Translated from *Uspekhi Khimii*, 47, 537-556 (1978) U.D.C. 547.233.551 + 542.954

The Mechanism of the Elimination of Ammonia in the Condensation of Primary Amino-compounds and Certain Syntheses of Nitrogen-containing Heterocycles

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Studies on the mechanism of the elimination of ammonia in the interaction of two amino(imino)-compounds or two amino-groups in the same compound, carried out using ^{15}N, are considered. Taking into account the difference between the properties of the amino-groups, several mechanisms, which explain the experimental findings, are proposed. The ideas developed have been used to interpret the mechanisms of reactions which have not been investigated by the ^{15}N isotopic method. The bibliography includes 70 references.

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I. INTRODUCTION

The reactions of amino-compounds with one another, accompanied by the elimination of ammonia, are very common in preparative and industrial practice and have therefore become important. These include the synthesis of secondary amines from primary amines, the synthesis of *N*-aryl- or *N*-alkyl-amides from unsubstituted amides and primary amines, the Fischer synthesis of indoles, the Bucherer or Borsche synthesis of carbazoles, and other reactions involving the formation of nitrogen-containing heterocycles. The determination of the pathways whereby nitrogen migrates in these processes constitutes a convenient and direct method for the elucidation of the relative reactivities of nitrogen atoms in the $-NH_2$, $=NH$, and NH_3^+ groups linked to various organic residues. The knowledge of the rules governing the variation of reactivity in series of amino-compounds is in its turn quite essential for the elucidation of the mechanisms of the corresponding processes and for the prediction of the pathways followed in new or hitherto uninvestigated reactions.

The study of the above reactions can also yield direct evidence for the relative reactivities of amino-groups. In other reactions of amines, such as, for example, solvolysis, interaction with aryl halides, acyl chlorides, etc., the mechanism of the process and its rate depend both on the nature of the amines and on the nature of the other reactant, so that the correlation between the rate constants and other parameters, on the one hand, and the properties of amines, on the other, frequently breaks down.

The pathways followed in the migration of nitrogen can naturally be elucidated only with the aid of the isotope technique. Isolated studies in this field began to be published from 1943 when concentrated ^{15}N preparations became available. Systematic research was carried out by the present author in 1954–1964 and by a group of German investigators in 1952–1967. The present author believes that the time has come to survey the results of all the studies carried out hitherto using heavy nitrogen and to describe the observed characteristics and mechanisms of the reactions. An attempt should also be made to use the results obtained with the aid of ^{15}N in order to elucidate the mechanisms of reactions which have not as yet been determined by the isotopic method.

II. CONDENSATION OF TWO AMINO-COMPOUNDS OR AMIDES

Reactions involving the condensation of two amines with elimination of ammonia have been known for more than 100 years. Nevertheless, the study of this process from the standpoint of the reactivity of the nitrogen atoms immediately poses a difficult problem: which nitrogen atom in the two amines is converted into ammonia? In certain cases a cautious prediction of the answer to this question can be made, as will be seen from the account below (for example, in the interaction of an amine with an amide). The general solution of this problem with the aid of the ^{15}N isotope can be achieved on the basis of the scheme

$$RNH_2 + R^1\overset{*}{N}H_2 \rightarrow RNHR^1 + \overset{*}{N}H_3 \ .$$

One of the initial amines is prepared with an increased content of ^{15}N in the amino-group relative to the natural abundance (0.365% ^{15}N) and the site from which the amino-group is eliminated can be determined from the concentration of ^{15}N in ammonia and (or) the secondary amine. The results of isotopic analyses obtained in the first studies on the amine condensation reactions[1-4] are presented in Tables 1 and 2.

The uniform distribution of ^{15}N between the reaction products on condensation of labelled aniline hydrochloride with unlabelled aniline indicates rapid proton exchange between the anilinium ion and the aniline molecule via the mechanism

$$Ph\overset{*}{N}H_3^+ + PhNH_2 \rightleftharpoons Ph\overset{*}{N}H_2 + PhNH_3^+ \ .$$

The ease of conversion of the arylammonium ion into an amine and conversely suggests that weakly basic amines can react under these conditions in the form of free bases. The catalytic role of the acid consists in facilitating proton transfer via the general mechanism of Brønsted acid–base catalysis[5].

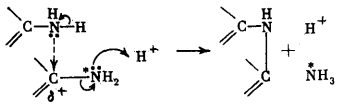
The results of the study of the condensation of [^{15}N]-benzamide with arylamines[1,2,6] are presented in Table 3. According to current ideas, ammonia is formed preferentially from the amide, which can be readily accounted for by the decrease of the basicity of the amide group NH_2 under the influence of the carbonyl group†.

Table 1. The condensation of primary amines in the presence of hydrochloric acid[1,2,6].

Starting substances				^{15}N content in reaction products, %	
labelled (% content of ^{15}N indicated in brackets)	$K_b \cdot 10^{10}$	unlabelled (0.37% ^{15}N)	$K_b \cdot 10^{10}$	secondary amine	NH_4Cl
Aniline (3.00)	3.82	Aniline	3.82	1.62	1.47
Aniline (2.15)	3.82	1-Naphthylamine	0.84	2.15	0.67
Aniline (9.3)	3.82	4-Aminophenol	66.0	9.0	0.46
1-Naphthylamine (9.3)	0.84	4-Aminophenol	66.0	3.25	5.35
1-Naphthylamine (8.4)	0.84	4-Chloroaniline	1.0	0.37	—
1-Naphthylamine (8.4)	0.84	3-Chloroaniline	0.3	0.40	—
Aniline (3.0)	3.82	n-Butylamine	$4 \cdot 10^4$	2.9	—

However, these studies firmly established that part of the amino-nitrogen is incorporated in *N*-arylbenzamide in reactions involving 1-naphthylamine and 9-aminophenanthrene; this unexpected result will be explained below.

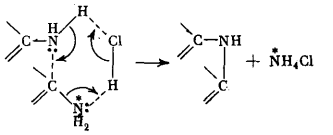
Since the essential feature of the condensation reaction involves the substitution of the amino-group by an arylamino-group, one can assume in principle that the reaction involves nucleophilic substitution:



(1)

The stronger base plays the role of the nucleophilic and adds to the positively charged carbon atom of the polarised C–N bond with the aid of the free electron pair of the nitrogen. On formation of the secondary amino-group, the previously more basic nitrogen atom loses a proton, which adds (evidently via the mediation of a catalyst) to the weakly basic amino-group, forming ammonia.

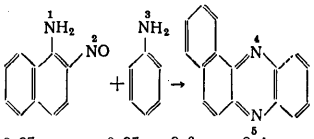
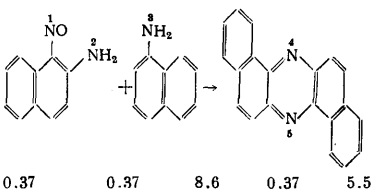
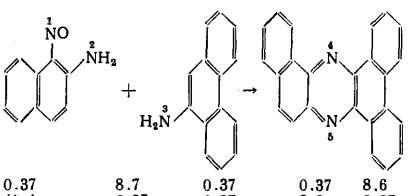
One cannot rule out the possibility that the reaction proceeds via an energetically favourable six-membered complex[7]; the possibility of the formation of such complexes has been pointed out by Shilov[8] and Syrkin[9]:



(2)

Comparison of the pathways leading to the elimination of amino-groups with the dissociation constants of the bases listed in Table 1 indicates the absence of a consistent relation between them. In the reaction of aniline with 1-naphthylamine the amino-group is split off from the weaker base, while in reactions of 3-chloroaniline with 1-naphthylamine or of aniline with n-butylamine it is split off from the stronger base; in the reaction of 4-chloroaniline with 1-naphthylamine, where the basicities of the two reactants are almost identical, the NH_2 group is split off wholly from only one component (1-naphthylamine), while in the condensation of nitrosonaphthylamine with 1-naphthylamine (Table 2) and of benzamide with polycyclic amines (Table 3), it is split off from both components. Nevertheless the mechanism described by Eqns. (1) and (2) provides for the elimination of the less basic amino-group. All the data obtained cannot therefore be accounted for by the S_N2 mechanism [described by Eqns. (1) and (2)] and, while remaining fundamentally correct, it needs to be revised. We may recall that the NH_2 groups attached to alkyl, aryl, or acyl residues differ sharply in their properties. Their basicity also varies within the limits of the same class of compounds as a function of the substituents, an increase of the number of benzene rings, steric hindrance, and other factors.

Table 2. Condensation of nitrosonaphthylamines with aromatic amines[3,4].

No. of expt.	^{15}N content, %				
	N (10)	N (2)	N (3)	N (4)*	N (5)*
					
1	0.37	0.37	8.6	8.4	0.37
2	0.37	8.7	0.37	0.37	8.6
					
3	0.37	0.37	8.6	0.37	5.5
					
4	0.37	8.7	0.37	0.37	8.6
5	10.1	0.37	0.37	9.9	0.37

*The ^{15}N content among the $N_{(4)}$ and $N_{(5)}$ atoms in the products was determined from the average ^{15}N concentration in both positions (by analysis) and the 0.37% content at one of them (known from the experimental conditions).

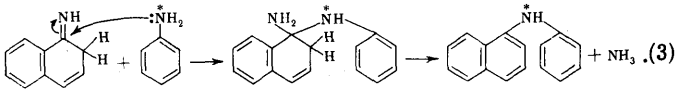
Taking into account these relations, one may suggest that there should be several mechanisms of the interaction of amino-compounds with one another. In the aromatic series, where the difference between the basicities of the amines are in most cases small, the possibility of the

† The elimination of the amide nitrogen of urea has been demonstrated using ^{15}N in well known studies on the synthesis of uric acid by the condensation of urea with uramil[20] or *diaminouracil*[20,21].

formation of quinonoid structures plays a significant role. In the instances investigated by the present author, where 1-naphthylamine always loses its amino-group on condensation with an amine of the benzene series (except 4-aminophenol which requires separate consideration), the monocyclic amine reacts with the quinonoid form of 1-naphthylamine. The basicity of the latter is suppressed and the reactive group



is subjected to nucleophilic attack by the NH_2 group:

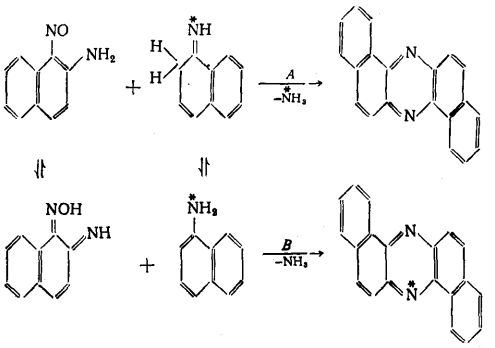


(3)

Table 3. Condensation of [^{15}N]-benzamide with amines[1,2,6].

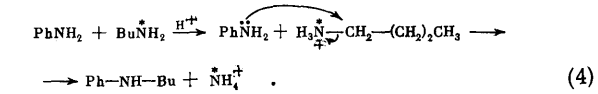
Amines	^{15}N content, %			Amount of benzamide nitrogen in N-aryl-benzamide, %
	in initial benzamide	in N-aryl-benzamide	in NH_4Cl	
Aniline	2.15	0.51	2.07	~0
4-Aminophenol	9.30	0.44	—	~0
1-Naphthylamine	8.16	0.77	7.25	5
9-Aminopenanthrene	8.75	2.1	5.7	21

When 1-naphthylamine condenses with 1-nitroso-2-naphthylamine, the stabilities of the quinonoid structures are approximately the same, which leads to the loss of nitrogen by both components (the nitroso-group is not split off; see Table 2). The reaction mechanism may be represented by the scheme



The results of isotopic analysis[3,4] showed that the contributions of pathways *A* and *B* are 38% and 62% respectively. This can be explained by the fact that the formation of the quinonoid form from nitrosonaphthylamine may be facilitated by the conjugation of the amino-group with the N=O group. Among the amines investigated by the present author, 9-aminophenanthrene shows the greatest tendency towards the formation of quinonoid structures. In the interaction with 1-nitroso-2-naphthylamine (Table 2) it therefore always reacts as the quinone imine and its amino-group is lost completely.

The condensation of aniline with n-butylamine[2] (which is 10^6 times stronger as a base) is accompanied by the elimination of the more basic amino-group only, in complete conflict with the mechanism involving reactions (1) and (2). One must suppose that the following reaction occurs in this instance:



(4)

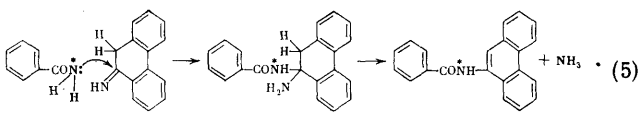
The very strong base therefore exists mainly as the alkylammonium ion, which is subjected to nucleophilic attack by the aromatic amine. Mechanism (4) must undoubtedly occupy an important place among amine condensation reactions, since these processes usually occur in the presence of acid catalysts. As will be shown below, the involvement of amines as ammonium ions can be postulated also in the interaction of amines with not quite so greatly different basicities and also in the cyclisation of the intermediate complexes containing two amino- or imino-groups.

The reactions with participation of 4-aminophenol may occur mainly (with aniline) or partly (with 1-naphthylamine) via mechanism (4), since 4-aminophenol is 17 times more basic than aniline. Furthermore, there exists a hydrolytic mechanism with preliminary formation of hydroquinone. This reaction pathway has been demonstrated experimentally[2].

The main pathway in the condensation of an amine with an amide is determined by the mechanism of the nucleophilic substitution at the carbonyl carbon atom, which is positively charged owing to the polarisation of the C=O group. An analogous mechanism has been adopted for the acylation or nitrosation of amines[10] and for the addition of nucleophiles to sulphonamides[11]. The same mechanism has also been proposed for the reaction of hydrazine with monoarylurea[12] and for the transamination of *N*-arylacetamides[13]. It may be that the condensation proceeds via a six-membered cyclic complex [see Scheme (2)]. A similar complex has been proposed by Syrkin and Moiseev[14] to account for the hydrolysis of benzamide in an acid medium. The role of the acid catalyst is to enhance the positive charge of the carbonyl carbon atom as a result of the protonation of the oxygen atom.

The second reaction pathway, leading to the elimination of amino-nitrogen, involves the participation of 9-aminophenanthrene or 1-naphthylamine in the quinonoid form and of benzamide as the nucleophile. The mechanism of this reaction can be represented by Scheme (5) below.

The results obtained in the condensation of amines with amides have shown that, in a system containing several benzene rings, the delocalisation of the electron density of the free electron pair of nitrogen and the concomitant formation of an imine may compete with the analogous phenomena in benzamide.



(5)

Further investigations[15-18] provided new evidence confirming the above mechanisms. Table 4 compiles the results obtained in these studies. They also show that, on condensation with both stronger and weaker amines of the benzene series, 1-naphthylamine usually loses its amino-group, but retains it on interaction with 9-aminoanthracene. Such behaviour of amines is fully consistent with the mechanism represented by Scheme (3), according to which the ability to split off NH_2 groups is determined

by the stability of the quinoid structures and increases in the sequence: monocyclic amine < dicyclic amine < tricyclic amine.

Table 4. Condensation of two amino-compounds[15-19].

Labelled component	Amine of benzene series	pK_b	Amount of nitrogen from the amine of the benzene series in the secondary amine formed, %
1-Naphthylamine (pK_b = 10.04)	*o*-Toluidine	9.48	100
	Aniline	9.35	100
	m-Toluidine	9.20	100
	p-Ethylaniline	–	99
	p-Toluidine	8.84	86.5
	p-t-Butylaniline	9.05	70
	p-Phenetidine	8.80	68
	2,4-Dimethylaniline	9.15	57
	p-Anisidine	8.56	32
	p-Phenylenediamine	7.92	20
	p-Aminoacetophenone	–	100
	p-Fluoroaniline	9.35	100
	p-Chloroaniline	9.93	100
	m-Chloroaniline	10.48	100
	m-Bromoaniline	10.42	100
	m-Iodoaniline	10.39	100
	9-Aminoanthracene	–	0
8-Aminoquinoline (pK_b = 10.01)	Aniline	9.35	81*
	p-Toluidine	8.84	95*
	p-Phenetidine	8.80	75*
	p-Anisidine	8.56	61*
5-Aminoquinoline	*p*-Toluidine	8.84	41*
	p-Phenetidine	8.80	35*

* Calculated by the present author from experimental literature data[17] (an incorrect calculation is quoted in the relevant paper[17]).

In many reactions (see Table 4) labelled nitrogen was found to be distributed within the reaction products—the secondary amine and ammonia[15-17]. Having noted that in these instances an amine more basic by 1-2 orders of magnitude reacts with 1-naphthylamine, one may assume that the former is partly converted into an $ArNH_3^+$ salt and then interacts via mechanism (4). Thus mechanisms (3) and (4) compete in this instance. The second reaction pathway should naturally be associated with the proton-accepting properties of the stronger base. Indeed the authors found that the degree of elimination of the imino-group is satisfactorily correlated with the dissociation constant of the amine of the benzene series and the Hammett σ constant of the substituent in the benzene ring. Individual straight lines were obtained for condensation with 1-naphthylamine, 8-aminoquinoline, and 5-amino-quinoline.

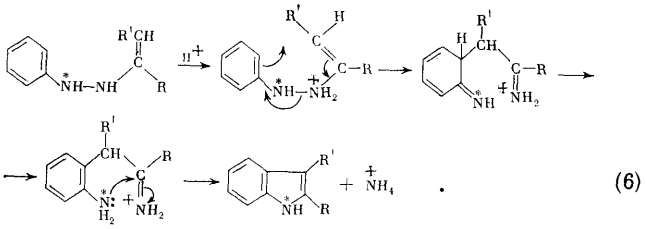
In the experiments on the condensation of urea with aniline and methylamine hydrochlorides an unexpected result was obtained—the elimination of the urea nitrogen[15]. The mechanism of the interesting reaction between urea and acetamide may be treated only qualitatively in the sense that ammonia is eliminated from both amides. The degrees of involvement of urea and acetamide nitrogen in the formation of acetylurea cannot be calculated from the analytical determination of ammonia (as was done by Krumbiegel and Hübner[15]), because the latter is obtained also from urea via a side reaction involving the formation of biuret.

Summarising the findings described above, one may say that mechanisms (1), (2), (3), (4), and (5),[1,2,6,7] as well as substitution at the carbonyl carbon atom of the amide[10], acting independently or competing with one another, can explain all the results obtained hitherto for the condensation of amines. The basicity of amines is correlated with the degree of elimination of the amino-group within narrow limits of pK_b values for reactions of similar amines with the same reactant (the second amino-compound)[19].

III. SYNTHESES OF HETEROCYCLIC COMPOUNDS

In certain syntheses of heterocycles from nitrogen-containing substances intermediates or short-lived complexes are formed in which there are at least two amino-groups. In most cases these reactions are complex, comprise many stages, and different aspects of their mechanisms may be discussed. Here they will be considered from only one standpoint—which amino-group is eliminated on cyclisation (in the form of ammonia) and the mechanism of such elimination.

The situation described is encountered in numerous Fischer syntheses of indole and carbazole derivatives from aldehyde or ketone arylhydrazones. It has been established with the aid of ^{15}N that, in the cyclisation of acetophenone[22] and acetone[23] phenylhydrazones, the amino-group attached to the aliphatic end of the intermediate diamine is eliminated, while the much less basic aromatic amino-group enters into the indole ring. This result can be readily explained by the mechanism developed on the basis of numerous studies[24,25], according to which the more basic $-NH_2$ (or =NH) group is protonated by the acid. This induces a positive charge on the carbon atom adjoining the nitrogen atom and the former is subjected to nucleophilic attack by the aromatic amino-group:

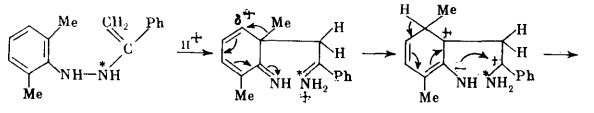


(6)

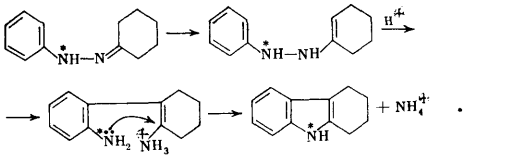
A special case of reaction (4), in which two amines with markedly different acid properties interact, may be seen in mechanism (6). The mechanism is in principle unaffected by the fact that two amino-groups in the intermediate complex (compound) interact rather than two different amines.

The migration of nitrogen in accordance with mechanism (6) has been confirmed by subsequent investigations. A study of the reductive contraction of the [2-^{15}N]-4-phenylcinnoline ring showed that the formation of the indole derivative is accompanied by the elimination of the aliphatic amino-group[26]. Suvorov et al.[27] cyclised acetaldehyde phenylhydrazone in order to obtain an indole labelled with ^{15}N, free from substituents in the pyrrole ring. Having labelled the nitrogen in the 1-position in the first experiment and that in the 2-position of phenylhydrazine in the second, they obtained results agreeing with elimination of the aliphatic amino-group from the intermediate diamine. A study of the reaction of acetophenone 2,6-dimethylphenylhydrazone also revealed the elimination of the amino-group from the aliphatic end of the intermediate complex[28]. In clear conflict with mechanism (6), the authors[28] present a mechanism where the less basic amino-group (aromatic amino-group and even the NH group of the secondary amine) is protonated twice.

The present author suggests that this mechanism is erroneous, particularly since a result consistent with experiment is obtained via mechanism (7), postulated here with correct allowance for the relative basicities. Results which can be explained by mechanism (4) have been obtained[29] in a study of the cyclisation of cyclohexanone phenylhydrazone. The 10.1% excess of ^{15}N among the nitrogen atoms in the 1-position of phenylhydrazine was fully incorporated in tetrahydrocarbazole [Scheme (8)].



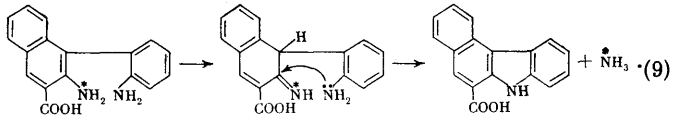
(7)



(8)

Analogous reactions involving aromatic compounds lead to carbazole derivatives. Clusius and Barsh[30] investigated one such reaction—the formation of benzocarbazole-carboxylic acid from 2,3-hydroxynaphthoic acid and phenylhydrazine labelled with ^{15}N. The main reaction pathway (the contribution of which amounts to 88.5%) involves the elimination of the amino-group from the naphthalene ring [Scheme (9)]‡. It is easily seen that mechanism (6) is unsuitable in this instance; it requires the elimination of the more basic amino-group from the benzene ring, which conflicts with experimental findings.

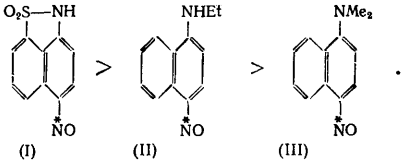
In order to account for these results, the present author suggests a mechanism of type (3), according to which the intermediate reacts as an iminoamine with a quinonoid structure of the naphthalene ring [Scheme (9)]. Cyclisation of this diamine leads to a carbazole derivative which does not contain ^{15}N, in agreement with experiment.



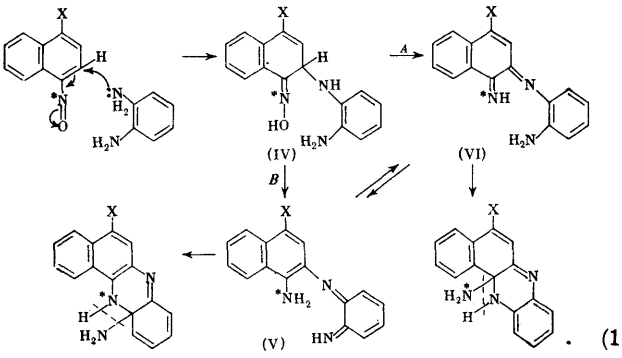
(9)

Holt and McNae[31] investigated the mechanisms of the interaction of [2-^{15}N]-phenylhydrazine with 2-naphthol. A small proportion of ^{15}N (~0.5%) was incorporated in the benzocarbazole formed under these conditions. It was shown that the labelled and unlabelled benzocarbazoles are formed by different reactions. The intermediate formation of the [2-^{15}N]-phenylhydrazone of 1,1-dihydro-2-oxonaphthalene followed by stages analogous to those in the Fischer synthesis of indole was postulated. The mechanism proposed for the main reaction pathway—the formation of unlabelled benzocarbazole with participation of the protonated "benzene" NH_2^- group—is unsuitable, because it would lead to the elimination of this group, which conflicts with the experimental results. The present author suggests that the main reaction proceeds via an intermediate diamine with participation of the quinonoid structure of 2-aminonaphthalene, by analogy with Scheme (9). The side reaction (its contribution is approximately 5%), leading to labelled benzocarbazole, evidently proceeds via the *ortho*-semidine rearrangement of the hydrazone. Other versions of the incorporation of ^{15}N into benzocarbazole proposed by the author[31] are erroneous, because they conflict with isotopic data for similar reactions.

The synthesis of phenazine derivatives from aromatic nitroso-compounds and *o*-phenylenediamine is accompanied by the evolution of ammonia. In the study of the pathway followed in the migration of nitrogen in such reactions it was found[32] that the nitroso-group labelled with ^{15}N is almost completely eliminated in the form of ammonia from the nitrosonaphthosultam (I), to the extent of 55% from *N*-ethyl-4-nitroso-1-naphthylamine (II), and to the extent of 23% from *NN*-dimethyl-4-nitroso-1-naphthylamine (III). The remainder of the ^{15}N is incorporated in the phenazine derivative.



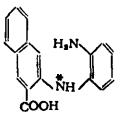
Scheme (10) was proposed to account for these results. The intermediate complex (IV) formed initially may be subsequently converted into compounds (V) and (VI), which are in equilibrium. This leads to the elimination of different imino-groups, with and without ^{15}N, which results in the distribution of heavy nitrogen among the reaction products.



(10)

The position of the (V) ⇌ (VI) equilibrium is determined by the nature of the substituent X. The sultam group has electron-accepting properties and promotes the formation of complex (VI), from which ^{15}N is eliminated; the contribution of the reaction via pathway *B* is insignificant—not more than 3% (which may even be due to experimental

‡ The side reaction involving the incorporation of ^{15}N in benzocarbazolecarboxylic acid proceeds to the extent of 11.5% (determined from its isotopic analysis) or to the extent of approximately 5% (found by the analytical determination of ammonia). The authors postulate the *ortho*-semidine rearrangement with formation of the intermediate



error). The introduction of an electron-donating substituent stabilises complex (V) and increases the basicity of the amino-group attached to the naphthelene ring; the reaction with the nitrosoamine (II) therefore proceeds to the extent of 50% via pathway *B*. The substituent with still more marked electron-donating properties in compound (III) promotes a further increase of the contribution of pathway *B*, which predominates in this instance.

IV. REACTION MECHANISMS

Examination of the literature data and the experimental studies described here lead to the conclusion that the dissociation constants of the bases do not always determine the mode of dissociation of the C–N bond in nucleophilic condensation reactions between two amines. The correspondence between the rate constants and the pK_b values for the amines breaks down also for other nucleophilic substitution reactions. For example, the rate of the reaction of 1-chloro-2,4-dinitrobenzene with chloroanilines and 1-naphthylamine decreases in a series which is not related to the variation of the basicity of the amines[32]:

p-Chloroaniline	*m*-Chloroaniline	1-Naphthylamine
$k_{45°}$ 2,8 · 10^{-3}	0,86 · 10^{-3}	0,36 · 10^{-3}
pK_b 10,0	10,52	10,04

The first stage of the interaction between the two amines [Scheme (1)] involves attack by the nitrogen atom of the nucleophilic component on the positively charged carbon atom of the second amine. This stage should therefore be promoted by a higher electronic charge density at the nitrogen atom and a positive charge on the carbon atom. Sixma[33] used the energy of the localisation of the free electron pair at the nitrogen atom as the criterion of nucleophilic reactivity. It has been shown[34] that the electronic charge is greater the lower the localisation energy. In the reactions of a series of polycyclic amines with 1-chloro-2,4-dinitrobenzene, Sixma found that the logarithms of the rate constants for the reactions vary linearly with the charge on the nitrogen§, provided that steric factors do not interfere.

The dissociation constants of the bases may also be to some extent proportional to the electronic charge on the nitrogen atom. For example, an approximately linear relation has been found between pK_a and the electronic charge q_N for a series of methylbenzacridines[35]. However, the correspondence between pK_a and q_N breaks down to a large extent for many bases with different molecular skeletons (Table 5).

The first stage of reaction (1) is promoted by electron-accepting substituents as well as other factors intensifying the positive charge on the carbon atom of the electrophilic molecule and ultimately increasing the amount of double-bond character of the C–N linkage. The increase of the C–N bond order leads ultimately to the formation of a quinonoid structure. Compounds with quinonoid structures show a greater tendency towards nucleophilic substitution reactions. Bunnett and Zahler[36] believe that this problem is still obscure, but quote evidence in support of the latter assertion. Thus halogenonitrobenzenes have a higher C–N bond order and react very readily with nucleophiles. It is also known that quinoneimines are more readily hydrolysed than amines. Thus, amino-compounds which readily give rise to quinonoid forms should combine with a nucleophile more readily, eliminating their amino-group at the same time. Presumably in the reaction of two aromatic amines the electrophile is the compound whose quinonoid form is more stable and which has a higher conjugation energy. It has been found experimentally that the degree of elimination of the amino-group increases in the sequence aniline < 1-naphthylamine < 9-aminophenanthrene[1,2]. This series has been compared (Table 6) with the electronic charges on the nitrogen atom q_N (calculated by the Slater–Pauling method[37]), the charges on the exocyclic carbon atom of the hydrocarbon analogue of the amine q_C, and the C–N bond orders[33]. Table 6 also shows that the oxidising potential of the corresponding quinone decreases, i.e. the stability of the quinonoid form increases, in the direction in which the ability of the amine to split off the amino-group increases[38].

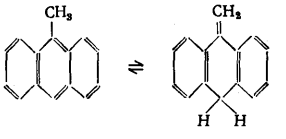
Table 5. Relation between the electronic charge on the nitrogen (q_N) and pK_a for the base[35].

Compound	q_N	pK_a
Pyridine	1,190	5,23
Isoquinoline	1,202	5,33
1-Aza-anthracene	1,205	5,05
Quinoline	1,221	4,91
Acridine	1,227	5,60

Table 6. Comparison of the reactivities of aromatic amines with the charges on the nitrogen (q_N), the charges on the exocyclic carbon atom (q_C), the bond orders P_{CN}, and the oxidation potentials of quinones (E).[7]

Parameter	Aniline	1-Naphthylamine	9-Aminophenanthrene
q_N	1,841	1,817	—
q_C	0,571	0,450	0,446
P_{CN}	1,160	1,180	—
E, *b*	0,794	0,576	0,460

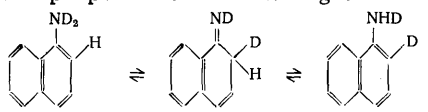
The increase of the ability to form quinonoid structures with increase of the number of benzene rings also follows from the benzenoid–quinonoid tautomerism of methyl derivatives or aromatic hydrocarbons. Thus, whereas 9-methylanthracene exists mainly in the benzenoid form [Scheme (11)], the quinonoid form predominates in methylpentacene. According to Syrkin and Dyatkina[39], this behaviour is caused by the increase of the π-electron energy of the quinonoid tautomer with increase of the number of rings:



(11)

§ For simplicity, the charge on the exocyclic carbon atom in the hydrocarbon analogue of the amine was calculated.

The formation of the quinonoid forms of polycyclic amines might serve as a convenient pathway for the migration of protons of the amino-groups to the ring and conversely. Such exchange has been investigated using deuterium introduced into the amino-group[40]. No exchange involving aniline was observed in a neutral medium, but it occurred at an appreciable rate at 180–200°C in the 2- and 4-positions of 1-naphthylamine. Since the rate of exchange was independent of the concentration of amine in the tetralin solution, the following intramolecular mechanism involving an intermediate quinonoid structure was proposed for the exchange:



(12)

This process could also proceed via a π-complex¶. An increase of electron density in the 2- and 4-positions promotes the addition of the amine proton in these positions with formations of a quinonoid tautomer†.

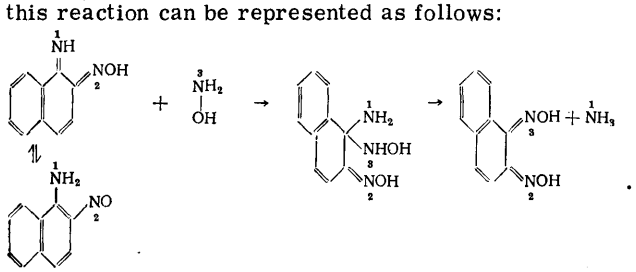
The foregoing discussion permits the conclusion that the benzenoid-quinonoid tautomerism in the reactions of polycyclic aromatic amines plays an important role. Here it was demonstrated in relation to the interaction of two amines, but there is no doubt that the conclusion is of more general validity.

The acid–base properties of amines also play a significant role in determining the mode of dissociation of the C–N bonds in the reactions under consideration. As we have seen quantitative relations have been observed in specific instances[19] between the reactivities of the amines, the pK_b values, and the Hammett σ constants. In elucidating the mechanism of the elimination of ammonia one must therefore take into account the relative basicities of the reacting amino-groups.

V. INTERPRETATION OF THE MECHANISMS OF PROCESSES WHICH HAVE NOT BEEN INVESTIGATED USING ^{15}N

In this section an attempt will be made to apply the ideas developed above for the mechanism of the condensation of amines to analogous reactions in which the nitrogen migration pathways have not been established by isotopic methods using ^{15}N.

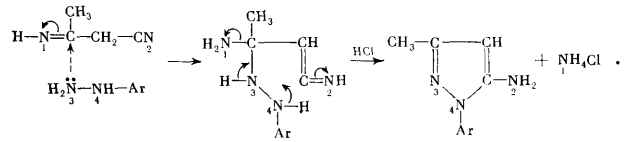
2-Nitroso-1-naphthylamine reacts with hydroxylamine to form 1,2-naphthoquinone dioxime[43]. The mechanism of this reaction can be represented as follows:



¶ An intramolecular mechanism involving π-complexes has been proposed for proton exchange involving toluidine hydrochloride in the solid phase[41].

† The four versions of the bimolecular mechanism proposed[42] for the self-exchange in aromatic amines do not conflict with these conclusions, because they refer to proton exchange in the presence of the alkaline catalyst PhNDK.

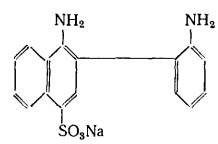
The reaction of diacetonitrile with arylhydrazines in the presence of hydrochloric acid[44] leads to 5-amino-1-aryl-3-methylpyrazoles (VII), which are used as the nitrogen-containing components in the synthesis of dyes. It appears that the arylhydrazine nitrogen atoms attack the carbon atoms of the nitrile and imino-groups to form $N_{(3)}$–C and $N_{(4)}$–C bonds. An intermediate complex (VIII) should be formed in the initial stage and ammonia containing the nitrogen atom of the imino-groups of the diacetonitrile is eliminated from it [Scheme (13)]. The polarisation of the $N_{(1)}$–C bond promotes the protonation of the $N_{(1)}$ atom by the acid present.



(VIII) (VII) (13)

When phenylhydrazine reacts with aminonaphthalene or naphthols, the products are hydrazo-compounds, which are converted into carbazole derivatives in the presence of acid[45]. In particular, the reaction of phenylhydrazine with 4-, 5-, 6-,[46] and 7-sulphonic acid of 1-naphthylamine[47] in the presence of sodium bisulphite yielded the corresponding benzocarbazolesulphonic acids. The hydrazo-compound detected in these studies is obtained by the nucleophilic substitution of the "naphthalene" amino-group by the phenylhydrazyl residue. The reaction is favoured by the tendency of the substituted naphthylamine to form a quinonoid structure containing the HN=C< group. This mechanism explains why such reactions proceed with bicyclic and tricyclic amines but not with amines of the benzene series: the conjugation of the free electron pair of the nitrogen with the π electrons of the ring, which largely determines the capacity for the formation of the quinonoid form, is insufficient for this purpose in the benzene series.

According to isotopic data, the cyclisation of the intermediate diamine (IX), which has also been detected in the reaction medium[46], should proceed in reactions of this kind[2, 3, 16, 31] with elimination of the amino-group from the naphthalene ring:

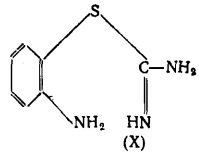


(IX)

The elimination of the "benzene" NH_2 group, which can be achieved, for example, by the *ortho*-semidine rearrangement of the hydrazo-derivative, is in this case still less likely than in the cyclisation of the [2-^{15}N]-phenylhydrazone of 1,1-dihydro-2-oxonaphthalene[31] owing to the presence of the sulpho-group. To demonstrate the occurrence of the side reaction (its contribution is probably less than 5%), an experimental test using ^{15}N is required.

The mechanism of the Fischer synthesis of indole derivatives from the phenylhydrazones of aliphatic or alicyclic ketones and aldehydes has been fairly clearly established (as a result of numerous studies, mainly those of Robinson's school). In the last stage of this mechanism ammonia is eliminated solely from the aliphatic component of the intermediate diamine. It has been shown[24, 31] that the

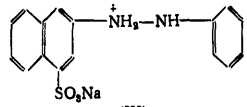
protonation of the aliphatic amino-group plays an important role in the elimination of ammonia. This mechanism is invoked in many investigations of the Fischer synthesis of indole derivatives[48,49]. In certain studies cyclisation mechanisms without protonation but with conversion of the aliphatic amino-group into an imino-group, for example, with formation of structure (X), [50-52] has been suggested:



(X)

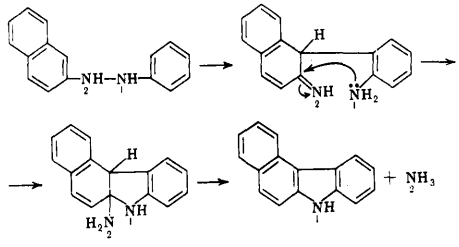
This mechanism should lead to the same ammonia elimination pathway, but it is in essence not unambiguous, because the aromatic amino-group can also be converted in certain cases into an imino-group and this would lead to its elimination in the form of ammonia, which conflicts with isotopic data.

Drawing an analogy between the Bucherer and Fischer syntheses, Seeboth[53] proposed a mechanism with the intermediate structure (XI):



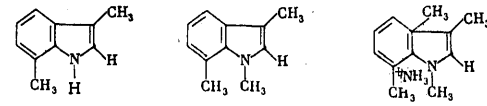
(XI)

The mechanism involving this structure, where the less basic nitrogen atom is protonated, appears to be doubtful. An analogous mechanism has been suggested in a paper[54] dealing specifically with the Bucherer reaction. Furthermore the Bucherer synthesis of benzocarbazole can be described by mechanism (14) with participation of the quinonoid form of naphthalene. The acid, which promotes the elimination of ammonia, catalyses the process via the general mechanism of acid catalysis:



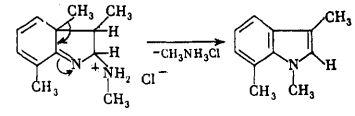
(14)

Mechanisms consistent with isotopic data are usually suggested in the literature for the interpretation of the Fischer syntheses of indoles and carbazoles, i.e. it is postulated that the amino-group attached to the aliphatic (or alicyclic) part of the molecule is always eliminated from the intermediate diamine (or dienoneimine). Only in two papers by the same workers[55,66] are mechanisms proposed in which the aromatic amino-group is eliminated to an equal extent. In these studies the interaction of *N'*-methyl-2,6-dimethylphenylhydrazine with propanal, 2-methylpropanal, and 2-methylcyclohexanone was investigated. Thus the reaction with propanal yielded a substance with structure (XIII) in addition to the normal indole (XII):



(XII) (XIII) (XIV)

To explain this, the authors postulate a side reaction involving the formation of the intermediate (XIV) from which compound (XIII) is obtained by the elimination of the aromatic amino-group. Apart from the fact that this mechanism conflicts with all isotopic data for reactions of this kind, it is by no means necessary for the explanation of the experimental data presented. Product (XIII) can be obtained from the intermediate (XV), the formation of which via mechanism (15) in the course of the normal Fischer synthesis was confirmed by the above authors themselves with the aid of ^{1}H NMR. The methyl group migrates from the benzene ring to the nitrogen atom and the quinonoid structure is converted into the more stable benzenoid structure:



(XV) (XIII) (15)

The interaction of amines with amides proceeds more readily than the reaction between two amines. Aniline reacts with urea at 160°C even in the absence of acids, forming diphenylurea[57]. Davis and Underwood[58] found a general method for the preparation of symmetrical diarylureas involving the heating of urea with primary aromatic amines. The mechanism of this reaction with aliphatic and aromatic amines of the benzene series gives rise to no doubts and evidently reduces to the elimination of the amide group. This can also be said of the reactions of mesidine with urea and of mesitylurea with hydrazine[12] as well as reactions of glycine and ethylglycine with urea[59] and of 2- and 3-aminopyridines with urea[60]. However, categorical predictions should not be made for the interaction of urea with 6-aminoquinoline[60], since, according to the present author's data[6], the dicyclic amine can lose part of its amino-nitrogen on reaction with an amide.

The reactions between an arylurea and an arenesulphonamide has been described[61]. One of the amides plays the role of the nucleophile:

$$RSO_2NH_2 + R'NHCONH_2 \rightarrow RSO_2NHCONHR' + NH_3 .$$

The site from which the aminogroup is eliminated may be determined only by introducing ^{15}N into one of them. Admittedly one may assume that the withdrawal of electron density from the nitrogen atom in the sulphonamide is more pronounced than the corresponding effect in urea and the latter therefore retains its nitrogen atoms.

In transamination reactions amines displace one another from secondary amines, *N*-arylamides, and other complex compounds. Since transamination is associated with the competition between the reactivities of the interacting amines, it is of interest to examine these amines.

Stavrovskaya[62] investigated the transamination of benzyldiethylamine with various aromatic amines in hydrochloric acid:

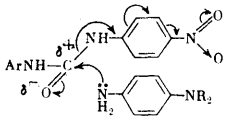
$$PhCH_2N(C_2H_5)_2 + ArNH_2 \xrightarrow{HCl} PhCH_2NHAr + NH(C_2H_5)_2 .$$

Although the K_b values for the aromatic amines investigated varied in the range $(4-2000)\times10^{-12}$, the yields of arylbenzylamines changed little (20–35%). The cause of this should be sought in the fact that all these weak amines displace diethylamine, which is a stronger base by 5–6 orders of magnitude. Evidently this possibility arises due to the presence of the acid, which converts the initial tertiary amines into the electrophilic ammonium ion. The low yields of the transamination product can be explained by the reversibility of the process and the more marked nucleophilic properties of diethylamine. A similar transamination involving n-aminobenzyldiethylamine was observed in another study[63].

Many instances of transamination have been observed in the series of urea derivatives. In the study already quoted[58] mention is made of the reaction of the symmetrical dimethylurea with aniline, which leads to the formation of diphenyl- and partly ethylphenyl-urea. Gerchuk et al.[64] carried out an extensive study of transamination in the series of substituted ureas. The results, which the present author compared with the basicities of the amines, permit the conclusion that the equilibrium in reaction (16) has shifted towards the displacement of the less basic amine. The authors propose a mechanism involving the preliminary decomposition of the arylurea to an aryl isocyanate, which reacts more readily with the stronger bases:

$$ArNHCONHAr + 2Ar'NH_2 \rightleftharpoons Ar'NHCONHAr' + 2ArNH_2 \quad . \quad (16)$$

The same view is held by Kutepov and Potashnik[65], who investigated the interaction of bis(trichlorophenyl)ureas with aniline. However, this mechanism conflicts with the stability of arylureas, which has been pointed out by Heintz[59]. One may add that this type of exchange of amines has been found in the series of entirely stable *N*-arylacetamides. One must therefore assume that transamination takes place (see also Kogan and Kutepov[66]) via a nucleophilic substitution reaction, evidently involving an S_N2 mechanism. The redistribution of electron density in the intermediate complex (XVI) promotes the elimination of the weaker base.

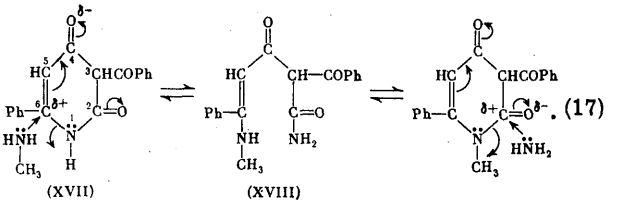


(XVI)

Transamination involving *N*-arylacetamides[13] takes place under very severe conditions (260°C, 100 atm, 2–5 days). The reaction of acetylpentylamine takes place more readily with aliphatic amines than with aniline. Primary amines also react more vigorously. The reactivity of amines in this process increases greatly as the phenyl groups become more remote, which can be seen from the following sequence:

aniline ≪ benzylamine < β-phenylethylamines.

The reactivity of the amino-groups is not correlated with their basicity. The authors therefore attribute much importance to steric hindrance. The mechanism of the transamination reaction is treated as a reversible nucleophilic substitution reaction; this conclusion has also been confirmed by other data[67]. Ridel' and Gerchuk[68] found that transamination takes place much more readily in the presence of hydrochloric acid, which can be accounted for by the induction of a positive charge on the carbonyl carbon atom on protonation. Like Porai-Koshits[69], they found that the strong base is displaced by the weak one. In certain cases this can be explained by the great excess (by a factor of 15–20) of the weaker base.



(XVII) (XVIII) . (17)

The exchange of amines has been observed by Petrenko-Kritchenko and Shettle[70] when the "ammonia derivative of dehydrobenzoylacetic acid" (XVII) was acted upon by methylamine or aniline: there is a reversible exchange of the R–N< residues, where R = H, Me, or Ph. The present author suggests that this exchange begins with the addition of the amine to the $C_{(2)}$ or $C_{(6)}$ atom [Scheme (17)]. After ring opening, the intermediate aminoamide (XVIII) is formed‡ and this can again cyclise, regenerating the starting substances or giving rise to substitution products, which can be accounted for by the reversibility of this reaction.

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‡ When the $C_{(2)}$ carbon atom is attacked by methylamine, the intermediate aminoamide has a different structure, but the nature of the reaction remains unaltered.

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