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NUCLEOPHILIC SUBSTITUTION OF HYDROGEN IN AZINES

OLEG N. CHUPAKHIN, VALERY N. CHARUSHIN
Laboratory of Organic Chemistry, Urals Polytechnic Institute, Sverdlovsk, 620002, USSR

and

HENK C. VAN DER PLAS*
Laboratory of Organic Chemistry, Agricultural University, De Dreijen 5, 6703 BC Wageningen, The Netherlands

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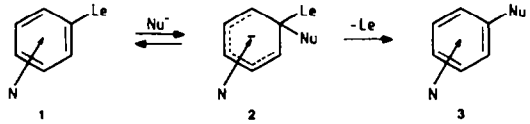
1. INTRODUCTION

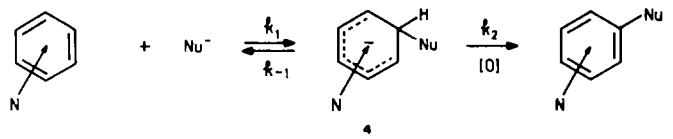
Most of the nucleophilic displacement reactions, studied with azines, take place with substrates (**1**) containing a substituent, that has a leaving group character (Le = Hal, OR, SO_2R, NO_2, SCH_3, SCN, CN, etc.). The nucleophilic substitution reaction leading to **3** usually occurs in a two-step mechanism, involving addition and elimination and having as intermediate the azacyclohexadiene **2**. The elimination of substituent Le is facilitated by the fact that the leaving group is stabilized in the form of its anion (Scheme 1).[1–4]



1 2 3

Scheme 1.

The substitution of hydrogen in electron-deficient azaaromatics by the action of nucleophilic agents, can formally be regarded as a hydride ion replacement. In the vast majority of cases also these reactions proceed via a two-stage mechanism (Scheme 2), involving intermediate **4**.



Scheme 2.

However the hydride ion has a low leaving group ability, is not solvated and does not show any tendency towards anionic stabilization. Therefore the reaction usually requires the presence of an oxidizing reagent to promote the removal of hydrogen provided that this role cannot be played by air, oxygen or the azaaromatic itself. In order to emphasize the specific nature of reactions in which hydrogen is substituted by a nucleophile the symbol S_NH has been suggested.[5] In a vast majority of cases it would seem justified to classify these reactions as $S_N(AO)$ reactions, indicating the two steps involved i.e. addition and oxidation of σ-adduct **2**. We believe, however, that the $S_N(AO)$ nomenclature has to be rejected since there are also many examples of hydrogen replacement in aromatics, in which no oxidant is involved and elimination of hydrogen occurs in the course of intramolecular auto-aromatization reaction, such as vicarious nucleophilic substitutions, nucleophilic telesubstitution reactions and others.† Since the replacement of hydrogen in (aza) aromatics also involves a two-step mechanism i.e. addition and elimination (whether or not promoted by an oxidizing reagent) we prefer the usual term $S_N(AE)^{ipso}$, in which an H is added in order to stress the specific character of the replacement reaction i.e. $S_N^H(AE)^{ipso}$, abbreviated in this review as S_N^H.

The reactions of the S_N^H-type are not the privileges of azines. They are also observed in the series of other heteroaromatic compounds, with arenes and quinones, but they are mostly applied in the chemistry of azines.

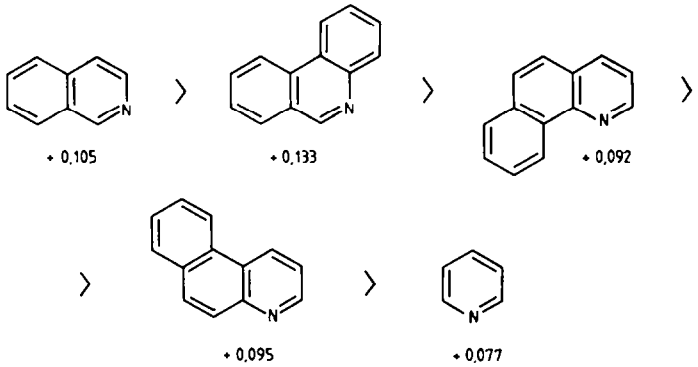
2. REACTIVITY OF AZINES IN THE S_N^H REACTIONS

2.1. *The Indices of Reactivity*

There have been attempts to characterize the reactivity of azines in the S_N^H reactions by various indices of quantum chemistry, such as π-charge on the C atoms (HMO,[6] SCF[7]), $(\sigma+\pi)$ charge (CNDO/2[8,9]), the charge on the N atom[10], etc.

2.1.1. *Relative reactivity of azines*

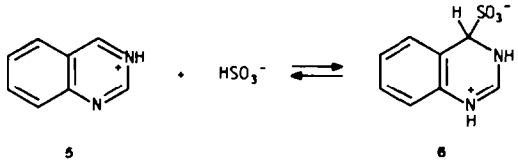
Both the relative reactivity of azaaromatic compounds as well as the site selectivity are mainly determined by the electron-deficiency of the C atom attacked by a nucleophile. However, from many studies it became clear that there is no straight dependence between the reactivity of azines in the S_N^H reactions and calculated positive charge values (Scheme 3). The reactivity of azines in the Chichibabin amination reaction evaluated by reaction parameters, such as temperature, duration and yields, follow the order as indicated, which is not in accordance with the order of the π-charge change (π-charges on the reactive C atoms are shown under the formulae).[11]



Scheme 3.

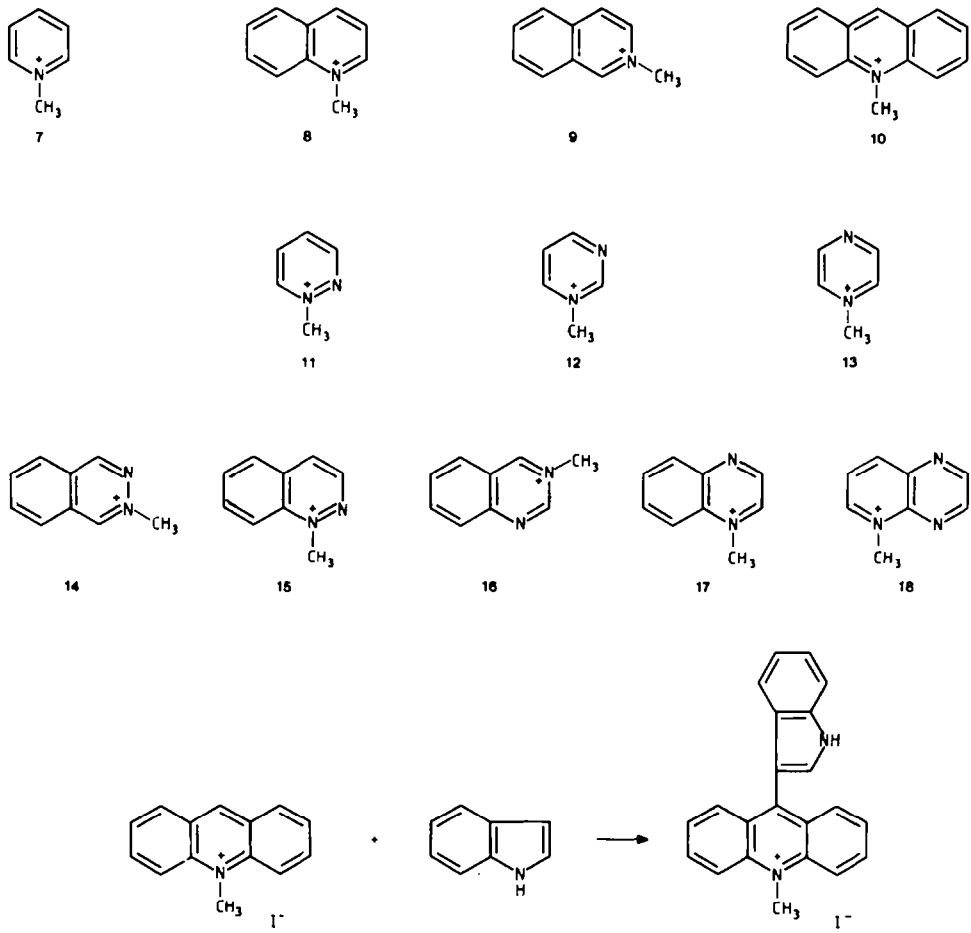
† For details see Section 3.3 of this review.

For the S_N^H reactions in which the addition of a nucleophilic reagent is a rate-determining step the observed rate depends on the electrophilicity of azines, being estimated by their electrochemical reduction potentials. Good linear relationship between the reactivity of some azinium cations, for example the quinazolinium cation **5** in the addition reaction with bisulphite-ion leading to the C-4 adduct **6**, and the potentials of their one-electron polarographic reduction has been obtained (Scheme 4).[12]



Scheme 4.

Looking for a correspondence between the data obtained by quantum chemistry methods and $E_{1/2}$ values as an indirect measure of estimating the reactivity, a series of azinium cations **7–18** (Scheme 5)[9] has been synthesized and their $E_{1/2}$ values measured.



Scheme 5.

It has been found that from all the reactivity indices the reduction potentials $E_{1/2}$ correlate best of all with the π-bonding energies per one electron (E_b^π/n), i.e. the indices characterizing the aromaticity of π-system (Table 1, Fig. 1). The data of chemical experiments also show that the reactivity of the cations **7–18** increases together with a decrease of their aromaticity.[9]

From these data it can also be concluded that the most reactive cation is certainly the acridinium

Table 1. Reactivity indices and the reduction potentials of N-methylazinium cations 7–18

Compound	N-methylazinium	$-E_{1/2}$, V	$-E_{LUMO}$ (HMO)	q_N^+ (HMO)	$C_{N^+}^2$ (HMO)	q_N^+ (SCF)	$C_{N^+}^2$ (SCF)	E_b^π, eV (SCF)	E_b^π/n, eV (SCF)	q_{max}^+ (SCF)
7	Pyridinium	1.269	0.507	1.590	0.167	1.288	0.291	−10.320	−1.290	0.216(2)
8	Quinolinium	0.842	0.317	1.630	0.108	1.318	0.216	−13.800	−1.150	0.225(2)
9	Isoquinolinium	1.046	0.404	1.598	0.111	1.290	0.130	−14.676	−1.223	0.071(1)
10	Acridinium	0.319	0.169	1.682	0.071	1.327	0.006	−16.016	−1.001	0.249(9)
11	Pyridazinium	0.741	0.397	1.560	0.183	1.283	0.293	−8.928	−1.116	0.214(4)
12	Pyrimidinium	0.938	0.497	1.954	0.159	1.299	0.116	−9.528	−1.191	0.244(4) 0.162(2)
13	Pyrazinium	0.728	0.381	1.566	0.170	1.244	0.286	−8.888	−1.111	0.053(2)
14	Phthalazinium	0.861	0.390	1.586	0.131	1.288	0.125	−13.776	−1.148	0.079(1)
15	Cinnolinium	0.533	0.206	1.594	0.134	1.311	0.219	−13.440	−1.120	0.223(4)
16	Quinazolinium	0.327	0.357	1.600	0.091	1.296	0.114	−12.060	−1.005	0.094(4) 0.069(2)
17	Quinoxalinium	0.368	0.195	1.596	0.123	1.265	0.242	−12.120	−1.010	0.058(2)
18	Pyrido [2,3-b]-pyrazinium	0.344	0.241	1.626	0.085	1.312	0.136	−12.096	−1.008	0.155(2) 0.141(3)

E_{LUMO}—Energies of the lowest unoccupied molecular orbitals. q_N^+—Positive charge on the nitrogen atom. $C_{N^+}^2$—Frontier orbital electron density on the nitrogen atom. E_b^π—π-Bonding energy. E_b^π/n—π-Bonding energy per one electron. q_{max}^+—Maximum positive charge value (position).

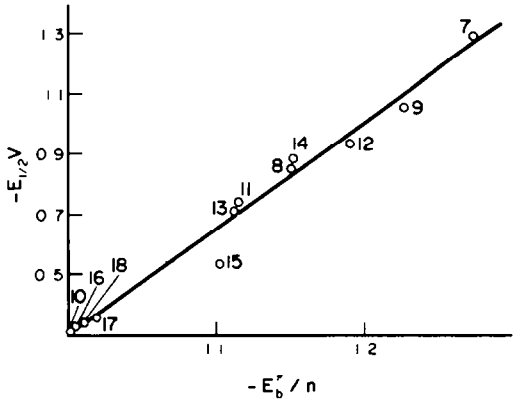


Fig. 1. Plot of $E_{1/2}$ against π-bonding energies per one π-electron E_b^π/n for N-methylazinium cations 7–18.

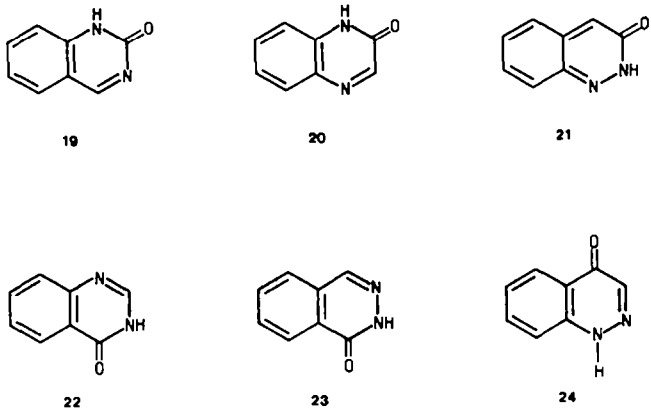
Table 2. Reactivity indices of diazanaphthalones

Compound	q_C	F_C	π_{CC}	$L_{\bar{N}u}$, β	L_R	DE_π, β	$DE\pi/n$, β
19	+0.193*	0.465	0.406	1.917	2.391	3.234	0.270
	+0.223†	0.550					
20	+0.098	0.547	0.502	0.186	1.991	3.166	0.264
	+0.155	0.602					
21	−0.178	0.061	0.524	2.224	1.055	2.983	0.249
	+0.041	0.587					
22	+0.203	0.447	0.416	1.940	2.221	3.300	0.275
	+0.168	0.508					
23	−0.201	0.577	0.481	2.493	2.074	3.604	0.300
	+0.128						
24	−0.157	0.519	0.463	2.584	2.172	3.645	0.304
	+0.147	0.544					

* HMO.
† PPP.
q_C—positive charge on the carbon atom ; F_C—free valence index ; π_{CC}—the self-polarizability index ; $L_{\bar{N}u}$—the energy of nucleophilic localization ; L_R.—the energy of radical localization ; DE_π—delocalization energy ; DE_π/n—delocalization energy per one π-electron.

salt **10**. Indeed, it undergoes the substitution of hydrogen at C-9 by the action of arylamines or indoles very easily (Scheme 5).[5]

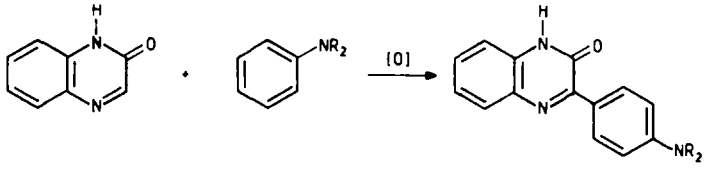
A similar conclusion has been reached when considering the series of isomeric diazanaphthalones **19–24** (Scheme 6) which take part in the reaction with N,N-dimethylanilines, as shown in Scheme 7 (Table 2).[13] It has been found that from the compounds **19–24**, those with the numbers **19–21** react smoothly with dimethylaniline to give the S_N^H products (Scheme 7), while **22–24** are unreactive under the same conditions.[13] Attempts were made to relate in those series chemical reactivity with reactivity indices. MO calculations indicate that among all methine carbons in the molecules **19–24** only the heterocyclic ones possess relatively large values of positive charge q_C, free valence index F_C and the self-polarizability index π_{CC} (Table 2). However these characteristics do not provide, qualitative understanding of the data obtained experimentally, in particular why the compounds **19–21** are more reactive than **22–24**.



Scheme 6.

A better correspondence has been found between the chemical behaviour of the compounds **19–24** and the energies of nucleophilic ($L_{\bar{N}u}$) and radical (L_R) localization (Table 2).

In order to characterize thermodynamic stability and aromaticity of the compounds **19–24** delocalization energies DE_π and delocalization energies per one π-electron ($DE_{\pi/n}$) have been calculated. One may conclude that only compounds with a low aromaticity are reactive enough to undergo the S_N^H process by action of dimethylaniline.[13]



Scheme 7.

Another approach used is based on the so-called delocalization model of reactivity. In this model one takes into consideration the nature of the nucleophile and compares the reactivity of different reactive centres of one molecule.[14] Since the compounds **19–24** have only one reactive site this method has been applied to estimate the reactivity of isomeric compounds (Fig. 2).[13]

Figure 2 shows distinctly that a nucleophilic attack by low active nucleophiles (δ from -0.6 to -3.0) is favoured for diazanaphthalones **19–21**; for the isomeric compounds **22–24** no reactivity is expected. This result is in full agreement with the experimental data.[13]

It is evident that aromaticity of azines influences both the initial addition of a nucleophile and in the second stage the aromatization of the σ-adduct. The lower the aromaticity of an azine, the lower is its activation barrier for the addition step and the more difficult the σ-adduct is to be aromatized.

As already mentioned, the potentials of polarographic reduction of azinium cations provide

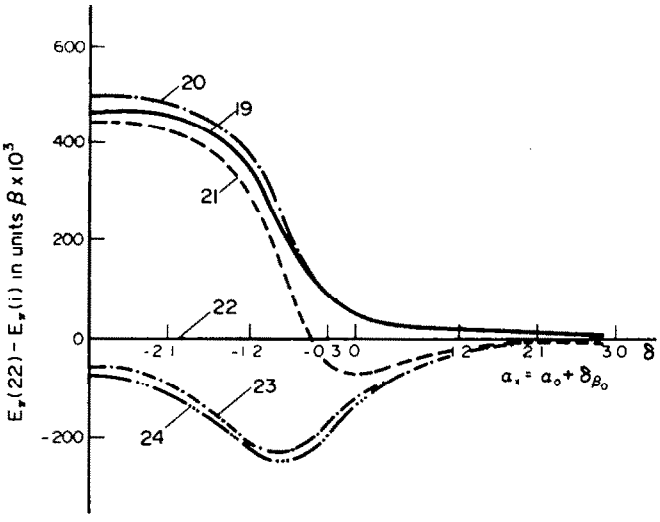


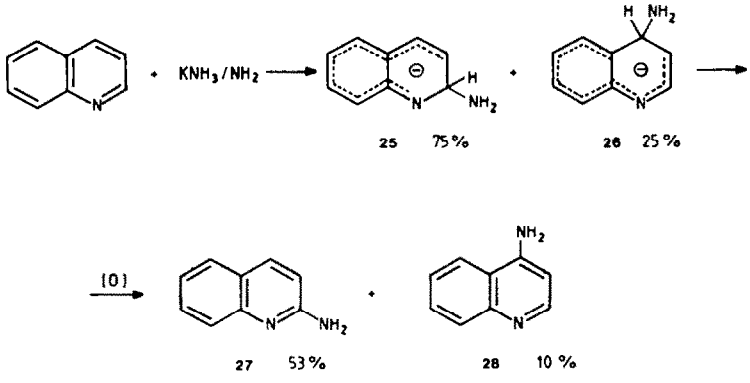
Fig. 2. The variation of the relative energies differences for nucleophilic attack on the azanaphthalones **19–24** with the nature of the reagent. α_x—coulomb integral for a nucleophile, HMO ; α_0—standard coulomb integral (for benzene) ; β_0—standard resonance integral HMO; δ—coulomb integral parameter, HMO.

useful information for predicting their behaviour in the S_N^H reactions. According to the data[9] the values $E_{1/2} \cong -0.5$ V correspond to the cations with the lowest electrophilicity which are but still able to react with uncharged nucleophiles. Cations reducing at more negative potentials are no longer able to react with arylamines or indoles.[9]

2.1.2. *The site selectivity*

When analysing the reactivity of azines towards nucleophilic reagents both the relative reactivity of different azine derivatives and the site selectivity are to be taken into account.

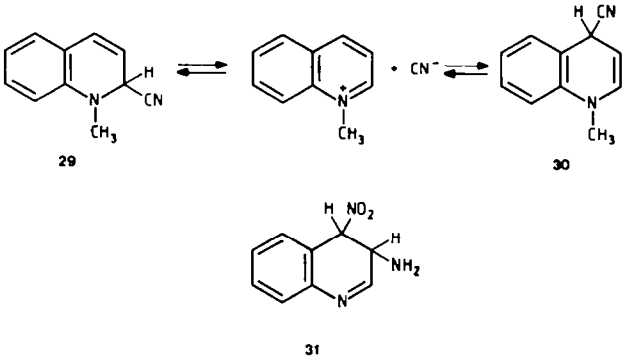
This is illustrated by the following example. When quinoline is added to a solution of potassium amide in liquid ammonia at −60°C, the 2-aminodihydroquinolinide (**25**) is formed.[15,16] However when the same solution is warmed to about +10°C the 4-aminodihydroquinolinide (**26**) is nearly exclusively present (Scheme 8). It is evident that at very low temperature the kinetically formed adduct **25** and at higher temperature the thermodynamically preferred **26** is obtained.[15,16] At intermediate temperatures, mixtures of **25** and **26** are obtained.[16] From this example it is evident that site selectivity seems to play an important role at the stage of the addition reaction. It determines mainly the final composition of reaction products, although the difference in rates of the aromatization (k_2, Scheme 1) for isomeric σ-adducts also affects the reaction outcome. As an illustration: quinoline, when dissolved in a solution of potassium amide in liquid ammonia at −40°C, forms a mixture of 2-amino-(**25**) and 4-amino-(**26**) adducts in the ratio 3 : 1, but after aromatization of these adducts at the same temperature the products **27** and **28** are obtained in 53% and 10% yields, respectively (Scheme 8).[15]



Scheme 8.

Site selectivity in relation to temperature have been extensively studied in Chichibabin aminations of all naphthyridines.[17-19] They follow the same addition rules as discussed above with quinoline.

Interestingly, the same behaviour was found for the reactions of pyridinium and quinolinium cations with cyanide ion.[20,21] It turns out that under kinetically controlled conditions (at −30 to −70°C) the addition takes place at C-2, yielding the σ-adduct **29**. Increase of the temperature up to −20 to +10°C[20,21] results in the formation of the 4-cyano adduct **30** (Scheme 9). Earlier experiments in which the addition of the cyanide ion was formed to add 'anomalously', i.e. exclusively at C-4, which behaviour was explained by means of MO calculations[22,23] on the basis of charge–transfer complexation between the reactants,[24] have neglected the temperature influence.



Scheme 9.

A vast majority of nucleophiles have been investigated in reactions with pyridinium and quinolinium cations. They all show the preferred additions at C-2.[3,4,20,21,25-30]

2.2. *Reactive Forms of Azines*

The S_N^H reaction of azines can be divided as follows depending on either the nature of reagents used or the type of their activation involved:

a. the reactions initiated by an anionic activation of the nucleophile employed;
b. the reactions involving the positively charged azaaromatic;
c. the reactions in which both reactive partners are activated by charge;
d. interactions between uncharged reactants.

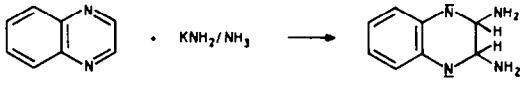
All these types of the S_N^H reactions are discussed below.

2.2.1. *Uncharged azines*

Azines belong to the π-deficient heteroaromatics because of the electron withdrawing effect of the aza group activating the system for a nucleophilic attack.[31] Therefore, azaactivation plays an exceptionally important role in S_N^H reactions. The polarizing effect of the aza group in pyridine is comparable to that of the nitro group in nitrobenzene. Due to this effect *o*- and *p*-positions of an azine ring are characterized by an enhanced activity towards nucleophiles which finds its reflection in the so-called local π-deficiency indices.[11,32] In principle, the aza group activation effect is less than that of the nitro group ($k_{NO_2}/k_{aza} > 1$).[33] This was also experimentally observed by a study on σ-adduct formation between 4-nitroquinoline and liquid ammonia, leading to the C-3 adduct **31** and not to the C-2 adduct.[16] The tendency towards specific proton solvation increases its activation power to a great extent, thus making ($k_{NO_2}/k_{aza} < 1$).[33]

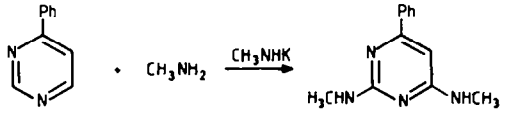
2.2.1.1. *Effects of aza groups, benzene annelation and of substituents.* The reactivity of azines in S_N^H reactions, as in any other chemical conversion, depends greatly on the electronic and steric effects of the substituents.

Introduction of each aza group increases the activity of azines making them able to react with weaker nucleophiles or under milder reaction conditions. Diazines and their benzo analogues are more active towards nucleophiles than the corresponding monoazine derivatives. When reacted with the amide ion, for example, pyrazine and quinoxaline undergo, unlike pyridine and quinoline, not mono- but the diaddition reaction (Scheme 10).[34]



Scheme 10.

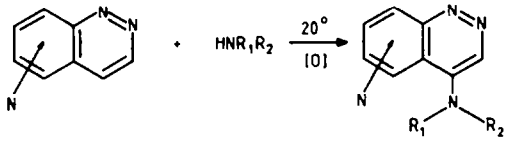
The reaction of 4-phenylpyrimidine with methylamine in the presence of potassium methylamide results in the disubstitution product (Scheme 11).[35]



Scheme 11.

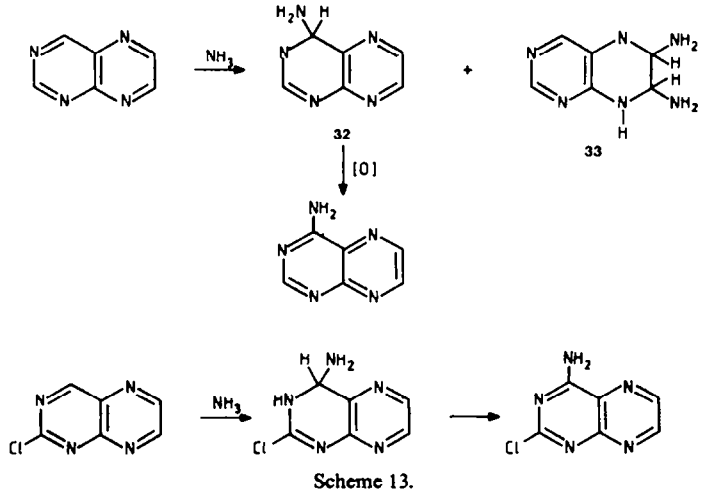
Triazines[36,37] and tetrazines[38] are even more reactive and convert into amino adducts in liquid ammonia, free of the amide ion.

Azaaromatic compounds with two fused rings exhibit, as a rule, higher reactivity than azine derivatives with one ring. Thus, triazanaphthalenes react with alkyl- and arylamines, thiols and other nucleophiles without any base catalysis into the S_N^H products (Scheme 12).[39]



Scheme 12.

Tetraazanaphthalenes are as expected more reactive than the triazanaphthalenes and have moreover more than one centre which is vulnerable for a nucleophilic attack. Thus, pteridine can react with ammonia, primary and secondary alcohols to afford both 1 : 1 and 1 : 2 adducts (Scheme 13).[40–42] These ratios are strongly dependent on the temperature. At low temperature C-4 addition is strongly favoured. With liquid ammonia the adducts **32** and **33** are obtained. In the presence of



Scheme 13.

an oxidant ($KMnO_4$) **32** is converted into 4-aminopteridine. Attempts to oxidize **33** into 6,7-diaminopteridine failed.[43] The amination of pteridines by liquid ammonia–potassium permanganate is also successfully applied with 7-phenyl-, 7(*p*-methoxyphenyl)-, 7-methyl-, 7-*t*-butyl-, 6,7-dimethyl- and 2-phenylpteridine yielding the corresponding 4-amino compounds.[44]

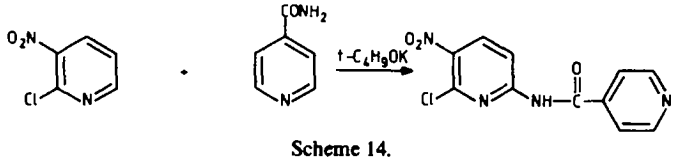
It is of interest that 2-chloropteridine, when reacted with liquid ammonia in the presence of an oxidant ($KMnO_4$), gave 4-amino-2-chloropteridine.[43] Despite the presence of the activated halogeno atom at C-2, the C-4 adduction is still favoured, showing the high π-deficiency of the pteridine ring at C-4 (Scheme 13).

Also the introduction of an alkylamino group at C-4 in pteridines, simply by reacting them with a primary alkylamine in the presence of potassium permanganate was easily performed. The precursors of these products, i.e. the σ-adducts at C-4, could be registered by ^{1}H-NMR spectroscopy.[43,45]

The effect of the benzene ring annelation is somewhat similar to that of introducing an aza group. If we try to estimate these effects quantitatively, considering the electrochemical reduction reaction as the simplest model of a nucleophilic addition, then, as found for the series of N-alkylazinium cations, the aza group shifts $E_{1/2}$ to more positive values of about 0.5 V, while annelation of the benzene ring causes shifts of 0.2–0.5 V.[9]

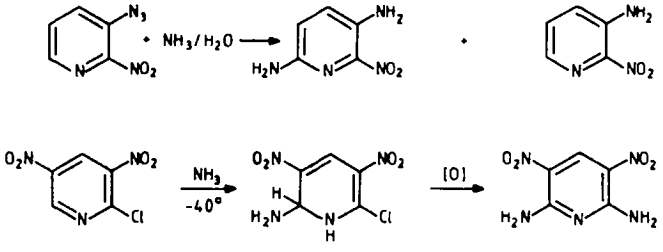
As might be expected mesomeric electron withdrawing groups, such as NO_2, CN, COR and others, increase the reactivity of azines in the S_N^H reactions, while electron donating groups, including alkyl substituents, decrease it considerably. Some examples are given below.

In 3-nitro-2-chloropyridine the hydrogen atom at C-6 is readily substituted by the pyridylcarbonylamino group in the presence of potassium *t*-butylate (Scheme 14).[66]



Scheme 14.

The presence of two electron acceptors in the pyridine ring makes 2-nitro-3-azidopyridine so reactive that nucleophilic substitution of hydrogen at C-6 takes place even by action of an aqueous solution of ammonia azide (Scheme 15).[17] In this reaction the azido-group acts as hydride acceptor undergoing both intra-and intermolecular reduction reactions.

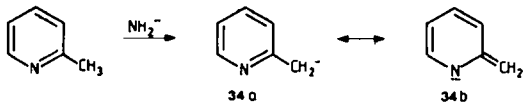


Scheme 15.

As one can see the activation of the nitro group is primarily directed to the C_6 position and not to C-2, containing the labile nitro group. This behaviour is very similar to that observed when 2-chloro-3,5-dinitropyridine reacts with liquid ammonia. At -60°C the C_4 adduct is formed, at -40°C the C_6 adduct. Apparently the C_6-adduct is the thermodynamically most stable one. In the presence of an oxidant ($KMnO_4$) the $S_N^H(AE)+S_N^{Cl}(AE)$ product i.e. 2,6-diamino-3,5-dinitropyridine is obtained in 70% yield.[48]

The activating effect of the nitro groups is also illustrated by the amination reaction of 3,6-dinitro-1,8-naphthyridines, which also proceeds easily in liquid ammonia[49] containing potassium permanganate.

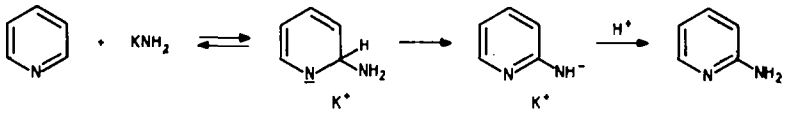
Contrary to that, amination of α- and γ-methyl substituted pyridines using potassium amide as aminating agent require more severe reaction conditions since α- and γ-picolines are easily depronated in the presence of potassium amide yielding the quite unreactive anions **34** (Scheme 16).[6]



Scheme 16.

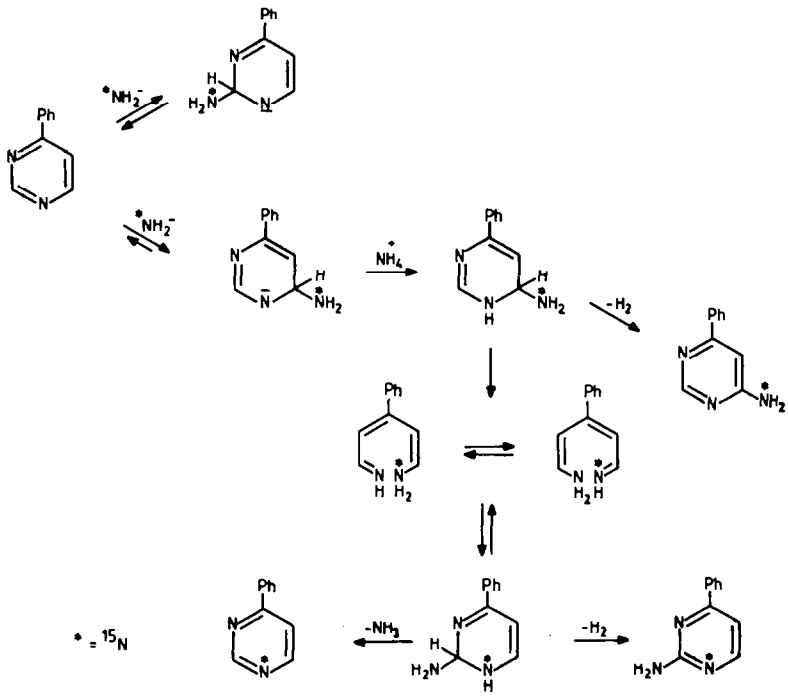
As might be expected, introduction of the amino group into the pyridine ring reduces its reactivity towards nucleophiles. Thus, 2-aminopyridine is converted into 2,6-diaminopyridine by action of potassium amide in an aprotic solvent only at 160–180°C, whereas the amination of pyridine in the same solvent takes place at 105–130°C.[6]

2.2.1.2. *Reactions with anions.* Among uncharged azine–anionic nucleophile interactions leading to a S_N^H substitution the Chichibabin amination reaction seems to be the best studied (Scheme 17). The reaction has been discussed in detail in a number of reviews.[6,19,50,51] The reaction mechanism is normally depicted as given in Scheme 17, i.e. addition and aromatization by hydride removal, that deprotonates the amino group under evolution of hydrogen. The mechanism will be discussed in extensive detail in Section 3.



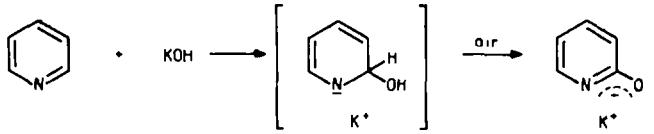
Scheme 17.

Also, it is worth mentioning that the animation of some diazines, triazines and tetraazanaphthalenes by action of potassium amide or ammonia may proceed via the ANRORC mechanism (Scheme 18).[52,53]



Scheme 18.

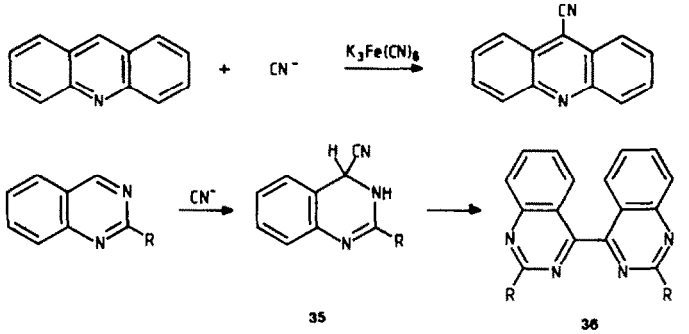
The hydroxylation of azines is somewhat similar to the amination process but it is usually carried out at rather high temperatures (about 300°C), (Scheme 19).



Scheme 19.

The hydroxylation of pyridine,[54] quinoline and isoquinoline,[55] acridine and phenanthridine[56] has been described in the literature. Pyrimidines and purines have been found to undergo the ring opening reaction initiated by the addition of the hydroxide ion.[57]

The cyanide ion is not nucleophilic enough to react with the neutral compounds, pyridine, quinoline and isoquinoline; however it adds to C-9 in acridine possessing a less aromatic character, and yields in the presence of an oxidant 9-cyanoacridine (Scheme 20).[58]



Scheme 20.

The addition of the cyanide ion to quinazoline and its derivatives results in the σ-adducts **35** which are, however, not oxidized to the expected 4-cyanoquinazolines. Instead the dimeric products **36** are formed (Scheme 20).[58,59]

Although they do not contain a pure carbanionic centre, alkyllithium and aryllithium derivatives and organomagnesium compounds also seem to be effective reagents for nucleophilic substitution of hydrogen in azines. Some samples of this type of reaction are presented in Tables 3 and 4.

Table 3. Nucleophilic substitution of hydrogen in pyridine

Reagent	Reaction product	Yield, %	Ref.
$NaNH_2$	2-Aminopyridine	66–76	6
Alk-NHNa	2-Alkylaminopyridine	12–79	60
NH_2NHNa	2-Hydrazinopyridine	16–29	61
KOH	Pyridin-2-one	low yield	62
Ar(Alk)Li	2-Aryl(alkyl)pyridines	60	63
ArMgCl	2-Arylpyridine	20	64
	4-Arylpyridine	80	64
$n\text{-}C_4H_9MgCl$	4-n-Butylpyridine	57	65
$n\text{-}C_5H_{11}MgBr$	4-Allylpyridine	9	66

Table 4. Nucleophilic substitution of hydrogen in quinoline

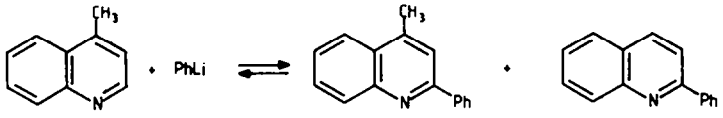
Reagent	Product	Yield	Ref.
$NaNH_2$	2-Aminoquinoline*	32	66
KNH_2	2-Aminoquinoline†	55	16
KNH_2	4-Aminoquinoline‡	65	16
$Ba(NH_2)_2$	2-Aminoquinoline§	80	67
	2-Aminoquinoline‖	53	67
	4-Aminoquinoline	10	67
$n\text{-}C_4H_9NHNa$	2-n-Butylaminoquinoline	40	68
$NaNHNH_2$	2,2-Hydrazoquinoline	45	61
KOH	Quinolin-2-one	80–90	62
$CH_2{=}CHMgBr$	2-Allylquinoline	56	69
CH_3SOCH_2Na	4-Methylquinoline	96	70
Alk(Ar)Li	2-Alkyl(aryl)quinoline	70	71

* In xylene at 130°.
† In liquid ammonia with $KMnO_4$ at −60°.
‡ In liquid ammonia with $KMnO_4$ at +10°.
§ In liquid ammonia at 20°.
‖ In liquid ammonia with KNO_3.

In reactions of pyridine and quinoline with organometallic compounds the 2-positions of the ring are usually the preferential site for a nucleophilic attack. However, if the reaction is carried out with an alkyl halogenide in the presence of lithium or magnesium forming organometallic compounds *in situ*, 4-substituted azine derivatives are yielded as main reaction products.[72]

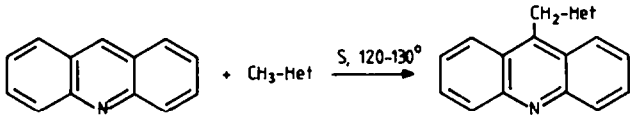
The regioselectivity for the addition of Grignard reagents to azaaromatic rings has recently been investigated.[73]

The reaction of lepidine with phenyllithium results in 4-methyl-2-phenylquinoline and 2-phenylquinoline in 96% and 3% yields, respectively (Scheme 21).[74] Both products are obtained as a result of the addition of the nucleophile at C-2, although the formation of 2-phenylquinoline is not quite clear.[74]



Scheme 21.

Reactions of azines with carbanions have been extensively studied and reported in many publications. Most of these papers deal with the addition of aliphatic and aromatic methylketones, acetylacetone, ethyl cyanoacetate and other CH-active compounds to acridine in the presence of sodium methoxide yielding the 9-substituted products.[67-77] It is interesting that acridine is also able to react with such reagents as α-methyl substituted azines and their quaternary salts without any base. Acridine itself seems to play the role of proton acceptor in this case (Scheme 22).[78]



Scheme 22.

The reaction is carried out by fusing the reactants with an excess of sulphur at 120–130° (Table 5). It is remarkable that no reaction has been observed in the absence of an oxidant.[78]

Table 5. The reaction of acridine with α-methylsubstituted azines

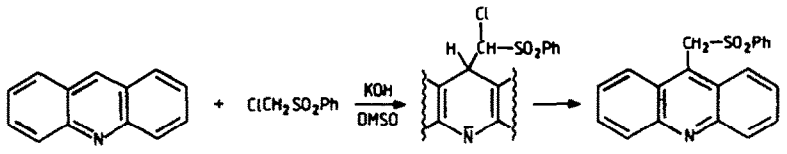
Reagent	The ratio of reagents—acridine : methylazine : sulphur	Reaction time, hours	Yield, %
2- and 4-Picolines	No reaction		
4-Picoline methiodide	1 : 2 : 3	5	11
Quinaldine	1 : 1 : 3	2	31
Lepidine	1 : 1 : 3	2	56

A useful synthetic methodology for the introduction of various functional groups into an azine ring is the so-called vicarious S_N^H reactions.

The characteristic feature of these reactions is that the presence of a good leaving group X in the carbanionic reagent employed leads after addition to a σ-adduct, in which the elimination of HX is facilitated, making the S_N^H process occur more easily.

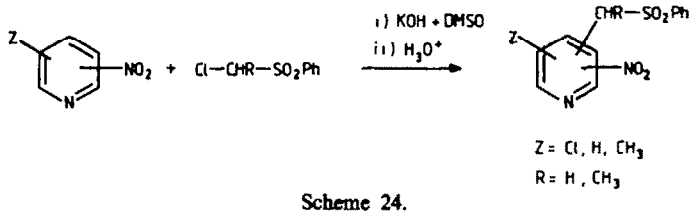
Numerous examples of vicarious nucleophilic substitution have been discovered in the reactions of nitro-activated substrates with halogenmethylsulfones, nitroalkanes and other CH-active compounds.[79] A number of vicarious S_N^H reactions have also been performed on azine derivatives.

Among uncharged azine derivatives only acridine with its low aromatic character proves to be reactive towards chloromethylsulfones in the presence of a base to form 9-methylsulfonylacridine in 72% yield (Scheme 23).



Scheme 23.

Pyridine and quinoline are inert towards chloroalkyl sulfones, but the nitropyridines and chloronitropyridines easily undergo the vicarious nucleophilic substitution of hydrogen at positions *o*- and *p*- to the nitro group (Scheme 24).[80]

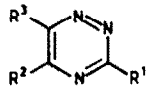


Scheme 24.

These examples again show that under appropriate conditions the displacement of hydrogen is faster than of nucleophugic substituents as halogen and the nitro group.

Substituted 1,2,4-triazines react in an analogous manner to form the S_N^H products **37** (Table 6).[81] Quinoxaline and naphthyridines react with chloromethylsulfones in a different way: not S_N^H products are yielded, but unexpectedly aziridine and cyclopropane derivatives.[82]

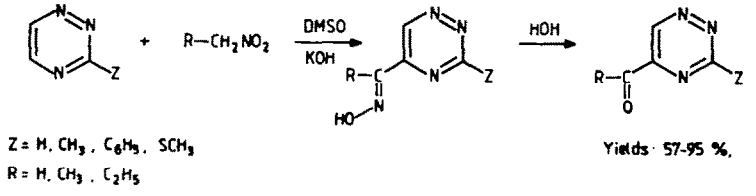
Table 6. Substituted 1,2,4-triazines **37a–e** obtained by the vicarious S_N^H reaction[81]



37

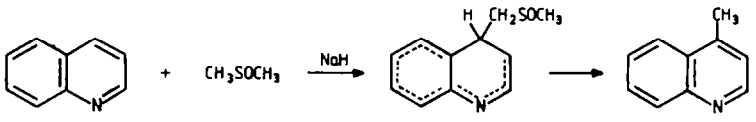
Compound	R^1	R^2	R^3	Yield, %
37a	H	$PhSO_2CH_2$	Ph	65
37b	Ph	$PhSO_2CH_2$	H	78
37c	MeS	$PhSO_2CH_2$	H	76
37d	$PhSO_2CH_2$	Ph	H	74
37e	MeS	Ph	$PhSO_2CH_2$	56

An interesting example of the vicarious S_N^H reaction is the very convenient and elegant method for direct nucleophilic acylation of azaaromatics including introduction of the formyl group into the triazine ring (Scheme 25).[83] In the intermediary σ-adduct an internal redox reaction takes place in which the leaving hydrogen reacts with the nitronate moiety[83] (also see Section 3).



Scheme 25.

The methylation of azines by action of the anions generated from dimethyl sulfoxides[70,83,84] and dimethylsulfones[84] in the presence of sodium hydride[70] or sodium *t*-butylate[83,84] (Scheme 26) is somewhat similar to vicarious displacement reactions.

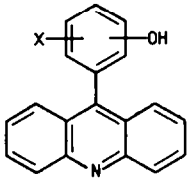


Scheme 26.

The method provides an effective one-step route to methylated azines. 1-Methylisoquinoline is formed quantitatively, and 4-methylquinoline, 9-methylacridine and 6-methylphenanthridine have been obtained in 74–98% yields.[70,85] Also non-aza activated anthracene and phenanthrene behave similarly giving rise to the corresponding methyl derivatives in 13% and 86% yields; the aza-activated but more aromatic pyridine proves to be unreactive towards these anions. This fact shows again that the reactivity of azines in the S_N^H reactions depends more on the aromaticity of these compounds as indicated by their aromaticity indices, than by the aza-activation.

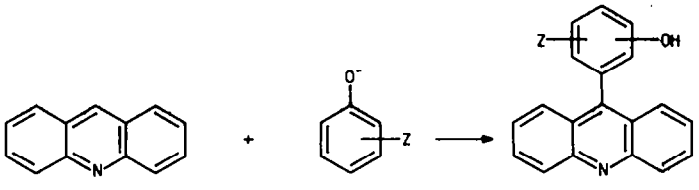
Ambident phenolate anions react with acridine as C-nucleophiles to afford hydroxyaryl acridines (Scheme 27, Table 7).[86] The reaction proceeds by heating a solution of acridine in DMF at 130–

Table 7. Yields of 9-hydroxyarylacridines



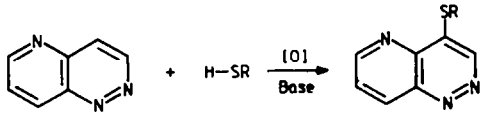
Starting phenol	The S_N^H product	Yield, %
Phenol	4-OH	33
o-Cresol	4-OH-3-CH_3	35
m-Cresol	4-OH-2-CH_3	51
p-Cresol	2-OH-5-CH_3	27
o-Bromophenol	4-OH-3-Br	91
m-Aminophenol	2-OH-4-NH_2	82
1-Naphthol	2-OH-3,4-benzo	74
2-Naphthol	2-OH-5,6-benzo	72
8-Hydroxyquinoline	4-OH-5,6-*β*-pyrido	81
o-Methoxyphenol	4-OH-3-OCH_3	15
m-Methoxyphenol	4-OH-2-OCH_3	43

140°C while air is led through the solution. Sodium salts of phenol and its derivatives with electron donating substituents in the ring participate in the reaction, whereas nitrophenols and hydroxybenzoic acids do not yield any S_N^H products (Table 7).[86] Unlike acridine, pyridine and quinoline do not interact with the phenolate anion.



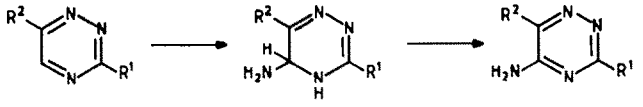
Scheme 27.

There are only a few examples of reaction between uncharged azines and S-nucleophiles. They include the addition of the bisulphite ion to acridine[87] and nucleophilic substitution of hydrogen in 5-azacinnoline by action of thiols (Scheme 28).[88]

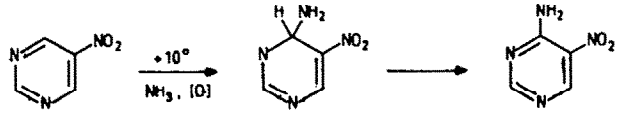


Scheme 28.

2.2.1.3. *Reactions with uncharged nucleophiles.* A great number of azaaromatics have been found to react easily with liquid ammonia (−40°C) in the presence of an oxidant ($KMnO_4$) into the corresponding amino compounds. These S_N^H amination reactions only occur with aza-activated heterocycles, i.e. triazines,[37] tetrazines,[38] pteridines,[38,42-45] or with azines activated by nitrogroups, such as nitropyrimidines,[89] nitroquinolines,[16] nitronaphthyridines.[18,49] In all these reactions NMR-evidence has been obtained[89,90] for the intermediary existence of σ-adducts (Scheme 29).



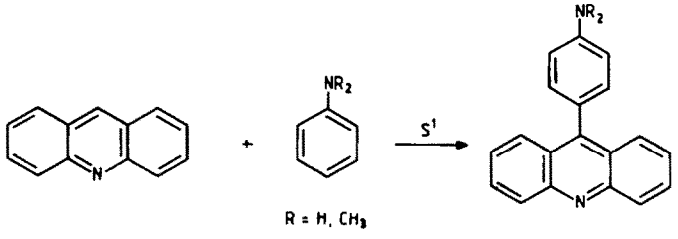
R^1 = H, CH_3, C_6H_5, OCH_3, NH_2, SCH_3, Cl
R^2 = H, C_6H_5, Br



Scheme 29.

The amination of 5-nitropyrimidine is strongly temperature dependent. At −75°C, mainly 2-amino-5-nitropyrimidine is formed, at +10°C the 4-amino-5-nitropyrimidine is exclusively obtained, again showing the kinetic and thermodynamic features of the amination (Scheme 29).[89]

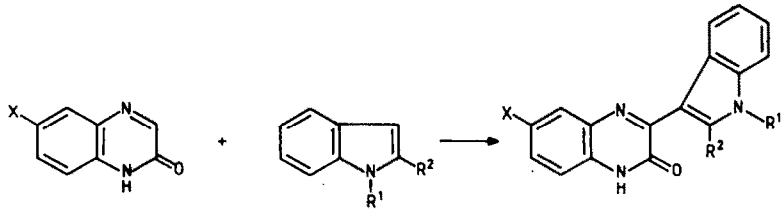
Substitution of hydrogen in azacinnolines has been observed on treatment with amines.[39] We should also mention here the reaction of acridine with lepidine and other methyl substituted heterocycles.[78] As far as reactivity is concerned acridine seems to be unique in the sense that it is able to react even with such weak nucleophiles as arylamines (Scheme 30).[91]



R = H, CH_3

Scheme 30.

Analogously quinazolin-2-one,[92] quinoxalin-2-one[93] and cinnolin-2-one[13] can undergo amino-arylation and heteroarylation reactions on treatment with arylamines, pyrroles and indoles (Scheme 31).

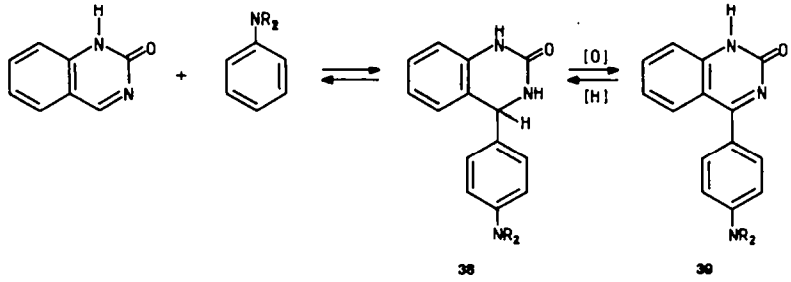


X = H, NO_2, R^1 = H, CH_3; R^2 = H, CH_3

Scheme 31.

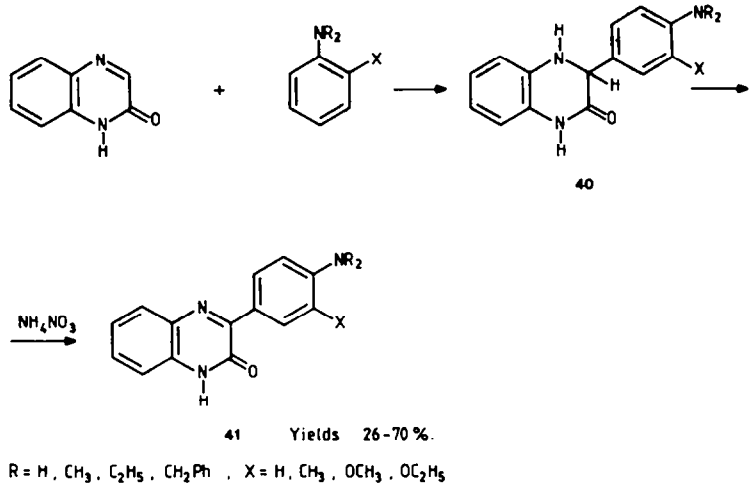
The arylation and heteroarylation of quinazolin-2-one proceeds smoothly when fused with sulphur or when reaction takes place in a DMF solution.[92] The compounds 39 can be reduced into

dihydroquinazolines **38** and then again be regenerated by dehydrogenation with sulphur; however all attempts to detect the formation of σ-adducts **38** chromatographically on mixing of the arylamine and quinazolin-2-one in an argon atmosphere have failed (Scheme 32).[92] It suggests that the intermediates **38** are present at a vanishingly low equilibrium concentration.



Scheme 32.

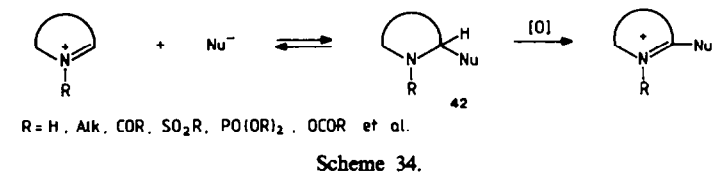
Quinoxalin-2-one reacts similarly with arylamines to give rise to σ-adducts **40** which unlike the dihydroquinazolines **38** can be registered in the ^{1}H NMR spectra. The adducts **40** are easily oxidized by ammonium nitrate under the reaction conditions (acetic acid, 130°C) into the corresponding S_N^H products **41** (Scheme 33).[93]



Scheme 33.

2.2.2. *Azinium cations*

Azinium cations are undoubtedly more reactive in the S_N^H reactions due to their enhanced electrophilicity facilitating the addition of nucleophiles. It should be taken into account, however, that electron withdrawing groups attached to the ring carbon or nitrogen atoms increase the stability of σ-adducts thus making the stage of their aromatization more difficult (Scheme 34).



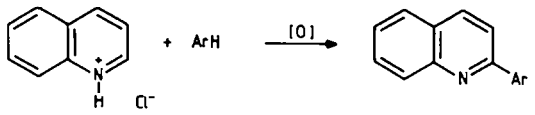
Scheme 34.

The addition of nucleophiles to azinium cations leads to the formation of neutral σ-adducts **42**, which are usually more stable than the corresponding azacyclohexadienate anions, formed from uncharged azines with anions. In this respect quaternary azinium salts seem to be more convenient

substrates to investigate the S_N^H process, since the structure of σ-adducts formed can be studied by means of a variety of physical methods including X-ray analysis which is especially important for understanding the transition state nature.

2.2.2.1. *NH-azinium salts.* The NH-azinium salts are comparatively seldom used in the S_N^H reactions, since often proton transfer from substrate to reagent occurs which leads to mutual deactivation or even decomposition of some nucleophilic reagents, such as, for instance, organometallic compounds.

NH-azinium salts seem to be more reactive towards nucleophilic reagents than the corresponding N-alkylazinium salts. Thus, N-alkylquinolinium and N-alkylisoquinolinium cations do not react with aromatic nucleophiles such as arylamines and phenols into substitution products[22] whereas protonated quinoline undergoes the S_N^H reaction smoothly (Scheme 35).[94]

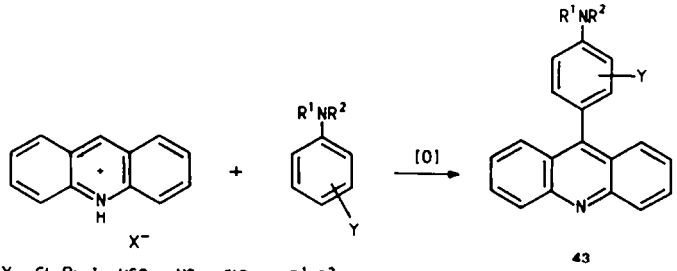


ArH C_6H_4-4-OH , C_6H_3-2-OH, 4-OH ; C_6H_3-2-CH_3, 4-OH , C_6H_4-4-OCH_3 , C_6H_4-NH_2 , C_6H_4-4-$N(CH_3)_2$, C_6H_3-2-CH_3 , 4-NH_2

Scheme 35.

NH-acridinium salts are reactive towards a variety of nucleophiles, such as arylamines and arylhydrazones, phenols, pyrroles and indoles, furan, picoline and other α-methyl substituted heterocycles.[5,95]

All these reactions take place under oxidizing conditions; suitable oxidants are sulphur (melt) or atmospheric oxygen bubbled through a DMF solution. Thus, arylamines containing various substituents both in the ring and in the amino group react with protonated acridine salts to produce aminoarylacridines **43** in 30–95% yields (Scheme 36).

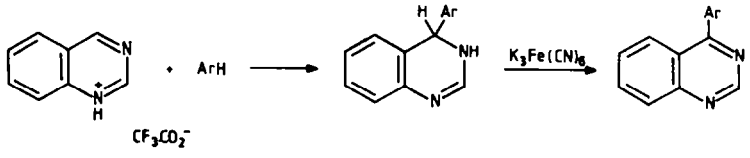


X = Cl, Br, I , HSO_4 , NO_3 , ClO_4 ; R^1, R^2 = H, Alk , N = CH-Ar ;
Y = Alk , Hal , OH , NH_2 , OR , NR_2 , benzo

Scheme 36.

The reaction of acridinium salts with anilines has recently been reinvestigated by Japanese authors.[96] They found that besides the same aminoarylacridines **43**, 9,10-dihydroacridine and 9,9′-diacridanyl are formed as by-products.[96]

Quinazoline trifluoracetate manifests a higher electrophilicity than diazonium salts. It easily adds not only phenol, pyrrole, anisole, dialkylanilines and thiomesitylene but also naphthalene, anthracene and mesitylene which additions are unusual for azinium cations (Scheme 37).[97,98] In all cases the aromatization of the adducts formed has been carried out by means of potassium ferricyanide.

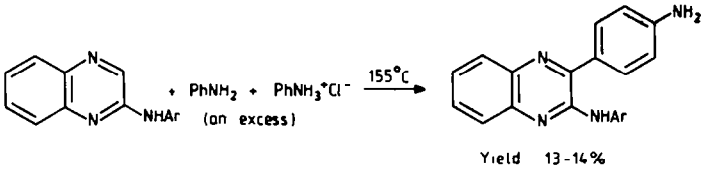


Scheme 37.

Pyridazine, pyrazine, pyrimidine and their derivatives react in a similar manner to produce the S_N^H products.[97,98] The reactivities of azines relative to anisole are changed as follows: quinazoline > pyrimidine > 5-methylpyrimidine ≫ 2-aminopyrimidine ~ 4-methylpyrimidine ~ 4-phenylpyrimidine > 2,4-dimethylpyrimidine.

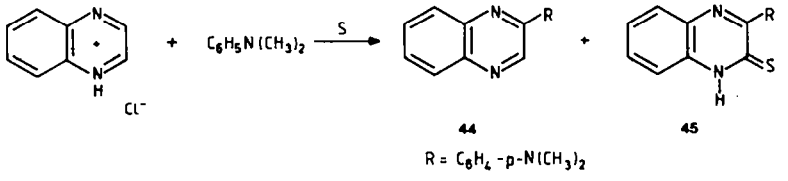
There are numerous examples of covalent hydration and bisulphite addition with protonated pyrimidines, quinazolines and pteridines.[12,99] Using these reactions as the first step of the S_N^H process the corresponding pyrimidine derivatives can be obtained.

The activation of quinoxaline derivatives by protonation also proved to be effective to cause the substitution of hydrogen when treated with arylamines (Scheme 38).[100]



Scheme 38.

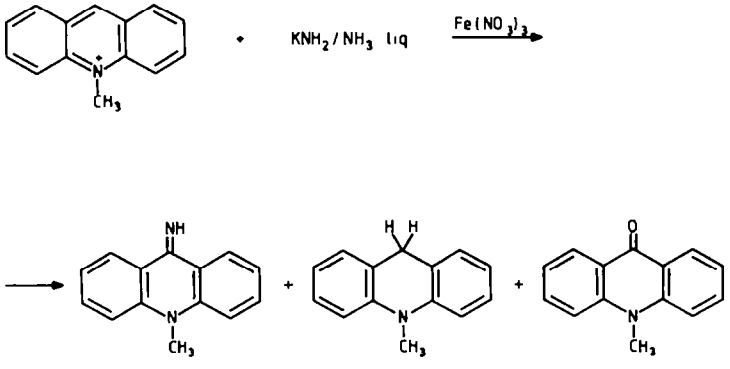
When quinoxaline hydrochloride, N,N-dimethylaniline and sulphur are heated up to 130°C in the ratio 1 : 1 : 3 besides aminoarylation into **44** (12%), subsequent thionation also takes place, leading to the formation of **45** (Scheme 39).[101]



Scheme 39.

2.2.2.2. *N-alkylazinium salts.* Although N-alkylazinium cations on the whole are less electrophilic than their N-protonated analogues (due to the electron donating properties of the alkyl group), nevertheless they are still rather reactive towards both anionic and uncharged nucleophiles.

Among reactions with anionic reagents one ought to mention the Chichibabin amination of some quaternary salts.[18] When N-methylacridinium salt reacts with potassium amide in liquid ammonia in the presence of ferric nitrate 9-imino-10-methyl-9,10-dihydroacridine is formed in 35% yield together with 10-methyl-9,10-dihydroacridine and N-methyacridone (Scheme 40).[102]

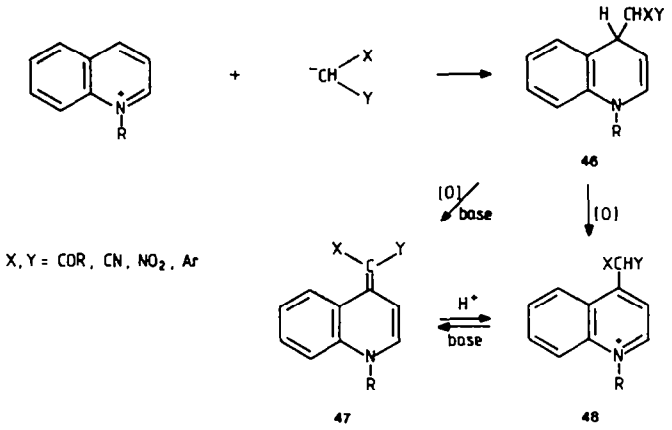


Scheme 40.

The formation of azinones as a result of the interaction of quaternary salts with hydroxide in the presence of an oxidant is an example of an easily occurring S_N^H substitution.[103]

Also the reactions of mono- and diazinium cations with carbanions of the type X-CH$^-$-Y leads

to substitution of hydrogen, provided that the reactions are carried out under oxidizing conditions (Scheme 41). N-Alkylpyridinium,[104-106] quinolinium[104-106] and quinazolinium[107] cations usually form 4-substituted products, while isoquinolinium,[104,105] acridinium[108] and quinoxalinium[109] salts form 1-, 9- and 2-substituted products respectively.

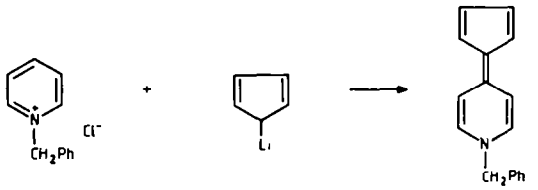


Scheme 41.

σ-Adducts like **46** can often be isolated from the reaction mixture. Their stability increases with annelation of the benzene ring or introduction of ring nitrogens. Dihydro compounds **46** are readily oxidized in air, and they can be dehydrogenated by chloroanil, lead tetraacetate in benzene, permanganate in acetone, etc.[76,77] In the presence of a base the oxidation of adducts **46** leads to the formation of the quinoid anhydrobases **47** due to deprotonation of the CH group at C-4 (Scheme 41).

On treatment with acids, compounds **47** are protonated into the azinium salts **48** (Scheme 41). Also the azabenzylation of acridine by action of methylpyridines discussed above proceeds more smoothly when quaternary acridine salts are used and given better yields of the S_N^H products.[110]

Organometallic nucleophiles with a highly polar character of the C–M bond have been used for the introduction of alkyl and aryl residues into N-alkylazinium salts (Scheme 42).[111-113]



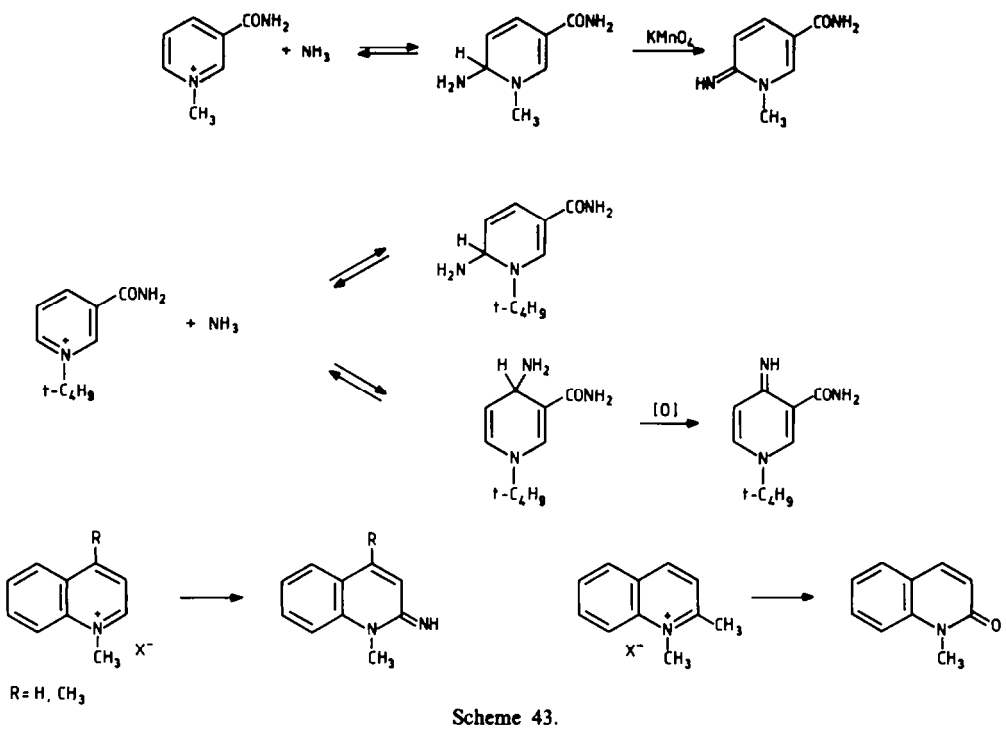
Scheme 42.

Among reactions of N-alkylazinium cations with uncharged nucleophiles the addition of ammonia[17,18,28,30] and water[25,26] are the most studied. In particular, the regioselective oxidative imination of 3-carbamoyl-1-methylpyridinium (Scheme 43),[114] N-methylquinolinium and 1,8-naphthyridinium[115] salts have recently been described.

It is of interest to mention that the 1-*t*-butyl-3-carboxamidopyridinium salt undergoes a regioselective imination at C-4. Apparently the bulky *t*-butyl-group at N-1 strongly hinders the addition at C-2.[30]

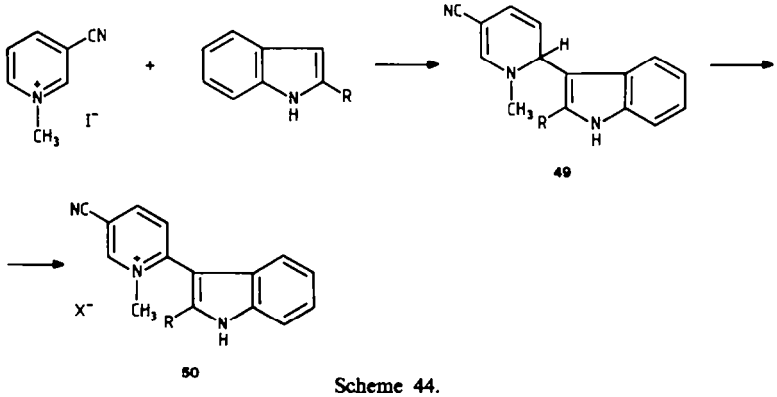
Later studies have shown that the presence of an electron withdrawing group, such as the carboxamide substituent, is not necessary, since the 1-methylpyridinium salt itself is already reactive enough to undergo the oxidative imination at very mild conditions.

Several papers have appeared, in which it is shown that N-methylquinolinium salts easily undergo S_N^H substitution at C-2.[114] 1-Methyl- and 1,4-dimethylquinolinium salts yield the corresponding 2-imino derivatives, when they are treated with liquid ammonia–potassium permanganate.[114,115] It is very striking that 1,2-dimethylquinolinium iodide, under identical conditions undergoes an oxidative-demethylation at C-2, yielding 1-methylquinolone-2 (Scheme 43).



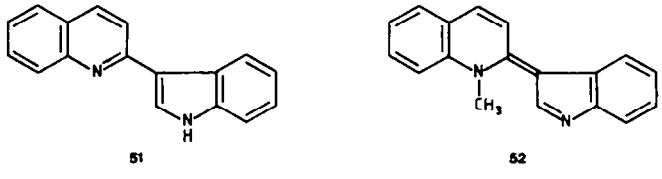
Scheme 43.

Also the N-methylnaphthyridinium salts when reacted with liquid ammonia, containing potassium permanganate easily undergo imination on the carbon adjacent to the nitrogen, carrying the methyl group, although many side reactions (e.g., ring contractions) occur.[116] 3-Cyano-1-methylpyridinium iodide reacts with the π-excessive indole in acetonitrile without an oxidant to yield product **50** (50%). The dihydropyridine intermediate **49** has been isolated from the reaction mixture in 12% yield (Scheme 44). In a similar reaction with 2-methylindole only the addition product **49** (R = CH_3) has been obtained.[117]



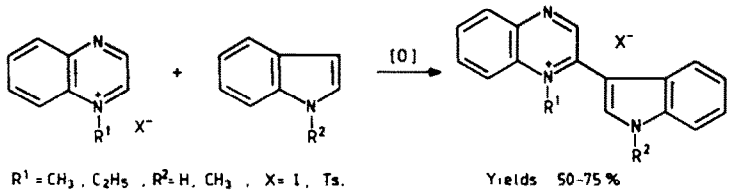
Scheme 44.

The S_N^H reaction of N-methylquinolinium salt with indole in the presence of sodium ethoxide leads to demethylation of the quinoline as well as deprotonation of the indole ring affording the compounds **51** and **52** in 10% and 70% yields (Scheme 45).[117]



Scheme 45.

Also the hydrogen at C-2 in N-alkylquinoxalinium salts (Scheme 46) is readily substituted by an indole moiety. The reaction proceeds at room temperature on bubbling air through an ethanolic solution.[118]

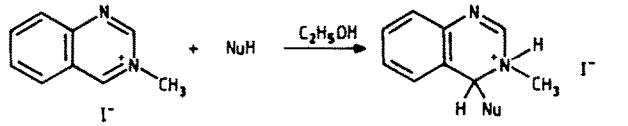


$R^1 = CH_3$, C_2H_5, $R^2 = H$, CH_3, X = I, Ts. Yields 50-75%

Scheme 46.

Products of a similar structure have been obtained in the reaction of N-alkylquinoxalinium iodide with polyphenols; phenol itself does not participate in the reaction.

N-Methylquinazolinium iodide when subjected to a reaction with uncharged aromatic nucleophiles yields the stable dihydro compounds **53**; unlike other dihydrodiazine analogues they resist oxidation (Scheme 47).[119]

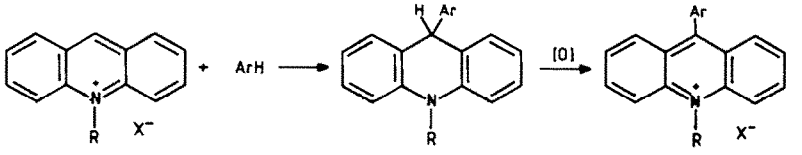


53 Yields 71-98%

Nu = 4-N(Alk)$_2$-C_6H_4, indol-3-yl, 2-methylindol-3-yl,

Scheme 47.

As already indicated on page 5 the quaternary salts of acridine are sufficiently reactive to undergo the S_N^H reaction when reacting with arylamines, arylhydrazones, indoles and phenoles (Scheme 48).[5]



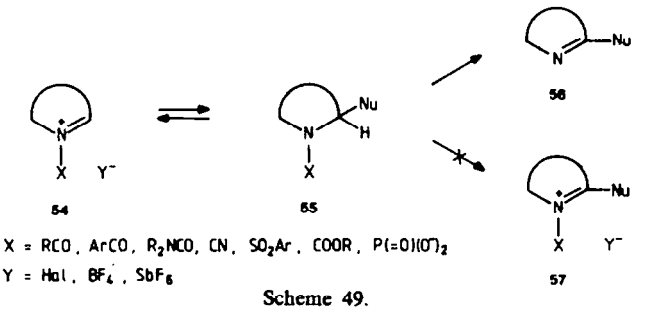
Yields 85-98%

Ar = 4-NH_2-C_6H_4, 4-$(CH_3)_2N$-C_6H_4, 4-$NH(CH_3)C_6H_4$, 4-NH_2-naphthyl, indol-3-yl, 4-NH=CH-C_6H_4

Scheme 48.

A great number of arylamines containing various substituents both in the ring and in the amino group has been reacted with N-alkylacridinium salts.[5] It has been established that the introduction of electron acceptors such as NO_2, COR and CN groups makes the arylamine unreactive toward the acridinium cation. *o*-Substituted dialkylanilines undergo dealkylation by action of the acridinium cation yielding monoalkylaminoarylacridines instead of the expected N,N-dialkylaminoarylacridinium salts.[120] When reacting with *p*-X-substituted N,N-dialkylanilines (X = Br, I and $HgOCOCH_3$) the acridinium cation reacts by an ipso-substitution of the substituent X.[121]

2.2.2.3. *N-acylazinium salts.* The N-acyl salts of pyridine, quinoline, isoquinoline, acridine, phenanthridine, pyrazine and other mono- and diazines have been investigated in their ability to undergo S_N^H reactions. N-acylazinium salts are easily prepared by reacting arylhalides with the appropriate azine in a dry apolar solvent and used *in situ*. Anhydrides of alkyl and aryl substituted carbonic acids, arylsulphonylchlorides, derivatives of phosphorous acids and other reagents are used to generate compounds **54**. The high reactivity of salts **54** allows the addition of dialkylanilines, π-excessive heterocycles (pyrrole, indole, furan), CH-active compounds (β-diketones, acetophenones etc.), trialkyl phosphites and other nucleophiles[1-3] (Scheme 49).

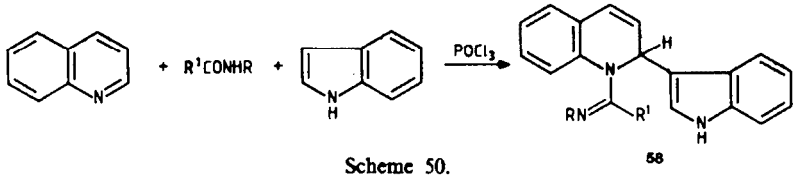


Scheme 49.

Several reviews deal with the chemistry of N-acylazinium salts,[122-126] but the S_N^H reactions are only studied to a limited extent. The use of N-acylazinium salts in the S_N^H reactions is limited since these salts are able to transfer the acyl-group to the free amino and hydroxy-groups, present in nucleophiles such as arylamines and phenols.[122] A majority of reactions between N-acylazinium salts and nucleophilic reagents appear to proceed according to Scheme 49.[122-126]

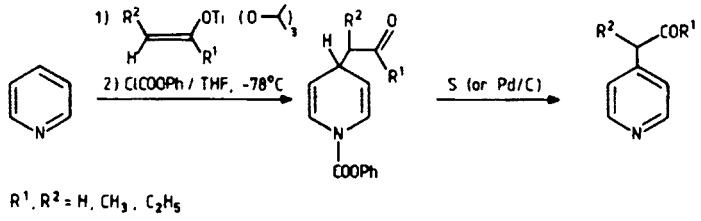
The electronwithdrawing effect of the N-acyl group increases the electrophilicity of the N-acylazinium cations and enhances the stability of their σ-adducts. Aromatization of σ-adducts **55** into **56** or **57** is hindered in many cases with the exception of pyridine derivatives. As a consequence, the reactions are often completed by either the formation of dihydro-compounds **55** or elimination of the acyl group affording product **56**. When reacting with nucleophilic reagents N-acylazinium cations, unlike their N-alkyl analogues, do not yield the substituted N-acylazinium derivatives **57** (Scheme 49).

It is of interest to mention that, whereas N-acylpyridinium salts usually form substitution products, the N-acylbenzopyridinium salts form dihydro-compounds **58** (Schemes 49 and 50)[127] with the exception of the N-acylacridinium cations which also yield S_N^H products like **56**.[128]



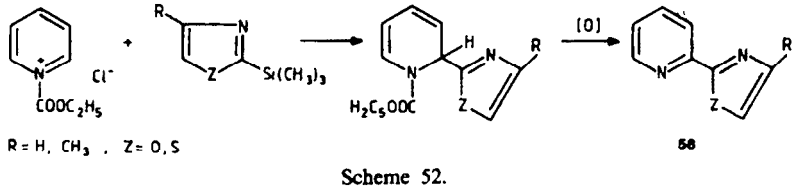
Scheme 50.

Recently alkoxy (aryloxy) pyridinium halides have been found to be appropriate substrates for the introduction of titanium enolates and silyl enol ethers into the pyridine ring (Scheme 51).[128,129]



Scheme 51.

Using pyridinium, quinolinium or isoquinolinium salts as starting materials the unsymmetrical diheteroaryls **58** have been obtained (Scheme 52).[130]

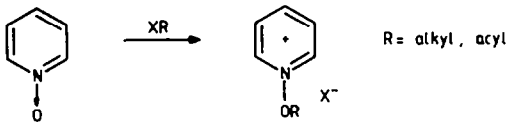


Scheme 52.

Many other pyridine derivatives have been obtained in a similar way.[27]

2.2.2.4. *N-oxides.* It is well established that a N-oxide, in which the nitrogen is a part of the azaaromatic ring, activates the ring to an electrophilic as well as a nucleophilic attack.[131]

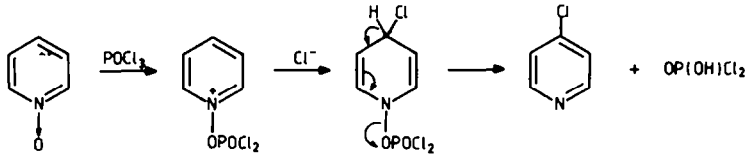
The nucleophilic substitution reaction usually takes place, if the N-oxide group is activated by the addition of an electrophilic reagent to form cationic structure of the type **59**; they are more active than the corresponding N-alkylazinium salts (Scheme 53).[132–134]



59

Scheme 53.

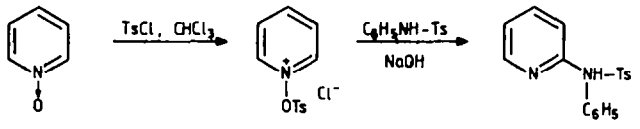
The well known nucleophilic chlorination of pyridine via its N-oxide involves the initial addition of $POCl_2^+$ to the oxygen atom followed by addition of the chloride ion at position 4 and elimination of $HOP(O)Cl_2$ (Scheme 54).[131]



Scheme 54.

In the reaction of 4-cyanopyridine 1-oxide with phosphorus oxychloride and phosphorus pentachloride under the same conditions 3-chloro-4-cyanopyridine is formed in 73% yield,[135] and not 2-chloro-4-cyanopyridine N-oxides as has been reported before.[136] The cyanation of 3-X substituted pyridine N-oxides by action of trimethylsilane-carbonitrile has also been described.[137] The reaction proceeds regioselectively yielding 3-X-pyridine-2-carbonitriles, where X = OCH_3, CH_3, OH, Cl, in 90% yields.

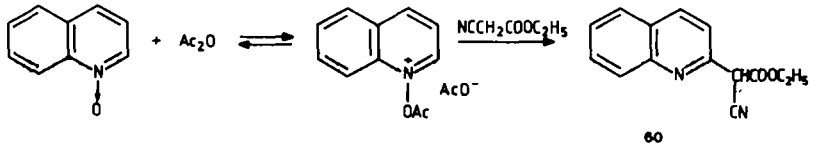
Anilides of sulfinic acids have been used to functionalize the pyridine ring via the N-oxide derivative (Scheme 55).[138]



Scheme 55.

A great deal of other S_N^H reactions aimed at the syntheses of various azine derivatives from their N-oxides[132,134,139] can be divided into two groups:

The first type of reaction is based on the use of acetic anhydride to activate azine N-oxides, and CH-active compounds as nucleophiles. Thus, quinoline N-oxide reacts with ethyl cyanoacetate in acetic anhydride at a low temperature to afford compound **60** in good yield (Scheme 56).

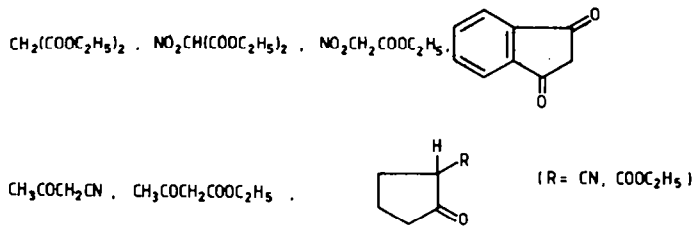


60

Scheme 56.

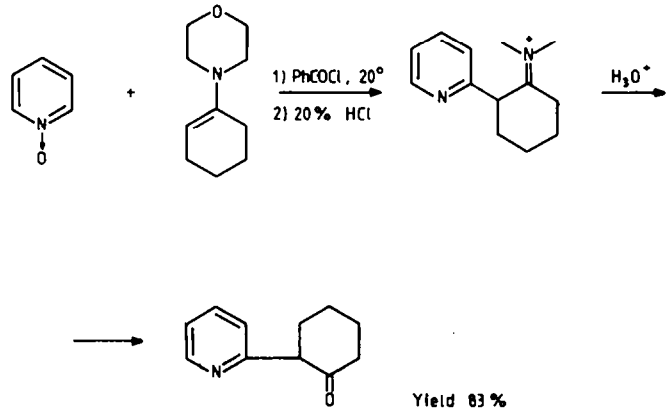
Pyridine N-oxides are much less reactive in analogous reactions yielding the corresponding products in 17–26% yields.[132] The use of this reaction has some limitation. It can be applied to a

series of CH-active nucleophiles shown below (Scheme 57),[132,140] however less acidic compounds, such as acetone and acetophenone, remain unreactive.



Scheme 57.

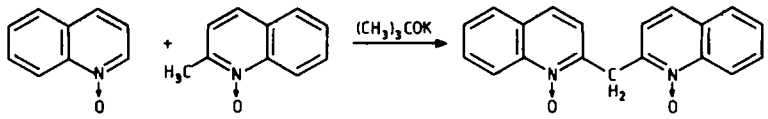
The second type of reaction involves interactions of azine N-oxides with enamines. For example, when an acyl halogenide is added to a mixture of pyridine N-oxide and 1-morpholinocyclohexene 2-(pyridyl-2)cyclohexanone is formed in good yield (Scheme 58).[141]



Scheme 58.

The addition step is considered to be a fast reaction since no products of the acylation of the enamine employed (the formation of which might be expected) have been discovered in the reaction mixtures.[142]

Other 'enamine-like' compounds such as dialkylanilines, indoles, enol ethers[132] and aromatic aldehyde cyanohydrins[134] participate in the similar reactions. The reaction of N-alkoxyquinolinium cations with ketone enamines is much more complicated. It results in the formation of the complex polycyclic compounds containing two quinoline fragments.[143] In a number of cases azine N-oxides can be used in the S_N^H reactions without activation by alkylation or acylation provided the nucleophiles are activated by conversion into anionic reagents using a base as deprotonating agent (Scheme 59).[144,145]



Scheme 59.

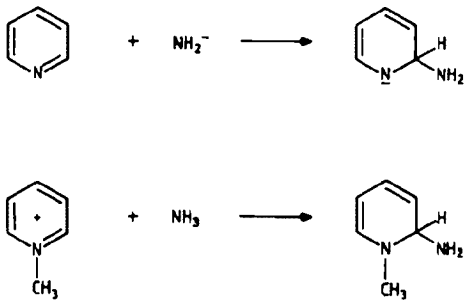
The recently published review on deoxydative substitution in pyridine N-oxide by thiols deals with the mechanism of the S_N^H reactions under consideration and shows their preparative value.[133]

3. MECHANISMS

The mechanisms involved in the S_N^H reactions of azines have not received considerable attention, especially the reactions with anionic nucleophiles for which practically no kinetic data are available.

The rate constants for the Chichibabin amination reaction obtained by measuring the volumes of hydrogen evolved, can be used for estimating the relative reactivities of azines only within the group investigated since the reaction has been carried out under the heterophase conditions.[146]

During the last two decades ^{1}H and ^{13}C NMR spectroscopy has provided new valuable data concerning mechanisms of the S_N^H reactions. Both anionic and neutral σ-adducts formed between pyridines,[2,25,30,34,50,114,147] quinolines and isoquinolines,[2,21,34,148] acridines,[149,150] pyrimidines,[2,34,50,89,151–156] other diazines and benzodiazines,[34,50,115,157–159] triazines,[36,37,50,160–164] pteridines,[40–45,165–167] naphthyridines[19,168,169] and s-tetrazines[38,50] with various nucleophilic reagents have been registered or even isolated in some cases. Two examples are shown below (Scheme 60).



Scheme 60.

The structure, rate and equilibrium constants for the formation of anionic σ-adducts arising from the reactions of azines with NH_2^-, OR^-, $XCYH_2^-$ and other anionic reagents have recently been reviewed.[2]

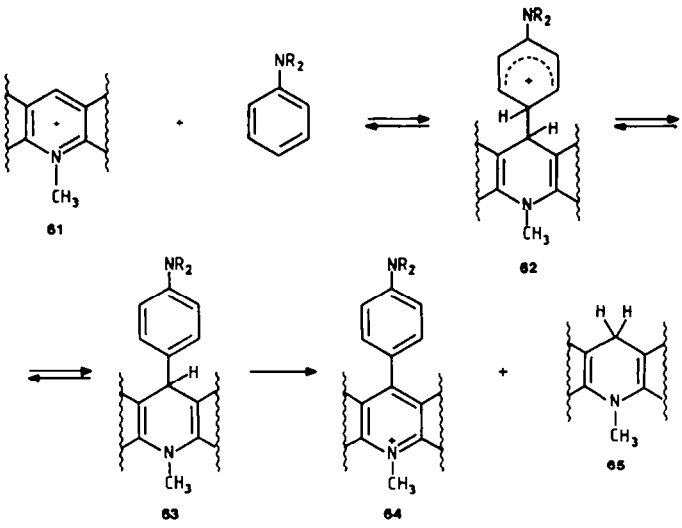
3.1. *Kinetic Measurements*

The mechanism of the S_N^H reactions including the Chichibabin one, has been postulated in many cases as the addition–elimination scheme. Attempts to investigate the kinetics of the Chichibabin amination by measuring hydrogen evolved have failed to answer the question whether the σ-adducts postulated by Ziegler[63] and registered by Zoltewicz[34] are on the reaction coordinate. Meanwhile this is the question to be answered. Huisgen in his review[170] on the kinetical elucidation of the reaction intermediates writes:

> "Nowadays scepticism is aroused by any claim to the isolation of a reactive intermediate as such. The substance in question is all too often a compound from a side-equilibrium of the kinetic system."[170]

The addition–elimination mechanism has been challenged. The so-called hetaryne mechanism involving an elimination–addition consequence has been proposed and discussed actively for the Chichibabin reaction.[171–173] However, it has been rejected by experimental facts such as the absence of a kinetic isotope effect for the amination of a mixture of 2-D and 3-D pyridines, and the amination of azine derivatives in which the formation of hetarynes is impossible still easily occurs. Also the principal possibility that the Chichibabin reaction proceeds via the ANRORC mechanism (Scheme 18) with the introduction of the amide nitrogen into the ring has been shown.[52]

The question of whether the σ-adducts are on the S_N^H reaction coordinates or not can be answered by means of a kinetic study provided that the measuring of concentration changes for the minimum of three components can be performed. This condition is usually not fulfilled and, therefore, suitable models are necessary. The reaction of the acridinium cation with arylamines can serve as one of them[174] because (i) the acridinium cation has only one electrophilic centre, therefore no isomeric adducts can be formed, (ii) the annelation of the pyridine ring with two benzene rings enhances the stabilities of the σ-adducts formed making it possible to register them by spectroscopic methods. The reaction can proceed under oxidizing conditions (air bubbling through the reaction solution) resulting in the formation of product **64**. In the absence of an oxidant cation **61** performs the hydrogenation of **63** into **64**. The hydride ion (or a hydride equivalent) is transferred from position C-γ in **63** to C-γ in **61** under formation of **64**, together with the dihydroacridine **65** (Scheme 61).



Scheme 61.

Rate constants for the reaction of N-methylacridinium iodide with arylamines in the presence of air bubbling through the solution of these reagents in DMF were obtained (Table 8).[174] The kinetic isotope effect measured for the reaction with 2,4,6-D_3-aniline $K_H/K_D = 2.2$ proved to be rather small; base catalysis was not found. ^1H NMR spectroscopy showed that the dihydroacridines **63** were almost always present in the reaction mixtures and, in a number of cases, these adducts could be isolated as crystalline substances.[149] The dihydroacridines **63** exhibit the typical properties of intermediates in a nucleophilic substitution. In an inert atmosphere they undergo the dissociation reaction of acetic acid to yield the starting materials, i.e. the cation **61** and the corresponding arylamine, while in the presence of an oxidant σ-adducts **63** are aromatized into the S_N^H products **64**.

Table 8. Rate constants ($\times 10^4$, 1 mol s^{-1}) for the reaction of N-methylacridinium iodide with arylamines.[152] Solvent DMF.

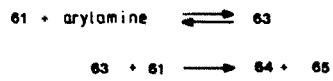
Arylamine	Temperature, °C 100	110	120	130
Aniline	81±2	124±2	216±2	293±3
N,N-Dimethylaniline	47±2	77±2	118±2	180±3
N-Methylaniline			170±2	
o-Toluidine			198±2	
2,4,6-D_3-Aniline			95±2	

These facts show that the reaction proceeds via a stepwise mechanism. The first step is the addition of arylamine to cation **61** to form adduct **62**. The abstraction of a proton from the arylamine moiety in **62** does not occur simultaneously with the addition process; it takes place at the next stage which is not a rate-determining one. The low value of the kinetic isotope effect indicates a considerable reversibility of the addition step, i.e. comparatively large values of k_{-1}.

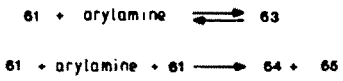
The fact that the presence of **63** could be proved indicates that the proton abstraction from adduct **62** does not occur simultaneously with the departure of the hydride ion.

The problem whether the dihydroacridines **63** are intermediates in the formation of **64** or are only side products of the kinetic systems has been solved by a ^1H NMR kinetic study of the reaction between N-methylacridinium iodide and o-toluidine in a DMSO-d_6 solution at 35°C in the absence of any outer oxidant. Experimental kinetic curves obtained by measuring concentrations of the cation **61**, the adduct **63** and the S_N^H product **64** have been compared with the data of theoretical calculation.[175] Two alternative mechanistic schemes have been simulated by the mathematical modelling of the reaction. The first one involves dihydroacridine **63** as the reaction intermediate

(Scheme 62), while the second Scheme corresponds to parallel reactions with dihydro-compounds **63** as the side products (Scheme 63).



Scheme 62.



Scheme 63.

A better correspondence between theoretical and experimental curves has been observed for the first variant. The usual criterion Δ of estimating the differences has been used.[176]

Thus all these results justify the conclusion that in σ-adduct **62** the abstraction of the proton and the hydride active hydrogen atom from adduct **62** is not a concerted process, but a two-step mechanism with the intermediacy of **63** (Schemes 61 and 62).

The same kinetic features have been established for the other examples of the S_N^H reactions.[177,178]

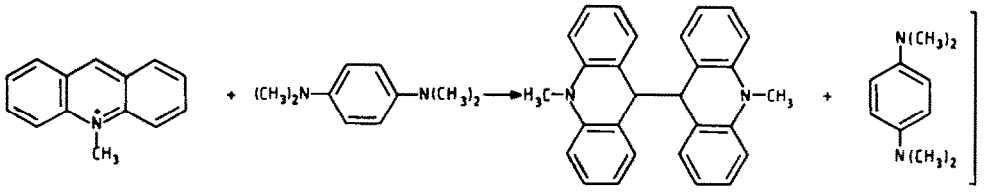
3.2. *The Addition Stage*

The initial interaction between azinium cations and nucleophilic reagents often involves a fast reversible electron transfer from the nucleophile to the substrate yielding charge–transfer complexes (CTC). Also in the reaction of acridinium salts with arylamines the formation of CTC has been observed.[179] Equilibrium constants (Table 9) and other thermodynamic characteristics have been determined. Judging from the ESR spectra of the reaction mixtures the full electron transfer does not occur. However, the formation of radical particles and their recombination in the cell cannot be excluded.

Table 9. Extinction coefficients (λ = 540 nm) and equilibrium constants for the formation of the electron transfer complex between N-methylacridinium iodide and N,N-dimethylaniline in ethanol[157]

Temperature, °C	$\varepsilon \pm 4$	$\varepsilon_{average}$	$K \pm 0.01$	$K_{average}$
15	500 500	500	1.09 1.11	1.099
25	487 500	496	1.05 1.04	1.045
35	476 485	480	0.98 0.99	0.99

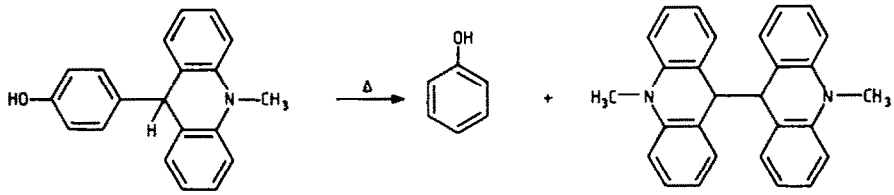
Electron transfer has been observed in the model reaction of N-methylacridinium cation with N,N-tetramethyl-*p*-phenylenediamine.[9] The electronic and ESR spectra of the 'Würsters Blues' are registered and diacridanyl could be isolated from the reaction mixture (Scheme 64).[9] This example shows that single electron transfer (SET) between a strong electron donor and the azinium cation seems a plausible elementary act in S_N^H substitutions.



Scheme 64.

One more example supporting the SET mechanism at the addition step is provided by the homolytic cleavage of the C–C bond in the σ-adduct **66** resulting from the reaction of N-methylacridinium cation with phenol. When heating adduct **66** in an aprotic solvent in inert atmosphere the formation of N,N-dimethyldiacridanyl is observed (Scheme 65). Acridine and phenol radicals

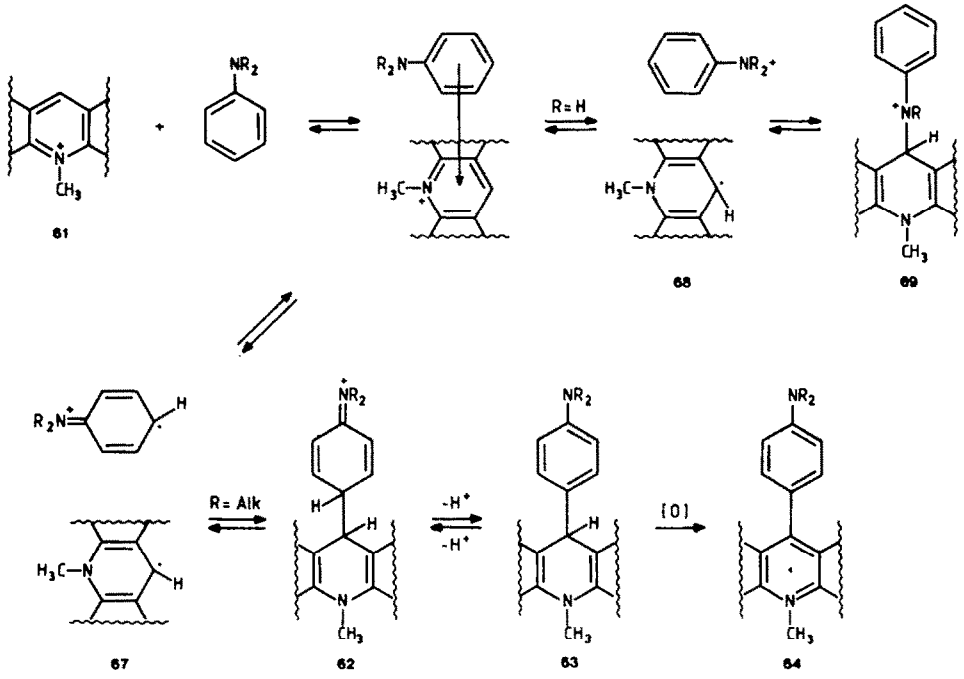
have not been registered because of their instabilities, but the evidence of their presence in the reaction mixture has been obtained by adding compounds, such as diphenylpicrilhydrazine or tri-*t*- butylphenol, giving stable radicals.[180]



Scheme 65.

It is worth mentioning that the homolysis of σ-adducts arising as intermediates in nucleophilic substitution reactions has never been observed before. These facts can be considered as an important point in the chain of evidences for the hidden radical nature of the addition step since if there is no radical dissociation of σ-adducts, the principle of microscopic reversibility is disturbed.

The ambident character of arylamines allows the formation of two types of derivatives due to both N- and C-addition reactions. UV and ^{1}H NMR study of the reaction between the acridinium cation and primary arylamines has revealed the formation of extremely unstable N-adducts **69** under kinetically controlled (−50°C) conditions.[150] At temperatures above 0°C the N-adducts **69** are converted into the thermodynamically favoured C-adducts **63**, apparently via the dissociative mechanism (Scheme 66).

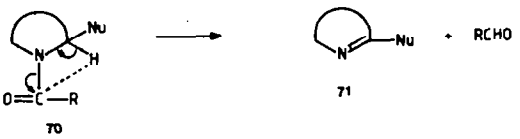


Scheme 66.

3.3. *The Aromatization Stage*

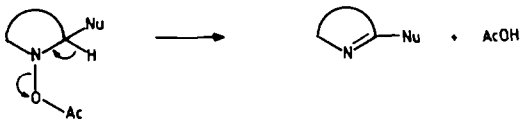
The aromatization of σ-adducts involves a C–H bond fission. Whether in the fission the hydrogen is eliminated as a hydride ion or a hydride equivalent depends on the nature of the reactants.

If the intermediate dihydroazines are capable of redistribution of the electron density in such a way as to facilitate the abstraction of proton, then the aromatization proceeds intramolecularly. Thus σ-adducts **70** undergo intramolecular shifts (the transfer of two electrons, then H^+) to yield the aromatic structure **71** and the aldehyde (Scheme 67).[133]



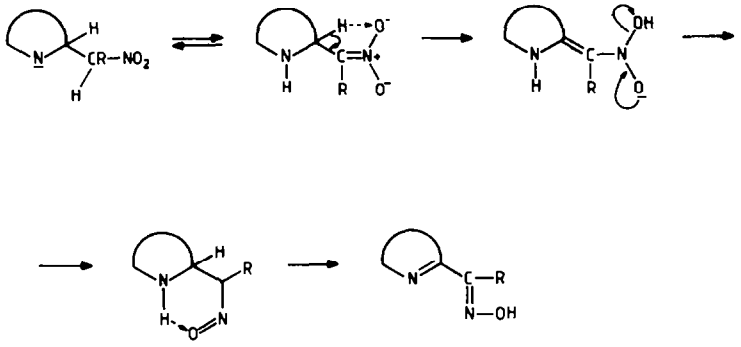
Scheme 67.

Dihydroazines resulting from N-alkyl (N-acyl) derivatives of the N-oxides are stabilized in a similar way (Scheme 68).



Scheme 68.

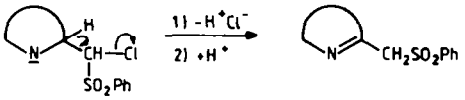
Another way of σ-adduct aromatization by means of an intramolecular hydrogen shift has recently been shown to occur by a process of redox stoichiometry involving the nitro group located in nucleophilic partner-nitronate anion[83] (Scheme 69).



Scheme 69.

The conversion of the dihydroazine intermediates into the stable state due to inner resources of the azine system is also observed in nucleophilic telesubstitution reactions. When anionic σ-adducts undergo the dehydro-halogenation reaction (even-telesubstitutions) or the shift of proton (odd-telesubstitutions), both cases correspond formally to the elimination of the hydride ion.

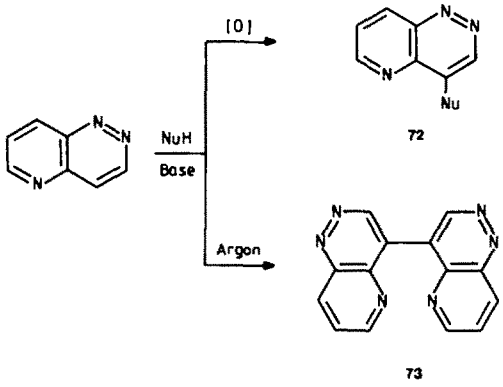
An interesting example of an auto-aromatization reaction is also provided by vicarious nucleophilic substitutions. In these reactions the abstraction of the hydrogen is assisted by the nucleophilic residue containing the readily leaving group X. The departing group X takes two electrons while hydrogen atom is eliminated as proton. In summary, the process is regarded as the β-elimination of HX (Scheme 70).



Scheme 70.

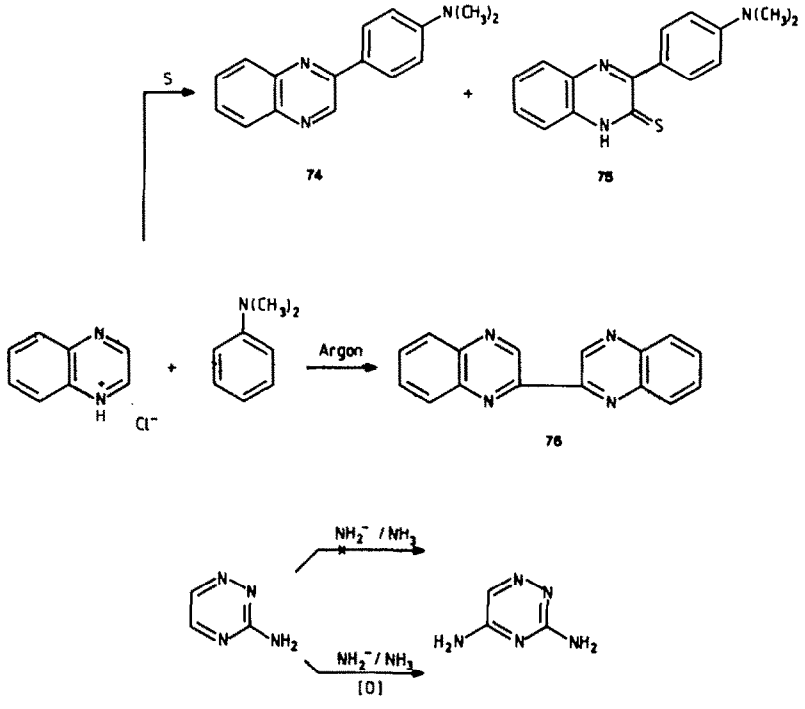
The auto-aromatization reactions discussed above can be considered as relay mechanisms because the carbon atom containing the mobile hydrogen atom passes the process to another reaction centre being either in the azine moiety or in the nucleophile fragment. If the reacting system has no built-in possibilities for hydrogen elimination an oxidant is necessary to promote the S_N^H reaction. The starting azine can serve as the oxidant of σ-adduct provided they have proper redox potentials, otherwise an outer oxidant should be introduced into the reaction mixture. Because of the reversibility of the addition step some S^H reactions take place only in the presence of an oxidant which is needed to shift the equilibrium.

Thus, 5-azacinnoline when reacting with N-, C-, S- and O-nucleophiles in the presence of oxygen readily forms the S_N^H products **72**. The same reaction being carried out in the sealed tubes in argon atmosphere results in the formation of dimeric products **73** (Scheme 71).[39,181,182]



Scheme 71.

In the reaction of quinoxaline hydrochloride in the melt with sulphur the S_N^H product **74** is formed together with its 2-thio analogue **75**, while in a DMF solution in an inert atmosphere it is 2,2-biquinoxaline **76** that is formed as the only product (Scheme 72).[101]

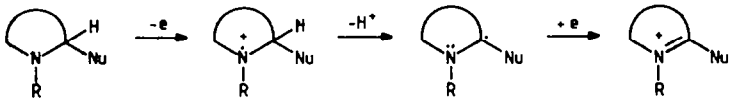


Scheme 72.

Reaction of 3-amino-1,2,4-triazine in the presence of potassium amide/liquid ammonia at −40°C does not give any reaction product; also no adduct formation at C-5 could be observed by NMR spectroscopy. When the same reaction is carried out in the presence of potassium permanganate in high yield 3.5-diamino-1,2,4-triazine is formed.[37]

There are many other examples when the S_N^H reactions do not take place in the absence of an oxidant or result in the formation of other products.[5,11]

The aromatization of dihydroazine intermediates by action of outer oxidants proceeds via a stepwise mechanism in the majority of cases and, like the auto-aromatization reaction, it is often completed by the proton abstraction (Scheme 73).



Scheme 73.

In general the idea of the stepped mechanism for dehydrogenation of organic compounds and in particular, for the dehydrogenation of ethanol belongs to Haber and Willstätter.[183] At the same time, the discussion concerning the intricate mechanism of dehydroaromatization of dihydroazines launched more than 30 years ago is still proceeding since these reactions are considered to be the models of the most important metabolism processes with participation of the coenzymes NAD, NADF and FAD.

In order to investigate how hydride ion is eliminated from dihydroazines the hydrogen exchange in the solvents of different polarities has been studied.[184] Other approaches are based on the analysis of the relationship between the rate constants for the hydrogen transfer from the donor to the acceptor and equilibrium constants for the nucleophilic addition of the cyanide ion to pyridinium salts,[185] the elucidation of the ESR spectra,[186] measuring of the isotope effects,[187] the electrochemical modelling of the reactions,[188,189] etc.

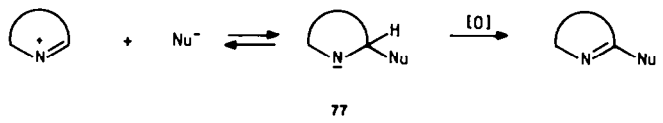
It should be stated that the data on the stepwise mechanism of the hydride ion elimination dominate the literature published during the last decade, although there are many reports on the one-stage transfer of the hydride ion.[190,191]

In order to solve the problem under discussion thorough kinetic studies have to be carried out by measuring concentrations of not only starting substances and final products but also the short lived intermediates by means of the stopped-flow method.

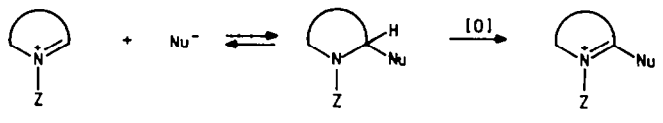
4. CONCLUSION

The data presented show that there are a great many reactions between azines and nucleophilic reagents the characteristic feature of which is the redox ability of the intermediate adducts (Scheme 74).

When compared with nucleophilic ipso-substitutions in heteroaromatics with a nucleophugic group reactions exhibit both similarities and differences. A similarity is that the S_N^H reactions also proceed via the addition–elimination mechanism involving the formation of the intermediate σ-adducts. However, characteristic differences between the S_N^H (= $S_N^H(AE)^{ipso}$) reactions and the $S_N(AE)^{ipso}$ substitutions which occur with substrates with a nucleophugic substituent, are the profound reversibility of the addition step, the enhanced stability of the σ-adducts as regard to the aromatization stage, their redox labilities, the specific nature of the leaving particle.



77



78

Scheme 74.

The σ-adducts **77** and **78** carrying hydrogen at the sp^3 carbon are much more stable relative to the corresponding σ-adducts with nucleophugic groups. They can be registered by spectroscopic methods and can often be isolated. In spite of the enhanced stability of such σ-adducts, they can be considered as anionic (or anionoid) analogues of the Wheland compounds.

The azacyclohexadienes **77** and **78**, are capable of dissociation in solutions or undergoing the aromatization process. There is however a great difference in the stabilities of intermediate σ-

adducts. As already mentioned, there are very stable adducts. For example, the adducts formed in the reactions of N-acylazinium salts with C-nucleophiles can hardly be dehydrogenated; sometimes they cannot be aromatized at all and the reaction is completed after the addition step. Contrary to that, there are short-lived σ-adducts which are present in the reaction mixtures at a vanishingly low quasistationary concentrations.

The second feature of the S_N^H reactions is the reversibility of the addition step, which is connected with a low tendency of σ-adducts to eliminate the hydride ion. It should be taken into account that especially at high values of k_{-1} (Scheme 1) the S_N^H process can only be developed by action of an outer oxidant.

The specific nature of the leaving group is the main feature of the S_N^H reactions. The tendency of σ-adducts to eliminate an anionic particle or group contradicts the nature of the hydride ion incapable of being stable in the form of an anion. The tendency of σ-adducts to convert into a more stable state is realized by other routes discussed above. When there are no ways for the intramolecular stabilization of the σ-adducts they can be aromatized by action of the outer oxidant.

The choice of the proper oxidant and searching for new aza aromatic substrates and nucleophiles yielding σ-adducts capable of the auto-aromatization will certainly expand the synthetic possibilities of the S_N^H reactions.

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