THESIS

presented by

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for the degree of

DOCTOR OF PHILOSOPHY

in the

UNIVERSITY OF ASTON IN BIRMINGHAM

Pharmacy Department

University of Aston in

Birmingham

June, 1972

SUMMARY

The preparation and properties of some known azetidine-2-ones are reviewed, and the biological properties are summarised. A series of new azetidinones have been synthesised.

The cycloaddition of diphenylketene or ketene to Schiff's bases yielded the 3,3-disubstituted and the 3-unsubstituted azetidinones respectively whilst the action of acid chlorides with Schiff's bases in the presence of triethylamine yielded the 3-phenyl and 3-phenyl-3-chloro azetidinones. Anils prepared from 9-fluorenone and aromatic amines yielded spiroazetidinones. In general it was found that diphenylketene and the fluorenone anils were the most reactive compounds.

The mechanism of these reactions are discussed in the light of the experimental results and the theoretical foundation of the Woodward-Hoffman rules for the Conservation of Orbital Symmetry.

Some nucleophilic ring opening reactions of azetidine-2-ones with sodium hydroxide, lithium aluminium hydride and methyl magnesium bromide are described and possible mechanisms for the reactions outlined.

Azetidine-2-ones have been shown to undergo acid-catalysed rearrangements to yield a variety of products. The reaction of 1-phenyl azetidinones with concentrated sulphuric acid yielded 3,4-dihydroquinoline-2(1H)-ones.

In the presence of boron trifluoride etherate and toluene as solvent the rearrangement of azetidine-2-ones results in the formation of a propionamide by ring opening of the azetidinone and electrophilic substitution of the intermediate into the aromatic ring of the solvent. Anisole has also been shown to undergo this reaction.

1,3,3,4-Tetraphenylazetidine-2-one also undergoes rearrangement in the presence of boron trifluoride etherate in toluene to yield the 2,3-diphenylindene-1-one rather than the propionamide by intramolecular electrophilic attack with the extrusion of aniline.

Rearrangement of 1,4-diphenylazetidine-2-one in the presence of boron trifluoride etherate in an inert aromatic solvent leads to rapid β -elimination

of the proton to yield cinnamanilide.

The mass spectra of a selection of azetidinones and 3,4-dihydroquinoline-2(1H)-ones are recorded and possible fragmentation pathways are suggested for these compounds.

ACKNOWLEDGEMENTS

The author would like to thank Dr. W.J. Irwin for his help and encouragement during the completion of this work; and Stirling - Winthrop Ltd. for the award of a research grant at the start of this work and the Pharmacy Department for a grant enabling this work to be completed.

"The great tragedy of Science - the slaying of a beautiful hypothesis by an ugly fact"

T.H. Huxley

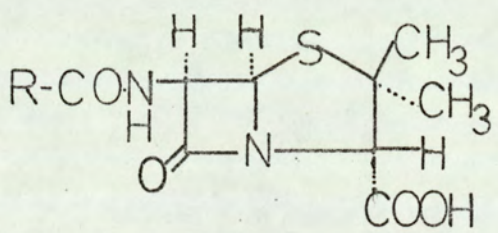
CONTENTS

INTRODUCTION

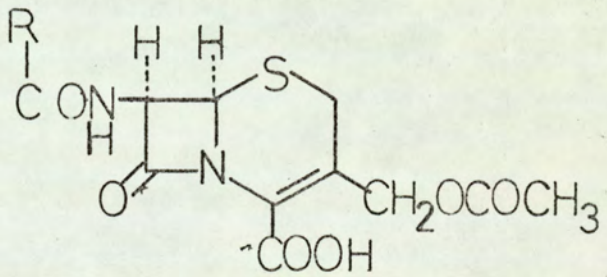
A. PREPARATION OF AZETIDINE-2-ONES

Perhaps the most important compounds to contain the azetidine-2-one structure are the penicillins (1). the antibacterial activity of which was first recognised by Fleming in 1928, when he observed that staphylococcus cultures were inhibited and were undergoing lysis in the vicinity of a contaminant mould, Penicillium notatum.

It was not until 1943 however, when the importance of penicillin was recognised, that a concerted effort was made by Britain and America to isolate and identify the active principal. The sodium salt of benzylpenicillin was isolated in 1943 and the structural elucidation, by chemical methods, electron density projections and infrared spectroscopic studies, was completed in 1945.[1]



(1)



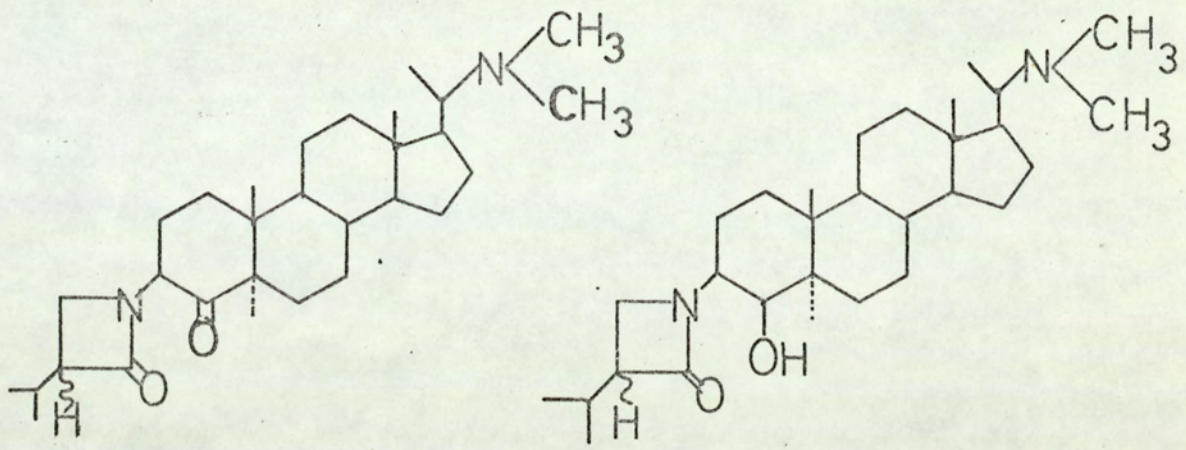
(2)

R = CH_2-Ph = benzylpenicillin

R= CH_2-CH_2-CH_2-CH(COO^-)(NH_3^+)

Cephalosporin C (2), another naturally occurring azetidinone with antibacterial activity, is a metabolite of Cephalosporiumacremonium and was isolated by Newton and Abraham in 1955.[2] The structure was established in 1961 through chemical [3] and X-ray crystallographic [4] studies and was shown to contain a fused azetidinone and dihydro-1,3-thiazene ring system.

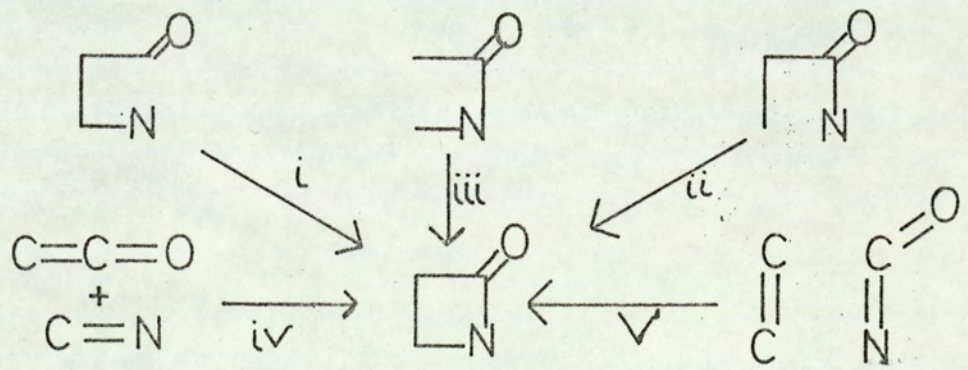
More recently the Japanese workers Kikuchi and Uyeo[5] have examined the alkaloids from Pachysandra Terminalis and isolated two components (3) which contain the azetidinone ring system.



(3)

Although[a] naturally occurring azetidine-2-one ring system was not recognised until 1945 the first synthetic azetidine-2-ones were reported by Staudinger in 1907.[6] After his initial work, however, few publications appeared until the post war interest in penicillins developed.

Azetidine-2-ones have been prepared by many different routes and the synthetic methods which follow are classified as far as possible by considering the bond which is formed during the cyclisation stage.



(i) Formation of bond 1 → 2

(ii) Formation of bond 1 → 4

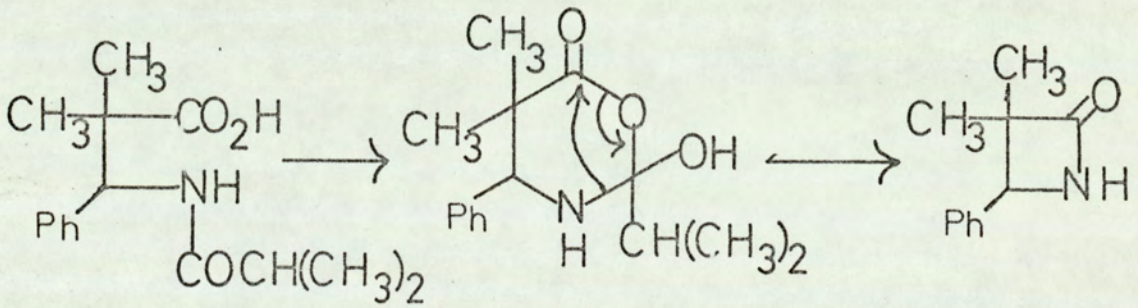
(iii) Formation of bond 3 → 4

(iv) Formation of bonds 1 → 2 and 3 → 4

(v) Formation of bonds 1 → 4 and 2 → 3

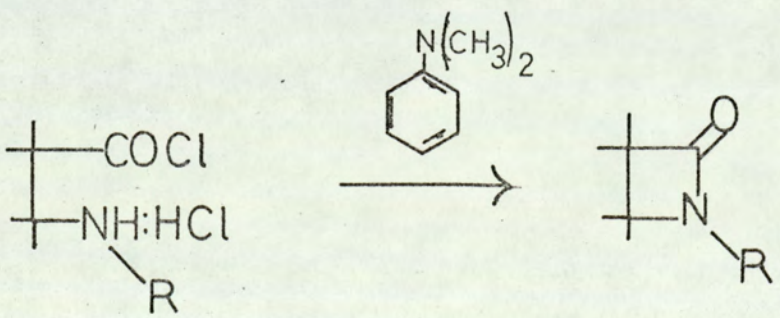
1) Ring Closure at the 1-2 Bond

The thermal dehydration of β-amino acids has never been accomplished but the cyclisation of β-amino derivatives to azetidine-2-ones has been shown to be a useful synthetic methods. Thus acyl amino derivatives undergo ring closure when heated above their melting points [7,8] with expulsion of a molecule of the acyl acid. Sheehan and Corey[9] have suggested that this ready cyclisation, compared to the failure of the ring closure with the free acids, may be due to the formation of a cyclic intermediate (4) which undergoes acyl migration to give the azetidinone. Cyclisation of the -β-amino acid by Staudinger[7] using acetyl chloride presumably proceeded by this mechanism but the intermediate β-acylamino acid was not isolated.



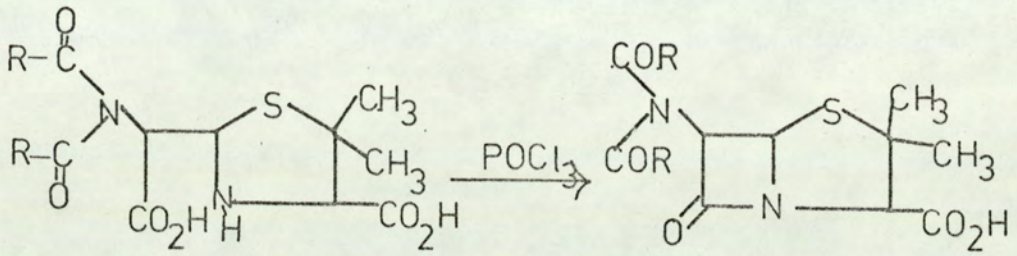
(4)

Blick and Gould [10] and Testa, Fontenella and Fava [11] independantly isolated the acid chloride hydrochlorides (5) from the β-amino acids and reported the base catalysed cyclisation to the azetidine-2-one.



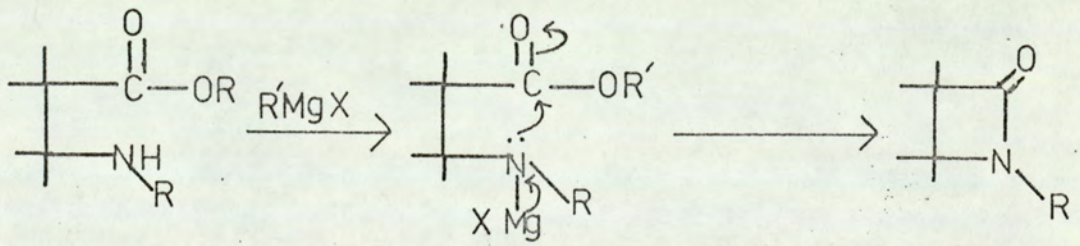
(5)

This method is an extension of that used by Sheehan and Cruikshank[12] who previously ring closed a thiazolidine acid (6) using thionyl chloride or phosphorous oxychloride, without isolating the intermediate acid chloride. Later the total synthesis of penicillin was achieved by Sheehan and Henry Logan[13] who used N, N' -dicyclohexyl-carbodiimide (D.C.C.) to effect the formation of the amide bond.



(6)

A further modification of the synthesis from β-amino acids is the ring closure of esters using a Grignard reagent which was first reported by Breckpot in 1932.[14] This reaction involves the conversion of the amine into its conjugate base to facilitate attack at the carbonyl group (7).

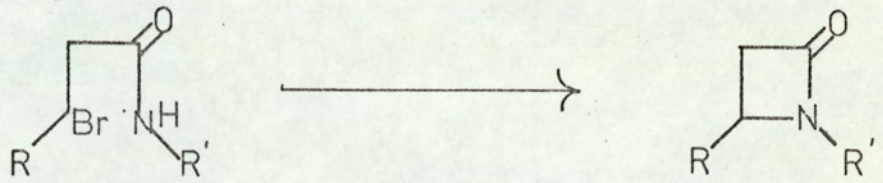


(7)

2) Ring Closure at the 1-4 Bond

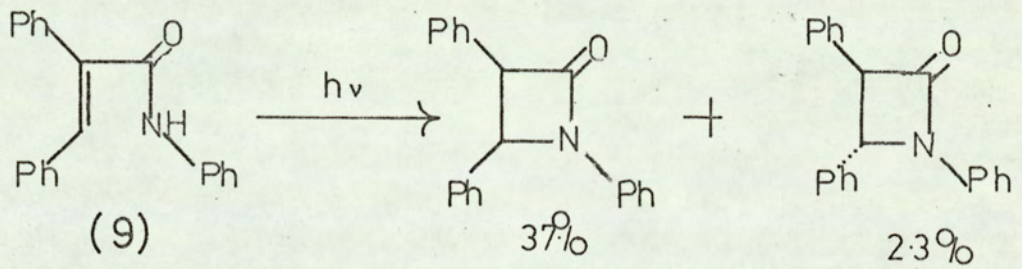
Knunyants and Gambaryan[15] successfully synthesised an azetidinone by the ring closure of β-bromo- β-phenylpropionamides (8) on treatment with sodium or potassium amide in liquid ammonia. When β -alkyl- β -bromopropion-amides were used some azetidinone was formed but the major product was the unsaturated amide. The extra stabilisation of the carbonium ion intermediate provided by the β-phenyl group reduces the β- elimination which gives the unsaturated amides.

Ring closure of N-benzyl β-bromopropionamide was effected by the use of sodium hydride in boiling toluene by Blick and Gould[10] and potassium butoxide by Manhas and Jeng.[16]



(8)

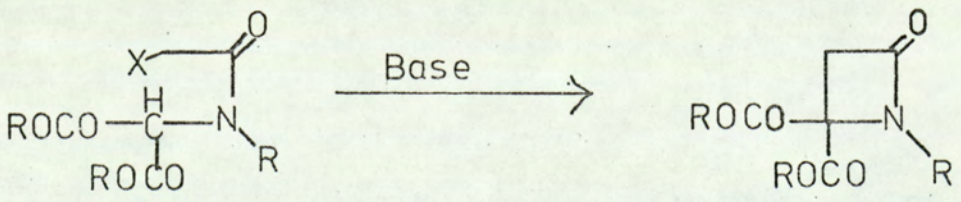
Chapman and Adams[17] have shown that U.V. irradiation of α-β-unsaturated amides (9) can produce both the Cis and the Trans isomers of some azetidinones.



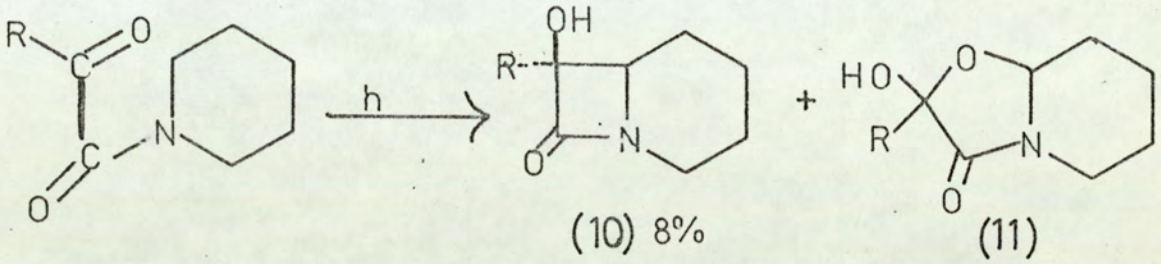
(9)

3) Ring Closure at the 3-4 Bond

Sheehan and Bose[18] reported the formation of an azetidinones by intramolecular alkylation of an α-haloacylaminomalonic ester. The reaction, which only occurs with secondary aminomalonates, is effected by a variety of weak bases. Ring closure of α-haloacylaminoacetic acid esters using potassium hydroxide has been reported by Chatterjee.[19] The ease of reaction and high yields are in contrast to the formation of cyclobutanes by an anolagous reaction, where strong bases are required.



Recently[20] a 3-hydroxy fused ring azetidine (10) has been formed by the U.V. irradiation of α- diketones. The yields were very poor and the major products are oxazolidones (11).

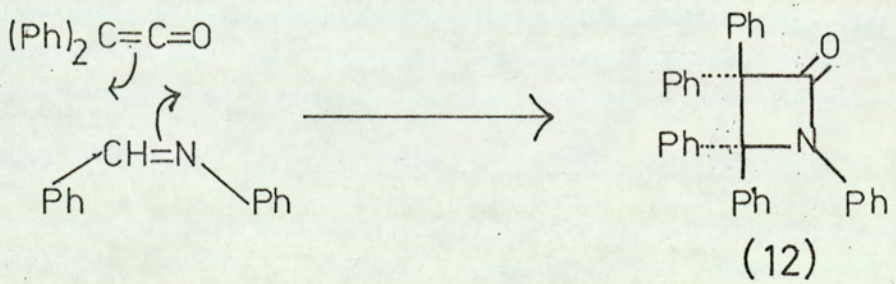


(10) 8% (11)

4) Ring Closure at the 3-4 and 1-2 Bonds

(a) Addition of Ketenes to Imines

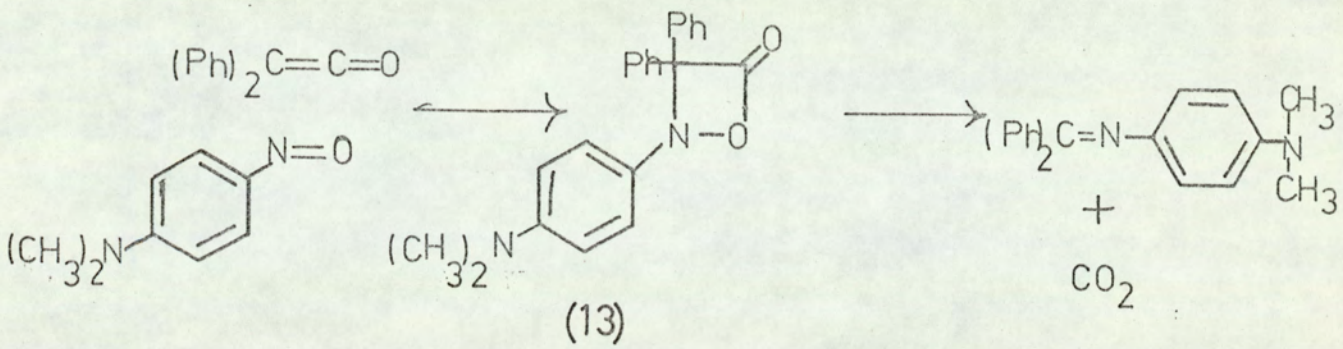
This reaction was used by Staudinger in the first reported synthesis[6] of an azetidine-2-one. For example the addition of diphenylketene to benzylidene aniline proceeded smoothly at room temperature to yield the tetraphenylazetidine-2-one (12). This reaction has been used extensively for the preparation of a great variety of azetidinones from different ketenes, which may be isolated or prepared in situ, and a large number of imines.



(12)

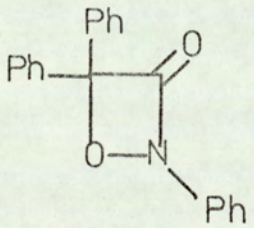
Staudinger and Jelagin[21] found that the addition of diphenylketene to p-nitrosodimethyl aniline yielded the penta substituted azetidine-2-one. This is thought to involve a cycloaddition to give the oxazetidinone (13) which loses carbon dioxide with the formation of the Schiff's base. Addition of

a second mole of ketene gives the azetidine-2-one.



(13)

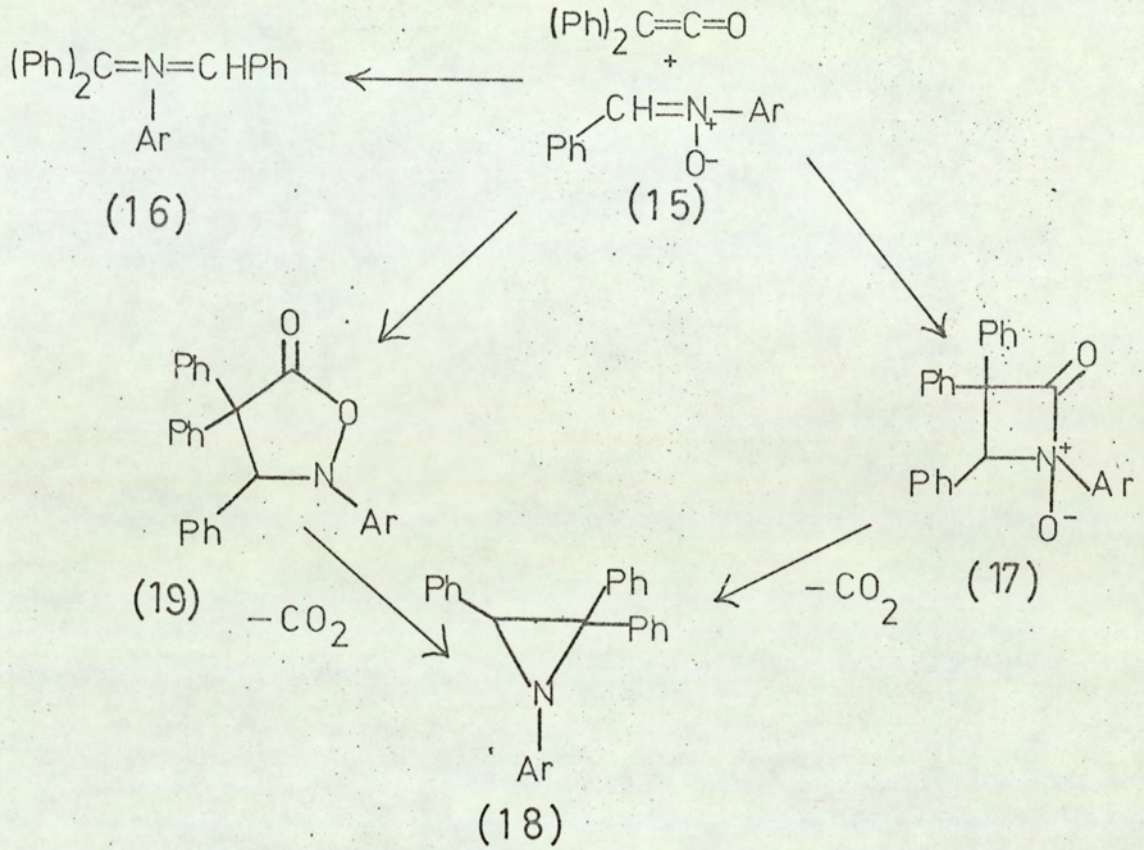
In the absence of the electron releasing dimethylamino group the polarity of the nitroso group is reversed and addition of diphenylketene yields the stable oxazetidine (14).



(14)

In the reaction between diphenylketene and nitrones (15) Staudinger and Miescher[22] proposed a similar reaction to the nitrosocompounds to give an intermediate which underwent decarboxylation yielding a compound formulated as (16).

This reaction was studied and re-evaluated by Taylor Owen and Whittaker[23] who proposed the azetidinone -N oxide structure (17) and the aziridine (18) as the intermediate.



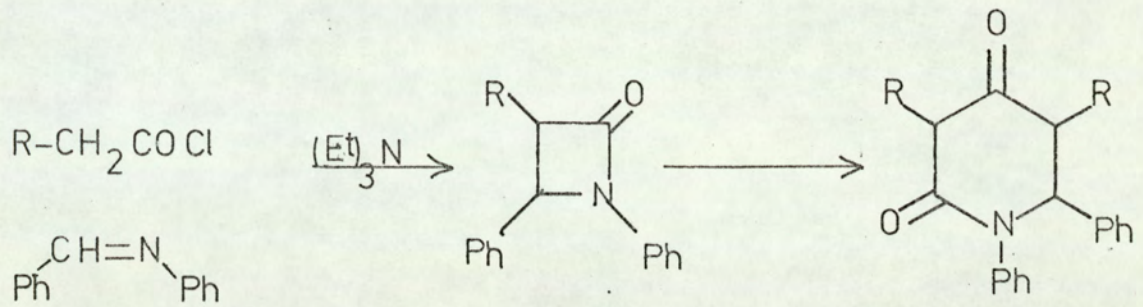
Further work by Hassell and Lippman[24] postulated attack by the ketene at the ortho-position of the N-phenyl ring in the nitrone.

In view of the lack of evidence for the structure for the intermediate and the known 1-3 dipolar additions of nitrones[25] a further interpretation may be the formulation of the intermediate as an isoxazolidin-5-one (19) which could then lose carbon dioxide to give the aziridine (18).

b) Addition of Acid chlorides to Imines.

This method was initially used by Sheehan and Ryan[26] for the preparation of 3-acyaminoazetidinones related to penicillins. It has been developed since[27,28,29,30,] to include many different acid chlorides to give a variety of 3-substituted azetidinones. The reaction usually proceeds quite rapidly

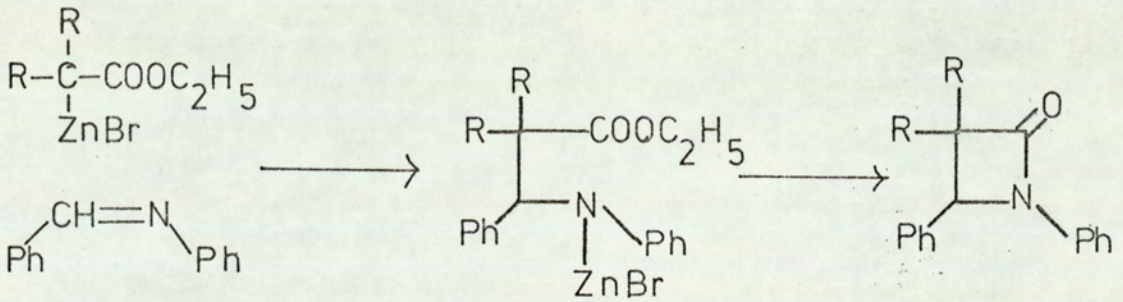
with triethylamine, using chloroform solvent and a high dilution to prevent the reaction with another molecule of acid chloride to produce a piperidinedione (20)



(20)

c) Reformatsky Reaction.

Gillman and Speeter[31] found that the reaction of a Schiff's base with an α-bromoester under the conditions of the Reformatsky reaction yielded azetidine-2-ones. Nucleophilic attack of the organozinc complex at the C = N of the Schiff's base to give a bromozinc complex (21) analogous to that formed during the cyclisation of β-amino esters by Grignard reagents is the most probable mechanistic pathway.

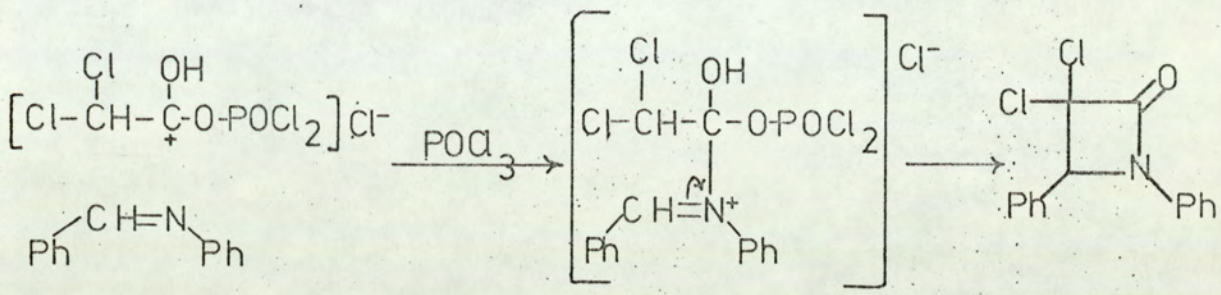


(21)

The stereospecificity of this reaction has been found by Kagan and Luche[32] to be modified by the polarity of the solvent used. The cis configuration of substitution at C-3 and C-4 is favoured by the more polar solvents whilst the trans -isomer is favoured by non-polar solvent.

d) α-Haloacids and Imines.

An interesting reaction between α-haloacids and Schiff's bases in dimethylformamide in the presence of phosphorous oxychloride has been found to yield the azetidinones[33] via unstable adducts (22).

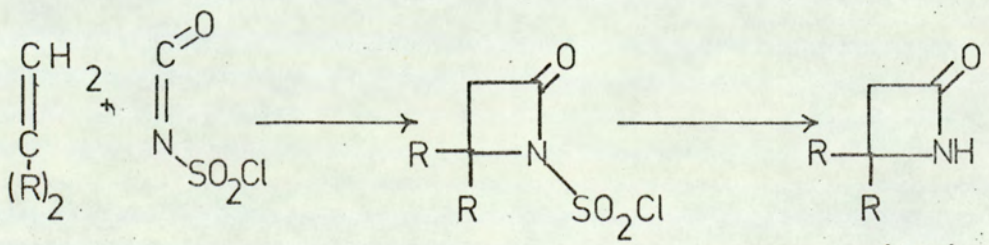


(22)

5) Ring Closure at the 1-4 and 2-3 Bonds.

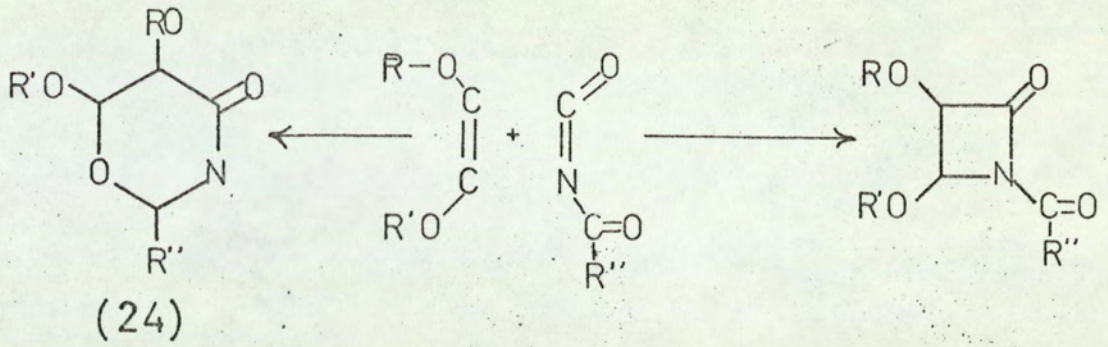
The addition of a simple isocyanate to an olefinic double bond has not been reported. However, azetidinones can be obtained if either of the reactants has been activated by electron withdrawing groups in the isocyanate or electron donating groups in the olefin.

Chlorosulphonylisocyanate addition to a terminal olefinic double bond to give azetidinones was reported by Graf in 1963[34]. The N unsubstituted azetidinones (23) which are often difficult to prepare, may be obtained by reduction of the sulphonyl halides in the presence of thiophenol and pyridine.



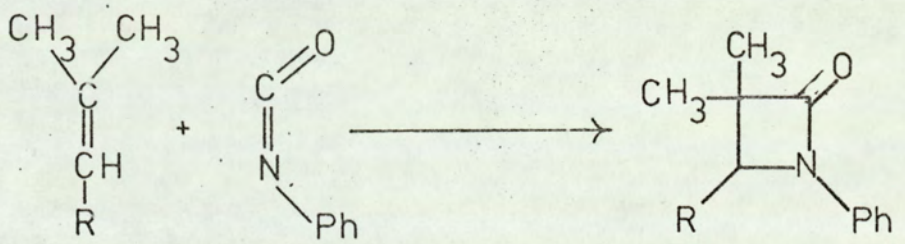
(23)

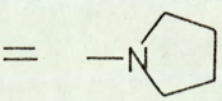
Benzoylisocyanates and acylisocyanates have been shown to react with vinyl ethers by Lattrel[35] to produce azetidinones and 1,3-oxazin-4-ones (24).



(24)

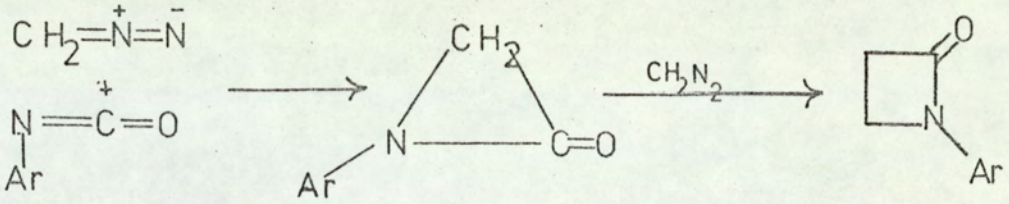
The reaction of phenylisocyanate with activated olefins such as vinyl ethers[36] and enamines[37] has been used to prepare azetidinones. This reaction must be kept extremely dry because the slightest trace of moisture is enough to hydrolyse the extremely labile 4-aminoazetidinones (25).



(25) R = 

= $-O-C_4H_9$

Sheehan and Izzo[38] found that two moles of diazomethane react with phenylisocyanate and p- bromophenylisocyanate to give the monosubstituted azetidinone. They thought that the reaction probably proceeds via an aziridinone (26). This method seems to be of limited scope, only the phenyl- and p-bromophenylisocyanate gave azetidinones from the several aryl isocyanates used.

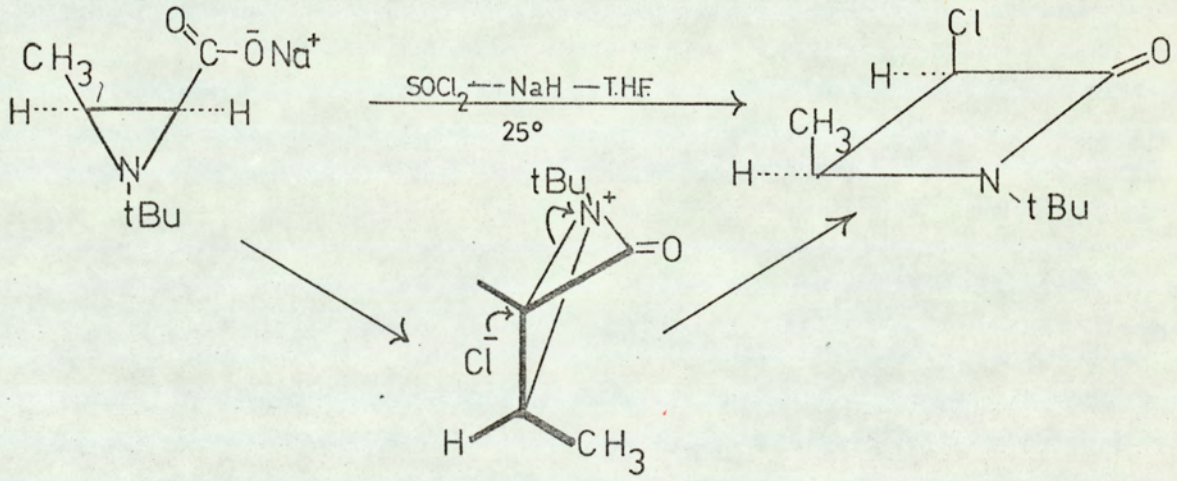


(26)

6) Rearrangements.

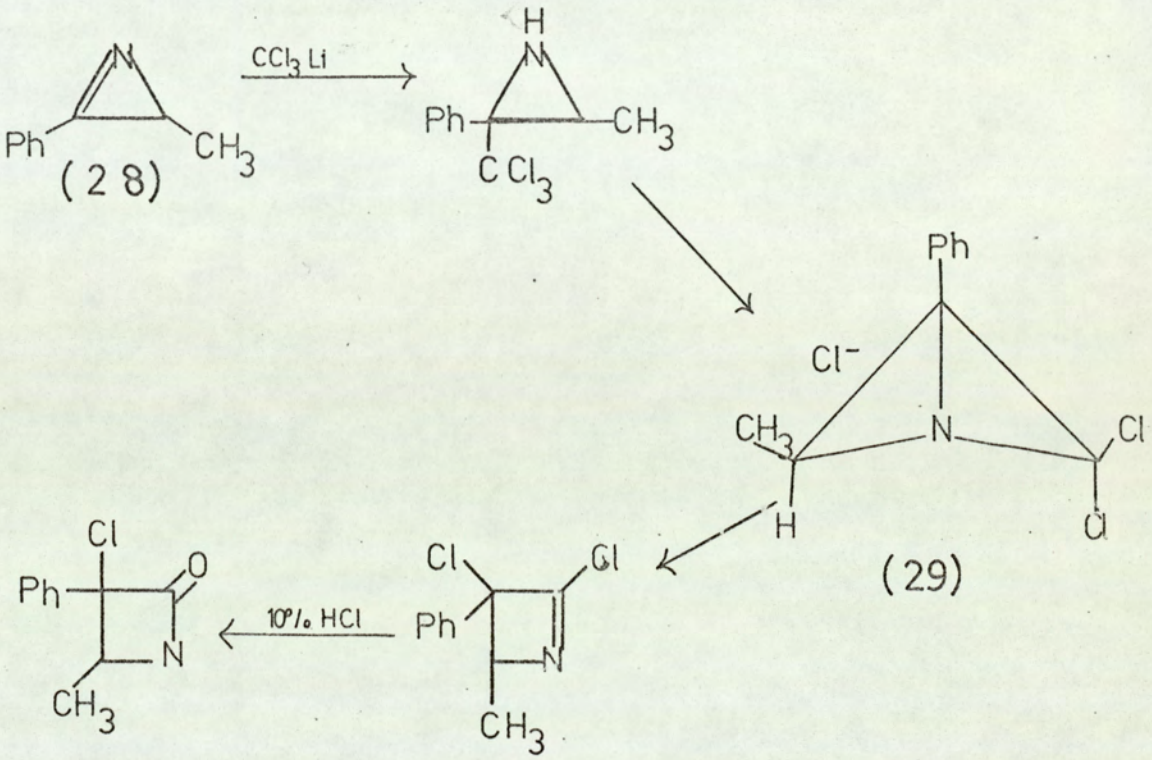
(a) Ring expansion.

Deyrup and Clough[39] found that when the sodium salt of an aziridine carboxylic acid was treated with thionyl chloride it did not give the acid chloride, but underwent ring expansion to the azetidinone. The stereospecificity, which is always a cis -substitution, indicated that the reaction proceeded via the azabicyclobutonium cation (27).

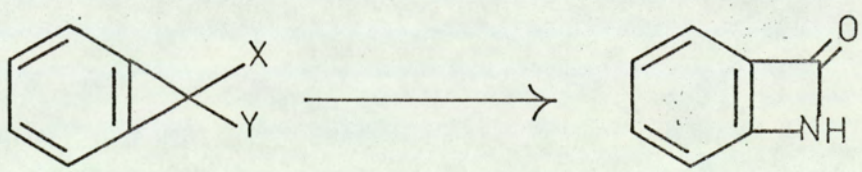


(27)

Hassner et al[40] found that azirines (28) underwent ring expansion via the postulated azabicyclobutane intermediate (29) to give an azetine which could be readily transformed to the azetidinone.



Recently Wasserman and Baird[41] have reported the expansion of a cyclopropane (30) to an azetidinone using sodium azide in tetrahydrofurane buffered to pH 5.5.

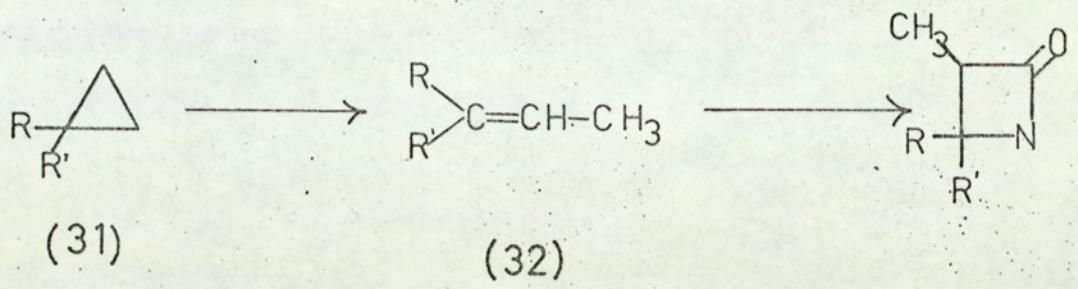


(30)

X=Y = N and X=OH, Y= N

Another cyclopropane ring expansion was carried out by Moriconi et al[42] when they treated cyclopropanes (31) with chlorosulphonylisocyanate to yield the

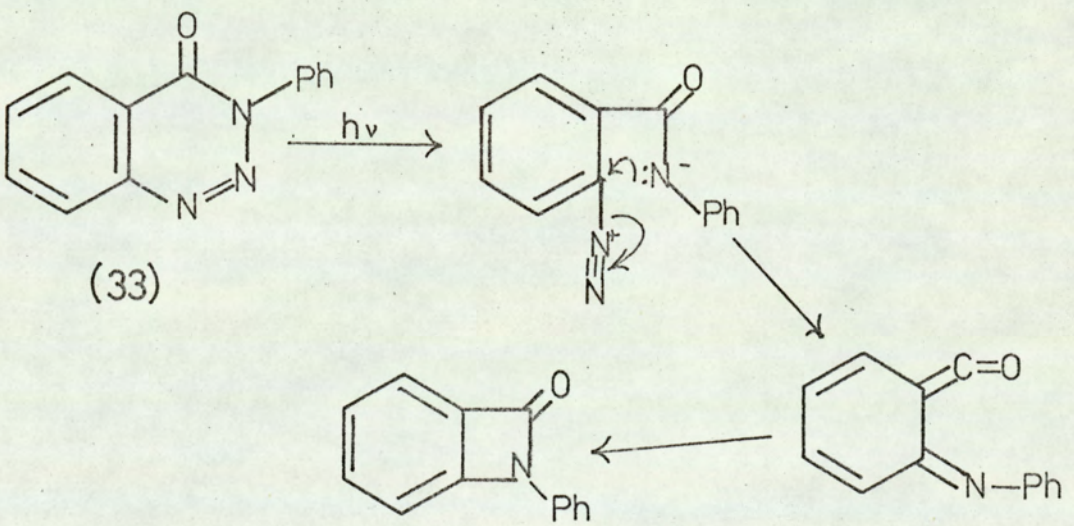
azetidinone. The most probable mechanistic pathway is ring opening of the cyclopropane to an olefin (32) and then addition of the isocyanate to the olefinic double bond (see section 5).



(31) (32)

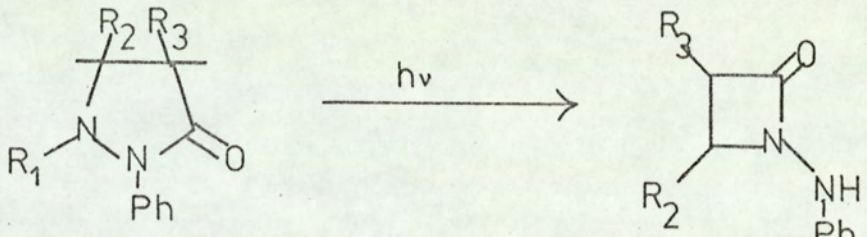
b) Ring Contraction

Photolysis of a 1,2,3-triazanapthalene-4-one (33) was shown by Ege and Pasedache[43] to yield a bicycloazetidinone with the expulsion of nitrogen.



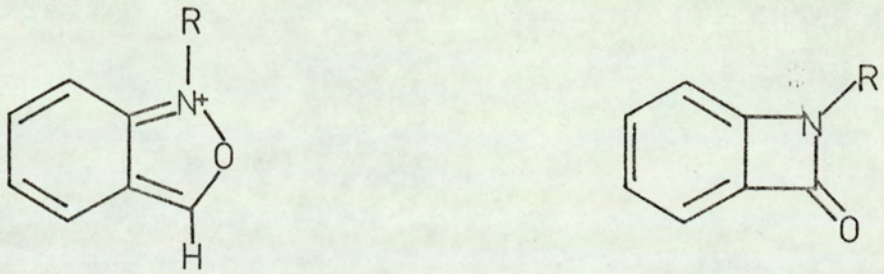
(33)

Similarly Ege[44] found that u.v. irradiation of pyrazolidin-5-one (34) caused a ring contraction to yield the azetidinone when R_1 = H. However, when R_1 = CH_3 the compound was completely stable to irradiation.



(34)

Recent reports by Olofson et al[45] have indicated that anthranilium salts (35) may be converted to azetidinones by the action of bases such as triethylamine. Only the more stable t - butyl derivatives have been isolated.



(35)

B) PROPERTIES AND REACTIONS OF AZETIDINE-2-ONES

1) Physical Properties

Azetidine-2-one was first obtained in 1949 [46] and is a colourless solid m.p. 73-74° which is soluble in ethanol and chloroform. The physical state of substitued azetidinones varies widely with both the nature and number of the substituents but in general they are stable crystalline compounds.

The X-ray data for azetidinones [47] indicates the ring to have the structure shown in Fig. 1. with the carbonyl in the plane of the ring. Cyclobutanones have also been shown to contain the coplanar ring carbonyl[48].

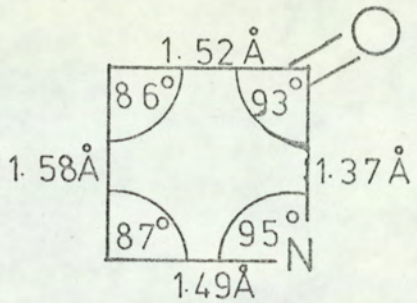


Fig 1

N-aryl substituents are shown to be approximately coplanar having an out of plane angle of 9.3°.

One extremely useful and highly characteristic property of these compounds is the infra red absorbtion spectrum. The stretching frequency of the carbonylgroup, which in open-chain amides appears at 1660 cm^{-1}, is shifted to higher wavenumbers , normally appearing at 1750 cm^{-1} in monocyclic azetidinones. In penicillins the fused thiazolidine ring adds further constraint to the N-C = O system and causes further hypsochromic shift to about 1790 cm^{-1}.

The increase in $\nu C = O$ with decreasing ring size is a general phenamenon, for example cyclohexanone absorbs at 1710 cm^{-1}, cyclobutanone at 1775 cm^{-1} and cyclopropanone at 1815 cm^{-1} [49] and is due in part to hybridisation changes due to ring strain.

Nuclear Magnetic Resonance (N.M.R.) spectroscopy has been an important method for the analysis of the stereochemistry of fused ring azetidinones. The cis and trans isomers have been designated by the difference in vicinal coupling constants of the protons on the C-3 and C-4. J cis is in the range 4.9-5.1 Hz whilst J trans is 2.2-2.5 Hz.

This has been particularly useful in determining the configuration of the azetidinone ring in the penicillins and cephalasporins and it has been shown that both contain the cis - configuration with the coupling constant in the range 4-5 Hz.

Mass spectral decomposition of azetidine-2-ones has been shown[50,51] to cleave the molecule in a reverse manner to the two basic modes of synthesis (fig2)

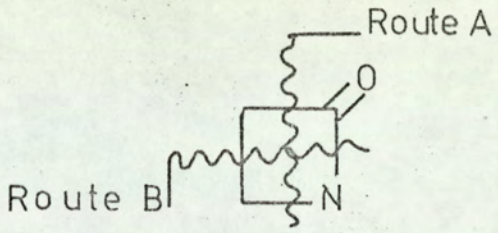


Fig 2

With an N-phenyl substituent route B is the dominant mode of fission.

2) Chemical Properties.

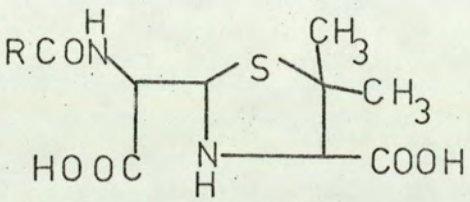
Azetidine-2-one is generally more reactive than the open chain amides. This observation can be related to the ring strain in the four-membered ring and is indicated by the high $\nu C = O$ of this compound. However, highly substituted azetidinones generally exhibit a marked drop in reactivity. This enhanced stability is perhaps due to the steric hindrance at the reaction centre.

(a) Hydrolysis

Alkaline hydrolysis is general and although there is a tremendous difference in reactivity the product is usually a β -aminoacid. The 1,4-diphenylazetidine-2-one is hydrolysed completely by refluxing for 1 hr. in methanolic 0.5 N potassium hydroxide whereas the 1,3,3,4-tetraphenylazetidine-2-one can only be hydrolysed by refluxing in 25% ethanolic potassium hydroxide for 48 hrs. In general the more substituted azetidinones are less easily hydrolysed.

Although some azetidinones have been hydrolysed by hydrochloric acid to the corresponding β -amino acids this reaction is by no means general, 1,4- diphenylazetidine-2-one is unaffected by boiling hydrochloric acid.

The acceptance of the fused azetidinone structure for the penicillins proposed by the Oxford and Merck groups in 1943 was considerably delayed by the discrepancies found between the rates of hydrolysis of penicillins and those of known azetidinones. Penicillins were found to be extremely labile to both acid and alkaline hydrolysis, undergoing ring opening to the penicilloic acids (36)



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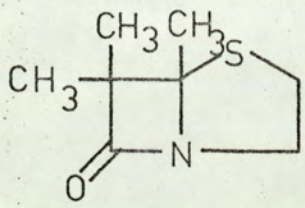


(37)

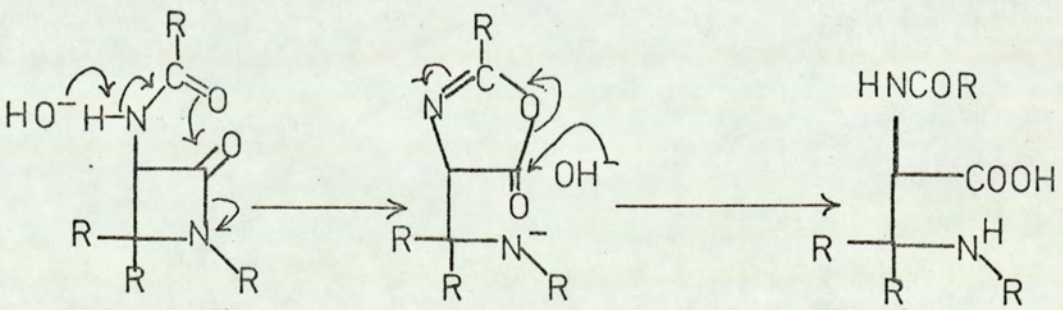
The synthetic azetidinones which were used as model compounds were all C-3-substituted monocyclic derivatives and the rates of hydrolysis were much slower than that of penicillins. However, the presence of a C-3 substituent has been shown[52] to considerably reduce the rate of hydrolysis of azetidinones (iii , table 1). This depression in the rate of hydrolysis of substituted azetidinones is attributed to steric interference with the attack of the base. A similar depression has been observed in α-substituted acyclic acid derivatives[53] (ethyl esters of phenyl and diphenylacetate, 45.3 and 3.14 10^3 k[l. mole^{-1} sec^{-1}] at 45°C respectively).

The rates of hydrolysis of unfused azetidinones have recently been compared with similar acyclic amide derivatives[73] and it has been found that azetidinones are not unusually stable to nucleophiles and in fact their lability closely follows that of the parent acyclic amides. However, there is less steric influence in 1,3- substituted azetidinones than in the corresponding linear amides. Hydrolysis of some alicyclic fused-ring azetidine-2-ones has indicated[54] that with a 1,4, - fused five membered ring (vii) the rate of hydrolysis is much greater than with a fused six membered ring (table 1 , viii)

	COMPOUND	k ($l.mole^{-1}$ Sec^{-1})
i	Azetidine-2-one	13.0[a]
ii	1-Benzyl-4-phenylazetidine-2-one	1.7[a]
iii	1-Benzyl-33-dimethylazetidine-2-one	0.04[a]
iv	1(2-isovalericacid)-3-phenylacetamido azetidine-2-one.(41).	4.0[a]
v	Benzylpenicillin	38[b]
vi	5,6,6-Trimethyl-4-thia-1-azabicyclo (3,2,0) -heptan-7-one.(38).	0.015[b]
vii	6-Phenyl-1-azabicyclo (3,2,0) heptan -7-one	3.45[c]
viii	7-Phenyl-1-azabicyclo (4,2,0) octan-8-one	0.124[d]
ix	N-methylacetamide	0.03[a]

a) 50° b) 0° c) 35° d) 44°

When a 3-acylamino substituent is present a substantial increase in the rate of hydrolysis is observed, this has been attributed to the direct participation of the acyl amino group (38)



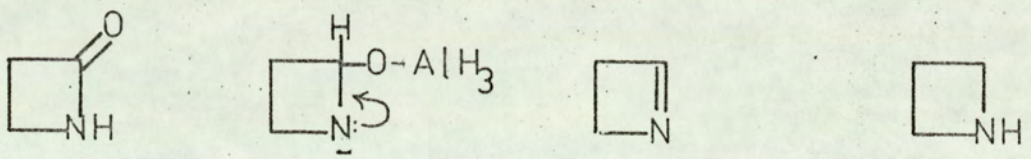
(38)

It can be seen that the increased rate of hydrolysis of penicillins can be attributed to two major functional groups on the azetidine-2-one ring (1) the 3-acylamino group which participates directly in the hydrolysis and (2) the fused five membered ring which increases the strain in the

azetidine-2-one ring.

b) Reduction.

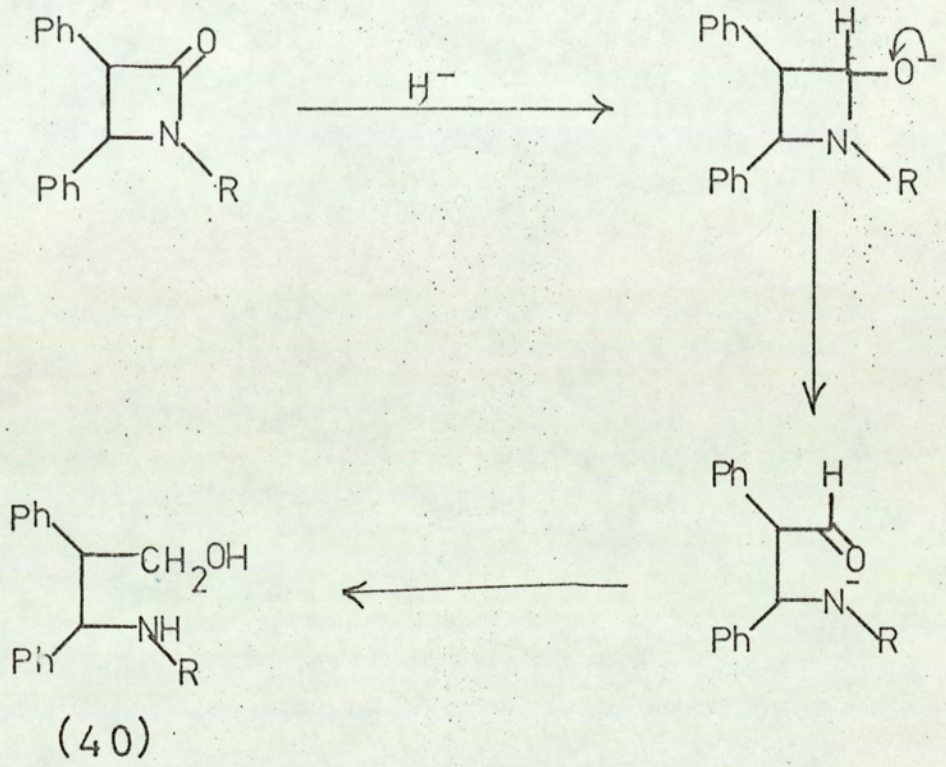
Reduction of azetidinones with lithium aluminium hydride has been used as a route to azetidine but it has only proved satisfactory with N-unsubstituted compounds.[55] This reaction probably goes via the azetine intermediate (39) which is then reduced to the azetidine. The difficulty in preparing 1,2,-unsubstituted azetidines makes this reduction as attractive synthetic method.



(38a) (39)

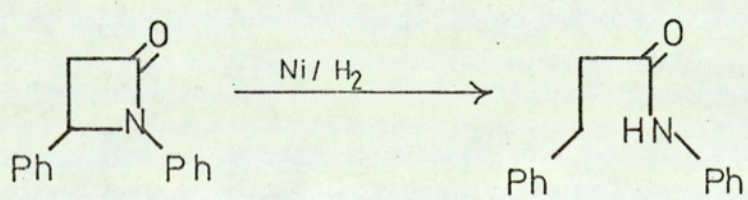
However, when N-substituents are present ring cleavage leading to γ-amino-propanols (40) invariable occurs.[56] This reaction is probably due to the relief of ring strain and can occur because of the departure of the nitrogen anion. This would be expected to be particularly favourable with 1-aryl substituents. Without a 1-substituent the azetidinone initially forms an anion (38a) which aids displacement of the aluminium moity, and retards ring-opening.

Reduction of 1,3,3,4,4-pentaphenylazetidine-2-one has been reported by Sarel et al[57] to yield the benzophenylidene aniline.

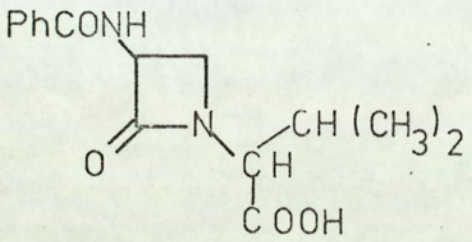


(40)

Catalytic hydrogenation, in general, does not cleave the azetidinone ring but in certain cases, such as 4-phenylazetidinones cleavage of the Ph-CH-N bond occurs to yield propionamides.[74] These compounds can be considered as derivatives of benzylamine and therefore susceptible to cleavage



When benzylpenicillin was treated with Raney nickel and hydrogen under pressure three desulphurised compounds were obtained. These compounds, desthiobenzylpenicillin (41), phenylacetyl-L-alanyl-D-valine (42) and the isobutylamide of phenylacetyl-L-alanine (43) played an important part in the elucidation of the structure of penicillin.



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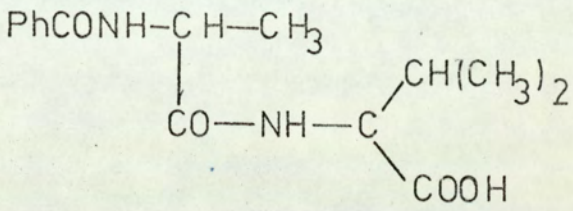

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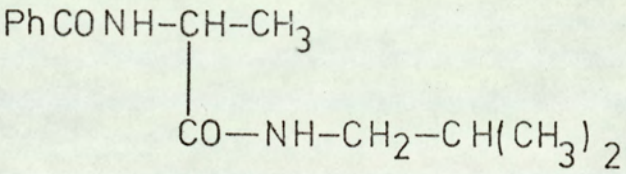
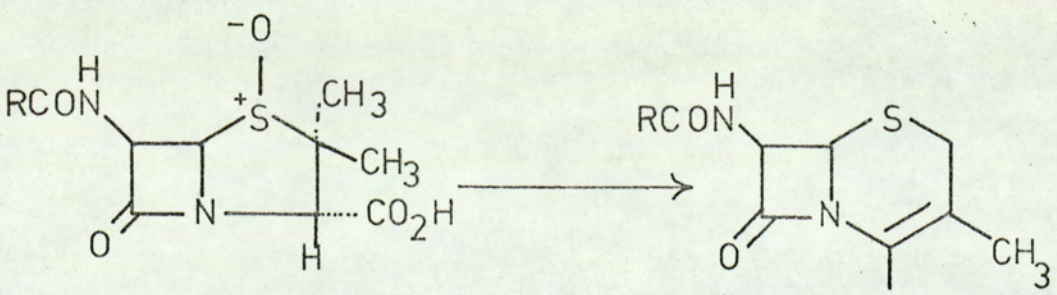


(43)

C). Rearrangements.

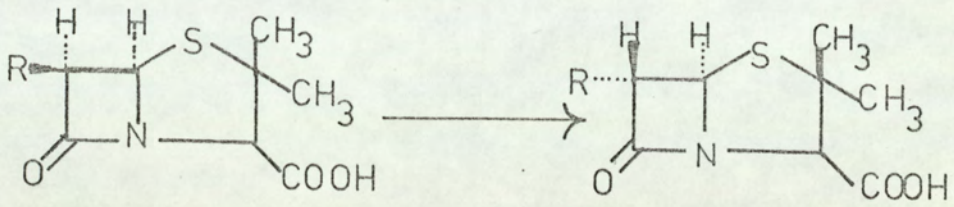
The azetidine system in penicillins takes part in many rearrangements, however a large proportion of these are due to the special lability of this system imparted by the fused thiazolidine ring. Perhaps one of the more interesting rearrangements is the ring expansion of the penicillin sulphone (44) to give a cephalosporin derivative (45).[58,59,60]



(44)

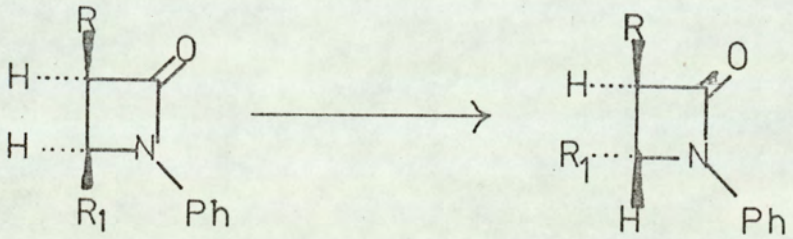
(45)

Much interest has been shown in the epimerisation in penicillins at C5-C6 to produce the epipenicillins (46) which have been shown to be considerably less active. Both aqueous alkali[61] and sodium hydride in tetrahydrofuran[62] have been used successfully to complete this inversion.



(46)

The epimerisation of cis-monocyclic azetidinones (47) has been carried out by Bose et al[63] in deuterobenzene using 1,5-diaza [4,3,0] Non-5-ene as catalyst to yield the trans-azetidinones (48).

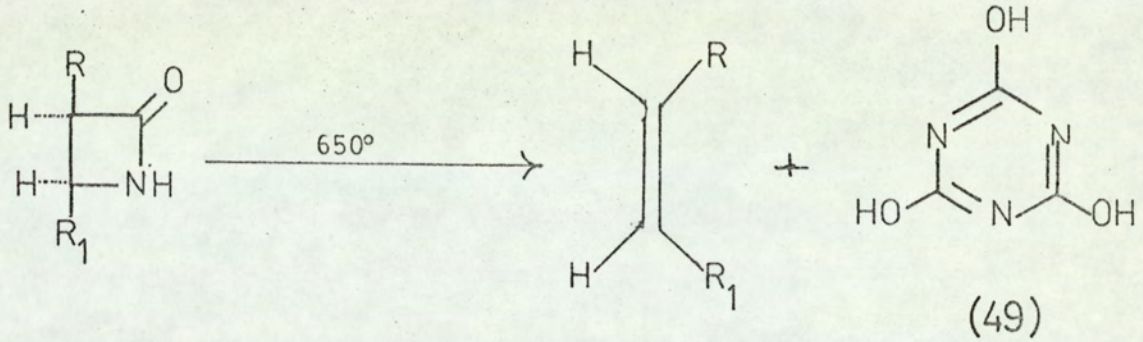


(47)

(48)

The thermal stability of azetidine-2-ones was examined by Staudinger[63] who observed both the reversal of the original cycloaddition to give a ketene and a Schiffs base and also an alternative mode of fission to give an olefin and anisocyanate.

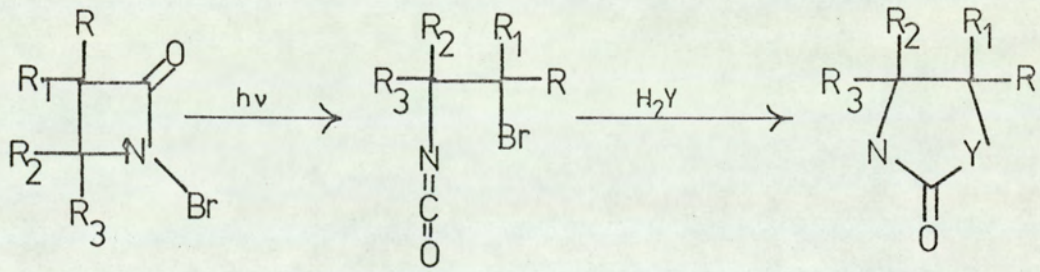
Paquette et al.[64] found that 1-unsubstituted azetidinones were thermally stable to 500° but underwent fission when heated above 650° to give an olefin, with complete retention of configuration, and cyanuric acid (49).



(49)

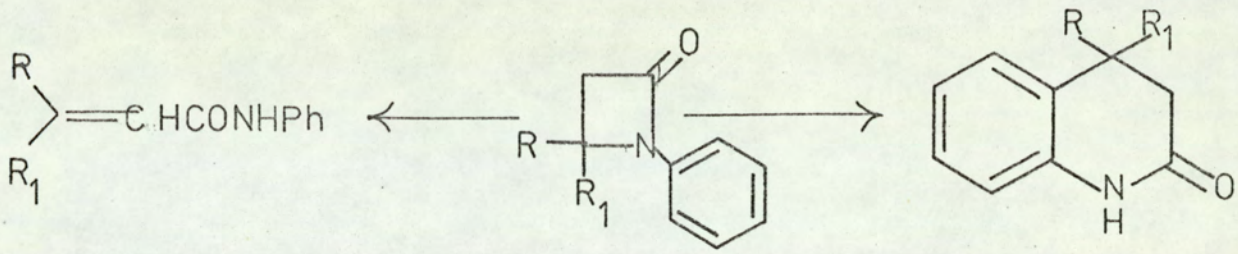
Fragmentation has also been initiated by means of ultra violet irradiation of azetidinones. Fischer[65] has found that the molecule fragments in a similar manner to the thermal fission reported by Staudinger.

Ultra violet irradiation of a 1-haloazetidine-2-one has been shown by Kampe[66] to produce a β-haloalkyl isocyanate (50). The tendency of bromine in the β-position towards neighbouring group participation can be demonstrated by means of a secondary cyclisation which occurs in some isocyanate additions of the bromoalkylisocyanates.[67]



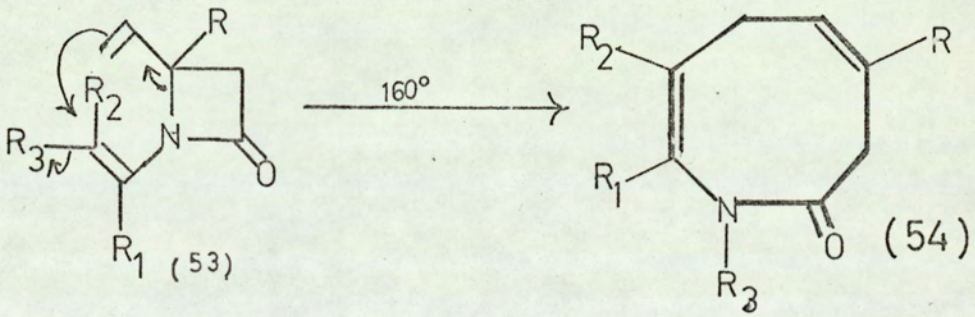
(50)

Knunyants and Gambaryan[15] found that in concentrated sulphuric acid an azetidine-2-one would ring-open at the C4-N bond and subsequent ring-closure gave the tetrahydroquinoline-2-one (51). When the substituents at C4 were alkyl residues a similar ring-cleavage gave the rearranged croton-amides (52).

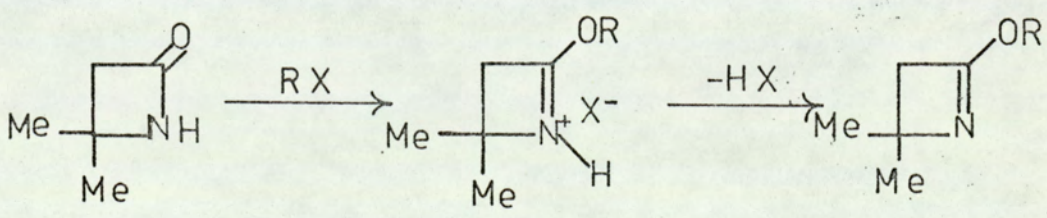


(52) R=R$_1$=Me (51) R=H, R$_1$=Ph

A Cope-type rearrangement of 1,4-divinylazetidine-2-one has been observed by Schrabel.[68] When the divinylazetidinone (53) was heated above 160° it rearranged to give the cycloazaoctadiene-2-one (54).

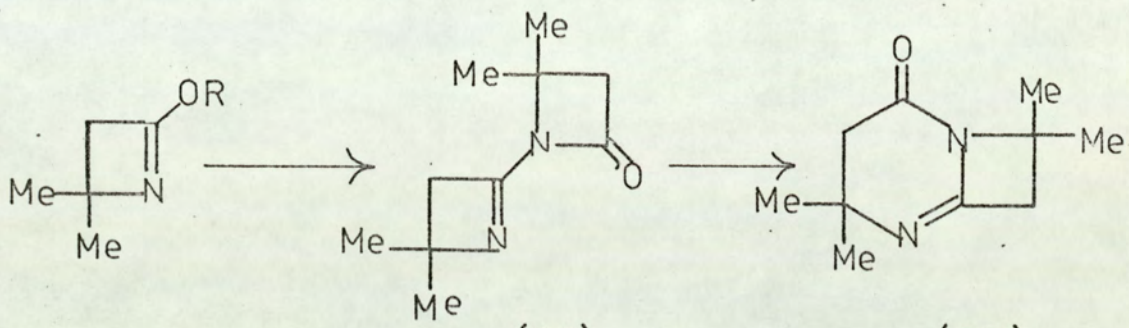


Alkylation of N-unsubstituted azetidinones[69] in the absence of bases leads to azetine ethers (55).



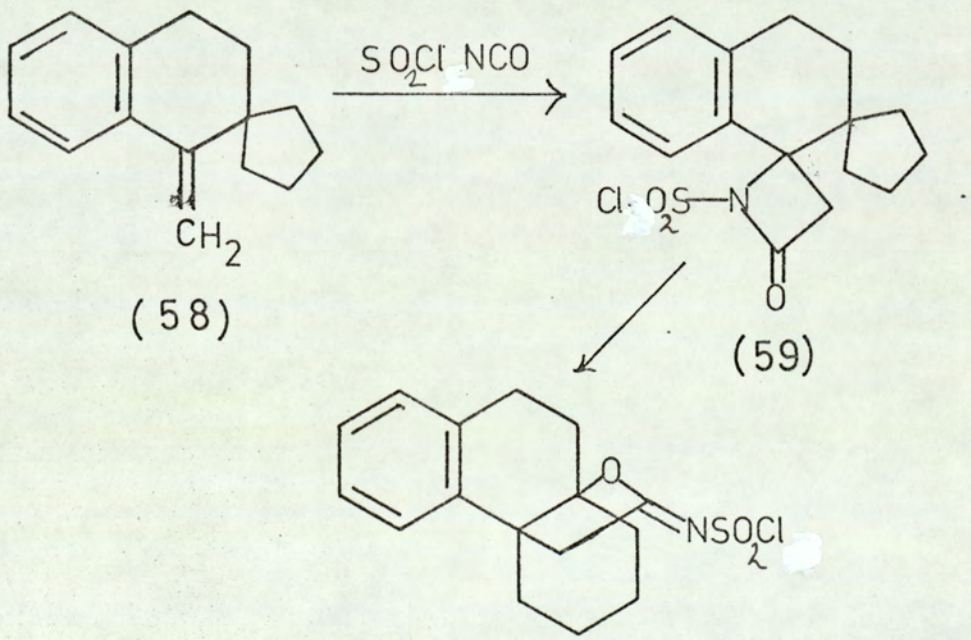
(55)

Barman found that the azetine ethers were very susceptable to nucleophilic attack at the 2-position and reaction with amines leads to the elimination of the alcohol and formation of a 2-aminoazetine (56). If, however, the reacting amine is the parent azetidinone then the aminoazetine immediately rearranges to give the 1,5-diazabicyclo [4,2,0] oct-5-ene-2-one (57).



(56) (57)

An azetidinone intermediate (59) which rearranges to give the expanded ring system (60) has been postulated by Doyle and Conway[70] in the reaction between chlorosulphonylisocyanate and the exocyclic double bond in the tetrahydronaphthalene (58), however, this has only been isolated as a transient compound at low temperatures.

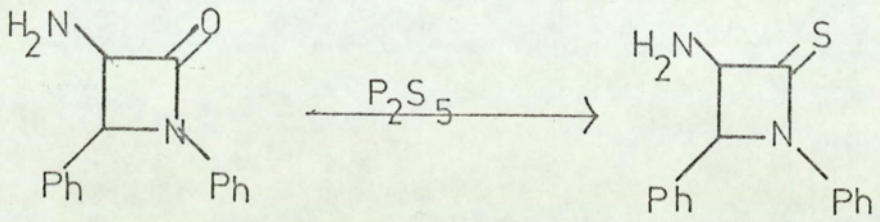


(58) (59)

(60)

d) Sulphurisation

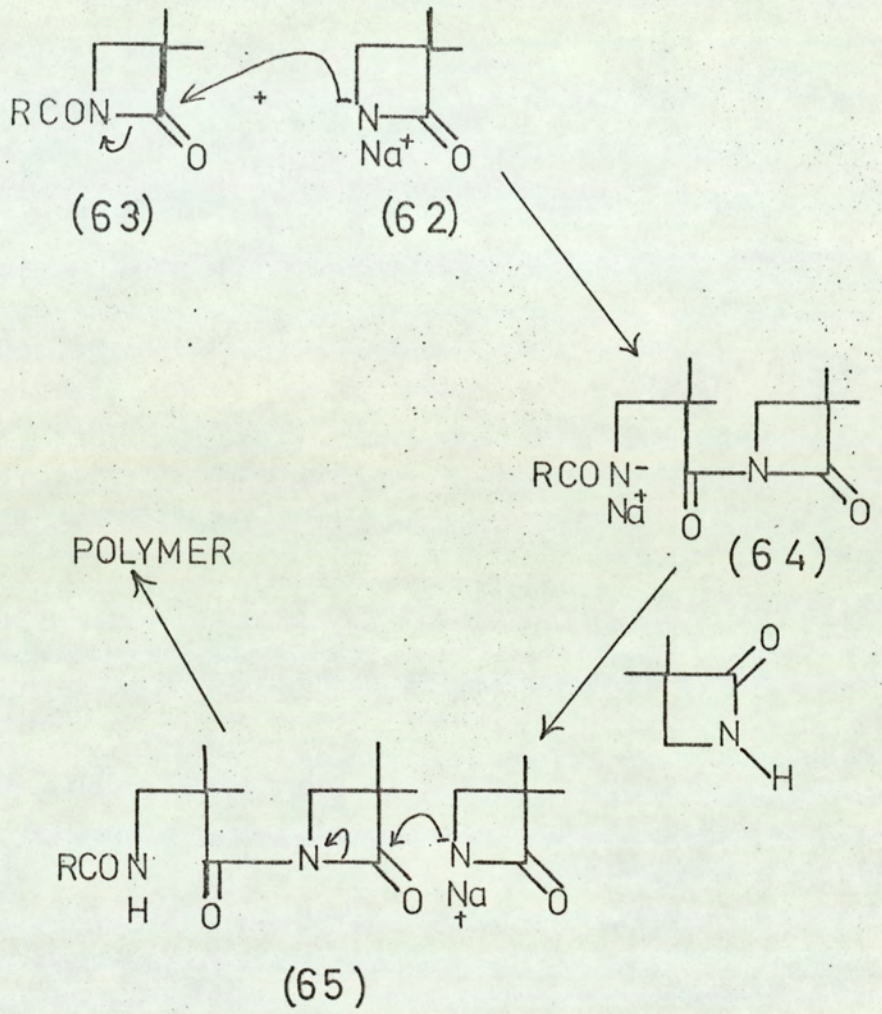
Thiazetidinones (61) can be prepared in good yields[71] by stirring the parent azetidine-2-one in benzene with phosphorous pentasulphide at room temperature.



(61)

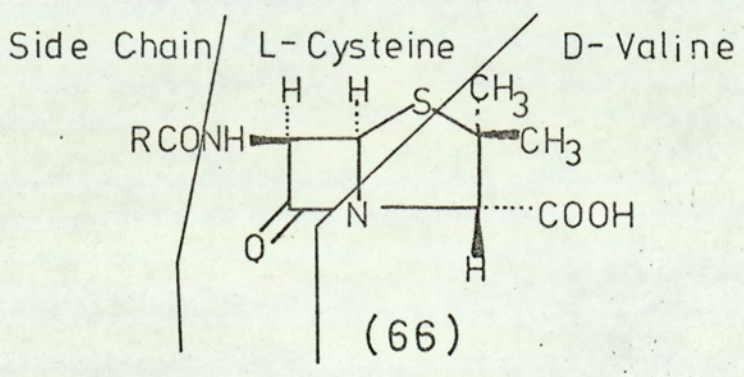
c) Polymerisation

Azetidine-2-ones polymerise quite readily in the presence of strongly basic catalysts to give polyamide chains. A great deal of work has been reported in the literature on many different azetidinones polymerised by a vast array of bases. The polymerisation is thought to begin[72] by addition of the alkali azetidinone (62) onto the acylazetidinone (63) accompanied by the opening of the acylazetidinone ring (64). This intermediate generates an anion from another azetidinone molecule which in turn reacts with the acylazetidinone group formed in the reaction (65).

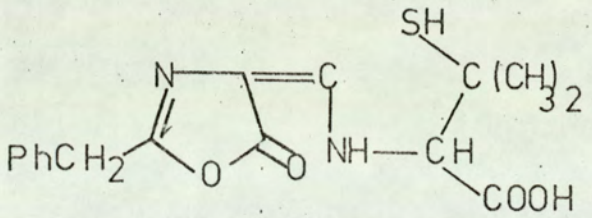


3) Biological Properties

Penicillins are cyclic dipeptides (66) consisting of a fused azetidine-2-one thiazolidine ring system. This may be regarded as an L-cysteine and a D-valine moiety attached to a side chain derived from a carboxylic acid.



Since the first tests were made on penicillins it has been recognised that they have a remarkably high activity against Gram-positive organisms. Their low toxicity makes them particularly useful in the treatment of infections caused by organisms such as staphalococci or streptococci. However, an allergic response has been noted and this is thought to be due to three major breakdown products of penicillin; benzylpenicillenic acid (67), D-penicillamine (68) and D-α-penicilloic acid (69).[114]



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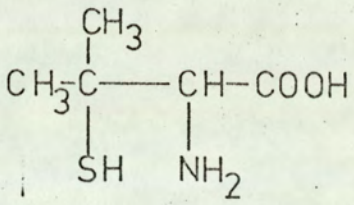

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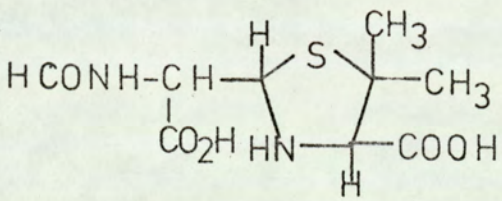
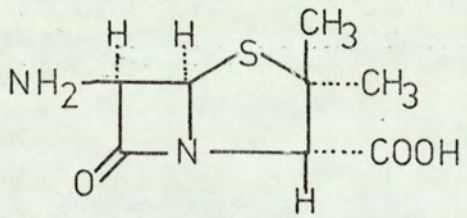


(69)

Perhaps one of the most serious disadvantages in the use of the penicillins is the resistance shown by many organisms which often may develop from the original sensitive strain. A principal cause of this is the production of β-lactamase enzymes which hydrolyse the azetidinone ring of the penicillin and thus inactivate it. It must be remembered however, that this is not the only mechanism whereby penicillin resistance is achieved as a number of Gram negative and some Gram positive organisms possess an intrinsic resistance which may be associated with permeability effects.[75]

The first two penicillins isolated (in 1943) were found to possess two different side chains, penicillin G also called benzylpenicillin had R = $Ph\text{-}CH_2$ (1) whilst penicillin F, 2-pentenylpenicillin had R = $CH_3\text{-}CH_2\text{-}CH = CH\text{-}CH_2$. The discovery that different penicillins could be formed by variation of the culture medium stimulated research into the semi-synthetic penicillins and it was found that if different acids were added to the mould culture they could be incorporated into the penicillin as the side chain residue. A different method of modification of this side chain, which has been particularly useful, has been the isolation of the 6-aminopenicillanic acid (70) from the culture broth and then acylation of this to provide many variations of the side-chain.

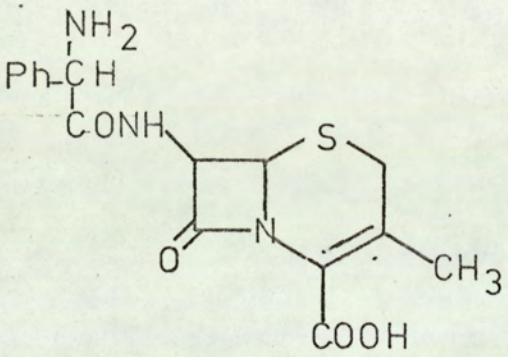


(70)

These modifications have been used to overcome the disadvantages of the earlierpenicillins, such as penicillin G which was acid unstable and not very active when administered orally. Penicillin V (1; R = Ph OCH_2), is acid stable and well absorbed orally. Further modifications of the side-chain have yielded broad spectrum penicillins such as the acid stable Ampicillin (1; R = Ph CH (NH_2) -) and Carbenicillin (1; R = Ph CH (COOH)-). The branched α-position in the side-chain apparently renders these compounds more resistant to the penicillinases.

The discovery of Cepholosporin C^2 has led to antibacterial agents with similar properties to the penicillins and although they do not possess the same antibacterial activity they do exhibit a broad spectrum of activity and are particularly useful in treating pathogens which have developed resistance to penicillins.

As with the penicillins, semisynthetic cephalosporins have been prepared. Thus cephaloridine (71), although not orally active, gives little pain on on injection , and Cephalaxin(72) is well absorbed from the gastro-intestinal tract when administered orally, and is useful for treating urinary tract infections.



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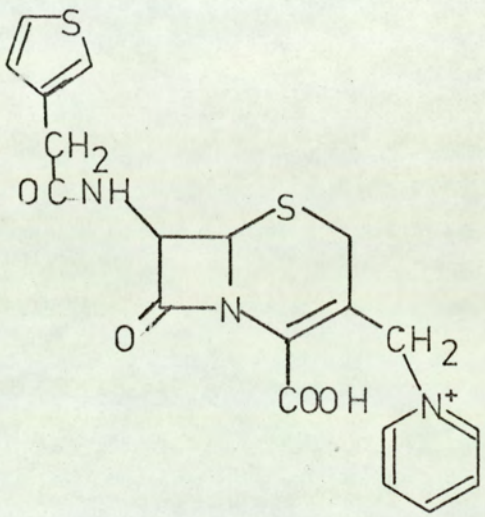
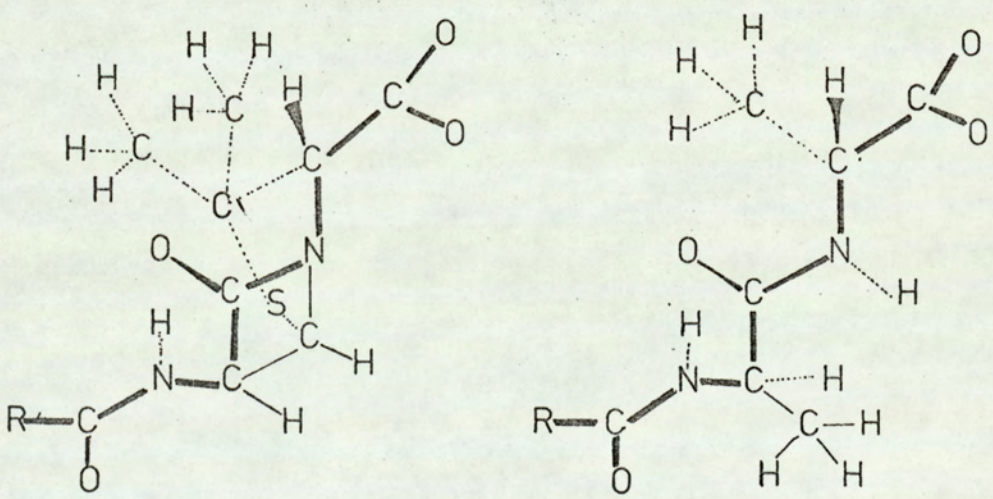


(71)

Penicillins destroy the dividing bacterial cell but they are inactive against the dormant cell. Further it has been observed[1] that growing cells in the presence of penicillins become mis-shapen and undergo lysis. Thus early work on the mode of action of penicillin suggested a surface phenomenon involving an attack on the cell wall.

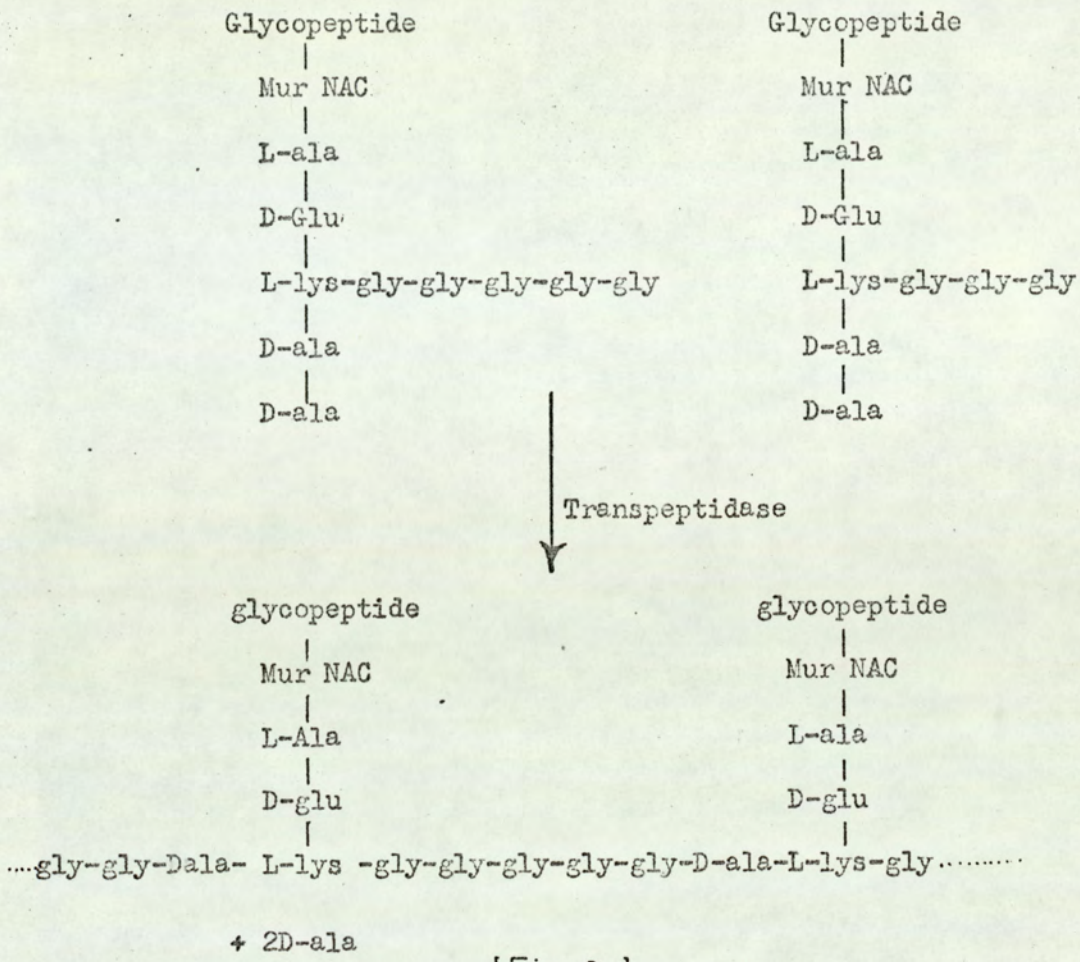
The bacterial cell wall consists of glycopeptide chains cross-linked by polypeptide bridges. These cross-links are completed by a glycopeptide transpeptidase which joins the D-alanine-D-alanine terminal amino acids to the glycopeptide chain (Fig. 3.).

Penicillin inhibits the formation of these polypeptide cross-links in the cell wall and causes accumulation of cell wall precursors. The resultant weakened cell wall cannot withstand the high osmotic pressures from inside the cell and rupture of the cell wall is inevitable.[76] It is the similarity of the penicillin to the terminal D-alanine-D-alanine peptide (73) which causes it to bind competitively onto the enzyme transpeptidase and so prevent the final peptide bond formation.[77]



DREIDING STEREO-MODELS OF PENICILLIN (left) AND D-ALANINE-D-ALANINE END OF THE GLYCOPEPTIDE (right)

(73)



[Fig 3]

Johnson and Maria[78] found that after epimerisation the epi-benzylpenicillin produced (46) showed negligable antibiotic activity. The change from a D-alanine D-alanine type residue to an L-alanine D-alanine residue means that it is now unable to bind to the transpeptidase and so it no longer inhibits the building of the bacterial cell wall.

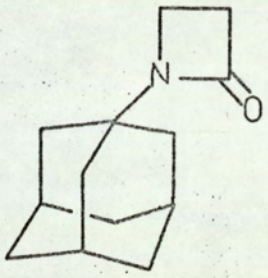
Desthio benzylpenicillin (41) produced in the penicillin programme[79] was tested against Gram positive bacteria and was found to have little, if any, activity.

Monocyclic azetidinones generally do not exhibit any marked antibacterial activity although a small zone of activity by N-alkyl azetidinones against E. Coli has been reported.[80]

Some azetidinones have been shown to exhibit a depression of C.N.S. activity similar to Phenobarbitone 1-phenyl-3-alkyl substituents tend to

increase this activity.[81]

An adamantyl derivative (74) has been reported to have some antiviral activity.[82]



(74)

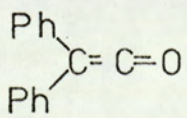
DISCUSSION

The preceding review indicates that only a small amount of data is available on the biological properties of simple azetidine-2-ones.

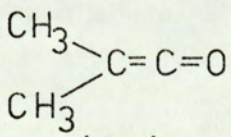
The aim of the work described in this thesis was to prepare some novel azetidine-2-ones for pharmacological evaluation and also to investigate their potential as intermediates in the synthesis of other novel compounds.

A) PREPARATION OF AZETIDINE-2-ONES.

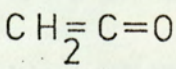
Ketenes were first shown to react with Schiff's bases to yield azetidine-2-ones by Staudinger in 1907[6]. Several different ketenes were used, some, such as diphenylketene(75), could be isolated whilst others, such as dimethylketene (76) were prepared *in situ* to prevent dimerisation Staudinger found that the order of reactivity of ketenes was aromatic substituted ketenes > aliphatic substituted ketenes > ketene.



(75)



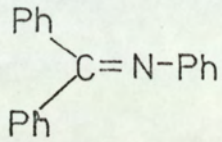
(76)



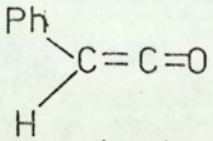
(77)

Ketene(77), the parent compound, was found to be the least reactive and only yielded an azetidinone with benzophenylidene aniline(78), a very reactive Schiff's base, at 200°C.

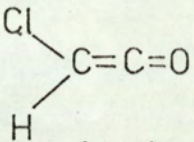
Many new ketenes have been synthesised since Staudinger's initial investigation and the preparation of unsymmetrical ketenes such as phenylketene(79)[83] and chloroketene(80)[84] have played an important part in the investigation of the stereochemistry of azetidine-2-ones.



(78)

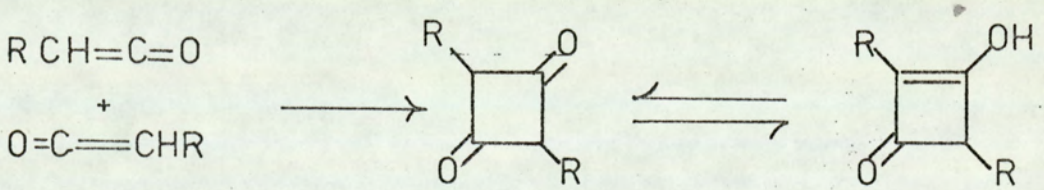


(79)

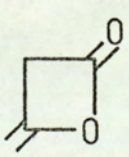


(80)

One disadvantage in the use of ketenes is their rapid dimerisation to give cyclobutenone derivatives(81). Great differences in the rates of dimerisation are observed, thus ketene and the monosubstituted derivatives have to be used immediately whereas diphenylketene can be distilled and stored quite readily. A crystal of hydroquinone is usually added to the distilled diphenylketene to prevent polymerisation. Ketene itself dimerises in a different manner, with the C = C bond adding to the C = O bond to give an unsaturated β-lactone(82).[85]



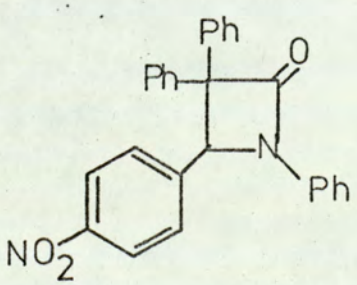
(81)



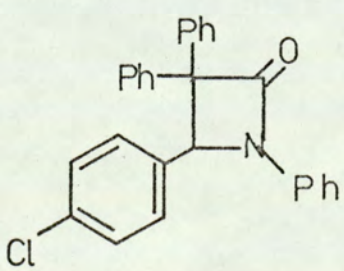
(82)

3,3-Diphenylazetidine-2-ones.

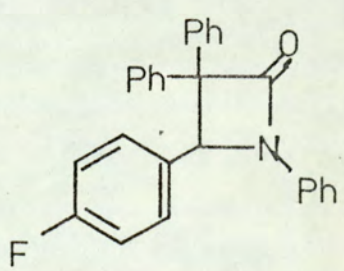
The synthesis of 3,3-diphenylazetidine-2-ones by the action of diphenylketene on a Schiff's bases was based on the successful method developed by Staudinger[6]. Diphenylazetidine was found to react smoothly with p-nitrobenzylidine aniline when warmed in benzene to give 4-p-nitrophenyl-1,3,3,triphenylazetidine-2-one (83) in good yield. This structure was confirmed by the infrared spectrum which showed a strong absorbtion at 1750 cm^{-1} indicating the presence of the azetidine-2-one carbonyl group. A singlet at 4.2τ in the N.M.R. spectrum which integrated for one proton showed the presence of the C4-H. This proton absorbed at 1.5τ in the anil before reaction with the diphenylketene. The mass spectrum showed a molecular ion peak at m/e 420 and an initial decomposition by loss of phenyl isocyanate to yield the fragment at m/e 301. In addition a peak at m/e 194, indicative of diphenylketene confirmed the typical azetidine-2-one mass spectral fragmentation pattern. p-Chlorobenzylidene aniline and diphenylketene also reacted readily to yield 4-p-chlorophenyl-1,3,3-triphenylazetidine-2-one(84). In view of the ease of these reactions it is surprising to find reports by Pfleger and Jager[83] which state that these compounds were not formed even after heating at 200°C. Other Schiff's bases containing electron - withdrawing substituents were also found to react smoothly with diphenylketene, and 4-p-fluorophenyl-1,3,3-triphenylazetidine-2-one (85) was prepared in a similar manner from p-fluorobenzylidene aniline. All of these azetidinones exhibited typical infrared absorption spectra having a strong peak at 1750 cm^{-1}.



(83)

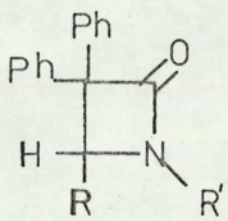


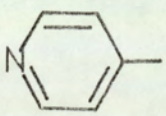
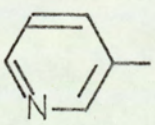
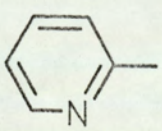
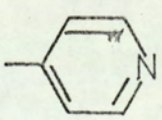
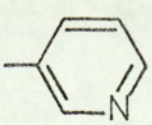
(84)



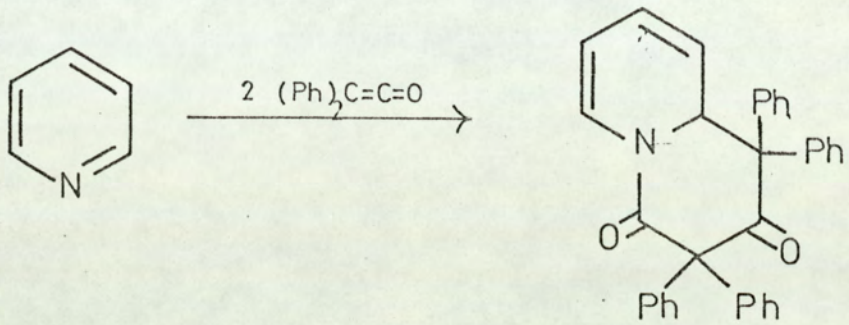
(85)

Previous work on the electronic factors which control these cycloaddition reactions has suggested that electron-donating substituents in the anil enhance reactivity whereas electron-withdrawal supresses formation of the azetidinone. In view of the result with p-chloro-, p-fluoro- and - p-nitrophenyl substituted anils further work with compounds deactivated by substitution with a pyridine nucleus was undertaken. Thus anils were obtained from 2,-3 - and 4-pyridine aldehydes and aniline and from 3- and 4- aminopyridines and benzaldehyde and were found to yield the desired 1,4-disubstituted 3,3-diphenyl-azetidinones (86-90) in good yields when treated with diphenylketene. Again the products were characterised by their strong $\nu C = O$ infrared absorption which occurred at 1755 cm^{-1} and also the characteristic mass spectral breakdown.



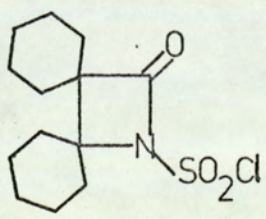
	R	R'
(86)		Ph
(87)		Ph
(88)		Ph
(89)	Ph	
(90)	Ph	

No reaction between diphenylketene and the pyridine nucleus could be detected although previous reports[7,8 6.] have indicated that two moles of ketene will react with pyridine to yield a piperidinone (91)

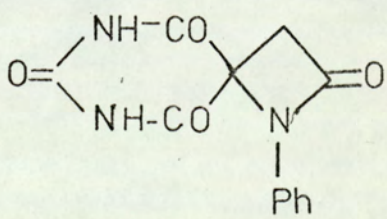


(91)

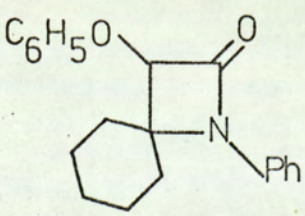
Very few spiroazetidinones have been reported in the literature although Graf[34] and Moriconi[87] have both prepared this type of compound (92) *via* the reactions of olefins and chlorosulphonyl isocyanate. Base and Garratt[88] cyclised an azetidinone 4,4-dicarboxylic ester to give a spirobarbituric acid derivative (93) and Manhas *et al*[89] prepared some 4-spiroazetidinones by the action of a ketene on a Schiff's base. However, it was found that only the most reactive ketenes, such as phenoxy ketenes, were capable of forming azetidinones (94).



(92)

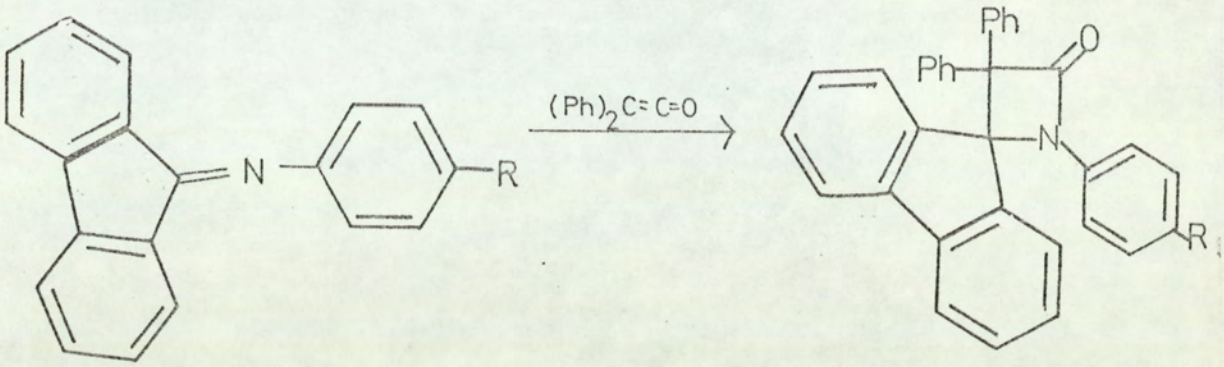


(93)



(94)

When diphenylketene was reacted with fluorenylidene anils (95→ 97), prepared from 9-fluorenone and aniline derivatives, at room temperature 4-spiroazetidinones (98→100) were rapidly formed as colourless crystalline compounds.



(95) R = H

(96) R = OCH_3

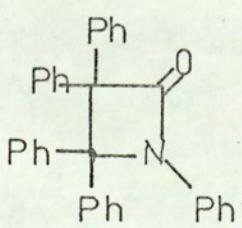
(97) R = Cl

(98) R = H

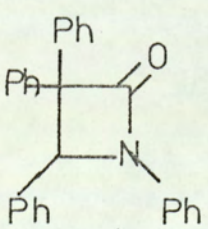
(99) R = OCH_3

(100) R = Cl

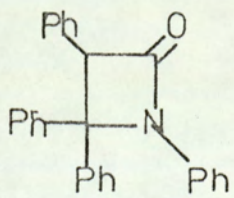
These compounds were readily identified by their infrared absorption spectrum, having a strong absorption at 1745 cm^{-1}. This figure is lower than the previously observed carbonyl stretching frequency and could be due to the relief of strain in the symmetrical fully substituted ring. A similar phenomenon was observed in the spectra of 1,3,3,4,4-pentaphenylazetidine-2-one (101) which absorbs at 1745 cm^{-1} compared with 1750 cm^{-1} for 1,3,3,4-tetraphenylazetidine-2-one (12) and 1755 cm^{-1} for 1,3,4,4-tetraphenylazetidine-2-one (102).



(101)



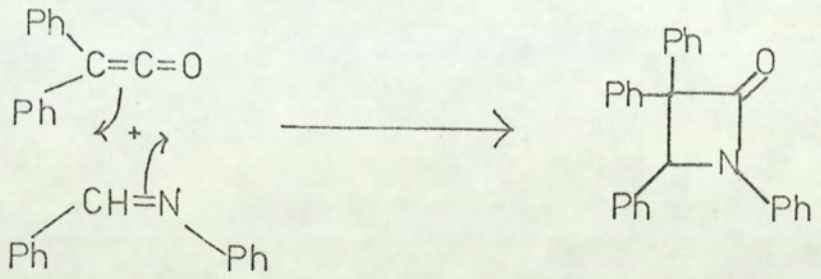
(12)



(102)

2 + 2 Cycloadditions

Cycloaddition of diphenylketene to a Schiff's base occurs quite readily even at room temperature and for many years was postulated as a concerted attack(103) to give the azetidinone



(103)

However with the formulation of the Woodward-Hoffman rules[90] it was seen that a concerted 2 + 2 cycloaddition reaction of this type was not thermally permissable. The principle of Conservation of Orbital Symmetry will only allow a concerted reaction to occur when all overlaps between the highest - occupied molecular orbital of one reactant and the lowest - unoccupied molecular orbital of the other are such that a positive lobe overlaps only with another positive lobe and a negative lobe only with a negative lobe. Thus in the case of a 4 + 2 concerted cycloaddition such as the Diels-Alder reaction the interacting orbitals may be represented as in figure 3a. This indicates that orbital overlap in the transition state will only involve lobes with the same wave-functional sign and consequently these reactions are expected to proceed readily.

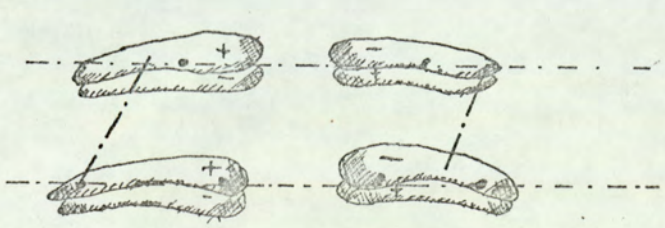


FIG 3a

However, in the apparently similar 2 + 2 reaction such as the dimerisation of olefins, the interacting orbitals may this time be represented as in figure 4. This indicates that the wave-functional signs of the lobes

to be involved in orbital overlap in the transition state do not allow a concerted pathway to operate. Generally, therefore, attempted reactions of this type give poor results.

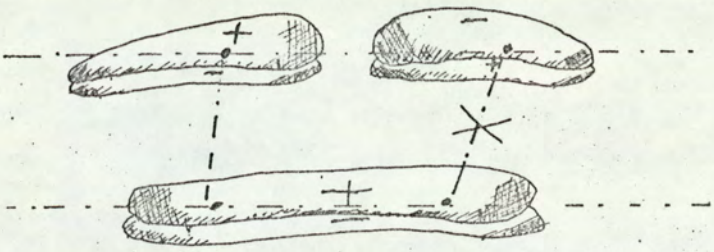


FIG 4

These considerations are reversed when ring closures are photochemically induced, since in such cases an electron is promoted to a vacant orbital before reaction occurs. This results in a change in the symmetry of the highest occupied orbital(FIGURE 5)and the reaction between two olefins is now allowed.

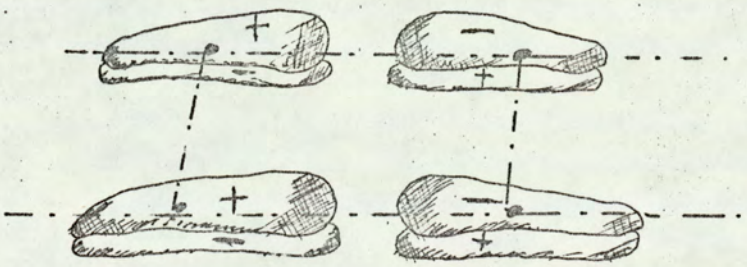
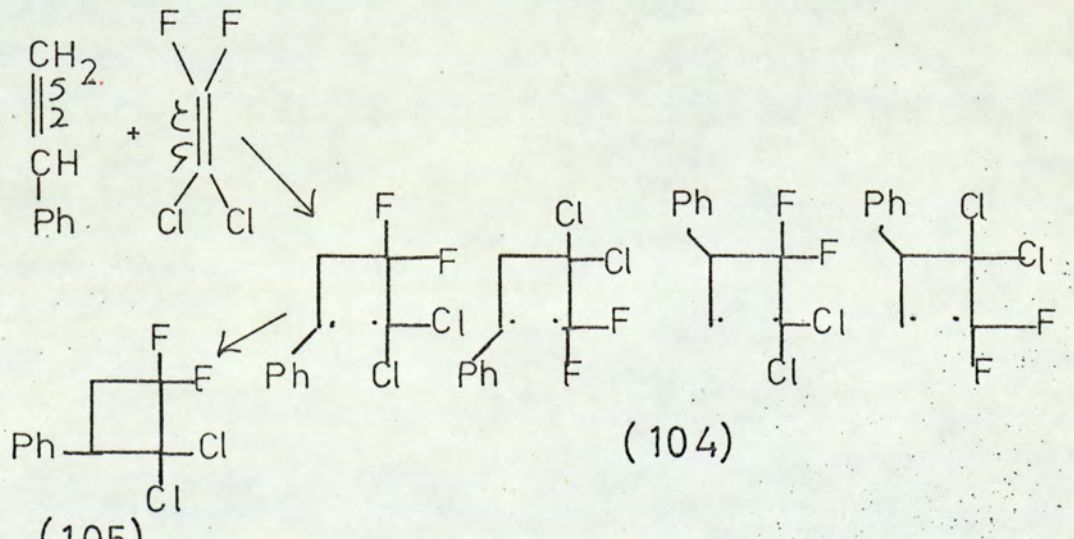


FIG 5

These rules do not apply to reactions which proceed via discrete intermediates in a multistage process. However, as 2 + 2 cycloadditions do occur they must proceed via a multistage process. The reaction between styrene and 1,1-difluoro-2,2-dichloroethane for example, has been postulated to proceed via a diradical intermediate and the relative stability of the four possible intermediates[04.)has been used to predict the structure of the product(105) .



(104)

(105)

Thus it can be seen that as the reaction between ketene and a Schiff's base is essentially a 2 + 2 cycloaddition it is not theoretically allowed by the Conservation of Orbital Symmetry rules. However, Woodward and Hoffman[91] have shown that for the cycloaddition of ketenes and olefins, the ketene molecule may be considered as a vinylium ion (106) and the vacant $\pi^*C=O$ orbital can contribute strong bonding interactions which aid antarafacial attack and which are absent from the reaction path for simple olefins FIG 6.

$$>C=C=O \longleftrightarrow >C=C^{+}-O^{-}$$

(106)

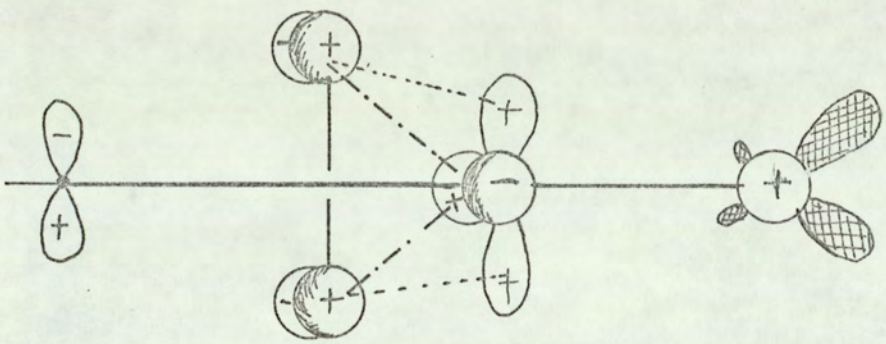
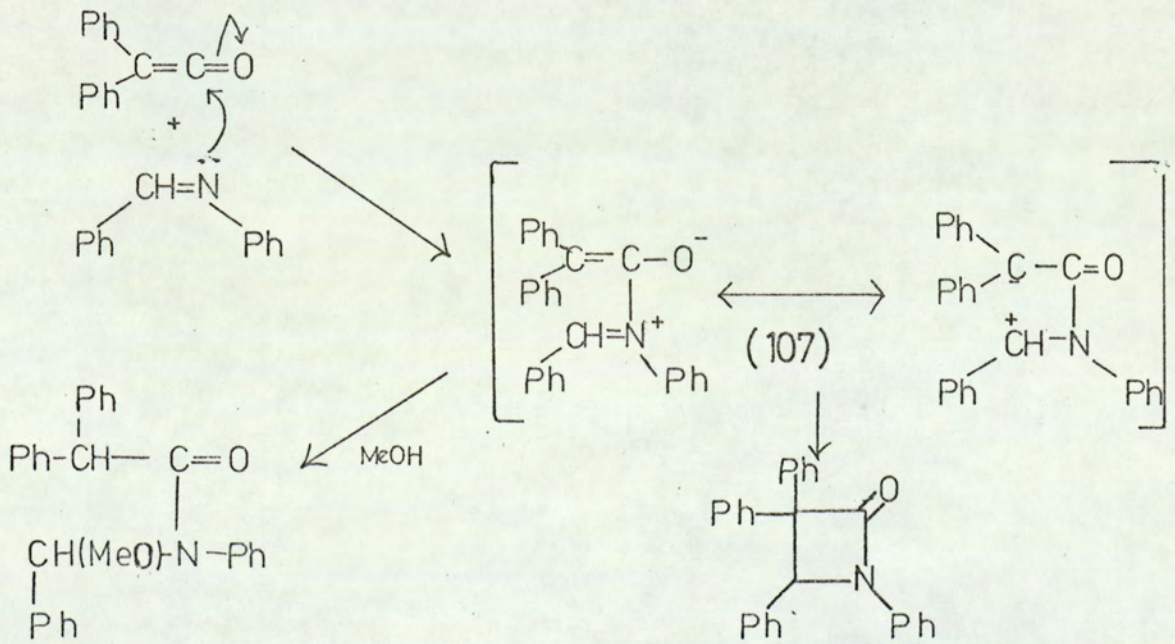


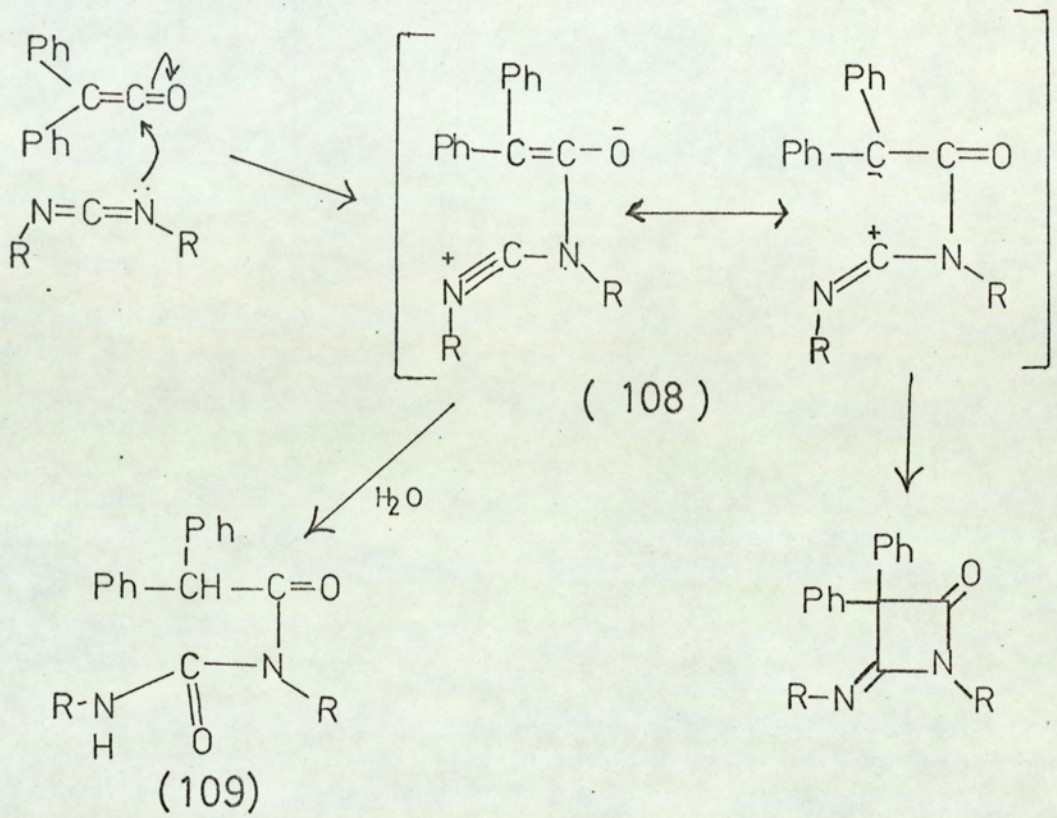
FIG 6

However, even though Conservation of Orbital Symmetry has shown that 2 + 2 concerted cycloadditions with ketene are possible, a large body of information concerning the isolation of intermediates has been built up.

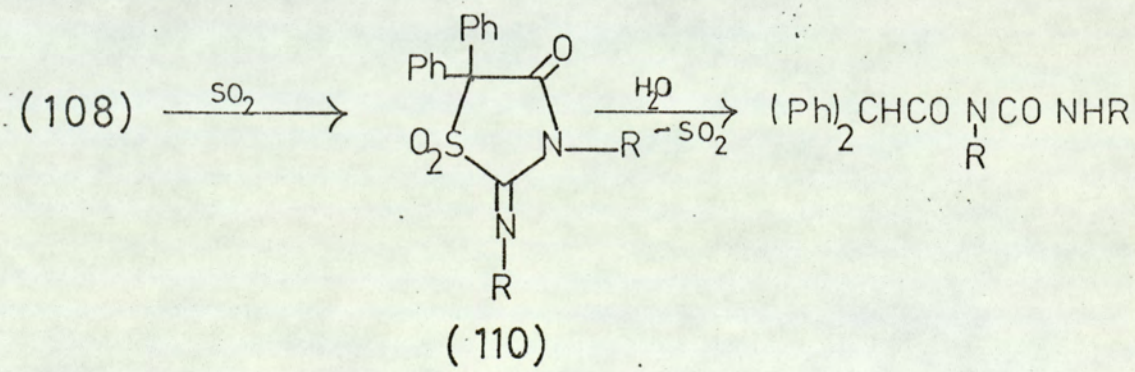
Recently Kagan and Luche[92] have shown that by quenching a reaction with methanol an intermediate zwitterion (107) may be trapped as a methanol adduct.



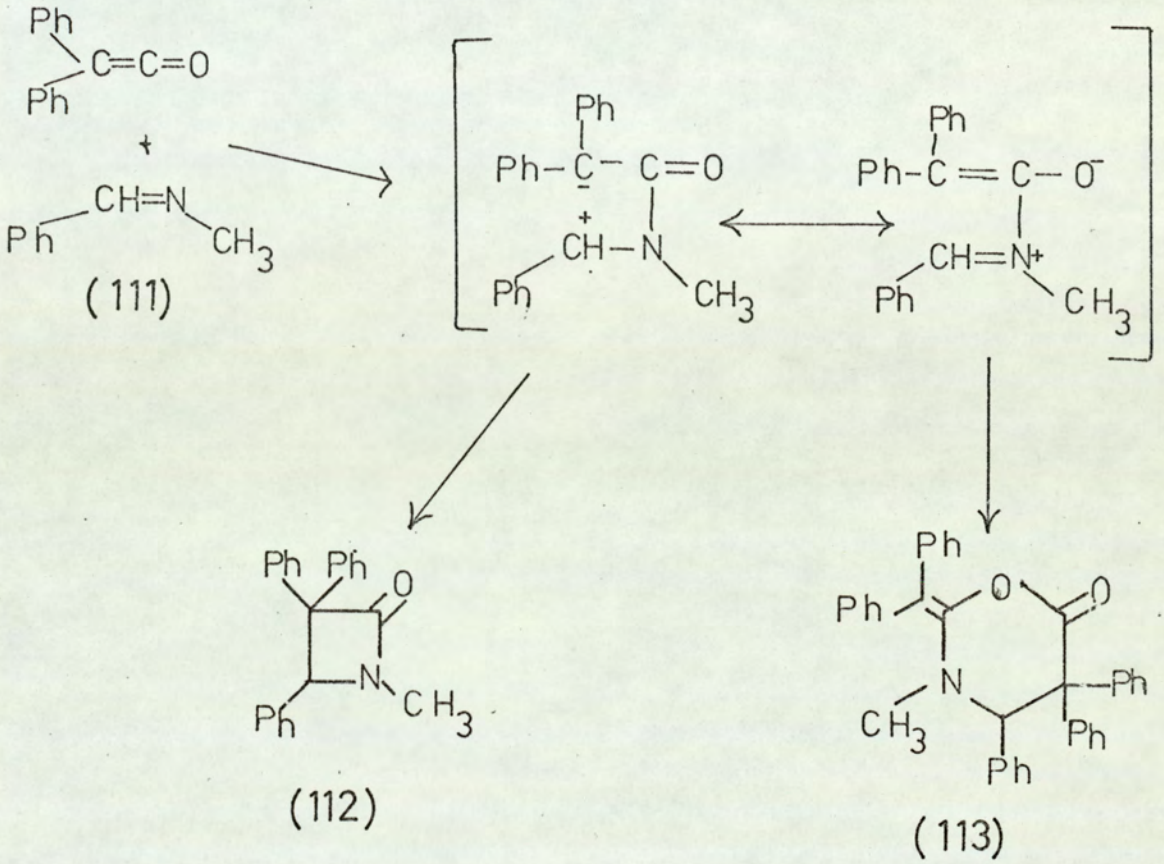
Brady and Dorsey[93] have also shown that the reaction between diphenylketene and carbodiimides which also yields azetidine-2-ones rather than the 1,3 adduct, also proceeds through an intermediate(108)which was trapped when the reaction was quenched with water after 4 min.



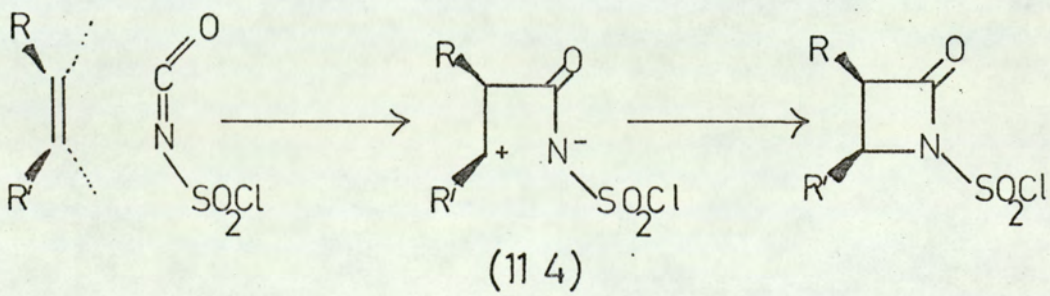
Further work by Brady and Dorsey using sulphur dioxide as a solvent has trapped the intermediate(108) as the thiazolidinone(110) which gives the same hydrolysis product(109) as the zwitterion(108)with loss of sulphur dioxide.



The reaction of diphenylketene with an azomethine(111)can yield two products, either the azetidinone(112)or the 1,3-oxazine-6-one(113).[94] These can both be derived from the same postulated intermediate, either by direct ring closure or by addition of another molecule of ketene and then ring closure.

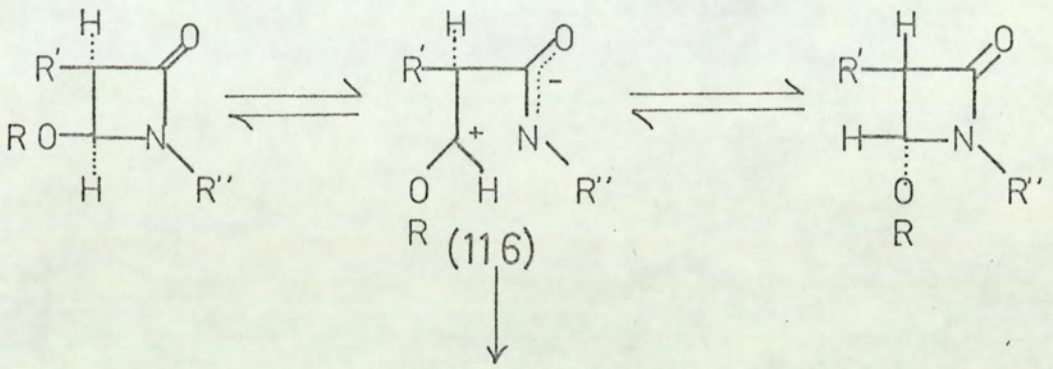


The reaction between chlorosulphonyl isocyanate and an olefin, the other mode of 2 + 2 cycloaddition to form an azetidinone has also been postulated to proceed via a dipolar intermediate.[95,96] Moriconi[97] found that the reaction proceeded stereospecifically and so postulated that it must proceed via the intermediate(114)before ring closing to yield the azetidinone.

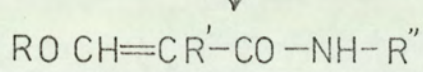


(114)

Effenberger[98] also found that the addition of an isocyanate to vinyl ethers proceeded stereospecifically but further postulated that as the azetidinone produced is also capable of undergoing irreversible fission to yield the vinyl ether(115)and an isomerisation to yield the isomeric azetidinone both reactionsproceed via the same dipolar intermediate.(116)



(116)

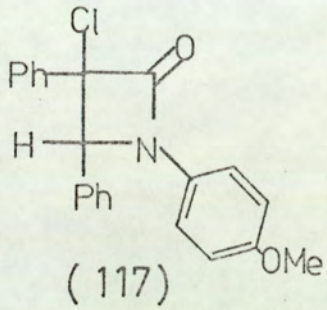


(115)

2) 3-Chloroazetidine-2-ones.

Acid chlorides will react with Schiff's bases in the presence of triethylamine to produce azetidine-2-ones[26,28,29,30,84,99]. and α-chloro subsituted acid chlorides yield the 3-chloroazetidinones. α-Chlorophenyl-acetyl chloride was prepared by dissolving d,l - mandelic acid in thionyl chloride and collecting the acid chloride by fractional distillation after removal of the excess thionyl chloride.[100] The reaction between the acid chloride and the Schiff's bases in the presence of base was very vigorous and good yields of the azetidinone were obtained. Thus benzylidene-p-methoxyaniline (120)and fluorenylidene-p-methoxyaniline(96)yielded 3-chloro-3,4-diphenyl-1-p-methoxyphenylazetidine-2-one(117)and 3-chloro-1-p-methoxyphenyl-3-phenyl-4-spirofluorenazetidine-2-one(118)respectively both of which exhibited high ν C = O peaks in the infrared spectrum. That of 3-chloro-3,4-diphenyl 1-p-methoxyphenylazetidine-2-one occurred at 1755 cm^{-1} whilst the absorption of 3-chloro-1-p-methoxy phenyl-3-phenyl-4-spirofluorenazetidine-2-one was somewhat higher at 1765 cm^{-1}. Such absorptions are not unexpected for compounds

containing a highly electronegative substituent in the α-position for example α-halo acids exhibit a similar shift to higher frequencies of 10-20 cm^{-1} compound to the unsubstituted acids.[101] Similar high absorptions have also been reported by Duran and Ghosez[84] for 3-chloroazetidinones, thus 3-chloro-1,4,4-triphenylazetidine-2-one was found to absorb at 1780 cm^{-1}.



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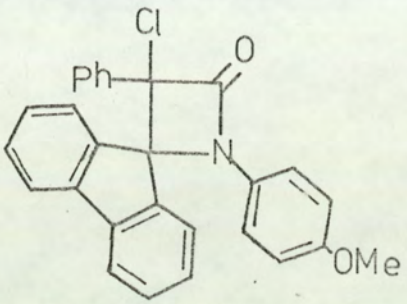
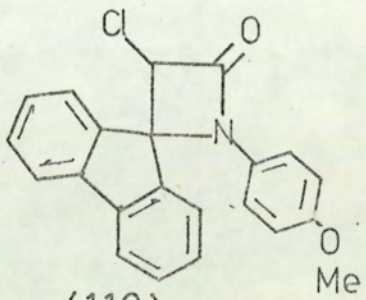


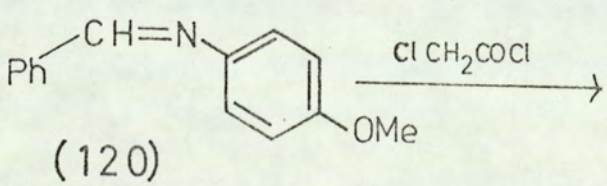
(118)



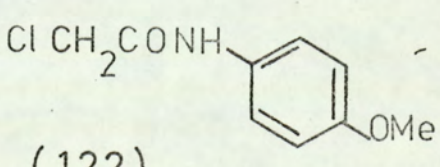
(119)

Similar reactions were carried out using chloro acetyl chloride. Thus fluorenylidene-p-methoxyaniline, the acid chloride and triethyl-amine yielded 3-chloro-1-p-methoxyphenyl-4-spirofluorenazetidine-2-one(119) which was readily identified by the high carbonyl stretching vibration at 1760 cm^{-1}, and the two singlets present in the N.M.R. spectrum that at 6.4 τ (3H) indicated the presence of the methoxyl groups and that at 4.7 τ (1H) confirmed the single proton at the 3 position.

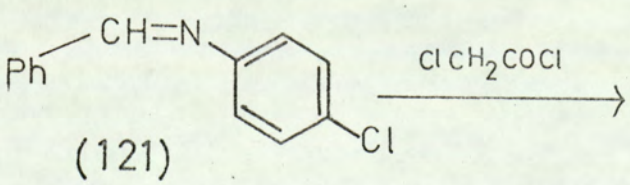
Chloroacetyl chloride also reacted with benzylidene-p-methoxyaniline (120) and benzylidene-p-chloroaniline(121) but the only products isolated were chloroacet-p-anisidide and chloroacet-p-chloroanilide respectively(122,123)



(120)



(122)



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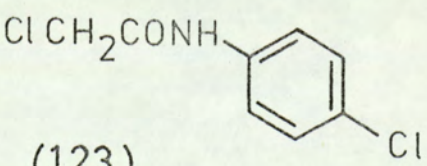
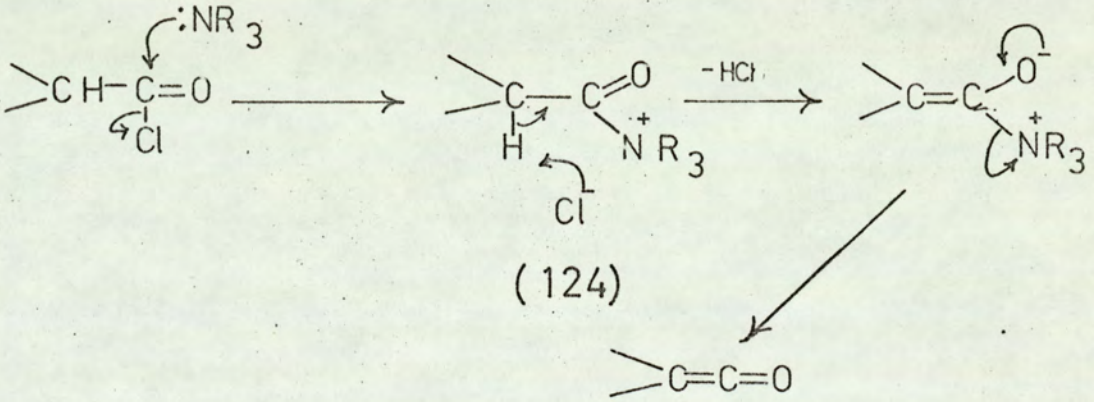


(123)

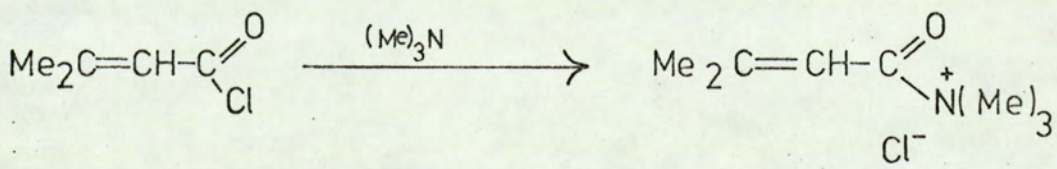
These observations are in agreement with those of Nelson[102] who found that in the absence of electron - donating groups in both aryl constituents of the anil the yield of azetidinone fell to about 5%.

The formation of the acetanilides suggests that an intermediate is formed during the addition of the acid chloride to the anils. A possible reaction pathway may involve the attack of triethylamine on the acid chloride to produce chloroketene in situ which undergoes reaction with the anils. According to Pracejus[103] a ketene is formed from the quaternary salt(124) via intermediate dipolar compounds.



(124)

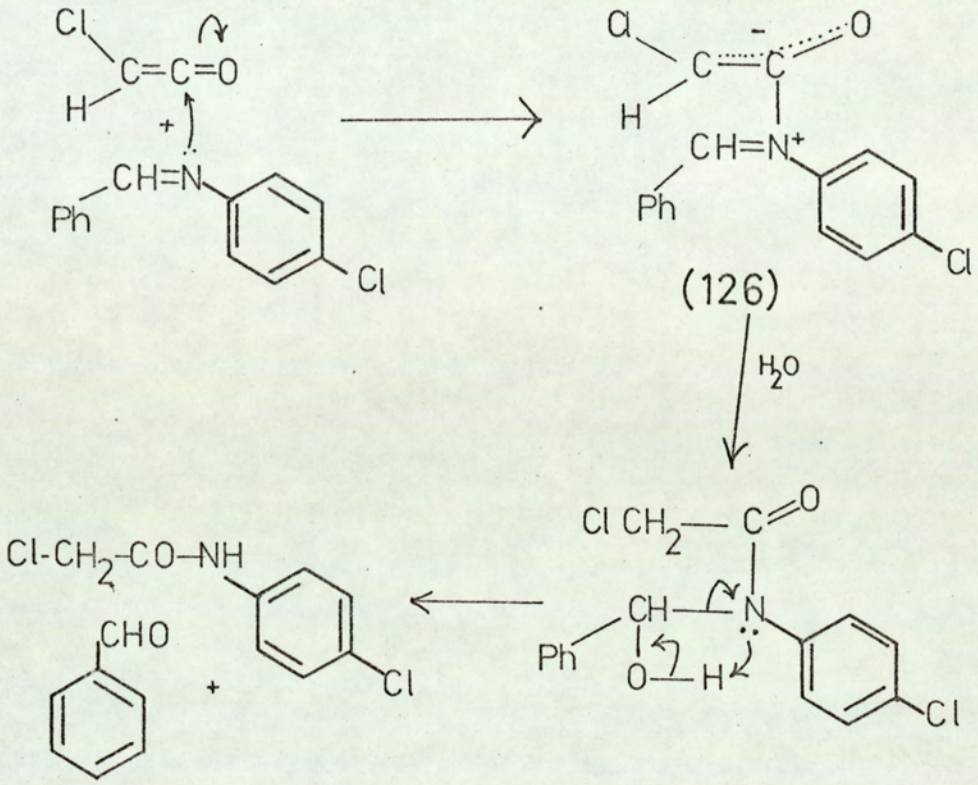
Quaternary salts from the adducts of acid halides and weak tertiary amines(125) have since been isolated by Payne[104]. This mechanism of formation of intermediate ketenes from quaternary ammonium salts, analogous to the Hoffmann degradation, is one of several which is possible.



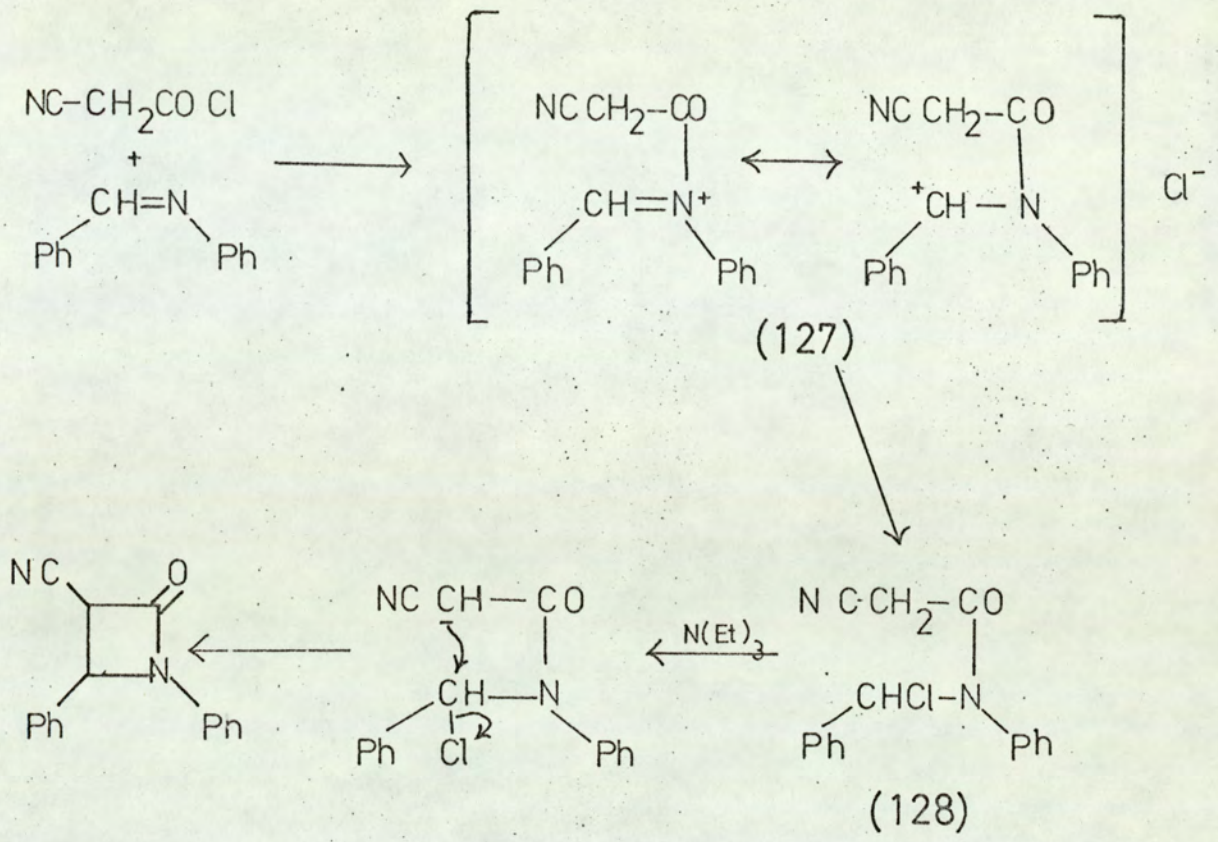
(125)

The reaction of the ketene produced in situ with the anil must proceed via an intermediate zwitterion(126)which is then able to undergo hydrolysis to yield the acetanilides. A similar intermediate has been postulated for the

action of chloroacetyl chloride on anils to yield the azetidinones.[102]

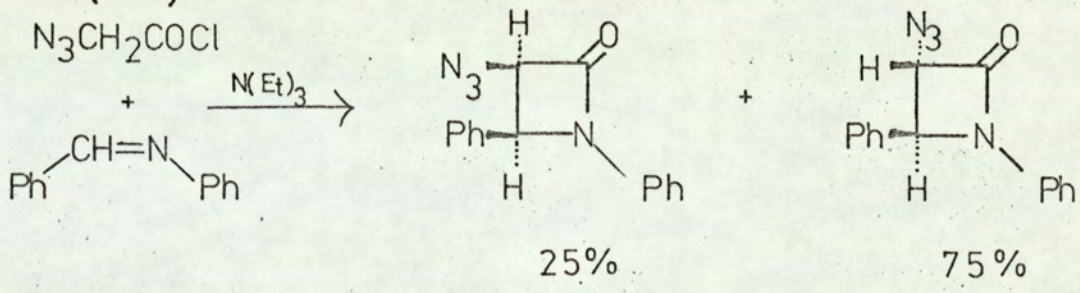


The reaction of acid chlorides with anils has also been postulated[30] to proceed via a similar type of intermediate(127) produced by direct attack of the acidchloride on the anil. This intermediate salt then rearranges to give the chloroamide(128)which can then be ring-closed using triethylamine. The chloroamide(128) was isolated from the reaction mixture at -70° as a hygroscopic crystalline compound which hydrolysed readily in solution.



A similar reaction was carried out by Bose[105] using azaacetyl-chloride (129), this yielded a mixture of cis and trans - azetidinones. The composition of this mixture was found to depend upon the method of addition of the acid chloride and seemed insensitive to other reaction conditions. If the acid chloride was added to a mixture of anil and triethylamine then the cis -azetidinone was the predominat reaction product, however, when the triethylamine was added to a mixture of the acid chloride and the anil the reaction yielded chiefly the trans-azetidinone. It was concluded that the reaction could proceed either via the salt (127) or the ketene addition (128) intermediates depending on the reaction conditions but as both cis and trans-azetidinones were always present both mechanisms must be operating, if only to a minor degree, concurrently.

(129)

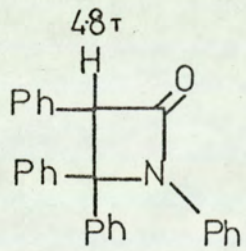


25% 75%

3) 3-Phenylazetidine-2-ones.

The preparation of 3-phenylazetidinones was accomplished quite readily by the action of phenylacetyl chloride added slowly to a hot, stirred mixture of anil and triethylamine.

Phenylacetyl chloride reacted readily with the fully substituted anils, benzophenylidene aniline and fluorenylidene-p-chloroaniline to give 1,3,4,4-tetraphenylazetidine-2-one(102) and 1-p-chlorophenyl-3-phenyl-4-spirofluoren-azetidine-2-one(130) respectively. The N.M.R. spectrum of these compounds shows that there is considerable deshielding of the 3-proton compound to the 4-monosubstituted azetidinones.



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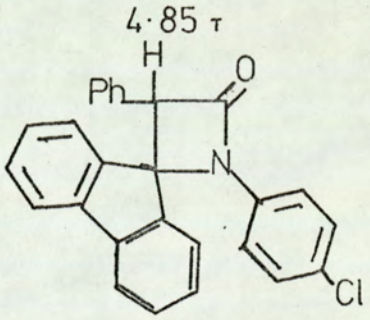
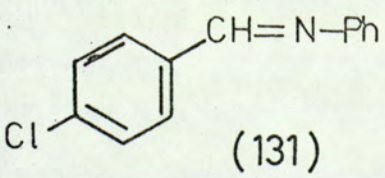
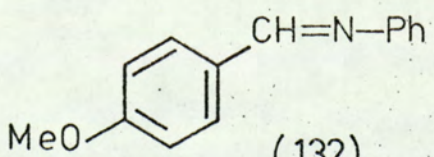


(130)

The action of phenylacetyl chloride on p-chlorobenzylidene aniline(131) and p methoxy benzylidene aniline(132) in the presence of triethylamine produced yellow oils which could not be induced to crystallise but which exhibited a typical infrared absorption spectrum (ν C = O 1750cm^{-1})



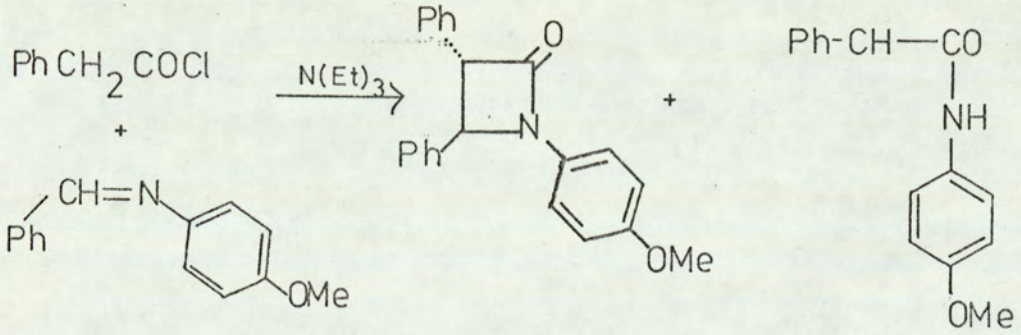
(131)



(132)

In attempts to alter the product composition resulting from the reaction between benzylidene-p-methoxyaniline and phenyl acetyl chloride this reaction was repeated at various temperatures from -70° up to the boiling point of the solvent (56°) and although the modes of addition of the phenylacetyl chloride were varied there was no evidence to indicate that any other than trans-isomer was formed.

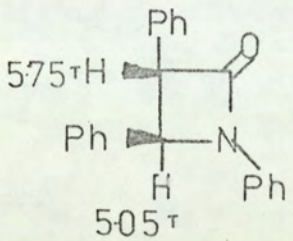
It can thus be concluded that the predominant pathway in this reaction is the formation of the ketene in situ and its addition to the anil to form an intermediate which cyclises via the least hindered pathway to yield the trans-azetidinones. It was found that if the solutions were not dry the yield of azetidinone was considerably reduced and the appearance of acetanilides (133) in the reaction mixture was observed. The formation of acetanilides in the presence of water indicates that this reaction proceeds via a labile intermediate similar to those (126) postulated for the addition of chloroacetyl chloride. Addition of triethylamine to a mixture of anil and acid chloride did not yield any appreciable amounts of azetidinone but resulted mainly in the preparation of acetanilides.



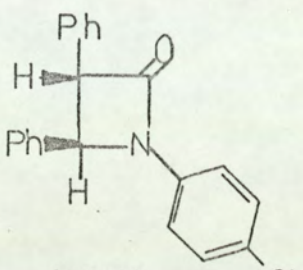
(134) (133)

All azetidinones prepared by this method exhibited a carbonyl absorption peak at 1750 cm^{-1} in their infrared spectrum. The N.M.R. spectrum of 1,3,4-triphenylazetidinone(135) 3,4-diphenyl-1-p-methoxyphenylazetidinone (134) and 3,4-diphenyl-1-p-chlorophenyl azetidinone (136) showed two characteristic doublets

at 5.75τ(3H) and 5.05τ(4-H) with J = 2.5 Hz. The small coupling constant exhibited by these compounds indicates that they are all in the trans - configuration. Similar trans - compounds have been shown to have a coupling constant J trans = 2.2-2.7 Hz.[106,107]



(135)



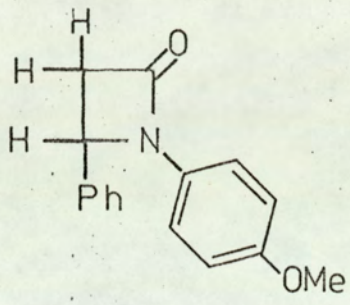
(136)

4) 3-Unsubstituted Azetidine-2-ones.

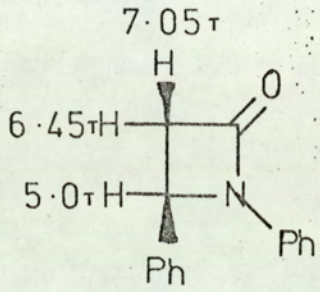
The reaction of ketene with anils has long been known to yield 3-unsubstituted azetidine-2-ones.[6] Ketene was prepared by thermal decomposition of acetone vapour over a hot Chromel wire[108] and was used immediately to prevent dimerisation. All of the reactions, with the exception of that with benzylidene p-methoxyaniline, were carried out in refluxing benzene. It was found that when ketene was bubbled through the anils at the elevated temperatures previously reported[6, 83] only a small yield of azetidinone was isolated from the many by-products obtained. If the solvent, benzene, was rigorously dried before use, the good yields of azetidinones could be recorded at relatively low temperatures. 4-Phenyl-1-p-methoxyphenylazetidine-2-one however, could not be prepared by bubbling ketene through a hot solution of Schiff's base in benzene but treatment of the molten Schiff's base at 130° with ketene produced a low yield of azetidinone after separation of the reaction mixture on an alumina column.

All azetidinones prepared by this method exhibited ν C = O at 1745-1750 cm^{-1}, The N.M.R. spectrum of 1,4-diphenylazetidine-2-one(138) exhibited a typical AMX splitting pattern, the two geminal protons in the 3 position showed a coupling constant of $J_{33'}$ = 15 Hz whilst exhibiting typical cis and trans

coupling constants with 4-proton J_{34} = 6 Hz and $J_{3'4}$ = 2.5 Hz respectively. These results were found to be in good agreement with others reported in the literature.[106]

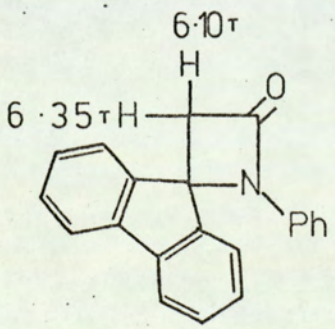


(137)

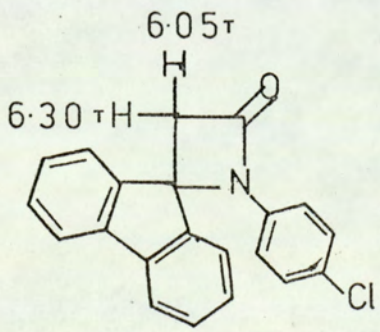


(138)

When 1-phenyl-4-spirofluorenazetidine-2-one (139) and 1-p-chlorophenyl-4-spirofluorenazetidine-2-one (140) were prepared it was found that the geminal coupling constants of the C-3 protons were reduced to 8 and 6 Hz respectively accompanied by a shift to lower τ . The geminal coupling constant of 1-p-methoxyphenyl-4-spirofluorenazetidine-2-one (141) could not be measured due to the close proximity of the large band from the methoxyl group.



(139)



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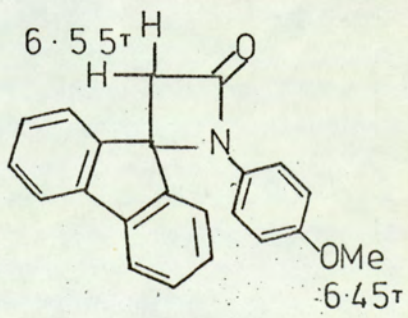
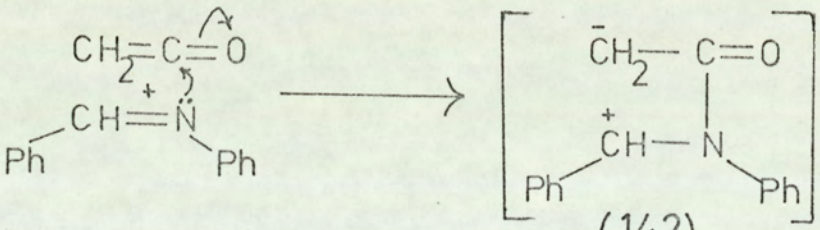
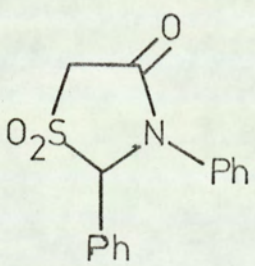


(141)

The reaction between ketene and a Schiff's base has been shown by Gomes and Jouille[109] to proceed via an intermediate(142) in a similar manner to the substituted ketenes. Although this intermediate has not been isolated, when ketene was reacted with benzylidene aniline in liquid sulphur dioxide a molecule of solvent was incorporated into the final product to yield a thiazalidinone(143). The reaction was thought to proceed via the intermediate rather than a trimolecular concerted attack.



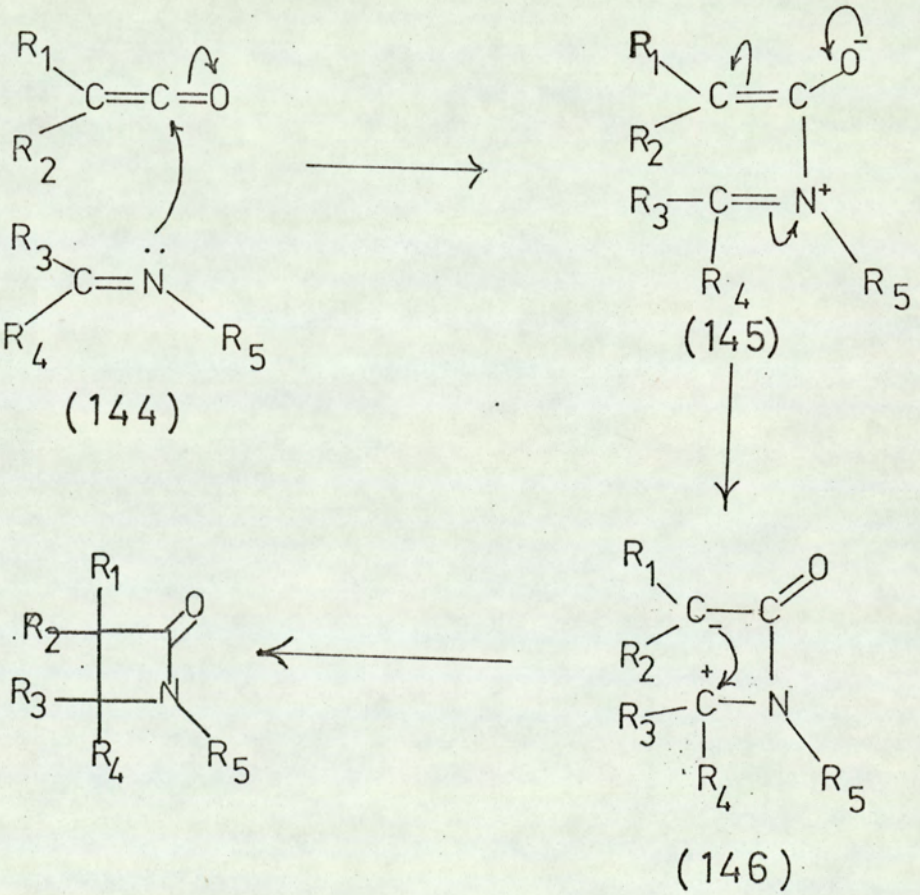
(142)



(143)

1,4-Diphenylazetidine-2-one was also prepared by the action of ethyl-bromo-acetate and zinc on benzylidene anilineusing a similar method to Gillman and Speeter[31] and although both this compound and the compound prepared by the action of ketene on the anil were identical when the infra-red spectrum, the N.M.R. spectrum and analysis figures were compared there was always a difference in the melting point of some 50°. The azetidinone prepared from the ketene could not be induced to melt above 106° even after repeated crystallisation where as all the literature reports[15,31,74,110] indicated a melting point of 154-155°.

The evidence presented in this investigation for the mechanism of the reaction between ketenes and Schiff's bases would suggest that a reaction pathway which involves discrete ionic intermediate is followed. Thus it would seem probable that the initial reaction involves the attack of the anil lone-pair of electrons at the powerfully electrophilic ketene carbonyl group (144) to yield a dipolar intermediate (145). Such a reaction would obviously be aided by electron donation in the anil, as noted by previous workers. Although as the present work shows a certain degree of latitute with electron - withdrawing substituent is possible.



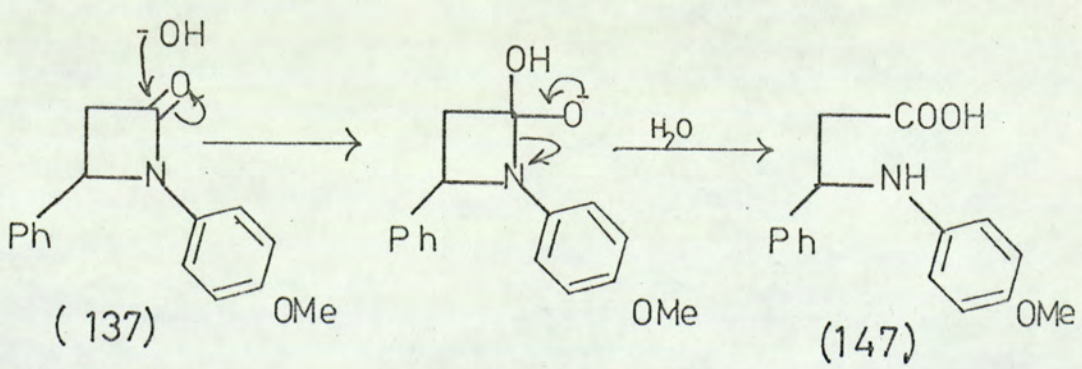
To enable cyclisation to take place this intermediate(145) can be represented in an alternative canonical structure(146). This places an anionic charge on the substituted ketene carbon atom and a cationic charge on the anil carbon atom and its existance can be effectively explain isolation of amides and the stereochemical route of the reaction. Those factors which stabilise the charges in this intermediate(146) might also be expected to aid cydisation and azetidinone formation. This was indeed found to be so. Diphenylketene, which would yield a stabilised diphenyl-methyl carbanion (146 $R_1=R_2=P_h$), was found to react very rapidly and smoothly with a variety of anils whereas ketene usually required longer reaction times and higher temperatures. Similarly anils derived from benzophenone or fluorenone, which would yield diphenylmethyl carbonium ion systems (146; $R_3=R_4=Ar$) , yielded azetidinones more readily than those obtained from aldehydes. Thus it would appear that electronic considerations are of importance in determining the case of cyclo addition if ketenes and anils despite the increased eclipsing strain which is produced in both transition state and azetidinone by these large phenyl substituents.

B. NUCLEOPHILIC REACTIONS

1) Hydrolysis.

The most extensively studied nucleophilic reaction of azetidine-2-ones is alkaline hydrolysis. In general the course of this reaction is similar to that of open-chain amides[115] and yields β-amino acids.

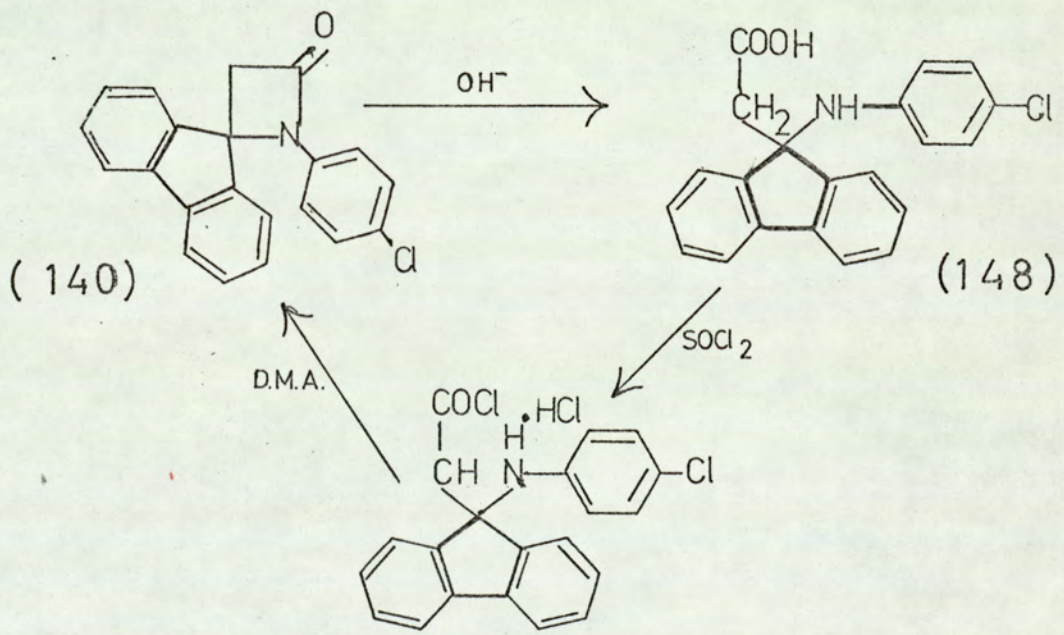
Thus complete hydrolysis of 1-p-methoxyphenyl-4-phenylazetidine-2-one (137) was achieved in two hours using 5% sodium hydroxide in ethanol and yielded β-(4-methoxyanilino)-β-phenylpropionic acid(147).



(137) (147)

This was identified by the ν C = O absorption shift from 1750 cm^{-1} to a typical acid absorption at 1700 cm^{-1} and the appearance of peaks for NH and bonded OH at 3300 and 2500 cm^{-1} respectively.

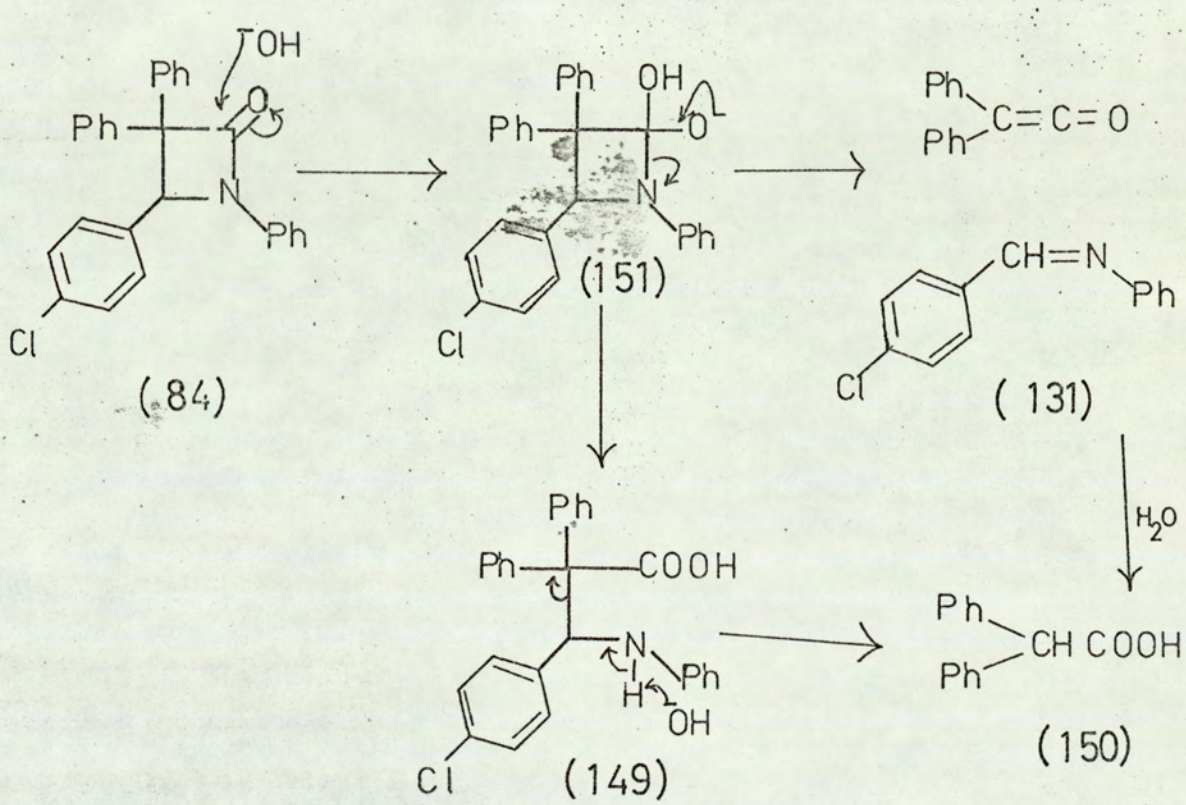
However, the hydrolysis of 1-p-chlorophenyl-4-spirofluorenazetidine-2-one(140)to 9(9-p-chloroanilinofluorene) acetic acid(148)could only be completed using 25% ethanolic sodium hydroxide for two hours or by heating it with a solution of sodium metal in damp ethanol for 1 hour. The acid was identified by its infrared spectrum and N.M.R. spectrum which showed the methylene protons as a singlet at 7.2 τ compared with two doublets at 6.05 and 6.3 τ due to the C-3 protons in the azetidine-2-one. The parent azetidinone was regenerated by treatment of the acid with thionyl chloride, to prepare the acid chloride hydrochloride, and subsequent cyclisation with N,N-dimethyl-aniline.



The hydrolysis of 4-p-chlorophenyl-1,3,3-triphenylazetidine-2-one(84)was found to require more vigorous conditions and 25% ethanolic sodium hydroxide for 24 hours was required. The products from this reaction were diphenyl acetic acid and p-chlorobenzylidene aniline(131)rather than the expected amino-

acid, β anilino-β(4-chlorophenyl)- α,α-diphenylpropionic acid.(149).

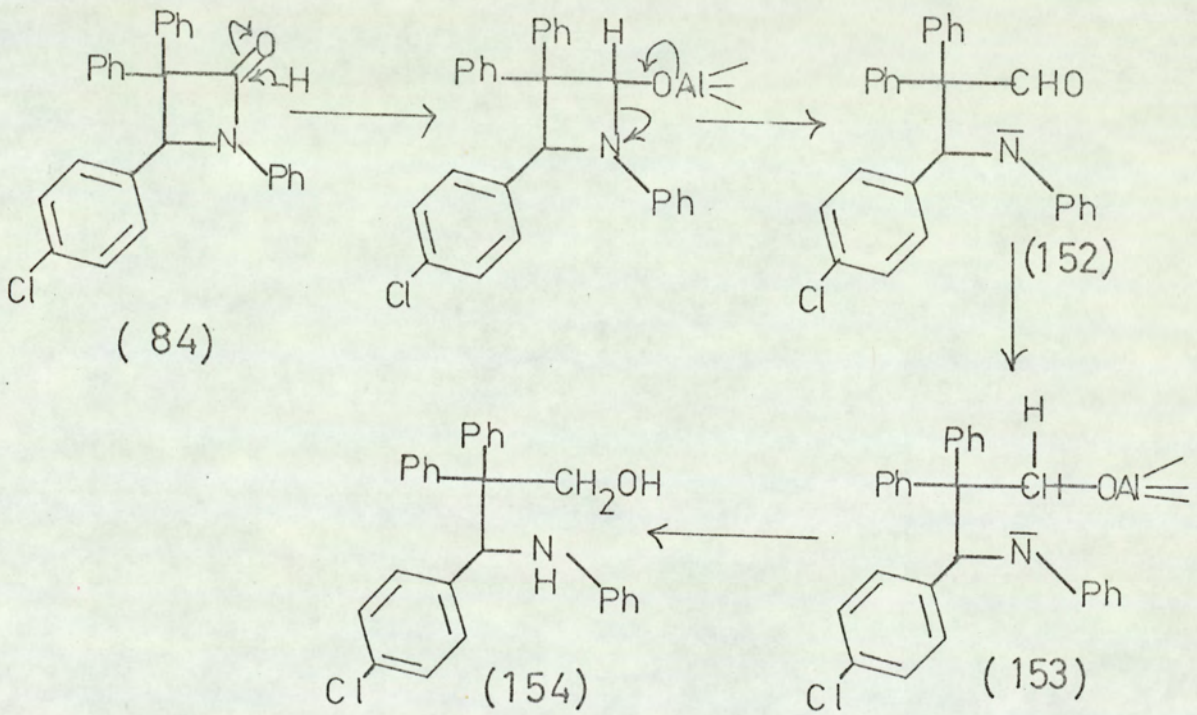
This reaction may proceed via a concerted fission(84,131)to yield diphenylketene which undergoes hydrolysis to give the acid (150) or via the slow elimination of diphenylacetic acid anion from the amide (149) resulting from hydrolytic ring opening. This latter possibility is more probable as similar eliminations are known and the driving force may be the departure of the stabilised diphenylacetic acid anion.



The considerable difference observed in the rates of hydrolysis of substituted azetidinones has been attributed mainly to steric effects[46,52] which may hinder the approach of reagents and also increase the energy associated with the tetrahedral intermediate(151) .

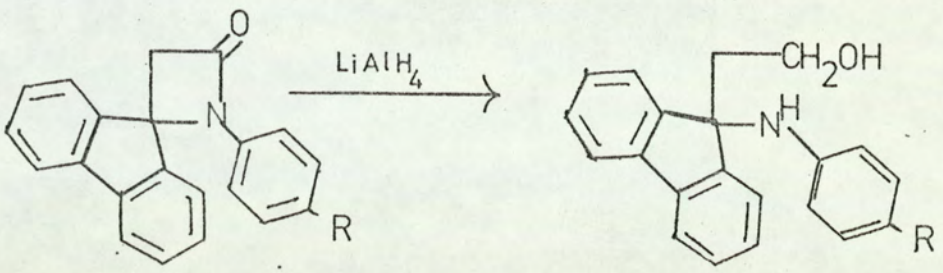
2) REDUCTION WITH LITHIUM ALUMINIUM HYDRIDE.

The reduction of 4-p-chlorophenyl-1,3,3-triphenylazetidine-2-one(84) with lithium aluminium hydride in ether gave 3-anilino-3-p-chlorophenyl-2,2-diphenylpropanol(154) in good yield (90%). This product was identified by the absence of carbonyl absorption and the appearance of a free OH peak at 3600 cm^{-1} and is produced from the azetidinone by ring-opening of the partially reduced intermediate(152) caused by the departure of the stabilised N-aryl anion, and a further subsequent reduction(153).



Similarly the reduction of 1-p-methoxyphenyl-4-spirofluorenazetidine-2-one (141)and 1-p-chlorophenyl-4-spirofluorenazetidine-2-one(140), yielded the 2(9-p-methoxyanilino-9-fluorene) ethanol(155) and 2(9-p-chloroanilino-9-fluorene) ethanol(156) respectively on reduction with lithium aluminium hydride in ether. Preparation of the alcohol was shown by the two peaks in the

N.M.R. spectrum at 6.3τand 7.75τwhich were triplets and integrated for two protons each.



(141) R = OCH_3 (155) R = OCH_3

(140) R = Cl (156) R = Cl

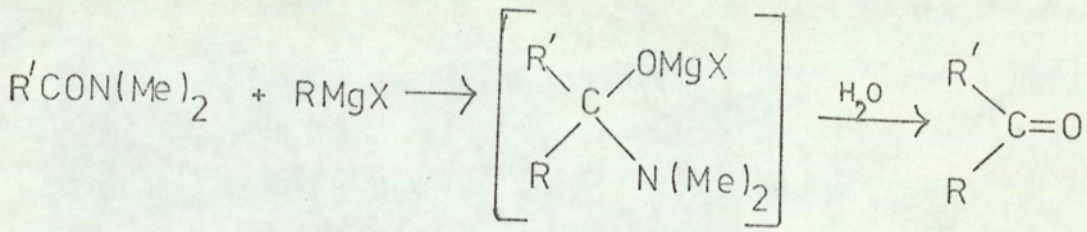
Attempts were made to isolate the intermediate aldehyde (152) from the reaction between lithium aluminium hydride and 4-p-chloro-phenyl-1,3,3,-triphenylazetidine-2-one (84) by using only one equivalent of the reducing agent, however, the only reaction product recovered was the propanol together with some azetidinone.

Sarel[57] found that 1,3,3,4,4-pentaphenylazetidine-2-one underwent fragmentation on treatment with lithium aluminium hydride in hot tetrahydrofurane to yield the Schiff's Base, benzophenylidene aniline.

This is probably due to the relief of ring strain causing cleavage of the C3 - C4 bond after the initial attack.

3. Reaction with Grignard Reagent.

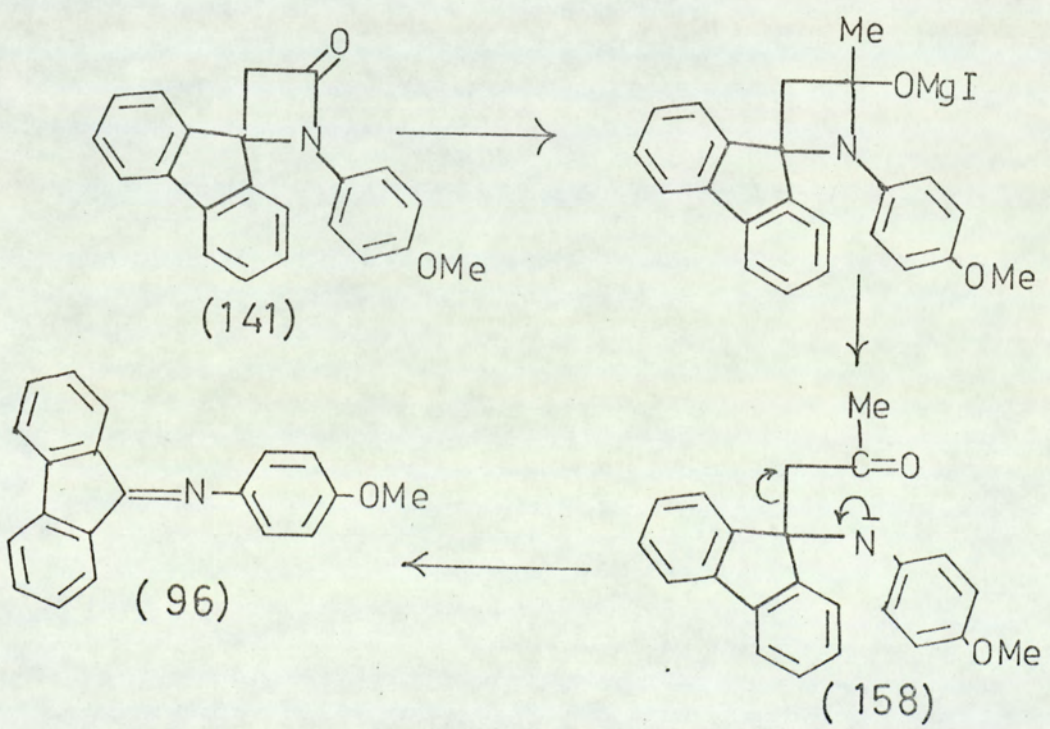
Nucleophilic addition to the amide carbonyl function also takes place with organometallic compounds such as Grignard Reagents. This process probably involves a concerted attack by the metal atom and the carbonium fragment on the amide oxygen and carbon atoms respectively. Tertiary amides react slowly with Grignard reagents to form a stable addition complex (157) which yields on hydrolysis a ketone[116]



(157)

Methyl magnesium iodide has been found to react with 1-p-methoxyphenyl-4-spirofluorenazetidine-2-one (141) to yield fluorenylidene-p-methoxyaniline (96) and some unchanged azetidinone. The product was shown to be identical with an authentic sample. No ketone was isolated from the reaction mixture. This reaction is similar to the reduction of azetidinones with lithium aluminium hydride in that both involve initial nucleophilic attack at the carbonyl group and it would thus appear to be an unusual result in that lithium aluminium hydride and the same azetidinone (141) yielded the alcohol.

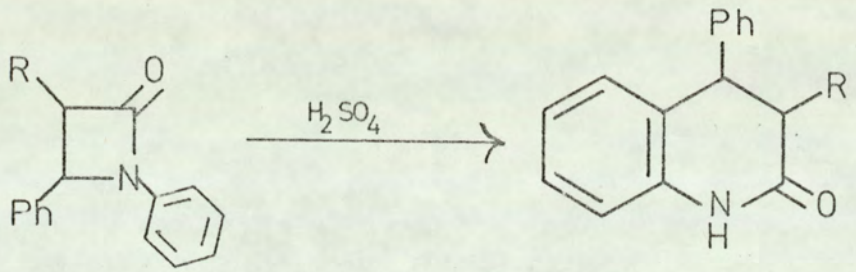
A similar intermediate (158) is probably produced in both reactions but the production of a stabilised anil (96) is probably the driving force which expels acetone as a stabilised α-keto carbanion more rapidly than the addition of a second molecule of Grignard reagent.



In the case of the hydride reductions it may be that the reduction of the ring-opened intermediate, already shown to be rapid compared to the rate of reduction of the azetidinone, is faster than ring fission.

C. REARRANGEMENTS.

Knunyants and Gambaryan[15] have reported the rearrangement of 1,4-diphenylazetidine-2-one (138) and 3-bromo-1,4-diphenylazetidine-2-one (159) in concentrated sulphuric acid to yield 4-phenyl-3,4-dihydroquinoline-2(1H)-one (51) and 3-bromo-4-phenyl-3,4-dihydroquinoline-2(1H)-one (160) respectively. In order to confirm that

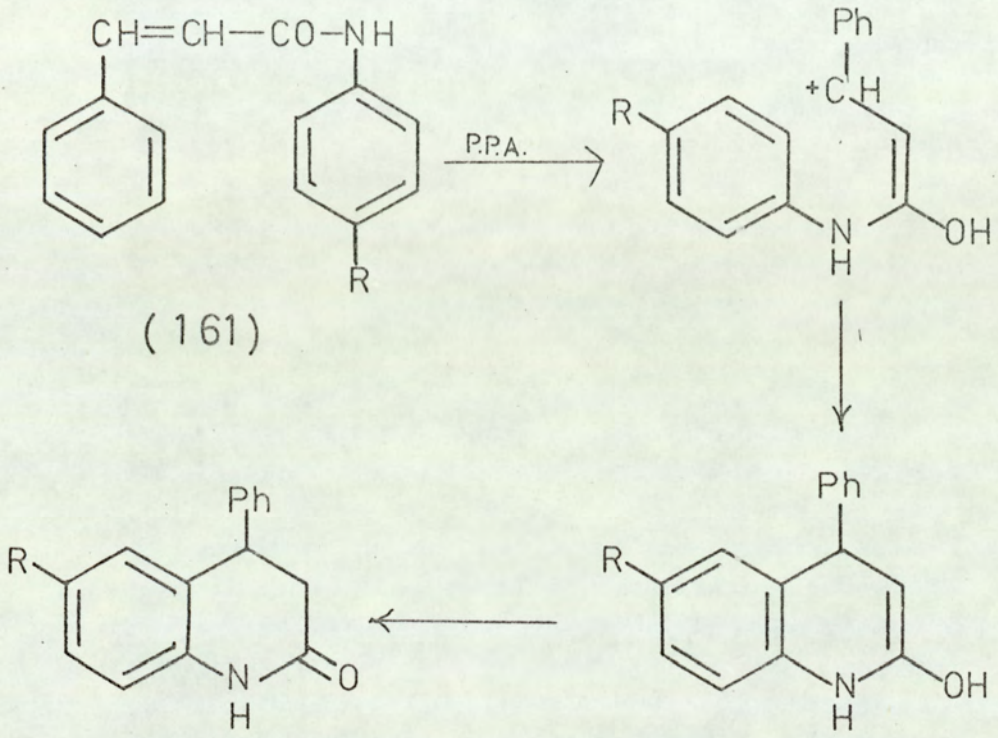


(138) R = H (51) R = H

(159) R = Br (160) R = Br

this rearrangement did indeed yield the formulated product, 1,4-diphenylazetidine-2-one(138) was dissolved in a small quantity of concentrated sulphuric acid and the solution stood at room temperature for 24 hours. Dilution of the reaction mixture with iced water yielded a solid, the infrared spectrum of which exhibited a peak at 1675 cm^{-1} (ν C = O) and also an NH absorption at 3250 $cm.^{-1}$ The distinctive geminal coupling of the C-3 protons exhibited in the N.M.R. spectrum of the azetidinone was replaced by peaks at 7.15 τ (d, J = 7.6 Hz) which integrated for 2 protons, and 5.75 τ (t, J = 7.5 Hz) and it was concluded that the azetidinone had rearranged to the isomeric 4-phenyl-3,4-dihydroquinoline-2(1H)-one(51) . Mass spectrometry confirmed this and showed that both the azetidinone and the dihydroquinolinone have the same molecular ion $^{m}/_{e}$ = 223 [M +] .

The structure of the product was finally proved by the synthesis of the quinolinone by the cyclisation of cinnamanilide (161) with polyphosphoric acid. The products from the two reactions were identical in all respects.



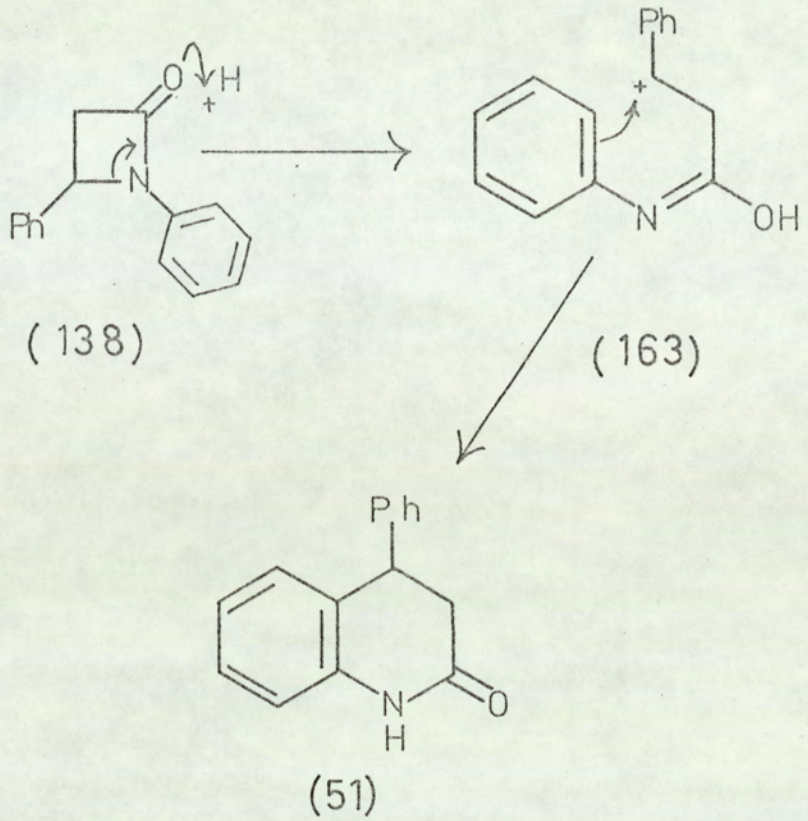
(161)

(51) R=H

(162) R=OMe

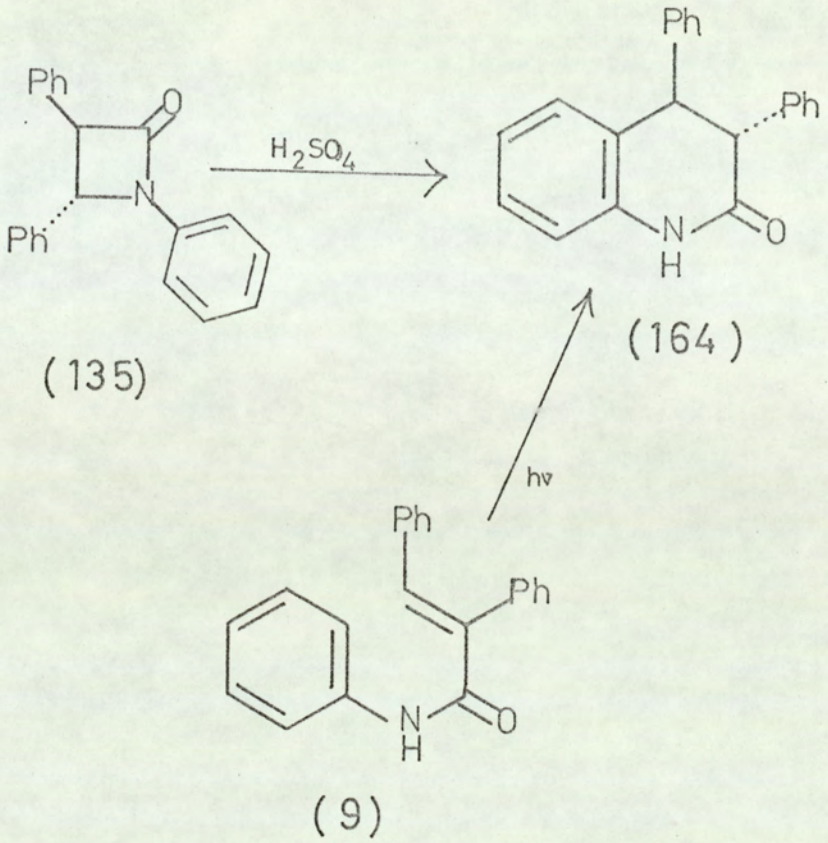
Treatment of 1-p-methoxyphenyl-4-phenylazetidine-2-one (137) with concentrated sulphuric acid in a similar reaction also resulted in rearrangement to yield 6-methoxy-4-phenyl-3,4-dihydroquinoline-2(1H)-one(162) . Again the structure of the product was confirmed by the cyclisation of cinnam-4-methoxy-anilide with polyphosphoric acid.

The rearrangement reaction probably proceeds via the carbonium ion(163) which is the initial product from the protonation of the azetidinone and which is a common intermediate in the synthesis of the quinolinone from cinnamanilide. Cyclisation of this intermediate can then be postulated as an intramolecular electrophilic substitution reaction to yield the dihydroquinolinone.

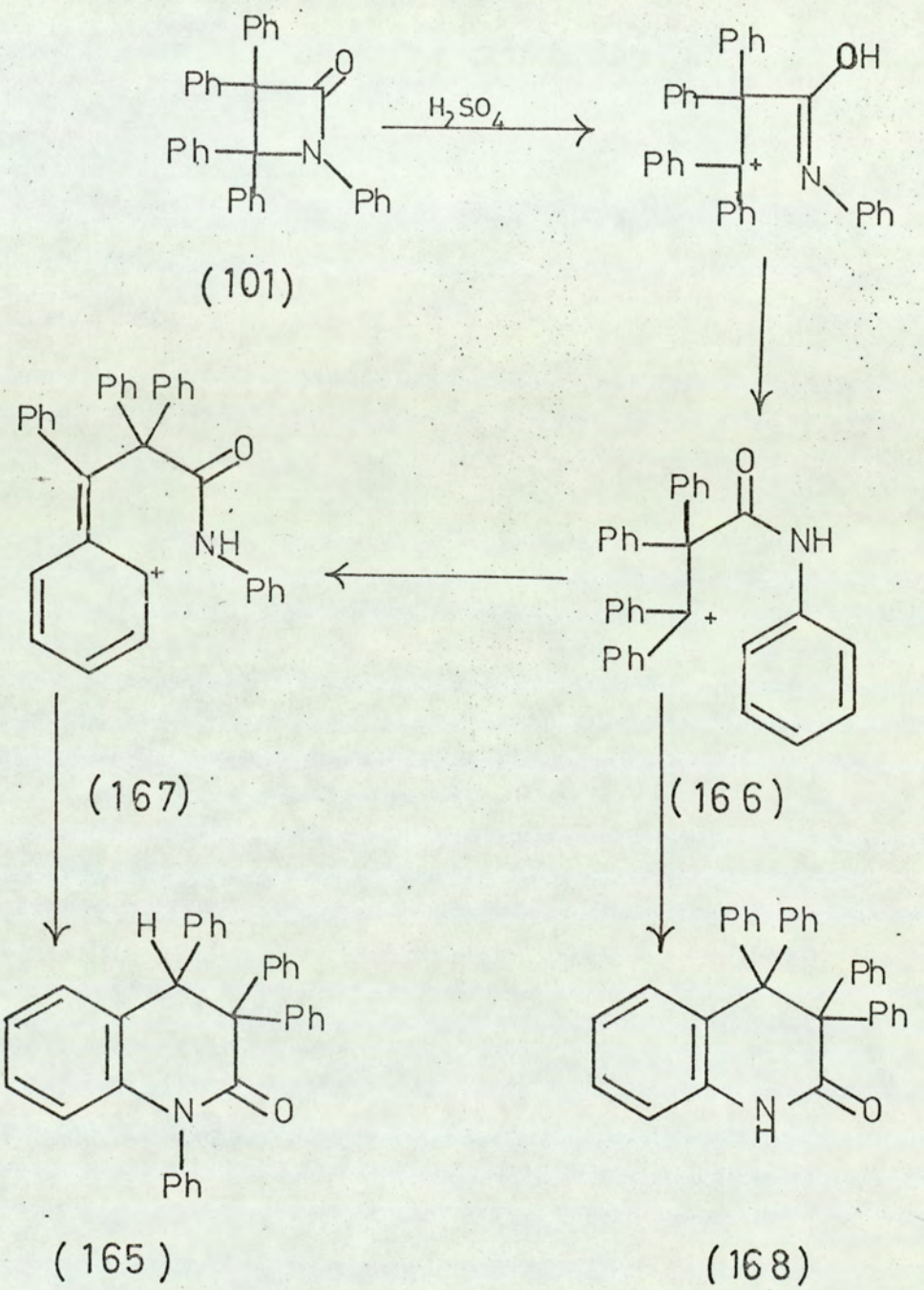


(138) (163) (51)

A similar reaction with 1,3,4-triphenylazetidine-2-one (135) yielded 3,4-diphenyl-3,4-dihydroquinoline-2(1H)-one (164). The N.M.R. spectrum of this compound showed two single proton doublets at 5.55 and 5.9 τ (J = 6Hz) in good agreement with another report of this compound prepared from the cyclisation of the cinnamanilide[107] (9) by U.V. irradiation. The coupling constant (J 6Hz) indicates that the 3 and 4-protons are probably in the diaxial positions. Calculations from the Karplus equation indicates that a coupling constant of the measured magnitude can be achieved if there is a small amount of rotation around the 3,4-bond to relieve some interaction between the two equatorial phenyl groups.



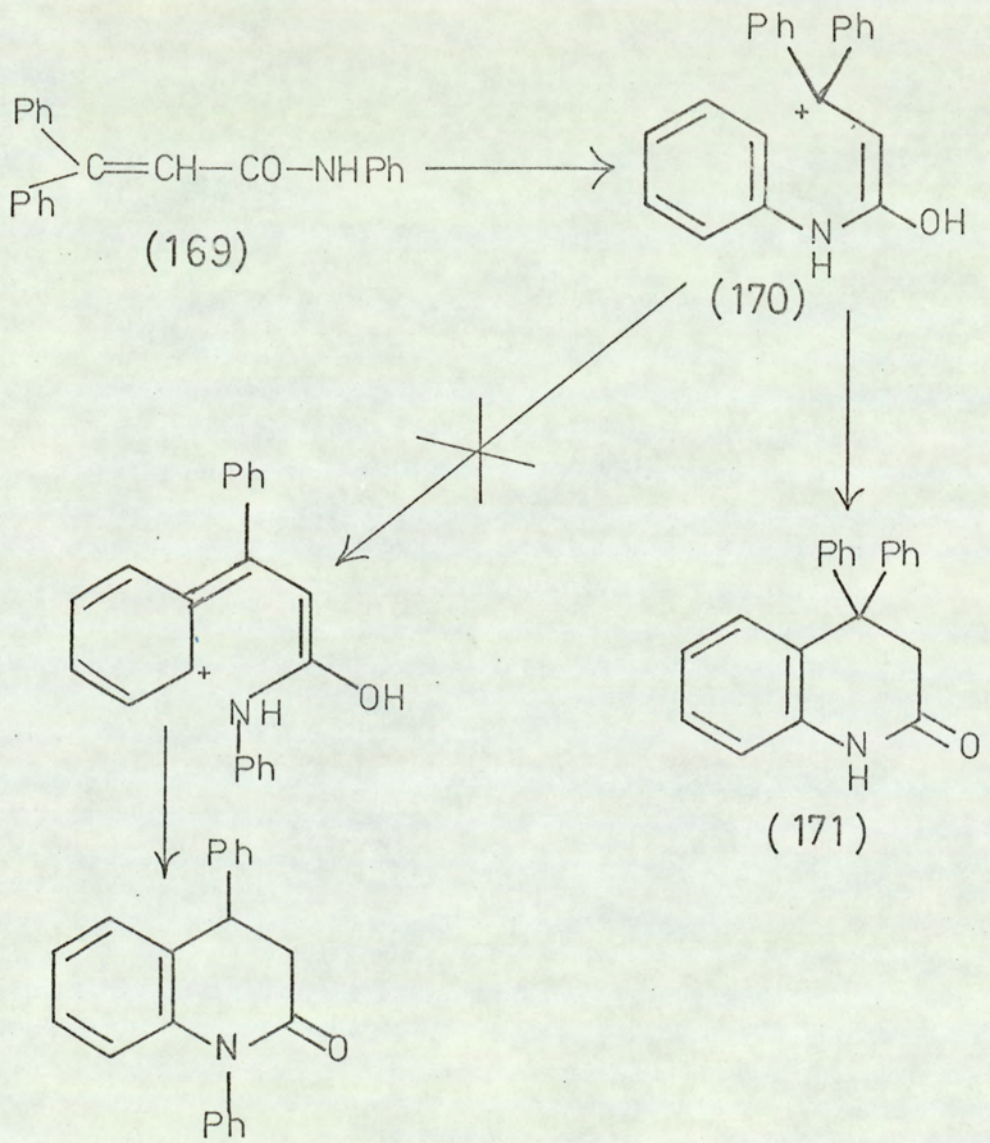
The reaction of concentrated sulphuric acid with the fully substituted 1,3,3,4,4-pentaphenylazetidine-2-one (101) was carried out by Sarel[57] and it was reported that the azetidinone rearranged to yield the isomeric 1,3,3,4-tetraphenyl-3,4-dihydroquinoline-2 - one (165) . This reaction requires a different mode of cyclisation to that observed with the 1,4-diphenylazetidinone rearrangement and it was concluded that steric hinderance around the carbonium ion (166) made the transition state (167) for this reaction the most favourable pathway. The ring closure presumably proceeded by a nucleophilic substitution reaction.



Repitition of the rearrangement reaction with 1,3,3,4,4-pentaphenyl-azetidine-2-one (101) indeed yielded a product with the expected high melting point and which was shown to be isomeric with the azetidinone by mass spectrometry ($^{m}/_{e}$ = 451 [M^{+}]). The product also showed an infrared absorption band at 1665 cm^{-1}, typical of a quinolinone, but also observed was a peak at 3350 cm^{-1} which suggested the presence of NH in this compound. In addition, the absorption band quoted to occur at 1630 cm^{-1} was not present in the infrared spectrum and the N.M.R. spectrum of the product did not show the singlet

expected of the proton at C4 which was quoted by Sarel to occur at 4.95τ. This evidence would suggest that in this instance the rearrangement has taken the expected course and has yielded 3,3,4,4-tetraphenyl-3,4-dihydroquinoline-2(1H)-one(168)via cyclisation of the stabilised carbonium ion(166) .

However, it is noteworthy that cyclisation of 3,3-diphenyl-acrylanilide (169) with concentrated sulphuric acid yields 4,4-diphenyl-3,4-dihydroquinoline-2 (1H)-one[134] (171)via a cyclisation of the diphenylmethylcarbonium ion(170) rather than ring-closure to the nitrogen atom expected from Sarel's work.



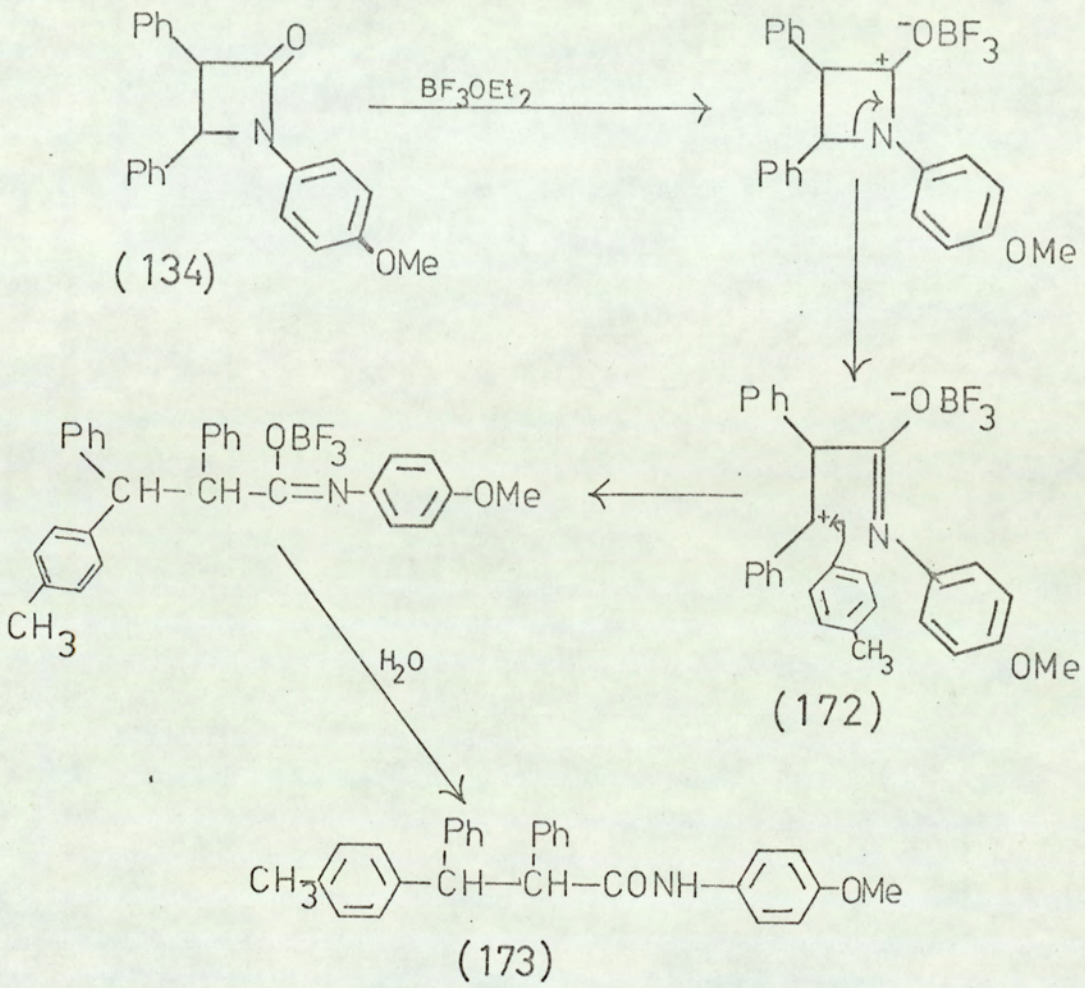
2) REARRANGEMENTS WITH BORON TRIFLUORIDE

a) Preparation of amides.

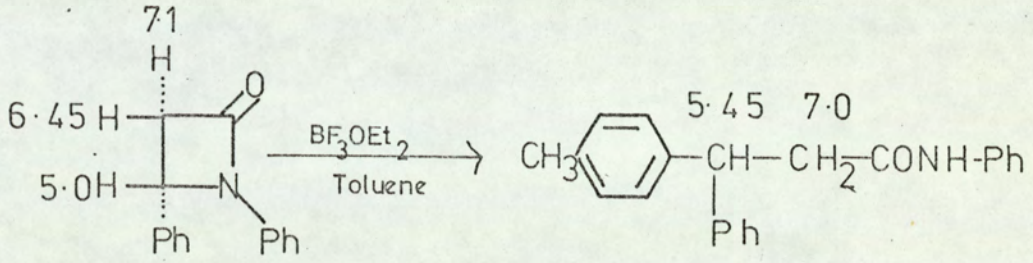
Reactions of azetidinones with concentrated sulphuric acid have shown that these compound will undergo rearrangement to yield 3,4-dihydroquinoline-2

(1H)-ones. If electrophilic attack by a proton generates the carbonium ion (163) as postulated, then, by changing the reaction conditions, it should be possible to isolate or trap the ring opened intermediates. This may be as further rearrangement or reaction products, or by elimination of a proton to yield olefins.

In an initial experiment 3,4-diphenyl-1-p-methoxyphenyphenylazetidine-2-one(134) was dissolved in boiling chloroform together with a little boron trifluoride etherate and the solution was heated under reflux for three days. However, over 70% unchanged azetidinone was recovered from the reaction mixture. In order to achieve more forcing conditions the azetidinone was dissolved in boiling toluene with boron trifluoride etherate. After a reflux period of 48 hours the reaction mixture showed no azetidinone carbonyl in the infrared spectrum, but a new peak at 1650 cm^{-1} together with a peak at 3300 cm^{-1} indicating an NH stretching vibration. The N.M.R. spectrum, which showed the presence of two doublets at 3.5 and 3.0τ(4H, J = Hz) and a three proton singlet at 6.4 (OMe) indicated that the p-methoxyphenyl group was retained. Other peaks in this spectrum were a singlet at 7.75 τ (3 protons) an AB quartet centered at 5.3 τ (2 protons, J = 12Hz) and a phenyl multiplet which integrated for 14 protons at 2.7 τ . Furthermore the mass spectrum showed that this compound had a small molecular ion at $\underline{m/e}$ = 421 and so could not be isomeric with the parent azetidinone ($\underline{m/e}$ = 329 [M +]). Thus it would appear that a molecule of toluene had been incorporated into the final product. If a carbonium ion had been formed(172)as postulated then the reaction conditions were ideal for a Friedel-Craft reaction to take place between it and the solvent, toluene, to produce a ring-opened subsituted propionamide (173) .

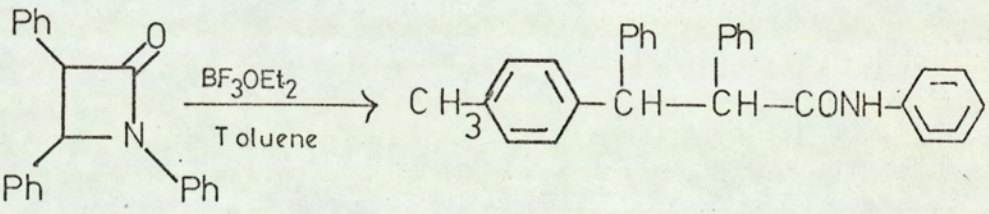


This reaction was repeated using 1,4-diphenylazetidine-2-one (138) to yield the 3-phenyl-3-tolyl propionanilide (174) which was identified by the infrared spectrum which showed a 1660 cm^{-1} absorption (ν C = O) and the N.M.R. spectrum, which showed three proton singlet at 7.75 τ and a doublet and triplet at 7.0τ(2 protons) and 5.45 τ (1 proton) respectively. This indicated that the azetidinone, which showed a typical AMX splitting pattern of quartets at 5.0, 6.45 and 7.1 τ had been broken down to yield the amide (174).

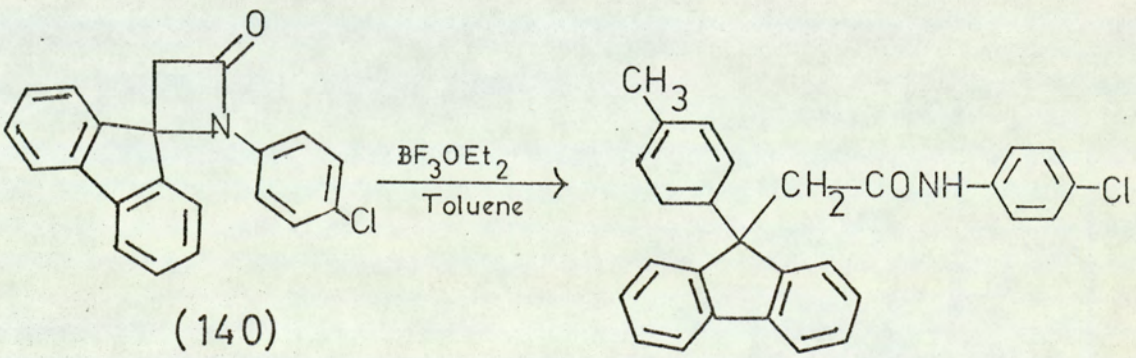


(138) (174)

Treatment of 1,3,4-triphenylazetidine-2-one (135) and 1-p-chlorophenyl-4-spirofluorenazetidine-2-one (140) with borontrifluoride and toluene yielded 2,3-diphenyl-3-p-tolylpropionanilide (175) and 9(9-p-tolylfluorene) acet (p-chloro) anilide (176) respectively.



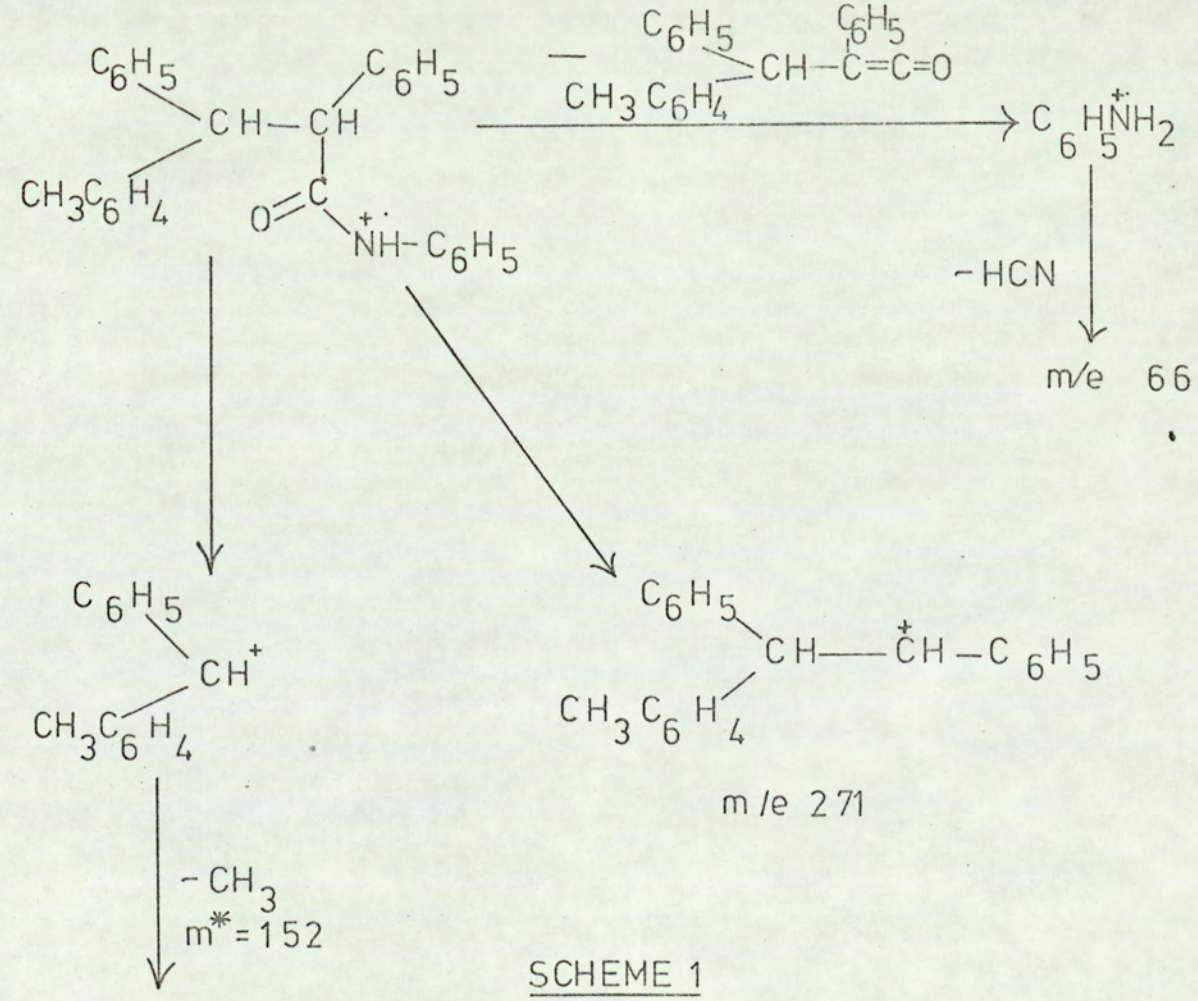
(135) (175)



(140)

(176)

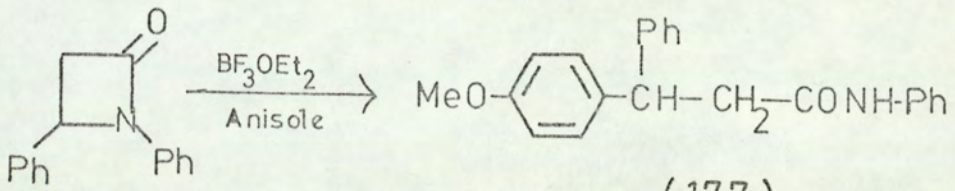
The structures of the amides produced in these reactions were confirmed by the mass spectral fragmentation pattern which showed decompositions typical of amides. Thus the mass spectrum of 2,3-diphenyl-3-p-tolylpropionanilide (175) showed a small molecular ion of m/e 391 (6 %) and those small peaks corresponding to phenyl and p-tolyl losses were observed at m/e 314 and m/e 300 respectively, the major breakdown was via β -cleavage to yield the base peak at m/e 181 (scheme 1). This fragment then further decomposes by loss of a methyl radical to m/e 166 as indicated by the appropriate metastable transition. Also present were small fragments due to the α -fission (m/e 271), the expulsion of a ketene (m/e 93) and also the production of the tropylium ion (m/e 91).



SCHEME 1

1,4-Diphenylazetidine-2-one was treated with boron trifluoride and anisole to ensure that this reaction could be carried out with other suitable aromatic compounds. This reaction yielded 3-p-methoxy-3-phenylpropionanilide

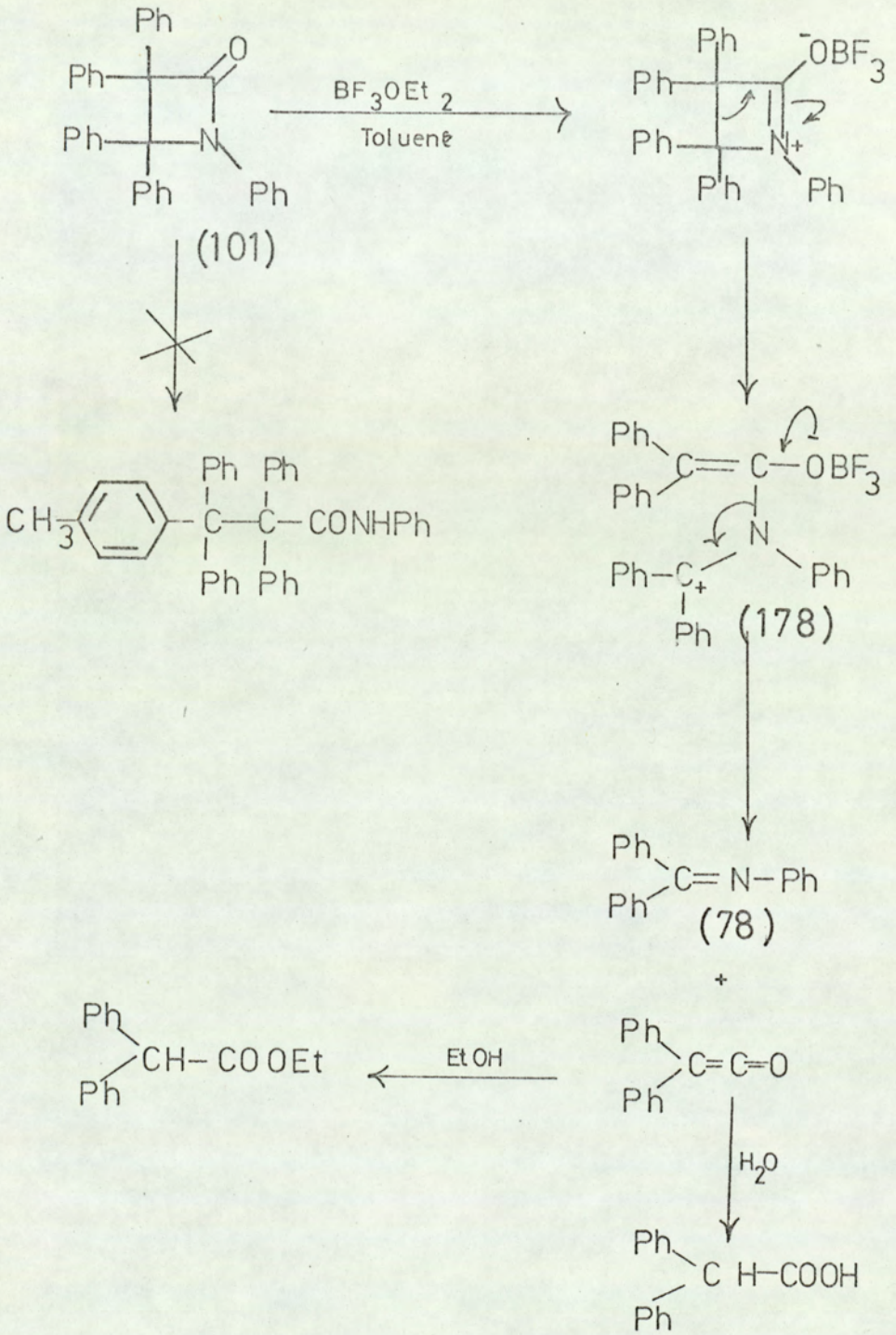
(177) as expected. The incorporation of the anisole into the final product was demonstrated by the appearance of a three proton singlet at 6.05 τ (OMe) in the N.M.R. spectrum.



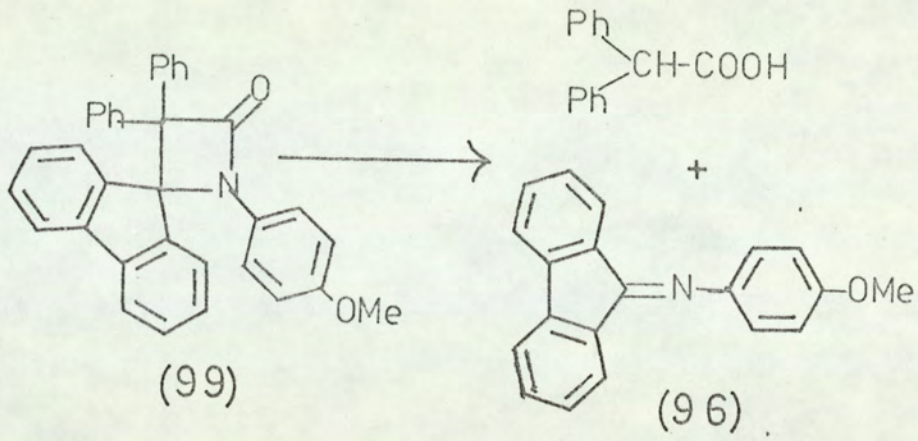
(177)

b) Ring Cleavage

The reaction between 1,3,3,4,4-pentaphenylazetidine-2-one (101) and boron trifluoride etherate in toluene did not give the expected fully substituted propionamide but instead yielded a mixture of two compounds. One fraction was obtained pure by recrystallisation from ethanol and was found to have an infrared spectrum and a melting point identical with those of benzophenylidene aniline (78) . After removal of the anil, extraction of the residue with aqueous sodium hydroxide and the neutralisation of the aqueous layer yielded a compound which could be recrystallised from hot water. This was identified as diphenylacetic acid from its infrared spectrum (ν C = O 1700 cm^{-1}), its melting point, 146° (lit. 146°) and comparison with an authentic sample. The isolation of these products indicates the complete breakdown of the azetidinone ring in a reverse manner to its formation. The presence of diphenylketene in the reaction was shown by rigorously drying the solvent used and adding dry ethanol to the reaction mixture before heating. Analysis of the products by N.M.R. spectroscopy showed the presence of a singlet proton singlet at 5.0 τ and a quartet (2H, J = 7Hz) and a triplet (3H, J = 7Hz) at 5.8 and 8.8 τ respectively indicating the formation of ethyl diphenyl acetate.



The reaction of 3,3-diphenyl-1-p-methoxyphenyl-4-spirofluorenazetidine-2-one (99) , another fully substituted azetidinone, with boron trifluoride etherate and toluene yielded fluorenylidene-p-methoxyaniline (96) and diphenyl acetic acid. Both compounds were identified by comparison with authentic samples.



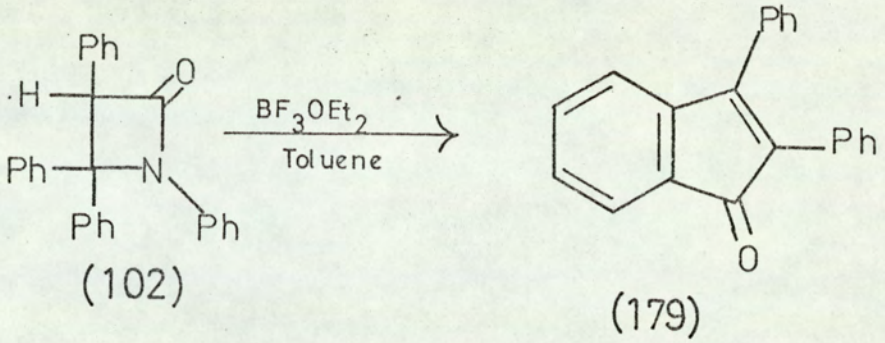
(99) (96)

This reaction appears to be limited to the fully substituted azetidinones. Both of the compounds used possess aromatic rings at the C3 and C4 positions which must be in the eclipsed conformation. This will exert a considerable strain on the C3-C4 bond and it is probable that the relief of this strain is the driving force for this reaction, rather than the production of a stable carbonium ion which has been observed previously. After the initial cleavage of the C3-C4 bond the formation of the stable anil(78) will probably proceed much more rapidly than the incorporation of toluene into the intermediate (178).

c) Formation of Indene-1-one.

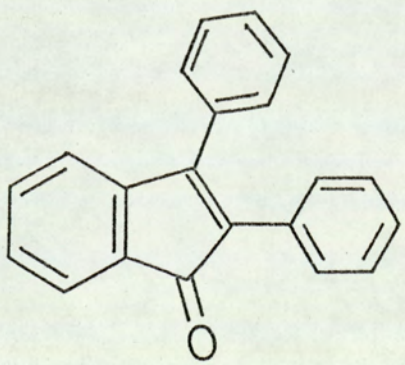
In the rearrangement of the penta-subsituted azetidinones it was found that there was no solvent incorporation due to an alternative mode of reaction being available. This was also found to be true with 1,3,4,4-tetraphenyl-azetidine-2-one (102)which on reaction with boron trifluoride etherate and toluene yielded a red crystalline product in good yields. The infrared spectrum (ν C = O 1700 cm^{-1}) indicated that this was not an amide, and indeed such an intense chromophore would not be expected from the toluene adduct. This compound was shown by N.M.R. analysis to possess only aromatic protons (2.6 τ). The mass spectrum showed that this compound was not isomeric with the azetidinone having a molecular ion at $^{m}/_{e}$ = 282. The product was eventually shown to be 2,3-diphenylindene-1-one(179) by comparison

with tabulated physical data.[118]

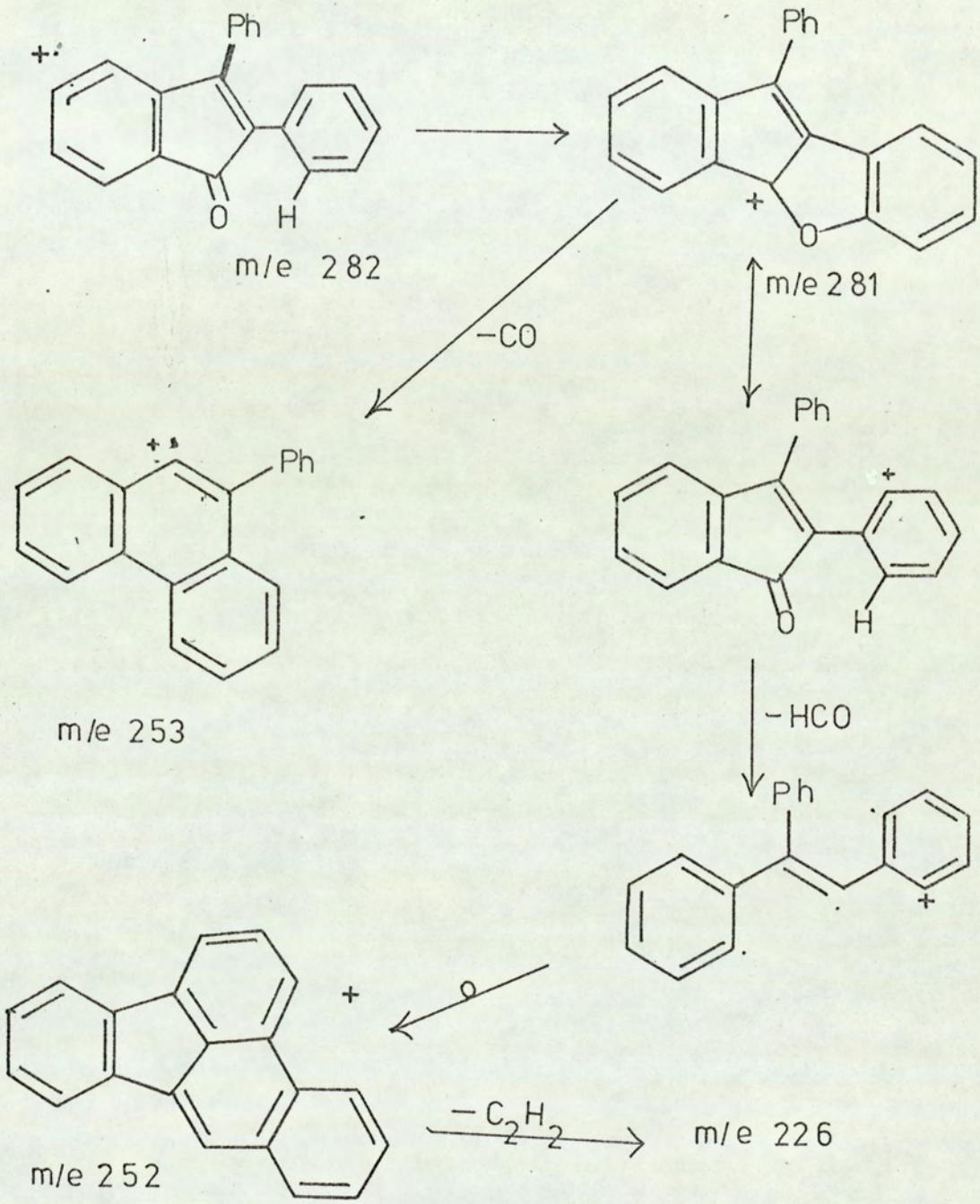


(102) (179)

The mass spectrum confirmed this formulation and shows a large molecular ion ($^{m}/_{e}$ 282). The first fragmentation was found to be a single hydrogen loss to give $^{m}/_{e}$ 281 which was followed by an HCO radical loss ($^{m}/_{e}$ 252). This successive loss of two radicals was confirmed by analysis of the metastable transitions and can be explained by proposing, as occurs for example with substituted polycyclic compounds, that a very stable hydrocarbon is formed during decomposition. Similarly a carbon monoxide extrusion after initial hydrogen loss could form a phenanthrene ($^{m}/_{e}$ 253), another a stable polycyclic hydrocarbon.



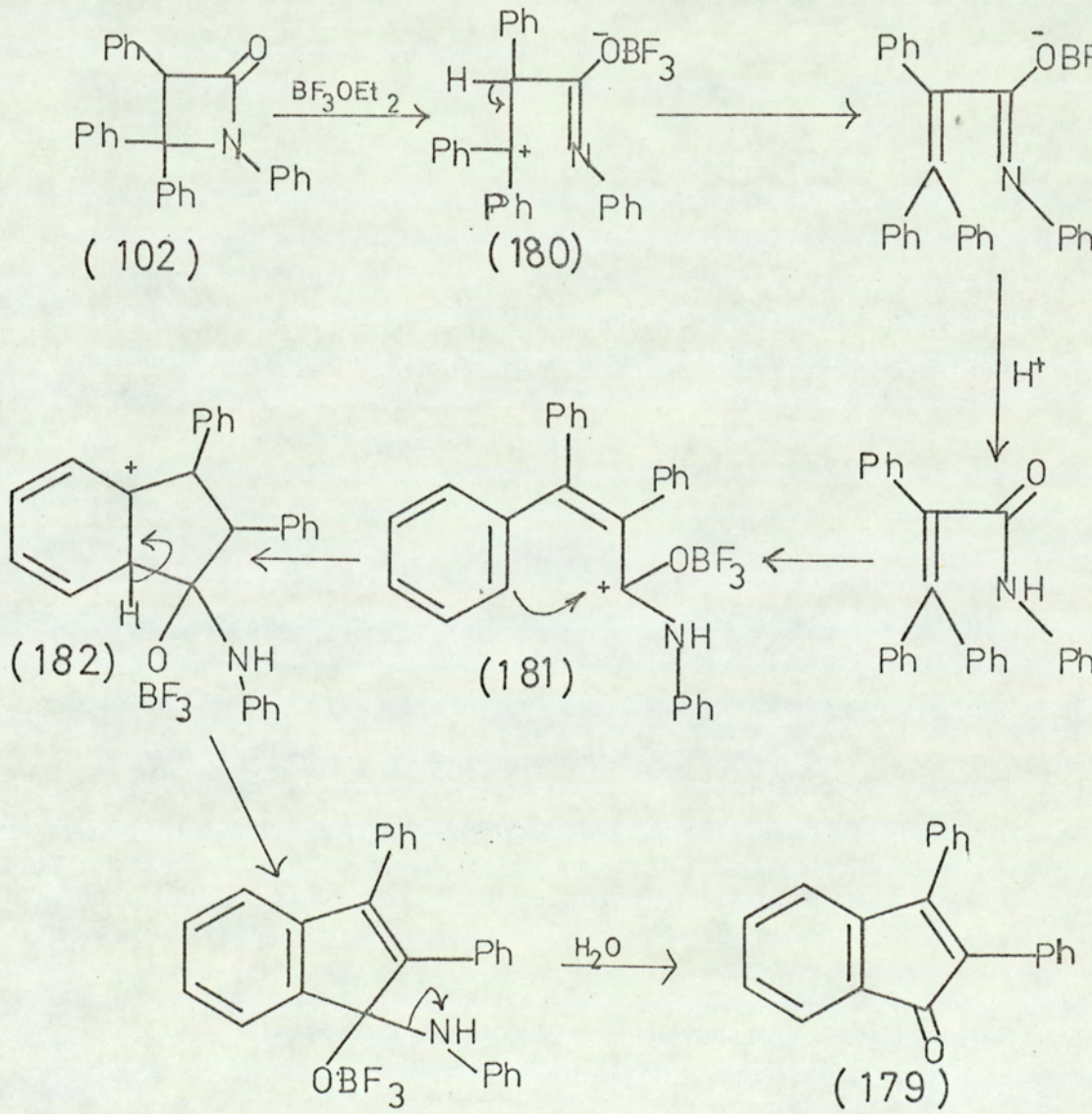
$^{m}/_{e}$ 282



The rather surprising results obtained from this reaction can be explained if, after initial production of the carbonium ion (180) there is a rapid formation of the olefin by loss of the β -proton. This can be regarded as the normal E1 elimination mechanism in which the formation of the carbonium ion is the rate determining step and the production of the conjugated olefin occurs very rapidly. Activation of this acrylamide by co-ordination with boron trifluoride would thus enable the formation of

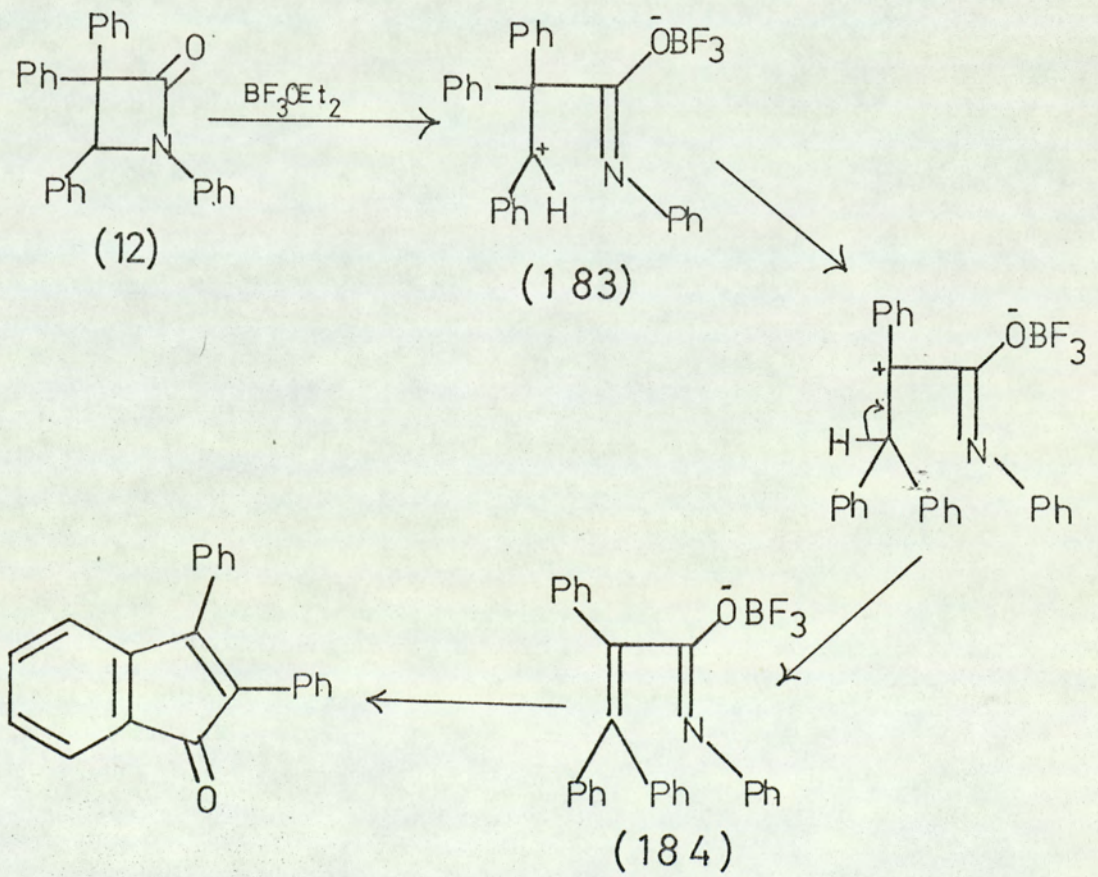
another incipient carbonium ion (181) which may initiate intramolecular electrophilic substitution leading to the formation of the indene skeleton. Further rapid β-elimination would stabilise the highly reactive σ-complex (182) and hydrolysis of the intermediate would yield the indene-1-one.

The rapid elimination of a proton from the carbonium ion (180) would preclude any substitution reactions with the solvent which may be expected to be somewhat slower. Similarly the rapid disappearance of the carbonium ion would also stop any intramolecular reactions to form the dihydroquinolinones. Although there will be some strain in the C3-C4 bond from the two eclipsed aryl residues this must be insufficient to cause fission of this bond.



A small amount of 2,3-diphenyindene-1-one was also obtained when 1,3,3,4-tetraphenylazetidine-2-one (12) was treated with boron trifluoride in boiling toluene, a large quantity of the st arting azetidinone however, was recovered from the reaction mixture and no propionamide was isolated.

The formation of the indene-1-one can proceed if, after the initial cleavage to form the carbonium ion, there is a 1-2 phenyl shift followed by a rapid β-elimination to yield the same intermediate (184) as that postulated in the rearrangement of 1,3,4,4-tetraphenylazetidine-2-one.



The reluctance of the reaction to proceed readily would suggest that the initial ring opening is indeed rate-determining and that the production of a benzyl carbonium ion(183)from 1,3,3,4-tetraphenylazetidine-2-one is a more energetic process than the formation of the diphenylmethyl carbonium ion (180) from the 1,3,4,4-isomer.

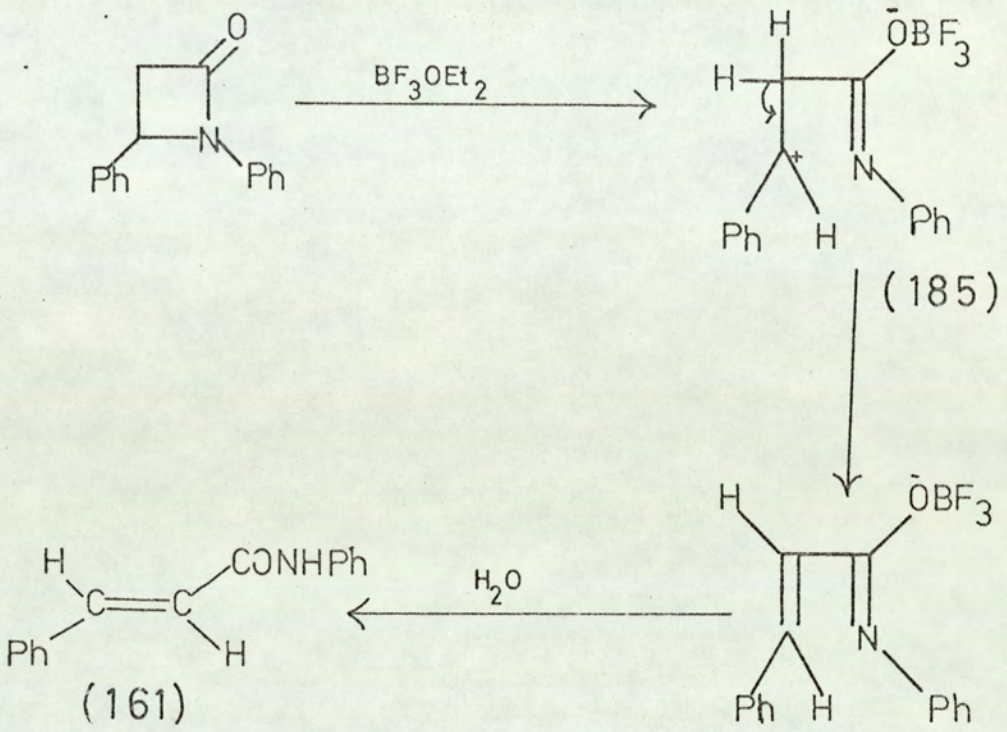
d) In Chlorobenzene.

The formulation of the reaction products from azetidinones boron trifloride etherate and aromatic solvents as ring-opened amides which had undergone electrophilic substitution into the aromatic solvent prompted the investigation of the reaction between the Lewis acid and the azetidinone in a high boiling solvent which was not susceptable to electrophilic attack. Chlorobenzene was selected as being suitable resistance to electrophilic attack and having a boiling point (132°) in the same region as toluene (110°).

1,4-Diphenylazetidine-2-one was heated with boron trifluoride etherate in chlorobenzene under reflux for 60 hours. This yielded a crystalline compound showing infrared absorption at 1665 cm^{-1} ($\nu C = O$) and a peak at 1630 $cm.^{-1}$ The N.M.R. spectrum showed a large phenyl absorption at 2.8 τ (10H) with two single proton doublets at 2.3 and 3.2τ(J = 16 Hz). This was strong evidence that there was a CH = CH group in the molecule and the absorption in the infrared spectrum at 1630 cm^{-1} supported this. Comparison of the physical properties of this compound with an authentic sample of cinnamanilide(161)showed the two to be identical. It can be seen that after the initial formation of the carbonium ion(185)β-elimination of a proton would yield the cinnamilide.

The intermediate carbonium ion did not react with the solvent presumably because the chlorobenzene was too deactivated and the reaction conditions were not forcing enough. The cinnamanilide formed is shown by the N.M.R. spectrum to be in the trans -configuration (J = 16 Hz) and consequently the phenyl group will be held away from the reaction centres necessary to form an indenone. As there is very little strain in the C3-C4 bond, compared to the penta-substituted azetidinone no fission products would be expected, and

indeed none were observed.



D) MASS SPECTRA.

(a) Azetidinones.

Table 2 records the mass spectral fragmentation of 18 azetidinones. All show a weak molecular ion and, in general, two distinctive modes of decomposition were found to occur. These may be considered as the reverse of possible 2 + 2 cycloadditions via which the azetidinones may be synthesises (Figure7). Thus fission by pathway I leads to fragment ions due to a ketene and an anil whereas pathway II produces an olefin and isocyanate residues. Usually all four of these possible decomposition ions are observed but the intensity is dependant upon the nature of substitution. The extrusion of HCO from the molecular ion was found to be an alternative mode of fragmentation but this usually accounted for only a very small proportion of the total ion current.

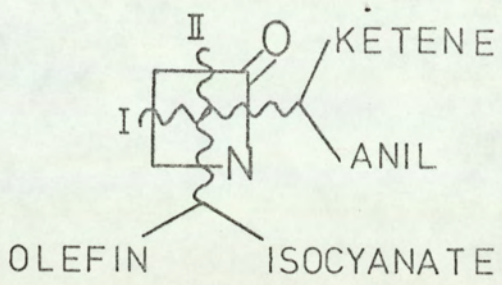
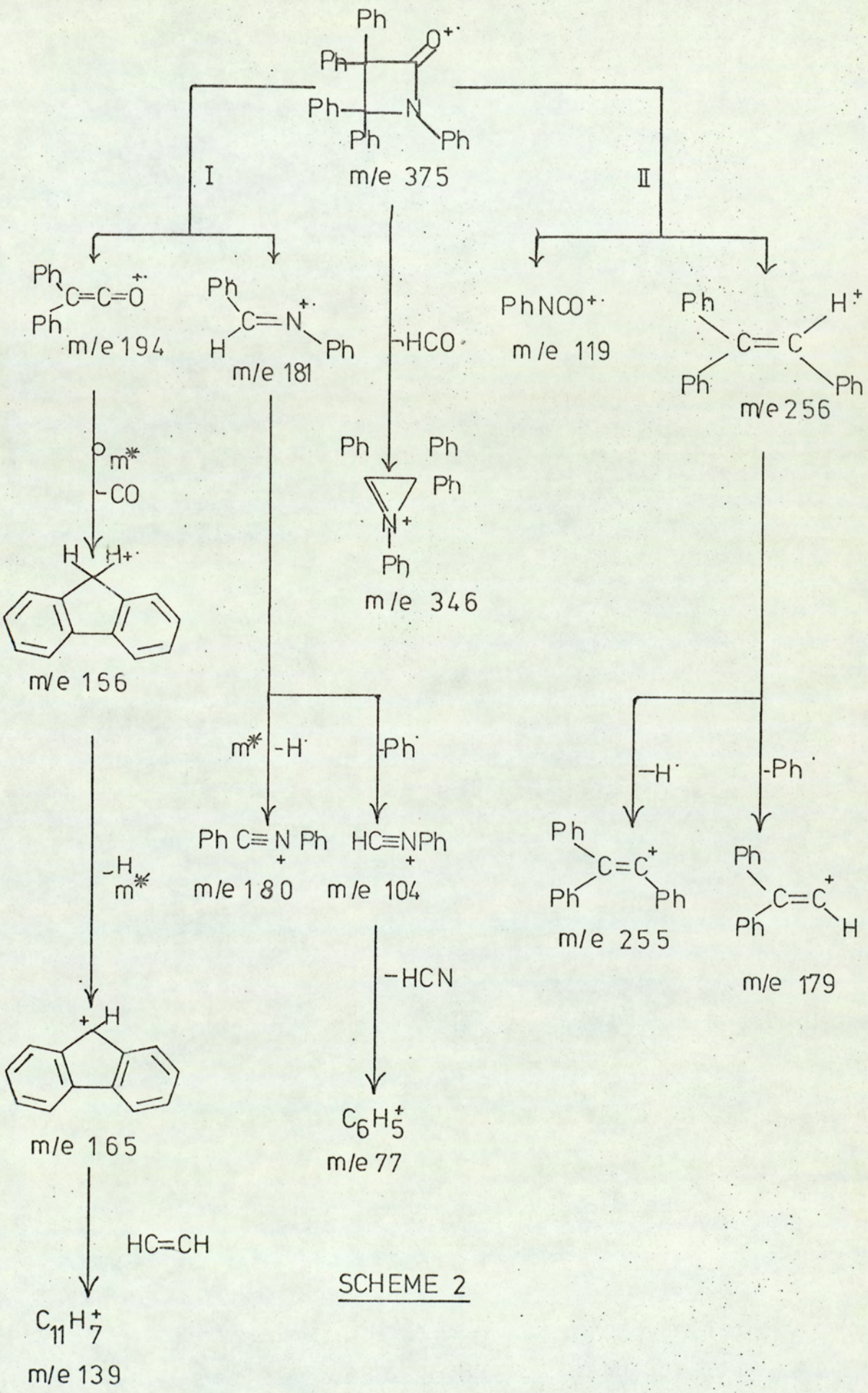


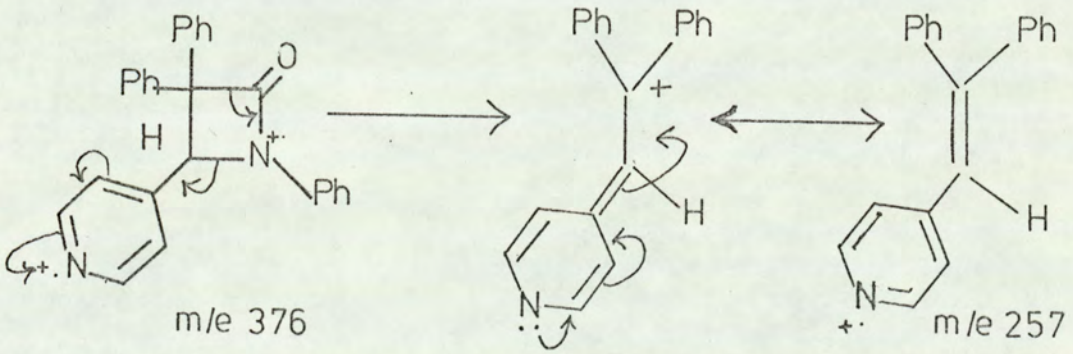
FIGURE 7

The mass spectra of the 3,3-diphenyl azetidinones(12,83,84,85,86,87,88, 89,90,98,99,100,101) were qualitatively similar and showed typical fragmentation pathways. Thus 1,3,3,4-tetraphenylazetidine-2-one (12) showed a small (3%) molecular ion ($^{m}/e$ 375) and principal decomposition via Pathway 1 (Scheme 2) to yield the diphenylketene radical ion ($^{m}/e$ 194) as the base peak and the benzylidene aniline radical ion ($^{m}/e$ 181). The base peak underwent further decomposition by successive losses of CO and H to yield the second most abudant ion ($^{m}/e$ 165). The first of these transitions (194-CO) generated an intense metastable ion (M* 141.9) which was an extremely characteristic feature of the mass spectra of all of the 3,3-diphenylazetidine-2-ones examined. The benzylidene aniline radical ion ($^{m}/e$ 181) also underwent further decomposition by H. ($^{m}/e$ 180), and phenyl radical loss ($^{m}/e$ 104). The alternative mode of fission was a relatively minor process yielding fragments corresponding to the olefin ($^{m}/e$ 256) and phenyl isocyanate ($^{m}/e$ 119). Decomposition of the molecular ion via HCO loss yielded a small (1%) ion ($^{m}/e$ 346).


m/e 375
I
II
m/e 194
m/e 181
m/e 119
m/e 256
m*
-CO
m/e 156
-HCO
m/e 346
m*
-H
-Ph
m/e 180
m/e 104
m/e 255
m/e 179
-HCN
-H
m*
m/e 165
m/e 77
HC≡CH
m/e 139

SCHEME 2

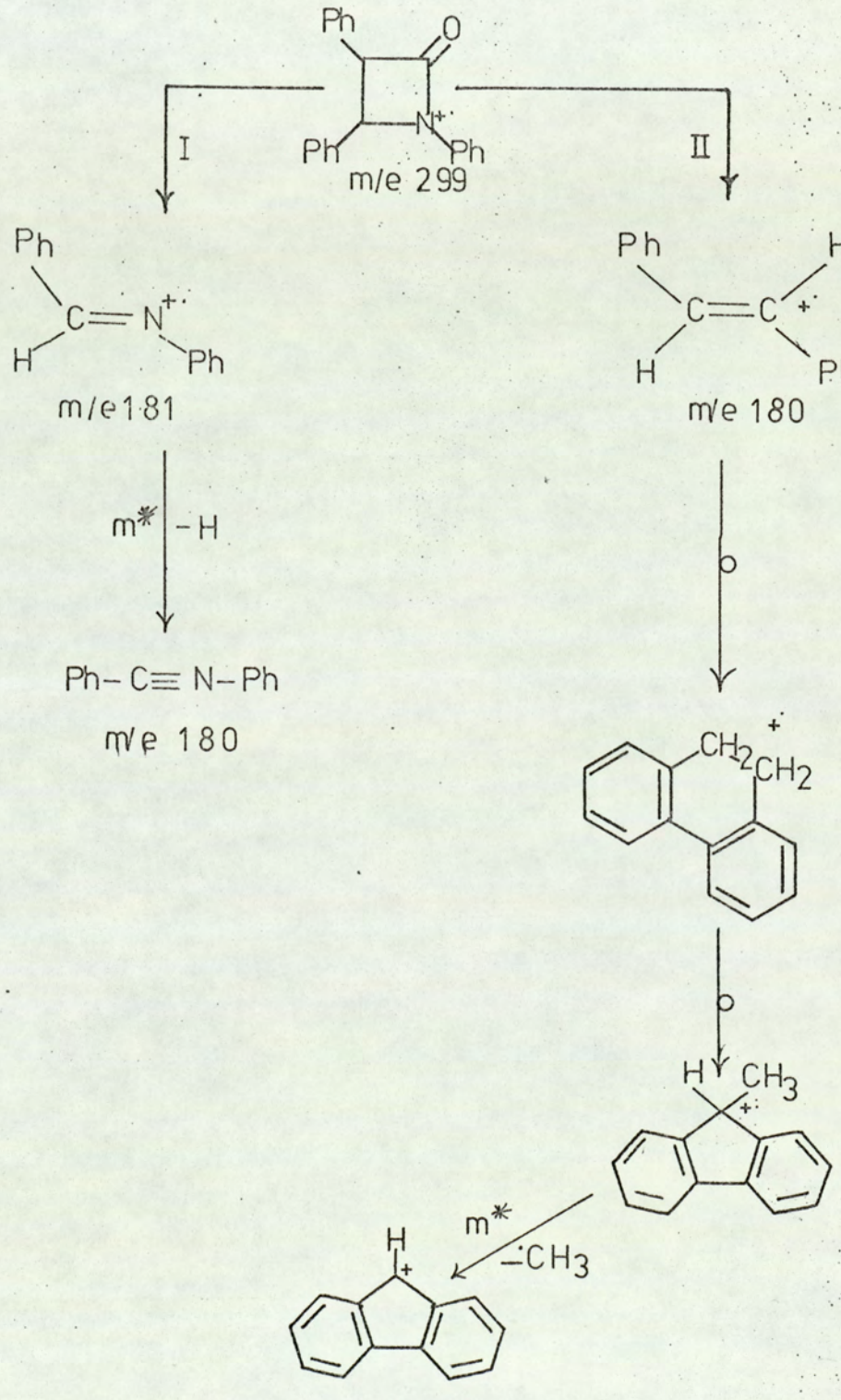
Halogen substitution in the 4-phenyl group (84) had little overall effect upon the fragmentation pattern but the ketene residue now accounted for far more of the total ion current *via* pathway I and a small reduction in the intensity of the olefin moity was apparent. However, with the 4-(4-nitrophenyl) derivative (83) although pathway I *via* the diphenylketene radical ion ($^{m}/_{e}$ 194) was still the preferred mode of decomposition a major fragment (76%) was now due to the olefin radical ion ($^{m}/_{e}$ 301). This trend was continued in the decomposition of the isomeric 4-(X -pyridyl) azetidinones (86 ⟶ 90) and although pathway I (base peak ($^{m}/_{e}$ 194) remained the predominant mode of fragmentation in the 4-(3-pyridyl) azetidinone (87) with the 4-(2- and 4-pyridyl) isomers (88,86) pathway II was the source of the base peak ($^{m}/_{e}$ 257). This effect may be due to the presence of a new centre with a low ionisation potential, i.e. 2-and 4-pyridyl residues, which controls subsequent fragmentation (SCHEME 3)



SCHEME 3

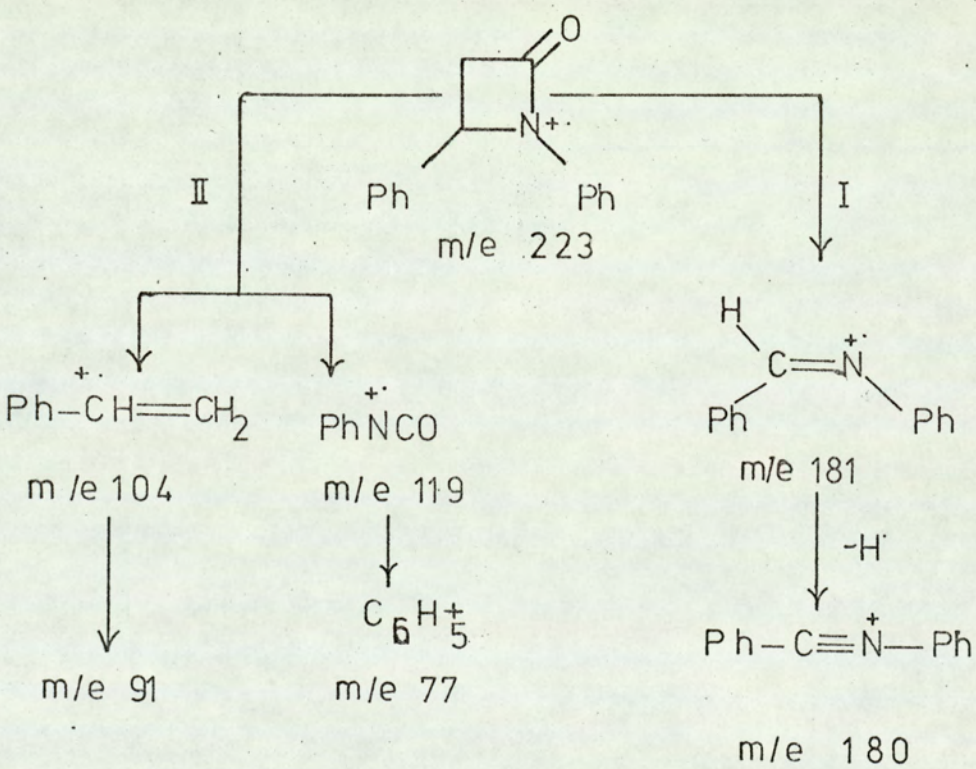
In the mass spectra of those azetidinones with only one 3-phenyl substituent ($_{102,130,134}$) Pathway I no longer appeared to be a major decomposition route. In contrast to 3,3-diphenyl compounds fission in this direction resulted in the anil fragment carrying most of the ion current. Thus the mass spectrum of 1,3,4-triphenylazetidinone (135) (SCHEME 4) showed a small (1%) molecular ion (^{m}/e 299) which underwent decomposition to yield the benzylidene aniline radical ion ($^{m}/_{e}$ 181) and the base peak at ^{m}/e 180. This latter ion was formulated as the stilbene radical ion and showed the characteristic loss of methyl typical of this sytem[135]. Afurther source of this ion

($^{m}/e$ 180), however, is hydrogen loss from the anil residue ($^{m}/e$ 180) and this was confirmed by high resolution measurement and was shown to account for 90% of the total peak. No such ambiguity was possible with 1-(4-chlorophenyl) -3,4-diphenylazetidine-2-one (136) and the base peak ($^{m}/e$ 180) was clearly due to the olefin residue.



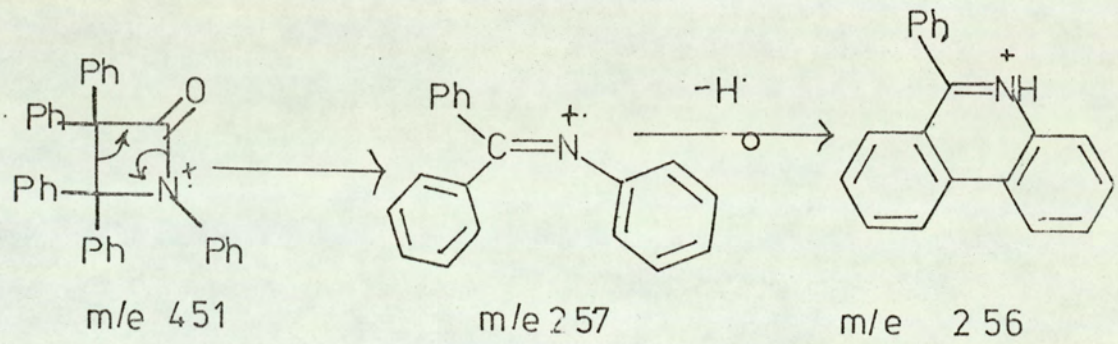
SCHEME 4

In the spectra of 3-unsubstituted azetidinones (138,141) pathway I was no longer the major decomposition route. A complete reversal of the mass spectral fragmentation of the 3,3-disubstituted azetidinones was found to occur and fragmentation by pathway II yielded the olefin radical ion which carried the major proportion of the ion current. Thus the mass spectrum of 1,4-diphenylazetidine-2-one (139 SCHEME 5) showed a molecular ion ($^{m}/_{e}$ 223, 10%) which underwent fragmentation by both pathway I and pathway II to yield a styryl radical ion ($^{m}/_{e}$ 104) as the base peak. However, a small amount (9%) of anil radical ions ($^{m}/_{e}$ 181) was formed by pathway I and these further decomposed by loss of a hydrogen radical ($^{m}/_{e}$ 180)



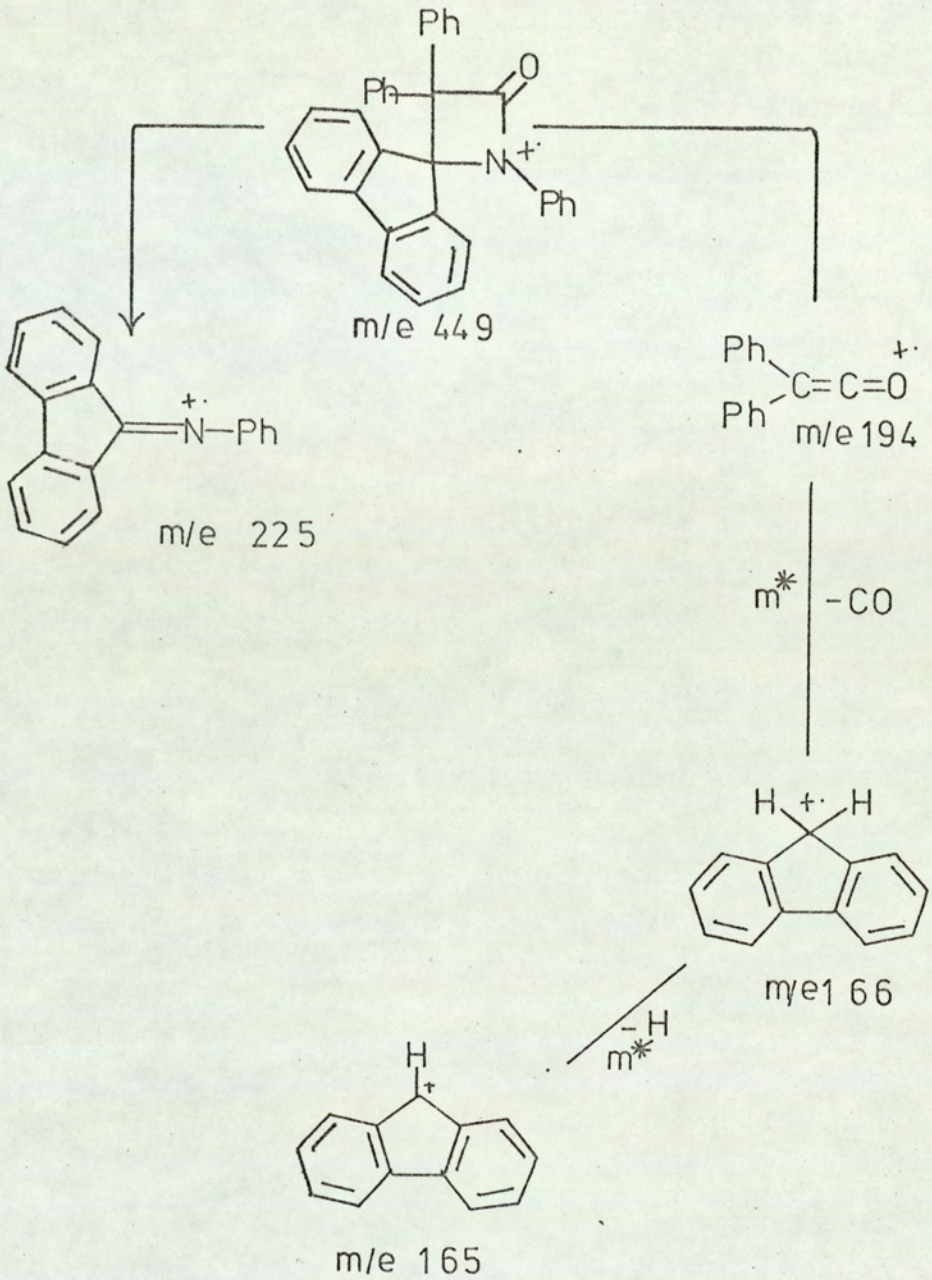
SCHEME 5

The spectra of 4,4-disubstituted azetidinones, which may be regarded as formally derived from the anils of ketones, showed enhanced decomposition *via* this anil fragment presumably due to the extra stabilisation caused by the second aromatic substituent. However, although pathway II was the major source of decomposition of 1,3,3,4,4-tetraphenylazetidine-2-one (101) the base peak (^{m}/e 256) was due to hydrogen loss from the anil radical ion (^{m}/e 257) (SCHEME 6)



SCHEME 6

In the case of the 4,4-spirofluorenazetidinone (98,99) (SCHEME 7) hydrogen loss was a much less significant process, and the base peak again was due to the anil fragment (^{m}/e 255) (SCHEME 7).

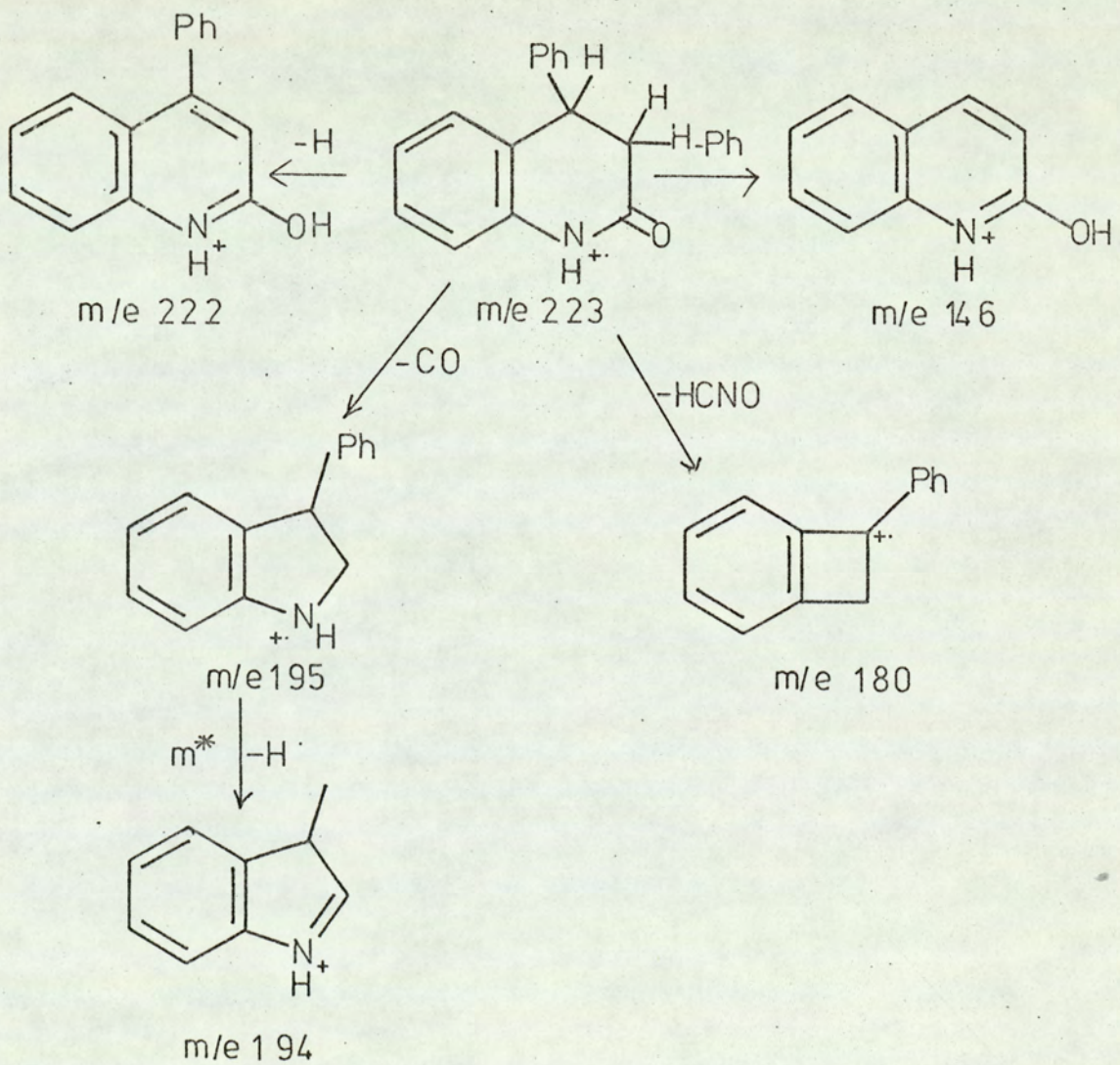


SCHEME 7

b) Dihydroquinoline-2(1H)-ones.

The mass spectrum of 4-phenyldihydroquinoline-2(1H)-one (51) showed the molecular ion as the base peak ($^{m}/_{e}$ 223) which underwent several modes of primary fragmentation (SCHEME 8). Thus loss of phenyl ($^{m}/_{e}$ 146) or hydrogen

($^{m}/e$ 222) radicals were important pathways (57% and 45% respectively) as was loss of isocyanate (95%) to yield the ion at $^{m}/e$ 180. The main fragmentation ion ($^{m}/e$ 194) resulted from the ejection of CO ($^{m}/e$ 195) from the molecular ion and the subsequent loss of a hydrogen radical. This fragmentation pattern was also clearly in the 6-methoxy-4-phenyl compound (162), however, the corresponding fragments were found 30 mass units higher. An additional decomposition pathway in this compound was due to loss of methyl ($^{m}/e$ 238).



SCHEME 8

EXPERIMENTAL

(i) SCHIFF'S BASES

General method for the preparation of the Schiff's Bases

The aldehyde (0.03 mole) was dissolved in ethanol (10 cm^3) and the amine (0.03 mole) was added slowly to the solution. The mixture was boiled for 10 min. and then cooled to yield the Schiff's base which was crystallised from ethanol.

Benzylidene 4 - Aminopyridine.

Benzaldehyde (5.0 g), 4 - amino-pyridine (5.0 g) and benzene (50 cm^3) were heated together with azeotropic distillation for 1 hour. After removal of the solvent the remaining solid was crystallised from petroleum ether to yield the Schiff's base (5.9 g., 59.5%), as colourless crystals, m.p. 68-69°.

ν max: 3050, 2900, 1630 (C = N), 1600, (aromatic nucleus), 1450, 1210, 820, 760 and 690 (aromatic CH) cm^{-1}.

(FOUND: $^m/_e$ 182.083983[M +] $C_{12}H_{10}N_2$ requires $^m/_e$ 182.084394[M +]).

2 - Pyridylidene Aniline.

Pyridine - 2 - aldehyde (5.0 g), aniline (5.0 g) and benzene (50 cm^3) were heated together with azeotropic distillation for 1 hour. After removal of the solvent the residual red oil was distilled (120° 2 mm. Hg.) to yield the Schiff's base (6.7 g., 79%) which slowly crystallised on cooling m.p. 34-5°

(FOUND: $^m/_e$ 182.083983[M +] $C_{12}H_{10}N_2$ requires $^m/_e$ 182.084394[M +]).

ν max: 3050, 2900, 1630 (C = N), 1600, 1480, 780 and 690 cm^{-1}.

3 - Pyridylidene Aniline.

Pyridine - 3 - aldehyde (5.0 g), aniline (5.0 g) and benzene (50 cm^3) were heated together with azeotropic distillation. Removal of the solvent afforded a light brown oil which on distillation (b.p. 131° 18 mm Hg) yielded the Schiff's base (5.2 g., 65%).

<u>SCHIFF'S BASES</u>

$$R_1R_2C = N - R_3$$

R_1	R_2	R_3	YIELD %	SOLVENT	OTHER INFORMATION	M. Pt.	REF.
C_6H_5	H	C_6H_5-	70	Ethanol	ν max. 1615 cm.$^{-1}$ $\tau(CDCl_3)$ 1.6(1H, S, - CH=) 2.6(10H, M, Phenyl).	53°	119
p-Cl-C_6H_4-	H	C_6H_5 -	58	Ethanol	ν max. 1615 cm.$^{-1}$	65-68°	123
p-NO_2-C_6H_4-	H	C_6H_5-	89	Benzene	ν max. 1620 cm.$^{-1}$ (a)	88°	119
p-F-C_6H_4-	H	C_6H_5-	73	Benzene	ν max. 1630 cm.$^{-1}$ (a)	45-47°	119
C_6H_5-	H	p-CH_3O-C_6H_4-	62	Ethanol	ν max. 1630 cm.$^{-1}$	71-72°	124
C_6H_5-	H	p-Cl-C_6H_4-	70	Ethanol	ν max. 1615 cm.$^{-1}$	61-62°	123

R_1	R_2	R_3	YIELD %	SOLVENT	OTHER INFORMATION	M. Pt.	REF.
p-CH_3O-C_6H_4-	H	C_6H_5	71	Ethanol	ν max. 1630 cm.$^{-1}$	56-57°	119
C_6H_5-	H	2-C_5H_4N	48	Benzene	ν max. 1630 (a)	b.pt. 220-230° at 18 mm Hg.	120
C_6H_5-	H	3-C_5H_4N-	61	Benzene	ν max. 1630 (a)	b. pt. 238-245 at 18 mm Hg.	120
9-$C_{13}H_8$-		C_6H_5	52	Chloroform		88.5-90°	125
9-$C_{13}H_8$		p-CH_3O-C_6H_4	74	Chloroform	ν max. 1650 cm.$^{-1}$	135-6°	121
9-$C_{13}H_8$-		p-Cl-C_6H_4-	92	Chloroform	ν max. 1640 cm.$^{-1}$	145-7°	121
C_6H_5	C_6H_5	C_6H_5	87		ν max. 1630 cm.$^{-1}$	106°	122

(a) azeotropic distillation

νmax: 3050, 2900, 1630, 1600, 1420, 1330, 1210 and 780 cm^{-1}

(FOUND: $^{m}/_{e}$ 182.082983[M^{+}] $C_{12}H_{10}N_2$ requires $^{m}/_{e}$ 182.084394[M^{+}]).

4-Pyridylidene Aniline

Pyridine-4-aldehyde (5.0 g) aniline (4.5 g) and benzene (50 cm^3) were heated together with azeotropic distillation for 1 hour. After removal of the solvent the remaining solid was crystallised twice from petroleum ether (60-80°) to yield the Schiff's base (5.2 g., 61%) as pale yellow plates, m.p. 74-75°.

νmax: 3000, 1635 (C = N) 1600, 1500 (aromatic nucleus) 820 and 690 cm^{-1}

(FOUND: $^{m}/_{e}$ 182.083983[M^{+}] $C_{12}H_{10}N_2$ requires $^{m}/_{e}$ 182.084394[M^{+}])

(ii) General method for the preparation of 3,3-Diphenylazetidine-2-ones

A solution of diphenylketene (0.16 mole) in ether (30 cm^3) was added to a stirred solution of the Schiff's base (0.16 mole) in ether (30 cm^3). An immediate precipitate was obtained which was crystallised from methanol to yield the azetidine-2-one.

Diphenylketene ($_{75}$).[127]

Benzil monohydrazone[126] (25 g., 0.164 mole), yellow mercuric oxide (40 g., 0.185 mole), anhydrous magnesium sulphate (20 g) and benzene (100 cm^3) were stirred together at 25-35° for 4 hours. After filtration the benzene was removed by slow addition of the red solution to a flask kept at 110-120°. The residual oil was distilled under a nitrogen atmosphere to yield the ketene (5.1 g., 21%), b.p. 110-130° 1-2 mm Hg (lit 119-121°). One crystal of hydroquinone was added to the ketene to prevent polymerisation.

νmax: 3050, 2150 (C = C = O) 1600, 1500, (aromatic nucleus) 1460, 770 and 700 cm^{-1}.

1,3,3,4,-Tetraphenyl-azetidine-2-one ($_{12}$).[6,128]

Benzylidene aniline (3.0 g) and diphenylketene (3.0 g) yielded the

azetidine-2-one (3.6 g., 62%) as colourless needles, m.p. 162°, (lit 161-161.5°) (from methanol).

(FOUND: C, 86.1; H, 5.7: N, 3.7: Calc. for $C_{27}H_{21}NO$
C, 86.4; H, 5.6; N, 3.7%)

ν max: 3050, 1750 (C = O), 1603, 1520 (aromatic nucleus) 1400 and 1150 cm^{-1}

τ(C D Cl_3): 2.2 - 3.1 (20H, m, Ph), 4.15 (1H, s, 4-H)

1,3,3 -Triphenyl-4-p-chlorophenylazetidine-2-one (84).

p-Chlorobenzylidene aniline (5.0 g) and diphenylketene yielded the azetidine-2-one (5.3 g., 56%) as colourless needles m.p. 157-158° (from methanol).

(FOUND: C, 79.1; H, 5.1; N, 3.6; Cl, 8.9: $C_{27}H_{20}NOCl$
requires C, 79.2; H, 4.9; N, 3.4, Cl, 8.7%)

ν max: 3050, 1750 (C = O), 1603, 1510 (aromatic nucleus), 1395, 1100 and 1020 cm^{-1}

τ(C D Cl_3): 2.3 - 2.9 (19H, m, Ph), 4.2 (1H, s, 4-H).

1-(3'-Pyridyl)-3,3,4-Triphenylazetidine-2-one (90).

Benzylidene 3-amino pyridine (5.0 g) and diphenylketene (5.0 g) yielded the azetidine-2-one (7.9 g., 77%) as colourless needles, m.p. 177-178° (from methanol).

T.L.C. silica with benzene: Methanol 9:1 indicated one component (Rf. 0.66).

(FOUND: C, 82.3; H, 5.3; N, 7.3 $C_{26}H_{20}N_2O$
requires C, 83.0; H, 5.3; N, 7.3%)

ν max: 3050, 1750 (C = O), 1600, 1490, 1450, 1390 and 1150 cm^{-1}

τ(C D Cl_3): 1.4 (1H, d, J2 H_z, 2-H-C_5H_4N), 1.6 (1H, d, J5 H_z, 6-H- C_5H_4N), 2.2-3.1 (17H, m, Ph and 4,5-H- C_5H_4N) 4.15 (1H, s, 4-H).

1-(4'-pyridyl) - 3,3,4-Triphenylazetidine-2-one (89).

Benzylidene 3-aminopyridine (5.0 g) and diphenyketene (5.0 g) yielded

the azetidine-2-one (7.1 g., 69%) as colourless needles m.p. 158-159° (from methanol).

(FOUND: $^{m}/e$ 376.157034[M^{+}] $C_{26}H_{20}N_2O$ requires $^{m}/e$ 376.157555[M^{+}]).

νmax: 3050, 1760 (C = O), 1603, 1510, 1390 and 1150 cm^{-1}

τ(C D Cl_3): 1.6 (2H, d, J5 Hz, 2 and 6 - H C_5H_4N), 2.2-3.1 (17 H, m, Ph and 3 and 5 - H C_5H_4N), 4.15 (1H, s, 4 - H).

4-(2' Pyridyl - 1,3,3-triphenylazetidine-2-one (88).

2-Pyridylidene aniline (3.0 g) and diphenylketene (3.0 g) yielded the azetidine-2-one (1.33 g., 21.4%) as colourless needles m.p. 162-164° (from methanol).

T.L.C. on silica with benzene: methanol indicated one component (Rf 0.63).

(FOUND: C, 83.1; H, 5.3; N, 7.4: $C_{26}H_{20}N_2O$ requires C, 83.0; H, 5.3; N, 7.3%)

ν max: 3050, 1750 (C = O) 1603, 1510, 1390 and 1150 cm^{-1}

τ(C D Cl_3): 1.4 (1H, m, 2-H C_5H_4N) 2.1 (2H, m, 4 and 5-H - C_5H_4N) 2.3-3.3 (16H, m, Ph and 3-H- C_5H_4N) 3.9 (1H, s, 4,-H).

4-(3' pyridyl)- 1,3,3-triphe nylazetidine-2-one (87).

3-pyridylidene aniline (3.0 g) and diphenyl ketene (3.0 g) yielded the azetidine-2-one (1.42 g., 22.8%) as colourless needles m.p. 137-138° (from methanol).

(FOUND: $^{m}/e$ 376.157786 M^{+} $C_{26}H_{20}N_2O$ requires $^{m}/e$ 376.157555 M^{+})

ν max: 3050, 1750 (C = O), 1603, 1510 (aromatic nucleus) 1390 and 1150 cm^{-1}

τ(C D Cl_4): 1.75 (2H, m, 2 and 6 H - C_5H_4N), 2.45-3.2 (17H, m, Ph and 4 and 5-H- C_5H_4N), 4.35 (1H, s, 4-H)

In this reaction a quantity of diphenyl acetanilide (0.25 g) was formed m.p. 185-186°

(FOUND: C, 83.6; H, 5.9; N, 4.9 Calc. for $C_{20}H_{17}NO$

C, 83.6; H, 6.0; N, 4.9%).

ν max: 3400, 3050, 1690, 1603, 1540, 1510, 1450 and 1120 cm^{-1}

τ(C D Cl_3): 2.7 (15H, s, Ph), 4.9 (1H, s, CH).

4-(4' pyridyl) - 1,3,3-triphenylazetidine-2-one (86).

4-Pyridylidene aniline (3.0 g) and diphenylketene (3.0 g) yielded the azetidine-2-one (3.8 g., 61.6%) as colourless prisms m.p. 147-148° (from petroleum ether, 60°-80°) T.L.C. on silica with benzene: methanol, 9:1 indicated are component (Rf. 0.348)

(FOUND: C, 81.8; H, 5.4; N, 7.2 $C_{26}H_{20}N_2O$ requires

C, 83.0; H, 5.3; N, 7.5%).

ν max: 3050, 1750 (C = O), 1603, 1510, 1390 and 1150 cm^{-1}

τ (C D Cl_3): 1.7 (2H, d, J5 Hz, 2 and 6 H C_5H_4N), 2.3-3.1 (17H, m, Ph and 3.5 - H-C_5H_4N), 4.25 (1H, s, 4 - H).

4-p Nitrophenyl-1,3,3 triphenylazetidine-2-one (83).

p-Nitro benzylidene aniline (4.0 g) and diphenylketene (3.2 g) yielded the azetidine-2-one (6.1 g., 81%) as yellow needles m.p. 180-181° (from methanol).

(FOUND: C, 77.6; H, 4.6; N, 6.7 $C_{27}H_{20}N_2O_3$ requires

C, 77.2; H, 4.8; N, 6.7%).

ν max: 3050, 1750 (C = O), 1603, 1540, 1510, 1390, 1350, 1150, 1110 and 860 cm^{-1}

τ(C D Cl_3): 2.3 (2H, d, J9 Hz, 2 and 6 H C_6H_4) 2.5-3.2 (17H, m, Ph and 3, 5 H - C_6H_4), 4.2 (1H, s, 4 - H).

4-p-Fluorophenyl-1,3,3-triphenylazetidine-2-one (85).

p-Fluorobenzylidene aniline (3.0 g) and diphenylketene (2.7 g) yielded the azetidine-2-one (3.5 g., 59%) as colourless needles m.p. 189-190° (from methanol).

(FOUND: C, 82.0; H, 5.2; N, 3.4 $C_{27}H_{20}FNO$ requires
C, 82.9; H, 5.1; N, 3.6%).

ν max: 3050, 1750 (C = O), 1603, 1510, 1390, 1240, 1150 and 850 cm^{-1}

τ(C D Cl_3): 2.2-3.2 (19H, m, Ph), 4.2 (1H, s, 4-H).

1-p Chlorophenyl-3,3-diphenyl-4-spirofluorene-azetidine-2-one (100).

Fluorenylidene p-chloroaniline (2.0 g) and diphenylketene (1.5 g) yielded the azetidine-2-one (3.0 g., 91%) as colourless prisms m.p. 255-258° (from methanol).

ν max: 3100, 1750 (C = O), 1603, 1510, 1460, 1390, 1100, and 840 cm^{-1}

(FOUND: $^{m}/_{e}$ 483.136912[M $^{+}$] $C_{33}H_{22}ClNO$ requires $^{m}/_{e}$ 483.138983[M $^{+}$]), for Cl 35).

4-Spirofluorene-1,3,3-triphenylazetidine-2-one (98).

Fluorenylidene aniline (3.0 g) and diphenylketene (2.7 g) yielded the azetidine-2-one (4.6 g., 87%) as colourless prisms m.p. 277-279° (from methanol).

ν max: (NUJOL): 1745 (C = O), 1603, 1510, 1250, 770, 750, 720 and 700 cm^{-1}

(FOUND: $^{m}/e$ 449.175393[M $^{+}$] $C_{33}H_{23}NO$ requires $^{m}/e$ 449.177955[M $^{+}$]).

3,3-Diphenyl-1-p-methoxyphenyl-4-spirofluorene-azetidine-2-one (99).

Fluorenylidene p-anisidine (1.0 g) and diphenylketene (0.75 g) yielded the azetidine-2-one (1.54 g., 91%) colourless prisms m.p. 240-242° (from methanol).

ν max: 3050, 2590 ($-OCH_3$), 1740 (C = O), 1603, 1590 and 1510 (aromatic nucleus) 1450, 1380, 1250 ($-OCH_3$) 1160, 1020, 830, 730 and 700 cm^{-1}

τ (C D Cl_3): 2.3-3.7 (17H, m, Ph, $C_{13}H_8$ and C_6H_4), 6.55 (3H, s, OCH_3).

1,3,3,4-pentaphenyl azetidine-2-one (101).

Benzophenylidene aniline (1.0 g) and diphenylketene (0.75 g) yielded the azetidine-2-one (1.53 g., 87%) as colourless needles m.p. 198-200° (lit.[21] 191-192°) from methanol.

(FOUND: C, 86.7: H, 5.9; N, 3.20: Calc. for $C_{33}H_{25}NO$ C, 87.8; H, 5.5; N, 3.10%)

ν max: 3050, 1745 (C = O), 1603, 1510 (aromatic nucleus) 1460, 1380 770 and 710 cm^{-1}.

(iii) 3-Chloro-3,4-diphenyl-1-p-methoxy phenyl-azetidine-2-one (117).

Benzylidene p-anisidine (1.4 g., 0.066 mole), triethylamine (2.0 g., 0.2 mole) and chloroacetyl chloride[13] (2.0 g., 0.1 mole) were dissolved in chloroform 25 cm^3) and the solution was stirred at room temperature for 15 hours. After washing the solution with water (50 cm^3) and drying ($MgSO_4$) the solvent was evaporated and the yellow oil triturated to yield the azetidine-2-one (1.0 g., 42%) as colourless needles m.p. 130-132° (from methanol).

(FOUND: C, 72.2; H, 4.9; N, 3.61 $C_{22}H_{18}ClNO_2$ requires C, 72.6; H, 4.9; N, 3.8).

ν max: 3050, 2950, 1745, 1520, 1450, 1390, 1300, 1250, 1140, 1030, 830, 750 and 690 cm^{-1}

τ($CDCl_3$) 2.5-3.3 (14H, m, Ph), 4.4 (1H s, 4-H), 6.25 (3H, s, -OMe)

3-chloro-1-p-methoxyphenyl-3-phenyl-4-spiro fluoreneazetidine-2-one (118).

-Chloroacetyl chloride (8.0 g) was added slowly to a cooled mixture of fluorenylidene p -anisidine (5 g), triethylamine (5.0 g) and chloroform (120 cm^3). The solution was stirred at room temperature for 30 minutes and then was washed with water (50 cm^3), was dried ($MgSO_4$) and was evaporated to low bulk. Trit uration of the residual yellow oil yielded the azetidine-2-one (6.3 g., 82%) as colourless prisms m.p. 160-162° (from methanol).

(FOUND: C, 76.7; H, 4.7; N, 3.1: $C_{28}H_{20}NO_2Cl$ requires C, 76.9; H, 4.6; N, 3.2%)

ν max: 3100, 1770 (C = O), 1530, 1260, 840 and 750 cm^{-1}

τ (C D Cl_3): 2.1-3.7 (17H, m, C_6 $\underline{H}_5$, C_6 H_4 and C_{13} $\underline{H}_8$), 6.4 (3H, s, -O CH_3).

(iv)

General method for the preparation of 3-Phenylazetidine-2-ones.

A stirred solution of the Schiff's base (0.16 mole), triethylamine (0.48 mole) and chloroform (50 cm^3) was cooled to 0°C and phenylacetyl chloride (0.32 mole) added slowly. The mixture was allowed to attain room temperature over a period of 1 hour and then was washed with water (50 cm^3), was dried (Mg SO_4) and was evaporated to low bulk. Trituration and crystallisation of the residual yellow oil yielded the 3-phenylazetidine-2-one.

1,3,4-Triphenylazetidine-2-one (135).

Benzylidene aniline (3.0 g), triethylamine (3.0 g), chloroform (30 cm^3), and phenylacetyl chloride (4.5 g) yielded the azetidine-2-one (1.9 g., 38%) as colourless prisms m.p. 128-130° (lit.[83,128] 133°) (from methanol/water).

(FOUND: C, 84.1; H, 5.8; N, 4.5: Calc. for C_{21} H_{17} NO

C, 84.3; H, 5.7: N, 4.7%).

νmax: 1750, 1603, 1510, 1390, 1150, 760 and 700 cm^{-1}

τ(C D Cl_3): 2.7 (15H, d, $\underline{Ph}$), 5.1 (1H, d, J2 Hz, 4-$\underline{H}$), 5.8 (1H,d, J2 Hz, 3-$\underline{H}$).

3,4-Diphenyl-1-p-methoxyphenylazetidine-2-one (134).

Benzylidene - p - anisidine (1.0 g), triethylamine (1.0 g), chloroform (20 cm^3) and phenylacetyl chloride (1.5 g) yielded the azetidine-2-one (0.55 g., 36%) as colourless needles m.p. 157-159° (lit.[83] 156°) (from methanol).

(FOUND: C, 80.6; H, 5.7; N, 4.2: Calc for C_{22} H_{19} NO_2

C, 80.5; H, 5.7; N, 4.2%).

νmax: 3100, 2950, 1745 (C = O), 1520, 1250 (-OCH_3), 820 760 and 700 cm^{-1}

τ(C D Cl_3): 2.54 (10H, d, $\underline{Ph}$), 2.67 (2H, d, J9 Hz, 3 and 5 $\underline{H}$ C_6 H_4),

3.2 (2H, d, J9 Hz, 2 and 6, $\underline{H}$ -C_6 H_4), 5.1 (1H, d, J2.5 Hz, 4-$\underline{H}$),

5.75 (1H, d, J2.5 Hz 3-$\underline{H}$), 6.3 (3H, s, -O$\underline{CH}_3$).

3,4-Diphenyl-1-p-chlorophenylazetidine-2-one (136).

Benzylidene-p-chloroaniline (1.0 g), triethylamine (1.0 g), chloroform (25 cm^3) and phenylacetyl chloride (1.5 g) yielded the azetidine-2-one (0.68 g., 44%) as colourless needles m.p. 148-150° (from methanol).

ν max: 3050, 1740 (C = O), 1505, 1135, 830, 750 and 700 $cm.^{-1}$

τ ($CDCl_3$): 2.69-2.9, (14H, m, Ph), 5.1 (1H, d, J2.5 Hz, 4-H)
5.75 (1H, d, J2.5 Hz, 3-H).

(FOUND: C, 75.9; H, 4.9; N, 4.2: C_{21} H_{16} Cl NO requires
C, 75.7; H, 4.8; N, 4.2%).

^{m}/e 333.09100 [M^+] C_{21} H_{16} Cl NO requires ^{m}/e 333.092035 [M^+]

1,3,4,4-Tetraphenylazetidine-2-one (102).

Benzophenylidene aniline (4.0 g), triethylamine (2.0 g), chloroform (30 cm^3) and phenylacetyl chloride (3.0 g) yielded the azetidine-2-one (3.2 g., 54%) as colourless needles m.p. 148-50 (lit.[83,128,147]°) (from methanol).

(FOUND: C, 86.5; H, 5.6; N, 3.7: Calc. for C_{27} H_{21} NO
C, 86.5; H, 5.6; N, 3.7%).

ν max: 3100, 1755 (C = O), 1603, 1510 (aromatic nucleus) 1460, 1380, 770 and 710 $cm.^{-1}$

τ($CDCl_3$): 2.3-3.3 (20H, m, Ph) 4.8 (1H, S, 3-H).

1-p-Chlorophenyl-3-phenyl-4-spirofluorenazetidine-2-one (130)

Fluorenylidene p-chloroaniline (2.5 g), triethylamine (1.0 g) chloroform (30 cm^3), and phenylacetyl chloride (1.5 g) yielded the azetidine-2-one (3.2 g., 89%) as colourless prisms, m.p. 205° (from methanol/chloroform)

(FOUND: C, 79.40; H, 4.5; N, 3.4: C_{27} H_{18} NOCl requires
C, 79.5; H, 4.4; N, 3.4%).

ν max: 3050, 1745 (C = O), 1603, 1500, 1460, 1390, 1100, 910, 830 and 720 cm^{-1}

τ($CDCl_3$): 2.2-3.2 (17H, m, Ph), 4.85 (1H, S, 3-H).

Attempted preparation of 4-p-chlorophenyl-1,3-Diphenyl azetidine-2-one.

Phenylacetyl chloride (0.75 g) was added slowly to a cooled, stirred solution of p-Chlorobenzylidene aniline (1.0 g), triethylamine (1.0 g) and chloroform (20 cm^3). After warming to room temperature the mixture was washed with water (50 cm^3), dried (Mg SO_4) and the solvent evaporated but the azetidine-2-one could not be crystalised from the residual yellow oil.

The infra red spectrum of the mixture showed max. 1750 cm^{-1} indicating some azetidine-2-one had been formed.

Similarly no product isolated from p-methoxybenzylidene aniline.

Phenylacet-(4-methoxy anilide) (133).

Benzylidene p-anisidine (1.0 g), chloroform (25 cm^3) and phenylacetyl chloride were heated together under reflux for 1 hr. triethylamine (0.5 g) was added slowly and after cooling the solution was washed with water (50 cm^3), dried (Mg SO_4) and evaporated to give a yellow oil. Trituration and crystallisation yielded the acetanilide (0.73 g., 64%) as colourless plates, m.p. 122-124° (lit.[129] 121.5°) from methanol.

ν max: 3360 (NH), 3000, 1680 (C = O), 1560, 1530, 1250 ($-OCH_3$), 840, 740 and 720 cm^{-1}.

$\tau(CDCl_3)$: 2.7 (5H, s, Ph), 2.7 (2H, d, J9 Hz, 3 and 5-H-C_6H_4), 3.23 (2H, d, J9 Hz, 2 and 6 H-C_6H_4), 6.3 (3H, S, $-OCH_3$) 6.4 (2H, S, $-CH_2-$).

3-Chloro-1-p methoxyphenyl-4-spirofluorenazetidine-2-one (119)

Chloroacetyl chloride (1.0 g) was added slowly to a cooled, stirred solution of fluorenylidene p-anisidine (1.35 g) chloroform (20 cm^3) and triethylamine (0.5 g) and the mixture was stirred for 10 min. The solution was washed with water (50 cm^3), was dried (Mg SO_4) and was evaporated to give a yellow oil. Trituration and crystallisation yielded the azetidine-2-one (1.02 g, 30%) as colourless needles, m.p. 174-5° (from ethanol)

(FOUND: C, 73.1; H, 4.6; N, 3.8: $C_{22}H_{16}NO_2Cl$ requires
C, 73.0; H, 4.4; N, 3.9%).

νmax: 3000 and 1760 (C = O) $cm.^{-1}$

τ($CDCl_3$): 2.2-2.85 (8H, m, $C_{13}\underline{H}_8$), 2.9 (2H, d, J9 Hz, 3 and 5 $\underline{H}$-C_6H_4), 3.4 (2H, d, J9 Hz, 2 and 6 - $\underline{H}$-C_6H_4), 4.7 (1H, S, 3-$\underline{H}$), 6.4 (3H, s, -$OC\underline{H}_3$).

Chloroacet (4-methoxyanilide) (122).

Benzylidene p-anisidine (1.0 g), chloroform (20 cm^3) and chloroacetyl chloride (1.0 g) were heated together under reflux for 2 hrs. Triethylamine (0.7 g) was added and the mixture was heated for a further 1 hr. The solution was washed with water (50 cm^3), dilute sodium hydroxide (30 cm^3), water (50 cm^3), was dried (Mg SO_4) and was evaporated to yield the acetanilide (0.5 g., 53%) as colourless plates, m.p. 122-125 (from methanol). (lit.[130] 121°)

νmax: 3350 (NH), 1670 (C = O), 1250 (OCH_3) 1040 and 840 cm^{-1}

τ($CDCl_3$) 2.52 (2H, d, J9 Hz, 3 and 5 -$\underline{H}$ C_6H_4), 3.12 (2H, d, J9 Hz, 2 and 6-$\underline{H}$ C_6H_4), 5.85 (2H, s, $C\underline{H}_2Cl$), 6.2 (3H, s, $OC\underline{H}_3$).

Chloroacet-(4-chloroanilide) (123).

Chloroacetyl chloride (0.5 g) was added to boiling solution of benzylidene p-chloroaniline (0.3 g) triethylamine (0.5 g) and chloroform (20 cm^3) and stirred for 10 mins. The solution was cooled, was washed with water (50 cm^3) was dried (Mg SO_4) and was evaporated to yield the acetanilide (0.2 g., 70%) as colourless plates m.p. 168-160° (from methanol) (lit.[131] 170°).

νmax: 3300 (NH), 1680 (C = O), 1620, 1560, 1410, 840 and 780 cm^{-1}

τ($(CH_3)_2CO$) :2.27 (2H, d, J9 Hz, 3 and 5 - $\underline{H}$ C_6H_4), 2.75 (2H, d, J9 Hz, 2 and 6 -$\underline{H}$ C_6H_4), 5.8 (2H, s, $C\underline{H}_2Cl$).

1,4-Diphenylazetidine-2-one (135)[110].

Ketene gas[198] was passed through a boiling solution of benzylidene aniline (2.0 g) and dry benzene (50 cm^3) for 6 hrs. After evaporation the residual red oil was dissolved in dichloromethane (5 cm^3) and passed down a column of alumina (20 x 1.5 cm) using dichloromethane as the eluent. The first yellow band yielded the azetidine-2-one (1.3 g. 52%) as colourless needles m.p. 104° (from methanol) (lit. 155°).

After sublimation the azetidine-2-one (m.p. 106°) was shown to be identical with an authentic sample.

(FOUND: C, 80.6; H, 6.0; N, 6.44: Calc. for $C_{15}H_{13}NO$
C, 80.7; H, 5.8; N, 6.3%)

1,4-Diphenylazetidine-2-one was also prepared by the action of ethylbromoacetate and zinc powder on benzylidene aniline in 52% yield, m.p. 157-158° (from methanol).

(FOUND: C, 80.7; H, 6.0; N, 6.4: Calc for $C_{15}H_{13}NO$
C, 80.7; H, 5.8; N, 6.3%).

ν max: 3050, 2950, 1750 (C = O), 1603 and 1510 (aromatic nucleus), 1380, 1150 and 710 cm^{-1}

τ ($CDCl_3$): 2.6-2.8 (10H, m, Ph), 5.0 (1H, q, J6 and 2.5 Hz, 4-H), 6.45 (1H, q, J6 and 15 Hz, 3-H-cis), 7.1 (1H, q, J2.5 and 15 Hz, 3-H trans).

Similar reactions using p-chlorobenzylidene aniline and benzylidene 2-aminopyridene produced very small quantities of azetidine-2-oneswhich were difficult to purify.

1-Phenyl-4-Spirofluorenazetidine-2-one (139).

Ketene gas was passed through a solution of fluorenylidene aniline (3.0 g) benzene (50 cm^3), heated under reflux, for 1 hr. Concentration of the solution to 5 cm^3 yielded the azetidine-2-one (2.7 g., 77%) as colourless prisms, m.p. 222-224° (from methanol).

(FOUND: $^{m}/e$ 297.115520 [M^{+}] $C_{21}H_{15}NO$ requires $^{m}/e$ 297.11535 [M^{+}])

νmax: 1745 (C = O), 1510, 1400, 1390 and 1140 $cm.^{-1}$

$\tau(CDCl_3)$ 2.0-3.1 (13H, m, $C_{13}\underline{H}_8$ and Ph), 6.1 (1H, d, J8, Hz, 3 H H) 6.4 (1H, d, J8 Hz, 3 H H).

1-p-Chlorophenyl-4-spirofluorenazetidine-2-one (140).

Ketene gas was passed through a boiling solution of fluorenylidene p-chloroaniline (5.0 g) in dry benzene (50 cm^3) for 2 hrs. Concentration of the solution to 15 cm^3 yielded the azetidine-2-one (5.1 g., 75%) as colourless prisms, m.p. 239-241°, (from methanol).

(FOUND: C, 75.9; H, 4.1; N, 4.0: $C_{21}H_{14}NOCl$ requires C, 76.1; H, 4.2; N, 4.2%).

νmax: 1750 (C = O), 1510, 1400, 1390, 1090 and 840 cm^{-1}

$\tau(CDCl_3)$: 2.0 (8H, m, $C_{13}H_8$), 3.0 (5H, s, $C_6\underline{H}_5$) 6.1, 1H, d, J8 Hz, C H H), 6.3 (1H, d, J8 Hz, C H H).

1-p-Methoxyphenyl-4-spirofluorenazetidine-2-one (141).

Ketene gas was passed through a boiling solution of fluorenylidene p-anisidine (3.0 g) dissolved in dry benzene (50 cm^3) for 1.5 hr. Concentration of the solution to 5 cm^3 yielded the azetidine-2-one (2.7 g., 78%) colourless prisms, m.p. 227-228° (from acetone).

(FOUND: C, 80.7; H, 5.4; N, 4.3 $C_{22}H_{17}NO_2$ requires C, 80.7; H, 5.2; N, 4.3%)

ν max: 3050, 2900, 1750 (C = O), 1520, 1460, 1400, 1310, 1260 (OCH_3) 1050 and 850 $cm.^{-1}$

$\tau(CDCl_3)$: 2.2-2.9 (8H, m, $C_{13}\underline{H}_8$) 3.1 (2H, d, J9 Hz, 3 and 5 $\underline{H}$ C_6H_4), 3.45 (2H, d, J9 Hz, 2 and 6 $\underline{H}$ C_6H_4), 6.45 (3H, s, $OC\underline{H}_3$) 6.55 (2H, s, 3-$C\underline{H}_2$).

A similar reaction using p-chlorobenzylidene aniline produced some azetidine-2-one which could not be isolated from the reaction mixture. Addition of BF_3 to the Schiff's base before reaction with ketene failed to improve the reaction products.

C. REACTIONS OF AZETIDINE-2-ONES

(1) Nucleophilic Attack

(a) Sodium Hydroxide

(9-p -methoxyphenyl-9-fluorenyl) acetic acid .

1-p-methoxyphenyl-4-spirofluorenazetidine-2-one (0.5 g) ethanol (50 cm^3) and 5% sodium hydroxide (10 cm^3) were heated together under reflux for, 2 hrs. The solution was cooled and was neutralised with dilute sulphuric acid to give a precipitate which was extracted with ether (2 x 50 cm^3). Evaporation of the ether gave a brown oil consisting of two compoents (T.L.C. on silica using benzene/methanol 9:1) which was resolved by acetylating the brown oil and separating on a dry alumina column (30 x 25 cm) using dichloromethane as eluent. Recovery from the column yielded the acetylated product as yellow prisms, m.p. 188-190°

ν max: 3050, 1680 (C = 0), 1530, 1260 ($-OCH_3$) and 850 cm^{-1}

3-p - Anisidine-3-phenylpropionic acid (147).

1-p-Methoxyphenyl-4-phenylazetidine-2-one (0.5 g), ethanol (40 cm^3) and 25% sodium hydroxide solution (10 cm^3) were heated together under reflux for 2 hr. The solution was cooled, was neutralised with dilute sulphuric acid and was extracted with ether (2 x 50 cm^3) evaporation of the solvent yielded the propionic acid (0.2 g., 37%) as colourless needles, m.p. 138-139° (from water).

ν max: 3400, 3050, 2850, 17100 (C = 0), 1520, 1470, 1250 (OCH_3) 1040, 830, 760 and 700 cm^{-1}.

(9-p- chloroaniline-9-fluorenyl) acetic Acid (148).

1-p-chlorophenyl-4-spirofluorena_zetidine-2-one (0.8 g), 25% sodium hydroxide (50 cm^3) and ethanol (20 cm^3) were heated together under reflux for 2 hrs. The solution was cooled neutralised with dilute sulphuric acid and extracted with ether (2 x 50 cm^3). Drying ($Mg SO_4$) and evaporation of the

ether yielded the acetic acid (0.2 g., 23%) as colourless plates m.p. 145° (decomp.) (from chloroform).

ν max: 3400 (NH), 3050, 2600 (OH), 1700 (C = O), 1600, 1500 1480, 1220, 1100, 820 and 670 cm^{-1}

The acid decorboxylates readily on heating to give 9-p-chloroaniline 9-methylfluorene as colourless microprisms, m.p. 115-117° (from benzene).

νmax: 3400 (NH), 1600, 1580, 1510, 1410, 1320 and 860 cm^{-1}

Hydrolysis of 4-p-chlorophenyl-1,3,3-triphenylazetidine-2-one (84).

4-p- chlorophenyl-1,33 -triphenylazetidine-2-one (1.0 g), 25% sodium hydroxide (50 cm^3) and ethanol (20 cm^3) were heated together under reflux for 24hrs. The solution was cooled and extracted with ether (2 x 50 cm^3). Drying ($Mg SO_4$) and evaporation of the ether yielded p chlorobenzylidene aniline (0.2 g., 38%), as colourless plates (from methanol), and some unchanged azetidine-2-one.

The basic fraction was acidified to yield diphenylacetic acid, as colourless needles m.p. 146° (from water).

b) Sodium Ethoxide.

(9-p-chloroaniline-9-fluorenyl) acetic acid (148).

1-p-chlorophenyl-4-spirofluorenazetidine-2-one (0.8 g) sodium ethoxide (3.0 g) and ethanol (20 cm^3) were heated together under reflux for 1 hr. and the solution was poured into water (150 cm^3). Neutrolisation with dilute sulphuric acid gave a turbid solution which was extracted with ether (2 x 50 cm^3). Evaporation of the solvent yielded the acetic acid (0.7 g 83%) as colourless needles m.p. 153-155° (decomp.) (from chloroform).

ν max: 3300 (NH), 2900 (CH_2) 1700 (C = O), 1600, 1500, 1480, and 820 cm^{-1}

τ($CDCl_3$): 1.6 (1H, s, N $\underline{H}$), 2.1-2.9 (8H, m, $C_{13}\underline{H}_8$), 3.25 (2H, d, J9 Hz, 3 and 5 $\underline{H}\,C_6H_4$ Cl), 4.05 (2H, d, J9 Hz 2 and 6 $\underline{H}\,C_6H_4$ Cl), 7.15 (2H, s, $C\underline{H}_2$).

$^m/_e$ 349 [M^+].

A similar reaction was carried out using 1-p-chlorophenyl-3,3-diphenyl-4-spirofluorenazetidine-2-one but no acid was recovered.

c) Lithium Aluminium Hydride [56]

β-(9-p-anisidino-9-fluorenyl) ethanol (155).

1-p-Methoxyphenyl-4-spirofluorenazetidine-2-one (1.0 g) lithium aluminium hydride (0.5 g) and ether (100 cm^3) were heated together under reflux for 40 hrs. After addition of water (2.0 cm^3) the solution was dried (Mg SO_4) and evaporated to yield the alcohol (0.7 g., 69%) as a colourless oil which discolours rapidly in air.

ν max: 3450, (NH), 3050, 1610, 1530, 1460, 1260 ($-OCH_3$) 1190, 1120, 1050 and 840 $cm.^{-1}$

τ($CDCl_3$): 2.2-2.9 (8H, m, $C_{13}\underline{H}_8$), 3.6 (2H, d, J9 Hz, 3 and 5 $\underline{H}\,C_6H_4OCH_3$), 3.95 (2H, d, J9 Hz, 2 and 6 $\underline{H}\,C_6H_4OCH_3$), 5.9 (2H, s, $-O\underline{H}$ and $N\underline{H}$), 6.5 (2H, t, J6 Hz $-C\underline{H}_2OH$), 6.55 (3H, s, $-OCH_3$) 7.9 (2H, t, J6 Hz $-C\underline{H}_2-$).

β-(9 p-chloroanilino-9-fluorene) ethanol (156).

1-p-chlorophenyl-4-spirofluorenazetidine-2-one (0.3 g), Lithium Aluminium Hydride (0.3 g) and ether (50 cm^3) were stirred together for 4 days at 20°. The complex was destroyed with 5% sodium hydroxide (5. cm^3) and the ether decanted, dried (Mg SO_4) and evaporated to yield the alcohol (0.25 g. 83%) as colourless prisms m.p. 175-176° from benzene.

ν max: 3350, (NH), 2950, 2850 (CH_2), 1603, 1500, 1300, 1100, 1020 and 820 $cm.^{-1}$

τ($CDCl_3$): 2.0-2.7 (8H, m, c, $\underline{H}_8$) 3.1 (2H, d, J9 Hz, 3 and 5 $\underline{H}\,C_6H_4Cl$) 3.95 (2H, d, J9 Hz, 2 and 6 $\underline{H}\,C_6H_4Cl$) 6.25 (2H, t, J6 Hz, $C\underline{H}_2OH$), 7.75 (2H, t, J6 Hz, $-C\underline{H}_2-$)

3-Anilino-3-p-chlorophenyl-2,2-diphenylpropanol (154)

4-p-Chlorophenyl-1,3,3 triphenylazetidine-2-one (2 g), Li AlH_4 (1.0 g) and ether (100 cm^3) were stirred together for 90 hrs. The complex was destroyed with dilute sodium hydroxide and water and the ether layer dried (Mg SO_4) and evaporated to yield the propanol (1.8 g., 90%) as colourless microprisms, m.p. 60°. (from petroleum ether (60-80°).

(FOUND: $^m/_e$ 413.154918 [M $^+$] C_{27} H_{24} NO Cl requires $^m/_e$ 413.154633 [M $^+$]) for Cl 35).

νmax: 3600 (OH), 3450 (NH), 2950 (CH_2) 1603 and 1510 (aromatic nucleus), 1330, 1020, 760 and 700 cm^{-1}.

τ($CDCl_3$): 2.4 - 3.6 (20H, m, Ph, C_6 H_4 and 3-CH), 4.6 (1H, s, -NH), 5.8 (2H, s, - CH_2-).

(FOUND: C, 79.7; H, 6.2; N, 3.3: C_{27} H_{24} Cl NO requires C, 78.5; H, 5.8; N, 3.4%).

Reductions using tetrahydrofurane as solvent gave similar results.

d) Grignard Reagent.

Magnesium turnings (3.0 g), ether (100 cm^3), methyl iodide (9 g) and iodine (0.1 g) were stirred together and warmed until the reaction started, the methyl iodide (9 g) was added slowly during 30 min. The mixture was heated under reflux for 30 min and 1-p-methoxyphenyl-4- spirofluorene azetidine-2-one (0.6 g) was added. After heating under reflux for a further 4 hrs. water (50 cm^3) was added and the ether layer was collected and dried (Mg SO_4). Evaporation of the ether yielded a solid which was recrystalised to yield the Schiffs base (0.05 g., 9.6%) and the azetidine-2-one (0.12 g).

2) REARRANGEMENTS

(a) With Sulphuric Acid.

General Method [15,57]

The azetidine-2-one was dissolved in concentrated sulphuric acid at room temperature for 16 hrs. and then poured into iced water. The solution was extracted with ether, was dried ($Mg SO_4$) and was evaporated to yield the 3,4-dihydro - 2 (1H) - quinolone which was crystallised from ethanol.

3,3,4,4-Tetraphenyl-3,4-dihydro-2 (1H)-quinolone (168).

1,3,3,4,4-Pentaphenylazetidine-2-one and concentrated sulphuric acid (7 cm^3) were mixed at room temperature for 24 hrs. and then poured onto iced water (50 cm^3). The solid was extracted with ether (2 x 50 cm^3) and the solvent was dried ($Mg SO_4$) and was evaporated to yield the dihydro-2 (1H) -quinolone (0.25 g., 50%) as colourless microprisms m.p. 245-247° (from methanol).

ν max: 3400, (NH), 3100, 1665 (C = O), 1603, 1510, 1460, 1360, 760 and 710 cm^{-1}

τ ($CDCl_3$) 2.5-3.2 (24H, m, Ph and $C_6 H_4$).

(FOUND: $^m/_e$ 451.190692 [M^+] $C_{33} H_{25} NO$ requires $^m/_e$ 451.193604 [M^+])

3,4-Dihydro-4-phenyl-2 (1H)- quinolone (51).

1,4-Diphenylazetidine-2-one (1.0 g) was dissolved in concentrated sulphuric acid (4 cm^3) at room temperature for 24 hrs. and then the mixture was poured into iced water (50 cm^3). The mixture was filtered to yield the dihydro-2 (1H)- quinolone. (0.4 g., 40%) as buff microprisms m.p. 177-179° (from methanol). (lit.[15,132] 177-178). Identical with a sample prepared from cinnamanilide and poly phosphoric acid.

ν max: 3250 (NH), 3100, 2950, 1675 (C = O), 1600 and 1500 (aromatic nucleus) 1400, 770 and 720 cm^{-1}

τ ($CDCl_3$ 2.5-3.2 (9H, m, $C_6 \underline{H}_5$ and $C_6 \underline{H}_4$), 5.75 (1H, t, J7 Hz, $C\underline{H}-CH_2$), 7.1 (2H, d, J7 Hz, $CH- C\underline{H}_2$)

6-Chloro-3,4-dihydro-3,4-diphenyl-2 (1H)-quinolone

1-p Chloro-3,4-diphenylazetidine-2-one (0.2 g) and concentrated sulphuric acid (2 cm^3) were mixed at room temperature for 18 hrs. and then poured into iced water (50 cm^3). Extraction with chloroform (2 x 50 cm^3) drying (Mg SO_4) and evaporation yielded the dihydro-2-(1H)-quinolone (0.1 g., 50% as colourless microprisms m.p. 194-196° (from methanol.)

νmax: 3300, 3000, 1670 (C = 0), 1603, 1490, 1370, 760 and 700 cm^{-1}

3,4-Dihydro-3,4-diphenyl- 2 (1H)-quinolone (164)

1,3,4-Triphenylazetidine-2-one (0.5 g) and concentrated sulphuric acid (4 cm^3) were mixed at room temperature for 2 hrs. and then poured into iced water (50 cm^3). Extraction with chloroform (2 x 50 cm^3), drying (Mg SO_4) and evaporation yielded the dihydro-2 (1H)-quinolone (0.2 g., 40%) as colourless needles, m.p. 200° (from methanol). (lit. 220°)[107]

ν max: 3300, 3050, 1675 (C = 0) 1600, 1530, 1450, 1320, 760 and 700 cm^{-1}

τ($CDCl_3$): 2.5-3.2 (16H, m, Ph and C_6H_4) 5.55 (1H, d, J6 Hz, 3H), 5.9 (1H, d, J6 Hz, 4H)

$^m/_e$ 299 [M +]

(FOUND: $^m/_e$ 299. 130931 [M +] C_{21} H_{17} NO requires $^m/_e$ 299.131007 [M +])

3,4-Dihydro-6-methoxy-4-phenyl-2 (1H)-quinolone (163.

1-p -Methoxyphenyl-4-phenylazetidine-2-one (0.6 g) and concentrated sulphuric acid (4 cm^3) were mixed at room temperature for 16 hrs. and then poured into iced water (50 cm^3). Extraction with ether (2 x 50 cm^3) drying (Mg SO_4) and evaporation yielded the dihydro - 2 (1H)-quinolone (0.3 g., 50%) as colourless needles m.p. 154-155° (from chloroform). (lit 155-156°)[117] identical with a sample prepared from cinnamoyl-4-methoxy anilide and polyphosphoric acid.

νmax: 3300, 2900, 1660 (C = O), 1510, 1240 (OCH_3), 830 and 700 cm^{-1}

τ($CDCl_3$) 2.5-3.6 (8H, m, Ph and $C_6 H_3$), 5.8 (1H, t, J7 Hz, 4-H), 6.4 (3H, s, OCH_3), 7.15 (2H, d, J7 Hz, 3- CH_2).

Similar reactions were carried out an 4-p-chlorophenyl 1,3,3-triphenylazetidine-2-one, 1 -p-chlorophenyl-4-spirofluoren azetidine-2-one, 1-p-methoxyphenyl-4-spirofluoren azetidine-2-one, 3,3-diphenyl-1-p-methoxyphenyl-4-spirofluorenazetidine-2-one, 3, 4-diphenyl-1-p-methoxyphenylazetidine-2-one, 1,3,3,4 tetraphenyl azetidine -2-one and 1,3,4,4-tetraphenylazetidine-2-one. All failed to give any appreciable amounts of the dihydro-2 (1H)-quinolone.

(b) WITH BORON TRIFLUORIDE

General Method

The azetidine-2-one and boron trifluoride diethyl etherate were heated together in a solvent for 60 hrs, Cooling, washing with water, drying ($Mg SO_4$) and evaporation yielded, on trituration, the propionanilide, crystallised from aqueous alcohol.

N-4-Methoxyphenyl-2,3-diphenyl-3-p -tolylpropionamide (173).

3,4-Diphenyl-1-p-methoxphenylenylazetidine-2-one (1.0 g), boron trifluoride diethyl etherate (1.0 cm^3) and toluene (100 cm^3) yielded the propionamide (0.45 g., 35%) as colourless microprisms, m.p. 157-159° (from ethanol)

(FOUND: C, 81.4; H, 6.6; N, 3.1: $C_{29} H_{27} NO_2$ requires C, 82.6; H, 6.4; N, 3.3%).

νmax: 3300 (NH), 3050, 2950, 1650, (C = O), 1603, 1520, 1250 ($-OCH_3$) 1170, 1040, 760 and 700 cm^{-1}

τ($CDCl_3$): 2.1 - 3.1 (14H, m, Ph and $C_6H_4 CH_3$) 3.05 (2H, d, J9, Hz, 3 and 5 H $C_6 H_4$ $-OCH_3$), 3.45 (2H, d, J9 Hz, 2 and 6- H $C_6 H_4$ $-OCH_3$), 5.1 (1H, d, J12 Hz, 2-CH), 5.75 (1H, d, J12 Hz, 3-CH), 6.4 (3H, s, $-OCH_3$), 7.8 (3H, S, $-CH_3$).

N-Phenyl-3-phenyl-3-p-tolylpropionamide (174).

1,4-Diphenylazetidine-2-one (1.0 g) boron trifluoride diethyl etherate (2.0 cm^3) and toluene (100 cm^3) yielded the propionamide (0.6 g., 42.5%) as colourless needles, m.p. 124-6° (from ethanol).

(FOUND: C, 84.1; H, 6.7; N, d.5: $C_{22}H_{21}NO$ requires C, 83.8; H, 6.7; N, 4.5%).

νmax: 3350, 1660 (C = O), 1603, 1555, 1450, 760 and 700 cm^{-1}

τ($CDCl_3$): 2.9 (14H, d, Ph and $C_6\underline{H}_4$), 5.45 (1H, t, J8 Hz, 3-H) 7.0 (2H, d, J8 Hz, 2-$C\underline{H}_2$), 7.75 (3H, s, -$C\underline{H}_3$).

N-Phenyl-2,3-diphenyl-3-p tolylpropionamide (175).

1,3,4-Triphenylazetidine-2-one (1.0 g) boron trifluoride diethyl etherate (2.0 cm^3) and toluene (100 cm^3) yielded the propionamide (0.54 g., 41%) as colourless needles, m.p. 210° (from ethanol).

(FOUND: $^m/_e$ 391.191751 [M^+] $C_{28}H_{25}NO$ requires $^m/_e$ 391.193604 [M^+])

νmax: 3350, 3100, 1665 (C = O), 1603,1560, 1510, 1460, 860 and 710 cm^{-1}

τ($CDCl_3$): 2.2-3.2 (19H, m, Ph and $C_6\underline{H}_4$) 5.1 (1H, d, J10 Hz, 2-C$\underline{H}$) 5.65 (1H, d, J10 Hz, 3-C$\underline{H}$) 7.8 (3H, s, $C\underline{H}_3$).

N-4 Chlorophenyl-2-phenyl-2-(9 p tolyl-9-fluorenyl) acetamide (176).

1-p-Chlorophenyl-3-phenyl-4-spirofluoreneazetidine-2-one (1.6 g), boron trifluoride diethyl etherate (2.0 cm^3) and toluene (100 cm^3) yielded the acetamide (0.28 g., 17%) as buff microprisms, m.p. 210° (from ethanol).

(FOUND: $^m/_e$ 499.170771 [M^+] $C_{34}H_{26}ClNO$ requires $^m/_e$ 499.170282 [M^+] for Cl 35).

νmax: 3250 (NH), 1650 (C = O), 1603, 1560, 1500, 1460, 1400, and 740 cm^{-1}

τ($CDCl_3$): 2.3-3.5 (21H, m, Ph, 2 x $C_6\underline{H}_4$ and $C_{13}\underline{H}_8$), 4.9 (1H, S, 2-H), 7.75 (3H, s, $C\underline{H}_3$).

N-Phenyl-3-p-methoxyphenyl-3-phenylpropionamide (177).

1,4-Diphenylazetidine-2-one (0.3 g) boron trifluoride diethyl etherate (2.0 cm^3) and anisole (100 cm^3) were heated together under reflux for 60 hrs. Cooling, washing with water (50 cm^3), drying ($Mg SO_4$) and evaporation yielded a red oil. Trituration and crystallisation yielded the propionamide (0.15 g., 34%) as colourless needles, m.p. 160-62° (from ethanol).

(FOUND: $^m/_e$ 331.156611 M^+ $C_{22} H_{21} NO_2$ requires $^m/_e$ 331.157220 M^+

ν max: 3300, 3100, 1660 (C = O), 1603, 1560, 1520, 1460, 1260 (OCH_3) 770 and 700 cm^{-1}

τ($CDCl_3$): 2.4-3.1 (14H, m, Ph and $C_6 H_4$), 5.35 (1H, t, J7 Hz, 3-CH), 4.05 (3H, s, OCH_3), 4.6 (2H, d, J7 Hz, 2-CH_2).

2,3-Diphenylindene-1-one (179).

1,3,4,4-Tetraphenylazetidine-2-one (1.4 g) boron trifluoride diethyl etherate (2.0 cm^3) and toluene (100 cm^3) were heated together under reflux for 60 hrs. The solution was cooled, extracted with water (50 cm^3) and dried ($Mg SO_4$). Evaporation of the solvent to a low bulk yielded the indene-1-one (0.71 g., 67.5%) as red prisms, m.p. 152-154° (from ethanol). (lit. 151.5-152°)[118]

(FOUND: C, 89.1; H, 5.1; Calc for $C_{21} H_{14} O$, C, 89.4; H, 5.0%)

ν max: 3100, 1710 (C = O), 1603, 1460, 1360, 770 and 710 cm^{-1}

τ($CDCl_3$) 2.3-2.9 (14H, d, Ph and $C_6 H_4$). $^m/_e$ = 282 M^+

A similar experiment with 1,3,3,4-tetraphenylazetidine-2-one also yielded 2,3-diphenylindene-1-one (5%) and starting material.

Under similar conditions 4-p-chlorophenyl-1,3,3-triphenylazetidine-2-one failed to react.

Reaction of Boron Trifluoride with 1,3,3,4,4-pentaphenylazetidine-2-one (101).

1,3,3,4,4-Pentaphenylazetidine-2-one (1.0 g) boron trifluoride diethyl etherate (2.0 cm^3) and toluene (100 cm^3) were heated together under reflux for 60 hrs. The solution was cooled, washed with water (50 cm^3) and dried.

Evaporation of the solvent yielded benzophenylidene aniline (0.4 g., 70%) as yellow plates, m.p. 107° (from ethanol) (lit. 106°)[122]

ν max: 3100, 1630 (C = N), 1600, 1500, 1460, 1330, 1300, 790 and 710 cm^{-1}

The filtrate from the crystallisation was evaporated and redissolved in chloroform (10 cm^3). The solution was washed with 10% sodium hydroxide (10 cm^3) and the aqueous layer neutralised with sulphuric acid. Filtration gave the diphenylacetic acid (0.2 g., 43%) as colourless needles, m.p. 146-147° (from water). (lit 146).

νmax: 3100, 2950, 1705 (C = 0), 1230, 950, 740 and 700 cm^{-1}

A further reaction of the azetidine-2-one with boron trifluoride in toluene was carried out with dry ethanol included in the reaction mixture. Ethyl diphenylacetate was isolated with the Schiff's base.

νmax: 3050, 1730, 1603, 1510, 1460, 1200, 1150, 1020, 760 and 710 cm^{-1}

τ($CDCl_3$): 2.7 (10H, s, Ph), 5.0 (1H, s, CH), 5.8 (2H, q, J7 and 14 Hz, CH_2-CH_3), 8.8 (3H, t, J7 Hz, CH_2-CH_3).

Benzophenone was also isolated.

Reaction of Boron Trifluoride with 3,3-Diphenyl-1-p-methoxyphenyl-4-spirofluoenazetidine-2-one (99).

3,3-Diphenyl-1-p-methoxyphenyl-4-spirofluorenazetidine-2-one (0.5 g), boron trifluoride diethyletherate (1.0 cm^3) and toluene (50 cm^3) were heated together under reflux for 60 hrs. The solution was cooled, washed with water (50 cm^3) and extracted with 5% sodium hydroxide (50 cm^3). The organic fraction contained unchanged azetidine-2-one and fluorenylidene-p anisidine (0.12 g., 40%) as orange prisms, m.p. 136° (from ethanol).

νmax: 3050, 2950, 2850, 1640 (C = N), 1603, 1510, 1455, 1240 (-OCH_3) 1100, 1040, 840, 800 and 735 cm^{-1}.

Acidification of the basic fraction yielded diphenyl acetic acid (0.15 g., 50%) as colourless needles, m.p. 146° (from water).

νmax: 3100, 3000, 2750 (-OH), 1710 (C = 0), 1510, 1420, 1330, 1230, 950, 740 and 710 cm^{-1}

Cinnamanilide (161).

1,4-Diphenylazetidine-2-one (1.0 g), boron trifluoride diethyl etherate (1.0 cm^3) and chlorobenzene (100 cm^3) were heated together under reflux for 60 hrs. Cooling, washing with water (50 cm^3), drying ($MgSO_4$) and evaporating the solution yielded cinnamanilide (0.7 g., 70%) as colourless needles, m.p. 153° (from chloroform). (lit.154). identical with a sample prepared from aniline and cinnamoyl chloride.

ν max: 3300 (NH), 3050, 1665 (C = O), 1630 (C = C), 1600, 1550, 1510, 1450 1350, 1190, 990, 770 and 700 cm^{-1}

τ($CDCl_3$): 2.0-3.2 (10H, m, Ph), 2.3 (1H, d, J16 Hz, = CH-CO), 3.15 (1H, d, J16 Hz, Ph-CH =).

MASS SPECTRAL TABLES

Table I, Azetidinones,

1,3,3,4,4-pentaphenylazetidine-2-one (101).

m/e (I%) 451 (2.2), 257 (20), 256 (100), 255 (21.4), 193 (16), 180 (10), 179 (71), 167 (6), 166 (23), 165 (60), 164 (5), 163 (4), 78 (5), 77 (66), 63 (4), 51 (21.4), 28 (9.9).

M * 254 (257 → 255), 164 (166 → 165), 106 (255 → 166).

4-Spirofluoren-1,3,3-triphenylazetidine-2-one (98).

m/e (I%) 449 (3), 330 (1), 229 (1), 257 (2), 256 (25), 255 (100), 254 (36), 253 (68), 252 (4), 212 (2), 195 (3), 194 (20), 168 (4), 167 (22), 166 (17), 165 (29), 164 (5), 163 (8), 152 (4), 105 (5), 82 (2), 78 (4), 77 (5), 63 (2), 51 (4).

3,3-Diphenyl-1-p-methoxyphenyl-4-spirofluorenazetidine-2-one (99).

m/e (I%) 479 (2), 286 (8), 285 (40), 272 (6), 271 (26), 241 (6), 203 (8), 202 (9), 194 (7), 179 (16), 178 (100), 76 (8), 166 (11), 165 (24), 101 (11), 89 (9), 88 (6), 76 (7), 63 (6), 51 (6).

M * 176 (479 → 285), 164 (166 → 165).

1,3,3,4-Tetraphenylazetidine-2-one (12).

m/e (I%) 375 (2), 257 (10), 256 (44), 255 (8), 241 (5), 239 (5), 195 (17), 181 (38), 180 (30), 179 (12), 178 (16), 167 (8), 166 (49), 165 (63), 152 (6), 104 (8), 91 (6), 79 (10), 78 (38), 51 (12).

M * 164 (166 → 165), 142 (194 → 166).

1-Phenyl-4-spirofluorenazetidine-2-one (139).

m/e (I%) 297 (1), 255 (7), 254 (9), 193 (16), 192 (100), 191 (24), 190 (5), 189 (8 165 (5), 28 (14).

M * 142 (254 → 192).

1-p-Chlorophenyl-3,4-diphenylazetidine-2-one (136).

m/e (I%) 333 (3), 217 (5), 216 (5), 215 (16), 214 (10), 181 (17), 180 (100), 179 (37), 178 (21), 165 (15), 118 (17), 111 (9), 91 (12), 90 (7), 89 (6), 78 (5), 77 (6), 75 (6), 51 (5).

M * 213 (215 → 214), 178 (180 → 179), 151 (215 → 179).

3,4-Diphenyl-1-p-methoxyphenylazetidine-2-one (134).

m/e (I%) 329 (1), 242 (6), 241 (24), 212 (6), 211 (24), 210 (6), 197 (5), 196 (19), 181 (19), 180 (112), 179 (33), 178 (16), 167 (6), 165 (14), 149 (15),

M * 151 (180 → 165).

1-(3'-pyridyl)-3,3,4-triphenylazetidine-2-one (90).

m/e (I%) 376 (4), 257 (6), 255 (6), 195 (16), 194 (100), 182 (9), 181, (14),179 (6), 178 (9), 167 (7), 166 (48), 165 (4), 78 (16), 77, (5), 51 (8).

M * 142 (194 → 166).

1-(4'-pyridyl)-3,3,4-triphenylazetidine-2-one (89).

m/e (I%) 376 (7), 257 (6), 256 (26), 255 (7), 253 (5), 239 (5), 195 (17) 194 (100), 182 (7), 181 (10), 179 (8), 178 (11), 167 (9), 166 (57), 165 (65), 164 (6), 139 (5), 78 (19), 77 (6), 51 (12).

M * 142 (194 → 166).

4-p-chlorophenyl-1,3,3-triphenylazetidine-2-one (84).

m/e (I%) 409 (3), 293 (8), 291 (6), 290 (23), 255 (5), 254 (6), 253 (7), 252 (6), 217 (6), 216 (7), 215 (17), 214 (16), 195 (17), 194 (100), 178 (6), 166 (34), 165 (44), 104 (5), 78 (23), 51 (7).

M * 142 (194 → 166).

4-p-Nitrophenyl-1,3,3-triphenylazetidine-2-one (83).

m/e (I%) 420 (2), 302 (18), 301 (76), 255 (5), 254 (9), 253 (11), 252 (9), 239 (9), 226 (11), 225 (7), 195 (17), 194 (100), 179 (12), 178 (7), 167 (8), 166 (50), 165 (67), 152 (5), 104 (6), 91 (5), 77 (22), 51 (6).

M * 216 (420 → 301), 142 (194 → 166).

4-p-Fluorophenyl-1,3,3-triphenylazetidine-2-one (85).

m/e (I%) 393 (5), 275 (7), 274 (32), 273 (5), 200 (5), 199 (25), 198 (19), 197 (4), 196 (8), 195 (16), 194 (100), 167 (6), 165 (47), 164 (4), 77 (24), 51 (8).

M * 142 (194 → 166).

4(4'-pyridyl)-1,3,3-triphenylazetidine-2-one (86).

m/e (I%) 376 (7), 258 (22), 257 (100), 256 (30), 254 (6), 242 (5), 228 (5), 195 (10), 194 (53), 182 (10), 181 (9), 180 (10), 179 (8), 167 (6), 166 (36), 165 (51), 165 (51), 164 (6), 139 (5), 104 (6), 91 (6), 79 (6), 77 (21), 51 (8).

M * 202 (257 → 228), 142 (194 → 166).

4 (3'-pyridyl)-1,3,3-triphenylazetidine-2-one (87).

m/e (I%) 376 (5), 258 (11), 257 (56), 256 (56), 254 (7), 195 (17), 194 (100), 182 (17), 181 (19), 179 (13), 167 (11), 166 (52), 165 (67), 139 (6), 104 (6), 91 (7), 79 (6), 78 (6), 77 (28), 51 (11).

M * 142 (194 → 166).

4 (2'-phenyl)-1,3,3-triphenylazetidine-2-one (88).

m/e (I%) 376 (3), 258 (5), 257 (32), 256 (100), 254 (5), 195 (5), 194 (33), 182 (6), 181 (11), 180 (6), 167 (5), 166 (18), 165 (25), 155 (6), 91 (5), 79 (7), 78 (7), 77 (14), 51 (7).

M * 142 (194 → 166).

1,3,4-Triphenylazetidine-2-one (135).

m/e (I%) 299 (3), 181 (26), 180 (100), 179 (26), 178 (12), 165 (9), 91 (4), 90 (4), 90 (4), 89 (3), 77 (16), 51 (6).

M * 179 (181 → 180), 152 (180 → 165).

1,4-Diphenylazetidine-2-one (138).

m/e (I%) 223 (10), 181 (9), 180 (14), 119 (10), 105 (10), 104 (100), 103 (8), 91 (5), 78 (10), 77 (20), 51 (9).

M * 179 (181 → 180), 102.5 (104 → 7103), 58.5 (103 → 77), 49.5 (223 → 104).

1-p-methoxyphenyl-4-spiroazetidine-2-one (141).

m/e (I%) 327 (4), 284 (18), 270 (20), 180 (10), 179 (20), 178 (100), 177 (8), 176 (10), 165 (10), 149 (26), 108 (14).

TABLE 2 3,4-DIHYDROQUINOLINE-2(1H)-ONES

4-Phenyl-3,4-dihydroquinoline-2(1H)-one (51).

m/e (I%) 223 (100), 222 (46), 204 (6), 196 (7), 195 (42), 194 (99), 193 (12), 181 (17), 180 (95), 179 (11), 178 (12), 153 (6), 152 (12), 151 (6), 147 (8), 146 (56), 145 (10), 131 (8), 128 (27), 118 (36), 117 (23), 116 (9), 115 (6), 112 (12), 103 (21), 102 (9), 96 (13), 91 (18), 90 (25), 89 (21), 83 (12), 77 (34), 76 (18), 51 (24).

M * 220 (223 → 222), 170 (222 → 194), 96 (223 → 146), 72.5 (146 → 103).

6-Methoxy-4-phenyl-3,4-dihydroquinoline-2(1H)-one (162).

m/e (I%) 253 (80), 252 (23), 239 (14), 238 (61), 225 (16), 224 (49), 222 (10), 211 (6), 210 (100), 196 (36), 193 (12), 192 (14), 181 (11), 180 (6), 178 (12), 177 (10), 176 (39), 168 (20), 167 (50), 166 (12), 165 (27), 152 (12), 115 (23), 105 (14), 104 (14), 103 (18), 91 (12), 90 (11), 89 (9), 80 (12), 79 (12), 78 (12), 77 (30), 51 (23).

M * 224 (253 → 238), 200 (253 → 224).

3,4-Diphenyl-3,4-dihydroquinoline-2(1H)-one (164).

m/e (I%) 299 (44), 208 (9), 207 (54), 180 (21), 179 (100), 178 (51), 177 (7), 176 (6), 152 (6), 93 (6), 93 (6), 77 (10), 51 (7).

M * 155 (207 → 179), 143 (299 → 207), 178 (180 → 179).

3,3,4,4-Tetraphenylquinoline-2 (1H)-one (168).

m/e (I%) 451 (32), 374 (6), 333 (14), 332 (47), 331 (43), 256 (12), 255 (45), 254 (69), 253 (27), 252 (20), 240 (7), 183 (5), 182 (27), 181 (8),

180 (5), 178 (5), 168 (6), 167 (27), 166 (6), 165 (14), 152 (7), 106 (7), 105 (100), 91 (6), 86 (49), 85 (62), 84 (76), 83 (95), 77 (56), 51 (27).

M * 244 (451 → 332), 194 (332 → 255), 56.5 (105 → 77).

2,3-Diphenylindine-1-one (179).

m/e (I%) 282 (100), 281 (51), 265 (10), 254 (6), 253 (24), 252 (40), 251 (5), 250 (12), 226 (4), 224 (4), 176 (7), 151 (4), 141 (4), 126 (12), 125 (6), 113 (5), 77 (6), 51 (6).

M * 280 (282 → 281), 228 (281 → 253).

Cinnamanilide (161).

m/e (I%) 223 (37), 132 (9), 131 (100), 103 (32), 93 (23), 77 (20), 51 (5).

M * 81 (131 → 103), 57.5 (103 → 77).

REFERENCES

1. H Clarke, J. Johnson & R. Robinson — The Chemistry of Penicillin, Princetown University Press, 1949

2. E. Abraham & G. Newton — Nature, 1955, 175, 548

3. E. Abraham & G. Newton. — Biochem.J., 1961, 79, 377.

4. D. Hodgkin & E. Maslen — I bid., 1961, 79, 393.

5. T. Kikuchi & S. Uyeo. — Tet., Lett. 1965, 3473

6. H. Staudinger — Ann., 1907, 356, 51

7. H. Staudinger & H. Klever. — I bid., 1910, 374, 1

8. H. Staudinger & L. Ruzicka. — I bid, 1911, 380, 278.

9. J. Sheehan & E. Corey. — Org. Reactions, 1958, 9, 388.

10. F. Blick & W. Gould. — J. Org. Chem., 1958, 23, 1102.

11. E.T. Esta, L. Fontenella & E. Fauna. — Il Farmaco (Pavia), Edig Sci, 1958, 13, 152.

12. J. Sheehan & P. Cruikshank. — J. Amer. Chem. Soc., 1956, 78, 3860, 3683.

13. J. Sheehan & K. Henery-Logan — I bid., , 1959, 81, 3089.

14. R. Breckpot. — Bull. Soc. Chim. Bel., 1923, 32, 412

15. I. Knunants & N. Gambaryan — Izvest. Akod, Nauk, S.S.S.R. Otdel Khim. Nauk., 1957, 7, 834

16. M. Manhas & S. Jeng. — J. Org. Chem., 1967, 32, 1246.

17. O. Chapman & W.A.Adams. — J. Amer. Chem. Soc., 1967, 89 4243.

18. J. Sheehan & A. Bose — I bid., 1950, 72, 5158.

19. B. Chaterjee. — Chem. Ber., 1969, 102, 2129.

20. B. Aker Mark and N. Johansson. — Tet. Lett., 1969, 371.

21. H. Staudinger and S. Jelagin. — Ber., 1911, 44, 365.

22. H. Staudinger and H. Miescher. — Helv. Chim. Acta., 1919, 2, 554.

23. T. Taylor, J. Owen & D. Whittaker. — J., 1938, 206.

24. C. Hassel & A. Lippman. — Ibid., 1953, 1059.

25. L. Smith. — Chem. Revs., 1938, 23, 229.

26. J. Sheehan & J. Ryan. — J. Amer. Chem. Soc., 1951, 73, 1204, 4367.

27. J. Wells & R. Lee. — J. Org. Chem., 1969, 34, 1477.

28. A. Bose and I. Kugajevsky. — Tetrahedron, 1967, 23, 957.

29. L. Paul, A. Draegar & G. Hilgetag. Chem. Ber. 1966, 99, 1957.

30. H. Bohne, S.Ebel & X. Hartke Ibid. 1965, 98, 1463.

31. H. Gilman & M. Speeter. J. Amer. Chem. Soc. 1943, 65, 2255.

32. H. Kagan & J. Luche Bull. Soc. Chim. Fr., 1969, 3500.

33. E. Zeigler et al. Monatsh, 1968, 99, 2128.

34. R. Graf. Ann., 1963, 661 111.

35. R. Lattrell. Ibid., 1969, 722, 142.

36. T. Mukaiyama et al Tet. Lett., 1966, 6247.

37. M. Perelman & S. Mizsak. J. Amer. Chem. Soc., 1962, 84,4988.

38. J. Sheehan & P. Izzo. Ibid., 1942, 71, 4059.

39. J. Deyrup & S. Clough. Ibid., 1969, 91, 4590.

40. A. Hassner et al. Ang. Chem., 1970, 9, 731.

41. Wasserman & Baird. Tet.Lett., 1971, 3721.

42. E. Morisoni, J. Kelly & R. Salomone. J. Org. Chem. 1968, 33, 3448.

43. G. Ege and F. Pas Edache. Chem. Ber. 1968, 101, 3089.

44. S.M. Ege Chem.Comm., 1968, 759.

45. R. Olofson, R. Vander Meer, S. Stournas. J. Amer, Chem. Soc.,1971, 93, 1543.

46. R. Holley & A. Holley. J. Amer. Chem. Soc.,1949, 71, 2129.

47. J. Luche et al Tetrahedron, 1968, 24, 1275.

48. T. Margulus & M. Fisher J. Amer. Chem. Soc., 1967, 89, 223.

49. L.J. Bellamy, The Infra Red Spectra of Complex Molecules Methuen & Co. Ltd. Pg 147.

50. T. Spotswood et al. Org. Mass Spec.,1968, 1, 857.

51. H. Kagan et al. Bull Chim, Soc. Fr.,1967, 2297.

52. A. Holley & R. Holley, J. Amer. Chem. Soc., 1950, 72, 2771.

53. H. Levenson & H. Smith Ibid, 1940, 62, 2324.

54. R. Earle, D. Hurst and M. Viney J.(C), 1969, 2093

55. E. Testa, L. Fontenella & G. Cristiani. Ann., 1959 626, 114.

56. M. Speeter & W. Maroney. J. Amer. Cehm Soc. 1954, 76, 5810.

57. S. Sarel et al. — Israel J. Chem., 1966, 4, 233.

58. R. Morin et al — J. Amer. Chem. Soc., 1963, 85, 1896.

59. J. Webber et al. — Ibid, 1969, 91, 5674.

60. D.O. Spry — Ibid., 1972, 92, 5006

61. J. Nayler et al. — Chem Comm., 1969, 129.

62. R. Cooper, P. DeMarco & D. Spry. — J. Amer. Chem. Soc. 1969, 91, 1528.

63. H. Staudinger — Die Ketene, Enke, Stuttgart, 1912.

64. L. Paquette, M. Wyuratt & G. Allen. — J. Amer. Chem. Soc. 1970, 92, 1763.

65. M. Fischer. — Che . Ber., 1968, 101, 2669.

66. K. Kampe. — Tet, lett., 1969, 117.

67. K. Kampe. — Ang. Chem. 1969, 8, 904

68. H. Schinabel. — Ibid., 1969, 8, 922

69. D. Barman. — Ibid., 1969, 8, 892

70. T. Doyle & T. Conway. — Tet Lett., 1969, 1889.

71. K. Hanery-Logan & H. Knoepfel — J. Het. Chem., 1968, 5,433.

72. R. Graf et al. — Ang. Chem.(Int). 1962 1, 483

73. R. Washkuhn & J. Robinson. — J. Pharm, chem., 1971, 60, 1175.

74. S. Ballard, D. Melstrom & C. Smith — The Chemistry of Penicillin, Princetown University Press (1949), 978

75. J. Hou & J. Poole. — J. Pharm, Sci., 1971, 60, 503

76. J. Park — Biochem. J., 70, 2P

77. P. Lawrence & J. Strominger. — J. Biol Chem., 1970, 245, 3653.

78. D. Johnson & D. Maria — Tet.lett., 1969, 267.

79. Ref 1. Pg. 256

80. J. Wells & O. Tarwater. — J. Med. Chem. 1971, 14, 242

81. G. Mafii. — Chem.Abs. 53: 205536 & 54:9105h

82. Ger Offer, 2,030, 989 — Through Chem. Abs, 74, 87810P

83. R. Pfleger & A. Jager — Chem Ber. 1957, 90, 2460.

84. F. Duran & LGHOSEZ — Tet.lett., 1970, 245.

85. Farnom et al — J. Amer. Chem. Soc., 1965, 87, 5191.

86. J. Berson & W. Jones. Ibid., 1956, 78, 1625.

87. E. Moriconi & J. Kelly. Ibid., 1966, 88, 3657.

88. A. Bose & S. Garratt Ibid., 1962, 84, 1310.

89. M. Manhas et al Tlt., 1969, 4421.

90. R. Woodward & R. Hoffman. J. Amer. Chem. Soc., 1965, 87, 2046.

91. R. Woodward & R. Hoffman The Conservation of Orbital Symmetry, Academic Press Inc. 1970 Pg 163.

92. H. Kagan & J. Luche. Tet. Lett., 1968, 3093.

93. W. Brady & E. Dorsey. Chem.Comm., 1968, 1638.

94. R. Huisgen, B. Davis and M. Morikowa. Angew (Int.)., 1968, I. 826.

95. E. Moriconi & W. Meyer. Tet.Lett., 1968, 3823.

96. F. Effenberger & G. Kiefer. Angew Chem. 1967, 6, 951.

97. E. Moriconi & J. Kelly. Tet.Lett., 1968, 1435.

98. F. Effenberger & G. Prossel. Ang. Chem., 1969, 8, 896.

99. W. Brady et al Tet.Lett., 1970, 819.

100. J. King & E. McMillan J. Amer. Chem. Soc., 1950, 72, 833.

101. Ref. 49 Pg. 167.

102. D.A. Nelson. Tet. Lett., 1971, 2543.

103. G. Pracejus. Ann., 1959, 622, 10.

104. G. Payne J. Org.Chem., 1966, 31, 78.

105. A. Bose. Tet., 1967, 23, 4769.

106. K. Barrow & T. Spotswood. Tet. Lett., 1965, 3325.

107 O. Chapman & W. Adams. J. Amer, Chem. Soc., 1968, 90, 2333.

108. A.Vogel, A Textbook of Practical Organic Chemistry, Longmans, 1964 Pg. 372.

109. A. Gomez & M. Jouille Chem. Comm., 1967, 935

110. H. Staudinger Ber., 1917, 50, 1035.

111. H. Kagan & J. Luche Bull. Soc. Chim. Fr., 1967, 2297.

112. M. Jackson, T. Spotswood & J. Bowie, Org. Mass Spec. 1968, 1, 881.

113. M. Manhas, J. Chib and A. Bose Tet., 1969, 25, 4421.

114. B. Levine. J. Exptl. Med., 1960, 117, 909.

115. Ref. 108 Pg. 798.

116. B. Castro. Bull. Soc. Chim. Fr., 1967, 1540.

117. R. Conley & W. Knopka. J. Org. Chem., 1964, 29, 496.

118. D. Curtin & J. Kauer. Ibid., 1960, 25, 880.

119. Organic Synthesis 1941, 1, 80.

120. A. Kirpal & Ereiter. Ber., 1927, 60, 666.

121. M. Taylor & T. Fletcher. J. Org. Chem., 1961, 26, 940.

122. H. Staudinger & S. Jelagin. Ber., 1911, 44, 373.

123. A. Hantzsh & G. Schwab. Ibid., 1901, 34, 832.

124. G. Reddelien & H. Danilof. Ibid., 1921, 54, 3132.

125. J. Billman & K. Tai J. Org. Chem., 1958, 23, 536.

126. Ref 119 Coll Vol. 3, 357.

127. Ref 119 Ibid., 356.

128. W. Kirmse & L. Horner. Chem.Ber. 1956, 89, 2759.

129. H. Saikachi & T. Hisano. Yakogaku Zasshi, 1961, 81, 59. through Chem. Abs. 55, 14432.

130. J. Halberkan. Ber., 1921, 54B, 1152.

131. I. ITO. Chem. Pharm. Bull., 1966, 14, 561.

132. E. Stephenson. J., 1956, 2557.

133. E. Chamberlin. J. Amer, Chem. Soc., 1957, 79, 456.

134. P. Petyunin & A. Pesis. J. Gen. Chem. U.S.S.R., 1952, 22 1187.

135. H. Budzikiewicz, C. Djerassi & D. Williams. Mass Spectrometry of Organic Compounds, Holden Day Inc. 1967, Pg. 89.