalkene. This approach is used rather than the generalized approach of describing first of all the Michael additions followed by the transformations of the addition products. The former approach was chosen, despite the possible problem of repetitiveness, since each Michael addition and subsequent reaction scheme required different reaction conditions. Prior to discussing the individual sequences a few general comments will be made regarding the key transformations, namely the Michael addition reactions and the nitroalkane to carbonyl conversion.

MICHAEL ADDITIONS TO 4-VINYL-2-AZETIDINONE

The initial step in the proposed scheme is the Michael addition of the β-lactam to the appropriate nitro olefin. The Michael reaction remains as one of the most efficient carbon-carbon bond forming processes available to the synthetic chemist. Baer[46] describes the reaction as:

> the base catalyzed addition of an addend or donor (A) containing a reactive ∝ -hydrogen atom to an activated carbon-carbon double bond in an acceptor (B).



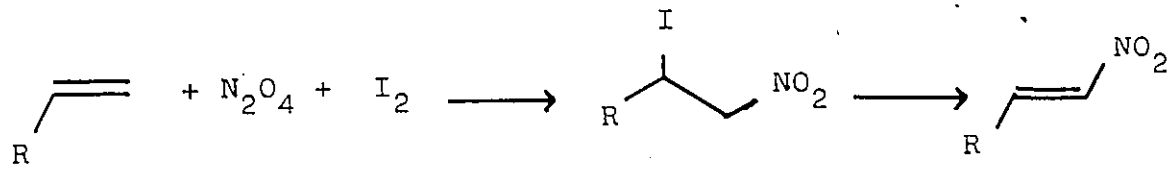
A B

In our case A (donor) is the β-lactam 81 possessing a reactive hydrogen atom in the form of an amide proton, the B (acceptor) is the nitro olefin, Y being the nitro group. The scope and limitations of the Michael reaction have been extensively reviewed by Bergmann, Ginsburg and Pappo[47] as well as Perekalin[48] and more recently Baer.[46]

As was previously alluded to, the preparation of the appropriate nitro olefin acceptor molecules was essential if the synthesis of the target molecules was to be achieved. The classical method for preparing nitro olefins consists of first performing a base-catalyzed condensation between the proper nitroalkane and aldehyde or ketone resulting in a nitro alcohol (Henry reaction). Next, the alcohol is dehydrated to the olefin. This may be accomplished by two means, use of chemical dehydrating agents such as phosphorus pentoxide, phthalic anhydride or by converting the alcohol group to a better leaving group through acety-

lation or mesylation followed by a base-catalysed elimination. In many cases, especially when the olefinic bond is part of a conjugated system, the dehydration is spontaneous, or occurs on acidic workup. In fact, isolation of the nitro alcohol intermediate is sometimes rather difficult. Yields are generally good in these condensations, with major interferences being unwanted self aldol condensations of the carbonyl components as well as products arising from further reactions of the initial condensation products. These can be avoided through control of amounts of reactants used.

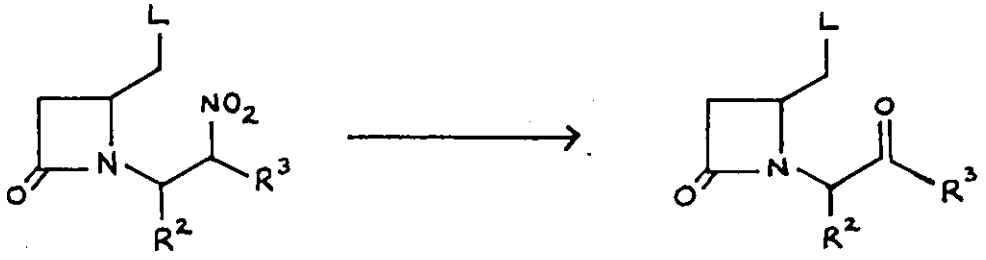
Another, much less commonly used route to nitroolefins is the addition of dinitrogen tetroxide/iodine to existing olefins. The resulting nitro-iodo compound is treated with base to effect elimination of hydrogen iodide.



In preparing the desired nitroolefins for this thesis, it was necesary to use all of the preparative methods discussed here.

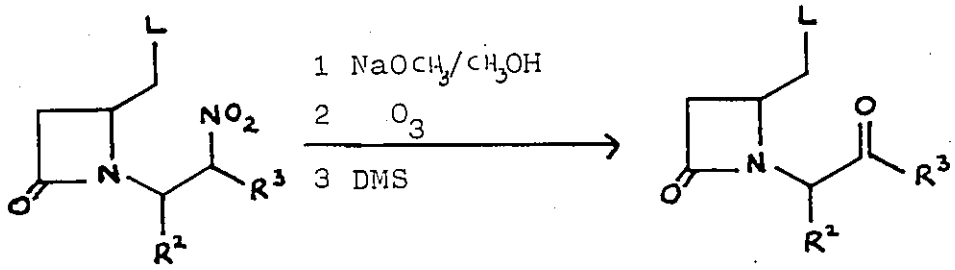
NITRO TO CARBONYL CONVERSION

The scheme leading to the 2-oxacephem derivatives requires the conversion of a nitro into a carbonyl group. (82 → 83).



82 83

In recent years, numerous methods have been published concerning nitro to carbonyl conversion.[49] These include: $NaOH/H_2SO_4$ (Nef reaction),[50] ozone/methoxide,[51] $KMnO_4$/methoxide,[52] $KMnO_4$/basic alumina,[53] ceric ammonium nitrate/triethylamine,[54] and titanium trichloride.[55] These reagents fall into three categories: strongly acidic, basic oxidative and neutral reductive. In choosing compounds such as β-lactams one must consider the severity of the reaction conditions. Unfortunately most of the above methods had to be rejected since their reaction conditions are too severe for survival of the β-lactam ring. The ozone/methoxide and permanganate/alumina methods seemed to hold promise for use in our scheme. The latter involves refluxing the nitro lactam in ethyl acetate with basic alumina, potassium permanganate and sodium periodate. This method gave good yield of the desired carbonyl compound in only one case. The ozone method consists of generating the sodium nitronate salt in dry methanol with sodium methoxide, followed by ozonolysis at -78°C. This method proved to be superior to the first, and was adopted as method of choice.

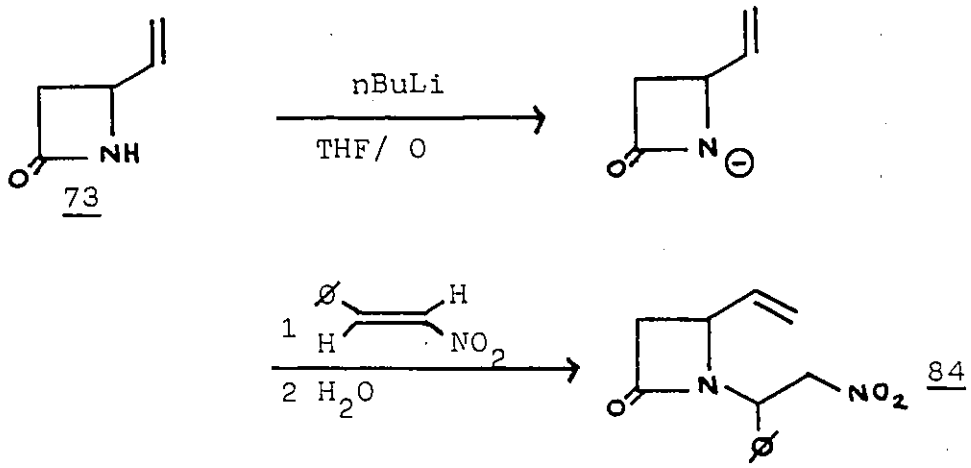


NITROSTYRENE ADDITION

The reaction between β-Nitrostyrene and 4-Vinyl-2-azetidinone was chosen as the model Michael addition reaction. β-Nitrostyrene, stable, easily purified crystalline material, is readily available from benzaldehyde and nitromethane. Furthermore, the proton NMR of the desired product

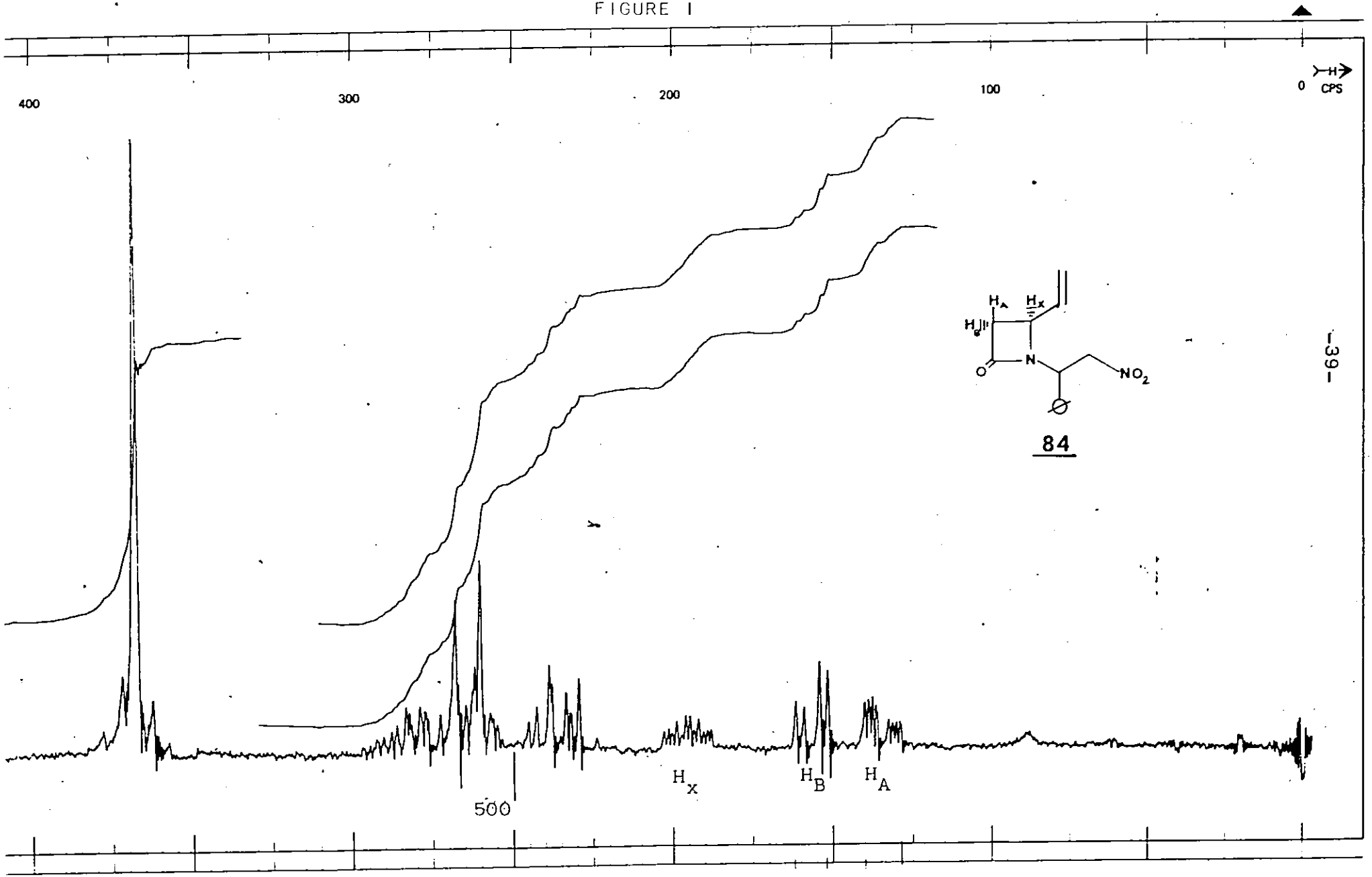
was easily predictable, and sufficiently different from either starting material to make its identification unambiguous.

The first base chosen to catalyze the reaction, n-butyllithium, proved to be the most effective. Reaction of the N-lithio salt of 73, generated in dry tetrahydrofuran at 0°C, with a tetrahydrofuran solution of nitrostyrene gave on aqueous workup, the adduct 84 as a yellow oil in 86% isolated yield. The use of other bases such as sodium hydride, triethylamine, DBN as well as phase transfer conditions failed and either starting material or polymers were obtained.



The proton and carbon-13 spectra of 84 are depicted in Figures 1 and 2 respectively. The proton spectrum shows the presence of the β-lactam ring. The three hydrogens on the ring represent an ABX system with H_A and H_B absorbing from δ 2.55 to δ 2.85 and δ 3.0 to δ 3.25 respectively. The observed coupling constants J_{AX} = 2Hz, J_{BX} = 5Hz are typical coupling constants observed for protons on a β-lactam ring having trans and cis relationships respectively. Proton H_X absorbs as a multiplet from δ = 3.75 to 4.1. The remaining non-aromatic hydrogens, namely those alpha to NO_2, alpha to phenyl and the three olefinic protons generate

FIGURE I



a complex multiplet from δ = 4.5 to 6.0. Part of the complexity of the spectrum is due to the fact that 84 is obtained as a diastereomeric mixture. This is, for example, suggested by the doubling of the peaks for the proton H_A, but fortuitously not for H_B. The existence of 84 as an essentially diastereomeric mixture is clearly established by the carbon-13 NMR, where each of the non-aromatic carbons are present as doublets. The various assignments shown in Figure 2 were supported by partial proton decoupling experiments.

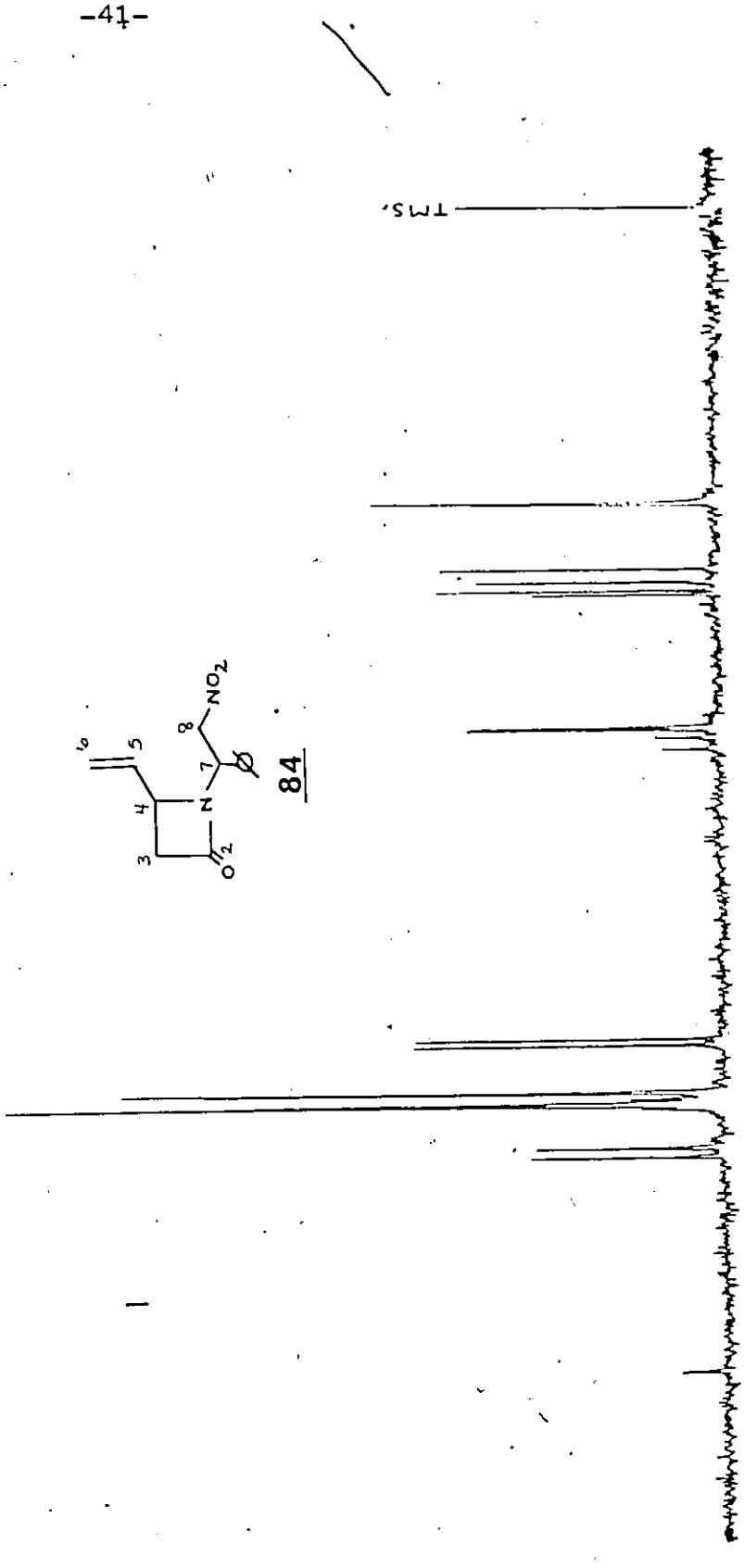
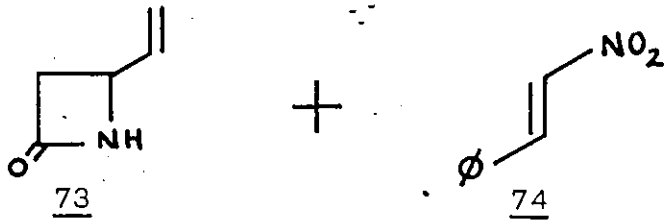
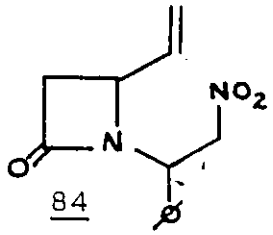


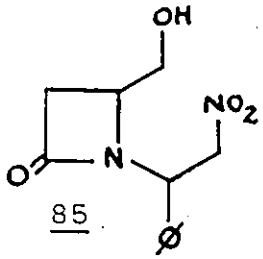
FIGURE 2



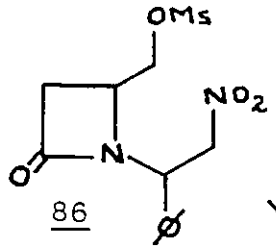
73 + 74



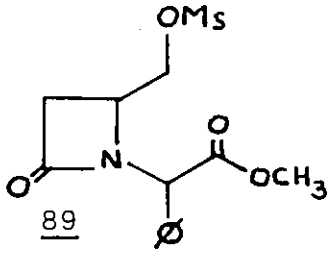
84



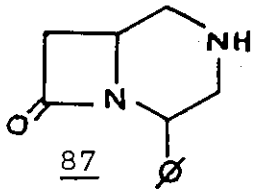
85



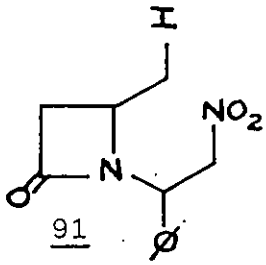
86



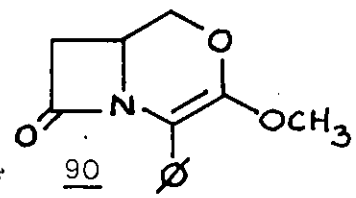
89



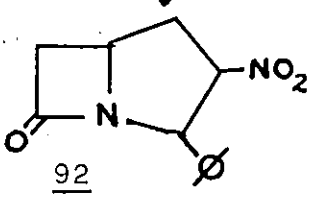
87



91



90



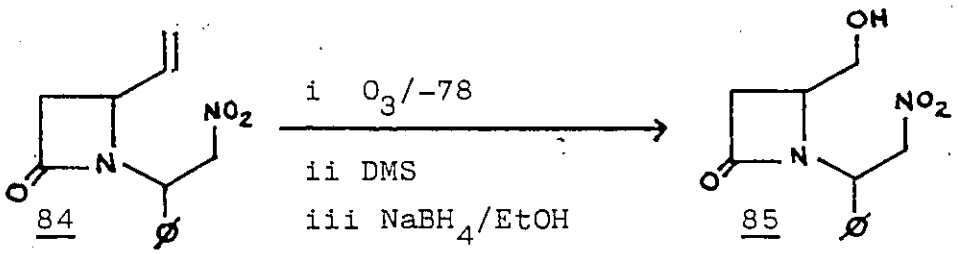
92

SCHEME VIII

The infrared spectrum of 84 shows characteristic absorptions at 1740 cm^{-1} (β-lactam C=O) and 1560, 1370 cm^{-1} (aliphatic NO_2).

With the desired adduct in hand, the next step of the reaction sequence was attempted. The adduct 84 was dissolved in methylene chloride containing a small amount of methanol, then ozonized at -78°C until the reaction mixture turned blue (excess ozone). The resulting ozonide was decomposed *in situ* with dimethyl sulfide, and the resulting mixture evaporated to a gummy residue. The crude aldehyde thus formed was reduced to the corresponding alcohol 85 ($NaBH_4$, EtOH).

The alcohol was obtained in 22% isolated yield after column chromatography, as a yellow foam.

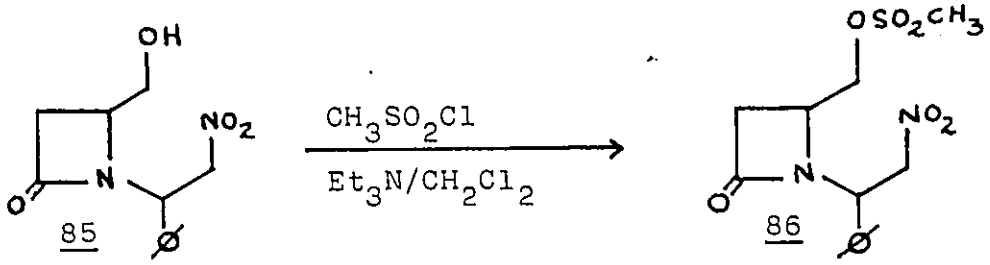


84 85

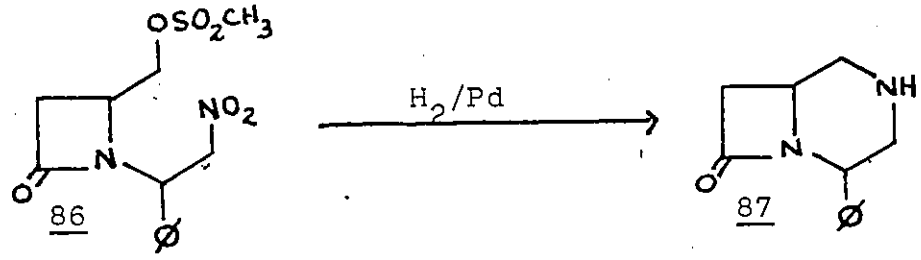
The infrared spectrum of 85 featured the expected absorption at 3200 - 3600 cm^{-1} (OH), 1740 cm^{-1} (C=O) 1560, 1380 cm^{-1} (NO_2). The proton NMR spectrum of 85 was difficult to analyze in detail. It showed (following D_2O exchange) multiplets from δ 2.5 - 3.0 (-CHC=O), 3.5 - 4.0 (-CHO- and N-CH), 4.6 - 5.8 ($-CH_2NO_2$ and OCHN-) and 7.3 - 7.6 (5H, aromatic). The carbon-13 spectrum of 85, again confirmed it as a mixture of diastereomers.

The alcohol 85 was converted to the mesylate 86 in 75% yield. The proton resonance spectrum of 86 showed the presence of two isomers in approximately equal amounts,

as shown by the presence of the two widely differing $OSO_2\underline{CH_3}$ absorptions (δ 2.9 vs 3.2). The infrared spectrum confirmed the presence of the OSO_2CH_3 group, 1370 and 1170 cm^{-1}. The β-lactam 1750 cm^{-1} (C=O) and NO_2 group 1350, 1560 cm^{-1} were observed. No OH group was detected.



Intermediate 86 is a very special compound in our reaction scheme. From here we may proceed via oxidation or reduction of the nitro group. Compound 86 was hydrogenated in 4:1 ethanol-ethyl acetate over palladium on charcoal. The reaction



was monitored by thin layer chromatography. When nearly all of 86 had disappeared, the reaction mixture was filtered, solvent evaporated and the residue eluted through a short silica column. A clear oil which slowly turned brown on standing was obtained. Its structure was assigned as 87 on the basis of its spectroscopic data. The yield was 24%.

The mass spectrum showed the molecular ion at m/e = 202 as expected on the basis of $C_{12}H_{14}N_2O$. The infrared spectrum shows a small sharp peak at 3550 cm^{-1} (NH) and

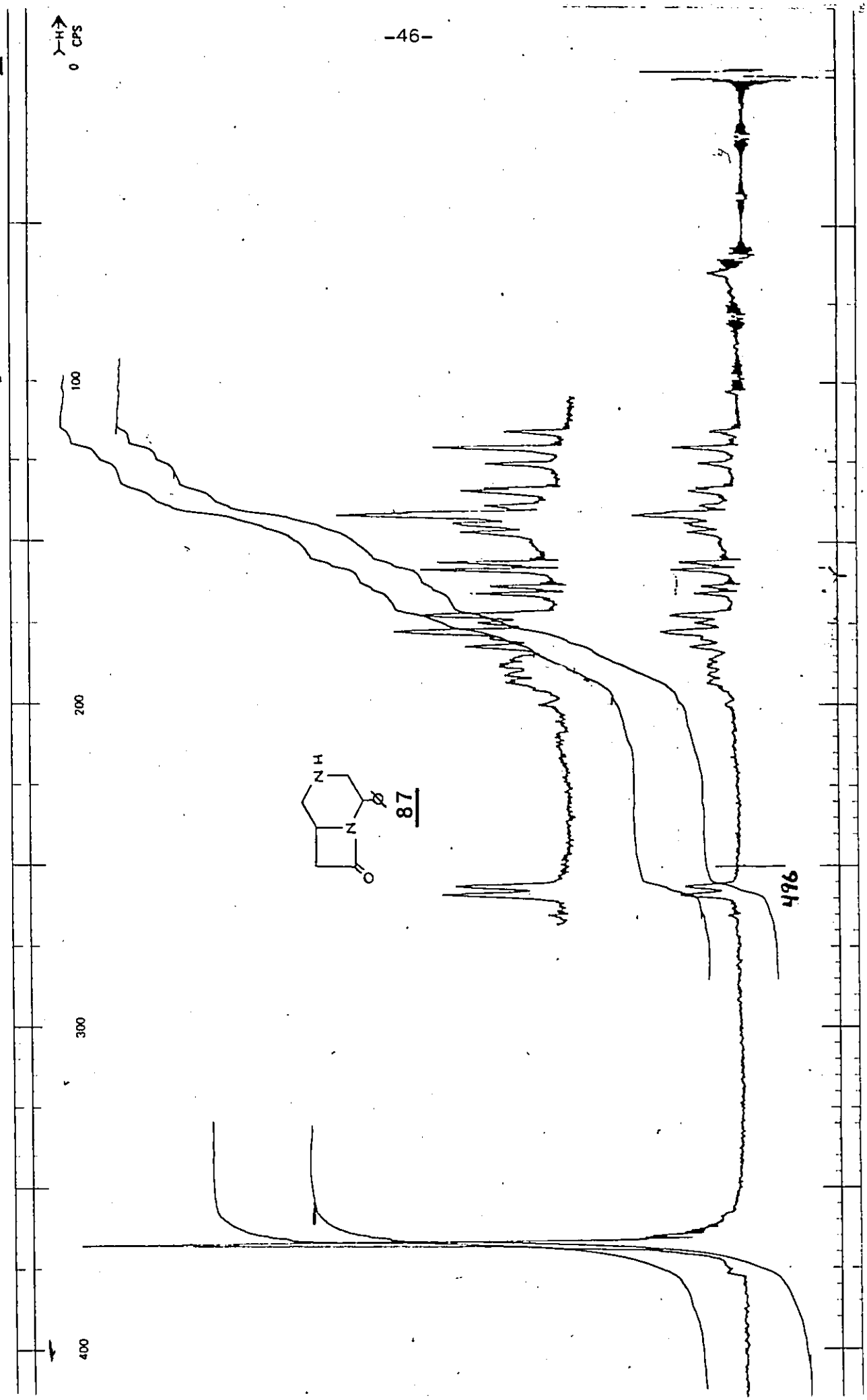
a broad peak from 3500 - 3000 cm^{-1} suggesting considerable hydrogen bonding. The reason for this is not clear. The β-lactam carbonyl absorbs at 1740 cm^{-1}.

The proton resonance spectrum for 87 is shown in Figure 3. It is quite complex and difficult to interpret due to considerable overlap of signals. The integration indicated the required aryl- to non-aryl hydrogen ratio of 5:8 The N-H proton could not be located, it may be highly broadened and therefore not visible. This would be in agreement with the strong H-bonding suggested by the infrared.

The signals expected for the diastereotopic CH_2 group on the β-lactam ring can readily be seen at δ = 3.26 and 3.82 (Figure 3); the bridgehead hydrogen is found at its usual position δ = 3.7 - 3.9. Surprisingly the benzylic hydrogen at δ = 5.20 occurs as a doublet (J = 6.0 Hz) rather than the expected quartet. Vicinal couplings in saturated heterocyclics are generally smaller than in cyclohexanes; it appears that J_{aa} in structure 87 is reduced to 6.0 Hz (10 Hz is typical J_{aa} in cyclohexanes) while the J_{ae}, typically 3Hz in cyclohexanes, has become less than 1 Hz and not measurable.

The most clearcut evidence for 87 comes from the carbon-13 spectrum (FIGURE 4), which shows six non-aromatic signals. Partial carbon-13 proton decoupling revealed that these signals represented one quaternary carbon, namely the C=O group at δ = 166.5, three CH_2 groups (triplets) at δ = 63.3, 61.4 and 43.1. The δ = 43.1 is assigned to the CH_2 group in the β-lactam ring by comparison with earlier compounds in the series and numerous other mono- and bicyclic β-lactams available in our laboratory. The other CH_2 groups, δ = 63.3 and 61.4 are due to either the carbon C1 or C3 The two CH groups required by structure 87 are present. The individual assignments are quite tentative.

FIGURE 3



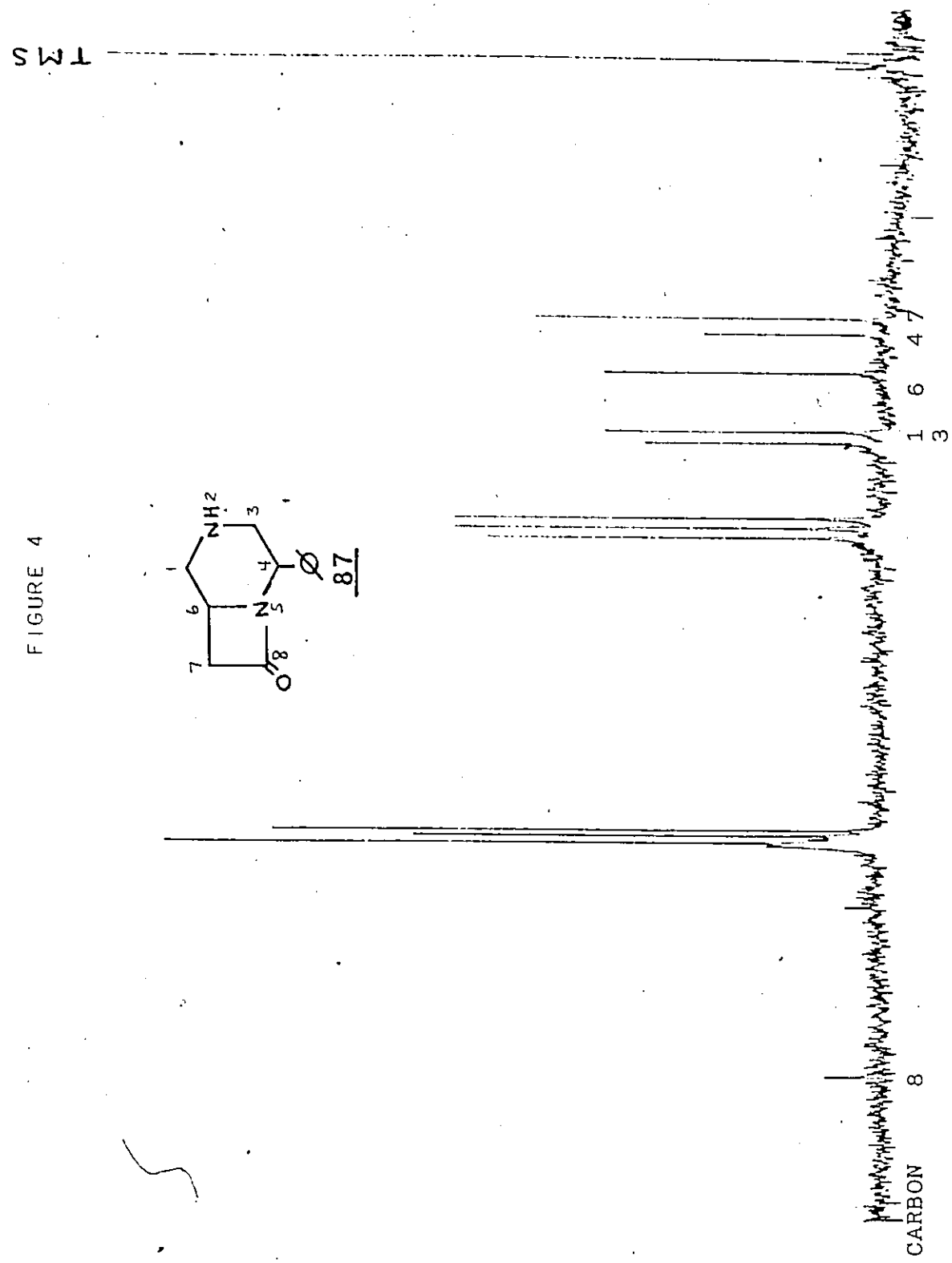
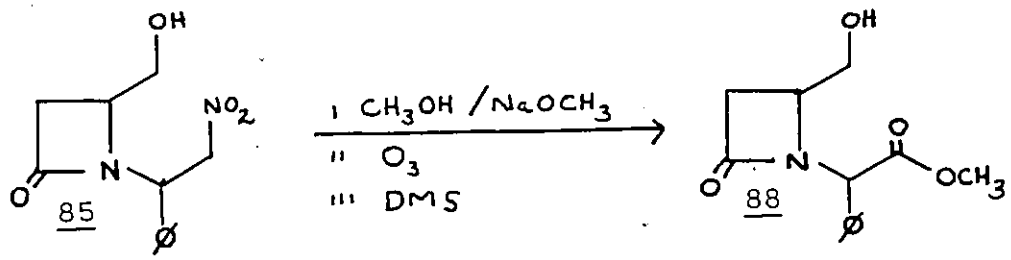


FIGURE 4

Anisotropy effects suggest that C4 should absorb at lower field that C6. However in a series of bicyclic β-lactams such as 87, the bridgehead carbon absorbs at $\delta = 50 \pm 3$, thereby suggesting that C6 is represented by the $\delta = 52$ peak. No better model structures could be found in the literature to help in these assignments. Overall the carbon-13 spectra show the features required for 87.

Attemps to acetylate 87 resulted in destruction of all of the material.

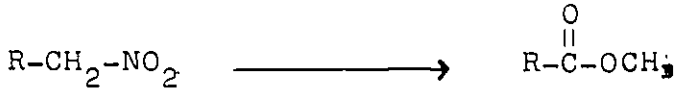
In order to study the oxidation of the nitro-lactam adduct, alcohol 85 was first used. Compound 85 was dissolved in dry methanol, and one equivalent of sodium methoxide in methanol was added to generate the sodium nitronate. Ozone was passed through the solution to a blue colour (-78°C). The reaction mixture was purged with nitrogen, the ozonide decomposed with dimethyl sulfide, and solvents were evaporated. A clear oil was isolated via silica gel chromatography to which the structure 88 was assigned. The yield was 42%.



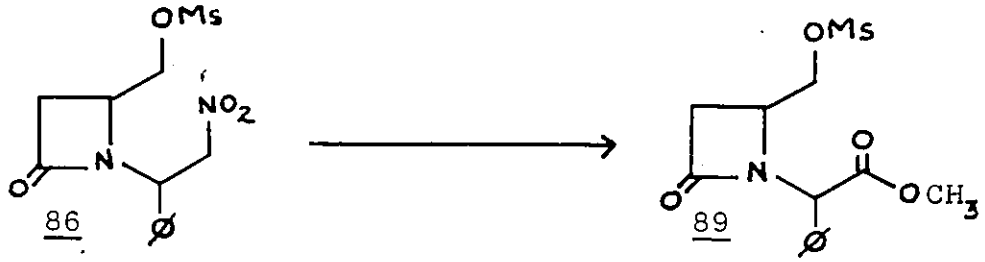
The proton magnetic resonance spectrum was in agreement with the assigned structure. It showed after D_2O exchange, two doublets of doublets at $\delta = 2.85$ (J = 12 and 5Hz) and 3.13 (J = 12 and 2Hz) assignable to the β-lactam CH_2 group. Other key features of the spectrum were a 3H singlet at δ = 3.89 (methyl ester) and a 1H singlet at $\delta = 5.89$ due to the benzylic hydrogen. The carbon-13 spectrum readily supported

the structure 88. It showed two carbonyl carbons at δ 167.1 and 172.9 together with five other non-aromatic carbons. These were found at 37.9 ($\underline{C}H_2C=O$), 52.5 ($\underline{C}HPh$), 53.4 ($O\underline{C}H_3$), 58.1 (bridgehead $\underline{C}H$) and 61.5 ($\underline{C}H_2OH$) when benzene was used as solvent. In $CDCl_3$ the benzylic CH_2 and OCH_3 groups were coincident. The infrared spectrum showed the required OH (3490 cm^{-1}), C=O's (1740, broad and very strong) and C-O (1200 cm^{-1}).

To the best of my knowledge there is no literature precedent for the direct conversion:



Earlier workers who described the conversion of primary nitroalkanes to aldehydes via ozonolysis of nitronates reported generally low yields of aldehydes but made no mention of the formation of methyl esters.

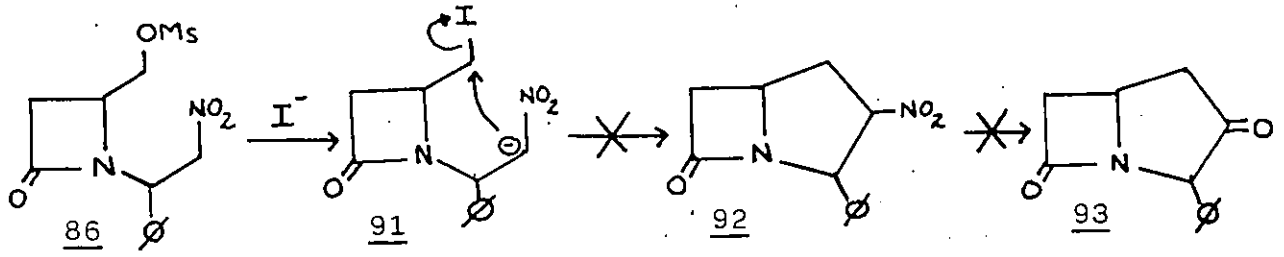


Ozonolysis of the mesylate 86 under the above conditions gave the mesylate methyl ester 89, thereby showing that the free hydroxyl group of 85 is not implicated in the ester formation mechanism. Spectroscopic data for 89 are in agreement with the proposed structure; they are tabulated in the Experimental Section. Furthermore 88 was converted

to 89 by simple mesylation in 46% yield.

Since compound 89 was readily available we attempted to convert it to the oxacephem 90 (SCHEME VIII), via cyclization with lithium diisopropylamide or NaOtBu. NaOtBu was successful in a related cyclization (99 → 100). Compounds similar to 90 have been prepared by Doyle and Belleau (see introduction). Unfortunately no ring closure could be detected under the above conditions and only starting ester was recovered.

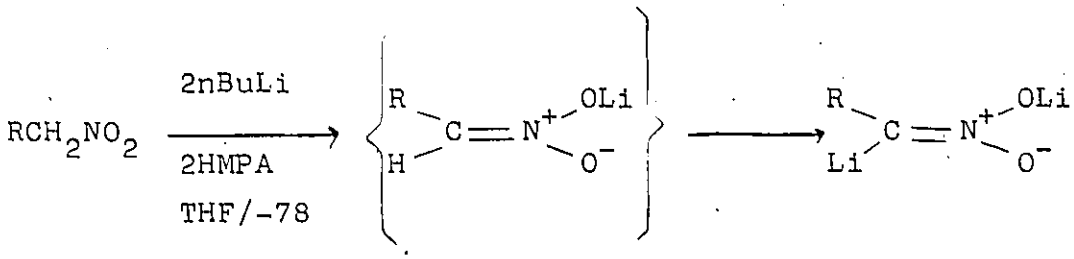
On inspection of 86 we envisaged the preparation of a nitro-iodo compound via nucleophilic substitution of iodine for the methanesulfonyl group. This iodo compound 91 could conceivably be cyclized to the penam derivative 92 by C-alkylation of the nitronate anion. Ozonolysis of the nitro group in 92 would generate the ketone 93. This keto-penam structure is a much sought-after intermediate in the preparation of thienamycin type antibiotics.[57]



Iodo derivative 91 was prepared by refluxing 86 with sodium iodide in dry acetone. It was obtained in 56% yield. The presence of 91 was detected by the disappearance of the $OSO_2\underline{CH}_3$ signal in the proton resonance spectrum and infrared as well as the presence of the highly characteristic chemical shift of $\underline{CH}_2I$ (δ = 5.5 and 6.5) in the carbon-13 spectrum (diastereomeric mixture).[65]

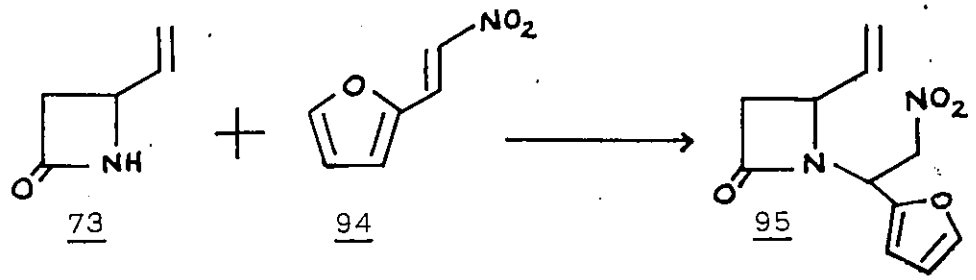
The cyclization of 1-iodo-3-nitropropane to nitrocyclopropane[58] has been reported; our cyclization would be similar. In general, the nucleophilic characteristics of the nitronate anion leave much to be desired, with O-alkylation

occurring in the majority of cases. Cyclization of 91 could not be accomplished using a number of bases. Seebach[59] had had success in increasing the nucleophilicity of nitronates through α , α double deprotonation at low temperature. This approach also failed in our case.



Finally, reaction of 91 with silver tetrafluoroborate also gave no evidence of any cyclization products.

The Michael addition product 95 of the nitro-furyl derivative 94 to the β-lactam 73 was obtained in 40% isolated yield. (See Figure 5 and Experimental Section for spectroscopic data). The furan ring of 95 can be considered a latent carboxylate function, which can be liberated by ozonolysis.



73 94 95

Unfortunately ozonolysis of 95 gave only a tarry residue from which no pure substance could be isolated. Thus this approach to the desired 4-carboxylate group was abandoned.

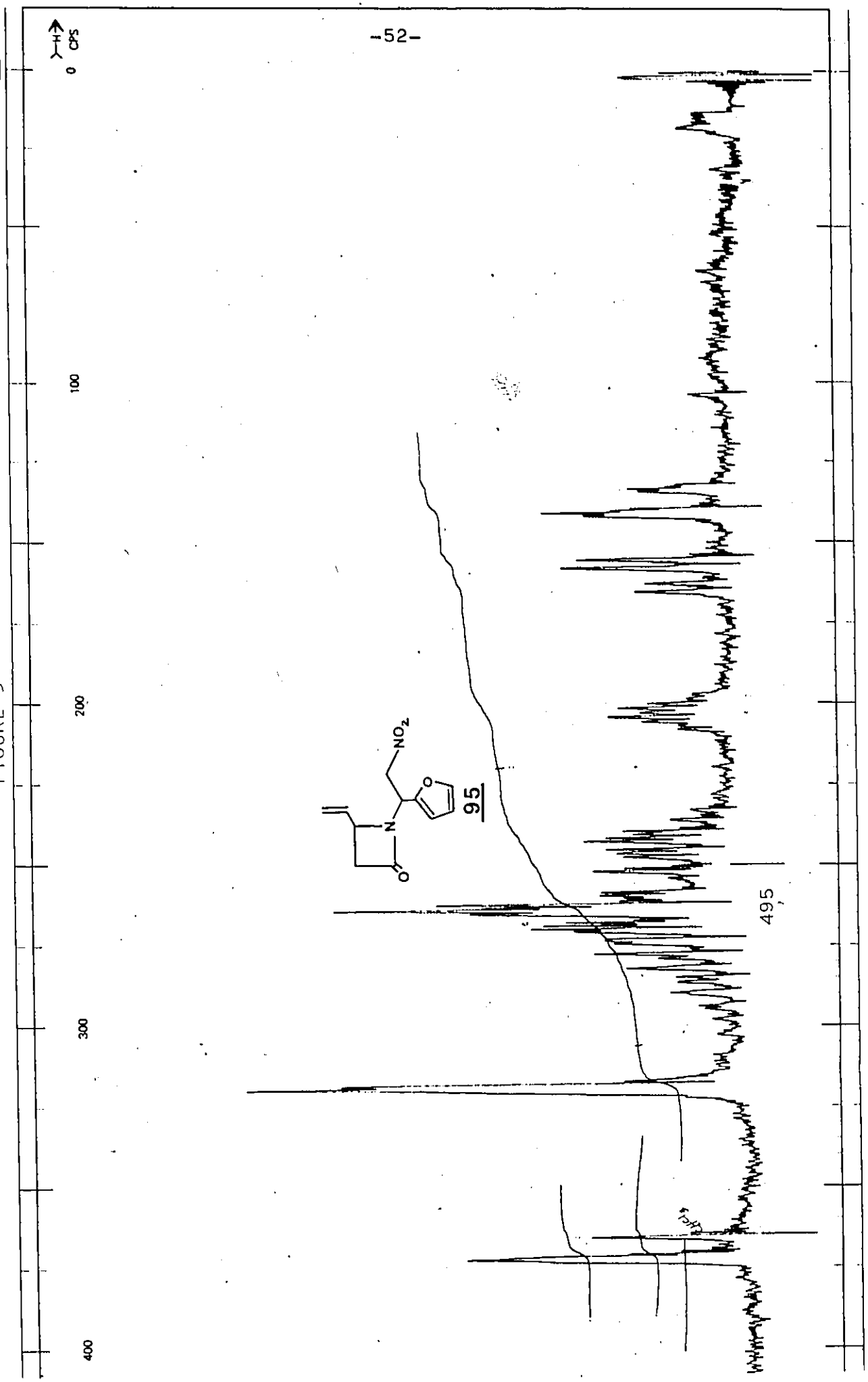


FIGURE 5

1-PHENYL-2-NITROPROP-1-ENE ADDITION

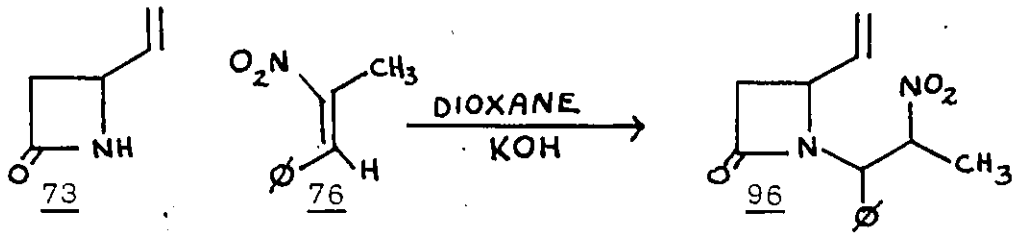
The title compound 76 was prepared by refluxing benzaldehyde and nitroethane in ethanol using a catalytic amount of n-butylamine as base. Compound 76 was obtained as easily handled yellow needles, much like nitrostyrene.

In comparing ease of reaction in Michael additions, one must consider: a) polarity of the double bond and b) the acidity of the donor molecule's reactive proton. In our reaction, the donor proton remains a constant, the amide proton of the β-lactam nucleus. In considering a), the nitro group polarizes the double bond, activating it to a Michael acceptor. However, its effect on the olefinic bond is not as pronounced as the effect groups such as CHO, CN or CO_2R have. Still, nitroethylenic acceptors do react, and most easily if the donor atom is highly acidic.

Nitroalkane to nitroolefin additions occur because the low order of reactivity of acceptor is offset by a highly reactive donor. Better still are acceptors that are doubly activated such as nitrostyrenes, nitrocrotonates and nitroacrylates. With this remaining, it would follow that 76, with a methyl group (mildly electron releasing) would counteract the effect of nitro and phenyl groups to some extent, making 76 a poorer acceptor than 75, nitrostyrene.

We in fact discovered that 76 would not add to the 4-vinyl azetidinone under normal anion conditions (nBuLi, THF, -78°). Fortunately, when the reaction was attempted under phase transfer conditions (50% aqueous NaOH, methylene chloride, benzyltriethyl ammonium chloride), thin layer monitoring showed the appearance of a new product of R_f value between those of the two reactants. Workup led to a crude product whose proton NMR gave indication that the addition had occurred. The success of LeBelle,[60] who added

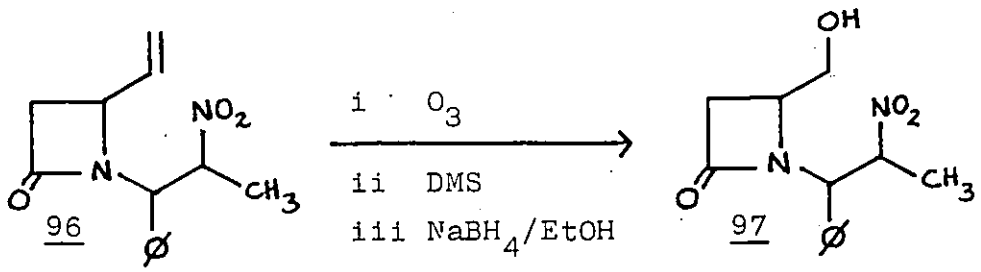
4-methyl-4-vinyl azetidinone to acrylonitrile using potassium hydroxide in dioxane, led us to attempt the addition 76 to 73 under these rather harsh conditions.



73 76 96

When the reactants were stirred at room temperature in dioxane, followed by addition of powdered potassium hydroxide, we found that the β-lactam would add to the olefin after only a short time (10 - 15 min.). Following neutralization and workup with water-ether and finally column chromatography, β-lactam 96 was isolated (40% yield). The proton NMR of 96 (FIGURE 6) showed the methyl protons as a pair of doublets at δ 1.35 and 1.85, again we see the ring protons represented as an ABX system with H_A and H_B absorbing from δ 2.45 to 3.0 and 3.05 to 3.4 respectively. Proton H_X occurs as a multiplet from δ 3.95 to 4.05. Proton Hα occurs as a doublet at δ 4.76. The vinyl protons and Hβ can be found as a multiplet from δ 5.1 to 6.1. Infrared spectra of 96 display peaks at 1740 cm^{-1} (C=O) and 1560, 1370 cm^{-1} (NO_2).

The next step in our reaction sequence is ozonolysis of 96 with subsequent reduction to alcohol 97.



96 97

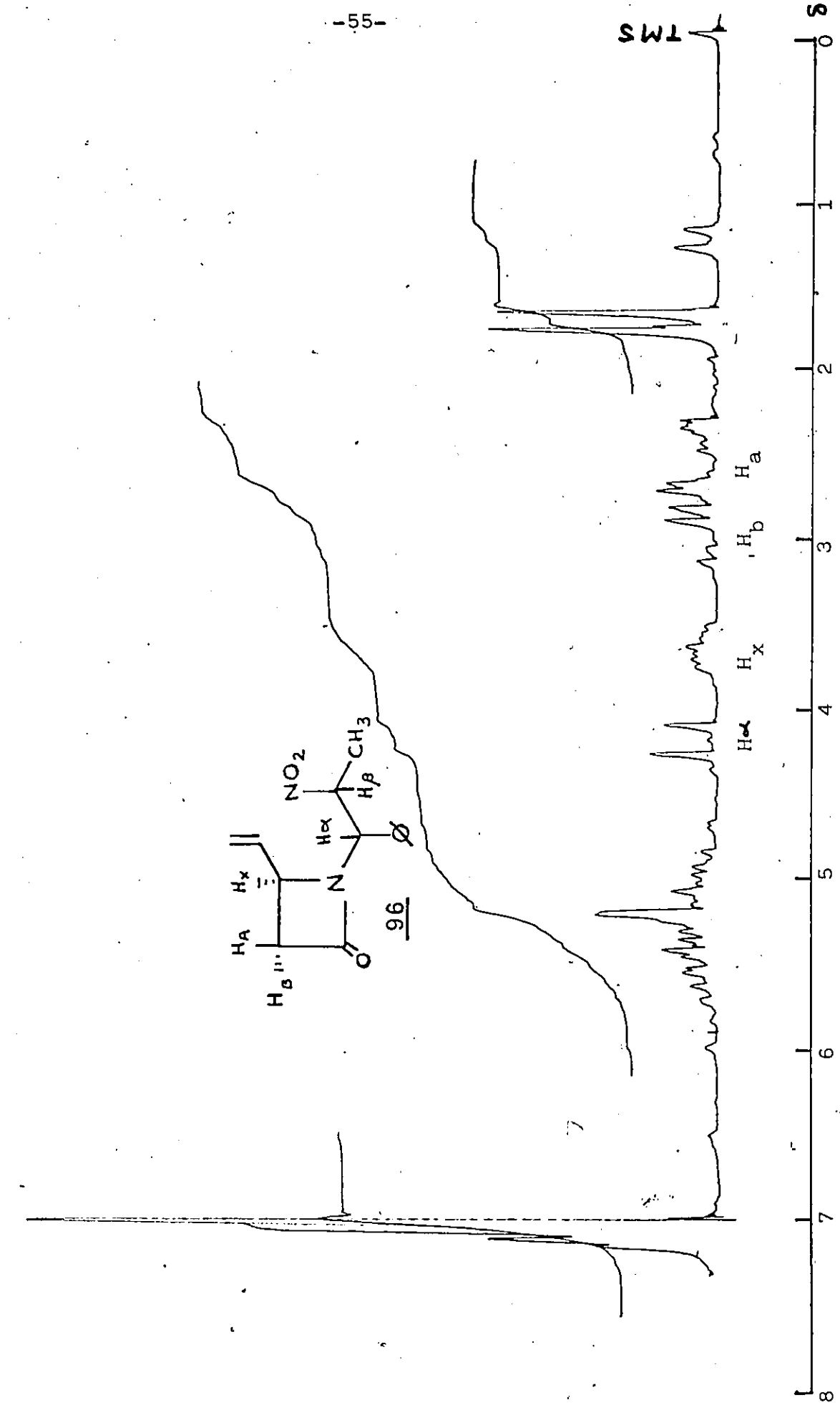
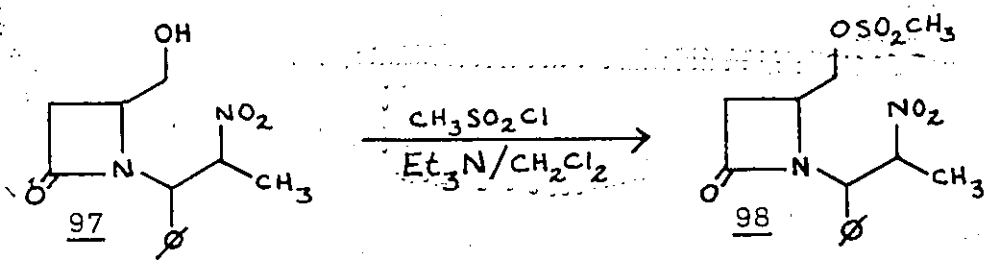

TMS
δ
0
1
2
3
4
5
6
7
8
H_a
H_b
H_x
H_α
NO_2
CH_3
H_β
H_α
H_x
H_A
H_B''
N
O
Ø
96

FIGURE 6

The reaction was performed under identical conditions used in preparing alcohol 85. The alcohol 97 was isolated as a yellow foam in 38% yield from starting olefin. The proton NMR of one isomer, which was obtained almost free of the other on chromatography, is shown in Figure 7. If features a doublet at δ 1.90 (CH_3), multiplet at 2.50 to 3.0 (Ha, Hb, OH), multiplet at 3.5 - 4.0 (Hx, $-CH_2OH$), doublet at 4.77 (Hd), multiplet from 5.5 to 5.95 (Hc) and singlet from 7.3 to 7.6 (phenyl). The infrared spectrum of 97 showed absorptions at 1740 cm^{-1} (C=O), 3200 - 3600 cm^{-1} (OH) and 1550, 1370 cm^{-1} (NO_2).

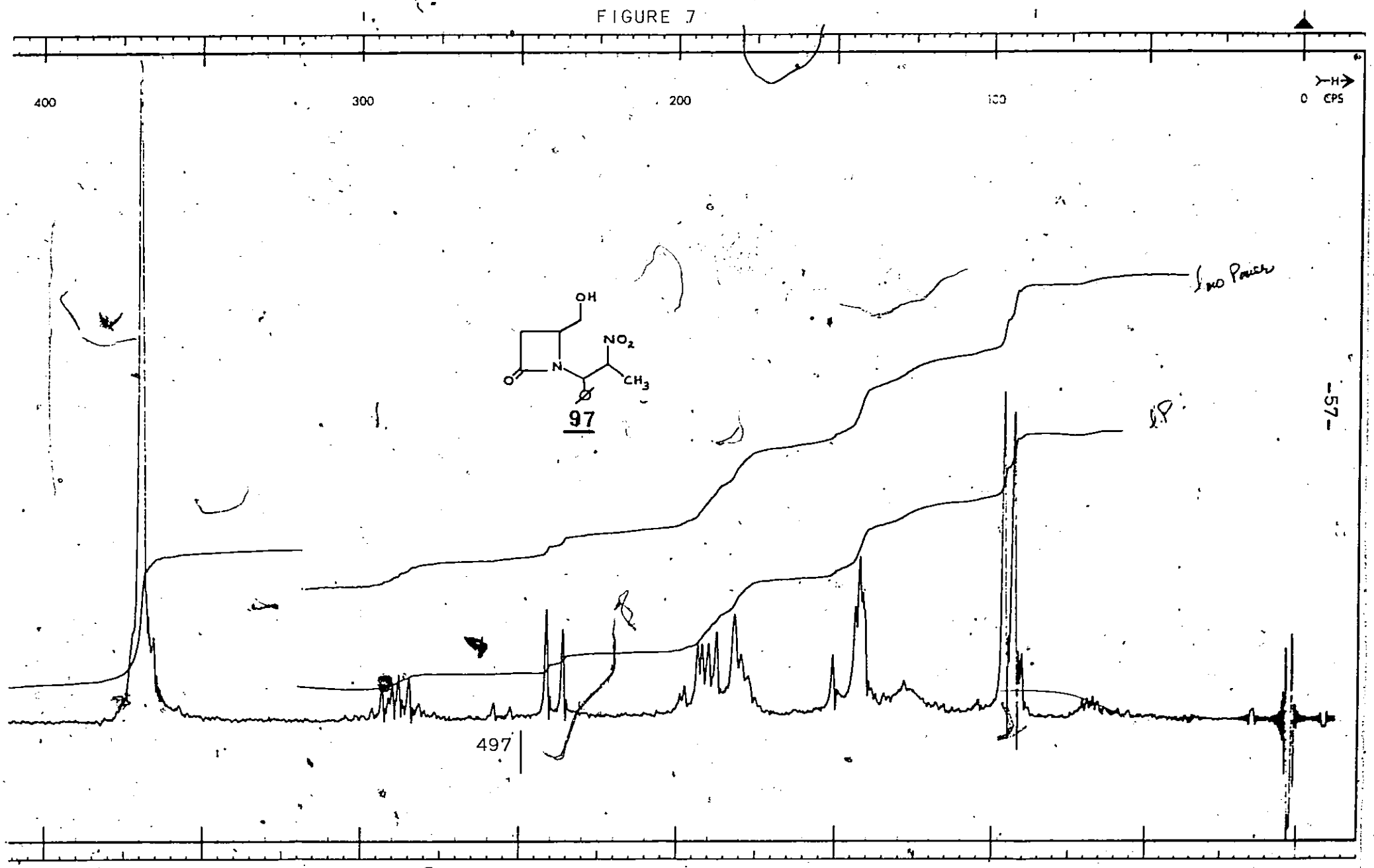
Conversion of 97 to the corresponding mesylate 98 was performed in 86% yield.



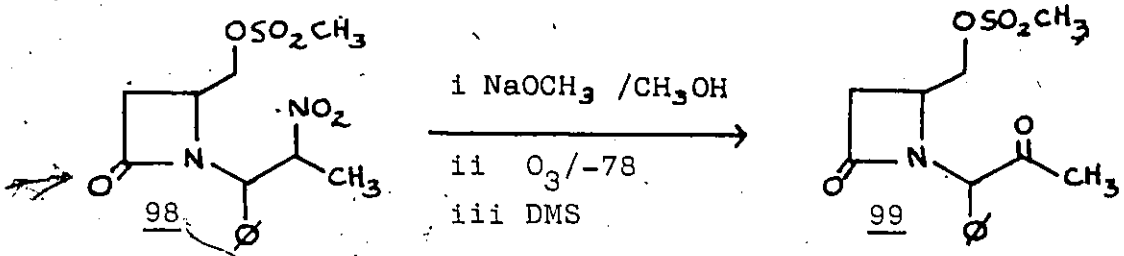
Compound 98 was hydrogenated in 4:1 ethanol: ethyl acetate over palladium on charcoal; no cyclized material could be detected. Other catalysts such as platinum oxide also failed. The reason for this is not clear, as starting mesylate 98 was recovered in each case. Thus, no 2-azacepham could be prepared by this route.

In order to prepare 2-oxo analogs we had to oxidize the nitro group of 98 to carbonyl. The mesylate was treated with one equivalent of sodium methoxide in methanol, then ozonized at -78°C until the blue color of excess ozone persisted. The system was purged with nitrogen and allowed to come to room temperature, then dimethyl sulfide was added. The solvent was evaporated and the product purified by silica gel chromatography. This time, no carbomethoxy group

FIGURE 7

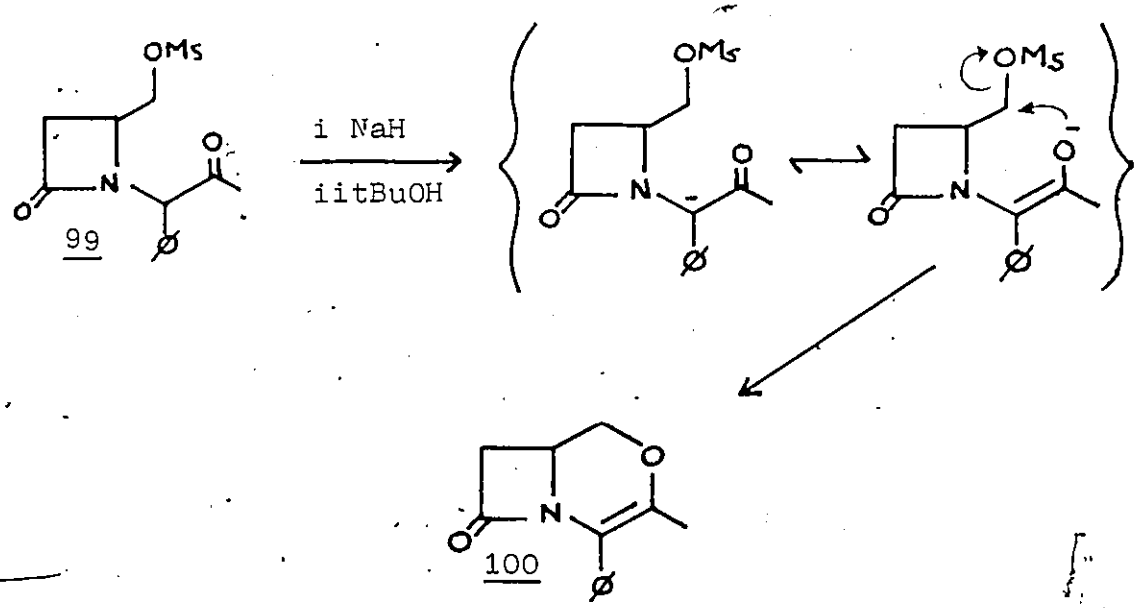


was detected, only the ketone 99 was obtained in 56% yield.



The proton NMR of 99 clearly indicates the presence of the ketone by the disappearance of the methyl doublet of 97, and the appearance of a methyl singlet of δ 2.1, typical of methyl ketones. Infrared confirmed the oxidation, as no nitro absorptions were detected and two carbonyl bands were observed, 1740 cm^{-1} (β-lactam) and 1720 cm^{-1} ($COCH_3$). The mesylate absorption at 1170 cm^{-1} was also present.

In an effort to cyclize 99, the compound was treated with lithium diisopropylamide in THF, however no reaction occurred. Sodium hydride in THF also failed, but when a few drops of tert-butyl alcohol were added to the sodium hydride/THF mixture the ketone 99 smoothly cyclized to the 2-oxacephem 100. Sodium tert-butoxide proved to be the base necessary to generate the enolate anion of 99; which displaced the mesylate and formed the Δ^3 bond.



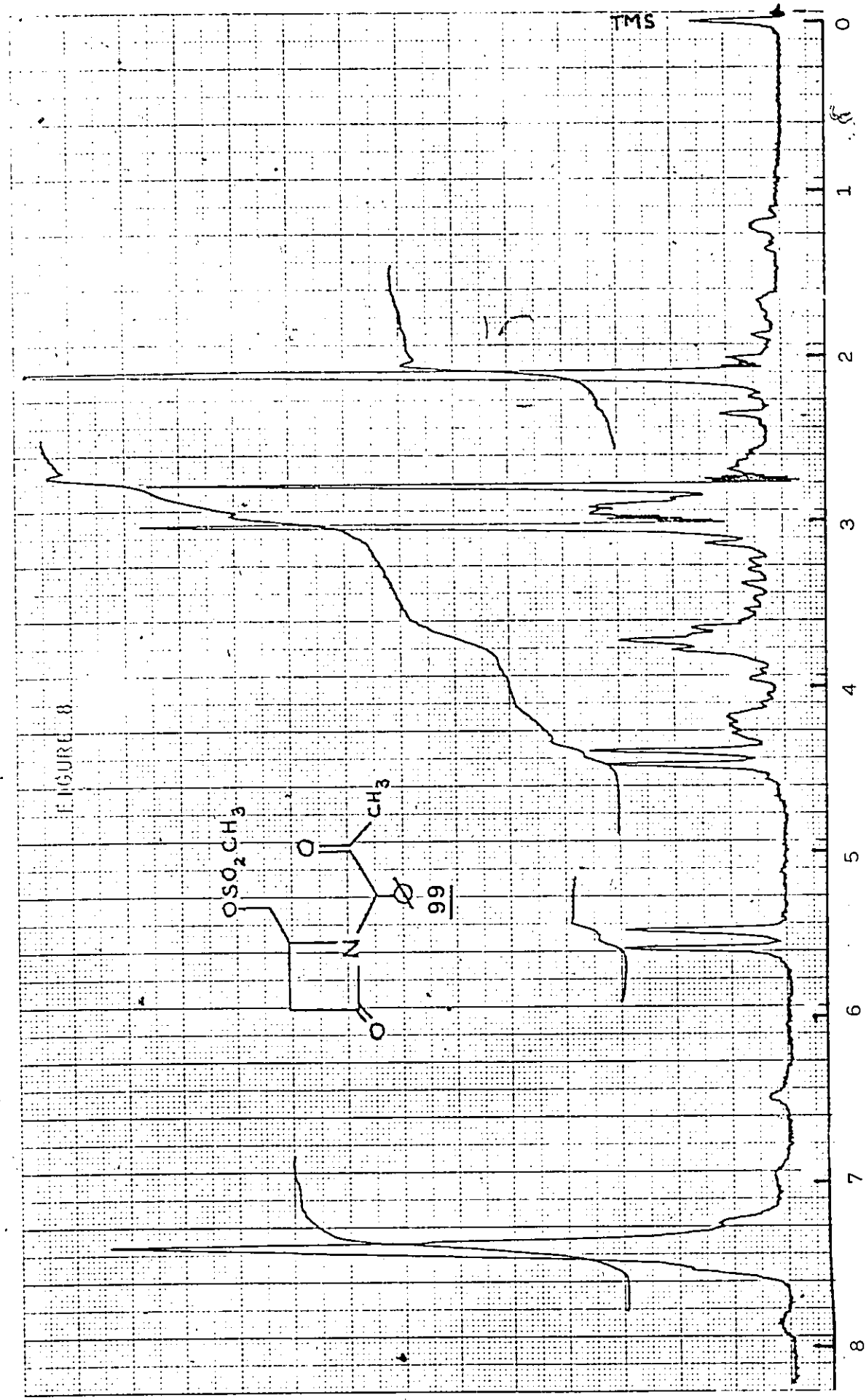
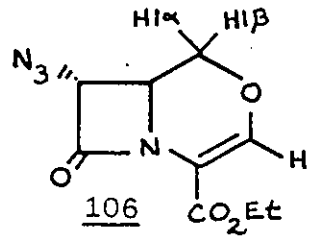


FIGURE 8

The 2-oxacephem 100 was isolated in 76% yield as white crystals (powder) melting at 132-133°C. The proton spectrum of 100 is depicted in Figure 10. The methyl singlet has shifted from δ 2.1 in mesylate 99 to 1.95, ring protons H_A and H_B appear as multiplets at δ 2.6 - 2.7 and 3.25 - 3.55 respectively. The proton H_X can be found along with the H1β proton at δ 3.6 - 3.7 as a multiplet, while H1α absorbs from δ 4.45 - 4.65. the large difference in chemical shift of protons H1α and H1β is similar to that reported by Doyle et al.[44] These authors found for the related compound 106 proton H1α absorbing at δ 4.63 while proton H1β and H6 absorb at δ 3.9 and 3.8 respectively.



106

The infrared spectrum of 100 shows only a carbonyl band at 1750 cm^{-1} as its prominent feature, no $-OSO_2CH_3$ absorption was detected. The carbon-13 spectrum of 100 confirms the presence of unsaturation by the appearance of two quaternary carbon signals along with the carbonyl and phenyl quaternary signals. The spectrum is shown in Figure 9, with assignments as indicated.

Once the ketone-mesylate route to 2-oxacephems had been established, we decided to prepare the saturated analog of 100. Reduction of 99 with $NaBH_4$ followed by treatment with NaH in dry DMSO afforded the 2-oxacepham 102 in 55% overall yield after isolation by PLC.

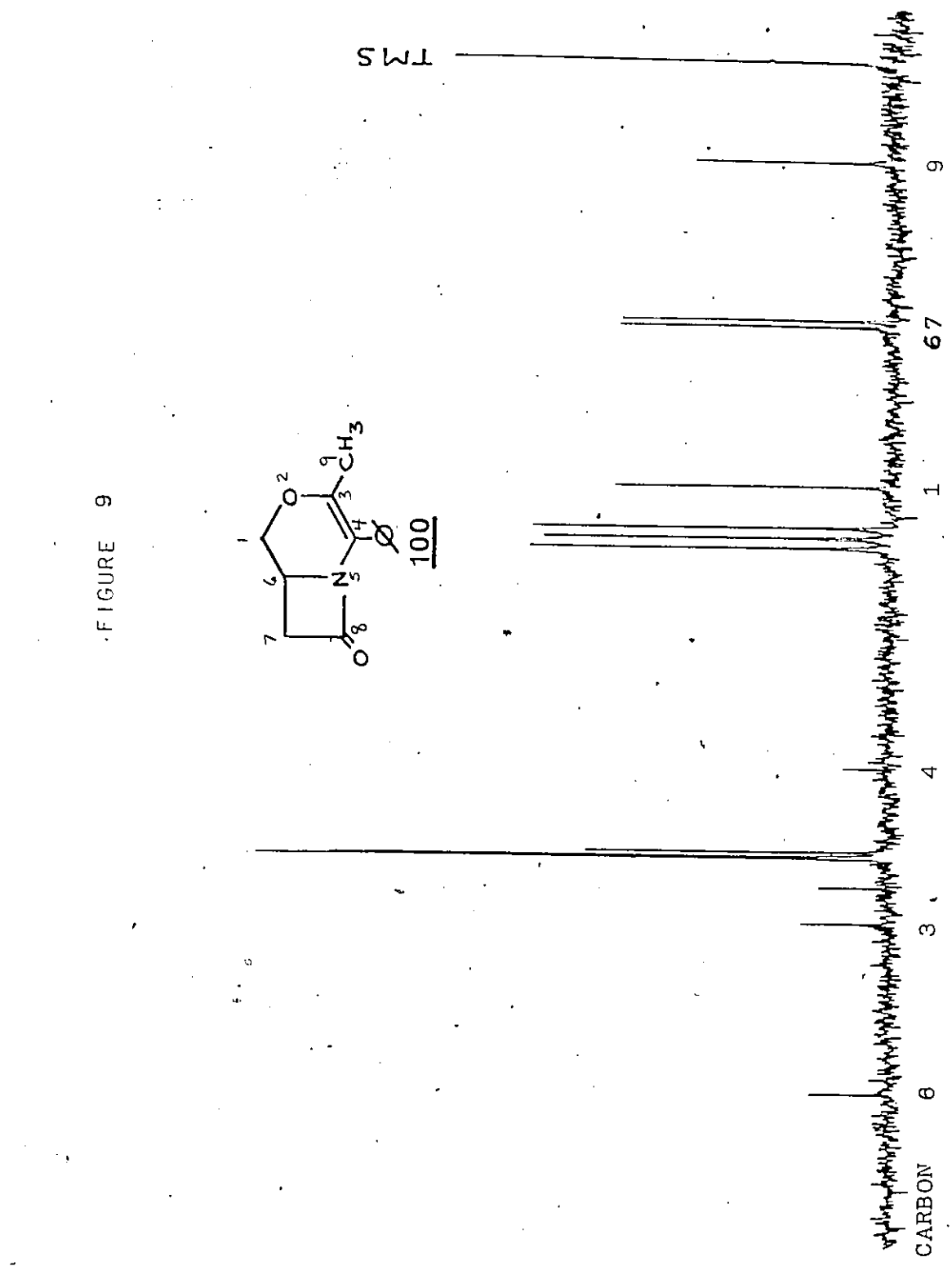
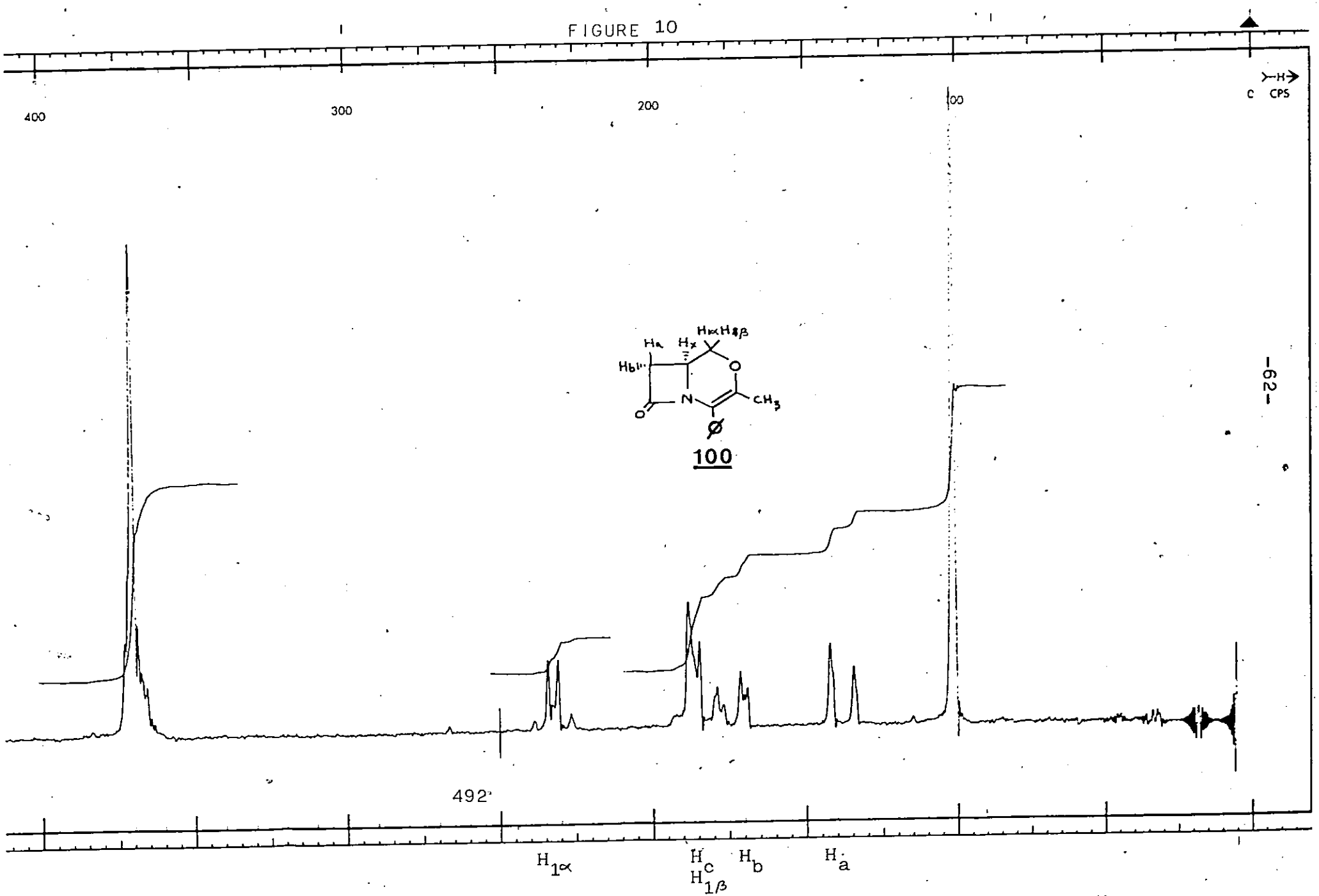
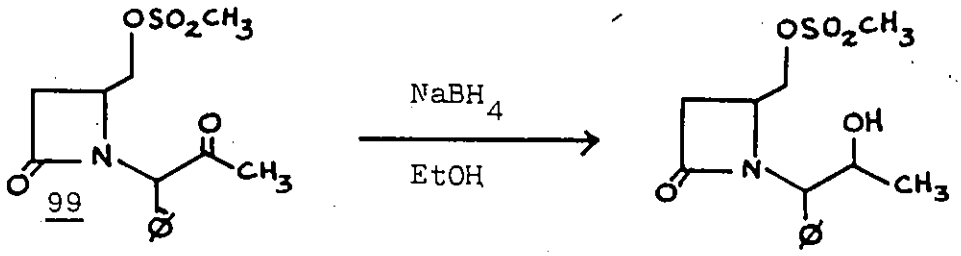


FIGURE 9

FIGURE 10

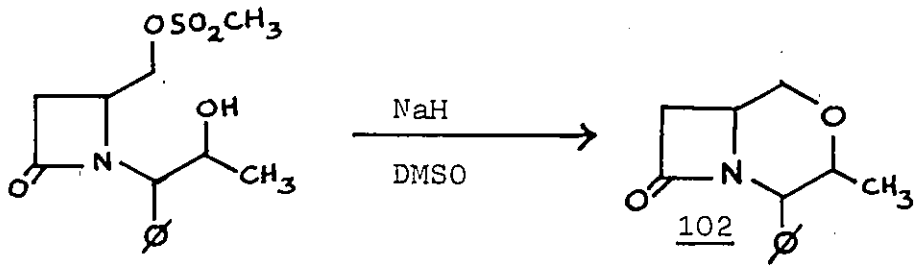


100



The important features of the proton NMR spectrum of 101 are the disappearance of the methyl singlet found in 99 and the appearance of a methyl doublet at δ 1.1. The remaining proton assignments can be found in the experimental section. The infrared spectrum of 101 shows absorptions at 3200 - 3600 cm^{-1} (OH), 1730 cm^{-1} (C=O) and 1170 cm^{-1} (OSO_2CH_3).

Cyclization of 101 to 102 proceeded in 71% isolated yield. Compound 102 was obtained as a clear oil following chromatography. The proton NMR of 102 appears in Figure 11. The methyl doublet appears at δ 1.0, protons Ha and Hb at δ 2.6 - 2.8 and δ 3.0 - 3.25 respectively, benzylic proton H4 at δ 4.5 - 4.6 appearing as a doublet, as was observed in the 2-N oxacepham 8 (see Figure 3). The remaining protons Hx, H1H2 and H3 all appear as a complex multiplet integrating to four protons from δ 3.65 to 4.3. The β-lactam carbonyl of 102 occurred at 1740 cm^{-1}.



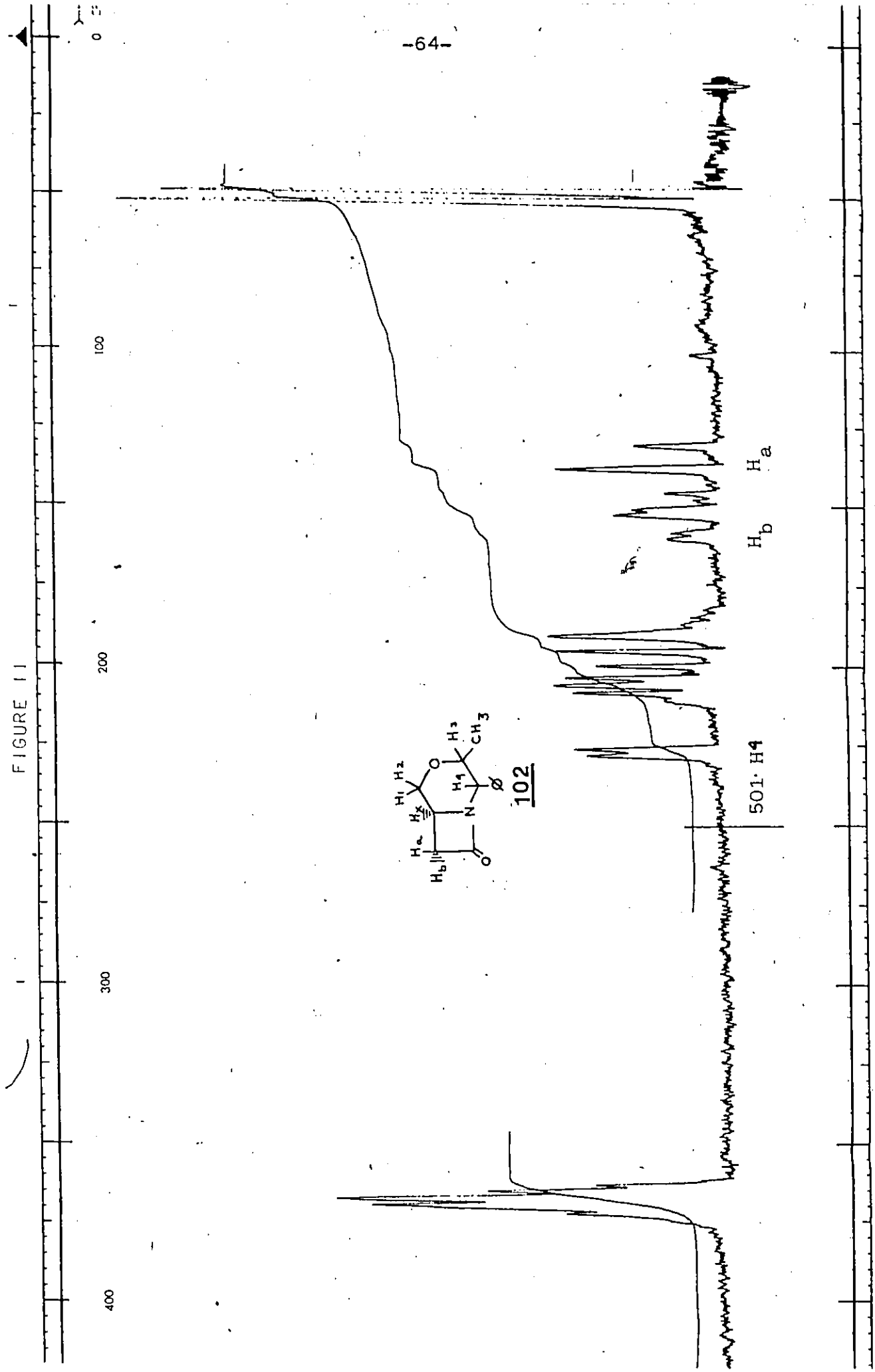


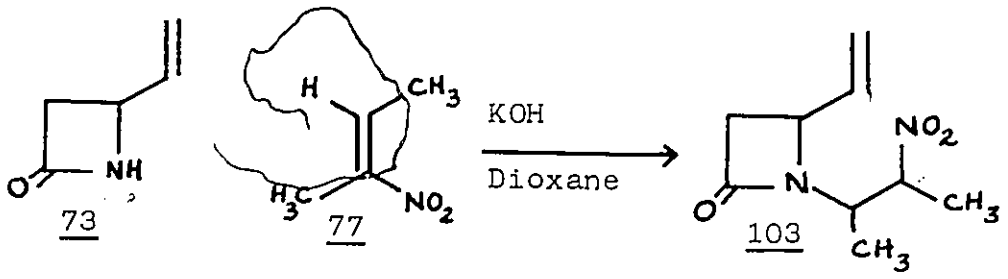
FIGURE 11

2-NITROBUT-2-ENE ADDITION

Up to this point in our study of nitro olefin additions to a β-lactam nucleus, olefins used had a phenyl group attached to one of the olefinic carbons. That is, both were nitrostyrene derivatives. In each case, addition gives an adduct that gives rise to a cyclized compound with phenyl group at C 4. We decided to investigate the addition of a nitro olefin that did not possess this phenyl ring, the choice of olefin being 2-nitrobut-2-ene 77. If successful, the addition of 77 would lead to a product containing a methyl group at C4 and a methyl group at C3.

Preparation of 77 was by the method of Melton and McMurry[61] who used methanesulfonyl chloride/triethylamine to dehydrate 3-nitro-2-butanol.

Addition of 77 to the 4-vinyl azetidinone again required drastic conditions, as the N-lithio salt of the β-lactam failed to add to the nitro olefin. Using experience gained in the addition of 1-phenyl-2-nitroprop-1-ene 76, we attempted the addition using powdered potassium hydroxide in dioxane. Under these conditions, 77 added to the 4-vinyl azetidinone 73 affording 103 in 40% isolated yield. This observation is consistent with regards to arguments put forth on ease of reactivity and polarity in the previous section.



73 77 103

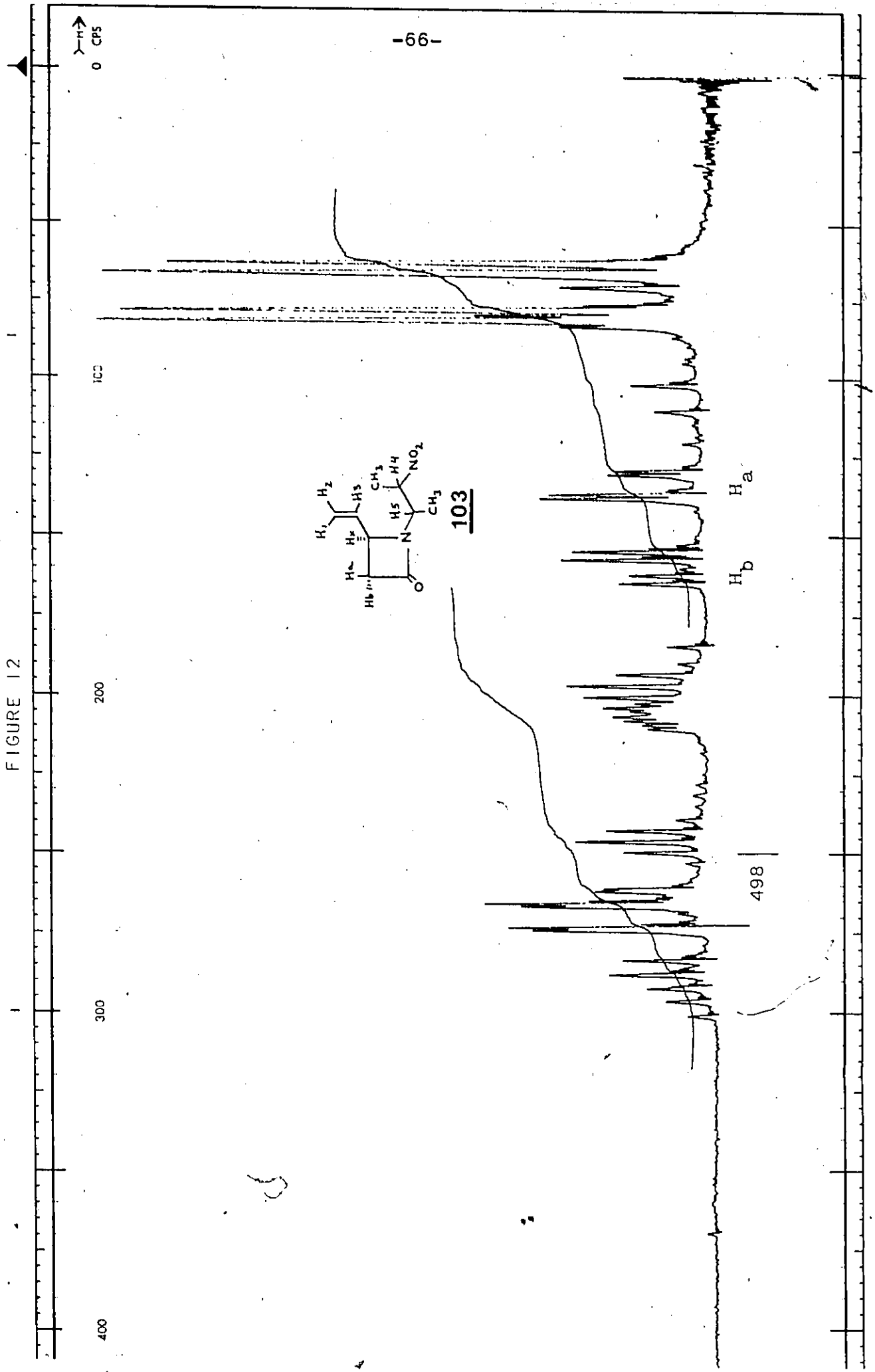
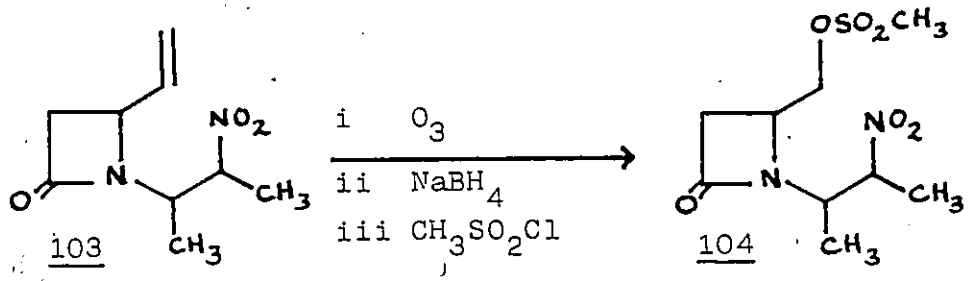
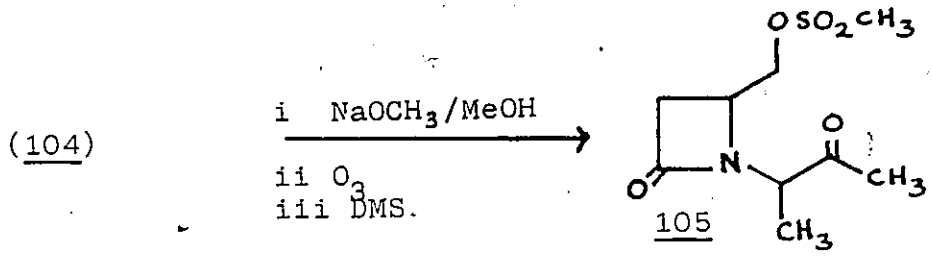


FIGURE 12

The proton NMR of 103, shown in Figure 12, features two methyl doublets, δ 1.6 and 1.3 assigned to the CH_3 alpha to nitro and the remaining CH_3 respectively. The spectrum also shows traces of a minor product, possibly due to another isomer. Protons H_A and H_B again appear at δ 2.6 - 2.8 and 3.1 - 3.3 respectively. The remaining portion of the spectrum is extremely complex but interpreted as follows: δ 3.7 - 4.3 (Hx, H5) and 4.7 - 6.1 (H1,H2,H3,H4).

The remaining sequence was applied to 103; that is, ozonolysis and reduction resulting in the alcohol isolated in 35% yield, mesylation (90%), ozonolysis of the nitro to a carbonyl group (70%), and finally NaOtBu cyclization to 107 in 69% yield.





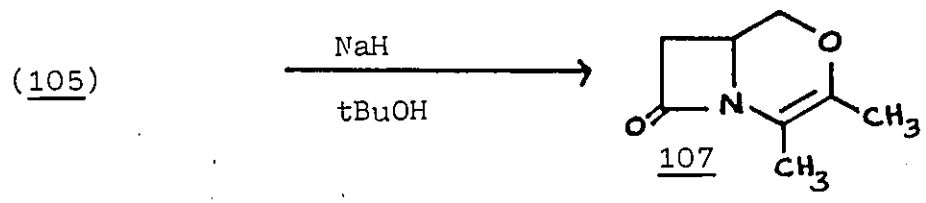
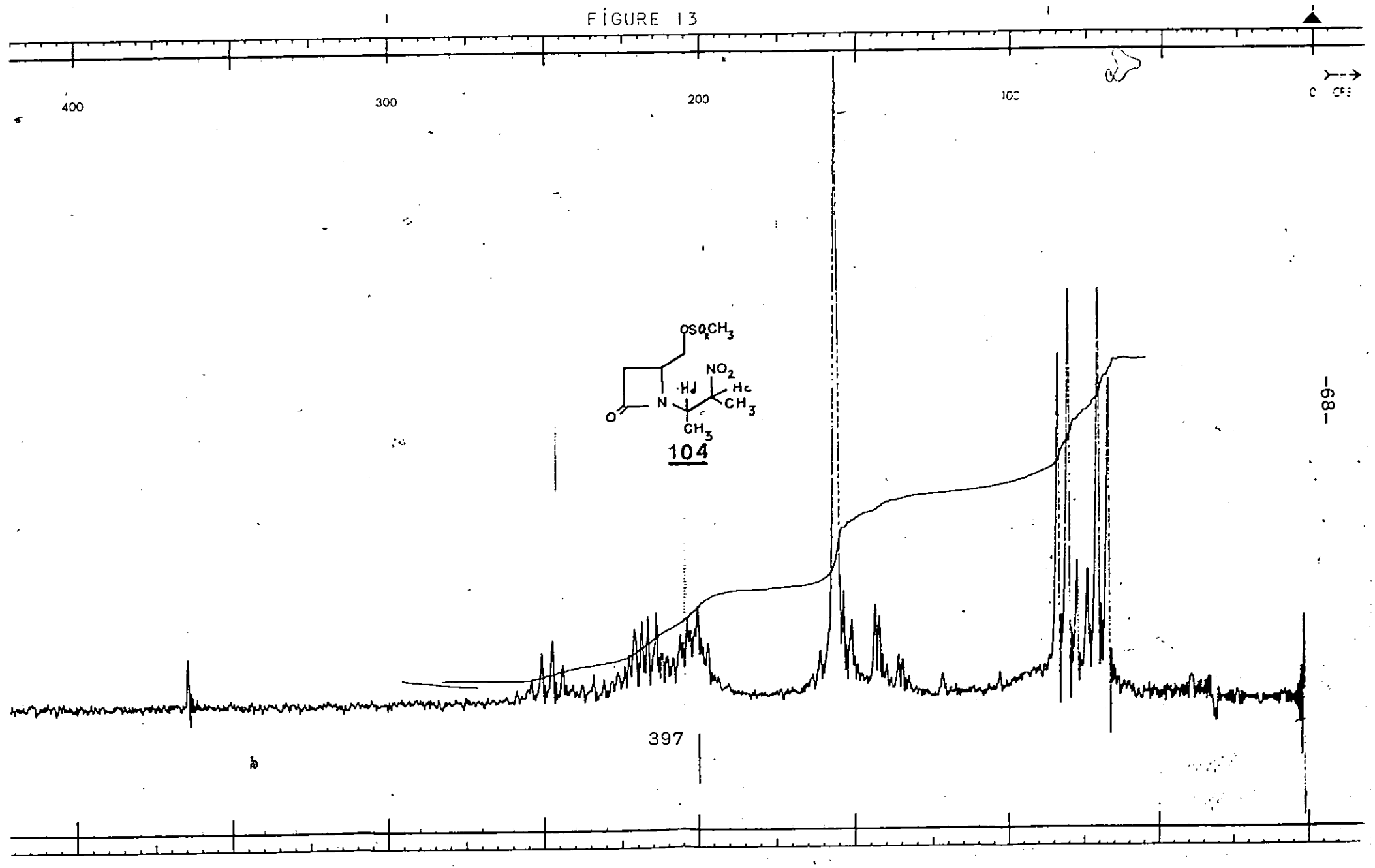
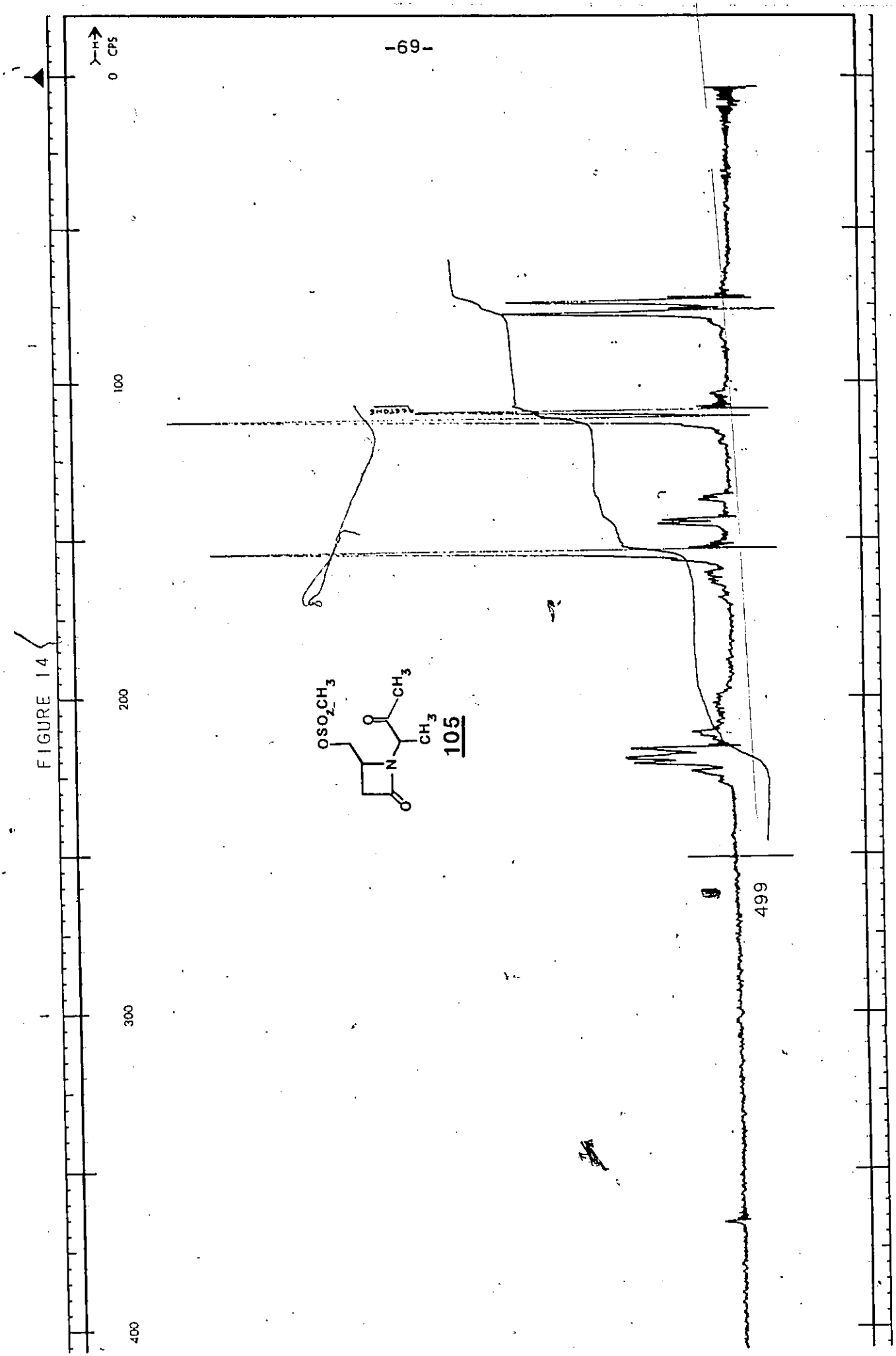


FIGURE 13



104



105

FIGURE 14

The structures of the key intermediates 104 and 105 were readily apparent from their spectroscopic properties, (See Experimental) and the method of synthesis. The desired bicyclic compound 107 showed two widely separated methyl signals at δ 1.75 (C4 methyl) and 2.05 (C3 methyl), a doublet of doublets (J=14, 2Hz) at 2.66 due to H_A, a multiplet at 3.1 - 3.6 (3H, due to H_B, Hx, and H1β). The remaining proton H1α is seen as a complex pattern near 4.4. The large difference in chemical shift of H1α and H1β is similar to that observed for compounds 100 and 106.

The carbon-13 spectrum displays all absorptions required by structure 107. It appears in Figure 16 along with the carbon assignments. The carbonyl absorption in the infrared occurred at 1740 cm^{-1}.

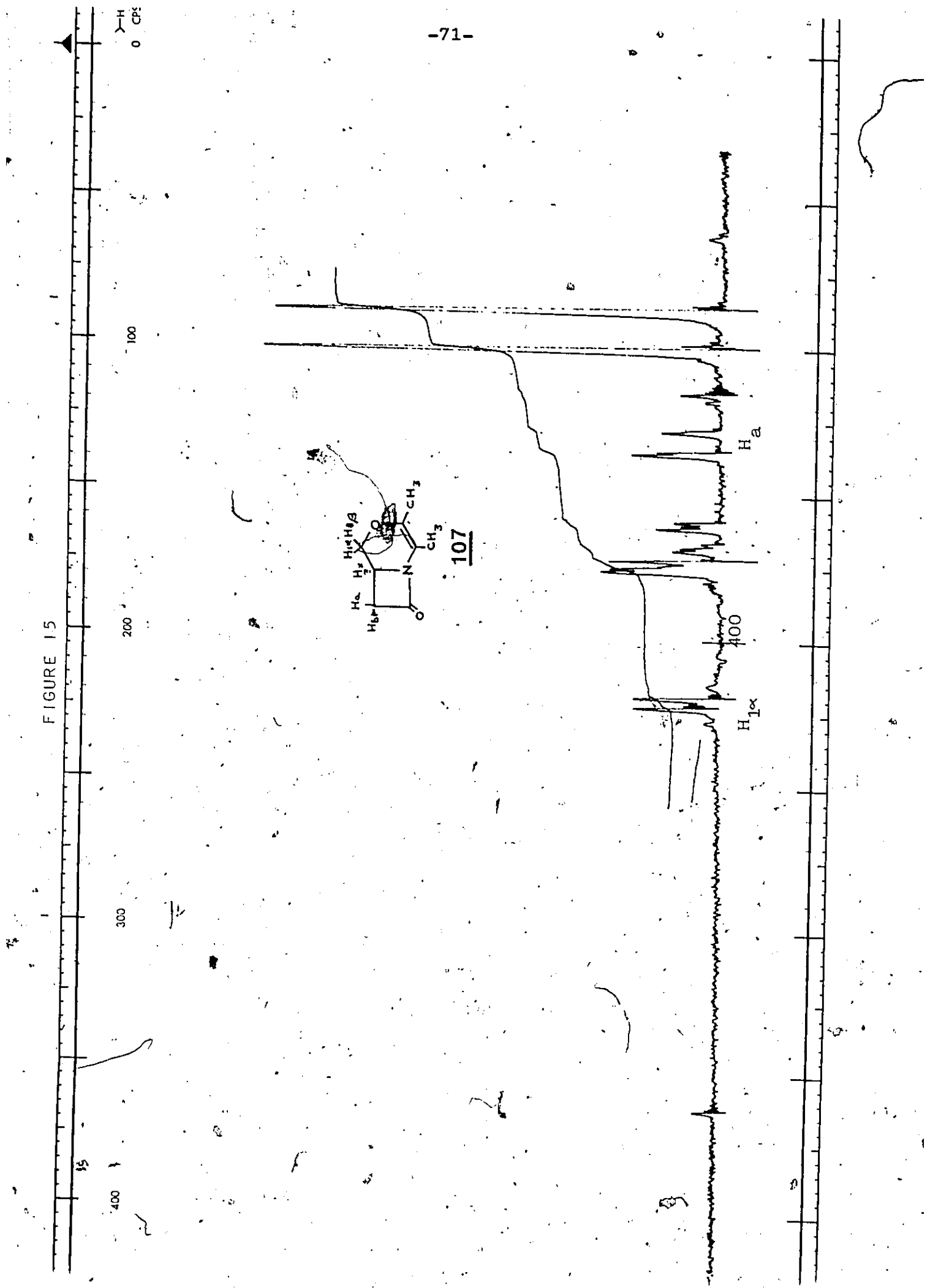
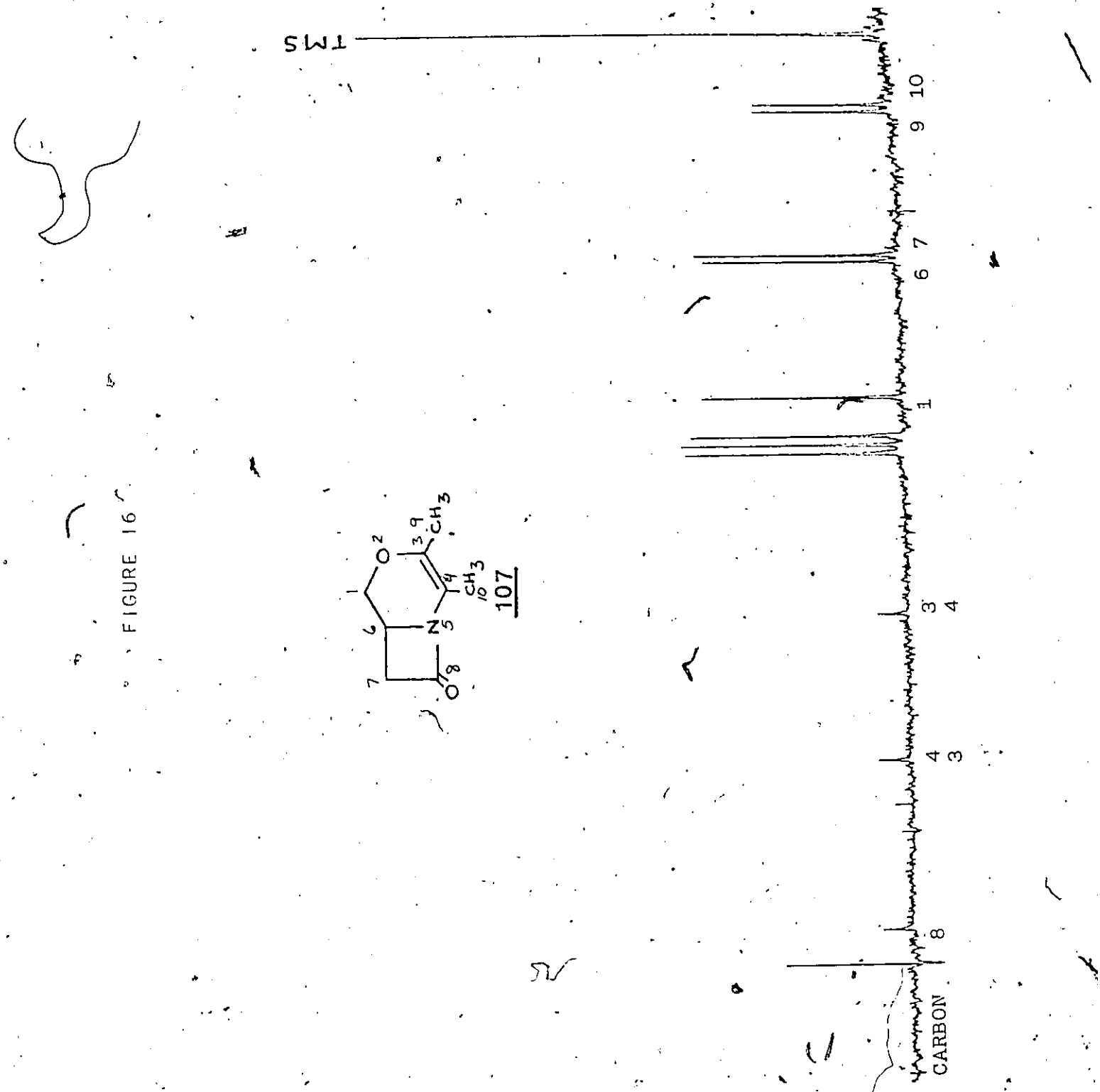


FIGURE 15

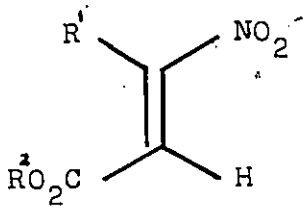


107

FIGURE 16

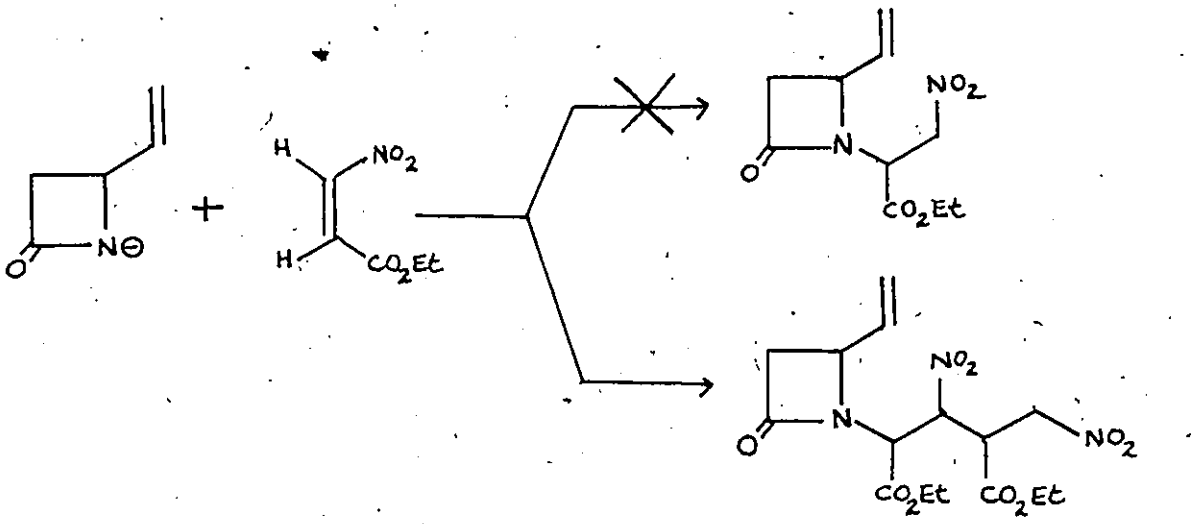
ETHYL 3-NITROACRYLATE, AND RELATED ADDITIONS

The bicyclic β-lactams synthesized to this point have been lacking one structural feature thought to be essential for antibiotic activity, the 3-carboxyl group. In order to generate such a structure via Michael addition, the nitro olefin acceptor must be of this type:



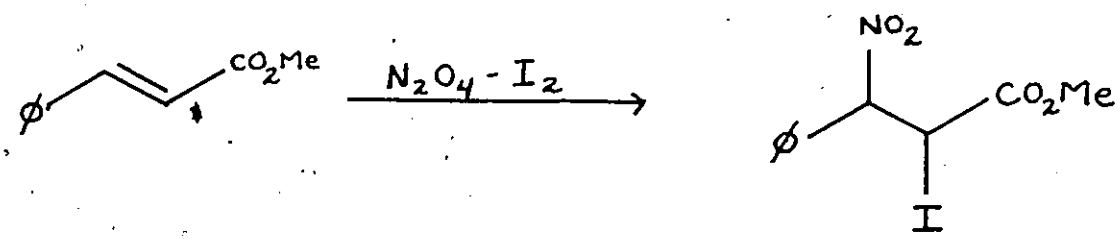
Compounds that fit this description include nitroacrylates (R^1=H), nitrobutenoates (R^1=CH_3) and nitrocinnamates (R^1=Ø). A search of the literature revealed that only ethyl nitroacrylate 78 (R^1=H, R^2=Et) was readily available. The preparation of this compound is described by McMurry,[62] who used the dinitrogen tetroxide-iodine approach. This involves injecting N_2O_4 (l) into an ethereal solution of iodine and ethyl acrylate, thus forming ethyl 2-iodo-3-nitropropionate. This intermediate is transformed into the olefin by refluxing with sodium acetate in ether. Since ethyl nitroacrylate is a doubly activated olefin, it should be the most reactive olefin studied yet in our Michael addition reaction. There are two electron withdrawing groups present, so it may be argued that the orientation of addition can be at either "end" of the olefin, or both. The direction of additions of this type was proved to be governed by the nitro group by McMurry,[62] who, in his synthesis of α-methylenebutyrolactone, demonstrated that the nitro group predominates over the ester group.

We added ethyl 3-nitroacrylate 78 to the N-lithio salt of β-lactam 73 at -78°C. On addition of the olefin to the solution of the anion, the reaction mixture turned a deep brown colour. On workup, only a small amount of, what appeared by NMR to be, a product of the addition of a further molecule of ethyl 3-nitroacrylate to the initial addition compound was obtained.



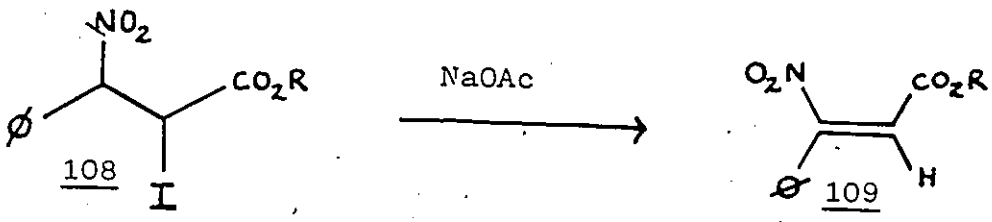
We were unable to adjust reaction conditions or find a suitable base which would give the simple addition product.

Reasoning that ethyl 3-nitroacrylate was far too reactive, it was hoped that a more substituted olefin (with a group other than H alpha to nitro) might display the proper reactivity. We attempted to synthesize β-nitrocinnamates from cinnamates, using the N_2O_4-I_2 reaction.



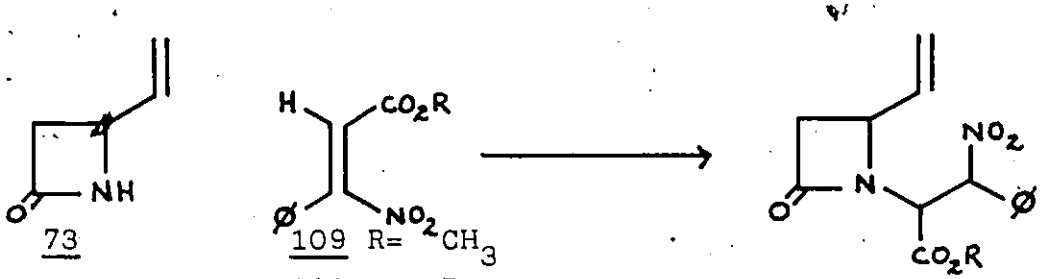
Treatment of methyl cinnamate with N_2O_4 and I_2 in ether resulted in a 20% yield of a compound initially identified as 108, yellow crystals, mp 80-82°C. The proton NMR of 108 showed protons H1 and H2 as an AB quartet (δ_A 5.91, δ_B 5.76)[64].

The carbon-13 spectrum of 108 showed all signals required for structure shown, including the iodine bearing carbon at its distinctive high field position δ 21.25.[65] Compound 108 was treated with sodium acetate to effect elimination of hydrogen iodide, giving 109 in 99% yield. The olefin was present as a mixture of



E, Z isomers as evident by the two singlet signals for the olefinic proton at δ 8.1 and 7.6 and the two methyl singlets at δ 3.95 and 3.90; the ratio was about 5:3. There were also two phenyl signals at δ 7.4 and 7.5. Judging by the chemical shift of the olefinic proton (downfield of the phenyl signal), we presumed that the nitro group was on the phenyl bearing carbon and not the ester bearing carbon, that is, the orientation of N_2O_4 addition was the same as observed with ethyl acrylate.

Using olefin 109, we proceeded, testing its addition to the β-lactam 73. As expected, it added smoothly to the N-lithio salt of 73, giving 110. Spectral data for 110 can be found in the experimental section.

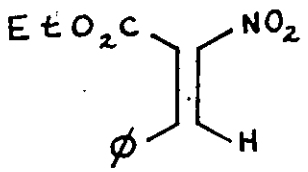


73 109 R= CH_3 111 = Bz 110 R= CH_3 112 = Bz

Seeing no further use for 110, as the methyl ester cannot be easily saponified to the free acid, we decided to prepare the benzyl ester.

Starting with benzyl cinnamate (from cinnamoyl chloride and benzyl alcohol), the N_2O_4-I_2 addition was performed and the β-nitrobenzyl cinnamate 111, R=Bz was prepared, and isolated as white crystals mp 87-88°C. Again the olefinic proton was well downfield of the phenyl signal in the NMR, occurring at δ 7.55. The Michael addition with 73 proceeded well, giving compound 112 R=Bz in 89% yield.

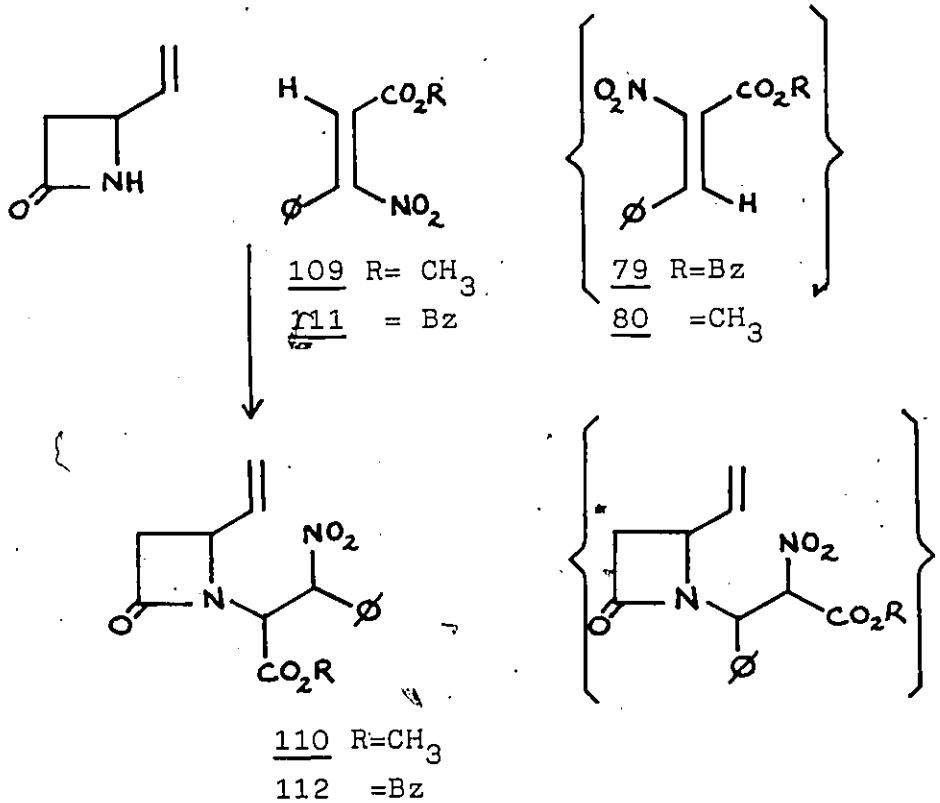
At this point we devised a means by which we could test the orientation of the N_2O_4 addition to the cinnamates. We were unsure of the position of the nitro and ester groups since the NMR spectra of the N_2O_4-I_2 addition and HI elimination products, tentatively identified as 108 and 109 did not allow us to exclude the alternate addition structures. Therefore we prepared 113 by an unambiguous route involving the $TiCl_4$-catalyzed condensation of ethyl nitroacetate with benzaldehyde, as described by Lehnert.[63]



113

Unfortunately the proton NMR of the ethyl ∝-nitrocinnamate 113 prepared by the Lehnert route was essentially identical (with the exception of the Et vs Me or Bz ester functions) with those of the compounds (109 and 111) obtained via the N_2O_4-I_2 route. Furthermore, $NaBH_4$ reduction of 113 and 111 furnished 120 and 121 whose NMR spectra were again virtually superimposable, except for the protons due to the ester function. We were thus forced to conclude that the "NO_2-I" addition occurred with the undesirable regiochemistry (opposite to that observed with ethyl acrylate). (Proper structures for all compounds are shown in brackets, SCHEME IX). Since the ultimate bicyclic structures would again possess phenyl groups at C 4, the pursuit of these compounds was discontinued.

A new approach to obtaining olefins that would give rise to final structures containing a C 4 carboxylate was needed. The obvious solution was to react the proper nitroparaffin with a glyoxyl derivative in a Henry type condensation. We had at

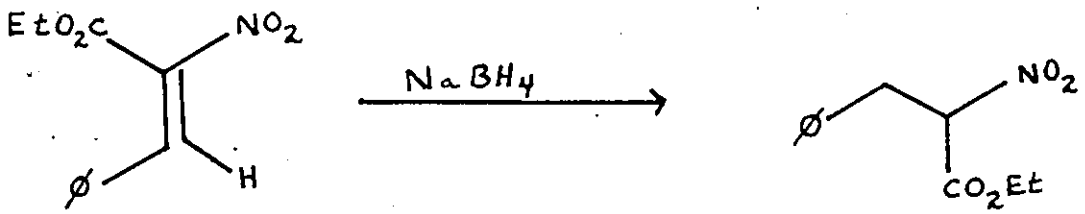


109 R= CH_3
111 = Bz

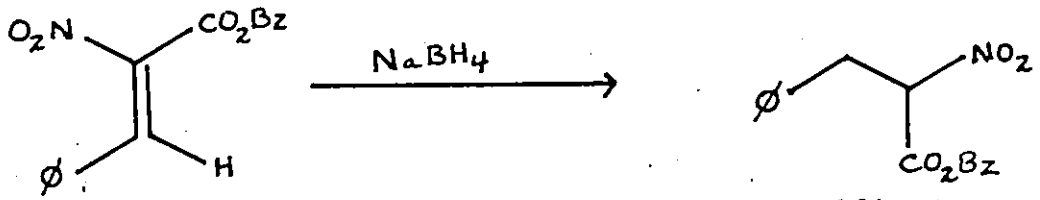
79 R=Bz
80 =CH_3

110 R=CH_3
112 =Bz

SCHEME IX

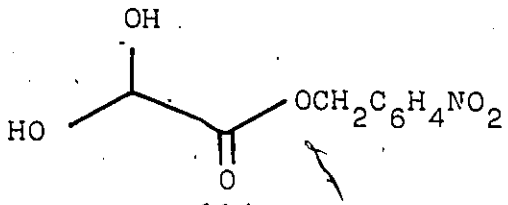


113 120



111 121

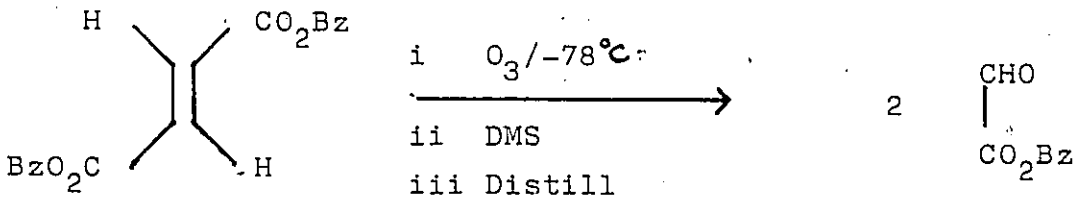
our disposal the p-nitrobenzyl ester of glyoyilic acid, the aldehyde being present in the hydrated "diol" form 114.



114

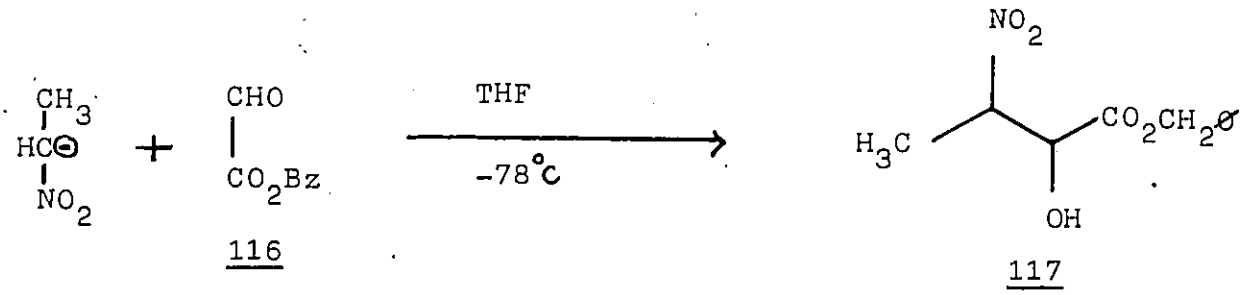
Numerous attempts to condense 114 with various nitroalkanes in the presence of different bases including triethylamine, pyridine and piperidine failed.

We reasoned that if the "free" aldehyde could be formed then the condensation might occur. Ozonolysis of the dibenzyl ester of fumaric acid 115 in dry methylene chloride followed by DMS reduction, nitrogen purge and distillation yielded a crude, but "free aldehyde" product, in 63%, bp 105°C at 0.5 mm. The crude benzyl



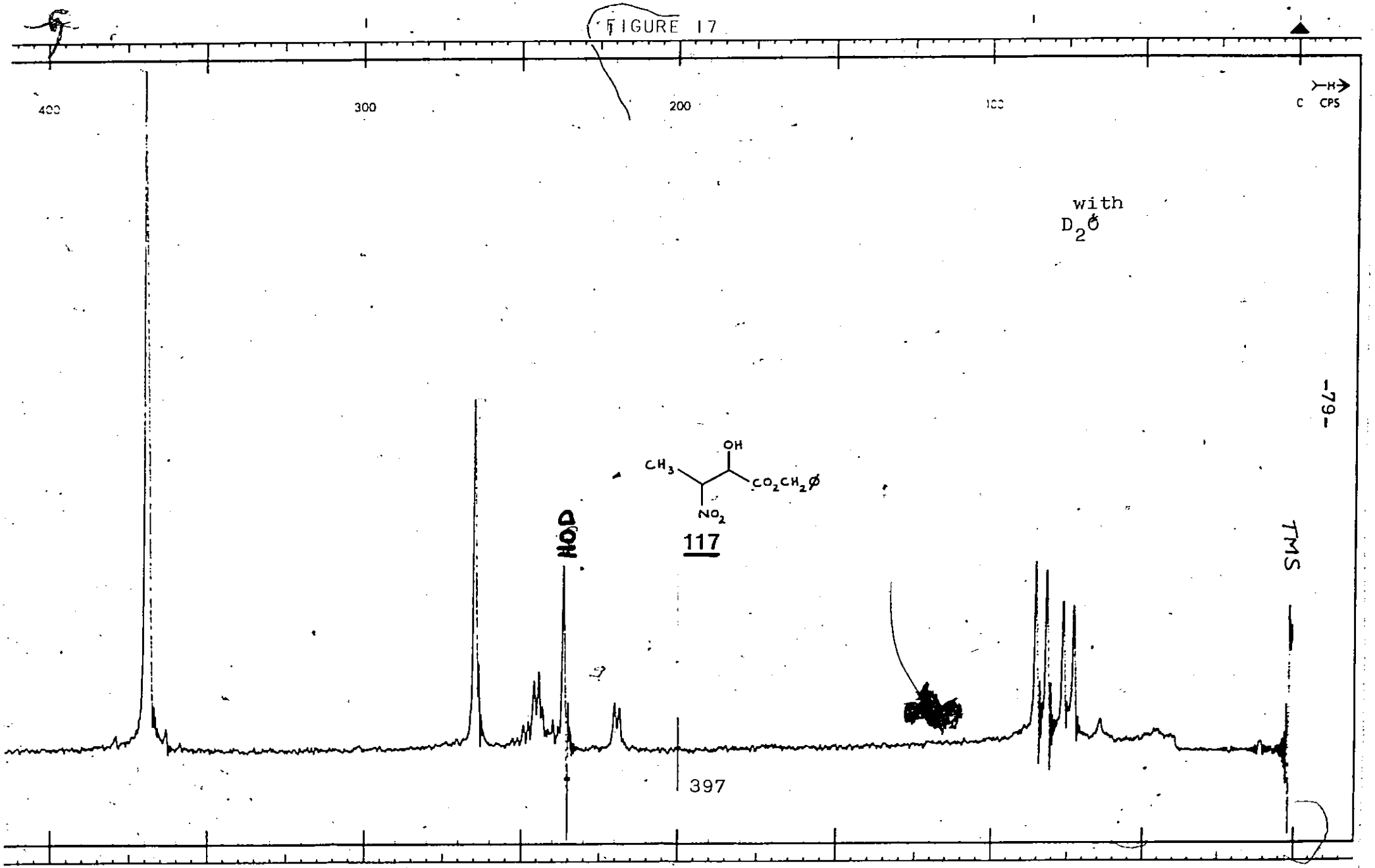
115 116

glyoxylate 116 was reacted with the lithium nitronate of nitroethane in dry THF, to give benzyl 2-hydroxy-3-nitrobutanoate 117 in 66% yield.



116 117

FIGURE 17

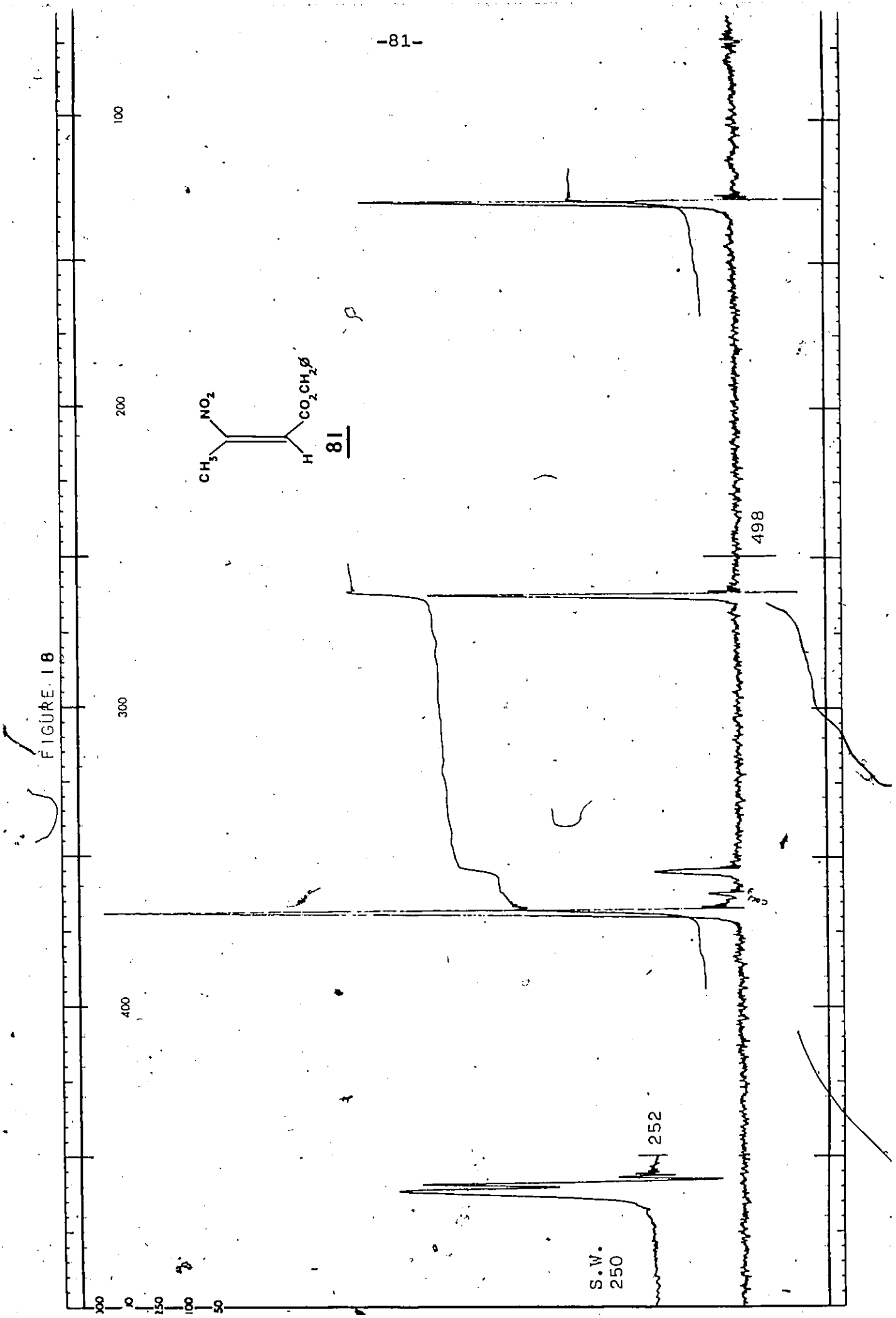


117

The proton NMR of 117 (after D_2O exchange) is shown in FIGURE 17. The methyl group appears as two doublets δ 1.45 to 1.7, the benzyl protons, a singlet at δ 5.3 and the phenyl a singlet at δ 7.4. Proton H1 on the hydroxyl bearing carbon appears as a doublet δ 4.4 (J=3Hz). The remaining proton H2 on the nitro bearing carbon appears as a complex multiplet δ 4.8 to 5.0. Infrared peaks occurred at 3430, 1740, and 1560 cm^{-1}. The nitro alcohol 117 was dehydrated to benzyl 3-nitrobut-2-enoate 81 in 98% yield via the Schmidt-Rutz reaction. NMR δ 2.6 (s, 3H), 5.3 (s, 2H), 7.1 (s, 1H) and 7.4 (5H); IR: 1730, 1670 and 1530 (cm^{-1}).

The appearance of the olefinic proton at higher field than phenyl gives further proof regarding our assignments of the nitro cinnamates 109 and 111.

In benzyl 3-nitrobut-2-enoate 81 we finally had the ideal nitro olefin to incorporate into a bicyclic β-lactam. This olefin would give a final cyclized product with a carboxylate ester which is easily hydrogenolyzed to the free acid, as well as a C3 methyl side chain. From our previous observations on orientation and reactivity arguments, its addition to 4-vinyl azetidinone 73 should be most facile of all olefins tested.



81

FIGURE 18

Unfortunately and inexplicably, all attempts to add 81 to 73 failed. Bases tried include n-BuLi, LDA, NaH, KOH, KF, Bu_4NF, $NaOCH_3$, NaOAc and Et_3N. In most cases starting olefin was recovered. Perhaps the preparation of the t-butyl ester of 81 will lead to satisfactory results.

EXPERIMENTAL

Proton NMR spectra were recorded on a Varian T60, EM 360 or HA-100 spectrometer using deuterochloroform as solvent with tetramethylsilane as internal standard. Carbon-13 spectra were recorded on a Varian FT80 instrument. Infrared spectra were recorded on a Beckmann IR-20 spectrometer.

Solvents used in reactions were dried prior to use; tetrahydrofuran was distilled from $LiALH_4$ or sodium-benzophenone ketyl, methylene chloride from P_2O_5, amines from CaH_2. Routine workup of reaction mixture refers to extracting with an organic solvent, washing with aqueous solutions and drying over $MgSO_4$. The organic phase was filtered and concentrated on a rotary evaporator. Chromatography was performed using Baker silica gel (60-200 mesh). High performance liquid chromatography was performed on a Waters PREP LC/SYSTEM 500 instrument (PrePak-500/silica, 325 g).

Melting points were determined on a Gallenkamp apparatus. Ozonolyses were performed with a Welsbach laboratory ozonator, operating on pure oxygen.

GENERAL PROCEDURES FOR LACTAM-OLEFIN CONDENSATIONS

(A) n-Butyllithium Method

To a solution of the β-lactam 73 in THF cooled to 0°C, was added 1 equivalent of n-BuLi in n-hexane. The solution was stirred for five minutes and a solution of nitro-olefin in THF (1 equivalent) was added dropwise. The mixture was quenched after 30 minutes with saturated NH_4Cl. Workup (ether 3x, $MgSO_4$) gave a crude product which was purified by column chromatography.

(B) Potassium Hydroxide Method

The β-lactam was dissolved in dioxane, then the nitro olefin (1 equivalent) was added and the solution was stirred at room temperature. An excess of finely crushed KOH was added in one portion, the flask equipped with a drying tube and the solution was stirred for 30 minutes. The reaction mixture was poured into an equal volume of water, then neutralized with 5% HCl. Workup (ether 4x, $MgSO_4$) gave an oil purified by column chromatography.

GENERAL PROCEDURE FOR PREPARATION OF ALCOHOLS

(C) The olefin-lactam was dissolved in dry CH_2Cl_2, then cooled to -78°C. A stream of ozone in oxygen was bubbled through the solution via a fritted glass without stirring until a faint blue colour persisted indicating excess ozone. The flask was purged with nitrogen for five minutes, then dimethyl sulfide (excess) was added to decompose the ozonide and the mixture was allowed to come to room temperature, then evaporated. The residue was partitioned between CH_2Cl_2 and brine, the CH_2Cl_2 dried over $MgSO_4$ and evaporated, giving a crude aldehyde.

The aldehyde was dissolved in ethanol and cooled to 0°C. A solution of $NaBH_4$ (2 equivalents) in ethanol was added to the aldehyde and stirred for 30 minutes at 0°C. The pH was adjusted to 4 with 5% HCl. Workup (ether 4x, brine, $MgSO_4$) gave a crude alcohol, purified by column chromatography.

GENERAL PROCEDURE FOR MESYLATIONS

(D) To a solution of the alcohol and CH_3SO_2Cl (1.2 equivalents in dry methylene chloride at 0°C was added dropwise 1.3 equivalents triethylamine. The resulting solution was stirred at 0°C for 30 min. Workup (water, 5% HCl, CH_2Cl_2,

5% $NaHCO_3$, brine $MgSO_4$) gave a crude mesylate that was purified by column chromatography.

GENERAL PROCEDURE FOR NITRO TO CARBONYL CONVERSION

(E) To a solution of the nitro compound to be oxidized and $NaOCH_3$ (1 equivalent) at -78°C was bubbled a stream of ozone in oxygen until the solution turned a faint blue colour (excess ozone). The solution was purged with nitrogen, dimethyl sulfide was added, and the mixture evaporated. The residue remaining was partitioned between CH_2Cl_2 - brine, the organic layer was dried over $MgSO_4$ and evaporated leaving the crude product of oxidation.

4-Vinyl-2-azetidinone 73

To a solution of 100 g (0.7 mole) chlorosulfonyl isocyanate in 200 ml benzene was added 54 g (1.0 mole) butadiene, followed by addition of 3 g anyhydrous K_2CO_3. The mixture was allowed to stand for one week (0 - 5°C), then it was transferred to a 500 ml separatory funnel and run dropwise into a solution of 176 g (1.4 mole) Na_2SO_3, 118 g (1.4 mole) $NaHCO_3$, 400 ml water and 200 ml ether at 0°C with vigorous stirring. The reaction mixture was filtered, separated and the aqueous layer extracted with ether (3 x 100 ml). Combined organic layers were dried over $MgSO_4$ and evaporated, giving 50 g crude β-lactam. This was distilled giving 45 g (66%) pure 73 (bp 95°C, 4mm).

β-nitrosytrene 75

Prepared as described by D.E. Worrall.[67]

N-(α-Phenyl-β-nitroethyl)-4-vinyl-2-azetidinone 84

Prepared via Method (A), using 2.5 mmole 73, 1.56 ml (1.6 nBuLi in n-hexane), 20 ml THF and 2.5 mmole 75. This

gave 0.57 g crude 84, which was chromatographed on silica gel using hexane-ethyl acetate (2:1) as eluent, affording 0.53 g (2.15 mmole) pure 84, (86%) as a yellow oil.

IR ($CHCl_3$) : 1740 (C=O), 1560, 1370 (NO_2)

NMR : δ 2.55 - 2.85 (Ha, dd, 1H) 3.0 - 3.25 (Hb, dd, 1H) (Jax = 2Hz, Jbx = 5Hz), 4.5 - 6.0 (complex multiplet, 4H, $C\underline{H}_2NO_2$, $C\underline{H} = CH_2$), 7.3 - 7.5 (phenyl, 5H)

N-(α-Phenyl-β-nitroethyl)-4-hydroxymethyl-2-azetidinone 85

Prepared via Method (C), using 4.46 g crude 84 in 50 ml CH_2Cl_2. Compound 84 was reduced in 20 ml EtOH using 0.51 g $NaBH_4$ in 5 ml EtOH, giving 4.13 g crude alcohol 85. This was chromatographed using hexane-ethyl acetate (1:2) as eluent, affording 1.36 g (5 mmole) pure 85 in 22% yield from nitrostyrene, as a yellow foam.

IR ($CHCl_3$) : 3200 - 3600 (OH), 1740 (C=O) 1560, 1380 (NO_2)

NMR : δ 2.5 - 3.0 ($C\underline{H}_2$ C=O), 3.5 - 4.0 ($-C\underline{H}_2O-$, N-C-H-), 4.6 - 5.8 ($-CH_2NO_2$, $C\underline{H}$) and 7.3 - 7.6 (phenyl)

N-(α-Phenyl-β-nitroethyl)-4-mesyloxymethyl-2-azetidinone 86

Prepared via Method (D), using 500 mg (2 mmole) 85, 275 mg (2.4 mmole) CH_3SO_2Cl and 263 mg (2.6 mmole) Et_3N in 10 ml CH_2Cl_2. This gave 600 mg crude mesylate 86. This was chromatographed on silica gel using hexane-ethyl acetate (1:2) as eluent, affording 478 mg (1.5 mmole) pure 86 (75%) as a yellow oil.

IR ($CHCl_3$) : 1370, 1170 (OSO_2CH_3), 1750 (C=O), 1350, 1560 (NO_2)

NMR : δ 2.9, 3.2 (s, OSO_2CH_3), 2.9 - 3.3 (Ha, Hb), 4.0 - 5.9 (complex multiplet, $-CH_2SO_2$ - CH_2NO_2, CH, Hx), 7.3 -7.5 (phenyl).

4-Phenyl-2-N-isocepham 87

In a long neck hydrogenation flask were placed 263 mg 86 (0.83) mmole), 263 mg 10% Pd on charcoal and 20 ml of 4:1 EtOH -EtOAc. Hydrogen was introduced and the flask was shaken for 22 hours. Reaction mixture was filtered and the solids were washed with EtOAc. The filtrate was evaporated with an equal volume of benzene, leaving 225 mg of a white solid. This was purified on a short silica column using EtOAc-hexane (2:1) This gave 40 mg of a clear oil tentatively identified as 87.

IR ($CHCl_3$) : 3500 (NH), 1740 (C=O)

NMR : δ 3.26, 3.82 ($CH_2C=O$), 3.7 - 3.9 ($-CH_2$ -CH-CH_2-) 5.20 (d, J=6.0 Hz, OCH) 7.3 - 7.5 (phenyl)

C-13 : ppm 166.5 (C=O), 63.3, 61.4 (C 3, C 1), 43.1, (C 7), 52.0, 45.7 (C 6, C 4)

MASS SPECTRUM: M^+ 202 (CALC. 202); base peak 103

N-(α -Phenyl-β-carbomethoxy)-4-hydroxymethyl-2-azetidinone 88

Following Method (E), 500 mg (2 mmole) of 85 in 20 ml CH_3OH was treated with 46 mg (2 mmole) of sodium in 5 ml CH_3OH. Ozonolysis gave 331 mg crude 88. This was applied to two 20 x 20 cm PLC plates and developed three times with ETOAc-hexane (1:1). This gave 75 mg of one isomer and 134 mg of another isomer (as evident by the benzylic proton singlet by NMR) for a total of 209 mg (42%) as clear oils.

IR ($CHCl_3$) : 3490 (OH), 1740 (C=O), 1200 (C-O)

NMR : δ 2.85 (dd, J=12, J=5 Hz), 3.13 (dd, J=12, J=2Hz, $C\underline{H}_2$ C=O), 3.89 (3H, singlet, $OC\underline{H}_3$), 5.89 (1H, singlet, $OC\underline{H}$), 7.2 - 7.6 (5H, singlet, phenyl)

MASS SPECTRUM: M^+ 249 (CALC. 249); base peak 190

N-(α-Phenyl-β-carbomethoxy)-4-mesyloxymethyl-2-azetidinone 89

FROM 86 - Following Method (E), 500 mg (1.54 mmole) of 86 was treated with 35 mg sodium metal in 5 ml CH_3OH (1 equivalent $NaOCH_3$). Ozonolysis resulted in 270 mg crude 89. This was purified by column chromatography giving 150 mg (0.46 mmole) pure 89 (30%) as clear oil.

FROM 88 - Following Method (D), 250 mg (1 mmole) of 88 was mesylated with 1.2 mmole CH_3SO_2Cl and 1.3 mmole Et_3N in 10 ml CH_2Cl_2, giving 237 mg crude mesylate. This was purified on a short column, affording 150 mg (0.46 mmole) pure 89 (46%) as a yellow oil.

IR ($CHCl_3$) : 1730 (C=O), 1170 (OSO_2CH_3)

NMR : δ 2.8 (S, 3H, OCH_3), 2.9-3.1 (dd, 1H, J=2Hz, Ha), 3.1 - 3.35 (dd, 1H, J=5Hz, Hb), 3.81 (s, 3H, OSO_2CH_3), 3.6 -3.9 (m, 2H, $-CH_2SO_2$), 4.3 -4.5 (m, 1H, $-C\underline{H}$), 5.60 (s, 1H, $OC\underline{H}$), 7.2 - 7.6 (s, 5H)

N-(α-Phenyl-β-nitroethyl)-4-iodomethyl-2-azetidinone 91

A mixture of 515 mg 86 (1.63 mmole) and 975 mg NaI (6.5 mmole, 4 equivalents) in 8 ml dry acetone was refluxed for 18 hours. The mixture was evaporated and the residue partitioned between brine and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated, leaving a crude iodide

that was purified on a short silica column using EtOAc-hexane (1:1) as eluent. This gave 330 mg (0.92 mmole) pure 91 as a yellow oil (56%). (SHOWN TO BE 2 ISOMERS BY C-13).

IR : 1750 (C=O), 1550, 1340 (NO_2)

C-13 : ppm 166.3 (C=O), 75.6 (CH_2NO_2), 57.4, 56.7 (OCH), 54.1, 51.2 (CH_2CHCH_2), 44.5, 44.4 ($CH_2C=O$) 6.5, 5.5 (CH_2I)

MASS SPECTRUM : M+ 360 (CALC. 359.9); base peak 105

N-(α-Furyl-β-nitroethyl)-4-vinyl-2-azetidinone 95

Following Method (A), 243 mg 73 (2.5 mmole) was condensed with 348 mg 2-(nitroethylene)-furan (2.5 mmole) using 1 equivalent nBuLi in n-hexane as base in 20 ml THF. This gave 508 mg crude 95. This was chromatographed on silica gel using EtOAc-hexane (2:1) as eluent giving 238 mg (1.0 mmole) pure 95 as a yellow oil (40%).

IR ($CHCl_3$) : 1740 (C=O), 1560, 1370 (NO_2)

NMR : δ 2.6 - 2.85 (m, 1H, Ha), 3.05 - 3.3 (dd, 1H, Hb, J=5Hz), 3.9 - 4.15 (m, 1H, Hx), 4.6 - 6.0 (complex multiplet, 6H, CH_2NO_2, $CH=CH_2$, $N-CH-CH_2NO_2$), 6.3 - 6.5 (d, 2H, J=2Hz, ring protons O-CH=CH), 7.4 - 7.5 (s, 1H, ring proton O-C=CH)

1-Phenyl-2-nitroprop-1-ene 76

Was prepared according to the method of H.B. Hass[68].

N-(α-Phenyl-β-nitropropyl)-4-vinyl-2-azetidinone 96

Prepared via Method (B), using 243 mg (2.5 mmole) 73 and 408 mg (2.5 mmole) 76 in 20 ml dioxane, and 2 pellets of finely crushed KOH. This gave 395 mg of crude 96 which yielded 258 mg (1.0 mmole) (40%) of pure 96 after column chromatography using EtOAc-hexane as eluent.

IR ($CHCl_3$) : 1740 (C=O), 1560, 1370 (NO_2)

NMR : δ 1.35, 1.85 (d, 3H, CH_3), 2.45 - 3.0 (dd, 1H, Ha), 3.05 - 3.4 (dd, 1H, Hb), 3.95 - 4.05 (m, 1H, Hx), 4.76 (dd, 1H, OCH), 5.1 - 6.1 (m, 4H, $CH=CH_2$ + $CH-NO_2$), 7.3 - 7.6 (s, 5H, Phenyl)

N-(∝-Phenyl-β-nitropropyl)-4-hydroxymethyl-2-azetidinone 97

Prepared via Method (C), using 5.71 g crude 96 dissolved in 50 ml, CH_2Cl_2. The residue was reduced in 20 ml EtOH using 0.5 g $NaBH_4$, giving 4.11 g crude alcohol 97. Chromatography performed on silica gel using EtOAc-hexane (2:1) as eluent, afforded 2.48 g (9.45) mmole) pure 97 (38% from 1-phenyl-2-nitroprop-1-ene).

IR ($CHCl_3$) : 3200 - 3600 (OH), (C=O), 1550, 1370 (NO_2)

NMR : δ 1.9 (d, 3H, CH_3), 2.5 - 3.0 (m, 3H, Ha, Hb, OH), 3.5 - 4.0 (m, 3H, Hx, $-CH_2OH$), 5.5 - 5.95 (m, 1H, $CHNO_2$).

N-(∝ -Phenyl-β-nitropropyl)-4-mesyloxymethyl-2-azetidinone 98

Prepared via Method (D), using 1.0 g alcohol (3.8 mmole) 97, 522 mg (4.56 mmole) CH_3SO_2Cl (1.2 equivalents) and 500 mg (4.9 mmole) Et_3N (1.3 equivalents) in 20 ml CH_2Cl_2. This gave 1.12 g pure mesylate (3.26 mmole) as a yellow oil (86%).

IR ($CHCl_3$) : 1740 (C=O), 1560, 1370 (NO_2) 1170 (OSO_2CH_3)

NMR : δ 1.9 (d, 3H, CH_3), 3.05 (s, 3H, OSO_2CH_3), 3.6 - 3.8 (m, 1H, Hx), 4.2 - 4.5 (m, 2H), CH_2OSO_2), 4.55-4.7 (d, 1H, OCH, J=9Hz), 5.65 - 5.9 (m, 1H, $CHNO_2$), 7.3 - 7.5 (s, 5H, phenyl), 2.8 - 3.05 (m, 2H, Ha, Hb)

N-(α-Phenyl-β-ketopropyl)-4-mesyloxymethyl-2-azetidinone 99

Prepared via Method (E), using 830 mg (2.43 mmole) 98, 2.43 ml (1n $NaOCH_3$, in CH_3OH) in 20 ml CH_3OH. Ozonolysis gave 686 mg crude 99. Column chromatography using 3:1 hexane-EtOAc gave 425 mg (1.37 mmole) pure ketone 99 as a clear oil (56%).

IR ($CHCl_3$) : 1740 (C=O), 1170 (SO_2CH_3)

NMR : δ 2.1 (s, 3H, CH_3), 2.8, 3.1 (s, 3H, OSO_2-CH_3), 2.5 - 4.3 (m, 5H, Ha, Hb, Hx, CH_2O), 5.55 (d, 1H, OCH, J= Hz), 7.2 - 7.6 (s, 5H, phenyl).

3-Methyl-4-phenyl-2-O-isocephem 100

Into a 10 ml round bottom flask was weighed 50.7 mg NaH dispersion (60.6%, 1.28 mmole). This was washed 3x with 5 ml hexane, then 8 ml THF was added and the slurry stirred at -78°C. A solution of 200 mg ketomesylate 99 (0.64 mmole) in 2 ml THF was added to the NaH slurry, followed by 1 ml of tert-butyl alcohol. The mixture was allowed to come to room temperature and stirred for 6 more hours., The mixture was poured into ether-water and neutralized with 5% HCl, the ether layer was dried over $MgSO_4$ and evaporated, giving 105 mg white crystalline material (76%). An analytical sample was recrystallized from CH_2Cl_2 - ether - hexane giving a white powder, mp 132-133°C.

IR ($CHCl_3$) : 1750 (C=O)

NMR : δ 1.95 (s, 3H, CH_3), 2.6 -2.7 (m, 1H, Ha), 3.25 - 3.55 (m, 1H, Hb), 3.6 - 3.7 (m, 2H, Hx, CH_2O), 4.45 - 4.65 (d.d., 1H, CH_2O), 6.15 - 6.45 (s, 5H, phenyl).

C-13 : ppm 166.2 (C=O), 138.9 (CH_3-C=O), 114.0 (NC=O), 68.9 (CH_2O), 43.3 (CH_2CHCH_2), 42.4 ($CH_2C=O$), 16.6 (CH_3)

MASS SPECTRUM: M+ 215 (CALC. 215); base peak 130

N-(α-Phenyl-β-hydroxypropyl)-4-mesyloxymethyl-2-azetidinone 101

A solution of 18.7 mg $NaBH_4$ in 5 ml EtOH was stirred at 0°C, then 155 mg of ketomesylate 99 was added in 2 ml EtOH. The mixture was stirred at 0°C for 24 hours. Workup (5% HCl, ether 4x brine, $MgSO_4$) gave crude alcohol 101. PLC using EtOAc-hexane (2:1) as eluent afforded 125 mg pure alcohol 101 in 79% yield.

IR ($CHCl_3$) : 3200 - 3600 (OH); 1730 (C=O), 1170 (SO_2CH_3)

NMR : δ 1.1 (d, 3H, CH_3, J=8Hz), 2.9 - 3.1 (m, 5H, SO_2CH_3, Ha, Hb), 3.5 - 3.7 (m, 1H, Hx), 4.0 - 4.8 (m, 4H, CH_2OSO_2, OCH).

3-Methyl-4-phenyl-2-0-isocepham 102

Into a 10 ml flask was weighed 21 mg NaH dispersion in oil (60.6%, 1.5 equivalents). This was washed 3x with hexane, then stirred in 5 ml dry DMSO. A solution of 110 mg 101 (0.35 mmole) in 2 ml DMSO was added dropwise to the NaH solution, and stirred at room temperature for 2 hours. The reaction was quenched with 5 ml water. Workup (CH_2Cl_2 (4 x 10 ml), brine, $MgSO_4$) gave a crude oil that, after eluting through a short silica column with CH_2Cl_2, gave 55 mg (0.25 mmole) pure 102. (71%).

IR ($CHCl_3$) : 1740 (C=O)

NMR : δ 1.0 (s, 3H, CH_3), 2.6 - 2.8 (m, 1H, Ha), 3.0 - 3.25, (m, 1H, Hb), 3.65 - 4.3 (m, 4H, Hx, CH_2O, $OCHCH_3$), 4.5 - 4.6 (d, 1H, OCH, J=4Hz).

2-Nitrobut-2-ene

Prepared *via* the method of Melton and McMurry.[61]

N-(α-Methyl-β-nitropropyl)-4-vinyl-2-azetidinone 103

Prepared *via* Method (B), using 2.91 g (30 mmole) 73, 3.03 g (30 mmole) 77 in 40 ml dioxane, and 2 g finely crushed KOH. This gave 2.4 g (12.1 mmole) pure 103, following HPLC using EtOAc-hexane (1:2) as eluent. Isolated yield was 40% (yellow oil).

IR ($CHCl_3$) : 1750 (C=O), 1550 (NO_2)

NMR : δ 1.3, 1.6 (d, 3H, CH_3), 2.6 - 2.8 (m, 1H, Ha), 3.1 - 3.3 (m, 1H, Hb), 3.7 - 4.3 (m, 2H, Hx, $CHCH_3$), 4.7 - 6.1 (m, 4H, $CH=CH_2$ $CHNO_2$).

MASS SPECTRUM: M^+ 198 (CALC. 198); base peak 54

N-(α-Methyl-β-nitropropyl)-4-hydroxymethyl-2-azetidinone

Prepared *via* Method (C), using 3.7 g (18.7 mmole) 103 in 100 ml CH_2Cl_2. The residue was reduced in 50 ml EtOH with 0.54 g NaBH in 5 ml EtOH, giving 2.1 g crude alcohol. Silica gel chromatography using EtOAc-hexane (4:1) as eluent gave 1.3 g (6.6 mmole) pure alcohol. (35%)

IR ($CHCl_3$) : 3250 - 3600 (OH), 1745 (C=O), 1550, 1370 (NO_2)

NMR : δ 1.1 - 1.25 (d, 3H, $NCHCH_3$, J=9Hz), 1.25 - 1.4 (d, 3H, CH_3CHNO_2, J=9Hz), remainder complex, integrates to 8H.

N-(α-Methyl-β-nitropropyl)-4-mesyloxymethyl-2-azetidinone 104

Prepared *via* Method (D), using 1.3 g (6.6 mmole) alcohol 118, 760 mg CH_3SO_2Cl and 670 mg Et_3N in 20 ml CH_2Cl_2.

This gave 1.93 g crude mesylate 104. Chromatography on silica gel using pure EtOAc as eluent gave 1.68 g (6 mmole) pure 104 (90%).

IR ($CHCl_3$) : 1750 (C=O), 1540 (NO_2), 1170 (OSO_2CH_3)

NMR : δ 1.4 (d, 3H, CH_3), 1.65 (d, 3H, $CHCH_3NO_2$) 2.7 - 2.9 (m, 1H, Ha), 3.0 -3.3 (m, 4H, Hb, SO_2CH_3), 3.9 - 5.2 (m, 5H, CH_2O, Hx, $CHCH_3$, $CHNO_2$).

N-(α-Methyl-β-ketopropyl)-4-mesyloxymethyl-2-azetidinone 105

Prepared via Method (E), 1.3 g (4.6 mmole) of 104 in 30 ml CH_3OH was treated with 4.6 ml of 1N $NaOCH_3$, in CH_3OH. Ozonolysis gave 950 mg crude ketone 105. Silica gel chromatography using EtOAc-hexane (4:1) gave 800 mg (3.2 mmole) pure 105 as a clear oil (70%).

IR ($CHCl_3$) : 1750 (β-lactam C=O), 1715 (C=O), 1190 (OSO_2CH_3)

NMR : δ 1.55 (d, 3H, CH_3, J=7Hz), 2.25 (s, 3H, CH_3 C=O), 2.7 - 2.95 (m, 1H, Ha), 3.15 - 3.35 (m, 4H, Hb, OSO_2CH_3), 3.95 - 4.6 (m, 4H, Hx, CH_2O, $CHCH_3$)

3, 4-Dimethyl-2-O-isocephem 107

Into a 10 ml flask was weighed 59.4 mg NaH dispersion in oil (60.6%, 1.5 equivalents). This was washed 3x with hexane, then 8 ml THF was added, and stirred at 0°C. To this 249 mg (1 mmole) 105 in 2 ml THF was added, followed by 2 ml tert-butyl alcohol. After 45 minutes the reaction mixture was quenched with water and neutralized with 5% HCl. Workup (CH_2Cl_2 (3 x 10 ml), brine, $MgSO_4$) gave a crude 107. Elution through a short silica column with CH_2Cl_2 gave 105 mg (0.69 mmole) pure 107 as a clear oil. (69%)

IR ($CHCl_3$) : 1740 (C=O)

NMR : δ 1.75 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.55 - 2.75 (m, 1H, Ha), 3.15 - 3.45 (m, 1H, Hb), 3.45 - 3.60 (m, HCHO, Hx), 4.3 - 4.55 (m, 1H, HCHO)

C-13 : ppm 166.4 (C=O), 135.4 (C=), 108.4 (C=) 68.5 ($\underline{C}H_2O$), 14.9 ($\underline{C}H_3$), 13.5 ($\underline{C}H_3$), 43.3 ($\underline{C}H$), 42.1 ($\underline{C}H_2$)

MASS SPECTRUM: M^+ 153 (CALC. 153); base peak 54

Ethyl 3-nitroacrylate 78

Prepared via the method of McMurry.[62]

Methyl 3-iodo-3-phenyl-2-nitropropionate 108

Into a 500 ml flask were placed, 150 ml dry ether, 10.16 g I_2 (0.04 mole) and 6.48 g methyl cinnamate (0.04 mole). The solution was cooled to 0°C under N_2 and protected by a cold finger filled with a dry ice acetone slurry. Then, with stirring, 3.6 ml (0.06 mole) N_2O_4 was injected. The reaction mixture was stirred at 0°C for 1 hour, then at room temperature for 5 hours. The mixture was washed with saturated $Na_2S_2O_3$ solution (until the ether layer was light yellow), 2x with saturated $NaHCO_3$, then brine. Evaporation of the ether left a reddish solid, recrystallized from cold ether giving 2.6 g yellow powder, mp 80-82°C. (20%)

NMR : δ 3.9 - 4.1 (s, 3H, OCH_3), 5.76, 5.91 (dd, $C\underline{H}NO_2$, $C\underline{H}I$), 7.2 - 7.7 (m, 5H, phenyl)

C-13 : ppm 162.7 (C=O), 93.3 ($\underline{C}HNO_2$), 54.3 ($\underline{C}H_3$) 21.3 ($\underline{C}HI$).

Methyl α-nitrocinnamate 80

In a 50 ml flask was placed 1.0 g (2.9 mmole) 108 and 25 ml dry ether, then 5 g dry NaOAc. The mixture was

refluxed under N_2 for 3 hours, washed with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, then brine. The ether layer was dried over $MgSO_4$ and evaporated giving 620 mg (2.9 mmole) pure 80 (99%)

IR (NEAT) : 1730 (C=O), 1640 (C=C) 1520 (NO_2)
NMR : δ (2 isomers) 8.1, 7.6 (s, 1H, C=CH), 3.95, 3.90 (s, 3H, CH_3), 7.4, 7.5 (s, 5H, phenyl)
MASS SPECTRUM: M^+ 207 (CALC. 207); base peak 77

N-(α-Phenyl-β-carbomethoxy-β-nitroethyl)-4-vinyl-2-azetidinone 110

Prepared via Method (A), using 145.5 mg (1.5 mmole) lactam 73, 0.94 ml (1.6 N nBuLi in n-hexane), 20 ml THF and 311 mg (1.5 mmole) 80. This gave 320 mg crude 110, chromatographed on silica gel using EtOAc-hexane (2:1) gave 248 mg (0.82 mmole) pure 110 as a yellow oil. (54%)

NMR : δ 2.5 - 2.8 (m, 1H, Ha), 2.9 - 3.2 (dd, 1H, Hb, J=5Hz), 3.4 - 4.0 (m, 4H, Hx, OCH_3), 4.85 - 6.55 (m, 5H, $CH=CH_2$, $CHNO_2$, NCH C=O)

Benzyl 2-nitro-3-iodo-3-phenylpropionate 119

Prepared by the same procedure used to prepare compound 80, using these amounts. In 150 ml ether, 8.89 g (0.035 mole) I_2, 8.25 g (0.035 mole) benzyl cinnamate and 3 ml N_2O_4. This gave 12.97 g crude 119, used without further purification. (91%)

Benzyl α-nitrocinnamate 79

To a solution of 5 g crude 119 in 100 ml dry ether was poured 20 g dry NaOAc. This was refluxed under N_2 for 3 hours, solution was washed 3X with $Na_2S_2O_3$, 1x with $NaHCO_3$

and 1x with brine. The ether layer was dried over $MgSO_4$ and evaporated, giving a yellow solid. Recrystallization from cold ether gave 1.0 g white needles, mp 87-88°C.

IR ($CHCl_3$) : 1730 (C=O), 1640 (C=C), 1530 (NO_2)
NMR : δ 5.2 - 5.3 (s, 2H, OCH_2), 7.2 - 7.4 (2s, 10H, OCH_2/OCH) 7.48 (s, 1H, C=CH)
C-13 : ppm 159.1 (C=O), 133.4 (C=), 132.2 (=CH), 68.4 (CH_2)
MASS SPECTRUM: M^+ 283 (CALC. 283); base peak 77

N-(α-Phenyl-β-carbobenzyl-β-nitroethyl)-4-vinyl-2-azetidinone 112

Prepared via Method (A), using 3.2 mmole lactam 73, 1.30 ml (2.4 nBuLi in n-hexane), 20 ml THF and 3.2 mmole 111. This gave, after column chromatography of the crude oil, 1.09 g (2.87 mmole) pure 112 as a yellow oil. (89%)

IR ($CHCl_3$) : 1750 (C=O), 1740 (C=O), 1570 (NO_2)
NMR : δ 2.30 - 2.9 (m, 1H, Ha), 2.95 - 3.3 (m, 1H, Hb), 3.6 - 4.05 (m, 1H, Hx), 4.75 - 7.1 (complex m, 7H, $CH=CH_2$, OCH_2. OCH, $CHNO_2$), 7.1 - 7.5 (2s, 10H, phenyl, benzyl)
MASS SPECTRUM: M^+ 380 (CALC. 380); base peak 144

Ethyl α-nitrocinnamate 113.

Prepared according to W. Lehnert.[63]

Ethyl 2-nitro-3-phenylpropionate 120

A solution of 76 mg $NaBH_4$ in 10 ml EtOH was stirred at 25°C. To this was added dropwise, a solution of 442 mg (2 mmole) 113 in 5 ml THF. The reaction mixture was stirred for 45 minutes. Workup (5% HCl, ether, $MgSO_4$) gave crude 120,

which, after elution through a 2 g pad of silica gel, gave 312 mg (1.4) mmole) 120 as a yellow oil (70%).

NMR : δ 1.3 (t, 3H, $CH_2\underline{CH_3}$, J=8Hz), 3.6 (d, 2H, $\underline{CH_2}O$, J=8Hz), 4.3 (q, 2H, $\underline{CH_2}$, CH_3, J=8Hz), 5.4 (t, 1H, $\underline{CH}NO_2$, J=8Hz), 7.2 - 7.5 (s, 5H, phenyl)

Benzyl 2-nitro-3-phenylpropionate 121

A solution of 37.8 mg $NaBH_4$ in 5 ml EtOH was stirred at 25°C. To this was added dropwise 283 mg (1 mmole) 79 in 2 ml THF. The mixture was stirred for 45 minutes. Workup (5% HCl, ether, $MgSO_4$) gave crude 121, which, after elution through a 2 g pad of silica gel gave 215 mg (0.76 mmole) 121 as a yellow oil (76%).

NMR : δ 3.6 (d, 2H, $\underline{CH_2}CO_2$, J=8Hz), 5.3 (s, 2H, $\underline{CH_2}O$), 5.4 (t, 1H, $\underline{CH}NO_2$, J=8Hz), 7.2 - 7.5 (2s, 10H, phenyl, benzyl)

Benzyl glyoxylate 116

In a 200 ml flask was weighed 0.12 g (45.5 mmole) dibenzyl fumarate. This was dissolved in 100 ml dry CH_2Cl_2 and cooled to -78°C. Ozone in a stream of O_2 was bubbled in at 0.2 l/min. for 3 hours, then N_2 bubbled for five minutes before adding 5 ml DMS. The solvent was evaporated, and the residue distilled, giving 9.4 g 116 (57.3 mmole) as a clear "gel". (63%) (highly unstable).

NMR : δ 5.3 (s, 2H, $O\underline{CH_2}$), 7.2 - 7.4 (s, 5H, CH_2O), 9.7 (s, 1H, $\underline{CH}O$)

IR (NEAT) : 1740 (C=O), 3200 - 3600 (OH)

-aldehyde mainly in free form, but some hydrate and polymer present.

Benzyl 2-hydroxy-3-nitrobutanoate 117

In a dry, N_2 swept, 100 ml flask was placed 780 mg (10.4 mmole) nitroethane, followed by 30 ml THF. This was cooled to -78°C. To the above solution was added 4.33 ml (2.4 M nBuLi in n-hexane), forming a milky white suspension. The reaction mixture was quenched with a solution of 1.7 g (10.4 mmole) benzyl glyoxylate in 10 ml THF, and stirred for 15 minutes. Workup (saturated NH_4Cl, ether, $MgSO_4$) gave 2.07 g crude alcohol 117. Column chromatography on silica gel using CH_2Cl_2 as eluent gave 1.65 g 117 (6.93 mmole) as a yellow oil. (66%)

IR ($CHCl_3$) : 1740 (C=O), 1560 (NO_2), 3420 -3440 (OH)
NMR ($\underline{W}D_2O$) : δ 1.45, 1.7 (dd, 3H, CH_3, J=7Hz), 4.4 (d, 1H, $\underline{H}COH$, J=2Hz), 4.8 - 5.0 (m, 1H, $C\underline{H}NO_2$), 5.3 (s, 2H, $C\underline{H}_2O$), 7.4 (s, 5H, phenyl).

Benzyl 3-nitrobut-2-enoate 81

In a 50 ml flask was weighed 380 mg (1.6 mmole) alcohol 117, then 5 ml acetic anhydride was added with 0.5 g dry NaOAc. The mixture was stirred at room temperature for 16 hours, then poured into saturated $NaHCO_3$. This solution was extracted with ether, the ether layer washed with 5% HCl, dried over $MgSO_4$ and evaporated, giving 370 mg crude olefin 81. An analytical sample was prepared by distilling some of the crude in a kugelrohr apparatus (125°C at 0.1 mm.)

IR (NEAT) : 1730 (C=O), 1530 (NO_2), 1670 (C=C)
NMR : δ 2.6 (s, 3H, CH_3), 5.3 (s, 2H, $C\underline{H}_2O$), 7.1 (s, 1H, C=C$\underline{H}$), 7.4 (s. 5H, phenyl).
C-13 : ppm 164.0 (C=O), 160.3 (C=), 121.1 (CH=), 67.5 (CH_2), 14.0 (CH_3).
MASS SPECTRUM: M^+ 221 (CALC. 221); base peak 91

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CLAIMS TO ORIGINAL RESEARCH

1. Synthesized 2-hetero-isocephams by base catalyzed condensation of 4-vinyl-azetidinone with nitro olefins followed by conversion of the vinyl group to a mesyloxymethyl group, oxidation or reduction of the nitro group, and final ring closure.

2. A novel primary nitro to carbomethoxy transformation is described.

3. Benzyl 3-nitrobut-2-enoate was prepared.

4. The following 2-isocephems were prepared:

   3,4-Dimethyl-2-0-isocephem
   3-Methyl-4-phenyl-2-0-isocephem

5. 3-Methyl-4-phenyl-2-0-isocepham was prepared.