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The Reactions of Azines on Treatment with 1,3-Bifunctional Nucleophiles

V.N.Charushin and O.N.Chupakhin

The literature data on the *o*-cyclisation reactions of azines with 1,3-bifunctional nucleophiles, which make it possible to annelate furan, pyrrole, imidazole, and other five-membered rings to an aromatic aza-ring are surveyed and described systematically. The cyclisation reactions leading to *m*-linked cyclic adducts or products of the transformation of azines *via* the intermediate formation of cyclic *m*- and *p*-adducts are also examined.
The bibliography includes 152 references.

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I. INTRODUCTION

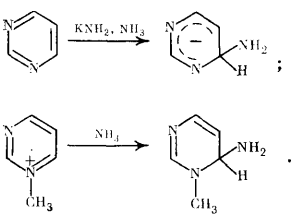
The reactions of azines with simple nucleophiles have been considered in fair detail in a whole series of books, monographs, and reviews.[1-12] Rules have been established for the nucleophilic substitution in the series of azines which make it possible to predict the rates of these reactions as a function of the number of aza-groups and their positions in the ring, the influence of other substituents, benzoannelation, the nature of the leaving group, and other factors.[1-3, 10,11] The characteristics of the nucleophilic substitution of hydrogen[7-9] as well as the wide variety of transformdtions of azines and azinium salts under the influence of ammonia, potassium amide, hydrazine, and other simple nucleophiles have been investigated.[4-6]

An increasing number of communications concerning the reactions of azines with 1,3-bifunctional nucleophiles have been published in recent years; as a rule, these reactions are more complex, more varied, and sometimes also unexpected, The present review is devoted to the rules governing these reactions and their characteristic features. Before discussing the reactions of azines with 1,3-dinucleophiles, we shall consider briefly certain reactions of azines with simple nucleophiles.

II. CHARACTERISTIC FEATURES OF REACTIONS OF AZINES WITH SIMPLE NUCLEOPHILES

1. σ-Adducts of Azines

It is nowadays considered as generally recognised that the first stage in many reactions of azines with nucleophiles is the formation of σ-adducts. The σ-adducts are understood to be both anionic σ-complexes of azines, which are close analogues of Meisenheimer complexes, and uncharged dihydrocompounds, which are formed as a result of the addition of neutral nucleophiles to an uncharged aromatic aza-ring or in reactions of azinium cations with anionic and neutral reagents.[13-42]. The anionic σ-complex of pyrimidine with potassium amide[33] and the neutral amino-adduct formed on dissolving an *N*-methylpyrimidinium salt in liquid ammonia[31] can serve as examples.



The development and application of the ^1H and ^{13}C NMR spectroscopic methods made it possible to accumulate during the last 10–15 years extensive factual data on the direct detection of anionic σ-complexes and neutral σ-adducts for the majority of azines (pyridine,[18-20] quinoline and isoquinoline,[18,21,22] acridine,[23,24] pyrimidine,[17,25-32] other diazines and benzodiazines,[17,18,33-36] triazines,[15,16] pteridine,[37-39] naphthyridines,[40,41] *s*-tetrazine,[42] as well as a series of aromatic polynitro-compounds related to the above substances in terms of a series of chemical properties[43-46]). For example, the series of *N*-adducts attained in the reactions of azines with liquid ammonia or with potassium amide in liquid ammonia is fairly varied and representative (Table 1). The *O*-adducts formed in the reactions involving the covalent hydration of *N*-alkylazinium cations[13] and the products of the *C*-addition of the cyanide anion to acylazinium salts (Reissert's compounds)[14] have also been fairly thoroughly investigated.

The data presented in Table 1 make it possible to compare the spectroscopic characteristics of the anionic and neutral amino-adducts of azines and also to trace their variation as a function of the position of the aza-group relative to the sp^3-carbon atom. A characteristic feature of the ^1H NMR spectra of both anionic and neutral σ-adducts is the signal in the range 3.7–5.5 p.p.m. (Table 1), i.e. the signal displaced upfield by 3.5–5.0 p.p.m. compared with the signals of the initial substrates, which has been assigned to the proton at the tetragonal carbon atom. In the anionic σ-complexes of pyridine, quinoline, and isoquinoline the proton at the sp^3-carbon atom (H_α) absorbs in weaker fields, while that at the neighbouring carbon atom ($H\beta$) absorbs in stronger fields compared with the corresponding signals of the uncharged *N*-methyl analogues (Table 1). It is also seen from the examples presented that the constants for the spin–spin interaction (CSSI) between the corresponding protons of the

heterocycle are reduced by ~1 Hz on passing from neutral σ-adducts to the anionic adducts, but overall their ^{1}H NMR spectra are extremely similar.

Table 1. ^{1}H NMR spectra of the anionic and neutral σ-adducts of azines in liquid ammonia.

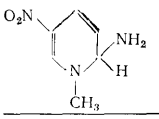
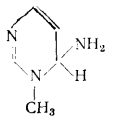
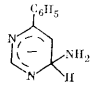
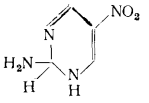
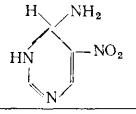
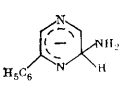
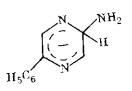
Adduct	δ, p.p.m.		CSSI, Hz	References
	proton at tetragonal carbon atom	protons of heterocycle		
	H(6):5.06	H(2):8.49; H(4):6.85; H(5):5.38	$J_{4,5}=10$; $J_{5,6}=4$	[18]
	H(6):4.57	H(2):6.94; H(4):6.27; H(5):4.91	$J_{4,5}=7$; $J_{5,6}=4.5$	[31]
	H(4):4.63	H(2):7.07; H(5):4.32	$J_{2,4}=J_{2,6}=0.5$; $J_{2,5}=1.5$; $J_{4,5}=3.5$; $J_{5,6}=6.5$	[33]
	H(2):4.26	H(5):5.43; H(6)*	$J_{5,6}=4.5$	[26]
	H(6):4.71	H(2):7.20; H(5):4.92	$J_{5,3}=4.0$	[26]
	H(2):5.33	H(4,6):8.18	$J_{2,4}=J_{2,6}=1.3$	[32]
	H(4):5.45	H(2):7.57; H(2):8.22	—	[32]
	H(4):3.73	H(3):6.55; H(5):4.27; H(6):6.70	$J_{3,4}=3.5$; $J_{3,5}=3.0$; $J_{3,6}=0.5$; $J_{4,5}=4.5$; $J_{5,6}=7.0$	[33]
	H(2):4.22	H(3):5.61; H(5):5.82; H(6):6.60	$J_{2,3}=3.0$; $J_{3,6}=0.5$; $J_{5,6}=3.0$	[33]
	H(6):4.33	H(3)*; H(5):5.70	$J_{5,6}=2.5$	[17]
	H(5):4.16	H(3)*; H(6):5.93	$J_{5,6}=2.5$	[17]

Table 1 (contd.).

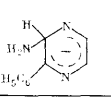
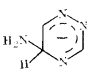
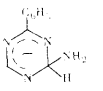
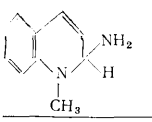
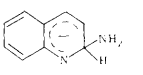
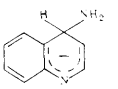
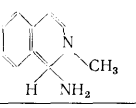
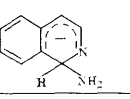
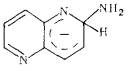
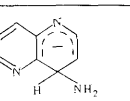
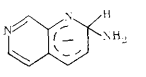
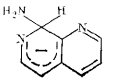
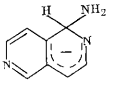
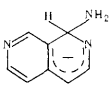
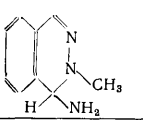
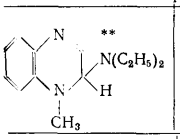
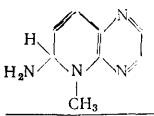
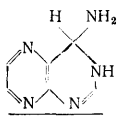
Adduct	δ, p.p.m.		CSSI, Hz	References
	proton at tetragonal carbon atom	protons of heterocycle		
	H(3):5.35	H(5):6.76; H(6):6.03	$J_{5,6}=2.5$	[17]
	H(5):4.15	H(3):7.40; H(6):6.65	—	[16]
	H(2):5.33	H(6):7.31	—	[15]
	H(2):4.79	H(3):5.86; H(4)*	$J_{2,3}=5.5$; $J_{3,4}=9.8$	[18]
	H(2):5.10	H(3):5.20; H(4)*	$J_{2,3}=4.3$; $J_{3,4}=9.0$	[21]
	H(4):4.70	H(2)* H(3):4.20	$J_{2,3}=6.5$; $J_{3,4}=4.3$	[21]
	H(1):5.15	H(3):6.37; H(4):5.45	$J_{1,3}=1.2$; $J_{3,4}=7.0$	[18]
	H(1):5.32	H(3)* H(4):4.87	$J_{3,4}=5.5$	[21]
	H(2):4.97	H(3):5.38; H(4)*	—	[40]
	H(4):4.59	H(2)*; H(3):4.18	—	[40]
	H(2):5.02	H(3):5.31; H(4):6.28	—	[40]
	H(8):5.13	H(5):4.52; H(6):7.01	—	[40]
	H(1):5.03	H(3):7.09; H(4):4.70	—	[41]
	H(1):5.03	H(3):7.16; H(4):4.59	—	[41]
	H(1):5.13	H(4):7.55	—	[18]

Table 1 (contd.).

Adduct	δ, p.p.m.		CSSI, Hz	References
	proton at tetragonal carbon atom	protons of heterocycle		
	H(2):4.70***	H(3):7.41	$J_{2,3} = 3.5$	[36]
	H(6):5.18	H(7):6.40; H(8):6.73	$J_{6,7} = 4.5$; $J_{7,8} = 10$	[18]
	H(4):5.52	H(2):7.64	—	[37]

*The signal of this proton is overlapped by the multiplet due to the aromatic protons in the range 7.0–7.7 e.p.m.
**The adduct with ammonia has not been described.
***In deuterochloroform.

The formation of σ-adducts as the primary σ-linked products of the interaction is characteristic of various types of reactions of azines with simple nucleophiles: nucleophilic substitution of hydrogen,[7,8,23,24,32,40] substitutions via the $S_N(ANRORC)$† mechanism,[6] reactions leading to transformations of the heterocyclic systems,[4,5] and other reactions.

2. The Polydentate Nature of Azines

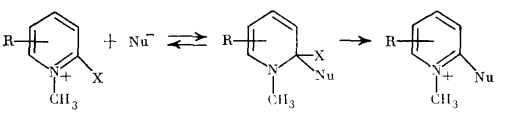
The outcome of the reactions of azines with nucleophiles and in general with 1,3-dinucleophiles in particular is in many respects determined by the properties of the σ-adducts, their stability, and the subsequent reactions which they undergo. The situation is complicated by the fact that many azines are polydentate and form two or even several types of σ-adducts with simple nucleophiles with respect to different positions in the heterocycle (Table 1). On the basis of the chemical shifts of the protons and the values of the CSSI in the ^{1}H NMR spectra of the σ-adducts, it is possible to determine accurately the reaction centre, i.e. the carbon atom which forms a covalent bond with the nucleophile. Since the values of CSSI characteristic of addition to a particular position in the azine ring change insignificantly as the substituent at the sp^3-carbon atom is varied, the data in Table 1 for the amino-adducts can be used to analyse the composition of the reaction mixtures of azines with other nucleophiles.

In cases of competitive addition of a nucleophile to two positions in the heterocycle an important factor is how the reaction is controlled under the given conditions—kinetically or thermodynamically. As a rule, the *o*-position relative to the heteroatom, i.e. the C(2) carbon atom, is more vulnerable to nucleophilic attack, while under the conditions of thermodynamic control more stable σ-adducts involving the C(4) position are formed. The formation of C(2)- and C(4)-linked σ-adducts in the reactions of pyridinium[19,20] and quinolinium[22] salts with *C*-nucleophiles as well as the formation of 2- and 4-amino-adducts of 1,5-naphthyridine[40] and 5-nitropyrimidine[32] in reactions with liquid ammonia (Table 1) may be quoted as examples of compounds obtained in recent years.

†Addition of the nucleophile, ring opening, and ring closure.

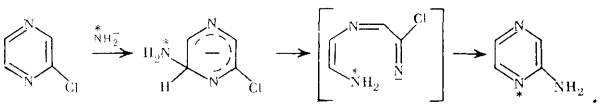
3. Chemical Reactions of the σ-Adducts

The stability of the σ-adducts depends both on the conditions of their formation and on the structure of the azines and varies within wide limits. The pathways whereby they can be stabilised are also varied. One of these pathways is the aromatisation of the σ-adducts as a result of the elimination of the substituent X, which represents overall aromatic nucleophilic substitution (S_NAE):



If X is a group which can be readily eliminated, then aromatisation usually proceeds so rapidly that the σ-adducts cannot be detected. This is true both of the series of azines and of the anionic σ-complexes of aromatic polynitrocompounds.[43–46] When X = H, the σ-adducts formed are relatively more stable and nucleophilic substitution of hydrogen is then known to require an oxidant.[7,8] The knowledge of the conditions governing the formation of the σ-adducts and the choice of a suitable oxidant make it possible to achieve successfully reactions involving the nucleophilic substitution of hydrogen in the series of azines. A number of recently published studies on the low-temperature oxidation of the σ-adducts of azines with ammonia demonstrate how attractive and promising is this direct amination method.[32,47,48]

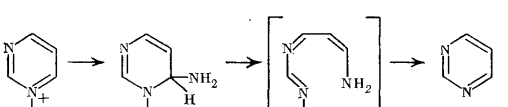
Another possible reaction pathway for the azine σ-adducts involves the opening of the heterocycle with subsequent formation of a new cyclic system; these are the so-called recyclisation reactions. The studies by Dutch chemists, namely van der Plas and co-workers,[4–6] have played a major role in the study of the recyclisation reactions of azines and other heterocyclic systems. These investigations showed that many outwardly simple nucleophilic substitution reactions of azines in reality proceed via the $S_N(ANRORC)$ mechanism.[4–6] The substitution of chlorine in 2-chloropyrazine on treatment with potassium amide in liquid ammonia can serve as an example of a reaction which takes place to the extent of 100% via the $S_N(ANRORC)$ mechanism:[49]



(I) (II)

Here and henceforth $\overset{*}{N}$ represents nitrogen enriched in the ^{15}N isotope.

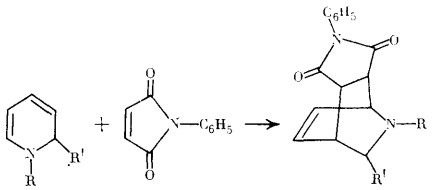
The observation of the demethylation of *N*-methylpyrimidinium salts in liquid ammonia[31] led to the concept of the so-called degenerate transformations of heterocycles,[5] i.e. reactions in which the initial heterocyclic system is restored as a result of recyclisation:



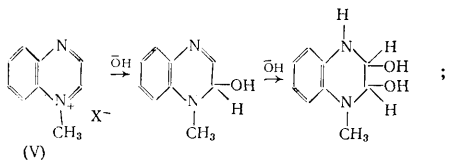
(III) (IV)

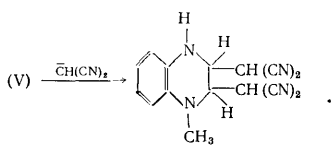
If the formation of the σ-adducts can be detected by NMR, then in the majority of studies on the recyclisation of azines[4-6] this is regarded as a stage preceding the opening of the heterocycle. The opening of the ring in the σ-adducts (I) and (III), formed in these and similar recyclisation reactions, is usually postulated on the basis of the results of experiments using ^{15}N isotope labels. It has been suggested[5] that the opening of the ring in the dihydropyrimidines (III) proceeds most probably as a thermally allowed $[\pi 4_S + \sigma 2_S]$-electrocyclic disrotary reaction. However, it must be emphasised that direct evidence for the involvement of the non-cyclic intermediates of type (II) and (IV) in the above reactions of the heterocycles has not so far been obtained.

As regards the σ-adducts of azines, they have long ceased to be merely hypothetical intermediates. Studies whose authors were enabled by the knowledge of the structure and conditions of the formation of the σ-adducts to employ them as starting materials for further syntheses are being published at an increasing frequency. Examples of such an approach have been quoted in a review[50] devoted to advances in the chemistry of dihydropyridines. The addition of nucleophiles to pyridines and pyridinium salts is regarded in this review as one of the methods of synthesis of 1,2- and 1,4-dihydropyridines. The σ-adducts formed can be used further as the starting materials in [4 + 2]- and [2 + 2]-cycloadditions, *N*-alkylation and *N*-acylation reactions, and other transformations:[50]



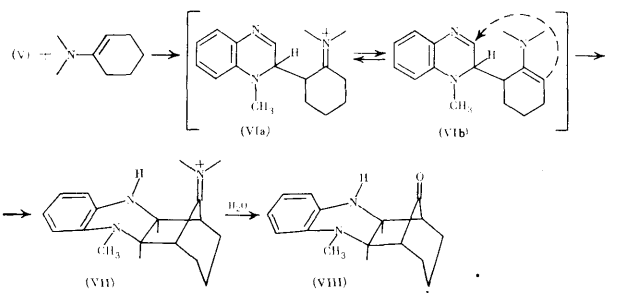
Yet another reaction pathway involving the σ-adducts is the secondary addition of a nucleophile with formation of bis-adducts. The presence of electron-accepting groups in the aromatic ring creates in many instances a structural situation where the remaining double bond (or bonds) of the σ-adduct is activated for secondary nucleophilic attack. Among azines, the tendency towards the formation of bis-adducts is most characteristic of compounds containing the pyrazine ring: pyrazines,[51] quinozalines,[18,35,51,52] pyrido[2,3-*b*]pyrazines,[53-55] and pteridines.[37-39] Thus the quinoxalinium salts (V) combine twice with both heteroanions[35] and carbanions:[52]





The bis-adducts formed in the reactions of pyrazines with heteroatomic nucleophiles usually exist in solution in equilibrium with the monoadducts, but are detected in the ^1H NMR spectra from the characteristic absorption of the H(2) and H(3) protons in the range 3.8–5.4 p.p.m. and the low values of the vicinal CSSI (Table 2). An important factor increasing the stability of the bis-adduct is the presence of an aromatic ring or an aromatic aza-ring condensed with the tetrahydropyrazine ring. It is not fortuitous that all the examples presented in Table 2 refer to bicyclic 1,4-diazines and the presence of a positive charge in the pyrazine ring in the initial substrates is not an obligatory condition for the formation of the bis-adducts (Table 2). Monocyclic pyrazines react with heteroatomic nucleophiles to form monoadducts (Table 1), but the more stable products of the addition of two *C*-nucleophile residues to pyrazines have been obtained on a preparative scale.[51] Bis-adducts with *C*-nucleophiles have also been obtained in the reactions of quinoxalinium[52] and pyrido[2,3-*b*]pyrazinium[53-55] cations.

It is readily seen that reactions involving diaddition to 1,4-diazines create conditions also for the formation of cyclic adducts when the reactant contains two nucleophilic centres. Thus, for example, the enamines derived from cyclic ketones, which exhibit the properties of 1,3-dicarbanionic reagents, react with quinoxalinium salts to form the cyclic adducts (VII) and (VIII):[59,60]



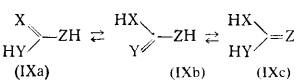
It has been suggested that the cyclisation takes place stepwise via a stage involving the formation of the σ-adduct (VI). Depending on the nature of the reactants, the reactions of azines with dinucleophiles can also proceed via other mechanisms (see below).

Bifunctional nucleophiles are usually classified in terms of the atoms which function as the nucleophilic centres (C,C-; C,N-; C,O-; N,N-; etc.) and also of their relative positions (1,2-, 1,3-, and 1,4-dinucleophiles). Analysis of the literature data shows that the 1,3-dinucleophiles are used most frequently because their cyclisations with azines lead to the formation of unstrained five- and six-membered rings.

In the present review an attempt has been made to summarise the data published during the last ten years on the cyclisations of azines with 1,3-dinucleophiles which make it possible to annelate to an aromatic aza-ring various carbocyclic and heterocyclic fragments; in addition, the cyclisation leading to *m*- and *p*-linked bicyclic adducts as well as the products of the transformation of azines under the influence of 1,3-dinucleophiles are examined.

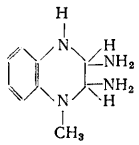
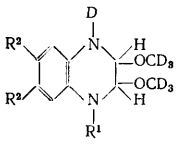
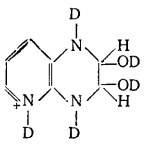
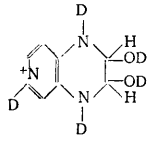
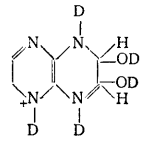
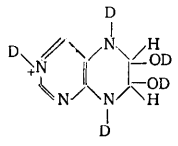
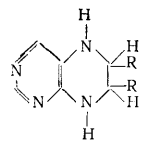
III. 1,3-BIFUNCTIONAL NUCLEOPHILES

Ketones,[61,62] ketone enamines,[59,60,63,64] β-diketones and their derivatives,[65-71] ureas, thioureas, and guanidines,[72-74] amidines,[75,76] α-substituted acetamidines[76-79] and iminoesters,[80-82] CH-active acetamides,[70,74,83] and other reagents described by formulae (IX, a–c) have been used as 1,3-dinucleophiles in reactions with azines;



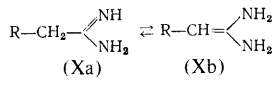
where X, Y, and Z are C-, N, O-, or S-substituted residues.

Table 2. ^{1}H NMR spectra of the diadducts of pyrazines with heteroatomic nucleophiles (δ = chemical shifts of the signals due to the protons of the tetrahydropyrazine ring).

Adduct	Solvent	δ, p.p.m.	CSSI, Hz	References
	NH_3 (liq.)	3.96; 4.07	$J_{2,3}=2.5$	[18]
 $R^1=CH_3$, $R^2=H$	CD_3OD	4.62 (2H)	—	[35]
$R^1=C_2H_5$, $R^2=H$	CD_3OD	4.71 (2H)	—	[36]
$R^1=CH_3$, $R^2=$ benzo-	CD_3OD	4.76 (2H)	—	[36]
	D_2O	5.17; 5.28	$J_{2,3}=3.0$	[56]
	D_2O	5.07; 5.15	$J_{2,3}=3.0$	[56]
	D_2O	5.27 (2H)	—	[56]
	D_2O	5.20; 5.35	$J_{6,7}=3.4$	[57]
 $R=NH_2$	NH_3 (liq.)	4.14; 4.20	—	[37]
$R=NHCH_3$	DMSO-d_6	3.83; 3.95	—	[58]

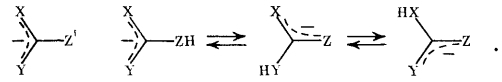
1. Tautomerism and Ambident Nature

A common structural feature of the 1,3-dinucleophiles considered is the presence of a double bond conjugated with a heteroatom having an unshared electron pair. A characteristic of such three-centre unsaturated systems is their capacity for prototropic tautomerism. The keto–enol,[84] thione–thiol, imino–enamine, lactim–lactam, and other types of triad tautomerism are known.[85] Certain types of tautomeric transformations, in particular, the existence of acetamidines (Xa) in the form of keten *N,N*-acetals (Xb), have been confirmed experimentally quite recently:[77,78]



(Xa) (Xb)

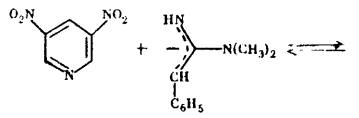
Many reactions of azines with 1,3-dinucleophiles take place only in the presence of bases. Tautomeric systems which exist solely in two forms give rise to the ambident anions (XI) on treatment with bases; in the case of three tautomeric forms, there is a possibility of the existence of the tautomeric anions (XII, a–c):

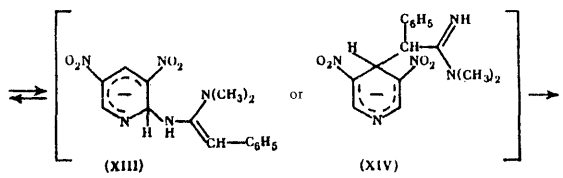


(XI) (XIIa) (XIIb) (XIIc)

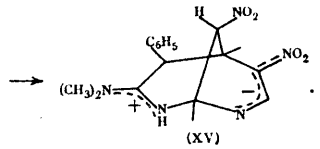
In the anions (XI) and (XII, a–c) the negative charge is distributed between the atoms of the triad and each of the terminal atoms can participate in the formation of a bond with the electrophile. Classical examples of 1,3-ambident anions are, for example, the enolates of β-diketones which form both *C*- and *O*-alkylation products.[86,87]

Thus the 1,3-ambident nature of nucleophiles combined with the behaviour of azines as polydentate species permits the formation of several types of mono-adducts which differ both in the site of the addition of the nucleophile to the azine nucleus and in the terminal atoms of the 1,3-anionic system involved in the formation of the bond. 1,3-Ambident systems are capable of reacting not only via each of its nucleophilic centres separately but also simultaneously via both such centres, which is the reason for the possibility of the formation of rings. Thus the reaction of 3,5-dinitropyridine with *N,N*-dimethyl-α-phenylacetamidine leads to the bridged cyclic adduct (XV)[88] and both the *N*- and *C*-adducts (XIII) and (XIV) can be regarded as probable intermediates:





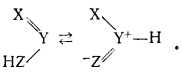
(XIII) (XIV)



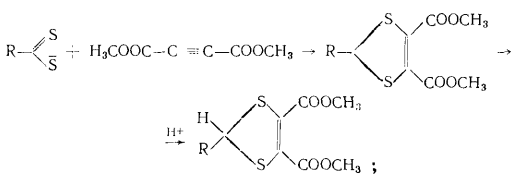
(XV)

2. Anionic and Dipolar Cycloaddition Reactions

It has been suggested in the literacture[89] that any triatomic systems of the type $\bar{Z}-X=Y$ and $\ddot{Z}-X=Y$, where Z is an atom with a free electron pair, are potential 1,3-dipoles. It has also been shown in a number of studies[90-94] that systems of the type X=Y−ZH are sources of 1,3-dipoles as a result of prototropic tautomerism:



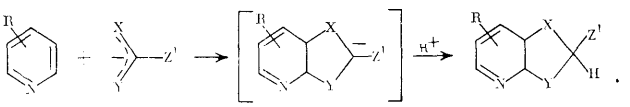
A number of studies have been published in recent years on the cycloaddition reactions with participation of heteroallyl anions.[68,69,80-82,95-108] For example, it has been found that the anions of dithiocarbamic[104] and also dithiocarbonic acid[101] react with a typical dipolarophile, namely dimethyl acetylenedicarboxylate, to form the 1,3-dithiols (XVI, a and b):



(XVI, a and b):

(a) R = $N(C_2H_6)_2$; (b) R = C_6H_5 .

Many of the dinucleophiles examined above conform to the principles, formuldted by Petrov et al.,[104] of the construction of systems capable of anionic cycloaddition. In the light of these requirements, we believe that the possibility of the concerted cycloaddition of 1,3-ambident anions to a double bond of the aromatic aza-system is entirely realistic.



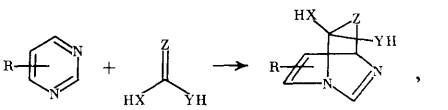
(XVII)

We shall consider the simplest case—the reaction of pyridine (pyridinium ion) with the 4π-electron heteroallyl system from the standpoint of the theory of molecular frontier orbitals.[109] The form of the highest occupied molecular orbitals (HOMO) of the heteroallyl anion and the lowest unoccupied molecular orbitals (LUMO) of the pyridinium cation, presented in the Figure, shows that the anionic cycloaddition at the C(2) and C(3) positions in the pyridine ring is prohibited owing to the phase incompatibility of the frontier orbitals but is possible at the C(3) and C(4) positions.

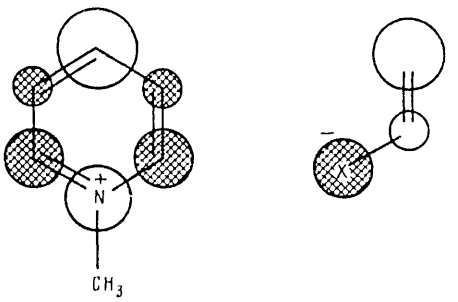
Apart from the limitations imposed by the theory of frontier molecular orbitals, the reaction via the anionic cycloaddition mechanism requires the stabilisation of the anionic intermediate (XVII), for example, as a result of protonation.[95] Furthermore, in the course of the anionic cycloaddition reactions the aromaticity of the azine ring is lost and the operation of this mechanism is therefore possible only for azines with an extremely low degree of aromaticity. Apparently, because of all these factors, clear-cut examples of anionic cycloaddition involving azines have not so far been found.

3. The Diels–Alder Reaction with Reverse Electronic Requirements

A number of 1,3-ambident nucleophiles contain a double bond enriched in electrons and can be regarded as 2π-components in reactions involving cycloaddition to the electron-deficient azadiene system of azines (the Diels–Alder reaction with reverse electronic requirements).[110,111] In a general form, such cyclisation can be described schematically as follows:



where XH and YH are electron-donating groups. Such reactions are at present known for azines containing at least two aza-groups in the *meta*-positions and yet another acceptor: nitropyrimidines, triazines, and tetrazines.



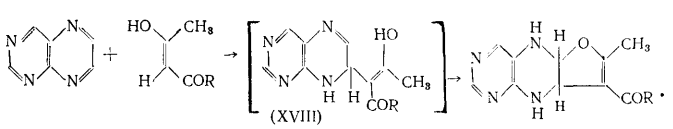
Schematic representation of the lowest unoccupied molecular orbital of the pyridinium cation and of the highest occupied molecular orbital of the heteroallyl anion.[109] The diameters of the circles are proportional to the coefficients of the atomic orbitals and cross-hatching indicates a change in the sign of the wave functions.

IV. THE CYCLISATION REACTIONS OF AZINES WITH 1,3-DINUCLEOPHILES

The reactions of azines with 1,3-dinucleophiles can in general lead to bicyclic systems with an *o*-, *m*-, or *p*-linked aza-ring. Despite a number of common features and the identity of the reagents capable of inducing all three types of cyclisation, the mechanisms of the formation of *o*-, *m*-, and *p*-linked cyclic adducts are different and merit separate consideration.

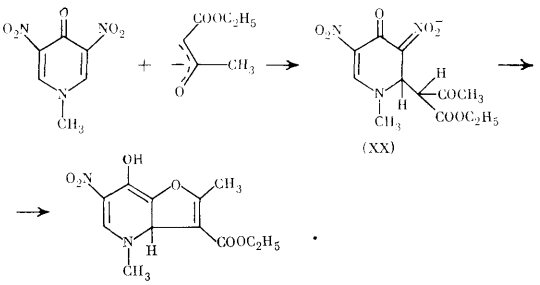
1. *ortho*-Cyclisations

One of the first examples of the *o*-cyclisations of azines with 1,3-dinucleophiles is the reaction of pteridine with β-dicarbonyl compounds.[71] The authors[71] suggested a stepwise cyclisation mechanism involving the intermediate formation of the monoadduct (XVIII). It is noteworthy that the structure of the cyclic adducts (XIX) has not been rigorously demonstrated and one cannot rule out the possibility of the reverse regio-orientation of the furan ring:



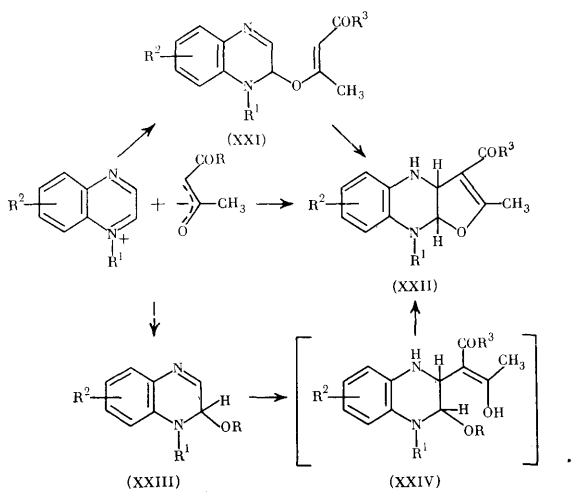
(XVIII) (XIX)

A similar mechanism with the initial formation of Michael adducts (XX) has also been proposed for the reactions of 3,5-dinitro-4-pyridone,[112] 3-bromo-4-nitropyridine *N*-oxide,[113] and 2,3,5,6-tetrachloropyrazine[114] with the anions of β-dicarbonyl compounds in which the furan ring is annelated as a result of the successive nucleophilic substitution of the halogen atoms or the nitro-group#:



(XX)

The mechanisms discussed in a number of studies[71,112-114] are inapplicable to the outwardly similar cyclisations of quinoxalinium salts with the enolates of β-dicarbonyl compounds in which the furan ring is also annealed but the C(2) atom, which is the most electrophilic in quinoxolinium salts, is linked during the reaction to the enolate oxygen. The reverse orientation of the furan ring presupposes either the initial formation of a C—O bond (charge control) in the stepwise course of the reaction via the σ-adduct (XXI) or the concerted formation of the C—O and C—C bonds via the anionic cycloaddition mechanism.[67-69] If the reaction is carried out in an alcoholic medium and is catalysed by bases, one cannot rule out also a mechanism in which the lyate complex (XXIII) is formed initially. Next there is a possibility either of the displacement of the OR group from the σ-adduct (XXIII) by the enolate anion, which leads to the formation of compound (XXI), or of the *C*-addition of the enolate to the 3-position. The complex (XXIII) can be detected in the ^{1}H NMR spectra and its conversion into the cyclic adduct (XXII) has been confirmed experimentally.[36]

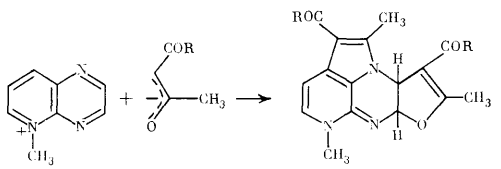


(XXI) (XXII) (XXIII) (XXIV)

#The cyclisations of azines with 1,3-dinucleophiles which take place as a result of the substitution of readily removed groups, as well as the cyclisations involving side groups, have their specific features and are not considered in this review.

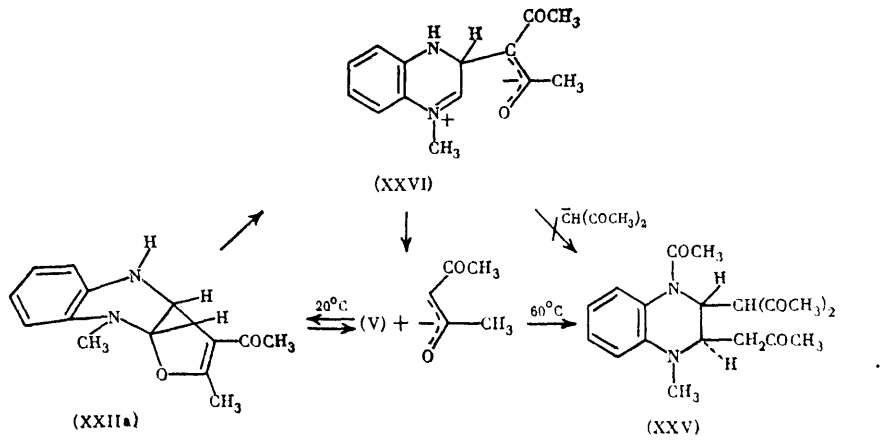
It has been shown by ^{1}H NMR and X-ray diffraction that, under the conditions of kinetic control, the reaction is highly regioselective and stereoselective and leads exclusively to the cyclic adducts (XXII) with the *endo*-configuration and *cis*-orientation of the bridgehead hydrogen atoms.[68] Quinoxalinium salts substituted in the benzene ring, including benzo[*g*]- and benzo[*f*]-annelated cations, react with the enolates to form cyclic adducts (XII) of analogous structure.[69]

The pyrido[2,3-*b*]pyrazinium cation reacts with the enolates in a more complex manner.[69] Apart from the annelation of the furan ring to the uncharged (as in pteridines[71]) pyrazine ring, in this case the second diketone residue undergoes *C*-addition to the *p*-position of the pyridinium ion with subsequent intramolecular cyclisation to the pyrrole ring:[69]

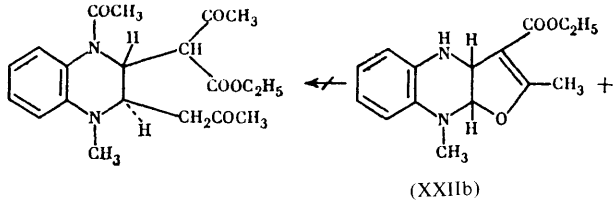


The question how the *o*-cyclisations discussed above take place—stepwise or as concerted pericyclic reactions—is common to these processes and is of fundamental importance. It is known[115-118] that the *cis*-principle is one of the main criteria of pericyclic reactions. The regiospecificity and stereospecificity of the cyclisation of β-diketones with aromatic 1,4-diaza-salts as well as their occurrence in conformity with the *cis*-principle constitute, as it were, arguments in support of anionic [3$^-$ + 2]-cycloaddition. However, it was noted above that the anionic cycloaddition at the C(2) and C(3) positions in the pyridinium ion is prohibited by the phase incompatibility of the frontier orbitals. Since it is difficult to expect a qualitative change in the properties of the LUMO on passing from the pyridinium to the pyrazinium (quinoxalinium) cation in view of their topological similarity, the question of the mechanism of the cyclisations considered remains open and requires both more profound quantum-chemical analysis and additional experimental data.

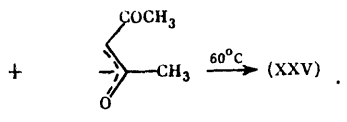
The experimental data demonstrating the concerted nature of the reverse cyclodecomposition reaction may serve as an additional argument in support of the concerted mechanism of the cyclisation of the enolates with quinoxalinium salts.[119] It has been shown that furo[2,3-*b*]quinoxaline (XXIIa) is formed only under the conditions of kinetic control at temperatures below 20 °C, but at 60 °C the reaction of *N*-methylquinoxalinium with acetylacetonate leads to the diadduct (XXV) with the *trans*-orientation of the hydrogen atoms located at the C(2) and C(3) atoms of the tetrahydropyrazine ring:[119]



Compound (XXV) is also formed when a solution of the cyclic adduct (XXIIa) in ethanol, heated to 60 °C, is treated with a second mole of acetylacetonate. The stepwise mechanism of this reaction via the intermediate (XXVI) in accordance with the scheme (XXIIa) → (XXVI) → (XXV) has been disproved by an experiment in which acetylacetonate was added at 60 °C to a solution of the cyclic adduct (XXIIb) having the ethoxycarbonyl group in the furan ring, which led to the diadduct (XXV) without the ester group:[119]



(XXIIb)

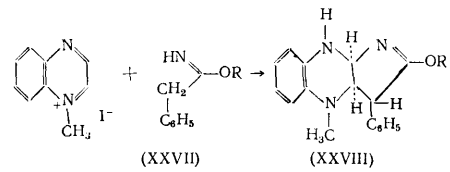


The result of this experiment demonstrates the reversibility of the cyclisation of the cation (V) with the enolates and also that the rupture of both σ-bonds (C–O and C–C) in the dissociation of the cyclic adduct (XXIIa) to give the starting materials most probably takes place via a concerted mechanism. The base-catalysed cycloreversions of tetrahydrofurans,[120] which have been discussed as concerted reactions,[118] constitute a fairly close analogy.

However, one cannot rule out fully the stepwise mechanism of the dissociation of the cyclic adduct (XXIIa) in accordance with the scheme (XXIIa) → (XXVI) → (V) + diketone. The absence of the reaction (XXVI) → (XXV), demonstrated by the experiment involving the transformation of compound (XXIIb) into (XXV), can be accounted for by the unduly short lifetime of the intermediate (XXVI) and its much faster dissociation compared with the rate of addition of the second diketone residue.

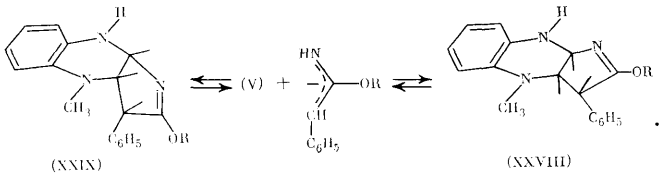
It is noteworthy that the cyclisation reactions of pyrazines with β-ketoenolates merit attention as a method of synthesis of furo[2,3-*b*]pyrazines regardless of the mechanism.

The annelation of the pyrrole ring to pyrazines is achieved in the reactions with N, C-dinucleophiles such as α-substituted acetiminoesters (XXVII),[80–82] acetamides, and β-ketoacid amides:[121]



(XXVII) (XXVIII)

Under the conditions of thermodynamic control, the interaction of quinoxalinium salts with iminoesters takes place regioselectively and stereoselectively and leads to the cyclic adduct (XXVIII) having the *exo*-structure.[81] In base catalysis the rate of cyclisation increases and two types of stereoisomeric cyclic adducts (XXVIII) and (XXIX) have been detected in the reaction mass by ^{1}H NMR. They have also been isolated on the preparative scale in the form of crystals:[80]

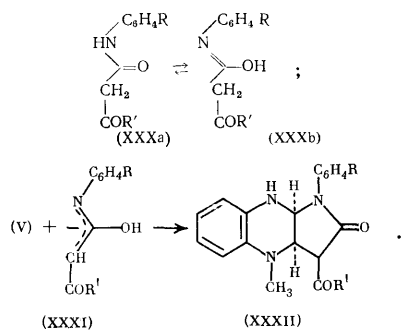


(XXIX) (XXVIII)

It has been shown chemically and spectroscopically that the *endo*-adducts (XXIX) are formed at a high rate in the initial period but under the reaction conditions the *endo*-adducts rearrange irreversibly to the more stable *exo*-isomers (XXVIII). It has been established that the rearrangement proceeds via a cycloelimination stage, i.e. via the decomposition of the *endo*-isomers to the starting materials.[80]

The above characteristics of the cyclisation of quinoxalinium salts with iminoesters repeat in broad outline the characteristics of the cycloaddition reactions[115–118] and, in particular, the anionic cycloaddition reactions.[95,97] It therefore appeared quite justifiable to regard these reactions as anionic [3$^-$ + 2]-cycloaddition of heteroallyl anions to the conjugated C=C bond of the pyrazine ring.[80]

The anilides of β-ketoacids (XXX) in the potentially tautomeric form (XXXb) are in essence analogues of iminoesters. They too react with quinoxalinium salts (V) to form the cyclic adducts (XXXII) containing the pyrrole ring:[121]

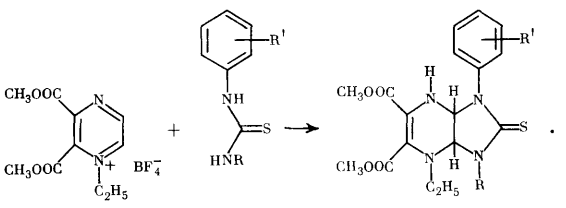


(XXXa) (XXXb)

(XXXI) (XXXII)

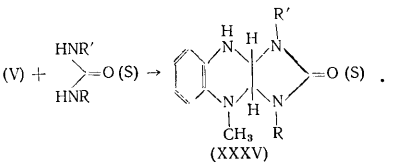
The high regioselectivity and stereoselectivity of the cyclisation is noteworthy. Despite the fact that the mesomeric anion (XXXI) participates in the reaction, no appreciable amounts of furo]2,3-*b*]quinoxalines or other cyclic adducts are formed.[121]

The annelation of the imidazole ring, leading to derivatives of imidazo[4,5-*b*]pyrazine (XXXIV), takes place in the reactions of pyrazinium salts with *N*-mono- and *N*,*N*′-di-aryl-substituted thioureas (XXXIII):[122]



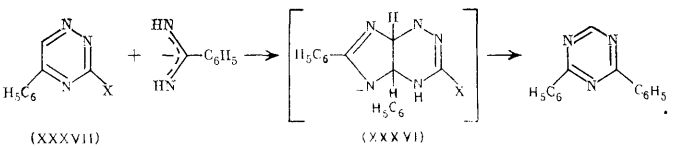
(XXXIII) (XXXIV)

Ureas and thioureas also behave as N,N′-dinucleophiles in reactions with quinoxalinium salts (V), giving rise to the products (XXXV):[122]



(XXXV)

The bicyclic adducts (XXXVI) with the annelated imidazole ring have also been regarded as the most probable intermediates in the transformation of 1,2,4-triazines (XXXVII) into 2,4-diphenyl-1,3,5-triazine, which has a fairly complex mechanism:[123]



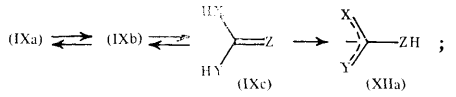
(XXXVII) (XXXVI)

We may mention again that the presence of the pyrazine fragment in the triazines (XXXVII) is structurally favourable for *o*-cyclisations.

A characteristic feature of the ^{1}H NMR spectra of all the cyclic adducts of pyrazinium and quinoxalinium salts with 1,3-dinucleophiles mentioned above is fairly high values of the vicinal CSSI between the protons at the bridgehead carbon atoms (^3J = 7–10 Hz), which indicates a *cis*-junction between the five-membered heterocycles and the pyrazine ring.[68,69,80,81,121,122]§ As already mentioned above, other vicinal constants $^3J_{2,3}$ = 2.5–3.5 Hz (Table 2), corresponding to the *trans*-orientation of the protons in the tetrahydropyrazine ring, are characteristic of the acyclic diadducts of pyrazines and quinoxalines.

If an attempt is made to formulate the empirical principles of the selection of 1,3-dinucleophiles (IX) capable of *o*-cyclisation, it is found that a common feature of different combinations of the heteroatoms X and Y remains, on the one hand, the presence of substituents stabilising the 1,3-ambident anions (XIIa) formed (this is frequently the phenyl or keto-group) and, on the other hand, the presence at the central atom of a triad of electron-donating groups of the type NR_2, OR, SR, or the methyl group, which activate these systems with respect to interaction with electron-deficient azines.

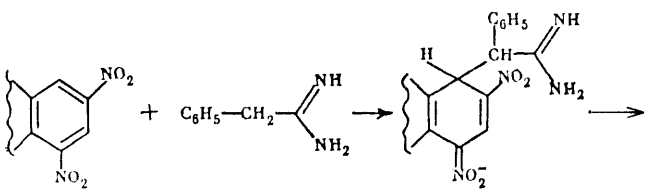
§ The ^{1}H NMR spectra of tetrahydroquinoxalines condensed with five-membered heterocycles have been discussed in detail by V.N.Charushin, A.I.Chernyshov, N.N.Sorokin, and O.N.Chupakhin, Org.Magnet.Resonance, 1984 (in the Press).



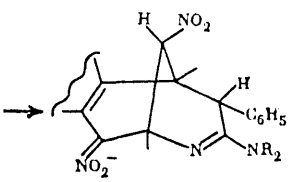
X, Y = N, O, S, CH, NH, NAr, CHAr, CHCOR;
ZH = NR_2, OR, SR

2. *meta*-Cyclisations

The characteristic features of *m*-cyclisations with 1,3-dinucleophiles were first formulated clearly by Strauss in a series of studies of the reactions of aromatic polynitro-compounds with enamines, α-phenylacetamidines, and urethanes:[124-130]



(XXXVIII)

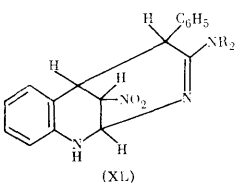


(XXXIX)

Cyclisations of this type, which have been called *meta*-bridging reactions,[124] immediately attracted attention as a direct and convenient method of synthesis of complex polycyclic structures. In particular, Strauss[126] demonstrated the applicability of these reactions to the direct synthesis of benzomorphans—potential antagonists of narcotic drugs.

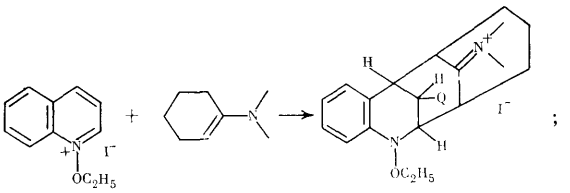
It has been suggested[124] that *m*-cyclisations take place in two stages via the intermediate formation of the anionic σ-complexes (XXXVIII), which can not only be detected spectroscopically but in a number of instances can be isolated, after which the second stage of the reaction can be carried out—the cyclisation of the σ-complexes (XXVIII) to *m*-linked cyclic adducts (XXXIX).[130]

The *m*-bridging reactions were subsequently extended to the aza-analogues of aromatic polynitro-compounds such as 3,5-dinitropyridine and 3-nitroquinoline.[88]



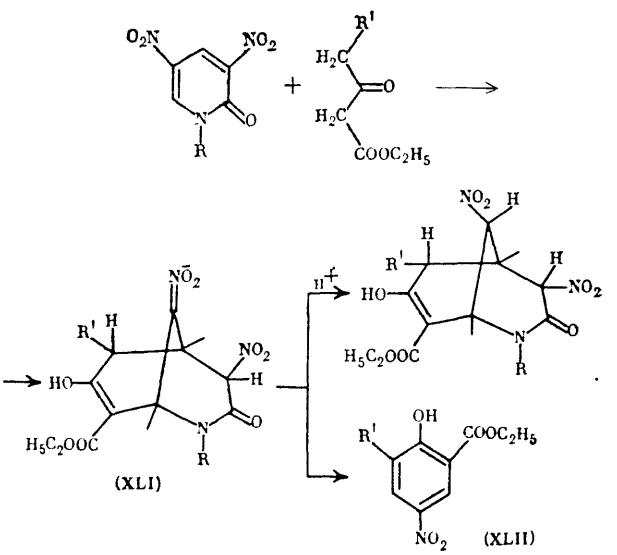
(XL)

The formation of the cyclic adducts (XV) and (XL) has been detected by ^{1}H NMR, but they could not be isolated.[88] This is due to the lower stability of the *m*-linked adducts of azines with 1,3-dinucleophiles compared with their nitro-analogues or with the *o*-annelated azines. In addition, the *m*-adducts undergo various chemical reactions. Thus the *m*-cyclisation of *N*-ethoxyquinolinium salts with enamines is accompanied by the addition of a second molecule of the initial cation:[61,64]



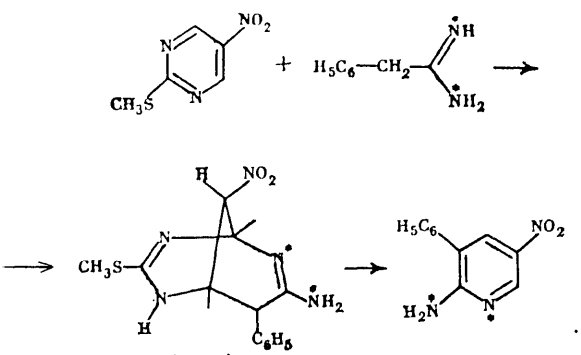
Q = 2-quinolinyl.

However, the most common reactions of the cyclic *m*-adducts are apparently their transformations into other heterocyclic systems. The sodium salts of β-ketoesters, for example, induce the transformation of 3,5-dinitropyridones into the nitrophenols (XLII) via the intermediate formation of bicyclic adducts (XLI), which can also be isolated on acidification of the medium:[66]



(XLI) (XLII)

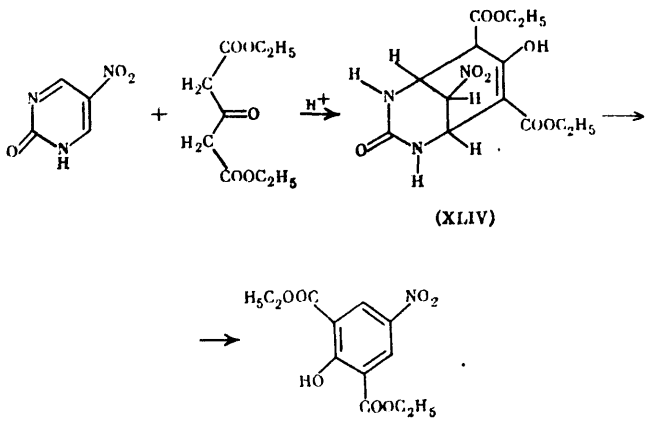
The formation of *m*-linked adducts has been postulated also in the transformation of 5-nitropyrimidines on treatment with the carbanions of keto-reagents[62] and also acetamidines[76]; however, experimental data confirming the feasibility of this mechanism of the transformation have been obtained quite recently.[78]



(XLIII)

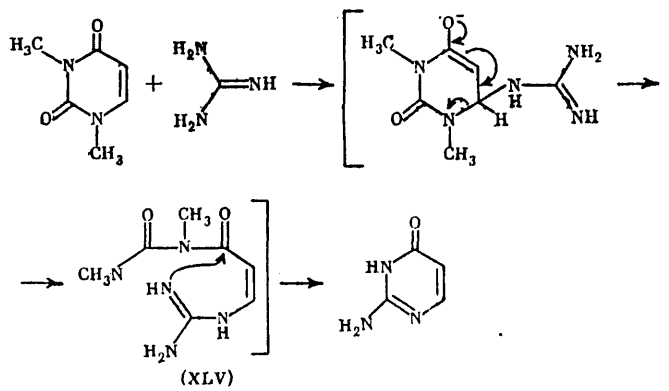
The formation of the cyclic *m*-adducts (XLIII) in the reaction of 2-methylthio-5-nitropyrimidine with α-phenylacetamidine has been detected by ^{1}H NMR and its involvement in the rearrangement is not inconsistent with experimental data obtained using [^{15}N]amidine.[78]

The involvement of bridged *m*-linked cyclic adducts (XLIV) in the transformations of 5-nitro-2*H*-pyrimidinone into nitrophenols on treatment with keto-reagents has been recently reported:[61]



(XLIV)

We may note that earlier in the majority of their investigations of similar transformations of uracils under the influence of 1,3-ambident nucleophiles American and Japanese chemists were inclined to adopt the *ANRORC* mechanism involving an acyclic intermediate of type (XLV):[70,72-74]

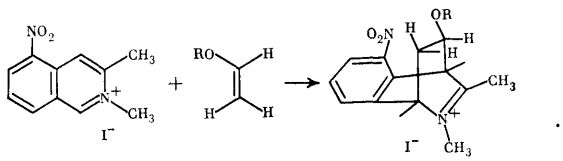


(XLV)

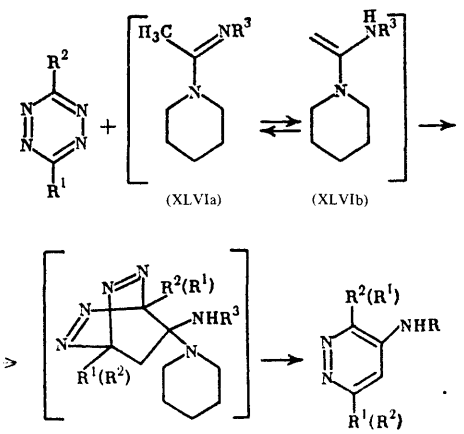
The question of the mechanism of the transformations of pyrimidines under the influence of 1,3-dinucleophiles still remains open, although studies in recent years have shown that the formation of bridged bicyclic intermediates in such reactions is extremely real.[61,66,78] Whereas the bridged cyclic adducts can nevertheless be detected in a number of instances,[61,66,78] the difficulties associated with the detection of the σ-adducts of azines with 1,3-dinucleophiles and even more so of the acyclic intermediates are evident. The σ-adducts formed on monoaddition of a 1,3-dinucleophile to azines with the *meta*-disposition of the electrophilic carbon atoms are extremely unstable, because their further reactions are greatly favoured by thermodynamic factors: they involve either the opening of the ring with rapid recyclisation or *m*-cyclisations with subsequent decomposition of the bridged cyclic adduct, leading to the transformation products.

3. *para*-Cyclisations

The most widely used method of synthesis of bicyclic systems with a bridge connecting the *p*-positions in the initial azine ring is the Diels–Alder reaction with reverse electronic requirements, in which the 4π-electron fragment of the azine system plays the role of the diene, while a wide variety of unsaturated compounds containing a double bond enriched in electrons are employed as dienophiles.[110,111] In conformity with the predictions of the theory of frontier orbitals, cyclisations of this type become energetically favourable only when several aza- or other electron-accepting groups have accumulated in the azine molecule or in the presence of a cationic centre, which all adequately reduce the energies of the lowest unoccupied molecular orbitals.[109,110,111,118] Derivatives of 1,2,4-triazine and 1,2,4,5-tetrazine,[111,131] as well as isoquinolinium and acridizinium cations, which readily enter into the cationic [4⁺ + 2]-cycloaddition reactions,[132-142] therefore show an extremely great tendency towards the formation of cyclic [4 + 2]-adducts:

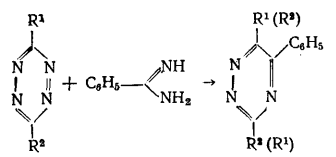


Many 1,3-ambident nucleophiles contain an electron-enriched double bond capable of participating in cycloaddition reactions with azadienes. Although there is no point in this connection to consider the manifestation of ambident properties by nucleophiles, these reactions nevertheless should be regarded as constituting another possibility for the involvement of 1,3-ambident systems in reaction with azines. This is particularly valid because the mode of many cyclisations is determined by tautomeric transformations characteristic precisely of 1,3-ambident systems and impossible in the case of isolated double bonds. Thus the acetamidines (XLVI) enter into reactions involving cycloaddition to tetrazines in the form of the enediamines (XLVIb) and it has been noted that the participation of acetamidines as C=C dienophiles is the first experimentally observed manifestation of the acetamidine–enediamine tautomerism.[77]

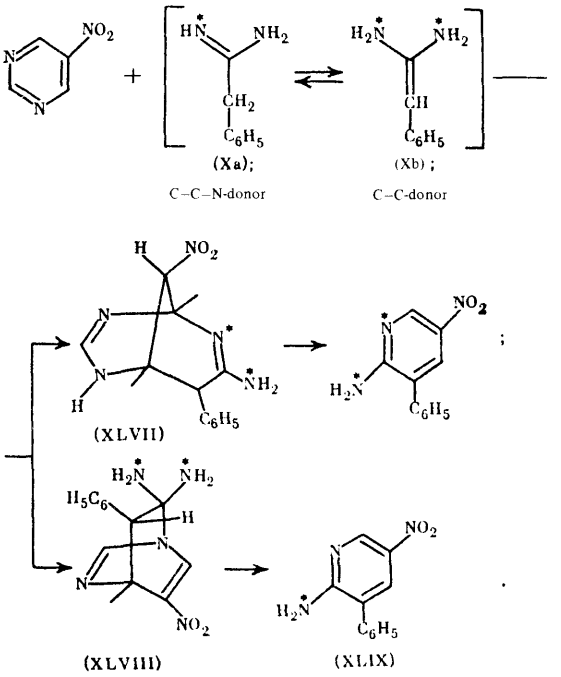


(XLVIa) (XLVIb)

In the absence of N,C-prototropic tautomerism, which obtains only in the presence of an active α-methylene group, amidines are capable of cyclising with tetrazines as C=N dienophiles:[143]

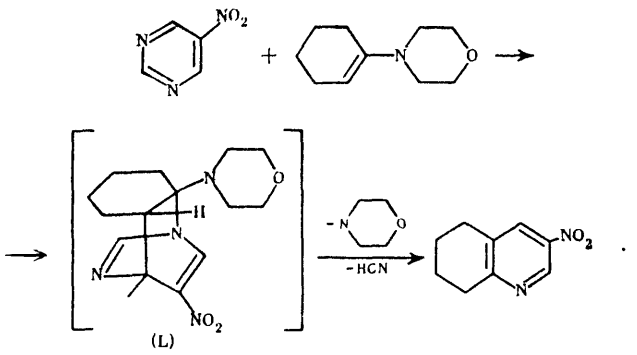


In some cases amidines are capable of exhibiting in their reactions with azines both the properties of 1,3-dinucleophiles and the functions of reverse dienophiles. It has been shown with the aid of ^{15}N isotope labels that the transformations of 5-nitropyrimidines on treatment with α-phenylacetamidines proceed via several mechanisms involving the formation of both bridged *m*-linked intermediates (XLVII) and *p*-linked cyclic adducts (XLVIII):[78]

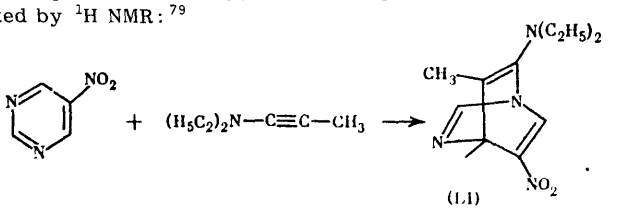


In the latter case the electron-enriched C=C bond of the enediamine (Xb) participates in the cyclisation, the enediamine thus behaving as a donor of the C–C fragment to the final transform5tion product, namely the pyridine (XLIX), which does not contain the ^{15}N isotope label in the ring.[78]

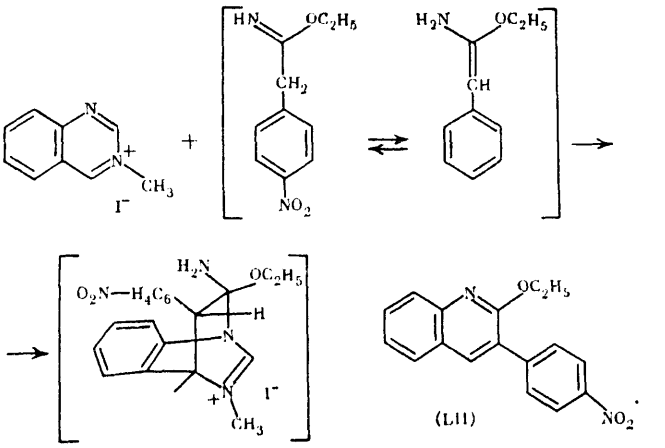
The transformations of pyrimidines based on the Diels–Alder reactions with reverse electronic requirements have been further confirmed and developed in a study[79] of the transformations of 5-nitropyrimidine on treatment with keten *O,O*- and *N,N*-acetals, enamines, and ynamines:



The postulated intermediates in these transformations, namely cyclic [4 + 2]-adducts of type (L), are unstable; on the other hand, in the case of *N,N*-diethylaminopropyne the stable cyclic adduct (LI) is formed as a result of addition to the 1,4-positions of the pyrimidine ring and has been detected by ^{1}H NMR:[79]

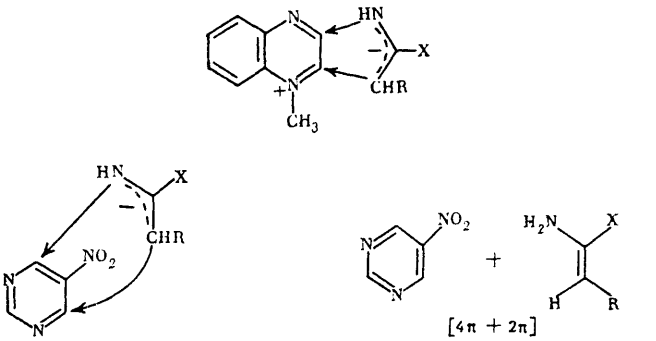


It is noteworthy that, whereas the formation of cyclic [4 + 2]-adducts with a *p*-linked 1,2,4-triazine or 1,2,4,5-tetrazine ring as intermediates in the transformations of the latter into other azine systems is generally accepted.[111,131] Charushin and van der Plas[78,79] were the first to conclude that systems with two heteroatoms can also participate in transformations proceeding via cyclic [4 + 2]-adducts. This result provides a more reasonable explanation of the previously described transformations of quinazolinium salts into the quinolines (LII) on treatment with methyl *p*-nitrophenylacetimidate[82] without resorting to open-chain intermediates and to *ANRORC* mechanisms usually postulated in such cases. This has been considered by Chupakhin et al.[82]



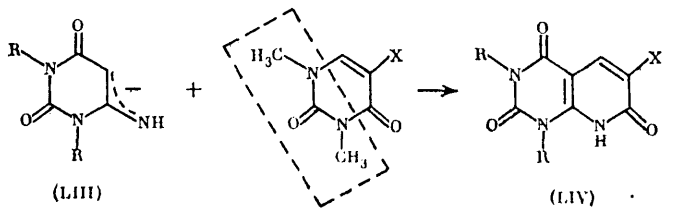
* * *

Thus the reactions of azines with ambident 1,3-nucleophiles are extremely varied and proceed via different pathways determined by the nature of the reactants, the structural and electronic factors, and the reaction conditions. The examples examined above show that, in reactions with ambident C,N-nucleophiles, such as, for example, acetamidines (acetimidates), there is a possibility of the formation of all three types of cyclic adducts: *ortho*-, *meta*-, and *para*-, the last two types of adducts being unstable and leading to the formation of transformation products.



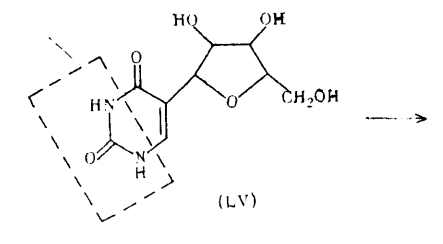
The data of Chupakhin et al.[82] for the reactivities of four isomeric benzodiazinium cations, namely quinoxalinium, cinnolinium, phthalazinium, and quinazolinium, with respect to *p*-nitrophenylacetimidate demonstrate a specific character of the *o*-, *m*-, and *p*-cyclisations rather than their common features.

The knowledge of the characteristics of the reactions of azines with ambident 1,3-nucleophiles and of the features of their occurrence in structurally different series of azines makes it possible to design new syntheses of azine systems and of annelated heterocycles based on them. Examples of such specific employment of cyclic ambident 1,3-nucleophiles (LIII) in the syntheses of pyrido[2,3-*d*]pyrimidines (LIV) have been described.[144,145] In the example presented in the scheme below the N–C–N fragment of 1,3-dimethyluracil is substituted by the C–C–N group of the 1,3-dinucleophile:[144]

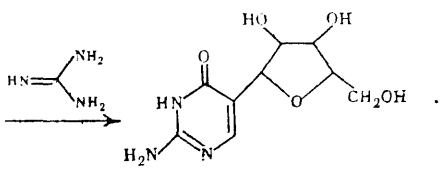


(LIII) (LIV)

A striking example of the practical use of the transformations of azines under the influence of 1,3-dinucleophiles has been given in a study[72] in which degenerate transformations of the pyrimidine ring were used for the modification of pyrimidine nucleosides. Thus pseudouridine (LV) can be converted under the influence of guanidine into pseudoisocytidine (LVI), which exhibits antileukaemic activity:[72]



(LV)



(LVI)

Further investigations of the cyclisation reactions and the transformations of azines on treatment with 1,3-dinucleophiles will make it possible to develop new easy methods of synthesis of practically useful compounds.

During the preparation of the manuscript for the press, a further series of studies on the cyclisation and transformations of azines under the influence of bifunctional 1,3-nucleophiles were published.[146–152] Among these, mention should be made of a novel one-stage method of synthesis of the familiar antitumour preparation 5-fluorouracil based on the transformation of 1,3-dimethyl-1,3,5-triazine-2,4-dione on treatment with fluoroacetamide.[147] This method undoubtedly merits attention, because transformations of this type can find applications also in the syntheses of other fluorinated heterocyclic compounds. We may also mention a review[150] of the Diels–Alder reactions of azadienes, which contains many examples of the participation of electron-deficient azines in cyclisations involving the *p*-position in the azine ring.

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Korov Urals Polytechnic
Institute, Sverdlovsk