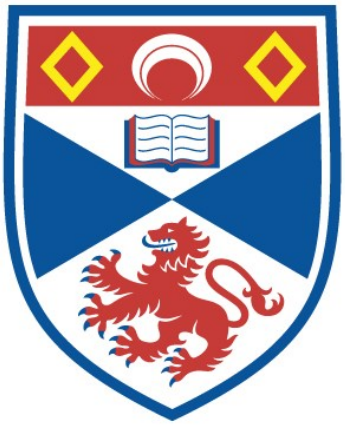
SOME HYDROLYTIC REACTIONS OF BETA-LACTAMS

Keith Freeman

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1976

SOME HYDROLYTIC REACTIONS OF BETA-LACTAMS

A Thesis

presented for the degree of

DOCTOR OF PHILOSOPHY

in the faculty of science of the

University of St. Andrews

by

Keith Freeman

St. Andrews

March, 1976

DECLARATION

I declare that this thesis is based on the results of experiments carried out by me, that it is my own composition, and that it has not previously been presented for a Higher Degree.

The work was carried out in the Department of Chemistry of the University of St. Andrews and at May & Baker Ltd., Dagenham under the direction of A.R. Butler and D.E. Wright, between October 1971 and July 1974.

CERTIFICATE

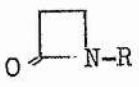
We hereby certify that Keith Freeman has spent eleven terms at research work under our supervision, has fulfilled the conditions of Ordinance General No. 12 and Resolution of the University Court 1967, No. 1 and is qualified to submit the accompanying thesis in application for the degree of Ph.D.

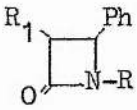
Directors of Research

The author would like to express his gratitude for the advice, assistance and patience of his supervisors Dr. A.R. Butler and Dr. D.E. Wright.

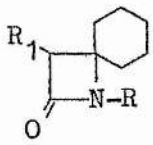
ABSTRACT

This thesis describes the synthesis and alkaline ring fission of some β-lactams. Three series of β-lactams were studied: those of type (A) bearing a substituent on the ring nitrogen; 1,3,4-trisubstituted β-lactams (B); and the spiro-β-lactams of type (C).





R=Ph, p-$NO_2C_6H_4$



(A) (B) (C)

Three synthetic routes were used for the synthesis of the β-lactams, namely (a) the Reformatsky Reaction using an imine and a bromoacetate ester, (b) the cyclization of a 3-bromopropionamide, and (c) the addition of an acid chloride across an imino group. In the acid chloride-imine reaction it was shown that, contrary to previous reports, the reaction will proceed successfully with an N-benzyloxycarbonylaminoacyl chloride, and that conditions of high-dilution are not necessary in order to obtain high yields.

The results of hydrolytic studies indicate that intramolecular assistance by an amido-group alpha to the β-lactam carbonyl is not of significance in the hydrolysis

of these β-lactams in the conditions employed (0.1-1.0 M sodium hydroxide).

Hydrolyses were also conducted in the presence of micelle forming agents and the results obtained show that the effect of these upon the rate of hydrolytic fission is dependant upon the nature of the substituents present on the β-lactam ring.

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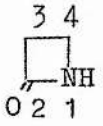
CHAPTER I

INTRODUCTION

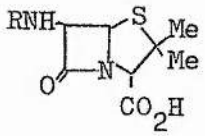
1. The Occasion for the Work

β-Lactams are cyclic amides with a four-membered ring. Monocyclic β-lactams are named as derivatives of the parent compound azetidin -2-one (1), the positions on the ring numbered as shown.



(1)

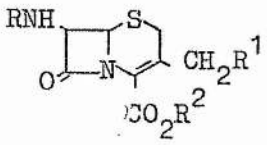
Although β-lactams were first synthesized in 1907,[1] it was not until the confirmation of the β-lactam-thiazolidine structure of penicillins[2] (2) that the compounds gained importance and interest.



(a) Penicillin G R=Ph.OCH_2.CO

(2)

Subsequently other natural products containing a β-lactam ring have been discovered: the cephalosporins[3] (3); the alkaloids of Pachysandris terminalis[4] (4); and wildfire toxin[5] (5).



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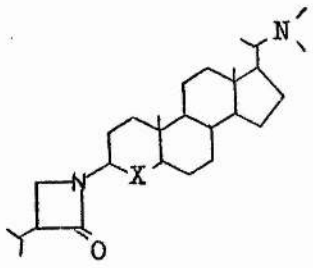
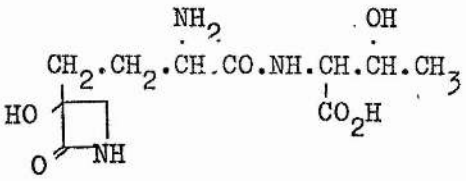


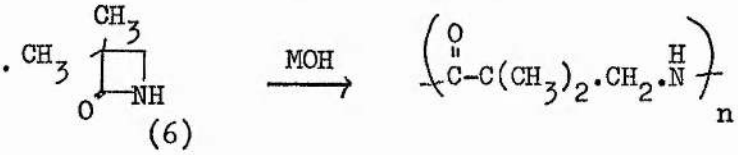
X=C=O, CHOH

(4)



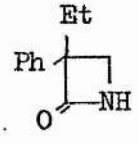
(5)

Interest in β-lactams has also been aroused by the possibility of the polymerization[6] of suitable β-lactams to polyamides (6), and by the reported physiological activity of some monocyclic β-lactams. The properties



(6)

reported include hypnotic activity similar to that of phenobarbitone, for 3,3-disubstituted β-lactams such as (7), anti-inflammatory activity[8] of some spiro-β-lactams (8), antiviral activity[9] of 1-adamantylazetidin-2-one (9), and antibacterial activity[10] of some trisubstituted β-lactams such as (10).



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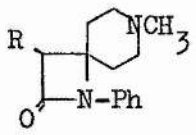

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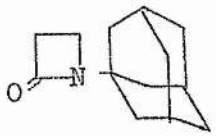

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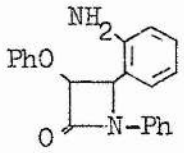
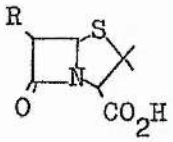


(10)

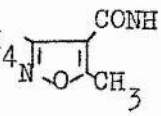
Consequently numerous β-lactams have been synthesized and, in particular, a large number of semisynthetic penicillins have been prepared from 6-aminopenicillanic acid (2b) or 6-iminopenicillanic acids (2c) in order to



(2)

(b) R=NH_2 (d) R=Ph.CH(NH_2)CONH

(c) R=N=CR^1R^2 (e) R= o-ClC_6H_4



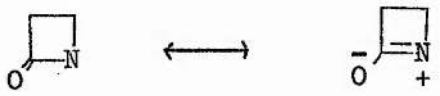
find compounds which possess a broader spectrum of antibacterial activity or which have a greater resistance to enzymic or hydrolytic fission of the β-lactam ring.

Among the more successful semi-synthetic penicillins are ampicillin (2d) and cloxacillin (2e).

The antibacterial properties of the penicillins (and of the cephalosporins) are believed to be due to interference in the final stage of cell wall synthesis,[11] i.e. the cross-linking of glycopeptide chains by a transpeptidase.[12] This enzyme replaces a C-terminal D-alanine residue on one chain with a free amino group on a neighbouring chain, and it was suggested by Strominger[13] that the antibiotics

are mistaken for a D-alanyl-D-alanine fragment by the enzyme which is then irreversibly acylated and thus rendered inactive. If the antibiotic activity is due to an acylation reaction then this activity may be reflected in the chemical reactivity of the β-lactam ring in such compounds.

It has been suggested[2b] that monocyclic β-lactams are less susceptible to hydrolysis than the penicillins owing to resonance stabilization[14] (11-12) which is not possible in the penicillins owing to the enforced



(11) (12)

tetrahedral geometry[15] at the β-lactam nitrogen. This is also indicated by the longer C-N bond length in active compounds as shown by X-ray analysis.[16,17] The degree of resonance stabilization and hence the stability of the β-lactam ring is also reflected in the frequency and intensity of absorption of the β-lactam carbonyl in the infra-red;[18,19] monocyclic β-lactams have an absorption in the region of 1740 cm^{-1} compared to 1770 to 1780 cm^{-1} for the active penicillins and cephalosporins. Molecular orbital calculations (using Extended Hückel and CNDO/2 methods) on model β-lactam structures have shown[18,20-22] that the C-N bond strengths and carbonyl carbon charge densities correlate with the

biological activity of some corresponding cephalosporins, although the nature of the side-chain may have a great effect on the electronic structure of the ring.[20,21] The biologically-active penicillins and cephalosporins are also usually found to undergo hydrolytic fission of the β-lactam C-N bond more readily than do inactive compounds. (This will be dealt with in more detail in section I.3.A.) Although active compounds in general possess a more reactive β-lactam ring, antibacterial activity must also depend upon a number of other factors[2c] such as cell permeability, β-lactamase resistance, and enzyme recognition.

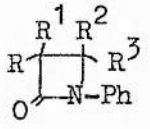
2. The Choice of β-Lactams for Study

Any study of the hydrolytic stability of the β-lactam ring in penicillins is necessarily complicated by a number of factors which may affect the rate of reaction. Rate enhancement with respect to simpler lactams may be due to any one or a combination of (a) the presence of an amido group in the 6-position, (b) the increase in ring strain due to the bicyclic nature of the system, (c) the presence of the sulphur atom in the 1-position, (d) the carboxyl function in the 3-position, and (e) the decrease in amide resonance brought about by the geometry of the molecule. It is therefore desirable to separate these factors and to examine them singly.

For a β-lactam to be considered as a useful model for the penicillin system in a hydrolytic study, the ring should

be opened readily under conditions similar to those in which penicillins react. This requires that the compounds react in aqueous base at hydroxide concentrations of 1 molar or less. Furthermore, for ease of study the reaction should be accompanied by a suitable change in some property of the system. One of the more convenient ways of following such a reaction is the use of spectrophotometric techniques, which imposes further restrictions on the choice of compounds for study.

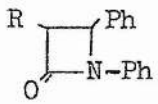
Azetidin-2-one has no u.v. absorption at wavelengths greater than 200 nm, but 1-phenylazetidin-2-ones (13) absorb strongly in the region of 250 nm and this absorption



(13)

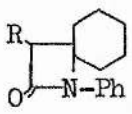
disappears on ring-opening. Therefore all the β-lactams prepared for study were of the type (13) with a phenyl or substituted phenyl group in position 1.

It has been shown[23] that the introduction of a 4-phenyl substituent on the β-lactam ring does not drastically affect the rate of base hydrolysis. As synthetic routes to 1,4-diphenylazetidin-2-ones (14) are known, compounds of this type were those first chosen for study.

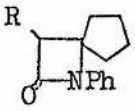


(14)

In addition the preparation of a series of β-lactams with a spirocyclohexyl (15) or spirocyclopentyl (16) group on C-4 was attempted. It was thought extra strain might be induced in the lactam ring by the distortion of the bond angle at the spiro ring from the normal tetrahedral angle and that this might be reflected in an increase in reactivity of the amide bond. It will be shown (II.2.C) that this



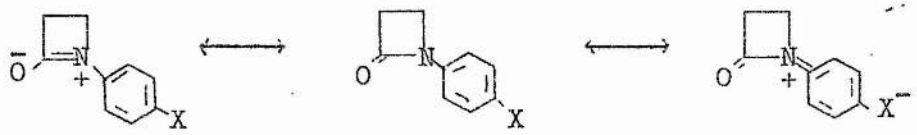
(15)



(16)

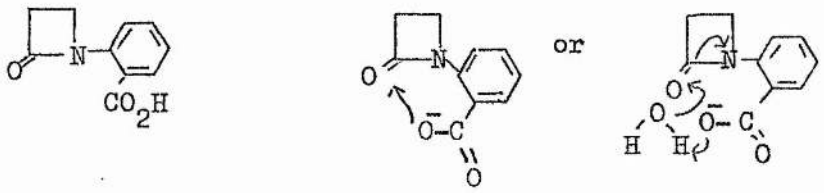
premise has some foundation as compounds of type (15) subsequently prepared exhibited greater integrated intensities of lactam carbonyl absorption in the infra-red region indicative of an increase in strain of the ring.

Azetidin-2-ones having only a phenyl or a para-nitrophenyl group on the nitrogen atom of the ring were prepared in order to determine the effect of decreasing the number of substituents on the rate of ring-opening and also to discover if the incorporation of an electron-withdrawing group in the phenyl moiety would affect the rate of ring-opening by its influence upon the amide resonance (structures 17b and c preferred to 17a).



(17a) (17b) (17c)

It was hoped to extend these findings to the 1,4-diphenylazetidin-2-ones (14) or the 1-phenyl-1-azaspiro[5.3]nonan-2-ones (15). Attempts also were made to prepare a β-lactam (18) with an o-carboxyphenyl group on the nitrogen atom in order to see if there would be any anchimeric assistance in the hydrolytic reaction brought about by intramolecular attack upon the carbonyl group of the lactam by the carboxyl group (19).



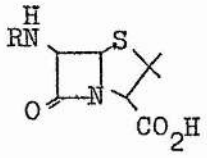
(18) (19)

3. Previous Kinetic Studies

Kinetic studies on the hydrolytic stability of the β-lactam ring may be divided into two types; studies of the enzyme-induced fission of the lactam ring and those of ring-fission in acidic or basic solution.

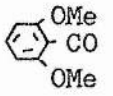
A. Structural Effects in the Enzymic Hydrolysis of Penicillins and Cephalosporins.

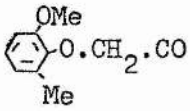
The effects of structure on the fission of the β-lactam ring by various lactamases has been investigated.[24,25] Structural changes have been shown to be qualitatively similar in their effect with the different enzymes. It has been shown[27] that in penicillins with large side chains the resistance to enzymic fission is a function of the size of the side chain, the presence of bulky substituents resulting in increased stability, although the effect is reduced[26] as the substituents are further removed from the ring. For example 2,6-dimethoxybenzoyl penicillin (2f) is more resistant to attack than is 2,6-dimethoxyphenoxyacetylpenicillin (2g).



(2)

R= (c) $Ph.CH(NH_2)CO$

(f) 

(g) 

(h) $Ph.S.CH_2CO$

(a) $Ph.O.CH_2.CO$

(j) $Ph.NH.CO$

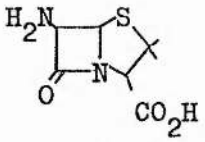
(k) $Ph.CH_2.CO$

This is largely due to a decrease in the binding of the substrate to the enzyme brought about by steric crowding. This decrease in affinity may also be produced by the incorporation of polar substituents in the side chain such

as the amino group in ampicillin (2c) and by the incorporation of a hetero-atom in the side chain, for example, phenylmercaptoacetylpenicillin (2h) is more resistant than phenoxyacetylpenicillin (2a) and similarly anilinopenicillin (2j) is attacked less readily than benzylpenicillin (2k).

B. Non-enzymatic β-Lactam Hydrolysis

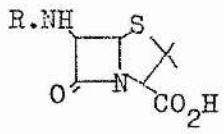
The hydrolytic fission of the lactam ring in 6-aminopenicillanic acid (2b) has been the subject of a



(2b)

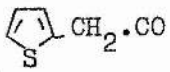
comprehensive study[27] dealing with the reaction in both acid and base. This work has shown that the reaction is subject to both specific and general base catalysis and that at the extremes of the pH range covered (pH 2.0 and 9.1) a positive primary salt effect is shown whilst at pH 3.3 there is no discernible salt effect. This may indicate that, at this pH, the reaction is proceeding by two independent reactions; the attack of an acid molecule on the cationic form of the substrate, and the reaction of a hydronium ion with the zwitterionic form of the substrate.

The substituent effect on the rate of basic hydrolysis of a series of penicillins (2) and cephalosporins (3) has been investigated[28] and it has been shown that acylation



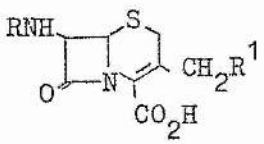
R=Ph.O.CH_2CO

Ph.CH_2CO



Ph.CH(NH_2).CO

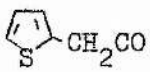
(2)



R=(a) H,

R=Ph.O.CH_2.CO

Ph.CH_2.CO

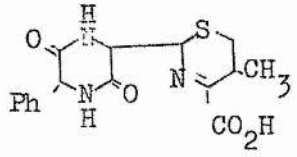


Ph.CH(NH_2)CO

NH_3^+.CH(CO_2^-)(CH_2)$_3$CO

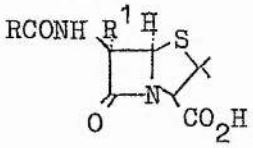
(3)

of 6-aminopenicillanic acid (2b) or 7-ACA (3a) produces an increase in the rate of ring opening but with little difference observed between the various acylated compounds. Correlations were found to exist for the rate of hydrolysis with both the infra-red frequency of the absorption of the lactam carbonyl and the lactam carbonyl change density as calculated by CNDO/2 methods. Evidence was produced for intra-molecular attack in cephalosporins having an α-amino group in the side-chain, reaction proceeding via a piperazine-2,5-dione (20). No evidence for this reaction route was found in the case



(20)

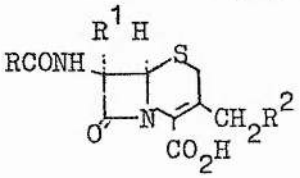
of ampicillin (2b) and this was accounted for on the basis of steric hindrance by the nearest proton on the gem-dimethyl group in penicillins. The effect of 6α-substitution of penicillins and 7α-substitution of cephalosporins was also investigated[29] and was found to be related to enzymic stability. The presence of a 6α-methyl, methoxy, or S-methyl group in the penicillin molecule (21) reduced the reactivity whereas a 7α-



$R^1 = CH_3, OCH_3, SCH_3$

(21)

methyl, methoxy, or S-methyl substituent in the cephalosporin molecule (22) produced little effect.

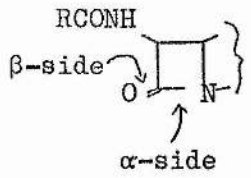


$R^1 = CH_3, CH_3O, CH_3S$

(22)

These results were accounted for by steric affects, since attack on the lactam ring in penicillins is hindered

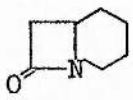
on one side of the molecule, the β-side (23) by the



(23)

amide group and the thiazolidine ring and the introduction of a 6α group results in hindrance to attack on both sides of the molecule and thus results in a lowering in the rate of reaction. The rate of ring opening of the bicyclic β-lactams (24 and 25) has been studied[30] and it has

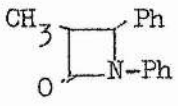
(24)



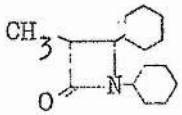
(25)

been shown that while (24) reacts in acid at a rate comparable with that of penicillins, (27) reacts at a rate two orders of magnitude smaller and is comparable[31] in reactivity to azetidin-2-one (1). The bicyclic lactams are found to react more readily in acidic than in basic solution which is in contrast to the behaviour of monocyclic β-lactams.[30]

Quantitative studies on reactivity have shown[32] that the reactivity of β-lactams is reduced by increasing the number of substituents on the ring and that the effect is proportional to the size of the substituents, and that β-lactams with aromatic substituents e.g. (26) react more rapidly than the alicyclic analogues e.g. (27).

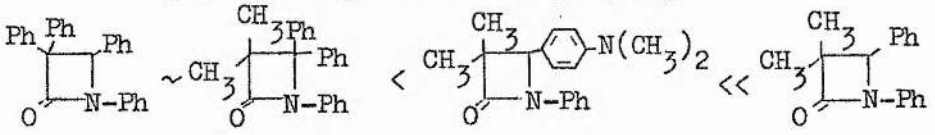


(26)

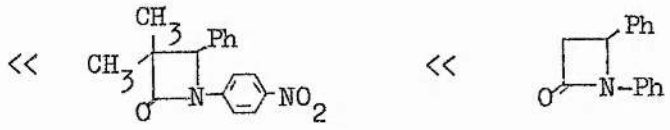


(27)

Studies of hydrolysis in aqueous alkali have confirmed[33] this substituent effect and have shown that the reaction rate is decreased by the presence of an electron donating group at position 4 e.g. (28c) and increased by an electron withdrawing group in position 1 e.g. (28e).

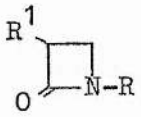


(28a) (28b) (28c) (28d)



(28e) (14f)

The effects of various substituents at positions 1 and 3 have been investigated.[34] In the series of type (29) the effects of the substituents were found[34] to obey the Taft



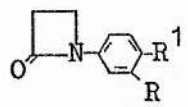
(29)

R=CH_2Ph, CH_3, CH_2CH_3

R^1=CH_3, H, Ph

equation where for example a 3-phenyl group enhanced and a 3-methyl group reduced reactivity and, in the 1 position, the order of reactivity was found to be benzyl > methyl > ethyl.

The effects of substitution at position 1 have also been correlated[35] with the Hammett σ^- constant in the series of type (30) with reactivity enhanced by electron-



(30)

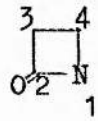
R=H, H, CH_3, H, H, Br, CF_3, NO_2, H.
R^1=OCH_3, CH_3, H, H, Br, H, H, H, NO_2.

withdrawing substituents and diminished by electron donating substituents.

4. Synthetic Routes Leading to the β-Lactam Ring

Since the first synthesis of β-lactams by Staudinger,[1] many reactions have been described which lead to the formation of this ring system and the subject has been comprehensively reviewed.[36]

Most synthetic routes to β-lactams can be classified conveniently on the basis of the bonds which are formed during the reaction. Among the possibilities are:



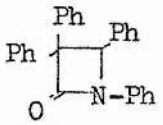
the simultaneous formation of bonds N-C2 and C3-C4 (route A); or of bonds C2-C3 and N-C4 (route B); cyclisation by the formation of bonds N-C2 (route C); C2-C3; C3-C4 (route D); or N-C4 (route E). All of these routes have been realised with the exception of that resulting in the formation of bond C2-C3. β-Lactams have been prepared also by ring expansion (route F) or ring contraction (route G) reactions

and by other methods (route H). The various synthetic routes are summarised below.

Route A: Simultaneous formation of bonds N-C2 and C3-C4

(a) The Addition of Ketenes to a Carbon Nitrogen Double Bond

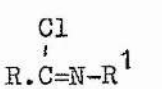
This reaction was used by Staudinger[1] who reacted diphenylketene with benzylideneaniline to give 2,3,3,4-tetraphenylazetidin -2-one (28a) and this reaction has subsequently been applied to the preparation of both monocyclic and bicyclic β-lactams.

$Ph_2.C=C=O + Ph-N=CH.Ph \longrightarrow$ 

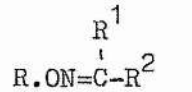
(28a)

Many ketenes have been employed in this reaction, including alkyl ketenes,[37,38] aryl ketenes,[1] acyl ketenes,[39] aryloxy ketenes,[38] and ketene[40] itself. Large differences in reactivity have been found[39] with different ketenes. Aryl ketenes are more reactive than alkyl ketenes, ketene itself often requires forcing conditions to bring about reaction, and diacyl ketenes are even less reactive.

Although the order of reactivity of the ketenes has been determined the requirements for the imine have not been investigated to any great extent. Imidoyl chlorides (31) and O-alkyloximes (32) do not react[1] to give β-lactams.

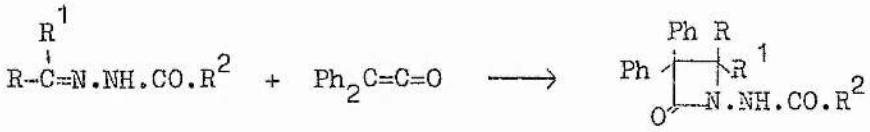


(31)

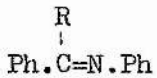


(32)

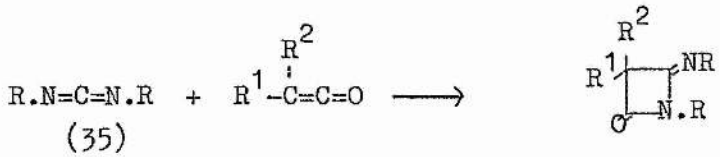
However acylhydrazones[41] (33) react readily, as do the imines (34, R=H,[1] CH_3,[42] SCH_3,[43]) and some carbodi-imides[44] (35). The last react to form imino-β-lactams (36).



(33)



(34)

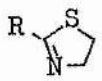


(35)

R=cyclohexyl, $(CH_3)_2CH$

(36)

In the preparation of bicyclic β-lactams it has been found that ketenes such as diphenylketene react rapidly with thiazolines[45,46] of the type (37a,b,c) although with compound (37d) the product obtained from the reaction has



(37)

R=(a) Ph

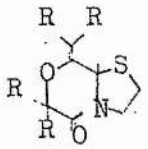
(b) NH_2 or $NHCOR^1$

(c) SH or $SCOR^1$

(d) CH_3

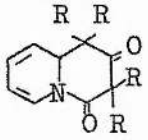
been assigned the structure (38)[47] or (39)[48] (into which compounds of type (38) are reported[49] to be converted in the presence of a base). Similar products have been

(38)



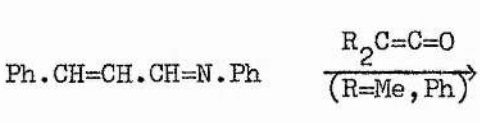
(39)

obtained with compounds in which the C=N bond is contained within a hetero-aromatic system, for example pyridine,[49] quinoline,[50] and phenanthridine[50] all give products of the type (40).

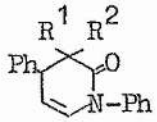


(40)

It is of interest that cinnamylideneaniline (41) reacts[45] with dimethyl ketene or diphenyl ketene to produce a β-lactam (42), but with ketene,[46] phenyl ketene[46] or dichloroketene[51] a δ-lactam (43) is formed.

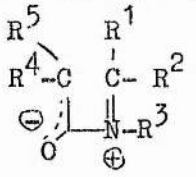


(41) (42)



(43)

The mechanism of the ketene/imine reaction has been investigated and evidence for an open-chain intermediate of the type (44) has been reported.[52]

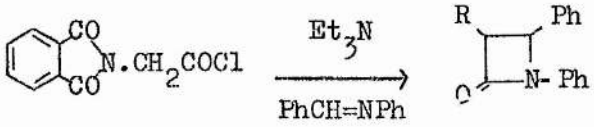


(44)

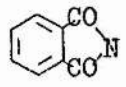
(b) The Reaction of Imines with Acid Chlorides

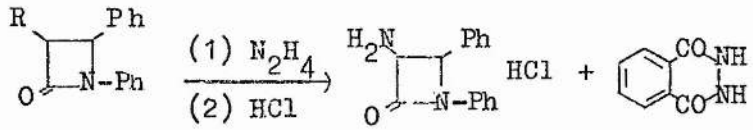
As suitable acid chlorides are known[53] to give ketenes on treatment with a tertiary amine, this reaction might be considered to be an extension of the ketene/imine reaction although it appears to be of much wider application.

The first synthesis by this route was described by Sheehan[54] who used phthalimidoacetyl chloride (45) to produce β-lactams. Removal of the phthaloyl group by



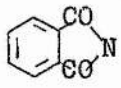
(45) (46) (a)R=





(46 a) (47)

R=

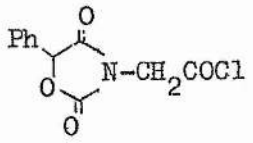


hydrazinolysis yielded the corresponding amino-lactam (47) which could then be acylated to give β-lactams with

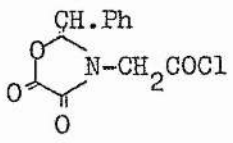
an amido function in the alpha position to the lactam carbonyl, similar to those present in the penicillins.

Many substituted acetyl chlorides have been employed in this reaction. These include dichloroacetyl chloride,[55] methoxyacetyl chloride,[56] and phenoxyacetyl chloride,[56] in addition to those which could subsequently be converted to an amido function, for example phthalomidoacetyl chloride.[54,57,58] (45) maleimidoacetyl chloride[58] (48a) succinimidoacetyl chloride[58] (48b), various cyanoacetyl chlorides,[59,60] (48c), azidoacetyl chlorides[56,61,62] (48d) and malonyl chlorides[65] (48e). Acid chlorides such as

2,4-dioxo-5-phenyl-1,3-oxazolidinoacetyl chloride[64] (49) and 2-benzylidene-4,5-dioxo-1,3-oxazolidinoacetyl chloride[65] (50) have also been successfully employed in this reaction.



(49)



(50)

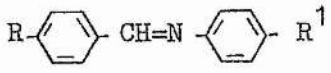
The latter two compounds gave β-lactams with a side chain that may be converted directly to a phenylacetamido group,

and their use had been occasioned because the production of acylaminoacetyl chlorides such as phenylacetamidoacetyl chloride commonly results in the formation of compounds such as (51).

$$Ph.CH_2.CO.NH.CH_2COCl \longrightarrow PhCH_2\text{-}(NH)\text{-}(CO)\text{-}O$$

(51)

As with the ketene/imine reaction the structural requirements of the imine have not been established although a large number of imines have been employed successfully in this reaction. A comprehensive series of benzylideneanilines,[66,67] substituted on either or both phenyl groups (52) or on the methine carbon, e.g. (53)

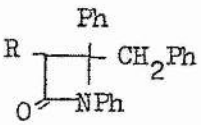


(52)

R	R^1
OCH_3	$COCH_3$
CO_2H	OCH_3
OCH_3	CO_2CH_3
OCH_3	H
H	H

react to give the expected products. Imines such as (54)[56] and (55)[68] may also be used.

$$Ph.C(CH_2Ph)=N.Ph \xrightarrow{R^1CH_2COCl}$$



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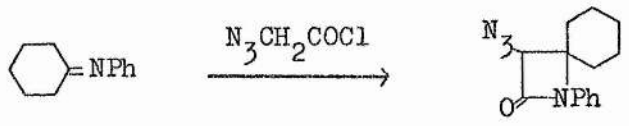
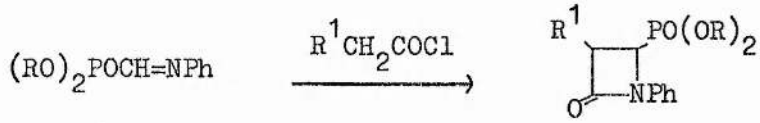
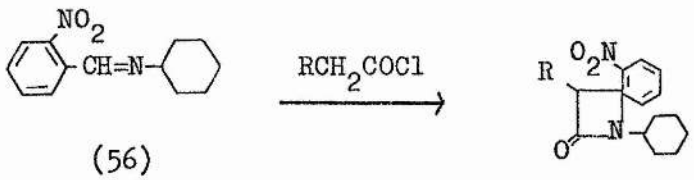


(54)

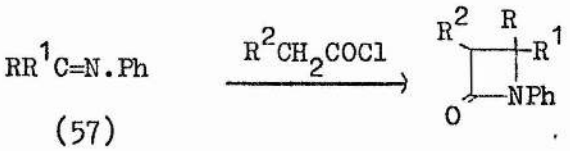


(55)

Imines with N-alkyl substituents,[10] such as (56), also react to give β-lactams as do imidates (57) and thoimidates.[69] Amidines[69,70] react with some acid chlorides yielding unstable 4-amino-β-lactams (58).

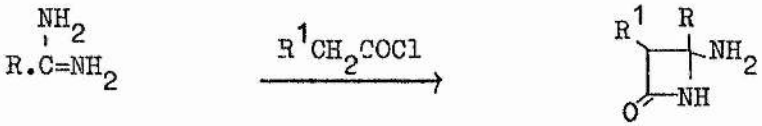


(56)



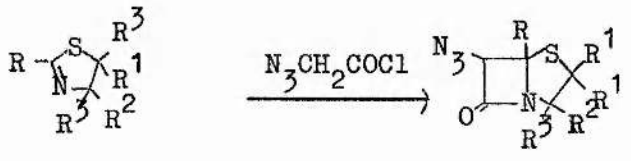
(57)

R	R^1
Ph	OCH_3
Ph	OC_2H_5
Ph	OC_3H_7
H	OC_2H_5
Ph	SCH_3
Ph	SC_2H_5



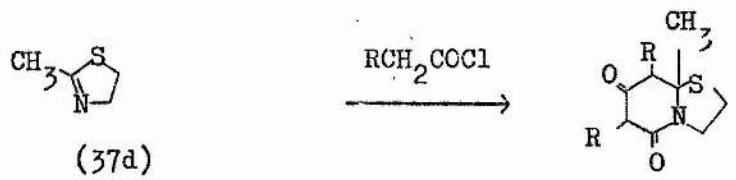
(58)

Amongst cyclic imines some thiazolines (59) have been found to react readily[64,65,71-73] although 2-methyl thiazoline[74,75] (37d) gives a product resulting from the addition of two molecules of acid chloride, which is similar to its reaction with ketenes. Similar products have been reported[76] in the reaction of phthalimidoacetyl



(59)

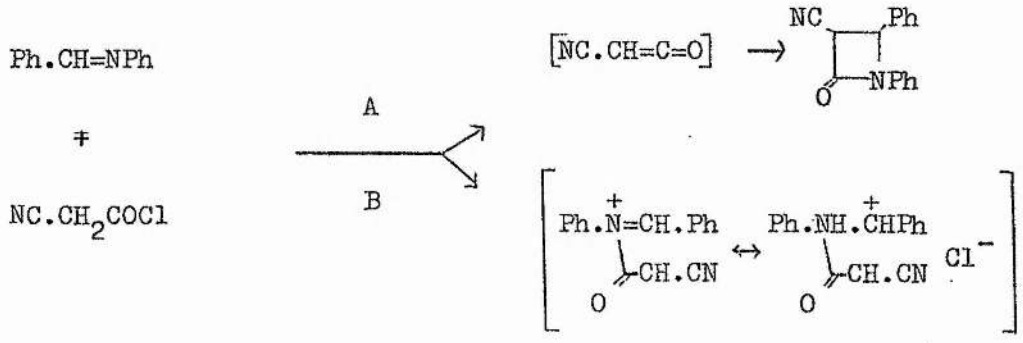
R	R^1	R^2	R^3
H	H	C_2H_5	C_2H_5
CO_2CH_3	CH_3	H	H
H	CH_3	CO_2CH_3	H
Ph	H	H	H
Ph	CH_3	CO_2CH_3	H
$pNO_2C_6H_4$	H	H	H



(37d)

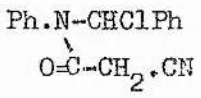
chloride with imines.

Although the reaction of an acid chloride with an imine may appear similar to that of a ketene with an imine, differences appear when the stereochemistry of the reactions are considered. The reaction of a ketene with an imine affords only one isomer[77] of the β-lactam, whereas the use of an acid chloride can lead to the production of both cis and trans isomers. In addition the isomer ratio may be altered to some extent by a change in the order of addition of reactants. This led to the proposal[36] that the reaction may proceed by two routes: either by initial formation of a ketene when the acid chloride is added to a solution of imine and base (route A), or the addition of base to a mixture of acid chloride and imine leads to the formation of an intermediate[59] such as (60) (route B) which is subsequently dehydrohalogenated to the β-lactam. However N.M.R. studies have indicated[77]



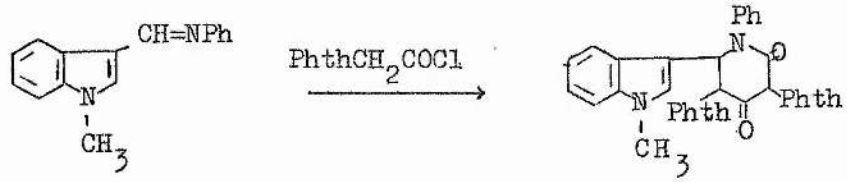
(60)

that the formation of a covalent intermediate of type (61) is more probable in this reaction. The reaction of phthalimidoacetyl chloride with certain imines has been

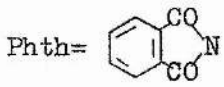


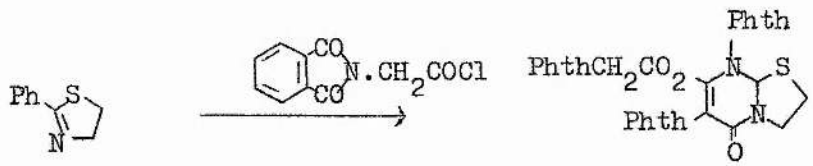
(61)

cited[76] as evidence in support of the ketene mechanism. For example when this acid chloride reacts with N-methyl-skatylideneaniline[78] (62) or 2-phenylthiazoline[76] the dioxopiperidines (63,64) are obtained, suggesting the addition of two molecules of ketene to the imines.



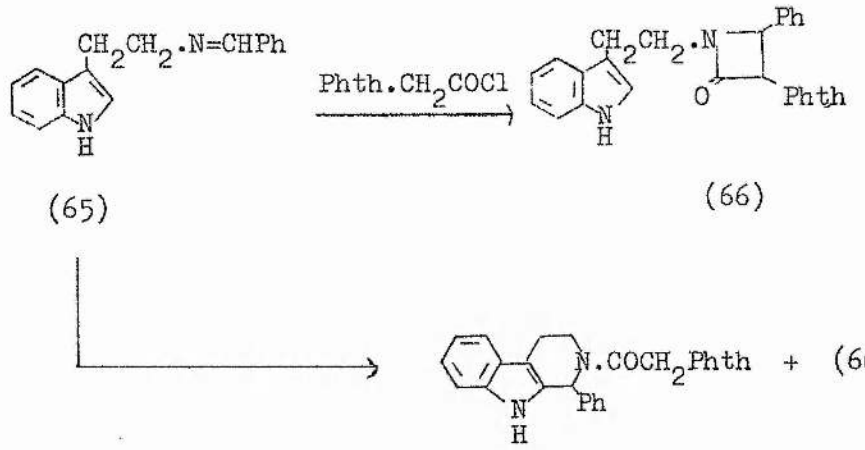
(62) (63)





(64)

The product obtained from the reaction of benzylidenetryptamine (65) with phthalimidoacetyl chloride depends on the order of addition.[79] When the acid chloride was added to the imine and base the β-lactam (66) was obtained whereas addition of the base to a solution of the acid chloride and imine gave (67) and a small quantity of the β-lactam.



(65) (66)

(67)

A recent investigation[80] of the acid chloride/imine reaction has suggested that additional factors are involved in determining the stereochemistry of the reaction. In a series of reactions of various acid chlorides with benzylidenaniline, cyclohexylideneaniline, and ethyl N-phenyl-formimidate it was found that the acid chlorides could be divided into two classes: those containing an atom with a lone pair of electrons on the carbon atom alpha to the carbonyl group, for example those of the type (48d-j) which reacted with all of the imines; and those acid chlorides with an alkyl or aryl group in this position (48k,l) which reacted only with benzylideneaniline. It was also found[80] that the addition of these acid chlorides

$R.CH_2.CO.Cl$

(48)

R=(d) N_3 (h) Cl

(e) Phthalimido (j) $PhCH_2S$

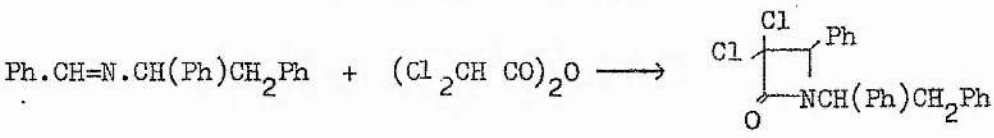
(f) PhO (k) Ph

(g) MeO (l) Me

to a mixture of imine and base resulted in a higher cis/trans ratio than did the addition of base to a mixture of acid chloride and imine.

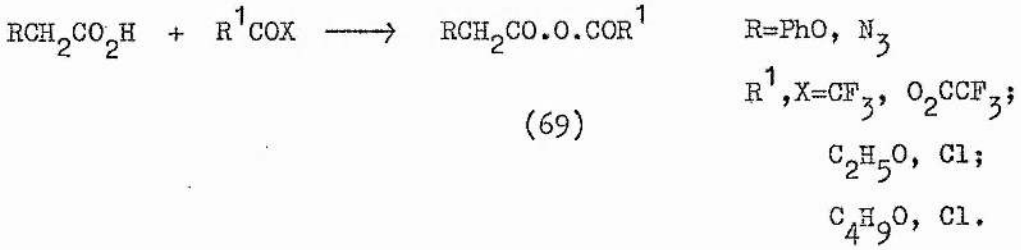
(c) Reaction of Imines with Acid Anhydrides

It has been found[81,82] that imines react with dichloracetic anhydride to give 3,3-dichloro-β-lactams such as (68). The mixed anhydrides (69) formed by treatment



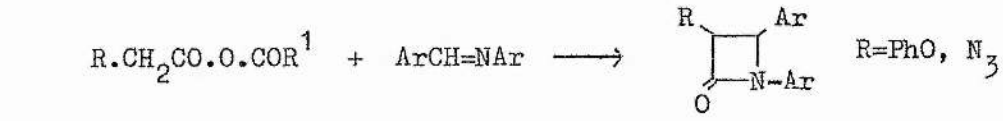
(68)

of phenoxyacetic acid or azidoacetic acid with trifluoroacetic anhydride, ethyl chloroformate, or butyl chloroformate also react with imines in the presence of a



(69)

base to give β-lactam of the type (70). The yields and stereochemistry of this preparative route are similar to those obtained from the acid chloride reaction.

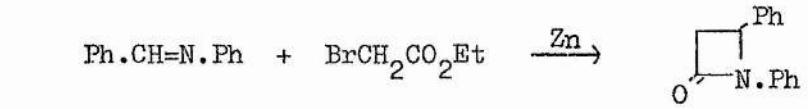


(70)

(d) Reaction of Imines with Bromoacetic Esters

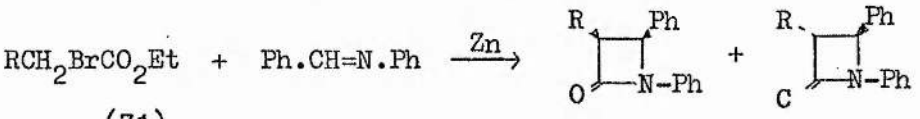
Ethyl bromoacetate reacts with benzylideneaniline under

Reformatsky conditions to give 1,4-diphenylazetidin-2-one[83] (14). This reaction has been investigated[84-86] using alkyl



(14)

and aryl substituted bromoacetic esters and imines other than benzylideneaniline. It has been found[87] that an increase in the size of the ester substituent (71) lowered the cis/trans ratio of the products. This ratio was also found[84,88] to be dependent on solvent polarity with an



(71)

R	% cis lactam
Me	73
Et	64
Pr^i	55
Bu^t	25
Ph	<5

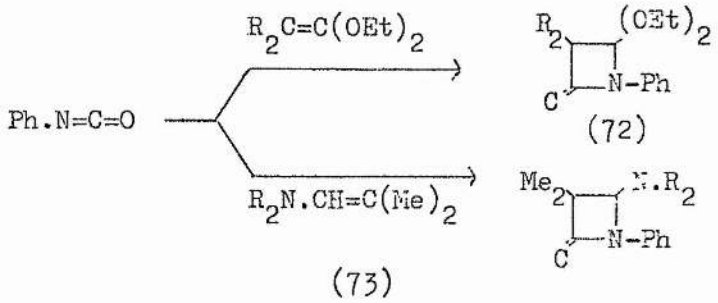
increase in the polarity of the solvent leading to an increase in the proportion of the cis-β-lactam.

Route B: Stimultaneous Formation of Bonds C2-C3 and N-C4

(a) The Addition of Isocyanates to Olefins

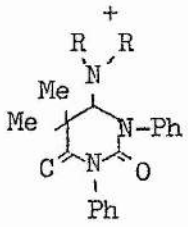
Phenyl isocyanate reacts with ketene acetals to produce β-lactams of the type (72),[89] and also with enamines of the type (73)[92,93] (to give unstable 4-amino-β-lactams).

However in this latter aminohydrouracils (74) may be formed[92]



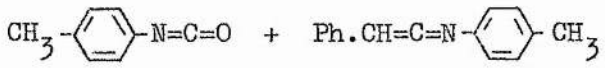
(72)

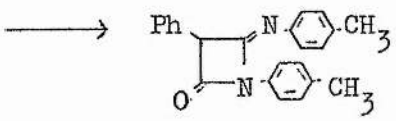
(73)



(74)

by the addition of two molecules of the isocyanate to the enamine. Methyl isocyanate and some substituted phenyl isocyanates react with keteneimines to produce 4-imino-β-lactams[93] (75).

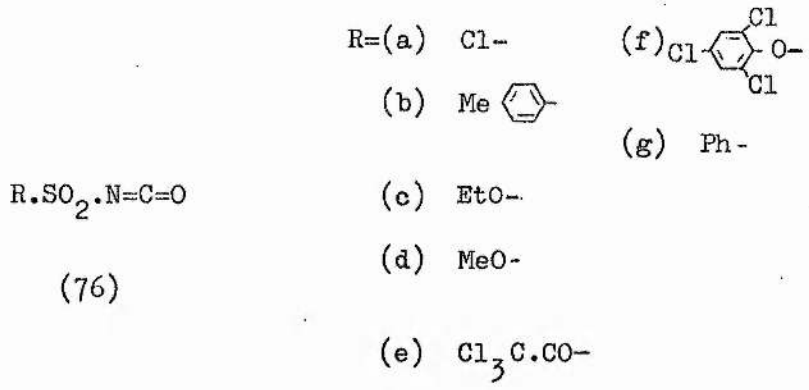




(75)

Whilst aryl isocyanates will react only with activated olefins, the use of sulphonyl isocyanates (76) permits the synthesis of β-lactams from a far greater range of olefins and the use of chlorosulphonyl isocyanate (76a) presents a route to N-unsubstituted

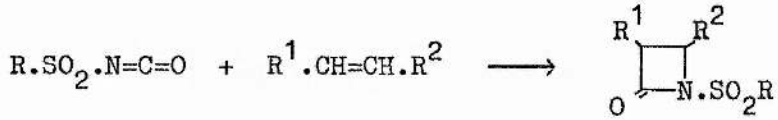
compounds since the N-chlorosulphonyl group is readily



removed[94] by treatment with thiophenol and pyridine.

Chlorosulphonyl isocyanate when treated with alkyl substituted olefins,[94] conjugated dienes,[95] or bisazomethines[95] reacts readily to produce β-lactams in good yield.[96,97]

A variety of sulphonyl isocyanates (76a-f) have been reacted with a series of olefins (77) to give both monocyclic and bicyclic β-lactams.[98]



(77)

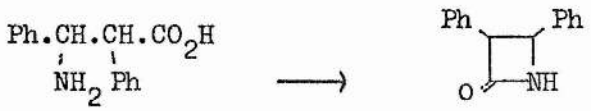
R^1,R^2=MeO, MeO; OCH_2O; $OC(CH_3)_2O$; $OCH(CH_3)O$; $O(CH_2)_2O$; $O(CH_2)_2S$; $PhCH_2S$, $PhCH_2S$.

or $R^1=C_2H_5O$, R^2=PhS.

Route C: Formation of the N-C2 Bond

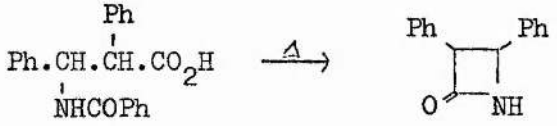
(a) Cyclization of β-aminoacid Derivatives

β-Aminoacids such as (78) have been cyclized to β-lactams with such reagents as acetic anhydride,[99] acetyl chloride,[100] phosphorus trichloride,[100] and thionyl



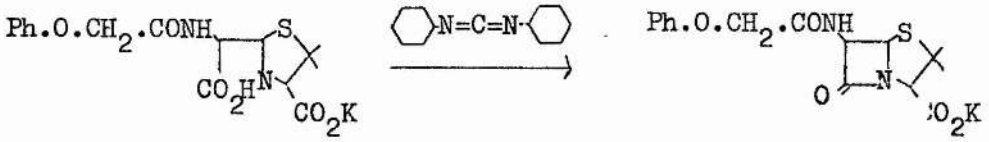
(78)

chloride.[100] Although a dehydrating agent is required for the cyclization of β-aminoacids, N-acyl-β-aminoacids e.g. (79) cyclise[101] readily on heating. Use has been



(79)

made of carbodiimides[102,103] and isonitriles[104] in the preparation of the bicyclic β-lactams (80) and (81) but these reagents have not been used in the preparation of monocyclic compounds.

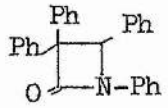


(80)

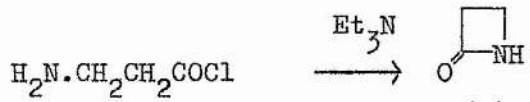
(81)

β-Aminoacid chlorides have been cyclised using tertiary

amines or ammonia.[105,106] The yield in this reaction is dependent[107] upon the degree of substitution of the acid chloride and whilst β-lactams such as (28a) can be prepared in high yield, when the method was applied to the preparation of azetidin-2-one (1) from β-aminopropionyl chloride it resulted in the formation of the β-lactam in a yield of only 4%.[105]

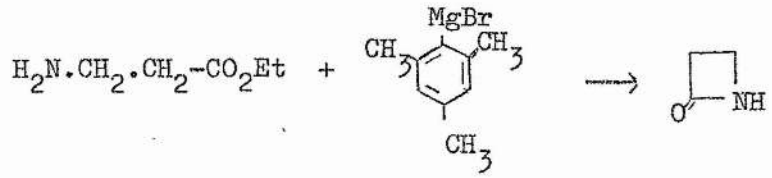


(28a)



(1)

β-Lactams are also produced from the reaction of β-aminoacid esters with Grignard reagents.[108] Investigations[109,110,111] of this reaction have shown that the yield may be improved by the use of an excess of the Grignard reagent, and also by employing a hindered Grignard reagent such as mesitylene magnesium bromide (82) which has much less tendency to add across the carbonyl bond resulting in reduction. Tri-isobutylaluminium[112] has been employed in



(82)

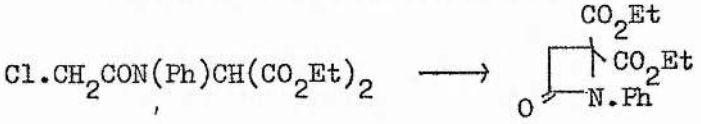
the cyclization of the ester (83).

(83)

Route D: Formation of the C3-C4 Bond

(a) Cyclization of α-Haloamides

This route to the production of β-lactams, which was developed in 1950, has been shown to proceed readily to give the required β-lactams in high yield.[113,114] The presence of a base is essential for the reaction to proceed. The amide (84) cyclises readily to (85) when heated in dimethylformamide although there is no reaction when the compound is refluxed in toluene or in the presence of a

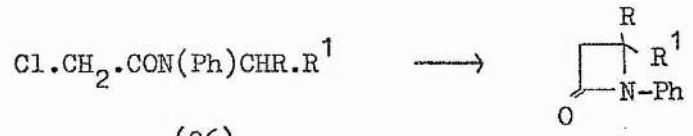


(84) (85)

non-basic hydrogen chloride acceptor such as α-pinene.[115] A variety of bases have been employed in this reaction including diethylamine,[114] triethylamine,[113,114] benzylamine,[114] alcoholic ammonia,[114] alcoholic potassium hydroxide,[114,116] and ion-exchange resins.[117]

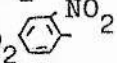
The haloamides originally employed in the synthetic route were N-aryl-N-chloroacetylmalonate esters such as (84), since it was found[114] that the corresponding iodoamides underwent quaternization rather than cyclization

under the reaction conditions used. A study[118] of the reaction has shown that activating groups other than ester groups also may be used, for example all the amides (86a-e) can be cyclised, although (86d) may produce[119] a dihydro-1,4-oxazine (87) or a mixture of products depending on the nature of the aryl substituent.

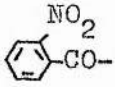


(86)

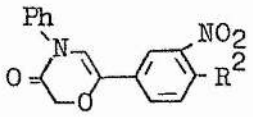
(a) R=Ph, $R^1=CO_2Et$

(b) R=H, $R^1=NO_2$ 

(c) R=H, $R^1=COPh$

(d) R=H, $R^1=$ Alkyl 

(e) R=H, $R^1=F$



(87)

(b) Carbene Insertion Reactions

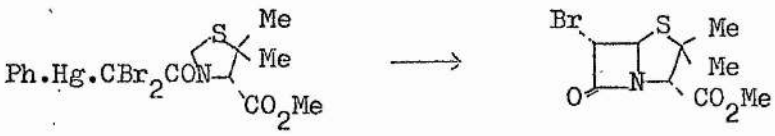
The bicyclic β-lactams (89a and b) have been prepared,[120] by a carbene insertion reaction, from (88) by refluxing in bromobenzene.

X=Cl, Br

(88)

(a) (b)

(89)

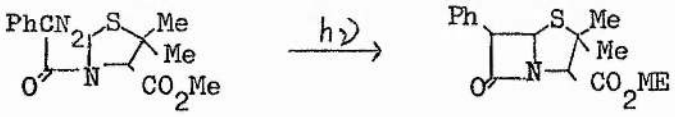


(90)

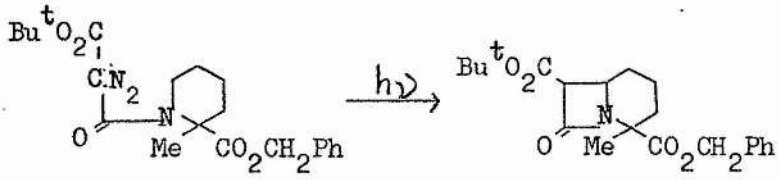
The synthesis has been extended[121] to the production of the 6-bromo-penicillin (90).

(c) Photochemical Reactions

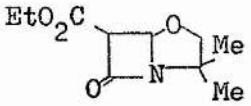
The photochemical ring closure of α-diazoamides has been used[122] in the synthesis of penicillin analogues such as (91), and the method has been extended[30,123-125] to the preparation of bicyclic β-lactams such as (92-94).



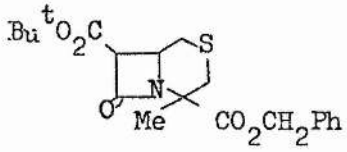
(91)



(92)

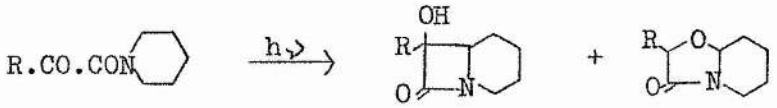


(93)

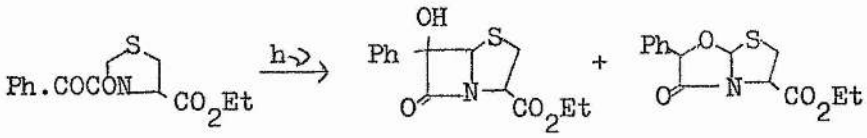


(94)

The irradiation of α-ketoamides such as (95) and (98) gave[126] the β-lactams (96) and (99) together with the compounds (97) and (100), which were the major products. This was the first synthesis of 3-lactams with a hydroxyl group in the alpha position to the lactam carbonyl group.

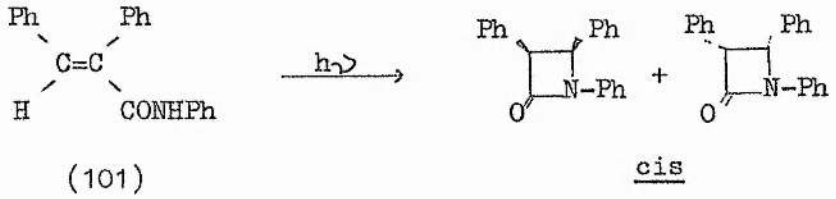


(95) (96) (97)

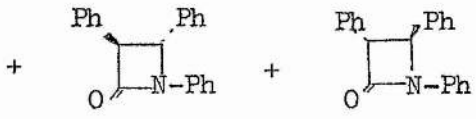


(98) (99) (100)

β-Lactams have also been produced by the photoisomerization of suitable cis-α-phenylcinnamic amides[127] such as (101), this reaction produces both the cis and trans isomer with the cis isomer predominating.



(101) cis



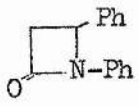
trans

Route E: Formation of the N-C4 Bond

In the presence of a strong base, such as sodamide,

β-halopropionamides such as (102) cyclise[128,129] to β-lactams in high yield. It has been found[130] that reaction is facilitated by the use of organic solvents rather than liquid ammonia as the reaction media and by the use of sodium hydride in dimethyl sulphoxide (Dimsyl-sodium) as the cyclising agent.[131,132]

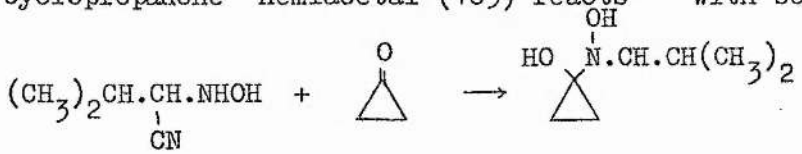
$$BrCH(Ph)CH_2CONHPh \xrightarrow{Na^+(CH_2\text{-}SOCH_3)^-}$$



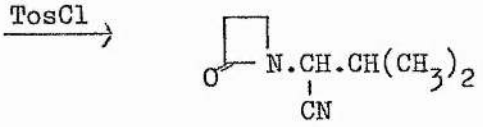
(102)

Route F: Ring Expansion Reactions Leading to β-Lactams

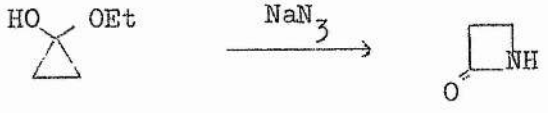
Cyclopropanones, aziridines, and α-lactams can undergo ring expansion reactions to give β-lactams. Cyclopropanone reacts[133] with N-substituted hydroxylamines such as (103) to form compounds of the type (104) which on treatment with toluenesulphonyl chloride rearrange to β-lactams. Cyclopropanone hemiacetal (105) reacts[134] with sodium azide



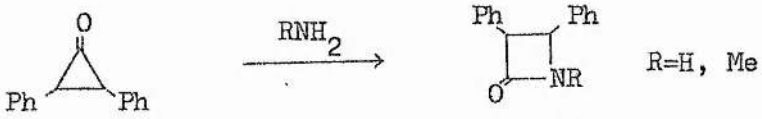
(103) (104)



under very mild conditions to produce azetidin -2-one (1) in fair yield. Diphenylcyclopropanone has been shown[135] to react with ammonia or methylamine to produce the β-lactam (106).

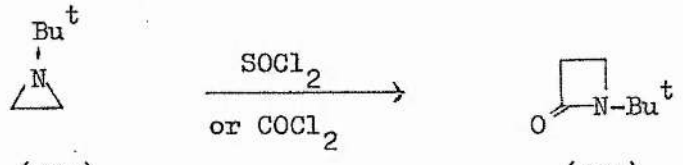


(105) (1)



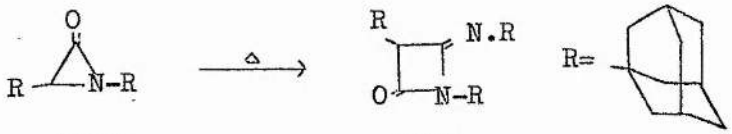
(106)

Treatment of the aziridine (107) with thionyl chloride or oxalyl chloride gave the β-lactam (108)[104] and during a study of the pyrolysis of 1,3-di(1-adamantyl)-



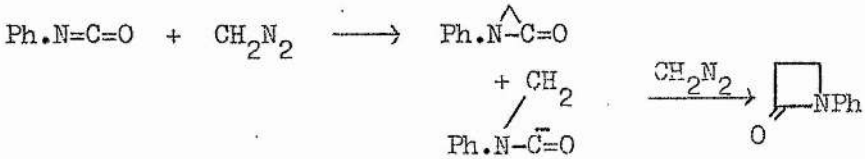
(107) (108)

aziridinone (109) it was found[137] that ring expansion had occurred affording the β-lactam (110).



(109) (110)

The reaction of phenyl isocyanate with diazomethane has been reported[138] to produce azetidin-2-one and it was proposed that the reaction proceeded via an α-lactam (111) or a zwitterionic intermediate. However attempted ring

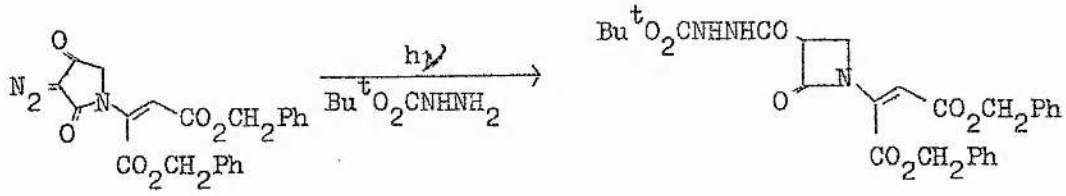


(111)

expansion reactions of α-lactams with diazomethane or dimethylsulphoxonium methylide have been unsuccessful.[139]

Route G: Ring Contraction Reactions Leading to β-Lactams

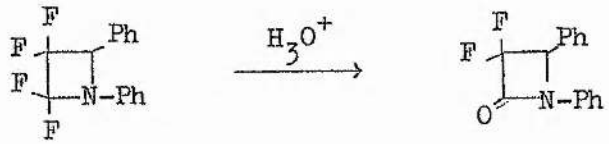
A recently developed[140] synthesis of β-lactams involves a photolytic Wolff rearrangement of a tetramic acid derivative such as (112).[141]



(112)

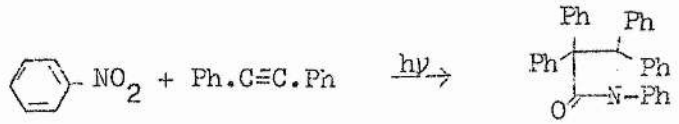
Route H: Miscellaneous Reactions Leading to β-Lactams

There are some reactions which either produce β-lactams or proceed via β-lactam intermediates, and these methods do not readily fit into the routes described above. For example the azetidine obtained from perfluoro-isobutene and benzylideneaniline can be hydrolysed in acid to the β-lactam (113).[142] Irradiation[145] of a mixture of



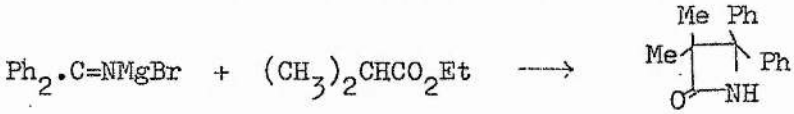
(113)

nitrobenzene and diphenylacetylene gave 1,3,3,4,4-pentaphenyl-azetidin-2-one (114) as one of the products. The β-lactam (117) was obtained[144] as a minor product from the reaction

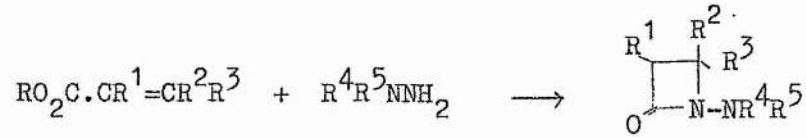


(114)

of the Grignard reagent (115) with the ester (116), and it has been found that acrylic esters will react with substituted hydrazines to produce N-amino-β-lactams (118).

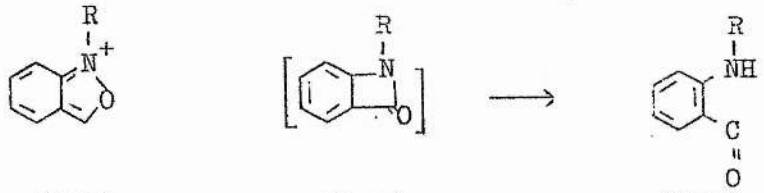


(115) (116) (117)



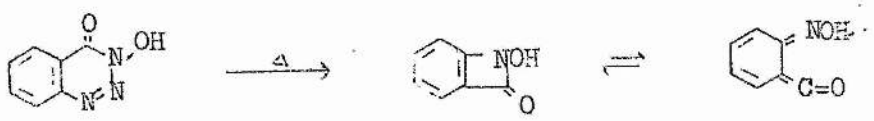
(118)

The formation of compounds of the type (121) by treatment of anthranilium salts (119) with a nucleophile is believed[146] to proceed via the β-lactam (120). Evidence has been presented[147] for the formation of the benzazetidinone



(119) (120) (121)

(120) (or the corresponding valence tautomer (122)) as an intermediate in the thermolysis of 3-hydroxy-1,2,3-benzotriazin-4-one (123).

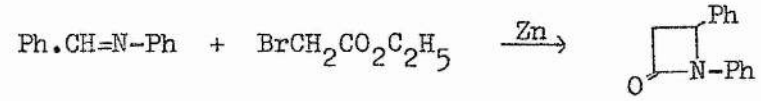


(123) (120) (122)

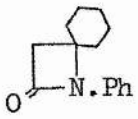
CHAPTER II

1. Routes Used for the Synthesis of β-Lactams for use in Hydrolytic Studies

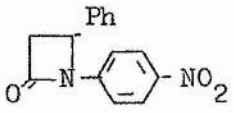
1,4-Diphenylazetidin-2-one (14) was prepared by a Reformatsky reaction of benzylideneaniline with ethyl bromoacetate by the method described.[8] A similar route



(14)

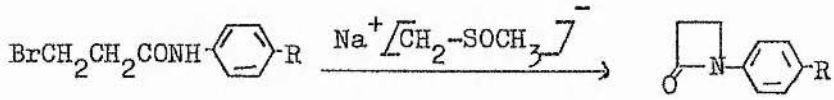


(15a)



(124)

was used in the attempted syntheses of 1-phenyl-1-azaspirononan-2-one (15a) and 1-(p-nitrophenyl)-4-phenyl-azetidin-2-one (124). N-phenylazetidin-2-one (30d) and N-(p-nitrophenyl)-azetidin-2-one (30j) were prepared from the corresponding 3-bromopropionamides by cyclization with Dimsyl sodium[132] and this method was also used in the

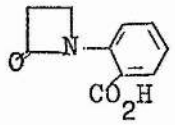


(30)

(d) R= H

(j) R=NO_2

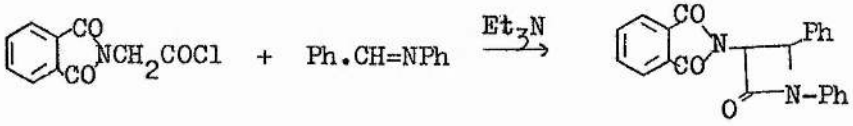
attempted synthesis of N(o-benzyloxycarbonylphenyl)-azetidin-2-one (18a) from which it was hoped to be able to prepare the free acid (18).



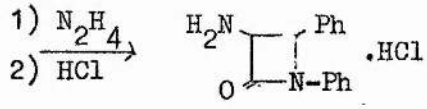
(a) = benzyl ester

(18)

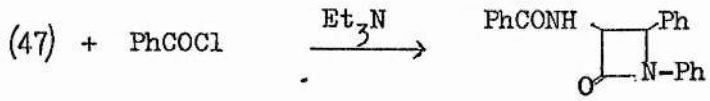
For the synthesis of the 3-substituted-1,4-diphenyl-β-lactams (46) the method of Sheehan[57] was employed with some modifications, conditions for the subsequent conversion of (46) to (47) and (47) to (47a) having been previously described.[57]



(46)

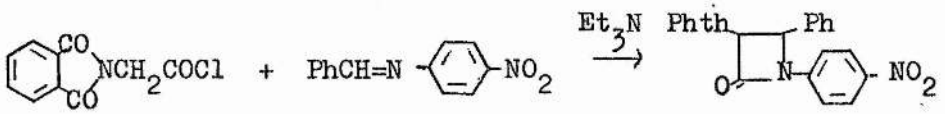


(47)

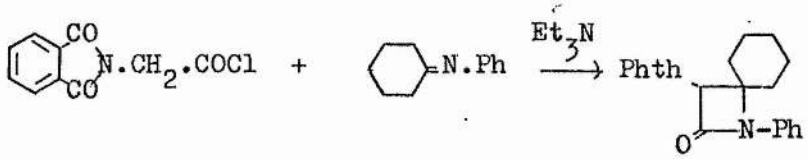


(47a)

This method was also used for the preparation of 1-(p-nitrophenyl)-4-phenyl-3-phthalimidoazetidin-2-one (46a).

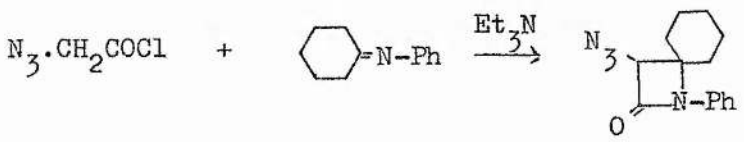


(46a)

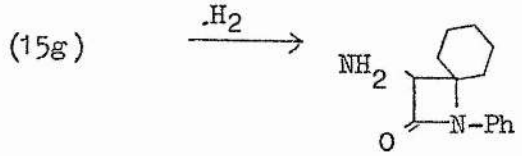


(15b)

The preparation of 1-phenyl-3-phthalimido-1-azaspiro [5.3]nonan-2-one (15b) (an intermediate to the amino-β-lactam (15a)) from phthalimidoacetyl chloride and cyclohexylideneaniline has been reported[80] but in our hands this method gave the β-lactam (15b) in an impure state and in low yield. Whilst this reaction was being further investigated (see Discussion of synthetic procedures, II, 3.A) an alternative synthesis leading to the amino-β-lactam (15a) was sought. The reaction of azidoacetyl chloride with cyclohexylideneaniline (to give (15g)) requires hydrogenation of the intermediate 3-azido-β-lactam (15g) to the 3-amino compound (15a). However, it

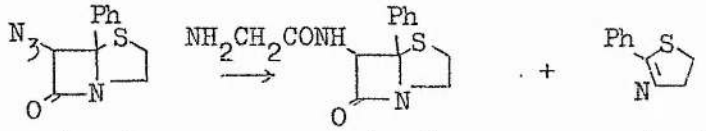


(15g)



(15a)

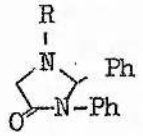
has been reported[148] that the hydrogenation of 3-azido-β-lactams can result in fission of the β-lactam ring (e.g. (125) gives (126) and (127)). This, and the explosive nature of some azidoacetyl compounds, resulting



(125) (126) (127)

in difficulties in purification (by distillation) led us to look elsewhere for a synthesis.

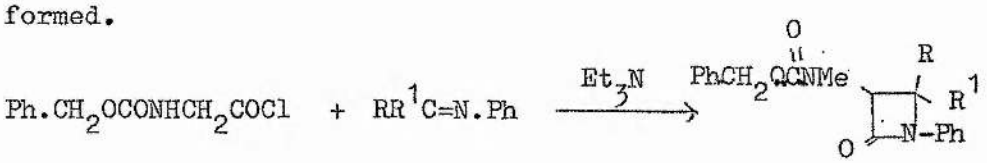
Amino-protecting groups other than the phthaloyl group and the azido group which can be removed under conditions sufficiently mild to avoid possible fission of the β-lactam ring include the benzenesulphonyl group and the benzyloxy-carbonyl group. Sheehan has reported[149] that the treatment of benzylideneaniline with either benzenesulphonylglycyl chloride or benzyloxycarbonylglycyl chloride gave the corresponding imidazolidinones (128). However in our hands this reaction using benzyloxycarbonylglycyl chloride



R=PhSO$_2$, Ph.CH$_2$OCO

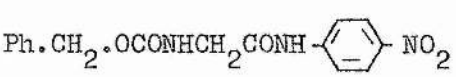
(128)

with cyclohexylideneaniline or benzylideneaniline was found to give the desired β-lactams (15c) and (46a). With benzylidene-(p-nitro)-aniline however the reaction produced only the amide (129) with none of the desired β-lactam being formed.



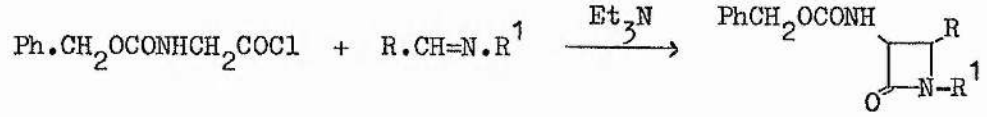
(15c) R,R^1=(CH$_2$)$_5$

(46a) R=H, R^1=Ph



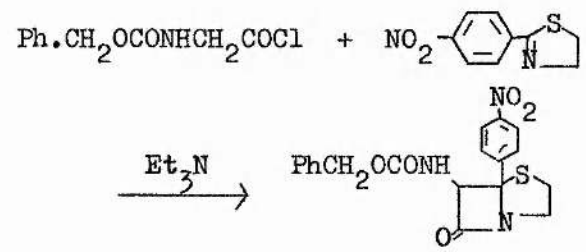
(129)

Whilst this work was in progress to determine the generality of this method for the preparation of β-lactams the use of benzyloxycarbonylglycyl chloride for the synthesis of β-lactams was reported by Bose and co-workers.[150] These workers described (with little preparative detail) the synthesis of the β-lactams (130), (131) and (132) by reaction of the acid chloride with the corresponding imines.

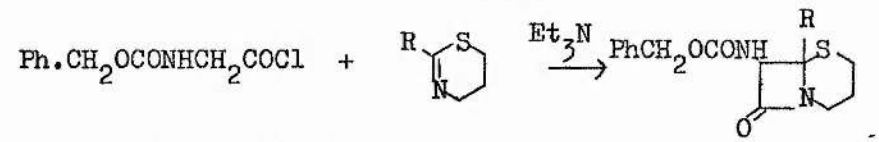


R=pCH$_3$.C$_6$H$_4$, pCH$_3$OC$_6$H$_4$
R^1=pCH$_3$OC$_6$H$_4$, 2-furyl

(130)



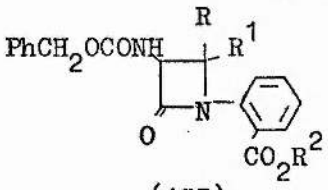
(131)



R=Ph, pNO$_2$.C$_6$H$_4$

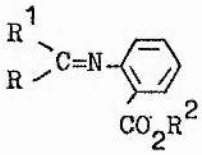
(132)

The preparation of 1-(o-benzyloxycarbonylphenyl)-β-lactams (133) by an acid chloride/imine reaction was not investigated owing to our inability to prepare the required imines (134).



R,R^1=Ph, H; -(CH$_2$)$_5$-

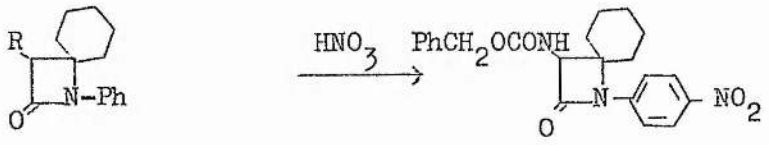
(133)



R,R^1=Ph, H; -(CH$_2$)$_5$-

(134)

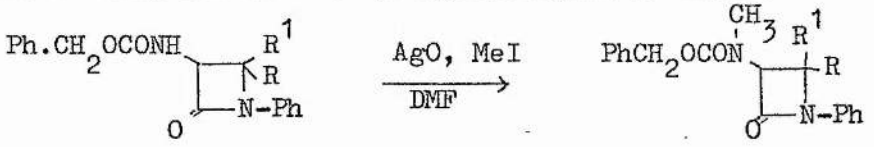
The preparation of a 3-benzylcarbamato-1-(p-nitrophenyl)-1-azaspiro[5.3]nonan-2-one (135) was attempted by nitration of the corresponding 1-phenyl compound (15c), but without success.



(15) (135)

(c) R=Ph.CH_2OCONH

The β-lactams (15d, 46b) were prepared by N-methylation of the corresponding 3-benzyloxycarbonylamino-β-lactams (15c) and (46a). The method used was based on that reported[151] for the N-methylation of alkyloxycarbonylamino-acids.



(15a) R,R^1=-$(CH_2)_5$-

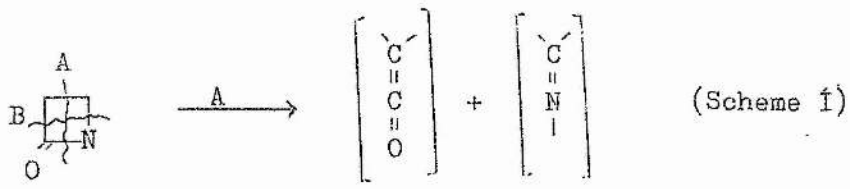
(46b) R=H, R^1=Ph

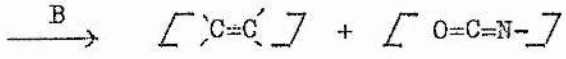
2. Physical Properties of β-Lactams

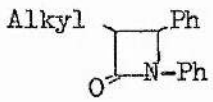
A. Mass Spectra

The mode of fragmentation of β-lactams in a mass spectrometer is similar to that observed[152] during thermolysis. Two main patterns are followed (Scheme I), the primary fragmentation process leading to the formation of either a ketene and an imine (Route A) or an olefin and an isocyanate (Route B). With N-aryl lactams fragmentation by Route B usually predominates, with the exception of

N-phenylazetidin-2-one where A is the major route.[153]







(26)

For 3-alkyl-1,4-diphenylazetidin-2-ones (26) it has been reported[154] that the fragmentation pattern is determined by the stereochemistry of the compounds, the cis-β-lactams showing a greater tendency to fragment by Route A than do the trans-β-lactams. The 3-substituted 1,4-diphenyl-β-lactams prepared in this work showed a similar effect of configuration upon the fragmentation pattern (Table 1). The β-lactams prepared from benzyloxycarbonylglycyl chloride and benzylidenaniline are of cis-conformation[150] and show a higher ratio of imine:isocyanate peaks in their fragmentation patterns than do the trans-isomers which were obtained from phthalimidoacetyl chloride and benzylideneaniline.

TABLE 1

Mass spectral fragmentation and stereochemistry (from n.m.r.) of β-lactams

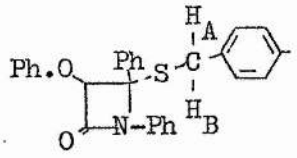
Relative Intensity	isocyanate	amine	stereochemistry
1-phenyl- (30d)	35	100	-
1-p-nitrophenyl- (30j)	20	100	-
1,4-diphenyl lactams			
1,4-diphenyl	15	10	-
3-amino	52	14	trans
3-phthalimido-	62	20	trans
3-benzamido-	85	32	trans
3-benzyloxycarbonylamino	1.5	30	cis
3-benzyloxycarbonyl-N-methylamino	0	25	cis
3-methylamino-HBr	0	75	cis
1-p-nitrophenyl-3-phthalimido-4-phenyl	4	4	trans

Table 1 (contd)

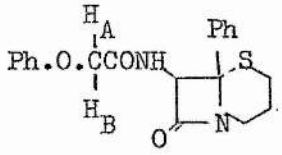
relative intensity	isocyanate	amine
1-phenyl-1-azaspiro-/5.3/nonan-2-ones		
3-phthalimide	9	22
3-amino HCl	4	8
3-amino HBr	5	11
3-benzyloxycarbonylamino	13	67
3-benzamide	17	100
3-p-bromobenzamido	41	100
3(2,6-dimethoxybenzamide)	0	5
3-p-nitrobenzamido	26	100
3-p-methoxybenzamido	15	56
3-benzenesulphonamido	7	88

B. Proton Magnetic Resonance Spectra

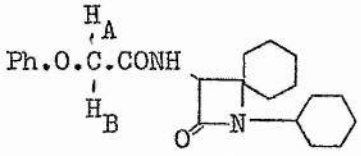
Proton magnetic resonance spectroscopy has been used mainly for the determination of configuration of β-lactams.[153,156] Compounds with a proton on C3 and C4 exhibit a difference in the magnitude of the coupling constant depending upon their stereochemistry. Cis-protons have a coupling constant of about 5 Hz compared to 0-2 Hz for trans-protons.[157] Use has also been made[158] of lanthanide shift reagents for the establishment of the configuration of β-lactams possessing a greater degree of substitution, and this has produced some unexpected results. In a study of lanthanide induced shifts[159] on diastereotopic protons in β-lactams of the type (136, 137, 138) using $Eu(DPM)_3$, $Yb(DPM)_3$, $Eu(FOD)_3$ and $Pr(FOD)_3$, it was found that the addition of the



(136)



(137)



(138)

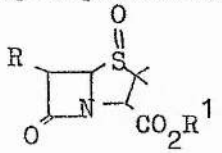
europium or ytterbium complexes reduced the non-equivalence of the protons (H_A and H_B in structures 136, 137, 138) and that with increased concentrations of the complexes the two signals merged to produce a singlet,

whereas the addition of the praseodymium complex increased the non-equivalence of the protons.

Of the two routes to 3-substituted-β-lactams which we employed, the addition of benzyloxycarbonylglycyl chloride to benzylideneaniline produced a cis β-lactam whilst the addition of phthalimidoacetyl chloride to the imine produced a trans β-lactam. This finding is substantially in accord with the results obtained by Bose[80] in his work on the preparation of similar compounds.

C. Infra-Red Spectra

Monocyclic β-lactams have a carbonyl absorption frequency of 1730-1760 cm^{-1}. This absorption frequency shifts to 1770-1780 cm^{-1} when the β-lactam is part of a fused ring system as in the penicillins and cephalosporins.[2d] It has been suggested[18] that the frequency and integrated intensity of the carbonyl absorption of a β-lactam might be considered as a measure of the lability of the amide bond and hence of the acylating ability of the compound, a higher frequency or greater intensity indicating increased reactivity of the compound and thus a potential for antibacterial activity. Correlations have been found[18,19] but there are some compounds which have a high carbonyl absorption frequency but possess little or no antibacterial activity - for example the penicillin sulphoxides (139) and anhydropenicillin (140).



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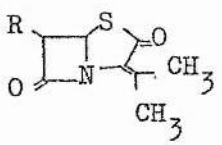
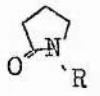


(140)

The integrated intensity of the carbonyl absorption peak in β-lactams is greater than that in pyrrolidin-2-ones (141) which is itself larger than that in piperidin-2-ones (142) and it has been suggested[161] that this is an effect of increased strain in the ring.



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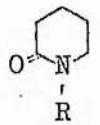


(142)

Of the β-lactams prepared in this work the spiro-β-lactams had a greater integrated intensity of the carbonyl absorption band than do the 1,4-diphenyl-β-lactams indicating that the incorporation of the spiro group had brought about an increase in the strain in the β-lactam ring (Table 2). The 3-phthalimido compounds are not included owing to overlap of the imido and lactam carbonyl bands.

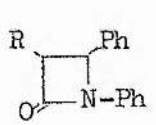
Table 2

Relative integrated intensity of the carbonyl absorption band of β-lactams. (Concentration 200 mg in 0.95 g KBr).

β-lactam	relative intensity
diphenyl lactams	
3-benzamido	1
3-amino	1.16
3-benzyloxycarbonylamino	1.24
spiro-lactams	
3-benzamido	1.88
3-amino	2.10
3-benzyloxy-carbonylamino	1.98
3-p-methoxybenzamido	1.86
3-p-nitrobenzamido	2.31
3-p-bromobenzamido	2.20
3-benzenesulphonamido	2.31
3-(2,6-dimethoxy-benzamido)	2.33

D. Biological Properties of β-Lactams

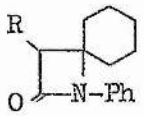
Certain of the compounds prepared in this study (46, a and b 15 h, 143) were tested for in vitro antibacterial activity, using the following standard procedure.



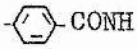
(46)

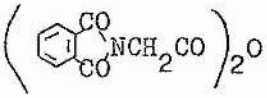
(a) R= 

(b) R=$PhCH_2OCONH$



(15)

R=pCH_3O 



(143)

(i) Solutions of the compounds were prepared in undiluted propylene glycol at a concentration of 0.1%, using the minimum of heat necessary to effect solution. The reference compound employed was ampicillin.

(ii) Serial two-fold dilutions were made in sulphonamide testing broth, usually ranging from 100 to 0.19 μg/ml. The broth solutions were innoculated with log phase cultures of Staphylococcus aureus (NCTC 6571A) the Oxford strain, and Escherichia coli (NCTC 4144) using ca. 100 cells per ml of broth.

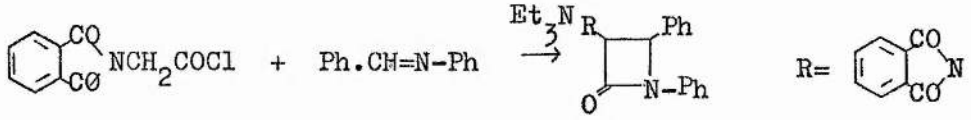
(iii) After overnight incubation at 37° the results were read as the minimal inhibitory concentration (μg/ml) according to the visible growth in comparison to broth without added drug.

None of the compounds tested showed antibacterial activity as measured by this method.

3. Discussion of Synthetic Procedures

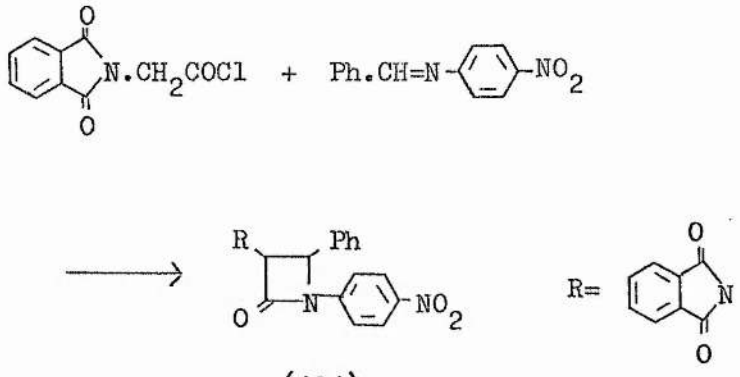
A. The Use of Phthalimidoacetyl Chloride in the Preparation of β-Lactams

The reaction of phthalimidoacetyl chloride with imines to give 3-phthalimido-β-lactams was first reported using benzene as the solvent.[57] It was later found[163] that the use of refluxing methylene chloride or chloroform as solvent, together with the use of a high-dilution cycle, minimized the formation of by-products. Following a synthesis of 1,4-diphenyl-3-phthalimidoazetidin-2-one (46a) in benzene from which the desired β-lactam (46a) was obtained in low yield (23%), it was found that much higher yields



(46)

(up to 72%) could be obtained by performing the reaction in methylene chloride. The use of a high-dilution cycle was found not to be necessary when the reaction was carried out at 0° and left for about 16 hours at ambient temperature, after addition of the reactants, before working up. The synthesis of 1-(p-nitrophenyl)-4-phenyl-3-phthalimidoazetidin-2-one (124) was found also to proceed readily using these conditions.



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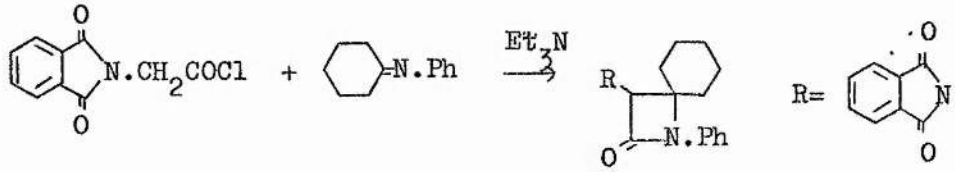
The synthesis of 1-phenyl-3-phthalimido-1-azaspiro[5.3]nonan-2-one (15b) from cyclohexylideneaniline and phthalimidoacetyl chloride has been reported[80] by Bose

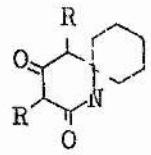


(15)

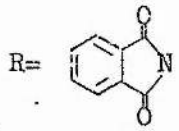
and co-workers but no experimental details have been published. For this synthesis, therefore, similar conditions were employed as for the synthesis of the 1,4-diphenyl compounds described above. This procedure resulted in a poor yield of the desired β-lactam. The main product of the reaction, which precipitated during the reaction, possessed an infra-red carbonyl absorption peak at 1740 cm^{-1} (similar to the β-lactam frequency) and in addition had an absorption peak at 1840 cm^{-1}. A small quantity of phthalimidoacetanilide was also isolated from the reaction.

It was initially thought that this major product from

the reaction of cyclohexylidene aniline with phthalimidoacetyl chloride might be the piperidin-2,4-dione (144) as the formation of such products from siliar reactions has been

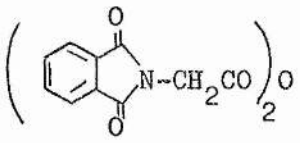


(144)



reported.[74-76,78] However the n.m.r. spectrum of the impure product from this reaction was not consistent with the proposed piperidin-2,4-dione structure.

Owing to the difficulty of purifying the compound because of its insolubility, the further investigation of the nature of the compound was held in abeyance whilst a method of increasing the yield of the β-lactam was sought. It was found that the yield of the desired β-lactam (15b) was markedly increased by the immediate use of freshly prepared phthalimidoacetyl chloride. When the pure acid chloride was added to a solution of the imine and triethylamine in methylene chloride the formation of the unidentified product was almost entirely inhibited and the yield of the β-lactam (15b) greatly improved. This suggested that the acid chloride was undergoing a reaction other than that with the imine and it was suspected that the compound formed was phthalimidoacetic anhydride (143). This premise was further supported by the deliberate use of a mixture of phthalimidoacetic acid and phthalimidoacetyl chloride

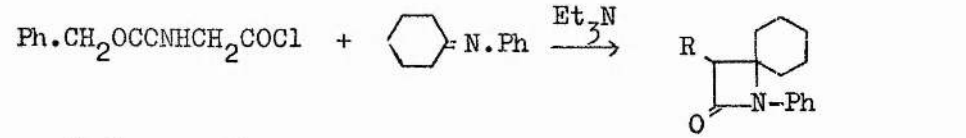


(143)

when a greater yield of the unknown compound was obtained. After continuous extraction of the compound with refluxing methylene chloride the residue was sufficiently pure to be identified as the anhydride (143).

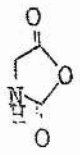
B. The Use of Other Acid Chlorides for the Preparation of β-Lactams

The reaction of N-benzyloxycarbonylglycyl chloride with cyclohexylideneaniline to produce 3-benzyloxycarbonylamino-1-phenyl-1-azaspiro[5.3]nonan-2-one (15d) proceeded readily under conditions similar to those employed for the preparation



(15) R=Ph.CH_2OCONH

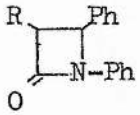
of the corresponding phthalimido-β-lactam. The acid chloride could be added in solution in methylene chloride at low temperatures or as a solid, without affecting the yield of the β-lactam. Owing to the rapid decomposition of benzyloxycarbonylglycyl chloride at 0° to the N-acyl anhydride (145) and in the presence of moisture to the polymer (146) the use of the solid compound was preferred.



$(-NHCH_2CO-)_n$

(145) (146)

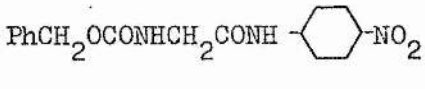
The synthesis of 3-benzyloxycarbonylamino-1,4-diphenylazetidin-3-one (46b) proceeded readily in similar conditions. However benzylidine-(4-nitro)-



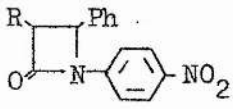
(b) $R=PhCH_2OCONH$

(46)

aniline with N-benzyloxycarbonylglycyl chloride gave the amide (147) and none of the required β-lactam (124c) was isolated.



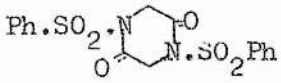
(147)



(124)

(c) $R=PhCH_2OCONH$

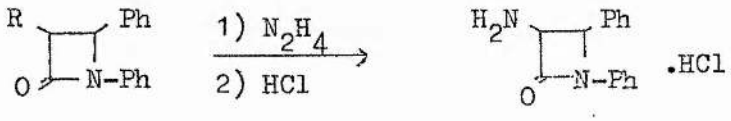
The reaction of benzenesulphonylglycyl chloride with benzylideneaniline led, in our hands to a compound which had no N-H absorption peak in the infra-red and a carbonyl absorption peak at 1705 cm^{-1} (too low for a β-lactam carbonyl). On the basis of the mass spectrum, nuclear magnetic resonance spectrum and elemental analysis the structure (148) has been proposed for this compound.



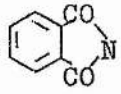
(148)

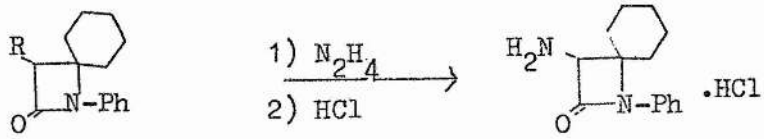
C. Preparation of 3-Amino-β-Lactams

The conversion of 3-phthalimido-β-lactams to 3-amino-β-lactams by treatment with hydrazine (Scheme 2) was reported[57] by Sheehan and co-workers. Of the 3-phthalimido-β-lactams which were prepared, 1,4-diphenyl-3-phthalimidoazetidin-2-one (46a) and 1-phenyl-3-phthalimido-1-azaspiro[5.3]nonan-2-one (15b) reacted with hydrazine in refluxing ethanol to give the corresponding

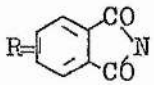


(46)

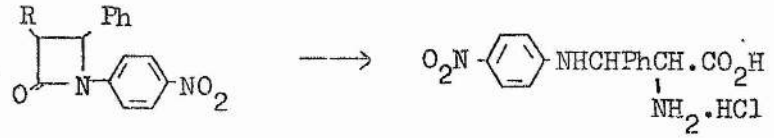
(a) R= 



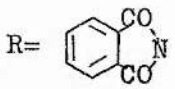
(15)

(b) R= 

3-amino-β-lactams. 1-(4-nitro-phenyl)-4-phenyl-3-phthalimidoazetidin-2-one (124b) reacted further under

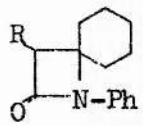


(124) (149)



these conditions to give a compound to which on the basis of infra-red and elemental analysis the structure (149) has been assigned. This compound was also isolated (with no β-lactam) when the reaction was carried out at room temperature for 30 minutes.

In peptide synthesis the benzyloxycarbonyl group is commonly removed by hydrogenolysis or by treatment with anhydrous hydrogen halide. Attempted hydrogenolysis of 3-benzyloxycarbonylamino-1-phenyl-1-azaspiro[5.3]nonan-2-one (15c) using palladised charcoal as catalyst was not successful, the starting material being the only compound

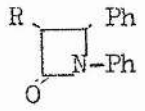


(15c)

R=Ph.CH_2O.CONH

isolated from the reaction. Treatment of the compound with hydrogen bromide in glacial acetic acid led to rapid reaction and the 3-amino compound was isolated as the hydrobromide in good yield. The reaction proceeded with similar facility with 3- benzyloxycarbonylamino-1,4

diphenylazetidin-2-one (46b), and with 3-(N-methyl-N-benzyloxycarboxylamino)-β-lactam (15e).



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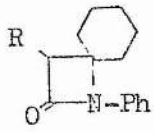
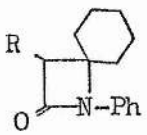


(15)

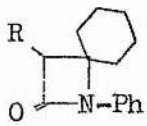
(b) R=$PhCH_2OCONH$ (e) R=$Ph.CH_2OCONMe$

D. Acylation of 3-amino-β-lactams

The preparation of 3-amido-β-lactams from the 3-amino compounds was effected by treatment of the amine with the requisite acid chloride in methylene chloride solution, the reaction generally producing a good yield of the desired amido compounds. The preparation of 3-phenoxyacetamido-1-phenyl-1-azaspiro [5.3]-nonan-2-one (15e) was attempted by acylation of the 3-amino-β-lactam with the mixed anhydride formed from phenoxyacetic acid and t-butyl chloroformate but none of the desired β-lactam (15e) was

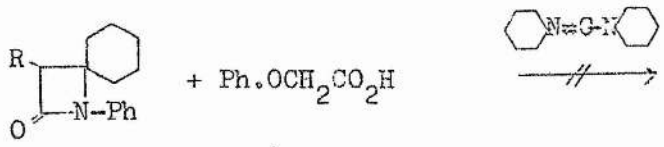


+ $Ph.O.CH_2CO_2CO_2Bu^t$ ⇏

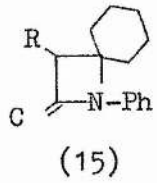


(15a) R=$NH_2.HCl$ (18) (e) R=$Ph.OCH_2CONH$

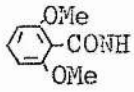
produced by this method. The preparation of the β-lactam (15e) and of 2,6-dimethoxybenzamido-1-phenyl-1-azaspiro [5.3]nonan-2-one (15f) was also attempted employing dicyclohexylcarbodiimide as the coupling agent. With phenoxyacetic acid only the acyl urea (150) was isolated



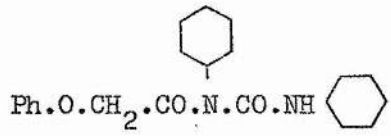
(15d) (a) R=NH_2.HCl



(e) R=Ph.O.CH_2.CONH

(f) R= 

(15)

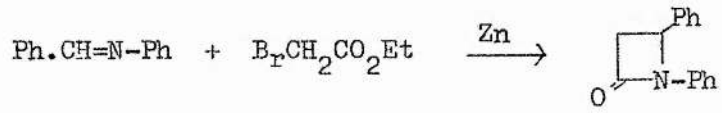


(150)

and with 2,6-dimethoxybenzoic acid no product was obtained on work up.

E. Preparation of β-Lactams by the Reformatsky Reaction

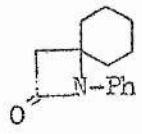
The preparation of 1,4-diphenylazetidin-2-one (14) by reaction[83] of benzylideneaniline with ethyl bromoacetate was found to proceed readily in refluxing toluene, but



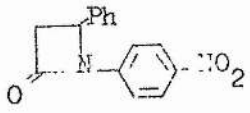
(14)

when this method was employed for the production of 1-phenyl-1-azaspiro[5.3]nonan-2-one (15g) and 1-(4-nitrophenyl)-4-phenylazetidin-2-one (124) there was no

reaction. The preparation of 1-(4-nitrophenyl)-4-



(15g)

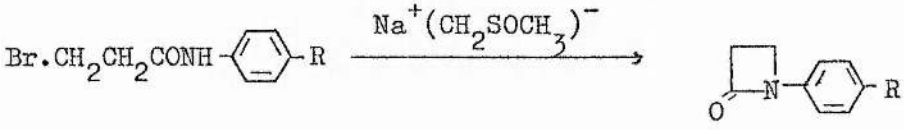


(124)

phenylazetidin-2-one (124) was also attempted using acetonitrile in place of toluene as solvent but again there was no reaction.

F. Cyclization of β-Bromopropionamides

The preparations of 1-phenylazetidin-2-one (30d) and 1-p-nitrophenylazetidin-2-one (30j) by cyclization



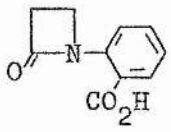
(30)

(d) R=H

(j) $R=NO_2$

of the corresponding β-bromopropionamides with Dimsyl sodium[132] were found to proceed readily and in good yield.

Preparation of 1-o-benzyloxycarbonylphenylazetidin-2-one (18a) gave the product as a gum which decomposed on



(18)

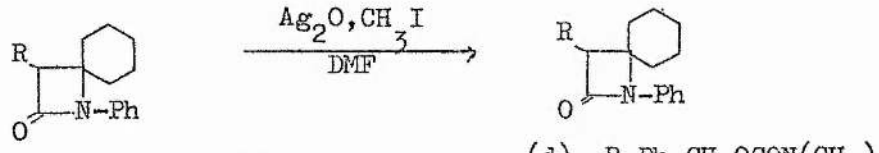
(a) = benzyl ester

attempted distillation, and on hydrogenolysis yielded a product which no longer showed a lactam carbonyl

absorption in the infra-red. The product could not be satisfactorily identified.

G. Methylation of 3-Amido-β-Lactams

Using a literature method[151] for the methylation of N-protected amino acids 3-benzyloxycarbonylamino-1-phenyl-1-azaspiro[5.3]nonan-2-one (15c) and 3-benzyloxycarbonylamino-1,4-diphenylazetidin-2-one (46a) were readily methylated on the side-chain nitrogen to produce the corresponding 3-N-benzyloxycarbonyl-N-methylamino-β-lactams.

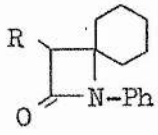


(c) R=Ph.CH_2OCONH (15)

(d) R=Ph.$CH_2OCON(CH_3)$ (15)

H. Nitration of 3-Benzyloxycarbonylamino-1-Phenyl-1-Aza-Spiro[5.3]Nonan-2-One

As a 1-p-nitrophenyl-1-azaspiro[5.3]nonan-2-one could not be prepared by an acid-chloride/imine reaction owing to an inability to prepare N-cyclohexylidene-p-nitro-aniline, entry to this system was attempted by nitration of 3-benzyloxycarbonylamino-1-phenyl-1- azaspiro[5.3]-nonan-2-one (15c) (the p-nitrobenzyloxycarbonyl group may be removed under conditions similar to those used in



(15)

(c) R=Ph.CH_2OCONH

removal of the benzyloxycarbonyl group). Nitration with either nitric acid/sulphuric acid or acetyl nitrate produced a compound with no β-lactam carbonyl absorption in the infra-red and the product was not identified.

Kinetic Measurements

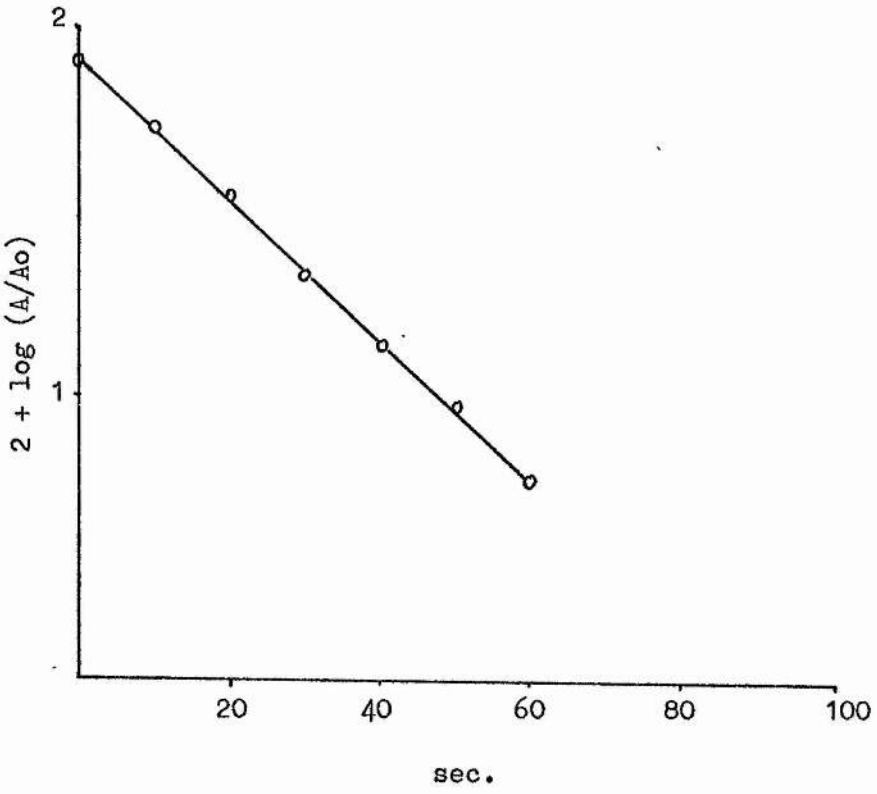
Method

All reactions were run in de-ionised water at an ionic strength of 1.0 (maintained by the addition of sodium chloride). The reaction of 1-p-nitrophenyl-4-phenylazetidin-2-one in surfactant solutions was followed by stopped flow methods, solutions of the lactam in surfactant solution (and dioxan to give a final dioxan concentration of 0.8%) and of sodium hydroxide being simultaneously introduced to the reaction chamber and the increase in absorption of 400 nm displayed on a cathode ray tube. For the other lactams reaction was initiated by the addition of one drop (ca. 0.02 ml) of a solution of the lactam in dioxan to the reaction medium contained in a thermostatted cuvette in a spectrophotometer. The reaction of 1-phenyl-β-lactams was followed by monitoring the disappearance of the β-lactam absorption at 255 nm, whilst for the 1-p-nitrophenyl-β-lactams it was more convenient to follow the increase of the product absorption at 400 nm. All the reactions displayed good first order kinetics over at least 3 half-lives and pseudo-first-order rate constants were obtained from plots of log $(A_t - A)$ against time (a typical plot is shown in Figure 1.).

For the slowest reactions the method of Swinbourne[161,162] was used.

For β-lactams which were soluble in dioxan/water (ca. 0.8% dioxan) the hydrolytic reaction was followed at hydroxide concentrations of 0.1 to 1 molar. Reaction rates for these compounds were determined at at least three temperatures to enable the calculation of activation parameters (Table 3).

Figure 1. First order plot for the hydrolysis of 3-benzamido-1,4-diphenylazetidin-2-one in 0.4M NaOH



The Use of Micelle Forming Agents in the Hydrolysis of β-Lactams

The use of micelle forming agents (surfactants) for solubilization and for the catalysis of various reactions has been comprehensively reviewed.[166] In aqueous solution both ionic and non-ionic surfactants have been used, the ionic surfactants being pyridinium or quaternary ammonium salts (cationic surfactants) or long-chain alkyl carboxylate or alkyl sulphate salts (anionic surfactants), and the non-ionic surfactants are commonly polyethers of high molecular weight.

The effect of a surfactant upon a particular reaction is dependant upon its type, the reaction generally being catalysed by only one kind of surfactant, the others having little effect or retarding the reaction. The effect shown is also dependant upon the concentration of the surfactant as below a certain concentration (the critical micelle concentration) the surfactant is present mainly as discrete molecules with little solubilizing or catalytic effect, whilst above this concentration most of the surfactant is present in large aggregates (micelles) and it is these aggregates with which the effects are associated. The critical micelle concentration is dependant upon the surfactant, the nature of the medium in which it is dissolved, and is also affected by the presence of salts or organic additives, which may increase the critical micelle concentration and the micelle size.

The effect of the surfactant as a catalyst is also dependant upon the nature of the reaction, and it is commonly found that the reaction is positively catalysed by only one type, the others having little or no effect on retarding the rate of reaction.

The surfactants investigated for use in the hydrolysis of β-lactams were cetyl trimethylammonium bromide (CTAB), sodium lauryl sulphate (NaLS), and 'Mulgofen G' (a proprietary polyether). The reaction of 1,4-diphenyl-3-phthalimidoazetidin-2-one (128) was followed in the presence of each of these surfactants in 1 M sodium hydroxide. NaLS (0.0001 M, the limit of its solubility in 1 M sodium hydroxide), and 'Mulgofen G' (5% w/v) depressed the rate of reaction to below that which could be conveniently measured (k less than 10^{-6} s^{-1}) whilst CTAB (0.01 M) increased the rate of reaction over that in aqueous sodium hydroxide. On the basis of these results only CTAB was further used.

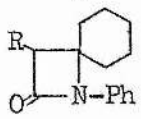
As the effect of the surfactant is concentration dependent, the critical micellar concentration (that concentration at which the surfactant has just become micellar) was determined. As the interior of the micelles of CTAB provide a non-polar environment it is possible to determine the critical micellar concentration by the shift in the wavelength of maximum absorption of a suitable compound in solution in the presence of the surfactant. Figure 2 shows a plot of the wavelength of

maximum absorption of diethylaniline against CTAB concentration from which the critical micellar concentration is shown to be at 0.003 M CTAB in 1 M NaOH.

The rates of reaction of the β-lactams which were soluble in aqueous dioxan were also determined in a range of CTAB concentrations about the critical micellar concentration so that comparisons could be made with the rates of reaction of the compounds which were insoluble in aqueous dioxan.

The results obtained in cetyl trimethylammonium bromide solution show that the increased strain in the lactam ring (as indicated by the carbonyl absorption in the infra-red) due to the bond distortion about C-4 occasioned by the spiro-cyclohexyl ring is not reflected in the rate of reaction.

The rates of hydrolysis show a dependence upon the electronegativity of the group in the para-position in 3-benzamido-β-lactams with an increase in the rate of ring fission with decreasing strength of the acid from which the side-chain is derived. The very slow rate of reaction of 3-(2-6-dimethoxybenzamido) -1-phenyl-1-azaspiro[5.3]nonan-2-one is in accord with the behaviour of the corresponding penicillin.



(15)

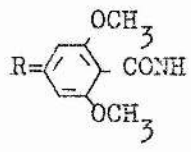
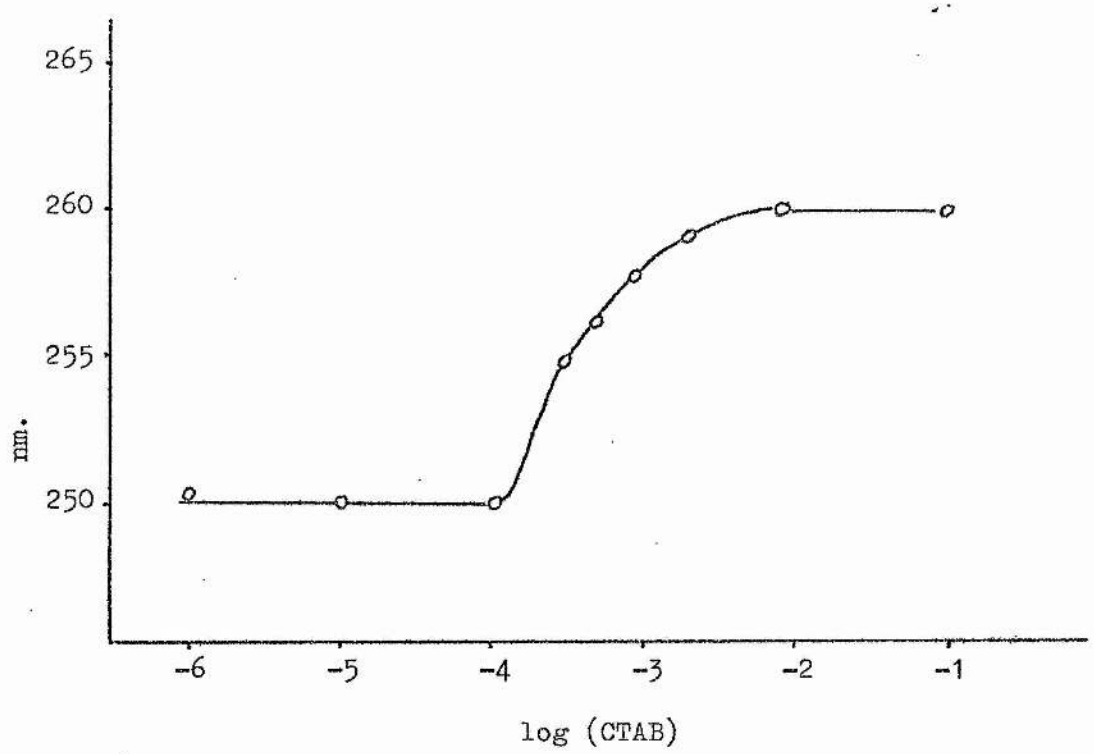
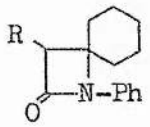


Figure 2. Variation of λ_{max} (diethylaniline) with CTAB concentration



Product Analysis

It has been shown[2] that 1-arylazetidin-2-ones, 1,4-diphenylazetidin-2-ones and 3-amido-1,4-diphenylazetidin-2-ones react with aqueous hydroxide to give the corresponding β-amino-acids. However, as no work has been reported on spiro-β-lactams such as those studied in this work 3-amino-1-phenyl-1-azaspiro [5.3]nonan-2-one (15a) and 3-benzyl-oxycarbonylamino-1-phenyl-1-azaspiro[5.3]nonan-2-one (15c)



(15)

(a) $R=NH_2$

(c) $R=Ph.CH_2OCONH$

were hydrolyzed on a preparative scale to ensure that these compounds reacted in a similar manner.

On hydrolysis each β-lactam afforded a single product (determined by thin layer chromatography) but it did not prove possible to isolate the product from either reaction in a pure state owing to rapid deterioration in air. The products were subjected to mass spectral analysis and assigned the structures of the respective β-amino-acids on the basis of a (small) peak at a mass 18 units greater than that of the β-lactam, and the lack of a peak at m/e=119.

Kinetics - Results

Of the lactams studied all of the spiro-lactams were insoluble in aqueous dioxan as were the 3-benzyloxycarbonylamino-1,4-diphenyl and 3-N-benzyloxy-carbonyl-N-methylamino-1,4-diphenyl lactams.

Hydrolyses in Aqueous Alkali

All the β-lactams which were soluble in aqueous dioxan showed a first order dependence of reaction rate on hydroxide concentration throughout the range of hydroxide concentration employed (Figures 3-9) and the rate data may be fitted by the equation:

$$k_{obs} = k[\overline{OH}] + k_1$$

where for all the compounds except 1-p-nitrophenyl-4-phenyl-3-phthalimidoazetidin-2-one k_1 is equal to zero.

Hydrolyses in Surfactant Solution

The 3-benzyloxycarbonylamino, 3-N-benzyloxycarbonyl-N-methyl lactams, and the 3-phthalimido and 3-benzenesulphonamido spiro lactams could not be kept in solution by even the highest concentrations of cetyl trimethylammonium bromide employed. The other β-lactams (with the exception of the 3-nitrobenzamido and 3-(2,6-dimethoxybenzamido) spiro lactams which with rate constants of less than $10^{-6}/s^{-1}$ were too slow to follow) exhibit similar behaviour (Table 4) showing a maximum reaction rate in the region of the critical micelle concentration. The decrease in rate at CTAB concentrations above the critical micelle concentration has been said[163] to be due to rate retardation by bromide ion.

Figure 3. 1-Phenyl-azetidin-2-one

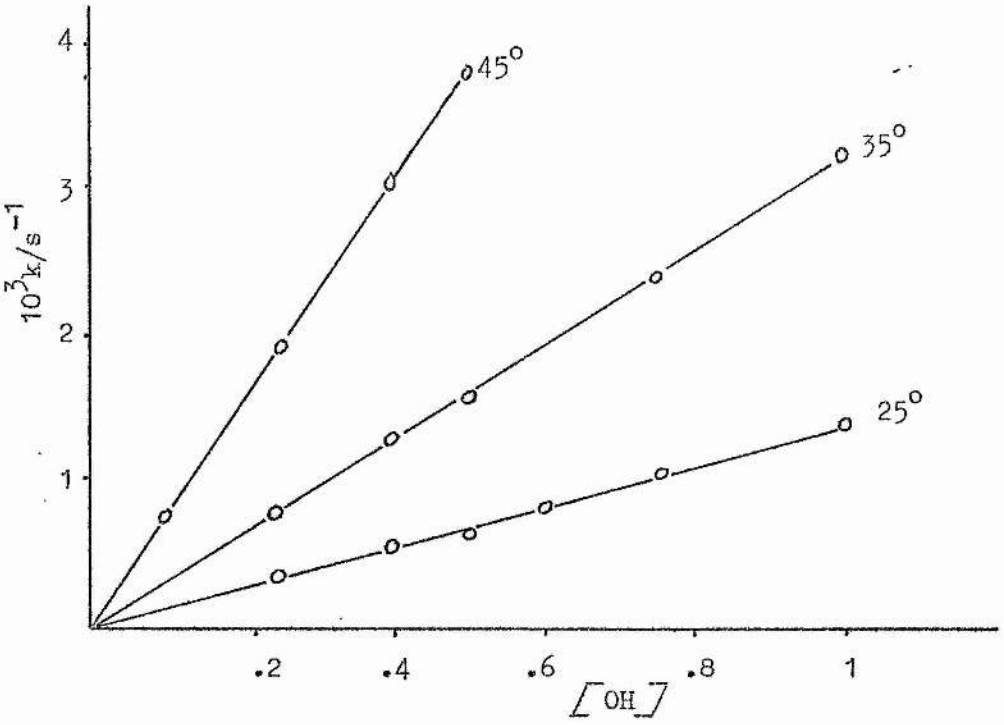


Figure 4. 1-(p-Nitrophenyl)-azetidin-2-one

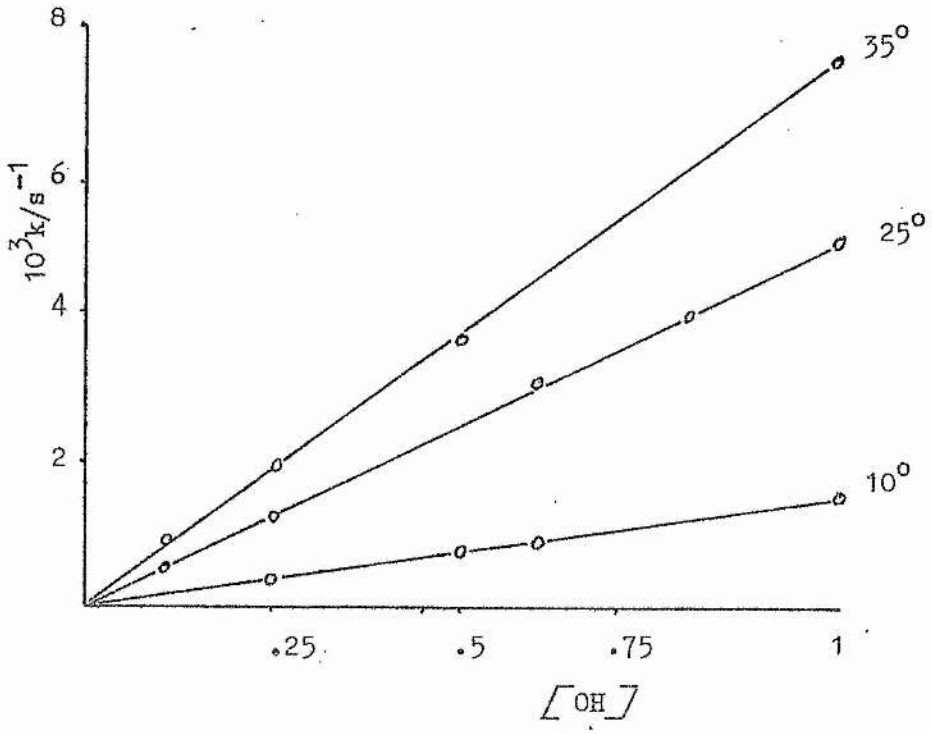


Figure 5. 1,4-Diphenyl azetidin-2-one

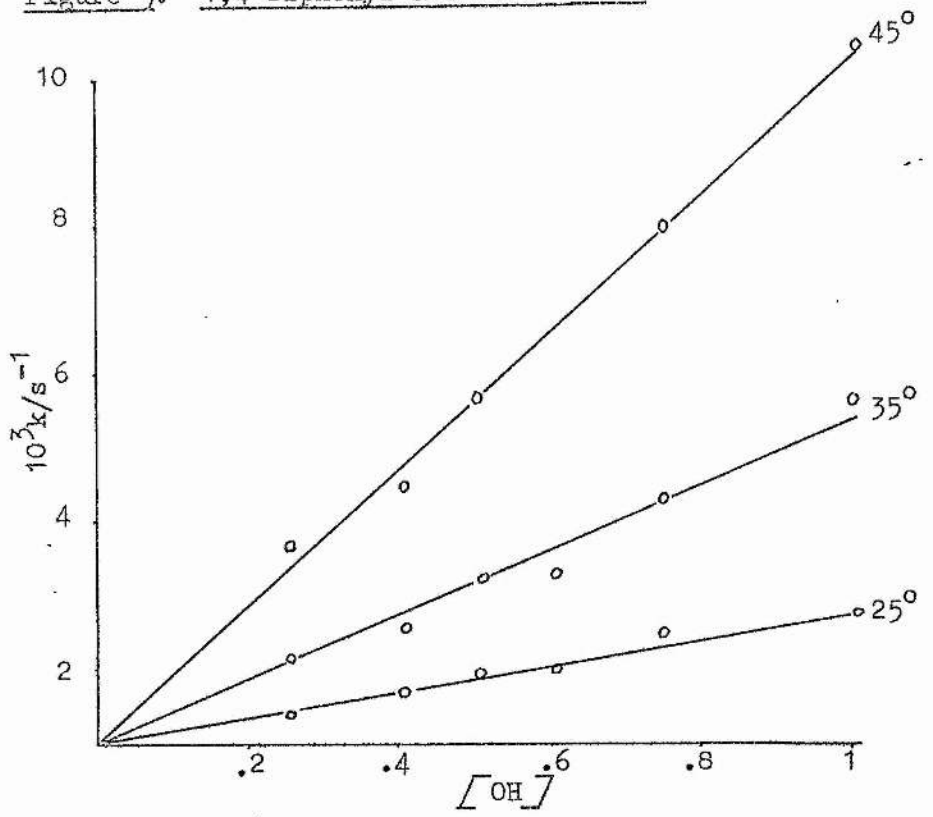


Figure 6. 3-Amino-1,4-diphenylazetidin-2-one hydrochloride

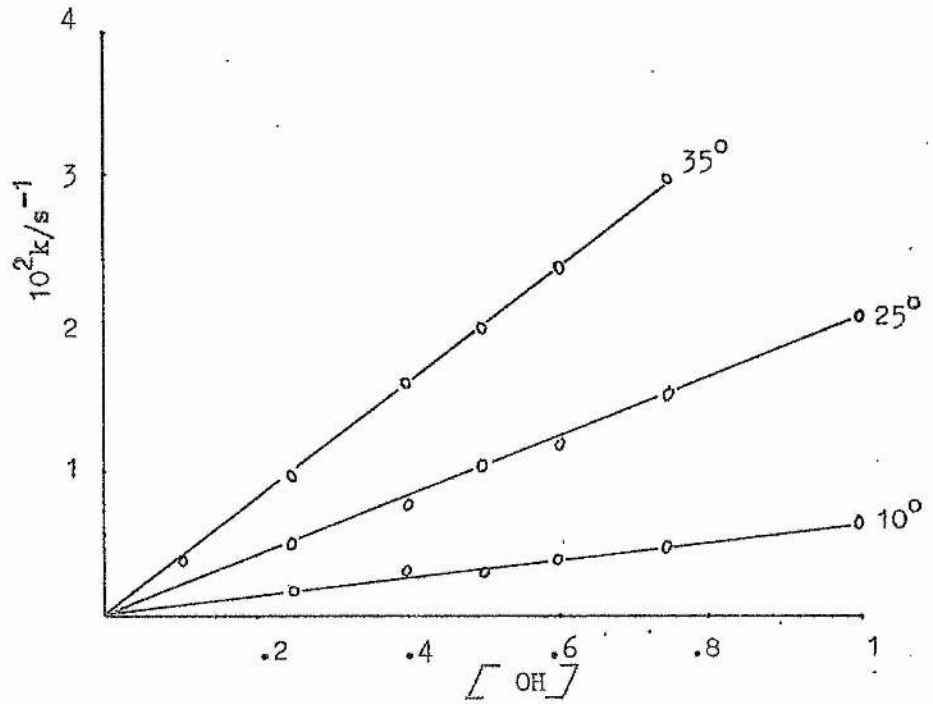


Figure 7. 1,4-diphenyl-3-phthalimidazetidin-2-one

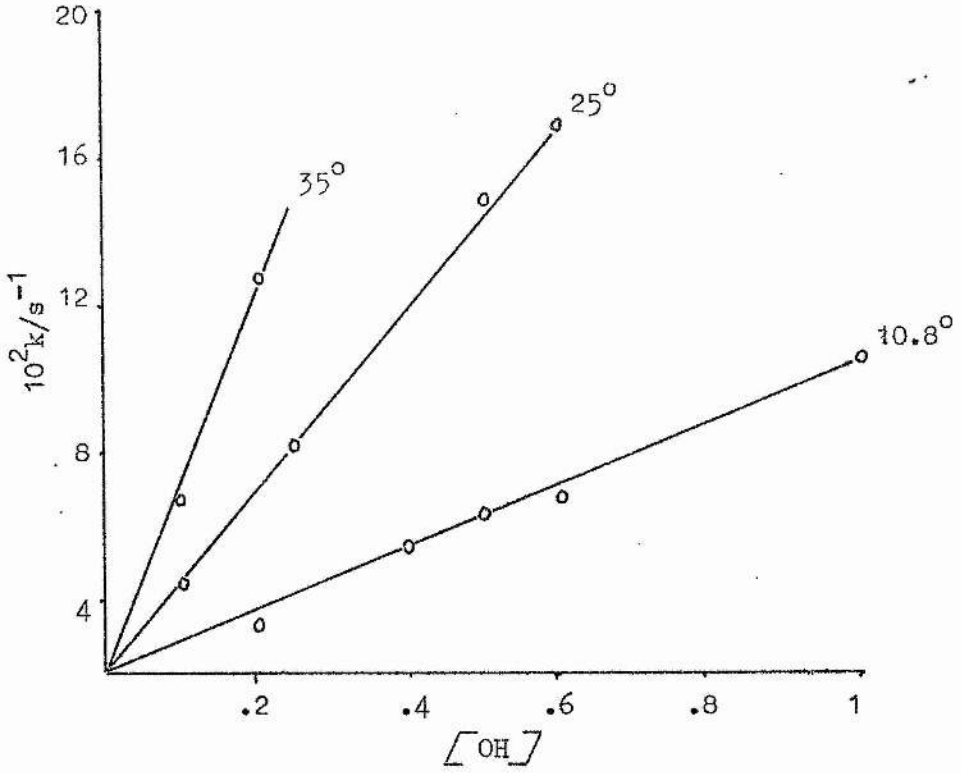


Figure 8. 3-benzamido-1,4-diphenylazetidin-2-one

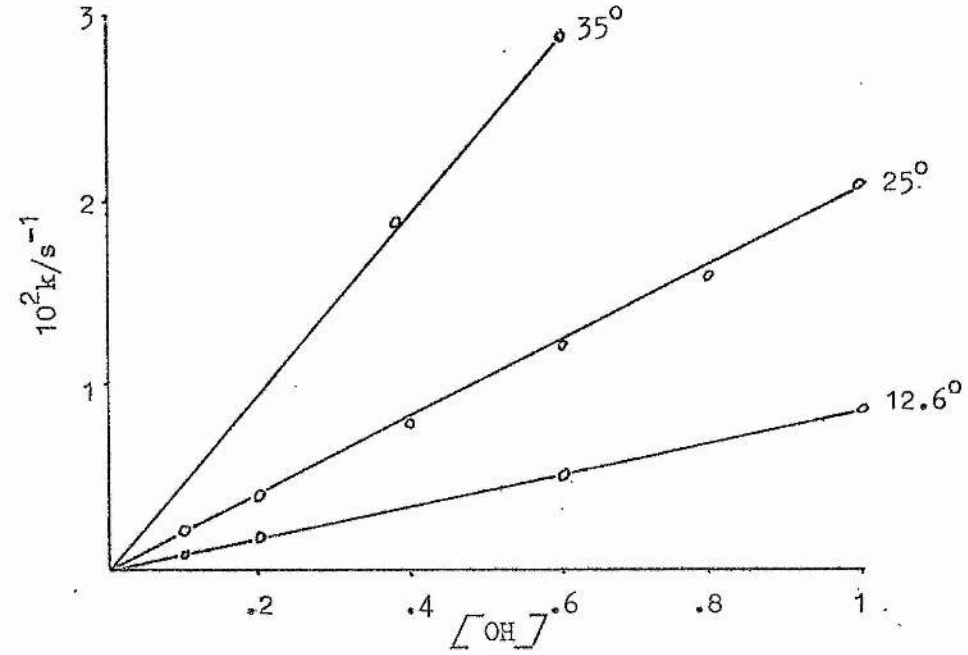


Figure 9. 1(p-nitrophenyl)-4-phenyl-3-phthalimidoazetidin-2-one

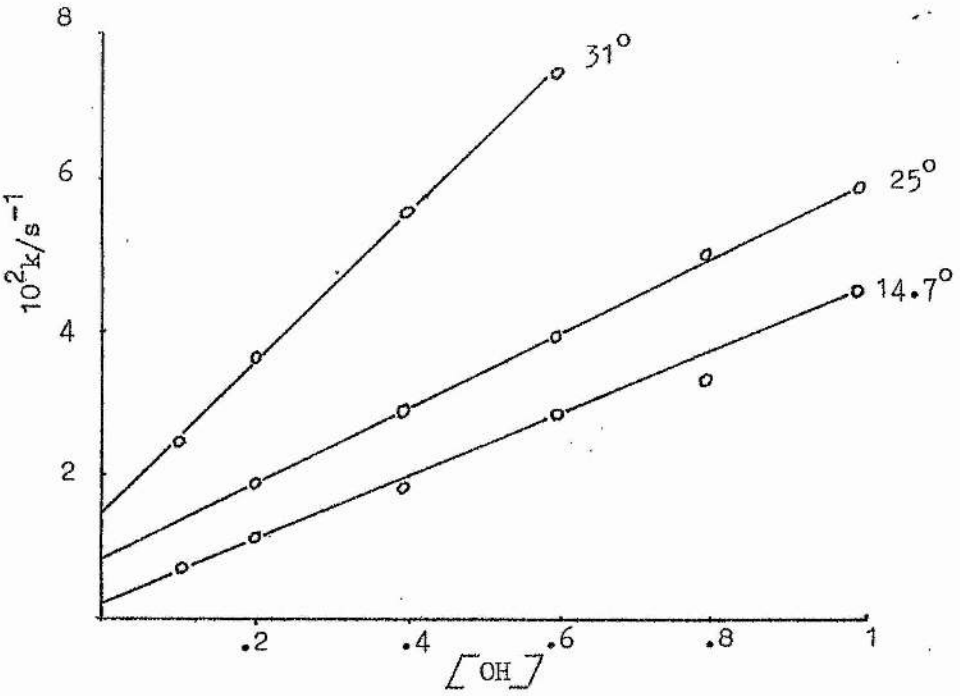
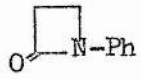
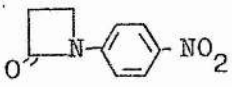
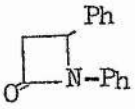
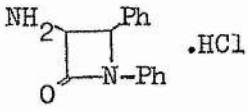
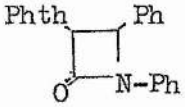
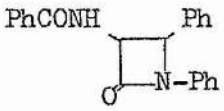
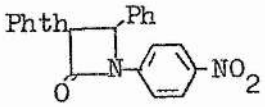


Table 3a

2nd order rate constants used for calculation of activation parameters.

$10^3 k/l.mol^{-1}s^{-1}$

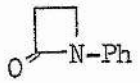
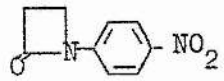
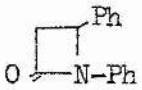
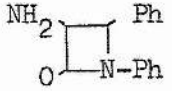
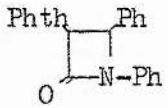
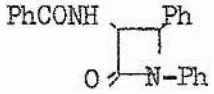
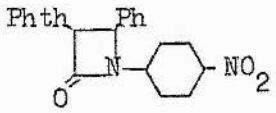
	°C	10	15	25	35	45
				1.4	3.2	4.6
		15.1		50.0	75.2	
				2.1	4.8	9.5
		6.2		20.0	37.4	
		8.6		25.1	55.6	
		7.2[a]		21.0	51.9	
			42.2	50.9	10.1	
			2.8[b]	8.3[b]	15.2	

a 13.6°;

b spontaneous reaction

Table 3b

Activation parameters for β-lactam hydrolysis. Calculated for T=25°C.

	$\Delta H^{\ddagger}$/kcal.mol^{-1}	$\Delta S^{\ddagger}$/cal.mol^{-1}k^{-1}	$\Delta G^{\ddagger}$/kcal.mol^{-1}
	15.3	-20.3	21.3
	13.3	-19.8	19.2
	14.1	-23.4	21.1
 .HCl	14.3	-18.3	19.8
	14.1	-18.5	19.6
	13.1	-21.5	19.5
	14.1 12.3[a]	-16.8 -26.8[a]	19.1 20.3[a]

a spontaneous reaction

Table 4

Variation of reaction rate

$10^3 k/s^{-1}$

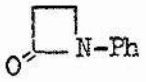
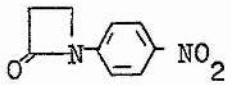
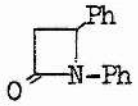
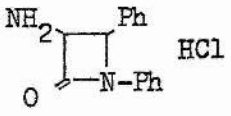
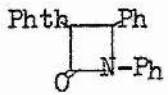
CTAB/mol.l^{-1}	.01	.005	.004	.003[a]	.002	.001	.0005	.0001
	1.0	1.1	1.1	1.2	1.0	1.7	0.7	-
	34.2	39.6	49.2	53.8	45.5	38.4		22.9
	1.0	1.1	1.2	1.6	1.6	1.1	1.0	1.0
	18.5	25.5	33.0	34.2	20.0	16.0	12.1	10.0
	21.3	23.3	24.5	27.9	26.9	25.8	18.5	12.4

Table 4 (contd)

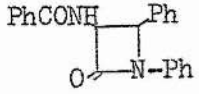
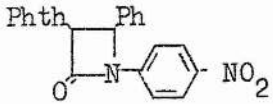
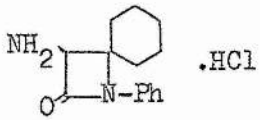
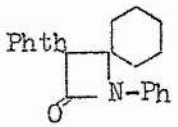
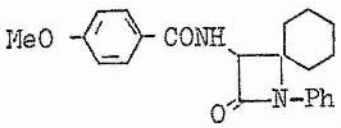
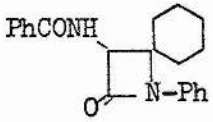
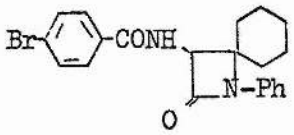
CTAB/mol.l^{-1}	.01	.005	.004	.003[a]	.002	.001	.0005	.0001
	12.1	21.8	24.3	24.3	22.4	20.5		19.7
	111	155	168	164	127	b		
 .HCl	16.3	21.7	25.8	26.4	15.0	12.2		8.2
	23.4	27.2	28.6	28.5	25.1	20.6		6.6
	7.0	12.0	14.7	20.0	19.7	17.3	11.9	9.6

Table 4 (contd)

CTAB/mol.l^{-1}	.01	.005	.004	.003[a]	.002	.001	.0005	.0001
	5.1	11.3	17.5	17.3	12.3	10.4		5.4
	8.1	9.2	9.8	10.2	9.3	8.9		7.6

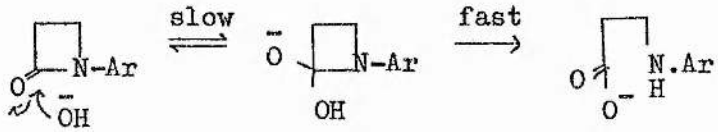
a critical micelle concentration

b precipitation occurred at this concentration.

Kinetics - Discussion

As the lactams which were sufficiently soluble to react in solution in aqueous alkali all show first order dependence on hydroxide concentration the second order rate constants may be directly compared and a number of conclusions drawn.

It is apparent that the substituents at positions 1 and 3 on the ring have a much greater effect upon the rate of hydrolysis than does the replacement of a hydrogen at position 4 with a phenyl group. The greater reactivity shown by lactams with a 1-p-nitrophenyl group than the 1-phenyl lactams is in accord with the results obtained by Blackburn and Plackett[35] who studied the effect on hydrolysis of aryl substituents and found their data fitted a Hammett plot with a ρ value + 1.225. This, with the absence of any increase in reaction order with increasing hydroxide concentration was interpreted to indicate rate-limiting attack by hydroxide (Scheme 2).



(Scheme 2)

Substitution in the 3-position with an amine, amido or imide group also occasions an increase in the rate of hydrolytic fission but with little difference in the effect of the three groups. This suggests that, for these lactams intramolecular assistance (Scheme 3) by the amido carbonyl is of little importance as this would require a large

——→ products (Scheme 3)

difference in the reaction rate of the three types of substituted compound. This conclusion is supported by the activation parameters for the reaction which are similar both for the unsubstituted and the substituted compounds.

From the results obtained it is apparent that the greatest effect upon the rate of hydrolysis is brought about by a p-nitrophenyl group on the lactam nitrogen. The electron-withdrawing effect of this group serves to reduce the double-bond character of the nitrogen-carbonyl bond leading to a carbonyl carbon more susceptible to attack by a nucleophile (in accord with rate-determining attack by hydroxide).

A decrease in amide resonance would also be caused by preventing a planar arrangement of bonds about the lactam nitrogen as in the penicillin system and the results obtained suggest that this may be a factor of greater importance in penicillin hydrolysis than the presence of the amido function.

EXPERIMENTAL

For kinetic measurements sodium hydroxide and sodium chloride were of 'Analar' standard. Cetyl trimethylammonium bromide was recrystallized from a mixture of methanol and ether[168] and had a melting point of 228-230° (lit.[168] 227-235°). Dioxan was purified by refluxing with sodium wire followed by distillation and was kept at 0°. Hydrolysis rates were measured in a Unicam SP 700 or SP 500 spectrophotomer, or Canterbury stopped flow spectrometer.

Dichloromethane was distilled from phosphorous pentoxide and the middle fraction (b.p. 40-41°) taken. Ether was dried over sodium wire. Benzene and toluene were dried with molecular sieve (Linde 4A) and triethylamine with potassium hydroxide.

Melting points quoted are uncorrected. Evaporation refers to removal of solvent under reduced pressure.

Unless otherwise stated, infra-red spectra were measured in potassium bromide, on a Unicam SP 200, and n.m.r. spectra in deuterochloroform with tetramethylsilane as internal standard using a Varian T60 spectrometer. Mass spectra were determined with a high resolution mass spectrometer. Only significant details of these spectra are quoted.

Thin layer chromatography was carried out using silica plates with a 1:1 mixture of benzene and ether as the developing solvent.

Petroleum ether refers to the fraction of boiling point 40-60°.

Hydrolysis of 3-amino-1-phenyl-1-azaspiro[5.3]nonan-2-one to 1-(1-phenylaminocyclohexyl)-glycine

A mixture of 3-amino-1-phenyl-1-azaspiro[5.3]-nonan-2-one hydrobromide (0.20 g), dioxan (20 ml) and sodium hydroxide (1 M, 30 ml) was stirred at 25°C for 1 hour. Water (200 ml) was added to the mixture and the resulting suspension was extracted with dichloromethane (3 x 50 ml). The extract was dried ($MgSO_4$) and evaporated to give 1-(1-phenylaminocyclohexyl)-glycine as a brown gum (0.7 g) which solidified on trituration with methanol m.p. 245 decomp. T.l.c. of this material using benzene:methanol (9:1) as solvent showed one spot at Rf 7.8 (M^+ 248 with no peak at 119 due to isocyanate, $C_{14}H_{30}N_2O_2$ requires M 248).

Hydrolysis of 3-benzyloxycarbonylamino-1-phenyl-1-aza-spiro[5.3]nonan-2-one to 1-(1-phenylaminocyclahexyl)-N-benzyloxycarbonylglycine

3-Benzyloxycarbonylamino-1-phenyl-1-azaspiro[5.3]nonan-2-one was hydrolyzed using similar conditions to those described above to give 1-(1-phenylaminocyclohexyl)-N-benzyloxycarbonylglycine as a brown gum Rf 8.2 (M^+ 382 with no peak at 119 due to isocyanate, $C_{22}H_{26}N_2O_4$ requires M 382).

Phthalimidoacetic Acid

A mixture of glycine (15 g), powdered phthalic anhydride (30 g) and triethylamine (2 g) in dry toluene (200 ml) was refluxed and the water produced was collected

in a Dean and Stark trap. The theoretical quantity of water (3.6 ml) was collected in 3 h. The toluene was evaporated and the residue recrystallized from chloroform to give the acid as large clear crystals (38 g, 93%), m.p. 192° (lit.[166] m.p. 192°) (Found: C, 58.4; H, 3.4; N, 6.8. Calc. for $C_{10}H_7NO_4$: C, 58.5; H, 3.4; N, 6.8%).

N-Benzyloxycarbonylglycine

To a stirred, cooled (ice-bath) solution of glycine (37.5 g) in sodium hydroxide (250 ml, 2 M) were added alternately in small aliquots benzylchloroformate (100 ml, 90% solution in toluene) and sodium hydroxide (250 ml, 4 M) over 30 minutes. The rate of addition was adjusted to maintain alkaline conditions. After completion of the addition the solution was stirred for a further 30 minutes. The solution was washed (x 3) with ether and the washings discarded. The aqueous solution was acidified (to pH 4) with concentrated hydrochloric acid and the precipitated product was allowed to stand for 1 hour at room temperature and filtered. Recrystallization from chloroform gave the acid as large clear crystals (88 g, 84%), m.p. 121° (lit.[167] m.p. 120-121°) (Found: C, 57.3; H, 5.4; N, 6.7. Calc. for $C_{10}H_{11}NO_4$: C, 57.4; H, 5.3; N, 6.7%).

N-Benzenesulphonylglycine

To a stirred solution of glycine (6 g) in sodium hydroxide (60 ml, 1 M) was added benzenesulphonyl chloride (14 g). The solution was stirred for 4 hours at room

temperature and then heated on a steam bath for 1 hour. Acidification of the cooled solution (to pH 3) with concentrated hydrochloric acid resulted in the separation of an oil which solidified on standing overnight at room temperature. The crude acid was purified by dissolution in water and precipitating with concentrated hydrochloric acid when it was obtained as a colourless power m.p. 108° (lit.,[168] m.p. 108-109°) (Found: C, 44.7; H, 4.2; N, 6.4; s, 14.9. Calc. for $C_8H_9NO_4S$: C, 44.8; H, 4.2; N, 6.2; s, 14.7%).

Phthalimidoacetyl Chloride

To a suspension of phthalimidoacetic acid (14.5 g) in dry toluene (200 ml) was added phosphorus pentachloride (15 g). The mixture was heated gently on a steam bath to maintain a steady rate of gas evolution. Solution was complete in 40 minutes and heating was continued for a further 1 hour. The solution was concentrated under reduced pressure to the point of precipitation and petroleum ether (100 ml) was added, with stirring to complete the precipitation of the acid chloride, which was obtained as a white powder (15 g, 95%) m.p. 83-84° (lit.[169] m.p. 83-85°). Recrystallization from toluene/petroleum ether gave the acid chloride as clear needles (m.p. 84°).

N-Benzyloxycarbonylglycyl Chloride

To a suspension of N-benzyloxycarbonylglycine (4.9 g) in dry ether (30 ml) at 0° was added phosphorus pentachloride (5.4 g). The mixture was stirred for 1 hour at 0°, cooled to -10° and filtered through glass wool

into dry petroleum ether at -70°. The acid chloride precipitated as a white powder which was filtered and washed with petroleum ether (4.8 g, 92%). The compound decomposed when a melting point determination was attempted (lit.,[170] m.p. 42°) and also on standing at room temperature for 30 minutes.

N-Benzenesulphonylglycyl Chloride

To N-benzenesulphonylglycine (10 g) was added thionyl chloride (6 g). The mixture was heated on a steam bath for 2 hours. On cooling, the acid chloride was obtained as brown crystals which were recrystallized from toluene-petroleum ether, when colourless crystals were obtained (4 g, 37%) m.p. 87-88° (lit.,[171] 87.5-88.5°).

3-Bromopropionyl Chloride

To a solution of 3-bromopropionic acid (7.5 g) in dry toluene (50 ml) was added phosphorus pentachloride (11 g). The mixture was heated gently on a steam bath to initiate the reaction and the heating was continued to maintain a steady evolution of gas. After 20 minutes visible reaction had ceased and the toluene was evaporated to give the acid chloride as a pale brown liquid. Distillation at 1 atm. afforded the acid chloride as a colourless liquid which darkened on continued exposure to light (5.8 g, 69%) b.p. 103-133° (lit.,[172] b.p. 131-133°).

N-Phenyl-3-bromopropionamide

To a stirred solution of redistilled aniline (4.7 g) and triethylamine (5 g) in dichloromethane (50 ml) was added,

dropwise over 15 minutes, a solution of 3-bromopropionyl chloride (8.5 g) in dichloromethane. The resulting solution was stirred for 30 minutes, washed (x 3) with water, dried ($MgSO_4$) and evaporated. The amide was obtained, on recrystallization of the residue from ethyl acetate, as large colourless crystals (9.3 g, 81%) m.p. 118° (lit.,[35] m.p. 118°) (Found: C, 47.4; H, 4.4; N, 6.0. Calc. for $C_9H_{10}BrNO_4$: C, 47.4; H, 4.4; N, 6.1%).

The following amides were prepared similarly:

N-(p-nitrophenyl)-3-bromopropionamide, which was obtained as yellow crystals (62%) m.p. 186° (lit.,[35] m.p. 186°) (Found: C, 39.5; H, 3.4; N, 10.2. Calc. for $C_9H_9BrN_2O_3$: C, 39.6; H, 3.3; N, 10.2%).

N-(o-benzyloxycarbonylphenyl)-3-bromopropionamide, which was obtained (42%) as a gum which could not be induced to crystallize and which decomposed on distillation at 3 mm Hg. Thin layer chromatography showed the presence of one compound (Rf 0.82) ν_{max} (film) 3320 (amide N-H), 1705 (benzyl ester carbonyl), and 1680 cm^{-1} (amide carbonyl); (M^+ 361, 363; $C_{17}H_{16}BrNO_3$ requires M 361, 363).

Benzyl Anthranilate

A suspension of anthranilic acid (3 g) in benzyl alcohol (125 ml) was cooled to 5°. To the stirred suspension was added thionyl chloride (10 ml) dropwise over 30 minutes. On each addition the temperature rose rapidly 2-3° and the rate of addition was controlled to keep the temperature below 10°. After leaving overnight

at room temperature the mixture was heated on a steam bath for 4 hours and then allowed to cool. Dry ether was added to precipitate the ester hydrochloride which was filtered after 6 hours. The hydrochloride was purified by precipitation from an ethanolic solution with dry ether, giving a colourless powder (3.8 g, 66%). The hydrochloride was dissolved in water (150 ml). The solution made alkaline with 5% sodium bicarbonate and the ester extracted into benzene. The extract was dried ($MgSO_4$) and the benzene evaporated to give an oil which crystallised on standing under petroleum ether at 0°, (2 g, 68%) m.p. 76-77° (lit.,[73] m.p. 77-77.5°) (Found: C, 74.0; H, 5.9; N, 6.0. Calc. for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.7; N, 6.2%).

N-Benzylideneaniline

To redistilled aniline (47 g) was added benzaldehyde (54 g). Reaction was immediate and slightly exothermic and the mixture became bright yellow. After 10 minutes the mixture was poured into ethanol (50 ml). The precipitated imine was crystallised from ethanol-water (2:1) and obtained as large yellow plates (78 g, 86%) m.p. 53° (lit.,[174] m.p. 52°) (Found: C, 86.2; H, 6.0; N, 7.7. Calc. for $C_{13}H_{11}N$: C, 86.2; H, 6.1; N, 7.7%).

N-Cyclohexylideneaniline

A solution of cyclohexanone (49 g) and redistilled aniline (47.5 g) in dry toluene (200 ml) with anhydrous zinc chloride (2 g) was refluxed, the water produced being collected in a Dean and Stark trap. The solution became

dark yellow and the theoretical quantity of water (9 ml) was collected in 2 hours. After evaporation of the toluene solution and filtration to remove the zinc chloride the residue was distilled to give the imine as a pale green liquid (72 g, 83%) b.p. 86-88° 0.3 mm Hg (lit.,[175] b.p. 85-89° 0.2 mm Hg) (Found: C, 83.3; H, 8.6; N, 8.1. Calc. for $C_{12}H_{15}N$: C, 83.3; H, 8.7; N, 8.1%).

N-Cyclopentylideneaniline

This compound was prepared from cyclopentanone and aniline by a method similar to that described for N-cyclohexylideneaniline. The reaction was complete in 3½ hours and the imine was obtained as a green liquid (1.6 g, 2%) b.p. 74-75°/0.3 mm Hg (lit.,[176] m.p. 75-80° 0.2 mm Hg). The compound decomposed rapidly on storage at 0° and a satisfactory analysis could not be obtained.

N-benzylidene-(p-nitro)-aniline

A mixture of benzaldehyde (11 g), p-nitroaniline (14 g) and p-toluenesulphonic acid (0.1 g) in dry toluene (150 ml) was refluxed and the water produced in the reaction was collected in a Dean and Stark trap. The theoretical quantity of water (1.7 ml) was collected in 6 hours by which time a dark brown solution had been formed. Evaporation of the toluene and repeated recrystallization of the residue from ethyl acetate gave the imine as orange crystals (11 g, 49%) m.p. 116-117° (lit.,[128] m.p. 117-118°) (Found: C, 69.2; H, 4.4; N, 13.3. Calc. for $C_{13}H_{10}N_2O_2$: C, 69.1; H, 4.4; N, 12.4%).

An attempt to prepare N-cyclohexylidene-(p-nitro)-aniline from cyclohexanone and aniline by a similar method failed to produce any of the desired product.

Also, attempts to prepare N-cyclohexylidene-(o-benzyloxycarbonyl)-aniline from cyclohexanone and benzyl anthranilate and N-benzylidene-(o-benzyloxycarbonyl)-aniline from benzaldehyde and benzyl anthranilate by a route similar to that described above were unsuccessful. In each case the residue after the removal of toluene showed strong N-H absorption in the infra-red (3350 cm^{-1}) and distillation of the crude product under reduced pressure (0.3-0.4 mm Hg) resulted in decomposition with benzyl alcohol being the only product isolated.

1,4-Diphenyl-3-phthalimidoazetidin-2-one

Method 1. - To a stirred solution of N-benzylidenaniline (57 g) and triethylamine (14 g) in dry benzene (550 ml) was added a solution of phthalimidoacetyl chloride (38 g) in dry benzene (350 ml) in small aliquots over 30 minutes at room temperature. The mixture became orange during the addition and a white precipitate of triethylammonium chloride formed accompanied by a small rise in reaction temperature. The mixture was stirred for 1 hour and filtered. The solid was washed with water and re-filtered to give a white powder. The benzene solution was evaporated and the orange residue was treated with ether/petroleum (1:1) in order to remove unreacted N-benzylideneaniline. The mixture was filtered, washed with ether/petroleum ether

and combined with the original solid which was then extracted with boiling ethanol. Recrystallization from dioxan/water (1:1) gave the β-lactam containing certainly 0.5 moles of dioxan of crystallization (25 g, 36%) m.p. 230-231° (lit.,[57] m.p. 230-231°) (Found: C, 72.9; H, 4.8; N, 6.8; Calc. for $C_{23}H_{16}N_2O_3 \cdot \frac{1}{2}C_4H_8O_2$: C, 72.8; H, 4.8; N, 6.8%).

Method 2. - To a stirred and cooled (ice-bath) solution of N-benzylideneaniline (9 g) and triethylamine (5 g) in dry dichloromethane (100 ml) was added a solution of phthialimidoacetyl chloride (10 g) in dry dichloromethane (200 ml) over 40 minutes; aliquots being added as the red colour produced on the addition of the previous aliquot faded. The solution was stirred for 1 hour and left overnight. The solution was then washed (x 3) with water, dried ($MgSO_4$) and the dichloromethane was evaporated to give an orange residue, which on treatment with a small quantity of methanol and filtration gave the β-lactam as a white powder (10 g, 62%) m.p. 268°. ν_{max} (Nujol) 1765, 1720, (imide carbonyls), and 1745 cm^{-1} (lactam carbonyl); τ ($CDCl_3$) 2.10-2.30 (4 H, m, $C_6H_4(CO)_2N$-), 2.63-3.04 (10 H, m, 2x Ph), 4.60 (1 H, d, J=2 Hz, H-4), 4.72 (1 H, d, J=2 Hz, H-3) (Found: C, 75.0; H, 4.4; N, 7.6; M^+ 368. $C_{23}H_{16}N_2O_3$ requires C, 75.0; H, 4.3; N, 7.6%; M 368).

3-Benzyloxycarbonylamino-1-phenyl-1-azaspiro[5.3]nonan-2-one

Method 1. - To a stirred and cooled (ice-bath) solution of N-cyclohexylideneaniline (5 g) and triethylamine (2.4 g) in dry dichloromethane (200 ml) a solution of freshly prepared

N-benzyloxycarboxylglycyl chloride (5.8 g) in dry methylene chloride (200 ml) pre-cooled to -40° was added over 40 minutes. The solution became red during the addition. The solution was stirred for a further 1 hour and left overnight to come to room temperature. After washing (x 3) with water the solution was dried ($MgSO_4$) and the dichloromethane was evaporated. Trituration of the residual red gum with a small quantity of methanol gave the lactam as a white powder which crystallised from methanol (3.5 g, 37%) m.p. 156° ν_{max} 3310 (carbamate N-H), 1740 (lactam carbonyl) and 1690 cm^{-1} (carbamate carbonyl); τ 2.50-2.90 (10 H, m, 2 x Ph), 4.04 (1 H, d, J=5 Hz, NH), 4.86 (2 H, s, $-CH_2O$), 5.12 (1 H, α, J= 5 Hz, H-3), 7.92-8.40 (10 H, m, $-C_5H_{10}-$) (Found: C, 72.4; H, 6.7; N, 7.6; M^+ 364. $C_{22}H_{24}N_2O_3$ requires C, 72.5; H, 6.6; N, 7.7% M 364).

Method 2. - Using the same conditions as above, the acid chloride was added as a solid in aliquots of ca. 0.5 g, each aliquot being added as the red colouration produced by the previous aliquot faded. The lactam was recrystallised from methanol (6.2 g, 65%) mp. 156° and was identical with that obtained by the method described above.

3-N-benzyloxycarbonylamino-1,4-diphenylazetidin-2-one

This was prepared from N-benzylideneaniline and N-benzyloxycarboxylglycyl chloride using the conditions described for method 2 above. The lactam was obtained as a white solid (3.4 g, 30%) m.p. 136-136.5° ν_{max} 3300 (carbomate NH), 1750 (lactam carbonyl) and 1690 cm^{-1}

(carbomate carbonyl); τ 2.65-2.95 (15 H, m, ArH), 4.60 (1 H, d, J=5 Hz, H-3), 4.95 (2 H, s, $-CH_2CO-$), 5.05 (1 H, d, J=5 Hz, H-4) (Found: C, 74.4; H, 5.4; N, 7.5; M^+ 372. $C_{23}H_{20}N_2O_3$ requires C, 74.2; H, 5.4; N, 7.5% M 372).

An attempted synthesis of 3-N-benzyloxycarbonylamino-1-phenyl-1-azaspiro[4.3]octan-2-one under similar conditions from N-cyclopentylideneaniline yielded N-benzyloxycarbonylglycylanilide m.p. 141° (lit., m.p. 141°) (Found: C, 67.6; H, 5.6; N, 9.8. Calc. for $C_{16}H_{16}N_2O_3$: C, 67.6; H, 5.6; N, 9.8%). An attempt to synthesise 3-N-benzyloxycarbonylamino-1-p-nitrophenyl-4-phenylazetidin-2-one from N-benzylidene-p-nitroaniline and N-benzyloxycarbonylglycyl chloride under similar conditions yielded N-benzyloxycarbonylglycyl-p-nitroaniline m.p. 161° (Found: C, 58.5; H, 4.6; N, 12.8. $C_{16}H_{15}N_3O_5$ requires: C, 58.4; H, 4.6; N, 12.8%).

1-p-Nitrophenyl-4-phenyl-3-phthalimidoazetidin-2-one

To a stirred and cooled (ice-bath) solution of N-benzylidene-p-nitroaniline (4.5 g) and triethylamine (3 g) in dry dichloromethane (200 ml) was added phthalimidoacetyl chloride (4.5 g) in small aliquots. Each addition produced a red colour in the solution and further addition was made as this faded. The solution was stirred for 1 hour at 5° and left to attain room temperature overnight during which time a precipitate (0.3 g) of phthalimidoacetic anhydride had formed which was filtered. The filtrate was washed (x 3) with water, dried ($MgSO_4$) and the dichloromethane was evaporated leaving a red gum. Treatment of the gum with a small quantity of methanol gave the β-lactam as a

yellow powder which on crystallization from methanol gave pale yellow crystals (2.6 g, 31%) m.p. 296° ν_{max} (Nujol) 1780, 1725 (imide carbonyl), 1770 (lactam carbonyl), 1515 and 1335 cm^{-1} (NO_2); τ 1.80-2.74 (13 H, m, Ar<u>H</u>), 4.55 (1 H, d, J=2 Hz, <u>H</u>-3), 4.64 (1 H, d, J=2 Hz, <u>H</u>-4) (Found: C, 66.9; H, 3.5; N, 10.0; M^+ 413. $C_{23}H_{15}N_3O_5$ requires C, 66.8; H, 3.6; N, 10.2% M 413).

<u>Reaction of benzenesulphonylglycyl chloride with benzylideneaniline</u>

To a cooled (ice-bath) solution of N-benzylideneaniline (4 g) and triethylamine (2 g) in dry dichloromethane (150 ml) was added a solution of benzenesulphonylglycyl chloride (4.7 g) in dry dichloromethane (200 ml) over 30 minutes. During the addition the solution became red and after 2 hours a precipitate had formed. After standing overnight to reach room temperature the mixture was filtered, and crystallization of the solid from dimethylsulphoxide gave 1,4-dibenzenesulphonylpiperidine-2,5-dione as pale yellow crystals (1.45 g) m.p. 294-296°. The filtrate was washed (x 3) with water, dried ($MgSO_4$) and the dichloromethane was evaporated to give a red gum. Treatment of this gum with methanol gave a further crop of the piperidin-dione (0.3 g) m.p. 293-296° but no other product could be isolated. ν_{max} 3450 (enolic OH), 1705 (carbonyl), 1365 and 1175 cm^{-1} (sulphonamide); τ (d_6-DMSO, 130°) 1.8-2.5 (1 OH, m, Ar<u>H</u>), 5.4 (2 H, s, .N.C<u>H</u>$_2$.CO), 7.0 (s, contribution from enol form) (Found: C, 48.7; H, 3.7; N, 7.0; S, 16.5; M^+ 394. $C_{16}H_{14}N_2O_6S_2$ requires: C, 48.7;

H, 3.6; N, 7.1; S, 16.2% M 394).

Reaction of phthalimidoacetyl chloride with N-cyclohexylideneaniline. Formation of phthalimidoacetic acid anhydride and 1-phenyl-3-phthalimido-1-azaspiro[5.3]nonan-2-one

To a stirred and cooled (ice-bath) solution of N-cyclohexylideneaniline (5 g) and triethylamine (3.6 g) in dry dichloromethane (200 ml), was added a solution of phthalimidoacetyl chloride (6.6 g) in dry dichloromethane (200 ml) over 40 minutes. As the acid chloride was added a red colour was produced in the solution. Precipitation of phthalimidoacetic anhydride began after 10 minutes. The mixture was stirred for 2 hours and left overnight to attain room temperature, by which time the solution had become yellow. The precipitated anhydride (2.4 g) was filtered off and washed with dichloromethane m.p. 231-232° (lit.,[179] m.p. 230-232°) ν_{max} (Nujol) 1840 (anhydride carbonyl), 1765 and 1720 cm^{-1} (imide carbonyls); (Found: C, 61.4; H, 3.0; N, 6.9; M^+ 392. Calc. for $C_{20}H_{12}N_2O_7$: C, 61.2; H, 3.1; N, 7.1% M 392).

The dichloromethane washings were combined with the previous filtrate and washed (x 3) with water. After drying ($MgSO_4$) the dichloromethane was evaporated, leaving a red gum. This gum was treated with a small quantity of methanol and filtered to give the ß-lactam as a white powder which was crystallised from methanol (0.2 g, 2%) m.p. 278-279° (lit.,[178] m.p. 278-279°) ν_{max} (Nujol) 1765, 1720 (imide carbonyl) and 1740 cm^{-1} (lactam carbonyl); τ 2.23-2.96 (9 H, m, $C_6\underline{H}_4(CO_2)N$- and $C_6\underline{H}_5$), 5.12 (1 H, s,

H-3), 8.02-8.40 (10 H, m, $-C_5\underline{H}_{10}-$); (Found: C, 73.1; H, 5.5; N, 7.9; M^+ 360. Calc. for $C_{22}H_{20}N_2O_3$: C, 73.3; H, 5.6; N, 7.8% M 360).

Concentration of the methanol filtrate yielded phthalimidoacetanilide which was recrystallised from acetone (0.02 g) m.p. 220-221° (lit.,[179] m.p. 220-221°) ν_{max} (Nujol) 1760, 1720 (imide carbonyl) and 1680 cm^{-1}, (amide carbonyl) (Found: C, 68.8; H, 4.3; N, 10.0. Calc. for $C_{16}H_{12}N_2O_3$: C, 68.6; H, 4.3; N, 10.0%).

The yields of the three products under varying conditions are given below, with the percentage purity of the acid chloride used.

% acid chloride	anhydride	β-lactam	anilide
100[a]	2.4 g (41%)	0.2 g (2%)	0.02 g
100[b]	0.4 g (7%)	3.9 g (38%)	0.01 g
100[c]	0.7 g (12%)	2.7 g (26%)	-
80[d]	2.4 g (41%)	1.1 g (10%)	0.01 g
50[d]	4.1 (70%)	0.2 g (2%)	-

a - a three day old sample of acid chloride

b - acid chloride added solid

c - acid chloride added in dichloromethane

d - plus phthalimidoacetic acid to 100%.

1-Phenylazetidin-2-one

To dry dimethylsulphoxide (10 ml) sodium hydride (0.6 g) was added under dry nitrogen. The mixture was stirred rapidly and heated to ca. 60° in an oil-bath. This temperature was maintained until gas evolution had ceased and a pale brown suspension had been obtained

(ca. 1 hour). The suspension was cooled to room temperature and a solution of 3-bromopropionanilide (4.6 g) in a mixture of dry dimethylsulphoxide (10 ml) and dry dichloromethane (40 ml) was added dropwise over 40 minutes. The mixture was then left to stand overnight, washed (x 3) with water, dried ($MgSO_4$) and the solvent evaporated. The residual gum crystallised on standing in ethylacetate and a recrystallization gave the β-lactam as large white crystals (2.1 g, 70%) m.p. 77-77.5° (lit.,[37] m.p. 77-78°), ν_{max} (Nujol) 1735 cm^{-1} (lactam carbonyl), τ 2.60-3.0 (5 H, m, Ar<u>H</u>), 6.40 (2 H, tr, J=2 Hz, <u>H</u>-3), 6.92 (2 H, tr, J=2 Hz, <u>H</u>-4) (Found: C, 73.4; H, 6.1; N, 9.5; M^+ 147. Calc. for C_9H_9NO: C, 73.5; H, 6.2; N, 9.5% M 147).

The following were similarly prepared from the corresponding anilides:

<u>1-p-nitrophenylazetidin-2-one</u>. - (58%) as yellow crystals m.p. 161° (lit.,[37] m.p. 161-162°) ν_{max} (Nujol) 1745 cm^{-1} (lactam carbonyl), τ 2.26 (4 H, dd, J=5 Hz, Ar<u>H</u>), 6.28 (2 H, b, J=2.5 Hz, <u>H</u>-3), 6.88 (2 H, tr, J=2.5 Hz, <u>H</u>-4), (Found: C, 56.3; H, 4.3; N, 14.6; M^+ 192. Calc. for $C_9H_8N_2O_3$: C, 56.2; H, 4.2; N, 14.6% M 192).

<u>1-o-benzyloxycarbonylphenylazetidin-2-one</u>. - (24%, crude) as a green gum (ν_{max} (Nujol) 1745 (lactam carbonyl), and 1705 cm^{-1} (benzyl ester)). T.l.c. on silica showed that the product was impure and attempts to purify by distillation (3 mm Hg) resulted in decomposition.

<u>1,4-diphenylazetidin-2-one</u>

A solution of N-benzylideneaniline (18 g) in dry

toluene (100 ml) was heated to reflux with zinc foil (6.8 g) and a crystal of iodine. Ethyl bromoacetate (16.6 g) was added in small aliquots to maintain a steady reflux. During the addition the solution became cloudy and the colour after 2 hours (all the ester having been added) was dark orange. The mixture was refluxed 30 minutes, allowed to cool and filtered. The toluene was evaporated to give a residual orange gum. Crystallization of the gum from ethylacetate gave the β-lactam as large clear plates (7 g, 31%) m.p. 154° (lit.,[85] m.p. 153-154°), ν_{max} (Nujol) 1745 cm^{-1} (lactam carbonyl), τ 2.64-2.86 (10 H, m, ArH), 6.7 (1 H, t, J=3 Hz, H-4), 7.10 (2 H, d, J=2.8 Hz, H-3) (Found: C, 80.8; H, 5.8; N, 6.4; M^+ 223. Calc. for $C_{15}H_{13}NO$: C, 80.7; H, 5.8; N, 6.3% M 223).

Similar conditions were used in the attempted preparation of 1-phenyl-1- azaspiro[5.3]nonan-2-one from cyclohexylidenaniline but no identifiable products were obtained. The attempted preparation of 1-p-nitrophenyl-4-phenylazetidin-2-one from N-benzylidene-p-nitroaniline was performed under similar conditions, and also using acetonitrile as solvent. From both reactions the only identifiable product was unreacted imine accompanied by a quantity of intractable oil.

3-Amino-1,4-diphenylazetidin-2-one hydrochloride

To a suspension of 1,4-diphenyl-3-phthalimidoazetidin-2-one (10 g) in ethanol was added hydrazine (28 ml, 1M) The suspension was refluxed for 3 hours and left overnight,

by which time a flocculant white precipitate had formed. The ethanol was evaporated and the residue stirred for 2 hours in hydrochloric acid (250 ml, 5M). The resulting suspension was filtered and the solid boiled (x 2) with distilled water (250 ml). After filtration the aqueous and acidic filtrates were combined, concentrated hydrochloric acid (30 ml) was added, and the mixture stood at 0°C for 24 hours. The β-lactam which separated was collected, dissolved in the minimum of water and re-precipitated with concentrated hydrochloric acid to give the pure β-lactam (3.2 g, 42%) as a white powder m.p. 237-238° (dec) (lit.,[181] m.p. 237-238° (dec)) ν_{max} (Nujol) 1740 cm^{-1} (lactam carbonyl) (Found: C, 65.5; H, 5.3; N, 10.3. Calc. for $C_{15}H_{15}ClN_2O$: C, 65.5; H, 5.5; N, 10.2%).

3-Amino-1-phenyl-1-azaspiro(5.3)nonan-2-one hydrochloride was prepared from 1-phenyl-3-phthalimido-1-azaspiro(5.3) nonan-2-one using similar conditions and was obtained as a white powder (38%) m.p. 236° (dec) ν_{max} (Nujol) 1745 cm^{-1} (lactam carbonyl) (Found: C, 63.0; H, 7.1; N, 10.3. $C_{14}H_{19}ClN_2O$ requires: C, 63.0; H, 7.2; N, 10.5%.

Attempted Preparation of 3-amino-1-p-nitrophenyl-4-phenylazetidin-2-one hydrochloride

Method 1. - A suspension of 1-p-nitrophenyl-4-phenyl-3-phthalimidoazetidin-2-one (10 g), ethanol (25 ml) and ethanolic hydrazine (27 ml, 1 M) was heated under reflux for 2 hours during which time a bulky precipitate was found. The mixture was left overnight at room temperature and the ethanol was evaporated. The residue was stirred

with hydrochloric acid (250 ml, 5 M) for 2 hours and filtered to give a yellow filtrate. Addition of concentrated hydrochloric acid to this failed to induce precipitation but on concentration of the solution a yellow solid (0.12 g) m.p. 195° (dec) was obtained which was shown by its infra-red spectrum not to be a lactam and was not identified ν_{max} (Nujol) 3400, and 1670 cm^{-1}.

Method 2. - A mixture of 1-p-nitrophenyl-4-phenyl-3-phthalimidoazetidin-2-one (1 g) ethanol (25 ml) and ethanolic hydrazine (2.7 ml, 1 M) was stirred at room temperature for 15 minutes when a bulky precipitate had formed. The ethanol was evaporated and the residue extracted with hydrochloric acid (25 ml, 5 M) for 30 minutes. The insoluble phthalhydrazide was filtered off and to the filtrate concentrated hydrochloric acid (15 ml) was added. Concentration under reduced pressure caused the separation of a yellow solid (0.08 g) m.p. 194-195° (dec) which was shown to be the same as the product from the previous reaction (mixed melting point 194-195°) and was not identified.

3-Amino-1-phenyl-1-azaspiro[5.3]nonan-2-one hydrobromide

3-N-benzyloxycarbonylamino-1-phenyl-1-azaspiro(5.3)-nonan-2-one (0.5 g) was shaken at room temperature with a solution of hydrogen bromide in glacial acetic acid (2.5 ml, 37%). The mixture effervesced and solution was complete in 5 minutes. The solution was shaken for a further 10 minutes and dry ether was added when the

β-lactam separated as a pink powder. Two precipitations from dry methanol with dry ether gave the β-lactam as a white powder (0.38 g, 88%) m.p. 228-230° dec. ν_{max} 1755 cm^{-1} (lactam carbonyl) (Found: C, 54.1; H, 6.2; N, 8.9; Br, 25.6. $C_{14}H_{19}BrN_2O$ requires: C, 54.0; H, 6.1; N, 9.0; Br, 25.7%).

The hydrobromides of the following 3-amino-β-lactams were similarly prepared from the corresponding benzyloxycarbonylamino compounds:

3-Methylamino-1-phenyl-1-azaspiro[5.3]nonan-2-one hydrobromide in 42% yield m.p. 231-232° dec ν_{max} (Nujol) 1745 cm^{-1} (lactam carbonyl) (Found: C, 55.4; H, 6.5; N, 8.7. $C_{15}H_{21}BrN_2O$ requires: C, 55.6; H, 6.5; N, 8.6%).

3-Methylamino-1,4-diphenylazetidin-2-one hydrobromide in 30% yield, m.p. 233° dec ν_{max} (Nujol) 1745 cm^{-1} (lactam carbonyl) (Found: C, 58.0; H, 5.0; N, 8.4. $C_{16}H_{17}BrN_2O$ requires: C, 57.8; H, 5.1; N, 8.4%).

Attempted Preparation of 1-o-carboxyphenylazetidin-2-one by hydrogenolysis of 1-o-benzyloxycarbonylphenylazetidin-2-one

A solution of 1-o-benzyloxycarbonylphenylazetidin-2-one (0.6 g) in ethyl acetate (100 ml) with palladised charcoal (5%, 0.2 g) was shaken under hydrogen at atmospheric pressure until the theoretical quantity of hydrogen (48 ml) had been absorbed. Uptake was initially rapid and was complete in 2 hours. The catalyst was filtered off and the ethylacetate was evaporated. Crystallization from ethyl acetate and petroleum ether

gave a white powder (0.2 g) m.p. 127°. Infra-red analysis showed that the product was not a β-lactam (absence of carbonyl absorption above 1720 cm^{-1}) and its identity was not ascertained.

3-(N-Benzyloxycarbonyl-N-methyl)-amino-1,4-diphenylazetidin-2-one

To a solution of 3-benzyloxycarbonylamino-1,4-diphenylazetidin-2-one (0.4 g) in dry dimethylformamide (10 ml) were added methyl iodide (0.6 ml) and silver oxide (1.0 g) The mixture was stirred for 12 hours at room temperature and then filtered. Dry chloroform (50 ml) was added to the filtrate to precipitate the silver iodide which was filtered off through a glass-fibre filter. The filtrate was washed (x 2) with 5% potassium cyanide solution and then with water until the washings were free of cyanide (tested with ferricyanide) and dried ($MgSO_4$). The chloroform was evaporated and the remaining dimethylformamide removed under high vacuum. Repeated recrystallization of the residual gum from methanol and finally from ethyl acetate gave the β-lactam as a white powder (0.3 g, 72%) m.p. 117° ν_{max} (Nujol) 1745 (lactam carbonyl) and 1690 cm^{-1} (carbamate carbonyl); τ 2.6-2.90 (15 H, m, Ar$\underline{H}$), 4.55 (1 H, d, J=5 Hz, $\underline{H}$-3), 4.94 (2 H, s, Ar.C$\underline{H}_2$.O.CO), 5.05 (1 H, d, J= Hz, $\underline{H}$-4), 7.5 (3 H, s, N-C$\underline{H}_3$) (Found: C, 74.6; H, 5.7; N, 7.3; M^+ 38.6. $C_{22}H_{22}N_2O_3$ requires C, 74.6; H, 5.7; N, 7.3%; M 386).

3-(N-Benzyloxycarbonyl-N-methyl)-amino-1-phenyl-1-azaspiro [5.3] nonan-2-one

Methylation of 3-benzyloxycarbonylamino-1-phenyl-1-azaspiro[5.3]nonan-2-one in conditions similar to those described above gave 3-(N-benzyloxycarbonyl-N-methyl)-amino-1-phenyl-1-azaspiro[5.3]nonan-2-one (78%) m.p. 94.5-95° ν_{max} 1740 (lactam carbonyl), and 1690 cm^{-1} (carbamate carbonyl); τ 2.40-2.94 (10 H, m, ArH), 4.82 (2 H, s, Ar.CH_2.O.CO), 5.12 (1 H, s, H-3), 7.88 (3 H, s, N-CH_3), 8.00-8.42 (10 H, m, -$(CH_2)_5$) (Found: C, 73.0; H, 7.0; N, 7.3; M^+ 378. $C_{23}H_{26}N_2O_3$ requires: C, 73.0; H, 6.9; N, 7.4%; M 378).

3-Benzamido-1,4-diphenylazetidin-2-one

To a stirred and cooled (ice-bath) suspension of 3-amino-1,4-diphenylazetidin-2-one hydrochloride (0.82 g) in dry dichloromethane (100 ml) was added triethylamine (0.7 g). When the β-lactam had dissolved a solution of benzoyl chloride (0.4 g) in dry dichloromethane (150 ml) was added over 40 minutes with stirring. The mixture was stirred for 1 hour and left to stand overnight at room temperature. The mixture was washed (x 3) with water, dried ($MgSO_4$) and the dichloromethane was evaporated. Trituration of the residue with methanol and crystallization from methanol of the solid which separated gave the β-lactam as a white powder (0.55 g, 54%) m.p. 156-157° (lit.,[183] m.p. 157°) ν_{max} (Nujol) 3350 (amide N-H), 1740 (lactam carbonyl), and 1665 cm^{-1} (amide carbonyl); τ 2.56-2.85

(15 H, m, ArH), 4.92 (1 H, d, J=2 Hz, H-3) and 5.16 (1 H, d, J=2 Hz, H-4). (Found: C, 77.2; H, 5.4; N, 8.2; M^+ 342. Calc. for $C_{22}H_{18}N_2O_2$: C, 77.2; H, 5.3; N, 8.2% M 342).

By similar methods the following 3-amido-β-lactams were prepared:

from 3-Methylamino-1-phenyl-1-azaspiro[5.3]nonan-2-one hydrobromide and benzoyl chloride there was obtained 3-N-Methylbenzamido-1-phenyl-1-azaspiro[5.3]nonan-2-one: (38%) m.p. 87° ν_{max} (Nujol) 1740 (lactam carbonyl) and 1660 cm^{-1} (amide carbonyl) τ 2.35-2.65 (10 H, m, ArHO, 4.83 (1 H, s, H-3) 7.86 (3 H, s, N-CH_3), and 7.98-8.42 (10 H, m, -$(CH_2)_5$-). (Found: C, 75.8; H, 6.9; N, 8.0; M^+ 348. $C_{22}H_{24}N_2O_2$: C, 75.9; H, 6.9; N, 8.0% M 348).

From 3-amino-1-phenyl-1-azaspiro[5.3]nonan-2-one hydrobromide and phenoxyacetyl chloride, 2,6-dimethoxybenzoyl chloride, benzoyl chloride, p-bromobenzoyl chloride, p-nitrobenzoyl chloride, benzenesulphonyl chloride and p-methoxybenzoyl chloride respectively, there was obtained:- 3-phenoxyacetamido-1-phenyl-1-azaspiro[5.3]nonan-2-one: (54%) m.p. 154° (lit.,[181] m.p. 154°) ν_{max} 3355 (Amide N-H), 1745 (lactam carbonyl), and 1670 cm^{-1} (amide carbonyl) τ 2.48-3.12 (10 H, m, ArH), 4.75 (1 H, s, H-3), 5.68 (2 H, s, .O.CH_2CO), and 7.98-8.43 (10 H, m, -$(CH_2)_5$) (Found: C, 72.3; H, 6.6; N, 7.5; M^+ 364. Calc. for $C_{22}H_{24}N_2O_3$: C, 72.5; H, 6.6; N, 7.7% M 364).

3-(2,6-Dimethoxybenzamido)-1-phenyl-1-azaspiro/5.3/nonan-2-one: (33%) m.p. 132° ν_{max} (Nujol) 3350 (amide N-H), 1745 (lactam carbonyl) and 1665 cm^{-1} (amide carbonyl) τ 2.75-2.91 (8 H, m, ArH), 4.85 (1 H, s, H-3), 6.18 (3 H, s, OCH_3), 6.72 (3 H, s, OCH_3), and 7.88-8.15 (10 H, m, $-(CH_2)_5$) (Found: C, 70.2; H, 6.5; N, 6.9; M^+ 394. $C_{23}H_{26}N_2O_4$ requires: C, 70.0; H, 6.6; N, 7.1% M 394).

3-Benzamido-1-phenyl-1-azaspiro/5.3/nonan-2-one: (56%) m.p. 157° ν_{max} (Nujol) 3350 (amide N-H), 1740 (lactam carboxyl), and 1660 cm^{-1} (amide carbonyl) τ 2.62-2.93 (10 H, m, ArH), 4.80 (1 H, s, H-3) and 7.92-8.34 (10 H, m, $-(CH_2)_5$) (Found: C, 75.4; H, 6.5; N, 8.2; M^+ 334. $C_{21}H_{22}N_2O_2$ requires C, 75.4; H, 6.6; N, 8.4%; M 334).

3-p-Bromobenzamido-1-phenyl-1-azaspiro/5.3/nonan-2-one: (42%) m.p. 218° ν_{max} (Nujol) 3350 (Amide N-H), 1740 (lactam carbonyl), and 1665 cm^{-1} (amide carbonyl), τ 2.68-2.96 (9 H, m, ArH), 4.86 (1 H, s, H-3), 7.90-8.43 (10 H, m, $-(CH_2)_5$) (Found: C, 60.8; H, 5.1; N, 6.7; M^+ 412. $C_{21}H_{21}BrN_2O_2$ requires C, 61.0; H, 5.1; N, 6.8% M 412, 414).

3-(p-nitrobenzamido)-1-phenyl-1-azaspiro/5.3/nonan-2-one: (36%) m.p. 207° ν_{max} (Nujol) 3355 (Amide N-H), 1745 (lactam carbonyl), and 1660 cm^{-1} (amide carbonyl), τ 2.54-2.86 (9 H, m, ArH), 4.84 (1 H, s, H-3) and 7.92-8.46 (10 H, m, $-CH_2)_5$-) (Found: C, 66.3; H, 5.6; N, 11.1; M^+ 379. $C_{21}H_{21}N_3O_4$ requires C, 66.5; H, 5.5; N, 11.1; M 379).

3-Benzenesulphonamido-1-phenyl-1-azaspiro/5.3/nonan-2-one: (18%) m.p. 235° dec., ν_{max} (Nujol) 3345 (Amide N-H), 1740 (lactam carbonyl), and 1350 cm^{-1} (sulphonamide) (Found:

C, 65.1; H, 5.8; N, 7.8; s, 8.9. $C_{20}H_{22}N_2O_2$ requires C, 64.9; H, 5.9; N, 7.6; S, 8.6%).

3-p-Methoxybenzamido)-1-phenyl-1-azaspiro[5.3]nonan-2-one (62%) m.p. 184° ν_{max} (Nujol) 3355 (amide N-H), 1740 (lactam carbonyl) and 1660 cm^{-1} (amide carbonyl) τ ($CDCl_3$) 2.68-2.96 (9H, m, ArH), 4.80 (1H, s), 7.94-8.44 (10 H, m, $-(CH_2)_5$). (Found: C, 72.4; H, 6.8; N, 7.6; M^+ 364. Calc. for $C_{22}H_{24}N_2O_3$ C, 72.5; H, 6.6; N, 7.7; M 364).

Attempted Acylation of 3-amino-1-phenyl-1-azaspiro[5.3]-nonan-2-one using dicyclohexycarbodiimide

(i) With Phenoxyacetic Acid

To a phenoxyacetic acid (0.49 g), 3-amino-1-phenyl-1-azaspiro[5.3]nonan-2-one hydrobromide (1.0 g), and triethylamine (0.33 g) in dichloromethane (12 ml) was added dicyclohexylcarbodiimide (0.63 g) the mixture was shaken and left for 3 days. The dichloromethane was evaporated and the residue extracted with ether. Evaporation of the ether gave phenoxyacetyldicyclohexylurea (0.8 g) which on recrystallisation from acetone had m.p. 103-104° ν_{max} 3340 (NH) and 1680 cm^{-1}.

(ii) With p-Methoxybenzoic Acid

Treatment of 3-amino-1-phenyl-1-azaspiro[5.3]nonan-2-one with p-methoxybenzoic acid using the conditions described above gave the p-methoxybenzyldicyclohexylurea m.p. 107-108° λ_{max} 3350 and 1680 cm^{-1}.

(iii) With 2,6-Dimethoxybenzoic Acid

Using the conditions described above 2,6-dimethoxybenzoic acid failed to react and was recovered unchanged on work up.

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