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Reactions of Aziridines with Ring Expansion

F.N.Gladysheva, A.P.Sineokov, and V.S.Etlis

The review gives a systematic account of the literature on the reactions of aziridines with the expansion of the three-membered ring by intramolecular and intermolecular cyclisation mechanisms. The intermolecular interaction of aziridines with aldehydes and ketones, CO_2, COS, and CS_2, and with isocyanates and isothiocyanates with formation of five-membered heterocyclic compounds (oxazolidines, thiazolidinones, thiazolidinethiones, imidazolidinones, and others) is discussed. The isomerisation of *N*-vinyl and *N*-acyl derivatives to the corresponding pyrrolines, oxazolines, and other five-membered heterocyclic compounds as well as dimerisation reactions of aziridines and their interaction with epoxy ethylene and nitrones are discussed.
The bibliography includes 88 references.

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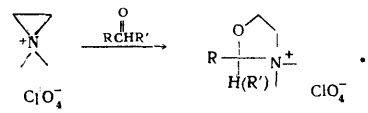
I. INTRODUCTION

The simplest nitrogen-containing three-membered heterocyclic compounds (aziridines) are extremely reactive [1-3]. They readily undergo addition reactions both with retention and opening of the aziridine ring. Under the action of acids, anhydrides, alcohols, amines, mercaptans, and other compounds, the three-membered ring opens and various *N*-substituted compounds are formed. In contrast to epoxy- and thioepoxy-alkanes, aziridines can react as amino-compounds with participation of the free electron pair of the nitrogen atom and the retention of the ring. They form aziridinium salts, add to the C=C double bond of keten, to activated double bonds of acrylic esters, and to conjugated double bonds of diene hydrocarbons, are acylated by acid anhydrides and chlorides to *N*-acylaziridines, cause ring opening of epoxyethane and ethylene sulphide, are dimerised to *N*-aminoethylaziridines, etc. A systematic account of the above reactions is given in the monograph of Gembitskii et al. [3], which contains the most complete description of the structure, properties, and methods of synthesis of aziridines and their reactions. Among the wide variety of the reactions of aziridines, a special place is occupied by reactions involving the expansion of the three-membered ring, which may be regarded as intermolecular and intramolecular interactions. The present review gives a systematic account of the literature on this problem up to 1968 inclusive.

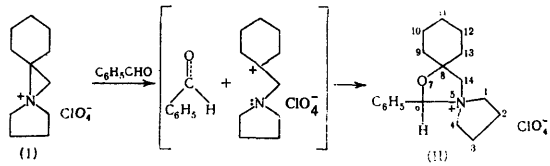
II. INTERMOLECULAR CYCLISATION

1. Reactions of Aziridines with Aldehydes and Ketones

The expansion of the aziridine ring in reactions with aldehydes and ketones was observed for the first time with aziridinium salts. Aziridinium salts were obtained by the nucleophilic attack of diazomethane on iminium compounds [4,5]. The proposed mechanism of the reaction of aziridinium salts with aldehydes [6] postulates the conversion of the three-membered cyclic ion to a five-membered ion with participation of the carbonyl group of the aldehyde or ketone:

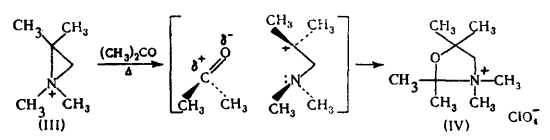


The mechanism consists of the opening of the aziridine ring to give a more stable positively charged tertiary β-aminocarbonium ion, which reacts with the polarised carbonyl group forming five-membered heterocyclic compounds—oxazolidinium salts. Thus, on heating, 5-azoniadispiro[4,0,5,1]dodecane perchlorate (I) in an excess of benzaldehyde at 60°C for 48 h, a new compound was isolated—6-phenyl-5-azonia-7-oxaspiro[4,2,5,1]tetradecane perchlorate (II):



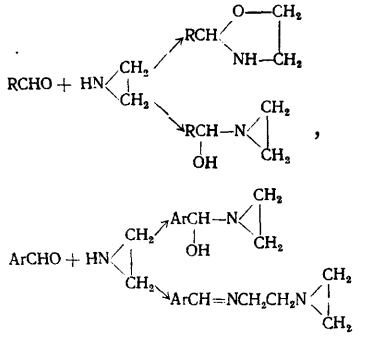
The infrared spectra of the compound isolated did not show absorptions characteristic of $^+$N–H or C=O bonds, which is evidence that the C=O bond breaks with formation of a five-membered heterocycle.

The above reaction is general, this being confirmed by the reaction of benzaldehyde with analogues of compound (I). Aziridinium perchlorate reacts with a number of aliphatic cyclic and aromatic ketones [7]. Thus the reaction of 1,1,2,2-tetramethylaziridinium perchlorate (III) on heating in an excess of acetone has been investigated. Analysis and NMR spectra indicate that the final reaction product is 2,2,3,3,5,5-hexamethyloxazolidinium perchlorate (IV):

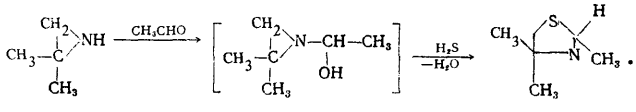


The reaction of the perchlorate (III) was carried out with cyclopentanone, cyclohexanone, methyl phenyl ketone, and other (cyclic and aromatic) ketones with heating to 65°C for 12–24 h. In each case stable oxazolidine derivatives were isolated and characterised. The interaction of aziridines unsubstituted at the nitrogen atom (in the form of free bases) with aldehydes does not lead to oxazolidines, as suggested by Doughty [8].

A number of investigations [9–15] have clearly demonstrated that under these conditions there is a possibility of the formation of *N*-aziridinemethanols or in certain cases *N*-(arylidene-β-aminoethyl)aziridines:



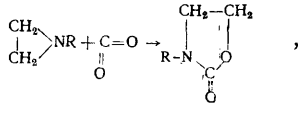
The formation of 2,4,4-trimethylthiazolidine [16] was observed in the reaction of acetaldehyde with 2,2-dimethylaziridine followed by saturation with hydrogen sulphide. One of the two possible mechanisms of reactions of this type postulates the formation of 2-alkyl-*N*-hydroxyaziridines, which yield thiazolidines under the action of hydrogen sulphide. In the second mechanism aziridine is converted into an amino-thiol, which is then converted into thiazolidine under the action of the carbonyl compound. The first mechanism is to be preferred in the case of the highly reactive acetaldehyde:



2. Interaction of Aziridines with Carbon Dioxide, Carbon Oxysulphide, and Carbon Disulphide

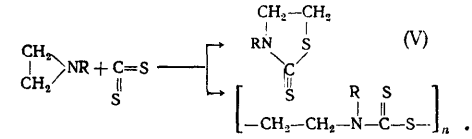
Oxirans and thi-irans react with carbon dioxide and its sulphur analogues with expansion of the three-membered rings [17]. In the reaction with carbon dioxide at room temperature, unsubstituted aziridine polymerises vigorously [18] and in the reaction with carbon monoxide, carbon oxysulphide, and carbon disulphide, it gives rise to thermoplastic resins [3].

Carbon dioxide does not react with aziridines in the absence of a catalyst. On heating with carbon dioxide in the presence of tetraethylammonium bromide (TEAB), equimolar amounts of *N*-arylaziridines give high yields of *N*-aryloxazolidinones [19,20]:

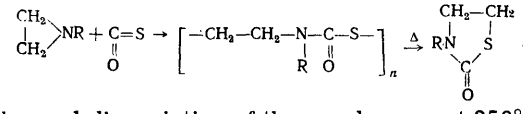


where R = C_6H_5, *p*-$CH_3C_6H_4$, *o*-$CH_3OC_6H_4$, or *p*-$CH_3OC_6H_4$. In the reaction of *o*- and *p*-methoxyphenylaziridines the corresponding *NN'*-diarylpiperazines were isolated as side products in yields up to 40%. In the reaction of *o*-tolylaziridine with carbon dioxide the formation of an oxazolidinone was not observed, the aziridine being dimerised due to the catalytic effect of TEAB. [21] Unsubstituted aziridine and its *C*-derivatives react with carbon disulphide forming thiothiazolidinones [22].

The reaction of carbon disulphide with *N*-arylaziridines under the conditions described for the reaction with carbon dioxide [19,20] leads to the expansion of the aziridine ring to that of *N*-arylthiazolidinethiones (V) (8–15%):



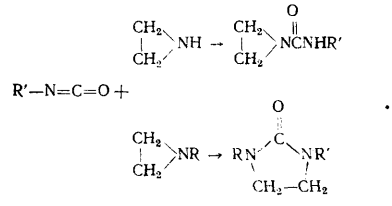
The main reaction products are characteristic copolymers of *N*-arylaziridines and carbon disulphide in molar proportions of 1 : 1. These copolymers are thermally unstable and on heating to 200–250°C dissociate with formation of the corresponding *N*-arylthiazolidinethiones (V) in a yield of 40–50%. The reaction of *N*-arylaziridines with carbon oxysulphide leads to the formation of ring expansion products only via the stage involving the copolymerisation of the reactant under the reaction conditions:



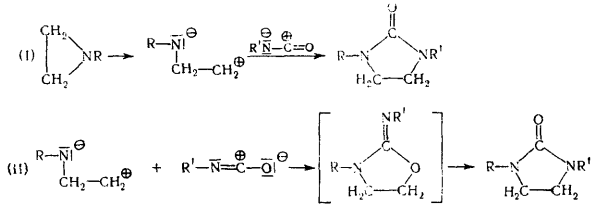
The thermal dissociation of the copolymers at 250°C leads to the formation of *N*-arylthiazolidinones (VI).

3. Interaction with Isocyanates and Isothiocyanates

The isocyanate molecule with the bond system N=C=O can react with aziridines with dissociation of the C=N or C=O bond. Aziridines unsubstituted at the nitrogen atom add to the C=N bond with formation of *NN'*-ethyleneureas [23–25]. In the reactions of *N*-substituted aziridines with isocyanates [26] the expansion of the aziridine rings to that of imidazolidinones was observed:

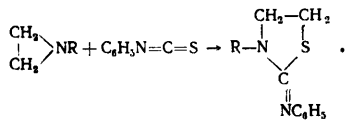


The reaction was carried out in the presence of a catalyst (lithium halides) at a temperature in excess of 100°C in an inert solvent. The interaction of *N*-acyl- and *N*-alkyl-aziridines with *N*-aryl, *N*-cyclohexyl, *N*-acyl, and *N*-sulphonyl isocyanates was investigated. For certain *N*-aryl and *N*-alkyl isocyanates, a competitive trimerisation reaction catalysed by tertiary amines was observed. The following two reaction mechanisms were proposed:



In the first mechanism the cleavage of a C–N bond of aziridine followed by the addition of the ion formed to the polarised N=C bond of the isocyanate with subsequent formation of an imidazolidinone is postulated. According to the second mechanism, an intermediate 2-imino-oxazolidine is formed and converted into a 1,3-disubstituted imidazolidin-2-one. The second mechanism is comparable with the mechanisms of the analogous reactions of epoxyethane [27].

Unsubstituted aziridines with an active hydrogen atom react with isothiocyanates with formation of *NN*-ethylenethioureas [28,29]. *N*-Aryl-substituted aziridines dissociate the C=S bond of the isothiocyanate in the presence of tetraethylammonium bromide, and are converted into the corresponding 3-aryl-2-phenyliminothiazolidines [21]:



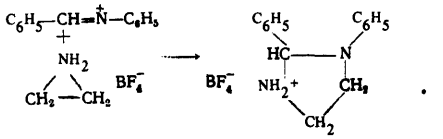
where R = C_6H_5, *o*-$CH_3C_6H_4$, *p*-$CH_3C_6H_4$, *o*-$CH_3OC_6H_4$, or *p*-$CH_3OC_6H_4$.

The infrared spectra of the compounds isolated show an intense absorption band in the region of 1632 cm^{-1}, which has been assigned to the vibration of the C=N bond.

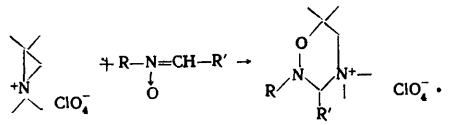
The reaction of *N*-phenylaziridine with methyl isothiocyanate under analogous conditions led to the isolation, together with 2-methylimino-3-phenylthiazolidine, of trimethyltrithioisocyanurate—the product of the trimerisation of the isothiocyanate. A similar reaction takes place with epoxyalkanes [30].

4. Interaction with Schiff Bases and Nitrones

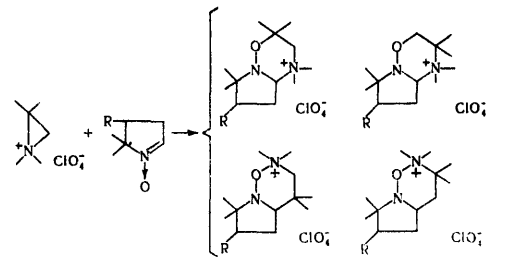
The possibility of the reaction of aziridine with the C=N bond of isocyanate is confirmed by the reaction of its derivatives with Schiff bases. Aziridinium salts readily add to the C=N bond of *N*-benzylideneaniline [31] with formation of 1,2-diphenylimidazolinium fluoroborate:



Nitrones, the structure of which includes the group O↑C=N, add to aziridine derivatives with formation of six-membered adducts in proportions of 1 : 1. [32]

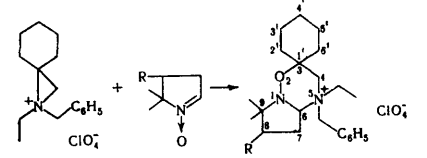


1,3-Dipolar addition to olefinic or acetylenic bonds with formation of isoxazolidine derivatives is characteristic of nitrones. Their interaction with aziridines can be explained similarly. Thus, the reaction of 1,1,2,2-tetramethylaziridinium perchlorate with 5,5-dimethyl- and 4,5,5-trimethyl-Δ^1-pyrroline-1-oxides at room temperature over a period of five days leads to the formation of one of a number of 1 : 1 adducts, since, depending on the course of the reaction, the C–N^+ bond of aziridine can disssociate in different ways:



where R = H or CH_3.

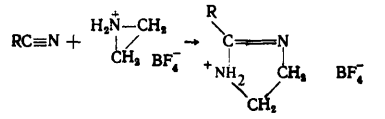
Under analogous conditions, 1-benzyl-1-ethyl-1-azoniaspiro[2,5]octane perchlorate gives rise to even more complex 1 : 1 adducts. Their analysis and infrared spectra confirm the formation of 5-benzyl-5-ethyl-8,9,9-trimethyl-1-aza-5-azonia-2-oxabicyclo[4,3,0]nonane-3-spiro-1′-cyclohexane perchlorate:



where R = H or CH_3.

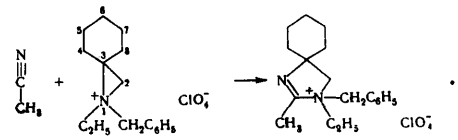
5. Interaction with Nitriles

The expansion of the aziridine ring is observed in the interaction with the C≡N bond of nitriles. Thus in the reaction between aziridinium tetrafluoroborate and various nitriles [31] the corresponding imidazolidinium salts were isolated:



where R = CH_3, C_6H_5, or $C_6H_5CH_2$.

After heating 1-benzyl-1-ethyl-1-azoniaspiro[2,5]-octane perchlorate with acetonitrile [33], a new compound was isolated—3-benzyl-3-ethyl-2-methyl-1-aza-3-azoniaspiro[4,5]dec-1-ene perchlorate, the infrared spectrum of which contains the absorption band $\nu_{C=N}$ = 1715 cm^{-1}. The structure of the compound was also demonstrated by NMR spectroscopy.

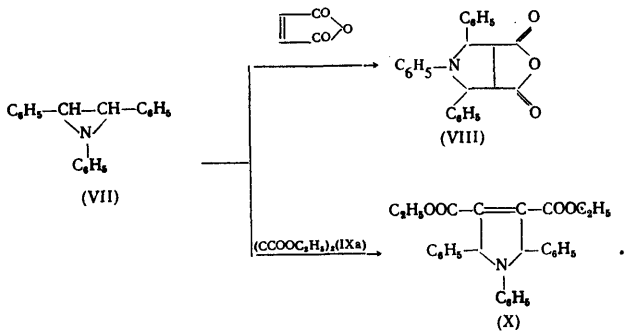


6. Interaction of Aziridines with Alkenes and Alkynes

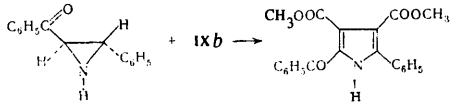
Aziridine ring expansion reactions are most often preceded by the rupture of the ring at carbon–nitrogen bonds. However, the carbon–carbon bond of the aziridine ring can also break with subsequent ring expansion. Such reaction takes place with reactive alkenes and alkynes [34–39].

The interaction of 1,2,3-triphenylaziridine (VII) with maleic anhydride takes place with formation of an expansion product of the three-membered ring in 94% yield, formed as a result of the dissociation of the C–C bond of aziridine and addition to the C=C bond of maleic anhydride [34]. The structure of the adduct (VIII) isolated was demonstrated by analysis and infrared spectroscopy.

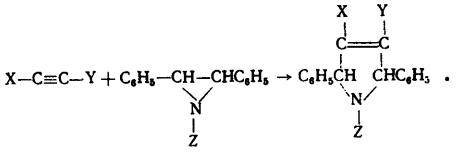
An example of the dissociation of the C–C bond in compound (VII) is provided by its reaction with diethyl acetylenedicarboxylate (IXa), which led to the isolation of a 98% yield of the pyrroline (X):



When *trans*-3-benzoyl-2-phenylaziridine was heated with dimethyl acetylenedicarboxylate (IXb) in xylene for 18 h, 2-benzyl-5-benzoyl-3,4-dimethoxycarbonylpyrrole was obtained in 80% yield [35]:



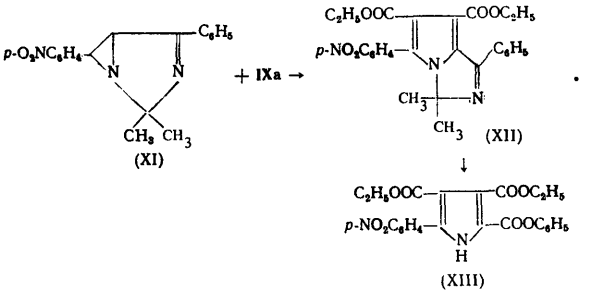
The interaction of triarylaziridines with various alkynes has been investigated [38]. When the reactions are carried out in toluene solution at room temperature (5 to 15 h), the corresponding Δ^3-pyrrolines are obtained in high yields:



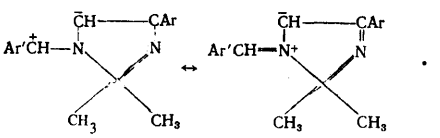
where X, Y = $COOC_2H_5$ and Z = C_6H_5; X = $COOC_2H_5$, Y = H, and Z = C_6H_5; X, Y = C_6H_5CO and Z = C_6H_5; X, Y = CF_3 and Z = C_6H_5; X, Y = $COOC_2H_5$ and Z = *p*-BrC_6H_4; X, Y = C_6H_5CO and Z = *p*-BrC_6H_4.

The reaction of aziridine with di(trifluoromethyl)acetylene was carried out in a sealed tube at 200°C for 12 h. The structures of the compounds isolated were confirmed by analysis of the infrared spectra. Their further chemical reactions were also studied.

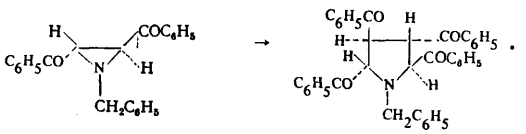
Similar interactions of aziridines with alkenes and alkynes, leading to the dissociation of the C–C bonds, were observed also in more complex heterocyclic systems [40]. When 1,3-diazabicyclo[3,1,0]hex-3-ene (XI) was heated in xylene with compound (IX), the diethyl ester of 3,3-dimethyl-5-(*p*-nitrophenyl)-1-phenyl-3*H*-pyrrolo[1,2-*c*]imidazole-6,7-dicarboxylic acid (XII) was obtained in a quantitative yield [38]:



The structure of compound (XII) was demonstrated by acid hydrolysis to the diethyl ester of 2-benzoyl-5-*p*-nitrophenylpyrroledicarboxylic acid (XIII) and acetone. The authors also synthesised and characterised the adducts (XI) with diethyl fumarate, diethyl azodicarboxylic ester, *N*-phenylmaleimide, and also *cis*- and *trans*-dibenzoylethylene. It was postulated that this interaction is preceded by the rearrangement of compound (XI), to a 1,3-dipolar compound which then reacts in this form:

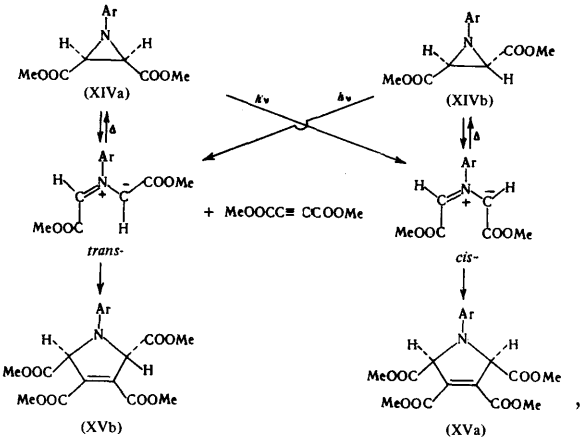


Attempts were also made earlier to account for the mechanism of this type of interaction by the 1,3-cycloaddition of the reactants to the aziridine derivatives [36]. 1-Benzyl-2,3-*trans*-dibenzoylaziridine is converted into *trans*-dibenzoylethylene (34% yield) and a certain amount of a ring expansion product—1-benzyl-1,2,3,4-(all-*trans*)-tetrabenzoylpyrrolidine:



The formation of the five-membered planar ring of the aziridine ring-expansion products gives rise to *cis*- and *trans*-isomerism. When dimethyl esters of 1-(4-methoxyphenyl)aziridine-2,3-dicarboxylic acid (XIVa, b) are heated in an excess of a "dipolarophile" ($CH_3OOCC{\equiv}CCOOCH_3$), a mixture of *cis*- and *trans*-isomers of the tetraesters (XVa, b) [39] is obtained, the proportions depending on the

reaction conditions. The equilibrium between the *cis*- and *trans*-isomers has been investigated by NMR spectroscopy



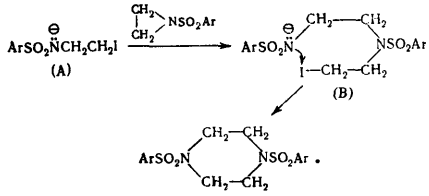
where Ar = $C_6H_4OCH_3$.

The thermal interaction of aziridines with a "dipolarophile" without solvent at 100–120°C takes place with the inversion of the configuration of the aziridine, while in the photochemical reaction the configuration is preserved. Thus, when 1 mole of compound (XIVa) and 10 moles of (IXb) were heated at 100°C for 14 h, compound (XVb) was isolated in 88% yield; under analogous conditions, compound (XIVb) is converted into compound (XVa) in 71% yield. Under the conditions of the photochemical reaction, compound (XIVb) is converted into compound (XVb) in 69% yield.

7. Dimerisation of Aziridine Derivatives and Interaction with Epoxyethane

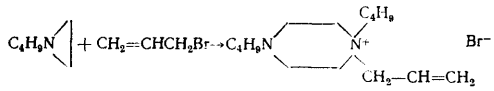
Oxygen- and sulphur-containing three-membered heterocyclic compounds dimerise under certain conditions to the corresponding dioxans[2] and dithians[41]. Aziridines also dimerise. The conversion of 1-methylaziridine into 1,4-dimethylpiperazine has been described[42]. The formation of piperazine derivatives in reactions of β-chloroethylamines has been observed. Kinetic studies of such reactions led to the conclusion[43,44] that chloroethylamines initially cyclise to aziridinium salts as intermediates, which then react further to give salts derived from piperazine. Piperazine derivatives were isolated after rearrangement of aziridines under the action of acids[45,46] and as side products in the isomerisation of aziridine derivatives[47].

1-Aroyl-2-alkylaziridines, 1-arylsulphonylaziridines, and 1-arylaziridines dimersie under the catalytic action of iodine. It is suggested that the first stage in the formation of piperazines[47] is a bimolecular substitution reaction of aziridine to give an ion derived from 2-iodoethylamine. Thus 1-arylsulphonylaziridines give rise to an ion (A) derived from *N*-(2-iodoethyl)arylsulphonimide, which attacks the methylene carbon of a second molecule of 1-arylsulphonylaziridine with formation of an intermediate ion (B):

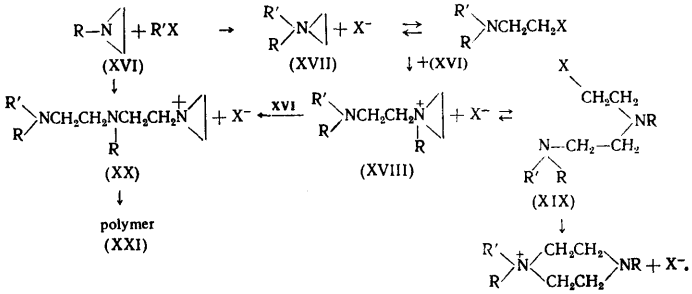


Piperazine is formed when an iodide ion is split off from the ion (B). The dimerisation of aziridine-1-carboxanilide to *NN*-di(phenylcarbamoyl) piperazine takes place similarly.

Dick[48] investigated the effect of alkylating agents on aziridine and succeeded in isolating piperazine derivatives. When allyl bromide is heated with 9 moles of *N*-butylaziridine in dry acetone, 1-allyl-1,4-di-*N*-butylpiperazinium bromide is formed in 96% yield:



Other alkylating agents have also been used: methyl iodide, methyl *p*-toluenesulphonate, ethyl *p*-toluenesulphonate, and ethyl bromide. The results of the experiments clearly show that in their reaction with aziridines alkylating agents favour the formation of piperazines. The mechanism of the opening of the ring of 1-alkylaziridines is known to involve catalysis by alkyl halides, including S_N2 attack by the nucleophilic agent on the aziridine ring. The following mechanism is proposed for the formation of piperazines:

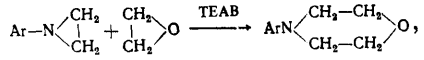


Aziridine (XVII) forms a dimer (XVIII) by an S_N2 reaction. Then, if X^- is a powerful nucleophilic agent, compound (XVIII) reacts with it to form compound (XIX), which cyclises. However, if X^- is a weak nucleophilic agent, for example the toluenesulphonate ion, compound (XVII) is not converted into compound (XIX) but causes ring opening in the next aziridine molecule, forming the trimer (XX) and then polymeric compounds (XXI). It is known that under certain conditions the reactions of acids or alkylating agents with aziridine derivatives yield polyaziridines. The reaction of aziridines with alkylating agents is significantly influenced by the solvent. For example, acetone favours the formation of piperazine, while more polar solvents favour the polymerisation (XVIII) → (XX) → (XXI).

The formation of 1,1-dialkylaziridinium salts of type (XVII) when aziridine interacts with alkylating agents was demonstrated also in earlier studies[49,50].

The dimerisation of *N*-aryl derivatives of aziridines was observed when the latter were heated in the presence

of a catalytic amount of tetraethylammonium bromide. The coupling of two three-membered heterocycles—*N*-aryl-aziridine and epoxyethane[51]—has been reported. Since the dimerisation of aziridine may compete with this type of interaction, the reaction was carried out in a large excess of epoxyethane:



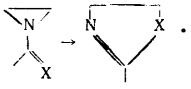
where Ar = C_6H_5, *o*-$CH_3C_6H_4$, *p*-$CH_3C_6H_4$, *o*-$CH_3OC_6H_4$, or *p*-$CH_3OC_6H_4$.

In the reactions of *N*-(*o*-methylphenyl)- and *N*-(*o*-methoxyphenyl)aziridines, *NN'*-diarylpiperazines were isolated in 30% yield together with morpholines. Ethylene sulphide does not take part in this reaction, undergoing quantitative polymerisation.

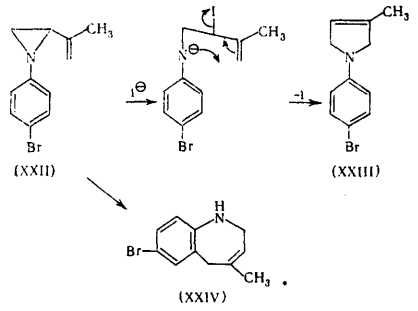
III. INTRAMOLECULAR CYCLISATION

1. Rearrangement of *N*-Vinyl Derivatives of Aziridines

Substituted aziridines undergo reactions typical for their hydrocarbon analogues—cyclopropanes. Under the action of nucleophiles and acids on heating, vinylcyclopropane isomerises to cyclopentene[52]. Similar processes have been observed for vinylaziridines:

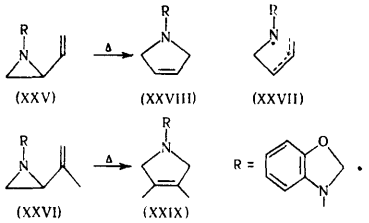


When *N*-methylvinyl(*p*-bromophenyl)aziridine (XXII) was heated with sodium iodide in dry acetone, 1-(*p*-bromophenyl)-3-methyl-3-pyrroline (XXIII) was isolated[53]:



The authors suggest that the mechanism of this reaction involves nucleophilic attack on aziridine by I^- with opening of the aziridine ring and subsequent displacement of iodine and formation of compound (XXIII). However, when *N*-vinylaziridine (XXII) is heated in xylene without a catalyst, the isomeric compound (XXIV), which is not a product of the expansion of the aziridine ring, is formed in a high yield. The structure of compound (XXIV) was demonstrated by the presence in its infrared spectrum of an absorption band characteristic of the NH group and also by the formation of the corresponding derivatives of phenylthiourea on heating with phenyl isothiocyanate.

Certain *N*-substituted 2-vinylaziridines [(XXV) and (XXVI)] undergo pyrolytic isomerisation in decalin solution at 180°C:[54]

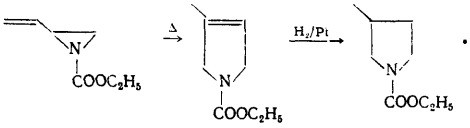


The products of the expansion of the aziridine ring (Δ^3-pyrrolines) are formed in 80% yield. The mechanism of their formation can be accounted for by postulating the opening of the aziridine ring with dissociation of the C–N bond. The reaction proceeds via the intermediate formation of the aza-allyl biradical (XXVII), the stability of which is higher than that of the alkylallyl biradical formed in the rearrangement of vinylcyclopropanes to cyclopentenes[52].

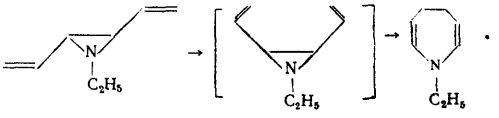
Comparison of the rates of conversion of the aziridines (XXV) and (XXVI) by heating in decalin at 150°C for 1 h shows that compound (XXVI) isomerises to compound (XXIX) to an extent of 100%, while the isomerisation of compound (XXV) to compound (XXVIII) takes place to the extent of 60% only. This can be explained by the greater stability of the tertiary allyl radical compared with the secondary radical.

The above aziridines (XXV) and (XXVI) are converted into Δ^3-pyrrolines under the action of a nucleophilic agent (sodium iodide) in boiling acetone with a yield of only 2% over a period of 24 h. In this case ring opening is not facilitated by the negative charge on the nitrogen atom. The conversion of three-membered rings into five-membered rings is possible only when the three-membered system is activated[55].

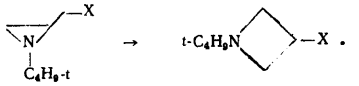
N-Ethoxycarbonyl-2-methyl-2-vinylaziridine isomerises in a gas-chromatographic column at 100°C or above with formation of *N*-ethoxycarbonyl-3-methyl-Δ^3-pyrroline[56]:



The presence of two vinyl substituents at the carbon atoms of aziridines leads to an unusual reaction involving the expansion of the three-membered ring to a seven-membered ring[57]: 2,3-divinylaziridine is converted into *N*-ethyldihydroazepine:



According to the latest literature data[58], certain aziridines rearrange to azetidine derivatives as a result of solvating ionisation:

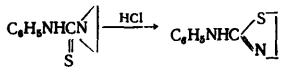


where X = OTs, OH, OC_2H_5, or Br.

2. Isomerisation of Aziridine Derivatives

The isomerisation of aziridine derivatives, which is an example of intramolecular cyclisation, constitutes the most thoroughly investigated type of rearrangements of aziridines. The rearrangement of *N*-acyl derivatives of aziridines, *NN'*-ethyleneureas, and thioureas, obtained by the interaction of aziridines unsubstituted at the nitrogen atom with isocyanic acid esters, benzoyl and thiobenzoyl chlorides, chlorocarbonic acid esters, and other compounds, led to the synthesis of many five-membered heterocyclic derivatives—oxazolines, oxazolidinones, thiazolidinones, imidazolidinones, and others.

In 1895 Gabriel [28] observed for the first time the conversion of aziridine-1-thiocarboxanilide into 2-anilino-Δ^2-thiazoline under the action of concentrated hydrochloric acid:

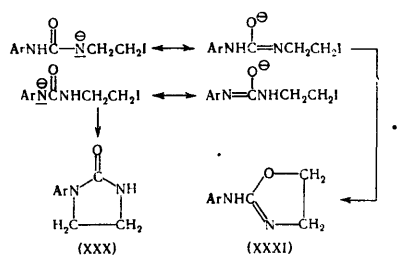


Later it was established that this type of reaction takes place readily in the presence of various nucleophilic agents which facilitate the dissociation of the C–N bond of the three-membered ring of aziridine.

Heine [59] proposed a mechanism for the nucleophilic catalytic isomerisation of aziridine derivatives, in which the formation of an anion derived from 2-iodoethylamine in the reaction in the presence of sodium iodide is postulated:



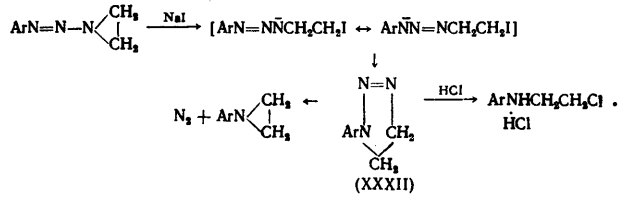
where R = ArCO, ArC(=NR')–, $Ar_2NC(=O)$–, or ArN=N–. The subsequent reaction of the anions formed can take place in different ways [47]; cyclisation may precede the tautomeric conversion of anions when there is a hydrogen atom at the nitrogen atom of *NN'*-ethyleneiminoureas:



(XXX) (XXXI)

For example, in the isomerisation of aziridine-1-carboxanilide in acetone solution in the presence of sodium iodide a mixture of products was isolated. The use of a small amount of acetone and an excess of sodium iodide leads to the formation of 1-phenylimidazolidin-2-one (XXX) in 85% yield. In an excess of acetone with a small amount of sodium iodide compound (XXX), the aziridine dimer, and a small amount of 2-anilino-Δ^2-oxazoline (XXXI) are formed.

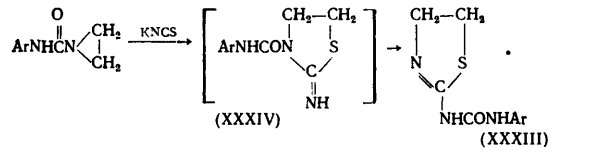
The synthesis of certain 1-arylazoaziridines [60], which are converted into 1-aryl-Δ^2-1,2,3-triazolines (XXXII) on heating in acetone solution containing iodide or thiocyanate ions, has been described:



(XXXII)

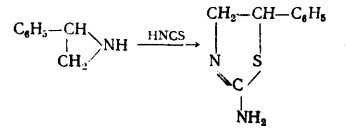
The products of the rearrangement of compound (XXXII) in turn serve as starting materials for the synthesis of a wide variety of *N*-arylaziridines which are difficult to obtain in other ways.

It should be noted that, apart from its catalytic effect, the thiocyanate ion can interact with aziridines, also yielding ring-expansion products. Thus, aziridine-1-carboxylic acid arylamides kept for 30 h in acetone with potassium thiocyanate are converted into 2-(3-arylureido)-Δ^2-thiazolines (XXXIII) [24], which are formed via the intermediate 2-imino-3-arylcarbamoyl-thiozilidines (XXXIV):

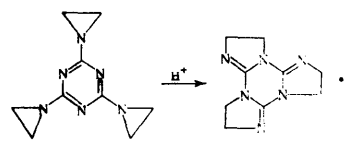


(XXXIV) (XXXIII)

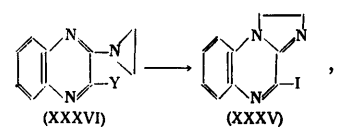
The mechanism of this interaction is consistent with the data of Gabriel [61], who described the effect of thiocyanic acid on 2-phenylaziridine:



The isomerisation of 2-alkyl-1-aroylaziridines, aziridine-1-thiocarboxanilides, and 1-arylsulphonylaziridines under the action of sodium iodide and thiocyanate ions in acetone [47] leads to the corresponding oxazolines and thiazolines—products of intramolecular cyclisation. 2,4,6-Tri-(1'-aziridino)-*s*-triazine isomerises on refluxing in acetonitrile solution in the presence of triethylammonium chloride to 2,3,6,7,10,11-hexahydrotrisimidazo-*s*-triazine:



New heterocyclic systems—1,2-dihydroimidazo[1,2-*a*]-quinoxamines (XXXVa, b)—have been obtained by the isomerisation of (1'-aziridino)quinoxamines (XXXVIa, b): [62]

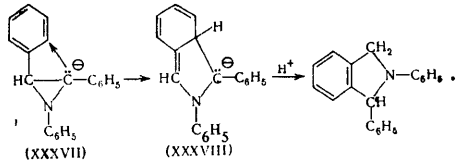


(XXXVI) (XXXV)

where (a) Y = Cl and (b) Y = CH_3O.

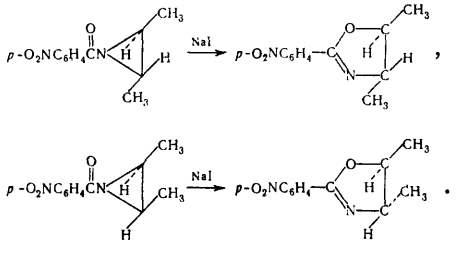
The conversion of compound (XXXVIa) into (XXXVa) takes place readily in acetone containing sodium iodide, while compound (XXXVIb), is converted into compound (XXXVb) in acetone solution containing sodium methoxide. The analogous isomerisation of 1-(*N*-arylbenzimidazolyl)-aziridine can be used to synthesise Δ^2-imidazolines [63].

The isomerisation of 1,2,3-triphenylaziridine is one of the first examples of carbanionic rearrangement involving the aziridine ring [64]. When 1,2,3-triphenylaziridine was heated in toluene in the presence of potassium t-butoxide in a sealed tube at 180°C, 1,2-diphenylisoindoline was isolated. The reaction may take place via the formation of the carbanion (XXXVII), which, after attack on the benzene ring, can be converted into the intermediate complex (XXXVIII); this undergoes a tautomeric conversion into 1,2-diphenylisoindoline:



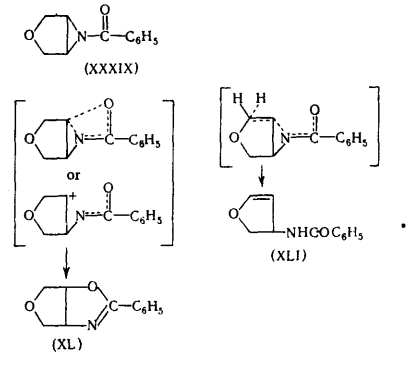
(XXXVII) (XXXVIII)

The isomerisation of certain 2,3-substituted *cis*- and *trans*-1-(*p*-nitrobenzoyl)aziridines, which are converted into the corresponding oxazolines under the action of iodide ions [65], is striking. The stereochemistry of this reaction has been investigated. In acetone solution containing iodide ions *trans*-2,3-dimethyl-1-(*p*-nitrobenzoyl)-aziridine isomerised to *trans*-4,5-dimethyl-2-(*p*-nitrophenyl)-Δ^2-oxazoline in 96% yield, while the *cis*-derivative of aziridine was converted into the corresponding *cis*-derivative of oxazoline:



The acid-catalysed isomerisation of 2,2-dimethyl-1-(*p*-nitrobenzoyl)aziridine [66] can take place via the intermediate formation of the tertiary carbonium ion $[ArCONHCH_2\overset{+}{C}(CH_3)_2]$.

The isomerisation has been observed also for more complex bicyclic aziridines (XXXIX), which also yield ring-opening products on heating in the presence of sodium iodide. The high probability of the rearrangement of aziridines into the corresponding oxazolines via the formation of amides has been demonstrated [67]:

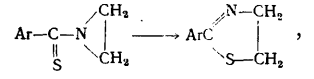


(XXXIX) (XLI) (XL)

When the aziridine derivative 6-aza-3-oxabicyclo[3,1,0]-hexane (XXXIX) and also its 6-methyl and 6-benzyl derivatives are heated, the oxazolines (XL) are formed but not the amides (XLI). The amide formed could be easily isolated under the experimental conditions, since it was shown that the amides are higher-melting less soluble products, which are more readily crystallised than oxazolines; the NMR spectra of compound (XL) differ from those of the isomeric amide (XLI). The hypothesis that the initially formed amide (XLI) cyclises under the reaction conditions is also unlikely, since it has been established that amides of this kind are stable on heating and cyclise to oxazolines only in concentrated sulphuric acid at room temperature [68].

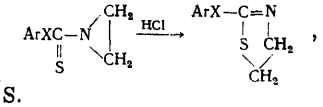
The oxazolines (XL) were also isolated after heating the benzoyl derivative of compound (XXXIX) with sodium iodide in acetone or acetonitrile. The mechanism of their formation is of the type of the isomerisation, described above, with formation of an ion derived from an iodoalkylamine [9].

Further studies [69] confirmed these findings in more complex heterocyclic systems. Conditions were found for the synthesis of 2,2-dimethyl-1-(*p*-nitrobenzoyl)-1-azaspiro[2,5]octane and 1-azaspiro[2,4-]heptane, which yield the corresponding *N*-nitrobenzoyl derivatives. The isomeric *N*-cycloalkenylmethyl-*p*-nitrobenzamides readily isomerise to spiro-oxazolines. Picric and *p*-toluenesulphonic acids have also been used as nucleophilic agents for the isomerisation; in their presence 1-thioaroylaziridines were converted into 2-arylthiazolidines in benzene solution [70]:



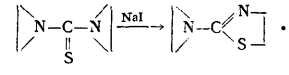
where Ar = *p*-ClC_6H_4, *p*-$CH_3C_6H_4$, or *p*-$CH_3OC_6H_4$.

1-(Aryloxythiocarbonyl)- and 1-(aryldithiocarbonyl)-aziridines readily polymerise on standing at room temperature and are converted into 2-aryloxythiazolines and 2-arylthiothiazolines by treatment with hydrochloric acid at 20°C:

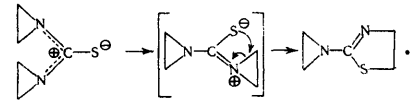


where X = O or S.

The extremely reactive 1,1'-(thiocarbonyl)bisaziridines readily isomerise in the presence of sodium iodide to a product formed as a result of the expansion of one of the aziridine rings [71,72]:

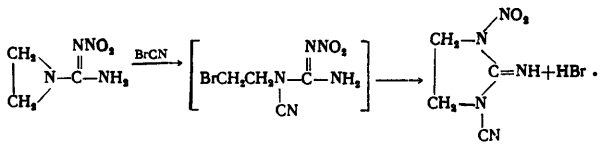


The reaction takes place quantitatively in 30 min at room temperature. The high reactivity of the bisaziridine can be explained by the high polarisation of the thiocarbonyl group in which the charge is delocalised between both aziridine nitrogen atoms:



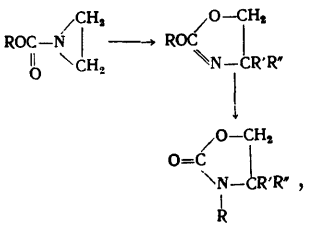
1-Nitroamidinoaziridines, obtained by the reaction of 2-methyl-1-nitro-2-thiopseudourea with aziridine and its 2-methyl derivative are examples of aziridines capable of isomerisation reactions [73]. In an acid medium the compounds isolated were converted into alkylnitroguanidines, while their cyanobromination leads to the formation of five-membered heterocycles—3-cyano-2-imino-1-nitroimidazolidine (XLII) and 2-amino-1-nitroimidazolidinium

bromide (XLIII)—in high yields. The cyanobromination of 1-nitroamidinoaziridine evidently takes place via the intermediate formation of *N*-(2-bromoethyl)-*N*-cyanonitroguanidine, which cyclises by an S_N2 mechanism with formation of compound (XLII) in 43% yield. The hydrogen bromide evolved reacts with aziridine to form 2-bromoethyl-3-nitroguanidine, which readily cyclises to compound (XLIII) in 41% yield.



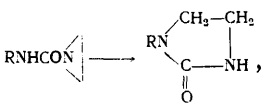
(XLII)

The aziridine derivatives of formic acid isomerise to oxazoline and oxazolidinone derivatives [74]. In this case the catalyst is sodium iodide in an aprotic solvent; an increase in the relative amount of sodium iodide in the initial mixture of reactants in excess of 0.1 mole leads to a decrease of the yield of the isomerisation products:

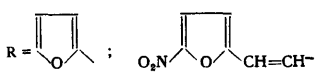


where R′ = R″ = H or R, R′, and R″ are hydrocarbons with more than 8 carbon atoms.

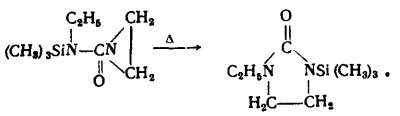
Japanese investigators [75] observed the isomerisation of *N*-[β-(5-nitro-2-furyl)vinyl]- and *N*-(2-furyl)-ethyleneureas at room temperature in acetone or acetonitrile solution in the presence of sodium iodide. The structure of the imidazolidin-2-ones formed in 85–90% yield was demonstrated by analyses, infrared spectroscopy, and syntheses. The mechanism of the rearrangement is consistent with that described previously:



where

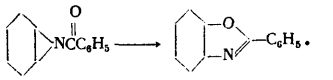


The aziridine ring-expansion reaction has been observed for ethyleneureas containing silicon atoms together with the aziridine ring [76]. *N*-Silylaziridines were obtained by the reaction of aziridine and trimethylchlorosilane. Their subsequent reaction with isocyanates leads to the formation of *N*-silylethyleneureas, which form imidazolidine derivatives of silicon on heat treatment:

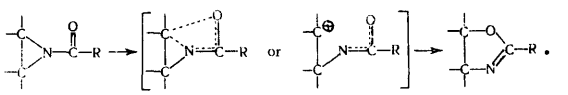


The structure of the imidazolidinones isolated was demonstrated by NMR spectroscopy, solvolysis of the product at the Si–N bond, and infrared spectroscopy of the decomposition products.

Many compounds, which readily isomerise under the influence of nucleophilic catalysts, undergo pyrolytic isomerisation to the corresponding ring-expansion products. Thus Gabriel [28] noted that redistilled 1-benzoylaziridine is converted on heating in a sealed tube to 240°C into 2-phenyl-Δ^2-oxazoline. The pyrolysis of *N*-benzoyl-*cis*-cyclohexeneimine leads to *trans*-4,5-tetramethylene-2-phenyl-Δ^2-oxazoline in 20% yield [59]:

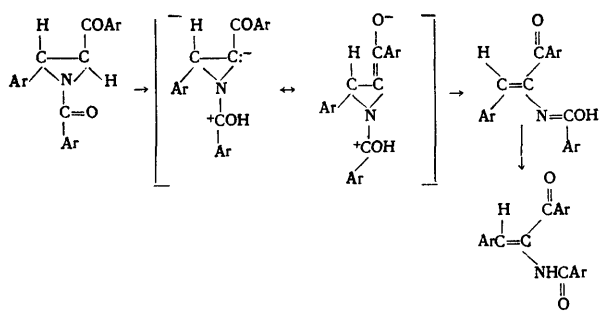


The thermolysis of the corresponding *cis*- and *trans*-1-(*p*-nitrobenzoyl)-2,3-diphenylaziridines leads to the *cis*- and *trans*-derivatives of oxazoline [66]. The mechanism of the pyrolytic isomerisations to oxazolines probably includes a four-centre displacement [59] or the intermediate contraction of the ion pair [67]:



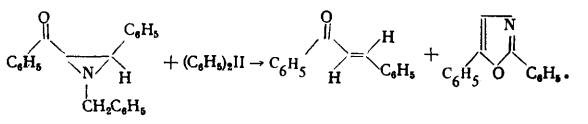
The study of the pyrolytic isomerisation of 1-acylaziridines taking into account stereochemical and kinetic data [66,77] led to the hypothesis that this intramolecular rearrangement consists of *cis*-elimination, including the displacement of the proton from the alkyl group to the amide oxygen. This displacement is impossible in the absence of an alkyl group at an aziridine carbon atom in 1-aroylaziridines or in the presence of steric factors preventing the formation of a bond between the amide oxygen and a proton.

On heating in boiling xylene, 1,3-diaroyl-2,3-arylaziridines [66] are converted into α-benzamidobenzoylacetophenone. In this case oxazolines are not formed, since there is a possibility of the displacement of the acid aziridine hydrogen atom to the amide oxygen atom and a reaction involving the dissociation of the carbon–nitrogen bond of the ring:

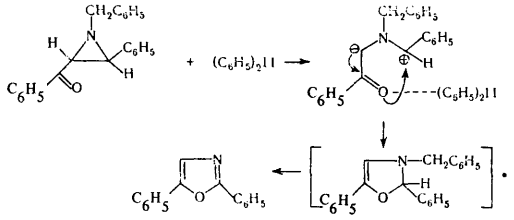


The isomerisation of aziridine derivatives involving the dissociation of the C–C bond of aziridine is known [78–81]. *trans*-3-Benzoyl-1-benzyl-2-phenylaziridine is converted into *trans*-benzylideneacetophenone (73% yield) and

2,5-diphenyloxazole (7% yield) on heating with diphenyliodonium iodide:



The following mechanism has been proposed for the isomerisation of aziridines to ring-expansion products [79]:

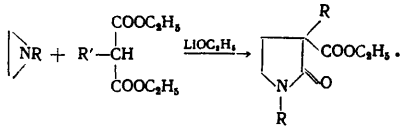


Diphenyliodonium iodide behaves as a Lewis acid and interacts with the C=O group, protonating the aziridine ring. The reaction of diphenyliodonium iodide with 2-benzoylaziridine yielded 2,5-diaryloxazoles and $\alpha\beta$-substituted ketones [80]. The aziridine ring-expansion product was not isolated when the reaction was carried out in anhydrous acetone and therefore the possibility of the formation of 2,3-dihydro-oxazoles cannot be explained, like the isomerisation of *N*-aroylaziridines, by the Heine mechanism. One of the possible mechanisms involves the interaction of diphenyliodonium iodide with the carbonyl group of the aziridine substituent and the dissociation of the aziridine C–C bond.

3. Interaction of Aziridines with Malonic Ester

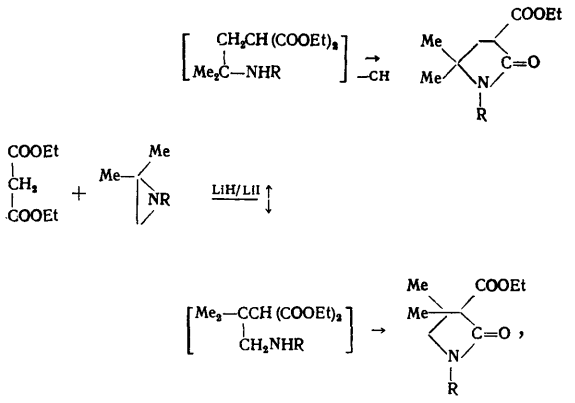
The reaction of aziridines with malonic ester leads to the formation of ring-expansion products—substituted pyrrolidinones. The first step in this reaction is aminoethylation, the subsequent intramolecular cyclisation with elimination of alcohol leading to the formation of pyrrolidinone derivatives.

In the reaction of *N*-phenylaziridine with malonic ester in the presence of lithium ethoxide, 3-ethoxycarbonyl-1-phenylpyrrolidin-2-one is formed [82,83]:



The reaction of 1-(β-phenylethyl)aziridine was carried out similarly [85]. In the presence of an excess of malonic ester aziridine is protonated. Under the influence of the enolate of malonic ester, the occurrence of competing processes is possible: *N*-alkylation (dimerisation of aziridine) and *C*-alkylation—formation of 3-ethoxycarbonyl-1-phenylethyl-pyrrolidin-2-one in 30% yield.

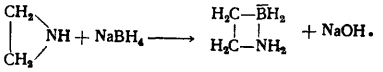
When malonic ester was heated with 2,2-dimethyl-1-(β-phenylethyl)aziridine in benzene [85] in the presence of LiH and LiI, 2-ethoxycarbonyl-5,5-dimethyl-1-(β-phenylethyl)pyrrolidin-2-one was isolated and then converted by alkaline hydrolysis into 5,5-dimethyl-1-(β-phenylethyl)-pyrrolidin-2-one:



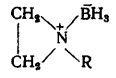
where R = $C_6H_5CH_2CH_2$.

Analysis and the NMR spectra led to the conclusion that the interaction of asymmetric aziridines with malonic ester involves an unsubstituted carbon atom with subsequent cyclisation to pyrrolidinone derivatives.

Earlier it was reported that unsubstituted aziridine reacts with sodium borohydride to forma four-membered heterocycle [86]:



Later investigations of this reaction confirmed the formation of aziridine salts (aminoboranes) in this process [87]:



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Whilst the present review was in the press, a paper dealing with the isomerisation of 1-(*p*-nitrobenzoyl)-2-vinylaziridine to a seven-membered derivative was published [88].

REFERENCES

1. Houben-Weyl, "Methoden der organischen Chemie", Vo. X1/2 1958.
2. R. C. Elderfield (Editor), "Heterocyclic Compounds" (Translated into Russian), Inostr. Lit., 1953, Vol. 1.
3. P. A. Gembitskii, D. S. Zhuk, and V. A. Kargin, "Khimiya Etilenimina" (The Chemistry of Aziridine), Izd. Nauka, 1966.
4. N. J. Leonard and K. Jann, J. Amer. Chem. Soc., 82, 6418 (1960).
5. N. J. Leonard, J. Org. Chem., 28, 1499 (1963).

6. N. J. Leonard, E. F. Kiefer, and L. E. Brady, J. Org. Chem., 28, 2850 (1963).
7. N. J. Leonard, J. V. Paukstelis, and L. E. Brady, J. Org. Chem., 29, 3383 (1964).
8. J. B. Doughty, C. L. Lazzell, and A. R. Collett, J. Amer. Chem. Soc., 72, 2866 (1950).
9. M. Lidaks and S. Hillers, Izv. Akad. Nauk Latv. SSR, 99 (1961).
10. R. G. Kostyanovskii, Dokl. Akad. Nauk SSSR, 139, 877 (1961).
11. R. G. Kostyanovskii and V. F. Bystrov, Izv. Akad. Nauk SSSR, Ser. Khim., 171 (1963).
12. W. J. Raburn and W. L. Howard, J. Org. Chem., 27, 1039 (1962).
13. S. Hillers and M. Lidaks, Symposium, "Puti Sinteza i Izyskaniya Protivoopukholevykh Preparatov" (Methods Used in the Synthesis and Search for Antitumour Preparations), Moscow, 1962.
14. R. G. Kostyanovskii, D. A. Pan'shin, and T. Z. Paponyan, Dokl. Akad. Nauk SSSR, 177, 1099 (1967).
15. J. Oshiro, K. Yamamoto, and S. Komori, J. Soc. Org. Syn. Chem., Japan, 24, 945 (1966); Chem. Abs., 66, 37706y (1967).
16. J. L. Larice, J. Roggero, and J. Metzger, Bull. Soc. chim. France, 3637 (1967).
17. L. N. Grobov, A. P. Sineokov, and V. S. Etlis, Uspekhi Khim., 35, 1575 (1966) [Russ. Chem. Rev., No. 9 (1966)].
18. A. Seher, Ann. Chem., 575, 173 (1952).
19. A. P. Sineokov, F. N. Gladysheva, and V. S. Etlis, Khim. Geterotsikl. Soed., 370 (1968).
20. A. P. Sineokov, F. N. Gladysheva, and V. S. Etlis, Khim. Geterotsikl. Soed., (in the Press).
21. A. P. Sineokov, F. N. Gladysheva, and V. S. Etlis, Khim. Geterotsikl. Soed., 567 (1968).
22. L. B. Clapp and J. W. Watjen, J. Amer. Chem. Soc., 75, 1490 (1953).
23. H. Bestian, Annalen, 566, 210 (1950).
24. H. Najer, R. Giudicelli, J. Menin, and C. Morel, Compt. rend., 253, 2369 (1961).
25. DBR P. 946 132; Chem. Abs., 52, 16754a (1958).
26. E. Gulbins, R. Morlock, and K. Hamann, Ann. Chem., 698, 180 (1966).
27. K. Gulbins and K. Hamann, Chem. Ber., 94, 3287 (1961).
28. S. Gabriel and R. Stelzner, Ber., 28, 2929 (1895).
29. Y. Iwakura and A. Nabeya, J. Chem. Soc. Japan, 77, 773 (1956); Chem. Abs., 52, 9028 (1958).
30. V. S. Etlis, A. P. Sineokov, and G. A. Razuvaev, Izv. Akad. Nauk SSSR, Ser. Khim., 737 (1964).
31. D. E. Pfeil and U. Harder, Angew. Chem., 77, 505 (1965).
32. N. J. Leonard, D. A. Durand, and F. Uchimaru, J. Org. Chem., 32, 3607 (1967).
33. N. J. Leonard and L. E. Brady, J. Org. Chem., 30, 817 (1965).
34. H. W. Heine and R. E. Peavy, Tetrahedron Letters, 3123 (1965).
35. A. Padwa and L. Hamilton, Tetrahedron Letters, 4364 (1965).
36. R. Huisgen, W. Scheer, G. Sreimies, and H. Hubr, Tetrahedron Letters, 397 (1966).
37. H. W. Heine, R. Peavy, and A. J. Durbetaki, J. Org. Chem., 31, 3924 (1966).
38. H. W. Heine, A. B. Smith III, and J. D. Bower, J. Org. Chem., 33, 1097 (1968).
39. H. Rolf, S. Wolfgang, and H. Helmut, J. Amer. Chem. Soc., 89, 1753 (1967).
40. H. W. Heine, R. H. Weese, R. A. Cooper, and A. J. Durbetaki, J. Org. Chem., 32, 2708 (1967).
41. Yu. K. Yur'ev and L. S. German, Zhur. Obshch. Khim., 25, 2527 (1955).
42. L. Knorr, Ber., 37, 3507 (1904).
43. P. D. Bartlett, S. D. Rass, and C. G. Swan, J. Amer. Chem. Soc., 69, 2971 (1947).
44. P. D. Bartlett, S. D. Rass, and C. G. Swan, J. Amer. Chem. Soc., 69, 2977 (1947).
45. L. B. Clapp, J. Amer. Chem. Soc., 70, 184 (1948).
46. L. B. Clapp, J. Amer. Chem. Soc., 73, 2584 (1951).
47. H. W. Heine, W. C. Kenyon, and E. M. Johnson, J. Amer. Chem. Soc., 83, 2570 (1961).
48. C. R. Dick, J. Org. Chem., 32, 72 (1967).
49. A. T. Bottini and R. L. Van Etten, J. Org. Chem., 30, 575 (1965).
50. G. K. Helmkamp, R. D. Clark, and J. R. Koskinen, J. Org. Chem., 30, 666 (1965).
51. A. P. Sineokov, F. N. Gladysheva, V. S. Etlis, and V. S. Kutyreva, Khim. Geterotsikl. Soed., (in the Press).
52. G. C. Overberger and A. E. Borchert, J. Amer. Chem. Soc., 28, 1007 (1960).
53. R. Scheiner, J. Org. Chem., 32, 2628 (1967).
54. R. S. Atkinson and C. W. Rees, Chem. Comm., 23, 1232 (1967).
55. E. L. Eliel, "Stereochemistry of Carbon Compounds" (Translated into Russian), Izd. Mir., 1965.
56. A. Mishra, S. N. Rice, and W. Lwowski, J. Org. Chem., 33, 481 (1968).
57. E. J. Stogryn and S. J. Brois, J. Org. Chem., 30, 88 (1965).
58. J. A. Deyrup and C. L. Moyer, Tetrahedron Letters, 6179 (1968).
59. H. W. Heine, Angew. Chem., 20, 772 (1962).
60. H. W. Heine and D. A. Tomalia, J. Amer. Chem. Soc., 84, 993 (1962).
61. S. Gabriel and J. Colman, Ber., 47, 1866 (1914).
62. H. W. Heine and A. C. Brooker, J. Org. Chem., 27, 2943 (1962).
63. H. W. Heine and H. S. Berder, J. Org. Chem., 25, 461 (1960).
64. H. W. Heine and F. Scholer, Tetrahedron Letters, 3667 (1964).
65. H. W. Heine, D. G. King, and L. A. Portland, J. Org. Chem., 31, 2662 (1966).
66. H. W. Heine and M. S. Kaplan, J. Org. Chem., 32, 3069 (1967).
67. P. E. Fanta and E. N. Walsh, J. Org. Chem., 31, 59 (1966).
68. P. D. Kashelikar and P. E. Fanta, J. Amer. Chem. Soc., 82, 4930 (1960).
69. P. E. Fanta, R. J. Smat, L. F. Piecz, and L. Clemens, J. Org. Chem., 31, 3113 (1966).
70. Y. Iwakura, A. Nabeya, and T. Nishiguchi, J. Org. Chem., 32, 2362 (1967).
71. D. A. Tomalia, J. Heterocycl. Chem., 3, 384 (1966).
72. D. A. Tomalia, J. Heterocycl. Chem., 4, 419 (1967).
73. J. U. Lowe, J. Takuhuko, A. Oda, and R. Evans, J. Org. Chem., 28, 1496 (1963).
74. G. E. Ham, US P. 3 247 220; Chem. Abs., 64, 19622h (1966).
75. T. Sasoki and Y. Yashioko, J. Chem. Soc. Japan, 41, 1258 (1968).
76. O. J. Scherer and M. Schmidt, Chem. Ber., 98, 2243 (1965).
77. P. E. Fanta and M. K. Kathan, J. Heterocycl. Chem., 1, 293 (1964).

78. A. Padwa and L. Hamilton, Tetrahedron Letters, 1861 (1967).
79. A. Padwa, D. Eastman, and L. Hamilton, J. Org. Chem., **33**, 1317 (1968).
80. A. Padwa and L. Hamilton, J. Heterocycl. Chem., **4**, 118 (1967).
81. A. Padwa and E. William, Chem. Comm., 380 (1968).
82. H. Stamm, Angew. Chem., **74**, 694 (1962).
83. H. Stamm, Angew. Chem., **77**, 546 (1965).
84. H. Stamm, Chem. Ber., **99**, 2556 (1966).
85. H. Stamm, Arch. Pharm., **299**, 965 (1966).
86. S. Akerfeldt and M. Hellstrom, Acta Chem. Scand., **20**, 1418 (1966); Chem. Abs., **65**, 16991b (1966).
87. B. P. Robinson and K. A. H. Adams, Tetrahedron Letters, 6169 (1968).
88. P. G. Mente, H. W. Heine, and G. R. Scharoulim, J. Org. Chem., **33**, 4547 (1968).