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Ioffe Physicotechnical Institute,
Academy of Sciences of the USSR

U.D.C. 547.717.1

AZIRIDINE: SYNTHESIS, STRUCTURE, PROPERTIES

P.A.Gembitskii, N.M.Loim, and D.S.Zhuk

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I. INTRODUCTION

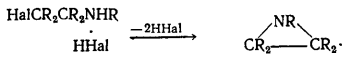
Aziridine and its derivatives have a number of very interesting physical, chemical, and biological properties, and they are attracting increasing attention of workers in different specialities. In addition to their theoretical and scientific interest, aziridine, some of its derivatives, and polyaziridine have found considerable practical uses. The object of the present review is to discuss briefly the main methods of synthesis, features of molecular structure and properties, and the chemical reactivity of aziridine together with its main uses in medicine and technology.

II. METHODS OF SYNTHESIS OF AZIRIDINE

The overwhelming majority of known methods of synthesis of aziridine and its derivatives may be divided according to reaction type into four groups of methods, leading to closure of a three-membered heterocycle: (1) intramolecular condensation reactions with elimination of the elements of an acid; (2) thermolysis of other nitrogen-containing heterocycles; (3) cyclisation reactions of nitrogen-substituted derivatives (oximes, hydrazones, dichloroamines); (4) addition reactions to C=C or C=N bonds.

Intramolecular condensation reactions. Aziridine was first synthesised by Gabriel in 1888 by the action of moist silver oxide on β-bromoethylamine hydrobromide[1]. Gabriel erroneously ascribed the structure of vinylamine to the compound obtained. This error was corrected by Marckwald, who showed that the product obtained by Gabriel was a secondary amine with a cyclic structure[2-4]; at the same time the true mechanism of

Gabriel's reaction for the cyclisation of β-halogenoethylamines, which is quite general, was discovered:

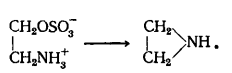


Thus, a whole series of free β-halogenoethylamines[5,6], *bis*-(β-chloroethyl)amine[7,8], and even *tris*-(β-chloroethyl)amine[9], are smoothly cyclised in aqueous, aqueous-alcoholic, or aqueous-acetone solutions with the formation of the corresponding aziridinium halides, which are then gradually hydrolysed with ring opening. In the absence of strong nucleophilic agents ($S_2O_3^{2-}$, HCO_3^-), aziridinium ions are comparatively stable and may accumulate in solutions in considerable quantities†. They may be detected titrimetrically (thiosulphate) and separated either as the poorly soluble picrates[12] and picrylsulphonates[6], or as free bases obtained by the addition of alkaline agents (Gabriel's reaction).

The rate of cyclisation of halogenoalkylamines depends on the nature of the halogen atom and the character of the substitution at both reactive centres of the molecule, the nitrogen atom and the carbon atom carrying the halogen. It increases in the order Cl < Br < I.[10] The negative inductive effect of the sulphonyl and acetyl groups in 2-chloro-3-sulphonamidobutane[13] and 1-bromo-1-acetyl-2-phenylamine[14] facilitates ring closure to such a degree that it occurs spontaneously with separation of the corresponding hydrogen halide. α-Methyl, αβ-cycloalkyl-, and even ββ-*gem*-dimethyl- substituents also have a favourable effect on the reaction centre[15-17]; this appears to be connected with corresponding changes in the conformations of the molecules of the initial halogenoalkylamines. The accumulation of bulky substituents, however, may cause steric hindrance at the reactive centre, preventing nucleophilic attack on the nitrogen atom, or even completely excluding cyclisation, as occurs with 1-chloro-2-(*N*-phenylamino)-1,1,2-triphenylethane[18] and 1-chloro-2-(*N*-acetyl)-1,1-diphenylethane[19].

Gabriel's reaction as a method of synthesising aziridines has been studied by various workers on numerous examples. It has been used for the preparation, apart from aziridine itself[20-27], of *N*- and *C*-alkyl-[28-35] and aryl-substituted[36-53] aziridines, bicyclic structures including the aziridine ring[33], and also *C*-acyl-[14], *C*-carboxy-[54], and *N*-sulphonyl-substituted[55-64] aziridine derivatives. It is inapplicable only in the case of *N*-acyl derivatives[65].

The second most widely used method of preparing aziridines after Gabriel's reaction is Wenker's synthesis, which is similar to it in principle[66-76]; this consists of cyclisation by the action of alkali of acid β-aminoalkylsulphates:



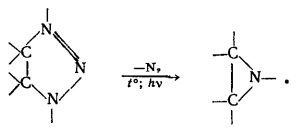
The most substantial differences between this method and Gabriel's reaction are the lower rates of cyclisation of β-aminoalkylsulphates compared with halogenoalkylamines[77]. However, since the aziridine formed remains in contact with hot alkaline solution for a longer period, the degree of hydrolytic cleavage increases and the yield correspondingly falls. A solution to the problem of the yield in Wenker's synthesis has been found by reducing the reaction time, either by increasing the reaction temperature[78], or by rapidly distilling off the aziridine formed by the slow addition of the aminoethyl sulphate to boiling aqueous alkali[79]. The yields thus obtained (up to 91%) correspond to the yields in Gabriel's reaction. The majority of industrial plants for the preparation of aziridine are based on Wenker's synthesis[80,81].

A study of the cyclisation of stereoisomeric β-halogenoalkylamines and β-aminoalkyl sulphates has shown that this is always accompanied by inversion of confirguration. Thus, the cyclisation of DL-*threo*- or L(+)-*threo*-3-aminobutan-2-ols leads to *meso*-2,3-dimethylaziridine (*cis*-isomer), but the L(+)-*erythro*-isomer gives L(-)-2,3-dimethylaziridine (*trans*-isomer)[82]. Similarly, *cis*-2,3-diphenylaziridine may be obtained by the cyclisation of *l*- or *dl*-iso-α-amino-β-chlorodibenzyls, and the *l*-*trans*- and *dl*-*trans*-isomers from *l*- and *dl*-α-amino-β-chlorodibenzyls respectively[37]. In systems in which *trans*-closure is impossible, the aziridine ring is not formed. Thus, when the stereoisomeric α-aminocyclohexyl sulphates are treated with alkali, only the *trans*-isomer gives an aziridine derivative (tetramethyleneaziridine)[83].

A large number of syntheses (mainly of various *C*-acyl substituted derivatives of aziridine) proceed in the same way as the Gabriel–Wenker reaction: vicinal dihalogeno-ketones[84-91], -ethers[92-94], -nitriles[95-97], or α-halogeno-substituted αβ-unsaturated ketones[98-100] and ethers[101-104] react with ammonia and amines, and there is also the analogous reaction of αβ-unsaturated ketones with iodine complexes of ammonia and amines[105,106]. The reaction with ammonia leads to aziridine derivatives unsubstituted at the nitrogen; the reaction with primary amines leads to substituted derivatives; and the reaction with secondary amines leads to the corresponding quaternary aziridinium compounds[99,100].

These reactions can be described in the most general way as cyclisation of bifunctional compounds of the type $(R_2CX)_2$ (R = H or a hydrocarbon group and X is a halogen atom, or a sulphate, nitrate, or other polar group) by ammonia or amines in the presence or absence of acid acceptors. One of these reactions — the condensation of dichloroethane with ammonia in the presence of calcium oxide — has proved such a successful method of synthesising aziridine that immediately after its discovery it was used on a production scale by the Dow Chemical Co.[107-109]. Experts of this firm consider that the successful development of the production of aziridine by this method will lead to a very considerable reduction in its cost in a short time[110].

Thermolysis of nitrogen-containing heterocycles. As in the synthesis of cyclopropanes by Kishner's method, thermal[111-116] or photolytic[117] decomposition of 1,2,3-triazolines leads to aziridine derivatives:

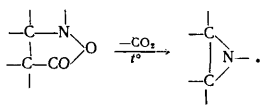


Evidently, the analogy in the structure of two strained rings may be extended to the thermolysis mechanism. In

† Since aziridine derivatives have an extremely high biological activity, the amount of aziridinium ions produced by decomposition is also reflected in the biological activity of the solutions[10,11].

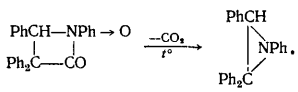
contrast to the pyrolysis of pyrazolines, which presupposes preliminary prototropic displacement of the double bond to the 1,2-position (catalysed by alkali), thermal decomposition of dihydrotriazoles, containing the ready-made azo-group in their ring, does not require the use of an alkaline catalyst.

A very similar thermolytic route is known for another five-membered heterocycle, oxazolid-2-one[118-120]:



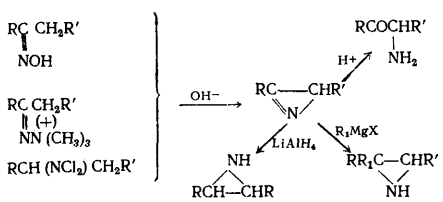
The two methods differ in that in the first contraction of the ring is accompanied by elimination of the azo-group as a nitrogen molecule, whereas in the second the $-C\begin{matrix}O\\O-\end{matrix}$ fragment of the lactam ring is removed as a molecule of carbon dioxide. Although simple heating is sufficient for decomposition of triazolines, pyrolysis of oxazolid-2-ones must be carried out in the presence of an alkaline solvent, since the carbon dioxide eliminated may react with the aziridine.

Mention should also be made of the formation of polyphenylated aziridine (1,2,3,3-tetraphenylaziridine) on heating the product of the addition of diphenylketene to benzaldehyde *N*-phenyloxime[18]:



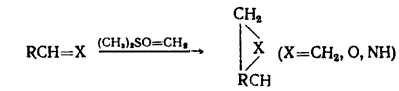
An attempt to prepare other aziridine derivatives in a similar way proved unsuccessful.

Cyclisation of oximes, hydrazones, and chloramines. The rearrangement of some derivatives of oximes (tosylates[121,122], magnesium halides[123-129]) and hydrazones (methyliodides of dimethylhydrazones[130]) of the structure $RC(=NX)CH_2R'$, where X = OH or $^+N(CH_3)_3$, and also *NN*-dichloro-s-alkylamines[131,132] of similar structure, to α-amino-ketones and -alcohols:

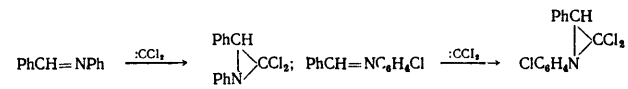


leads to common cyclic intermediate products, the corresponding azirines or alkoxyaziridines. Reduction of the latter with lithium aluminium hydride or Grignard reagents and the use of mild conditions for hydrolysis of the reaction products (ice + ammonium chloride) enabled the rearrangements mentioned to be used as a method of synthesis of the corresponding substituted aziridines.

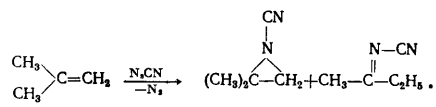
Addition to C=C and C=N bonds. Cyclisations by addition to C=C or C=N bonds include a number of recently discovered reactions in which the C=N bonds of imines, which are susceptible to nucleophilic attack, are methylenated, and reactions in which activated alkene C=C bonds are iminated with the aid of unstable and extremely active compounds of radical or ionic character. Thus, it has very recently been shown that sulphonium ylides, formed by the decomposition of the corresponding sulphonium salts by strong alkalis in anhydrous dimethylsulphoxide, react with polar C=C, C=O or C=N bonds to give good yields of derivatives of cyclopropane, ethylene oxide and aziridine respectively[133-136]:



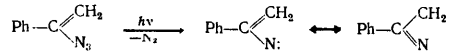
An analogous route is also known for radical reagents, carbenes and their nitrogen analogues — nitrenes or azocarbenes. The addition of hydrocarbon carbenes to C=N bonds of imines[137,138], or of azocarbenes to alkene C=C bonds[139,140] unambiguously leads to derivatives of aziridine, for example,



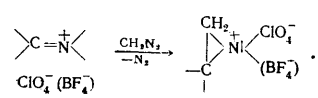
Since nitrenes are produced by the thermal or photolytic decomposition of azides, this mechanism is obviously also the basis of the synthesis of aziridine derivatives described in the literature in which alkenes react directly with certain azides (sulphonyl azides[141-143], cyanazide[144], and carbamoyl azide[145]), for example:



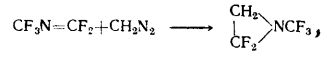
Apart from adding to multiple bonds, some nitrenes can undergo intramolecular cyclisation reactions[146-148]. For example, photolysis of t-butylazide and α-azidostyrene gives good yields of 2,2-dimethylaziridine[146] and 2-phenylazirine[147]:



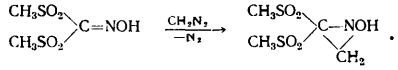
Diazomethane is another widely used methylenating agent; the addition of diazomethane to C=N bonds of imines gives triazolines, which are starting materials for the synthesis of aziridines by thermolysis (see above). In the case of tertiary iminium salts with weakly nucleophilic anions (perchlorates and fluoroborates) similar nucleophilic attack of diazomethane leads directly to the corresponding aziridine derivatives in high yield[149-152]:



Polyfluorinated imines react in a similar way, for example[153]:

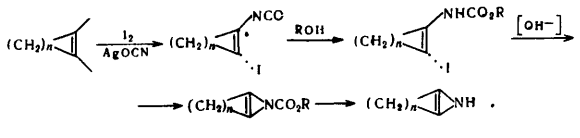


and also *bis*-methanesulphonylisonitrosomethane[154]:



Mention should also be made of the synthesis of condensed aziridines from cyclic alkenes (mainly in the

steroid series) by hydrolysis of the corresponding iodocarbamates, obtained by the reaction of alkenes with iodine in the presence of an excess of silver cyanate[155,156]:



III. STRUCTURE AND PROPERTIES

Physical properties. Closure of the three-membered C–C–N heterocycle is accompanied by a considerable increase in boiling point, specific gravity, and some other physical constants connected with intermolecular interactions (Table 1).

This effect is connected with the increased strength of H–N...H-hydrogen bonding (both in comparison with non-cyclic analogues and in comparison with isologues), which is characteristic of aziridine.

Thermochemical properties. The following are the main thermochemical values for aziridine:

		kcal mole^{-1}
Heat of combustion	C_2H_5N(liq.)	380.34 ± 0.15
Heat of formation	C_2H_5N(liq.)	21.96 ± 0.14
Heat of formation	C_2H_5N(gas)	26
Heat of evaporation	C_2H_5N	4

Comparison of the given experimental values[109,160] for the energy of formation of aziridine with those calculated from the summation of the bond energies (12 kcal mole^{-1}) gives a value of 14 kcal mole^{-1} for the strain energy of the three-membered heterocycle.

Solubility and properties of aqueous solutions. Examination of the three-component system aziridine–water–sodium hydroxide is of considerable practical interest. The relevant ternary diagram (Fig. 1) gives valuable information on the division into and composition of phases in this system[161]. Here each point inside the region bounded by the binodal curve and the upper tie-line corresponds to a system divided into two liquid phases. Their composition can be determined from the points of intersection of the corresponding tie-lines with the binodal curve and the base of the triangle.

Detailed study of the dependence on concentration of density, refraction, melting point, boiling point, surface tension, and viscosity of aqueous solutions of aziridine shows that all these undergo sharp changes at the point with an aziridine : water ratio of 1 : 2.[161] The nature of these changes (minima, breaks, and points of inflexion on the curves) indicates the formation of a characteristic chemical compound of aziridine and water of this composition. Infrared spectroscopic examination of the 1 : 2 compound of aziridine and water shows that the characteristic

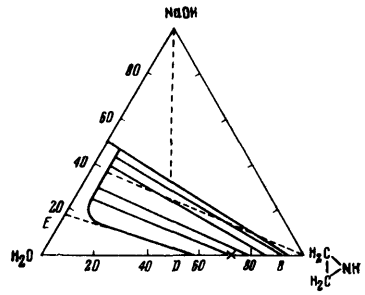


Fig. 1. Ternary diagram of the aziridine–water–sodium hydroxide system at 20°.

frequencies of aziridine are absent and suggests a cyclic chelate hydrate structure formed by intermolecular OH- and NH-bonding. It is interesting to note that the parachor and thermochemical properties of this compound also indicate that the three-membered heterocycle in it must be opened‡.

Molecular structure. As with cyclopropane, closure of the three-membered C–C–N ring is accompanied by considerable distortion of the valence angles, which in turn leads to the development of substantial ring strain. Clearly this strain is primarily reflected in the molecular structure of aziridine, that is, in bond energies, interatomic distances and angles, etc. Such methods as spectroscopy, microwave spectroscopy, mass spectroscopy, and electron diffraction give interesting information on this point. Thus, analysis of the microwave spectrum of aziridine shows that the imine hydrogen (NH bond) of aziridine does not lie in the plane of the ring[162–165]. Comparison of the experimental intensity of the bands with the calculated intensity confirms that the molecule is not coplanar. Structural parameters of the molecule and values of the components of the dipole moment (Table 2) have been determined from the microwave spectrum of aziridine[166,167].

The values in Table 2 agree with those calculated from electron-diffraction data[168].

Some conclusions on the structure of the aziridine molecule may also be drawn from an analysis of its infrared and

TABLE 2. Structural parameters of the aziridine molecule (from microwave spectroscopic data).

Bond	Bond length, Å	Angle	Value of angle	Component μ	Value of μ (D)
C–C	1.480	C_2NH	112°	μ_a	1.670
C–N	1.488	H_2CC	159°45′	μ_c	0.890
C–H	1.083	HCH	116°41′	μ_{total}	1.890

TABLE 1. Physical properties of aziridine and dimethylamine.

Compound	B.p., °C	M.p., °C	d_4^{20}	γ, dyn cm^{-1}	η, cP	Flash-point, °C	Refs.
Aziridine	55–56	–78.0	0.837	32.8	0.418	–11.1	157,158
Dimethylamine	7.4	–96.0	0.680	18	0.37	—	159

‡ Similar results obtained by workers by the Dow Company are given in the prospectus of this company published in 1965. This also gives some original physical constants of aziridine, and also recommendations for its transport and storage together with safety precautions for working with it, and the stability of various constructional materials in contact with aziridine.

Raman spectra[169-174]. The presence of increased (3012–3078 cm^{-1} compared with 2800–2980 cm^{-1} in aliphatic amines) CH stretching vibration frequencies indicates considerable strain in the three-membered heterocycle. The ring strain in aziridine leads to an increase in the polarity of the NH bond and to some reduction in its characteristic vibration frequencies compared with aliphatic amines[175]. This fact is in agreement with the low basicity constants of aziridine and its derivatives. A considerable shift in NH frequencies (from 3357 to 3280 cm^{-1}) in liquid compared with gaseous aziridine is explained by intensive NH. . . H-hydrogen bonding[176]. Deformation vibrations of the ring in the 1210 and 857–820 cm^{-1} regions, also noted in the spectra of cyclopropane and ethylene oxide, agree with calculations based on a triangular model consisting of three parts. Examination of the vibrational spectra of substituted aziridine derivatives shows that these frequencies sharply change in intensity and are even displaced when hydrogen atoms in the ring are replaced[177,178].

The dipole moment of aziridine, calculated from the results of measurements of the dielectric constant of a benzene solution, is 1.73 ± 0.1 *D*.[179] The component WKB constants for aziridine are x_{aa} = 0.69 mc/s; x_{bb} = = 2.17 mc/s; x_{cc} = -2.86 mc/s.[180]

The ionisation potential of aziridine, determined by mass spectroscopy, is 9.94 ± 0.15 eV.[181,182]

Stereoisomerism. As with cyclopropane, the planar structure of the aziridine ring leads to the existence of two (*cis*- and *trans*-) geometric isomers for 2,3-disubstituted derivatives. As in the case of cyclopropane, the internally compensated *cis*- form is optically inactive (*meso*-form), but the *trans*-isomer and also the *C*-monosubstituted derivatives may be separated into optical antipodes. The isomeric aziridines differ somewhat in physical constants. Differences between the geometric isomers in their ability to transfer strain between two unsaturated groups are also interesting. *Cis-trans*-isomerisation of 2,3-disubstituted aziridine is catalysed by irradiation or by dry hydrogen chloride[183].

Still another form of stereoisomerism of aziridine derivatives is connected with the presence of a nitrogen atom in the ring. The existence of optical isomers, due to the asymmetry of the tervalent pyramidal nitrogen, in *N*-substituted aziridine had long been suspected[184], but it has only recently been demonstrated definitely by nuclear magnetic resonance, which showed the presence of two triplet resonances of ring protons[185-189].

Electronic structure. Since two hybrid atomic *sp*-orbitals cannot form an angle of less than 90° with each other, the structure of the three-membered rings of cyclopropane, ethylene oxide, and aziridine cannot be explained by Pauling's hypothesis of directed valencies. In this case it must be assumed that the corresponding bonding orbitals are not aligned directly one towards the other, as this hypothesis requires, but are bent to form "banana" bonds (Fig. 2).

To form a ring, hydrocarbon atoms use their hybrid $(2s-2p)\sigma$-orbitals (at an angle of 92°).[190] This type of bonding is intermediate between lateral π-bonding and terminal σ-bonding modes of overlap[191-193]. Less overlap of the bent bonds is compensated by less distortion for the orbitals with less bending. Theoretical calculations show that these orbitals of the ring now become $sp^{4,12}$-orbitals instead of the usual tetrahedral sp^3-orbitals[194,195]. A study

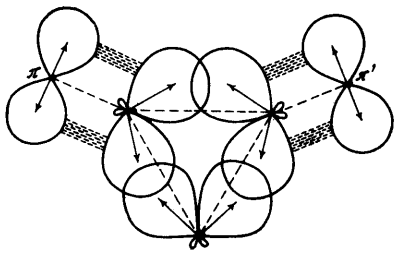


Fig. 2. Electronic structure of the aziridine molecule (plane projection: π and π' atoms, containing *p*-electrons, linked to both carbon atoms of the ring).

of the molecular structure of aziridine shows that the $sp^{4,12}$-bonds formed are shorter than normal single C–C or C–N bonds. The strong *p*-character of the *endo*-orbitals of the ring leads to a strong *s*-character of the external bonds ($sp^{2,28}$-*exo*-bonds). These bonds form an angle of 116° with one another, which exceeds the value of 109.5° for the tetrahedral angle. This strained structure is reflected in all the properties of compounds with a three-membered ring. The most important of these is overlapping (shown dotted on Fig. 2) of the deformed bonds of the ring with the *p*-orbitals of substituents (for example, a double bond or benzene ring) or free electron pairs of halogen atoms, known by the term conjugation.

A quantitative evaluation of conjugation with the aziridine ring is given by a comparison of Hammet's σ constants for ethylenimino-, dimethylamino-, and amino-groups, calculated from chemical shifts of the fluorine (^{19}F) signal in the NMR spectra of the corresponding *m*- and *p*-fluorophenylamines[196].

Ethylenimino-group	σ_{para} = + 0.066	σ_{meta} = −0.290
Dimethylamino-group	+ 0.098	−0.530
Amino-group	+ 0.115	−0.486

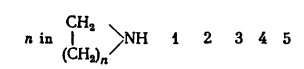
This comparison shows that, although the inductive effect of the three-membered heterocycle is close to the effects of non-cyclic groups, the capacity of its nitrogen atom for conjugation with the benzene ring is greatly reduced. This effect of the inclusion of the nitrogen atom in the three-membered ring is connected with a reduction of overlapping of rehybridised *endo*-orbitals of quadrivalent nitrogen with the π-orbitals of the benzene ring.

The position of aziridine in the cyclic imine series. In the series of cyclic imines the strained three-membered ring of aziridine occupies a special place. Thus, in the infrared spectra, a gradual shift of the upper limit of C–H bond frequencies (from 2919 cm^{-1} for hexamethyleneimine to 3078 cm^{-1} for aziridine) occurs on going from rings with a large number of atoms, in which there is no material strain, to strained three- and four-membered rings[197]. The N–H frequencies change in the reverse order (with increasing strain in the ring the N–H frequencies are reduced) and the basicity of the cyclic imines increases.

Comparison of the ultraviolet absorption intensities of *N*-phenylsubstituted cyclic imines and dimethylaniline in the 250 and 290 mμm§ regions shows that the conjugation energy of the nitrogen atom with the benzene ring increases

§ Linearly related to benzene ring–nitrogen delocalisation interaction.

in higher cyclic imines and dimethylaniline compared with aziridine[198]. In the same way, there is a regular reduction in ionisation potential as the ring increases in size:



and also in the stability of the corresponding complexes with trimethylboron[199].

These facts are most generally and basically reflected in the chemical shifts of the NMR spectra of cyclic imines. Results obtained show that the nitrogen atom of the three-membered ring has the minimum electron density[200]. It would be expected to have the minimum capacity for adding a proton and therefore the minimum basicity.

IV. REACTIONS OF AZIRIDINE AND ITS DERIVATIVES

All the diverse reactions of aziridine and its derivatives may be divided into two approximately equally large groups. The first of these comprises reactions in which only the free electron pair of the nitrogen atom participates and aziridine behaves simply as an amino-compound. The basic feature of reactions of this type is the relative ease with which they are transformed to reactions of the second group, because of the instability of the strained three-membered heterocycle. In this connection they require special precautions in that acids and strong nucleophilic reagents must be absent.

Reactions of the second group, which lead to opening of the three-membered heterocycle, constitute the most interesting feature of the chemistry of aziridine, a unique compound that combines the properties of saturated and unsaturated carbon and nitrogen atoms. Polymerisation¶ is a special ring-opening reaction; this proceeds by the step-wise stringing together of aziridine molecules by a polymer chain with an aziridinium ion at its growing end.

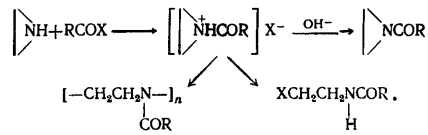
1. Reactions with Retention of the Aziridine Ring

Protonation. Potentiometric titration of aziridine with hydrochloric or perchloric acid in aqueous solutions of neutral salts has been used to determine the thermodynamic protonation constant[201-205]. The titration curves obtained in this way have the form characteristic of weak bases. Comparison of the calculated pK_a value (7.88) for aziridine with the corresponding constants for dimethylamine (10.72) and ammonia (9.25) shows a considerable reduction in the basicity of the nitrogen atom in the three-membered ring (see above)[202].

The temperature dependence of aziridine protonation has been studied and its heat of neutralisation has been determined as $\Delta H^\circ = 11.6$ kcal mole^{-1}.[206] This is lower than the corresponding value for ammonia, which also indicates the low basicity of aziridine.

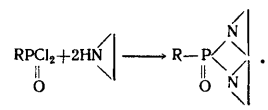
Complex formation. The ability of aziridine to act as a donor of the free electron pair of the nitrogen atom is also reflected in complex formation with transition metal ions[179,206-208]. The type of bond that aziridine forms as a ligand with metal ions and their coordination numbers in these compounds are similar to those of the corresponding ammine complexes. In agreement with the reduced basicity of aziridine, the stability of these compounds is lower than that of the analogous ammine complexes.

Acylation and alkylation. The reaction of aziridine with acid anhydrides or acid chlorides leads to the corresponding *N*-acylaziridines only when the acid formed is immediately removed from the site of reaction with some acid acceptor[209-214]. Otherwise the *N*-acylaziridinium compounds formed undergo further conversion with ring opening and the formation of substituted β-acylethylamides or their polymers:



The *N*-acylaziridines obtained in this way are very unstable compounds[210]. Some of them have interesting biological properties and are used industrially. Special mention should be made of tris-(1-aziridinyl)-*s*-triazine[215-217] (triethylenemelamine or TEM), the first aziridine preparation that was found to have a therapeutic effect in the treatment of cancer and sarcoma[218]. This discovery at once led to numerous syntheses of other aziridine derivatives of triazine and some heterocyclic systems, such as pyrimidine, purine, tetrazine, and others of similar structure.

The reaction between aziridine and phosphorus oxychloride formed the basis of the most numerous class of anti-cancer compounds of aziridine, the aziridinylphosphine oxide derivatives[219,220]. The possibility of varying their properties was discovered by first introducing a substituent (or two substituents) into phosphorus oxychloride and then treating it with aziridine[221]:



An analogous series of aziridinylphosphine sulphides based on the acid chlorides of thiophosphoric and thiophosphonic acids has been obtained[222,223].

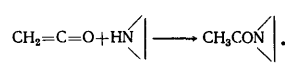
A recently proposed method of acylating aziridines differs in principle from the reactions considered[224]. It starts directly from aziridine and the corresponding free acid and does not require the use of alkaline agents. In this method *NN*-dicyclohexylcarbodiimide is used as a unique dehydrating agent. This method is particularly convenient in the preparation of amino-acyl aziridines; it is also applicable to carboxylic and sulphonic acids.

Since, as a rule, alkylation of amines requires more drastic conditions than acylation, its application to aziridine does not usually give individual monomeric *N*-alkylaziridines; the successful use of alkylation is limited to a few reactions with the most active alkyl halides[215,225]. It is interesting to note that the aziridine ring, stabilised by two alkyl substitutents at the ring carbon atoms[226] or by inclusion in the bicyclic structures of tetramethyleneaziridine[227] and spiro-cyclohexylaziridine[228], can be

¶ Polymerisation of aziridine and the properties of polyaziridine, see Uspekhi Khim., 34, 1249 (1965) [Russ. Chem. Rev., 515 (1965)].

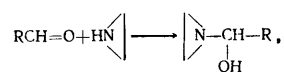
normally alkylated and even gives stable quaternary aziridinium compounds on reaction with an excess of alkyl halides.

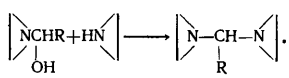
Addition to multiple bonds. While these reactions lead to products considered in the previous section, they proceed much more smoothly, because they are not accompanied by the elimination of any acid or nucleophilic compounds. Thus, the addition of aziridine to the C=C bonds of ketones gives the corresponding 1-acylaziridines in nearly quantitative yield[229,230], for example,



Similarly, aziridine readily adds to the activated double bonds of esters[231-234] and nitriles[235-237] of $\alpha\beta$-unsaturated acids; in the presence of catalytic quantities of metallic sodium, it also adds to the conjugated double bonds of dienes[238,239] and styrenes[238,240]. An analogous reaction of aziridine with quinone formed the basis of a new class of anti-tumour preparations, aziridinoquinones and hydroquinones[241,242].

The addition of aziridine to the carbonyl bonds of aldehydes and ketones at first leads to the corresponding aziridinyl carbinols, which are unstable compounds that tend to undergo polymerisation and cleavage to the starting components[215,243-248]. Aziridinyl carbinols can combine with a second molecule of aziridine, another amine or ammonia to form diaminomethanes[249-253]:

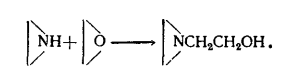




This mechanism is quite general. In the reaction of aziridine with $\alpha\beta$-unsaturated aldehydes and ketones the first stage is addition to the C=C bond[254,255]. A second molecule of aziridine combines with the C=O bond to form diaziridinyl carbinols, which have an appreciable anti-tumour effect[256].

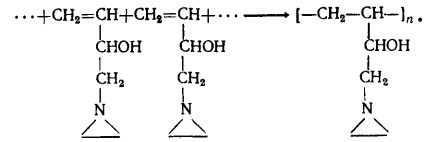
Of the addition reactions of aziridine to C=N bonds, the most widely studied is the reaction with cyanuric acid and its esters[215,257-260], which leads to aziridinylureas. Aziridinylureas, and particularly bisaziridinylureas (based on diisocyanates), are used in the textile industry for the treatment of synthetic and natural fibres and fabrics.

Addition as a result of opening of strained rings. In common with other amines, aziridine opens vigorously the three-membered rings of epoxides, adding the β-hydroxyethyl group formed to its nitrogen atom[261-263]:



Tetramin is a compound of this kind; it is the product of the addition of aziridine to divinyl monoepoxide and is the most powerful cytostat of the aziridine derivatives[264-267].

An interesting anti-cancer preparation has also been synthesised by the radical polymerisation of tetramin[268]:



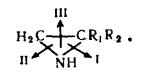
In this polymer, which is less toxic than tetramin, the aziridine rings with their anti-tumour activity are retained.

A similar reaction with thiiran has also been described[269]. Dimerisation of aziridine is an example of this reaction involving aziridine itself[270].

Of the other reactions of aziridine common to other amines, mention should be made of condensation with diborane[271], trimethylboron[199], alkali metals[272], and organometallic compounds[273], and also the formation of halogenoamines by the action of hypohalites[274-277].

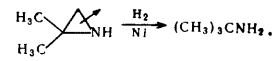
2. Reactions with Opening of the Aziridine Ring

In the general case of asymmetrically substituted aziridines a variety of products is to be expected, corresponding to three possible ways of ring opening:



Clearly, these three ways of ring opening will not always occur. Examination of the nature of the attacking reagent enables definite conclusions to be drawn as to the structure of the products formed. In this respect homolytic reactions (non-polar reagents) are distinguished from heterolytic reactions (polar reagents). All homolytic reactions rigorously follow the route predicted by rupture of the least polar bond, but the reverse does not necessarily hold for heterolytic reactions. Here the nucleophilic properties of the attacking reagent must also be taken into account. Rearrangements of aziridine derivatives that usually proceed with participation of a polar substituent in the three-membered ring form an independent group of ring-opening reactions.

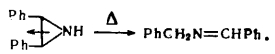
Homolytic opening of the aziridine ring. Hydrogenolysis of the three-membered ring of asymmetrically substituted aziridines proceeds exclusively homolytically at the least polar bond. Thus, the sole product of the hydrogenolysis of 2,2-dimethylaziridine (on a nickel catalyst at 130°) is t-butylamine[278-280].



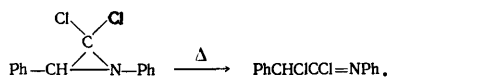
Catalytic hydrogenolysis of the three-membered heterocycle is somewhat more difficult than that of a multiple bond; the C≡N bond in β-(2,2-dimethylaziridinyl)propionitrile, or the C=C bond in *N*-vinylaziridine, can be selectively hydrogenated in the presence of the aziridine ring[235,281].

Another example of the homolytic opening of the three-membered heterocycle is thermal isomerisation of aziridine derivatives. Here the comparatively rare opening

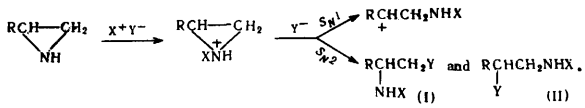
of the ring at the C–C bond corresponds to the requirement of minimum polarity of the bond undergoing homolysis, for example[282,283]:



In 2,2-dichloro-1,3-diphenylaziridine the considerable polarisation of the bonds adjacent to the CCl_2 group results in the opposite group (C–N) in the ring undergoing pyrolytic rupture[284]:

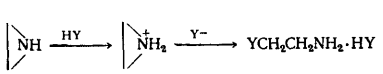


Heterolytic opening of the aziridine ring by various nucleophilic agents. When the three-membered ring in asymmetric aziridines is opened by polar reagent XY, two types of products (I) and (II) may be formed.



One of these may predominate or be formed exclusively, depending on the nature of the reagent and the substituents in the aziridine ring. Thus, in most cases hydrolysis of alkylated aziridines in acid solutions gives type (II) products, corresponding to preferential rupture of the bond at the tertiary carbon atom; ammonolysis with ammonia and amines is not so specific and leads to a mixture of products (I) and (II), and all remaining modes of nucleophilic ring opening mainly lead to products of type (I). In fact, heterolysis of the aziridine ring may proceed by two different mechanisms, depending on the nucleophilic character of the attacking reagent: (1) cationic addition, which includes protonation of the nitrogen atom, rupture of the ring with the formation of a carbonium cation, and addition of the nucleophilic agent (type S_N1 unimolecular mechanism), and (2) rupture as a result of nucleophilic attack by the anion Y^- on the protonated ring (type S_N2 bimolecular mechanism). Because of greater stability of the substituted carbonium cation, the first mechanism leads exclusively to type (II) products, but the second mechanism leads preferentially to the formation of type (I) products, because of the lower electron density of the methylene group and reduced steric hindrance to attack.

The action of acids on aziridine is accompanied by rapid opening of the protonated three-membered ring as a result of nucleophilic attack of the acid anion and addition of this anion to one of the carbon atoms of the ring with the formation of the corresponding β-substituted ethylamine:



With asymmetrically substituted aziridines the reaction leads to two isomeric products; however, in each individual case one or other of the two routes predominates. Thus, the main products of the reaction of 2-methylaziridine with hydrogen halides are β-halogenoisopropylamines[29,30]; with 2-phenylaziridine, α-isomers are preferentially formed[36,39–41].

A study of the kinetics of the opening of aziridine rings by a number of strong nucleophilic agents (see Table 3) has shown that in all the cases examined the reaction is of second order[285–288]; this means that heterolysis of the ring by strong nucleophilic agents proceeds preferentially by the bimolecular S_N2 mechanism. The most probable mechanism of these reactions is nucleophilic attack on the methylene link in the protonated aziridine ring according to the following mechanism:

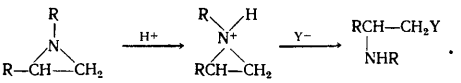
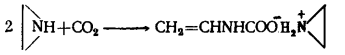


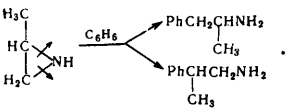
Table 3 also shows that the rate of these reactions is mainly determined by the nucleophilic character of the anion and depends to a lesser degree on substitution in the aziridine ring.

Study of the stereochemistry of the reaction of diastereoisomers of aziridines with acids shows that, as with ring closure, ring opening of three-membered aziridine derivatives is accompanied by inversion of configuration. Thus, as a result of *trans*-opening of the ring, reaction of *cis*- and L(-)-*trans*-2,3-dimethylaziridine with acetic acid gives DL-*threo*-2-acetoxy-3-aminobutane in the first case and L(-)-*erythro*-2-acetoxy-3-aminobutane in the second[289]. In the same way reaction of DL-*erythro*-3-methyl-2-phenylaziridine with hydrogen chloride gives DL-*threo*-2-amino-1-chloro-1-phenylpropane, which gives the starting aziridine when boiled with 50% potassium hydroxide[290].

Other reactions in which the aziridine ring is opened by acid agents include the unique reaction of aziridine with carbon dioxide which leads to derivatives of the unstable *N*-vinylamine[291]:



and also the aminoethylation of hydrocarbons by aziridine and its derivatives which is initiated by Lewis acids[292].



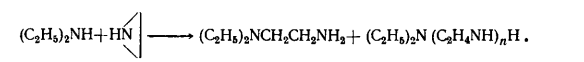
Here too asymmetrically substituted aziridines give two products corresponding to the two mechanisms of ring opening[293,294].

Such important reactions as ring opening by ammonolysis with ammonia and amines and by hydrolysis deserve special examination.

TABLE 3. Kinetics of the opening of aziridine rings by various nucleophilic agents.

Nucleophilic agent	10^6k, mole^{-1} s^{-1} at 25°			
	aziridine	2-methylaziridine	2,2-dimethylaziridine	N-butylaziridine
Cl^-	5.48	3.56	7.56	1
Br^-	28.5	17 8	33	8.3
CNS^-	230	145	243	110
I^-	436	168	297	—
$S_2O_3^-$	5360	5920	4880	3500

Ammonolysis. In the pure form, aziridine and most of its derivatives do not react with ammonia and amines even on prolonged heating[295,296]. In the presence of catalysts such as water, alcohols, and various acid agents (including ammonium chloride and Lewis acids) reaction occurs, leading to the formation of the corresponding ethylenediamine derivatives together with polymeric products of their further conversion[295-300]:



The ratio of ethylenediamine to polymer depends on the reaction conditions and the catalyst used. Considerable amounts of polyamines are formed in reactions catalysed by water[295-297] or ammonium chloride[298,299] at room temperature; lesser amounts are formed at increased temperature and pressure. An ideal catalyst for the preparation of ethylenediamines is aluminium chloride, which forms a stable complex with the reaction product[300].

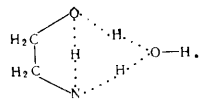
Ammonolysis of asymmetric aziridine is characterised by preferential rupture of the ring at the primary C atom, although in a number of cases considerable quantities of isomeric compounds are also formed. Thus, 2-ethylaziridine forms only one isomer with morpholine, *N*-β-aminobutylmorpholine, but with aniline a small quantity of the second isomer is formed; 2,2-dimethylaziridine forms equal quantities of both isomers with aniline[298].

The ammonolysis of "activated" aziridines without catalysts of any kind is of special interest. For most derivatives of aziridine preliminary protonation or coordination of their nitrogen atoms with a suitable Lewis acid is a condition for nucleophilic attack leading to opening of the aziridine ring, but "activated" aziridines undergo ring opening with great ease even in the absence of acid catalysts[301]. The ammonolysis of *O*-ethyl-*NN*-(1-aziridinyl)-urethane by aniline and a number of its substituted derivatives is an example of such a reaction[296]. Results of the kinetic investigation of this reaction suggest a bimolecular mechanism in which a carbon atom of the three-membered 1-aziridinylurethane ring is replaced by the amino-group of aniline.

Study of the steric course of ammonolysis shows that an overwhelming proportion of product is formed with inversion of configuration, and therefore results from *trans*-opening of the aziridine ring. Thus, DL-*threo*-2,3-aminobutane has been obtained by the ammonolysis of *meso*-2,3-dimethylaziridine with ammonia, and *meso*-2,3-diaminobutane by the reaction of L(-)-*trans*-2,3-dimethylaziridine with ammonia[302]. In the same way D(-)-*erythro*-2-amino-3-ethylaminobutane was obtained from L(-)-*trans*-2,3-dimethylaziridine by the action of ethylamine[303], and *meso*-2,2-bisethylaminobutane was obtained from L(+)-*trans*-*N*-ethyl-2,3-dimethylaziridine. In the latter case, in addition to the optically inactive *meso*-isomer, a small quantity of the optically active product, L(+)-2,3-bisethylaminobutane was observed; this corresponds to the contribution of the S_N1-reaction with frontal attack by the amine on the corresponding carbonium ion.

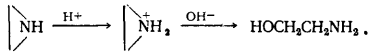
Hydrazinolysis of the aziridine ring, which is analogous to ammonolysis, has also been described[304].

Alcoholysis and hydrolysis. As has already been mentioned above, in aqueous solutions of aziridine a reaction occurs leading to the formation of a unique cyclic chelate hydrate, linked by hydrogen bonds and containing two molecules of water per molecule of aziridine[161], for example,



The addition of alkali suppresses this reaction, and heating of the solution converts the chelate hydrate in to a mixture of ethanolamine and water.

In acid solutions the mechanism of hydrolytic opening of aziridine rings is essentially different. Here the three-membered ring, previously protonated by acid, is opened as a result of nucleophilic attack of the hydroxide ion:



In the absence of catalysts, alcohols do not generally react with aziridine, but in the presence of strong acids or boron trifluoride, acid alcoholysis, similar to hydrolysis, occurs with the formation of the corresponding β-amino-ethers:



Numerous attempts to study the acid hydrolysis of aziridine derivatives under the action of aqueous hydrochloric acid have not given definite results, because of the competition between chloride ions and water molecules for opening of aziridine rings in aqueous hydrochloric acid solutions[306-309]. The ratio of the products obtained (four) largely depends on the reaction conditions.

Hydrolysis uncomplicated by other nucleophilic ring-opening reactions can only be studied for reactions catalysed by acids with very weakly nucleophilic anions (for example perchloric, picric, or fluoroboric acid) incapable of this kind of competition to an appreciable degree. The work of Clapp on the hydrolysis of aziridine, 2-ethylaziridine and 2,2-dimethylaziridine by a solution of perchloric acid is an example of this kind of reaction[286]. Study of the kinetics, activation energies, and entropies and also the composition of the products of these reactions shows (Table 4) that, although with 2,2-dimethylaziridine and 2-ethyl-2-phenylaziridine hydrolysis is mainly a unimolecular process, both uni- and bimolecular mechanisms operate with 2-ethylaziridine, and aziridine is probably hydrolysed exclusively by an S_N2 mechanism[310].

Table 4 shows that 2-ethyl-2-phenylaziridine is hydrolysed at the fastest rate. The rate of the S_N2 reaction at the primary carbon of aziridine is approximately equal to the overall rate of the S_N1 and S_N2 reactions at the secondary carbon of 2-ethylaziridine, but appreciably less

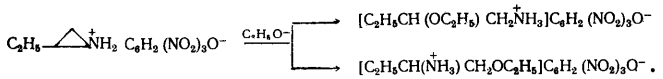
TABLE 4. Hydrolysis of aziridines by aqueous perchloric acid at 21°.

Compound	Composition of hydrolysate		10^7k	ΔH, kcal mole^{-1}	ΔS, e.u.
	S_N1, %	S_N2, %			
Aziridine	—	—	4.61	23.0±0.6	−9.4±1.0
2-Ethylaziridine	22	61	2.64	23.1±0.1	−10.0±0.5
2,2-Dimethylaziridine	80	—	21.0	24.3±0.4	−1.9±1.0
2-Ethyl-2-phenylaziridine	100	—	1400	23.6	1.1

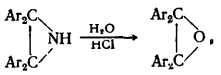
than the rates of the S_N1 reaction at the tertiary carbon of 2,2-dimethyl and 2-ethyl-2-phenylaziridine.

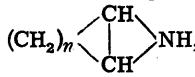
The results of the study of the steric course of hydrolysis of stereoisomeric aziridines are also ambiguous. With *cis*- and L(-)-*trans*-2,3-dimethylaziridine[302] *trans*--opening with inversion of configuration occurs, but hydration of 1,2-dimethyl-3-phenylaziridine (from *dl*-pseudoephedrine) leads to the formation of about equal quantities of *dl*-ephedrine and pseudoephedrine[311]. Finally, study of the hydrolysis of four stereoisomeric forms (*cis*, *d*, *l*, and *dl*) of 2,3-diphenylaziridine shows the predominance of *cis*-addition with retention of configuration at both asymmetric carbon atoms[312]. To a small extent *trans*-addition occurs in all the cases considered; this leads to Walden inversion at the carbon atom undergoing nucleophilic attack. The fact that racemisation does not occur in hydrolysis experiments on pure optical antipodes indicates that the configuration at the second carbon atom remains unchanged, and therefore only the C–N bond of the ring undergoes hydrolytic cleavage. Therefore, all the results mentioned indicate the presence in the hydrolysis reactions in some proportion of both (uni- and bimolecular) components of the ring-opening reaction.

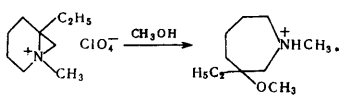
These principles are also valid for the acid alcoholysis of aziridines. Thus, alcoholysis (with methanol or ethanol) of 2,2-dimethylaziridine picrate is accompanied by preferential opening of the ring at the bond with the tertiary carbon atom, but 2-ethylaziridine picrate opens in ethanol to give a mixture of approximately equal quantities of both isomeric β-amino-ethers[235,305].



Mention should be made of an interesting hydrolytic reaction of tetra-arylaziridines, leading to derivatives of another strained three-membered heterocycle, ethylene oxide[313]:



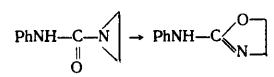
and also of the increased stability to hydrolytic cleavage of aziridine rings included in bicyclic structures of the type , which increases further with the number *n*. Thus, trimethyleneaziridine[314], tetramethyleneaziridine[315], and pentamethyleneaziridine[316] are only hydrolysed by prolonged boiling with perchloric acid; hexamethyleneaziridine is hydrolysed by perchloric acid only at 150°;[317] and octamethyleneaziridine is not hydrolysed at all. Bicyclic aziridine derivatives with a common nitrogen atom are hydrolysed with rupture of the bridge bond and enlargement of the ring[74,318]:



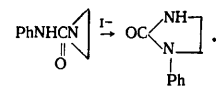
Rearrangement of aziridine derivatives occurs on heating or in the presence of catalysts. The best known catalysts are nucelophilic reagents, aluminium chloride, and acids. As a result of the reaction one C–N bond of the ring opens and a new bond is formed, usually with participation of a polar substituent in the ring.

Some rearrangements of aziridine derivatives are used for the preparation of other nitrogen heterocycles — oxazolines, imidazolines, thiazolines, etc., and also allyl amides and isocyanates.

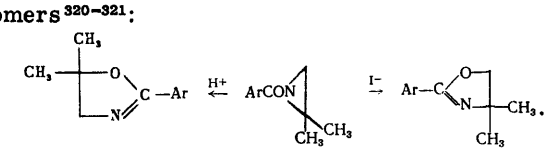
As with the aziridine ring-opening reactions by various reagents described above, the same two main ring-opening mechanisms operate in the rearrangements considered here: (1) intramolecular ionisation following rupture of the protonated ring, and (2) nucleophilic attack of the catalyst on one of the carbon atoms of the three-membered ring. The first type is most characteristic of rearrangements in the presence of acids; the second is catalysed by nucleophilic agents. Thus, in the presence of acids or simply on heating aziridinylureas rearrange by the first mechanism with the formation of corresponding derivatives of 2-oxazoline[319]



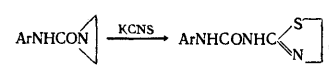
while in the presence of a large excess of a nucleophilic catalyst (for example sodium iodide) the rearrangement proceeds by the second mechanism, leading to 2-imidazoline derivatives[320]:



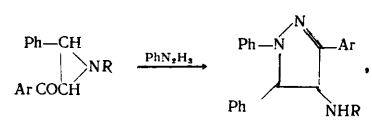
Rearrangement in the presence of a small quantity of a nucleophilic catalyst leads to a mixture of both isomerisation products[320]. Rearrangements of 1-acylaziridines, which lead to 2-oxazolines[320–324], proceed by one of the two mechanisms, depending on the catalyst, and in the case of asymmetric aziridines lead to one of the two 2-oxazoline isomers[320–321]:



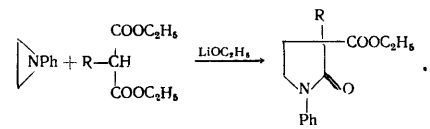
Another type of rearrangement of aziridine derivatives is that in which a molecule of the attacking reagent is included in the new ring. Examples of this mechanism include rearrangements of aziridinylureas in the presence of potassium thiocyanate, leading to 2-thiazolines[325]:



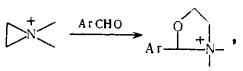
the formation of pyrazolines and pyrazoles by the reaction of β-arylaroylaziridines with phenylhydrazine[43,182,326–328]:



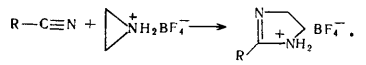
the condensation of 1-phenylaziridine with malonic ester[329]:



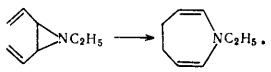
and the reaction of aziridinium salts with aromatic aldehydes[330]:



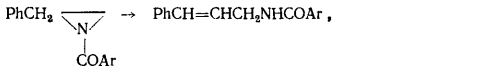
and nitriles[331]:



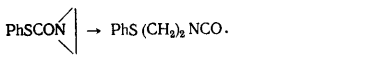
Mention should also be made of an interesting type of valence-tautomeric rearrangements of *cis*-2,3-divinylaziridine derivatives to dihydroazepines[332]:



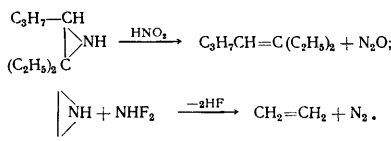
Examples of rearrangements of aziridine derivatives leading to non-cyclic compounds include the stereospecific thermal isomerisation of 1-acyl-2-alkylaziridines to the corresponding allyl amides[323,333-339]:



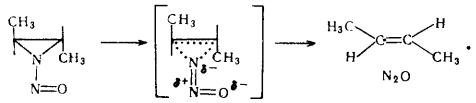
and the rearrangement of *NN*-(1-aziridinyl)-*S*-phenylthiourethane to isocyanate[340]:



Other reactions of aziridine. Deamination. Deamination of aziridine derivatives by the action of nitrosating agents[341-345] or difluoramine[346] is an interesting reaction in which both C–N bonds of the ring are simultaneously ruptured:



A study of this reaction based on the geometric isomers of 2,3-dimethylaziridine has shown that it is highly (> 90%) stereospecific[344]. The rate of deamination of aziridine derivatives is kinetically unimolecular. These facts suggest a mechanism for deamination in which simultaneous opening occurs of both C–N bonds of the ring in the *N*-nitrosoaziridine intermediate:



Reactions with natural compounds. The reaction of aziridine with cellulose, on which industrially important methods of modifying the properties of the latter are based, is of the greatest practical importance[347]. In this reaction the aziridine rings are opened by the free hydroxy-groups of the cellulose and β-aminoethylated cellulose is formed. The presence of basic amino-groups in the cellulose macromolecule does not change its mechanical properties but renders it capable of being dyed like wool with acid dyes and improves its adhesion to various fire-resisting, water-repellant and crease-resisting materials and additives. A somewhat different modification of the properties of cellulose is that produced by treatment with polyfunctional aziridine derivatives, for example, bisethyleneureas. This treatment leads to joining of the thread-like cellulose molecules by bis-(β-ureylene)alkoxy--bridges and is used industrially for the dry spinning of cellulose fibre.

The reaction of aziridine and its acyl derivatives with proteins, which is of biological interest, should also be mentioned[348]. The reactivity of proteins towards aziridine derivatives is due to the presence of acid groups in the protein molecules; the reaction probably proceeds by a mechanism in which various functional groups of the protein molecule are alkylated by protonated aziridine rings.

V. IDENTIFICATION AND QUANTITATIVE DETERMINATION OF AZIRIDINE DERIVATIVES

Numerous complex-formation[1,3,4,215] and salt-formation[6,12,21,349,350] reactions, leading to intensely coloured or poorly soluble compounds, have been proposed for the qualitative identification of aziridines. A basic disadvantage of these methods is that the reactions are common to the majority of amino-compounds, and in the presence of the latter they are of little use or entirely inapplicable. Methods based on opening of the three--membered ring, for example, the colour reaction with thiourea[351], and spectroscopy are more specific for aziridine.

The spectroscopic determination of aziridine derivatives is based on the presence in their vibrational spectra of high frequency (above 3000 cm^{-1}) C–H vibrations, due to bond strain in the three-membered rings[169-174,177,178]. The only limitation of this method is the requirement that multiple bonds and aromatic rings, which absorb in the same region, should be absent. This method is most convenient for detecting aziridine in mixtures with other aliphatic amines or in its polymerisation products.

Acidimetric titration and colorimetric methods have been described for the quantitative determination of aziridine. Recently a number of methods based on ring opening have been proposed. Obviously, these are the most specific methods.

Direct acidimetric titration is the least successful method for the quantitative determination of aziridine, because of the considerable number of side-reactions; these include polymerisation, hydrolysis, and nucleophilic ring opening by acids[20,199,202-204]. Colorimetric methods based on double decomposition with the potassium salt of 1,2-naphthoquinone-4-sulphonic acid are also not specific for aziridine[351,352]. Extraction with chloroform of the dye formed in aqueous solution has been proposed to increase the sensitivity of this method.

As with qualitative identification, the most specific and reliable quantitative methods are based on reactions in which the aziridine ring is opened by various nucleophilic agents. These methods include the extremely sensitive colorimetric determination of the product of the reaction of aziridine with γ(-4-nitrobenzyl)pyridine, proposed for the determination of very small quantities of aziridine in water and in air[353]. Reactions of this group suffer from one general disadvantage: they have a very low velocity,

which is characteristic of non-ionic reactions. Because of this the methods are generally used indirectly. Attempts to improve them involve a search for effective nucleophilic agents that would give the maximum reduction in the time of reaction with aziridine.

The most widely used method of this group, the thiosulphate method[354-357] and its latest modification in which thiocyanate is used[358], are based on the determination of alkali formed as a result of rupture of the aziridine ring by $S_2O_3^{2-}$ or CNS^- ions in an acidified solution. The second method of this group is a combination of the acidimetric method and ring opening by acid. The sample containing aziridine is boiled with an excess of acid, which is then determined by back titration[215]. The latest modification of this method comprises direct titration of aziridine derivatives with a solution of perchloric acid in acetic acid or dioxan in the presence of an excess of quaternary ammonium iodide[359]. The method is based on the rapid opening of the aziridine ring by hydriodic acid immediately it is formed (by displacement with perchloric acid from the quaternary ammonium salt). Verification of the results obtained by means of the thiocyanate method shows that direct titration is of sufficiently high accuracy.

VI. ACTION ON LIVING ORGANISMS

Aziridine and its derivatives surpass all known chemical compounds in their biological activity and in their many-sided action on living organisms (toxicity, mutagenesis, cytostatic properties). Since their action is very similar to that of penetrating radiation, they have been called radiomimetic compounds. The biological effect of aziridine derivatives is widely used in various fields of science and technology and therefore deserves special consideration.

Toxicity. Aziridine is extremely poisonous[360-366]. A single oral dose of 15 mg per kg of body weight is lethal. Death usually occurs in 1 to 24 hours as a result of respiratory paralysis[361]. It has been noted that in aziridine poisoning death can occur even 10 days after a symptomless period as a result of a combination of pulmonary and renal lesions with leukopenia[365-367].

The danger of poisoning by aziridine vapour is aggravated by the great similarity of its odour to that of ammonia, and also by the absence of symptoms during exposure[368]. The first signs of aziridine poisoning only appear after 2–8 h in the form of nausea and vomiting, and inflammation and oedema of the mucous membrane of the mouth, throat, and eyes[368,369]. A single exposure for 30–60 minutes to a concentration of 250 parts per million in air is dangerous to life[369]. Hydration, antihistamines, steroids, antibiotics, expectorants, and enzyme therapy are used in the treatment of aziridine poisoning[370]. It has been noted that, when suitable safety measures are taken, work with aziridine in the laboratory can be carried on for a long time without danger to health[368]. An ordinary gas mask provides individual protection against aziridine vapour.

Aziridine is readily absorbed by the skin and produces blisters and rashes that are difficult to heal[371]. Prolonged action of aziridine on the unprotected skin produces symptoms of systemic poisoning.

Mutagenic activity. Aziridine and its derivatives are the most powerful chemical mutagens. The mechanism of chemical mutagenesis by aziridine derivatives involves attack by the aziridine molecule on the pyrimidine precursors of deoxyribonucleic acid[372,373]. Compared with irradiation by ultraviolet light and X-rays, aziridine derivatives produce the maximum number of mutations per thousand surviving spores[374]. The combined effect of irradiation and the action of aziridine derivatives has a much greater mutagenic effect than each of these separately[375]. Aziridine and its derivatives are widely used in agricultural and industrial selection to increase the productivity of agricultural crops and for the selection and growth of strains of antibiotic producers.

Cytostatic activity. The discovery that triethylenemelamine, phosphoraziridates, and certain other aziridine derivatives can prevent the reproduction (mitosis) of plant and animal cells has prompted an extensive search for similar compounds amongst other aziridine derivatives. The exceptional interest in these compounds is due to the wide use of their cytostatic activity in the treatment of various forms of neoplastic disease, such as cancer, sarcoma, and malignant blood diseases.

VII. MAIN TECHNICAL USES

It has been noted above that the unique chemical, physicochemical, and biological properties of aziridine find considerable use in various branches of science and technology. We shall consider some of them briefly.

Judging from the number of publications, aziridine and its derivatives are most widely used in the textile and paper industries. Aziridines, which are fairly powerful alkylating agents (as a result of the opening of the three-membered ring), readily react with most compounds that form natural and synthetic fibres and paper; since amino-groups are introduced into the compounds, their properties are modified. Cellulose, acetylcellulose, viscose, and other cotton fibres acquire the capacity to take acid dyes in the same way as wool[376]. This also holds for most synthetic fibres; these include polyacrylic[377], vinylidene cyanide[378] and polyvinyl-alcohol[379] fibres. Polyalkene fibres, which have the best mechanical properties but contain no reactive groups in the molecule, must be partially oxidised[380] or subjected to γ-irradiation[381] before treatment with aziridine[381]. Treatment of synthetic and natural fibres with aziridine derivatives greatly increases their water-resistance[382,383]. Wool and other protein fibres acquire resistance to laundering[384], do not shrink, and do not break off after they have been treated with bisalkyleneureas, or other aziridine derivatives containing at least two aziridine rings in the molecule (because of the formation of cross-linking bonds in the keratin). Synthetic fibres and fabrics made from them do not accumulate electric charges when they have been treated with aqueous solutions of polyaziridine and some aziridine derivatives[385].

The addition of 0.3–0.6% of aziridine or polyaziridine in the process of paper making accelerates the coagulation of the paper mass and increases the productivity of the paper-making machines[386]; it also permits the use of raw material with low drainage properties, activates the cellulose fibres, increasing their adhesion to fillers[387], and increases (by about 60%) the mechanical strength of the paper under wet conditions and also its ability to fix dyes and pigments[388].

Some aziridine and polyaziridine derivatives are used in photography to strengthen the emulsion gelatin[389] and to fix a colour image on it[390], to sensitise photographic materials[391], and as developers of colour photographs[392].

Some cytostatically active aziridine derivatives find a very interesting use in the control of mosquitos, flies, and other blood-sucking insects[393,394]. The active compound (usually triaziridinylphosphine oxide or sulphide) is added in the proportion of 0.5% to the insect food (a corn bait); when the individuals that have eaten it are distributed amongst the natural populations, the latter are exterminated in about three generations[395].

The use of aziridine and a number of its derivatives in rocket engineering should also be mentioned. The high heat of formation, associated with the closure of the three-membered ring, the tendency to ignite spontaneously with most oxidising agents, and also the low melting point and relatively high density make aziridine[396,397] and 1-aminoaziridine[398] attractive combustible components of highly effective fuels for liquid rocket motors. Aziridine derivatives containing several aziridine groups in the molecule (for example, triaziridinylphosphine oxide and sulphide and triethylenemelamine) are used for hardening the composition of a mixed solid rocket fuel based on synthetic polymers containing terminal acid groups[399,400]. The fuels thus obtained have better physicomechanical characteristics compared with similar compositions hardened by epoxides[399].

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Institute of Petrochemical Synthesis,
USSR Academy of Sciences

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ADVANCES IN THE CHEMISTRY OF IMIDAZOLE

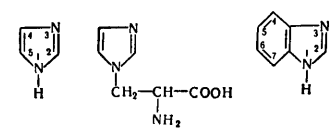
A. F. Pozharskii, A. D. Garnovskii, and A. M. Simonov

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I. INTRODUCTION

In recent times progress in the chemistry of certain classes of organic compounds has been closely related to advances in molecular biology. A striking example of this is the chemistry of imidazole (I) and its derivatives. Numerous natural compounds (enzymes, nucleic acids, alkaloids, etc.), which include in their composition the imidazole group, have been known for a long time. A new antibiotic, azomycin (2-nitroimidazole)[1-3] and a new amino-acid, isohistidine (II)[4], are further additions to this series of compounds.



(I) (II) (III)

At the beginning of the 1950's it was shown that purines are not the only condensed imidazole system which plays a role in vital processes. It was found that the structure of vitamin B_{12} incorporates a 5,6-dimethylbenzimidazole fragment[5]. This finding greatly stimulated the development of the chemistry of imidazoles condensed with aromatic rings, and in the first place of benzimidazole (III).

The advances in the elucidation of the role of the imidazole group of enzymes and nucleic acids in the chemistry of the most important living processes has been particularly remarkable[6,7]. All these discoveries naturally enough also required a considerable effort in research on the chemistry of imidazole. In terms of the volume and importance of the studies on imidazole and its derivatives the last decade may be compared to the entire preceding period. In this connection it is necessary to sum up all this work, particularly as the latest reviews on the chemistry of imidazole[8] and benzimidazole[9] cover the literature only up to 1951. In a number of monographs on the chemistry of heterocyclic compounds[10-15] the chemistry of imidazole is dealt with in a very brief and incomplete manner.

The present review covers the literature on the chemistry of imidazole and the most important imidazole derivatives condensed with aromatic rings from 1952 to 1963