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Advances in the Study of the Chichibabin Reaction

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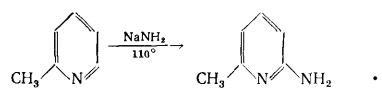
The state of research into one of the most important reactions of heterocyclic compounds—their amination by sodium amide (the Chichibabin reaction)—is described. The mechanism of the reaction, its application to specific classes of nitrogen-containing heterocycles, and certain reactions related to the Chichibabin reaction, namely amination of heterocycles by organic derivatives of metal amides, substitutional amination with elimination of hydrocarbon groups, amination of *N*-heteroaromatic cations, and hydrazination and hydroxylation, are discussed.
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I. INTRODUCTION

In 1914 Chichibabin and Zaide reported that, when they attempted to metallate the CH_3 group of α-picoline by sodium amide in toluene, they unexpectedly observed the amination of the pyridine ring in the free α-position[1]:



Later Chichibabin and his students extended this amination method to many pyridine, quinoline, and isoquinoline derivatives. The Chichibabin reaction has had an enormous influence on the development of the entire chemistry of pyridine and has acquired great practical importance. Its application to condensed imidazole systems, achieved for the first time by Simonov and coworkers[2], proved to be particularly fruitful. A view widely expressed in textbooks and reference literature (see, for example, Surrey[9]) is that the Chichibabin reaction is most typical for pyridine and its benzologues. Nevertheless, we shall show that this is not altogether the case.

There exist two fundamental reviews on the Chichibabin reaction[3,4]. The first, published more than 30 years ago, is naturally obsolete. The second has unfortunately remained little known and since its publication many fundamental new data concerning this reaction have accumulated in the literature. In a number of other reviews the discussion is restricted to reactions of pyridine[5-7] or imidazole[8] derivatives.

The aim of the present review is to give an account of the present state of research into the Chichibabin reaction and certain related reactions, primarily processes such as hydroxylation of heterocycles by alkalies and their hydrazination by metal hydrazides. The review reflects as far as possible the entire literature on the given problem published up to 1st June, 1976.

II. REACTION MECHANISM

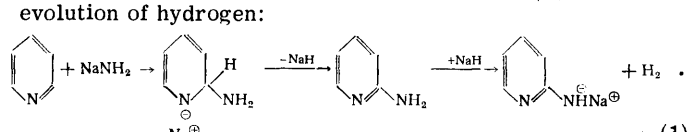
Owing to the high basicity of the amide ion, the Chichibabin reaction is usually carried out in aprotic solvents inert with respect to $NaNH_2$. Aromatic hydrocarbons, dimethylaniline, and liquid paraffin are most commonly used. Sodium amide is almost insoluble in these solvents, so that the reaction takes place under heterogeneous conditions. The only solven in which $NaNH_2$ (and to a greater extent KNH_2) is soluble proved to be liquid ammonia[10]. The Chichibabin reaction in liquid ammonia, achieved for the first time by Bergstrom[11-15], requires specific conditions: the use of sealed tubes and a long process time (up to several days); at the same time it is difficult to follow the course of the reaction. Furthermore, many heterocycles (pyridine, condensed imidazoles, etc.) are not aminated in liquid ammonia. The Chichibabin reaction can be carried out also without a solvent, in the melt, but this usually leads to less satisfactory results. In most instances the reaction begins at a comparatively high temperature (100-130°C), which is regulated in such a way that the evolution of hydrogen (a characteristic feature of amination) is uniform.

The mechanism of the Chichibabin reaction has been studied much less than those of other nucleophilic substitution reactions and is still not entirely clear. This is to a large extent due to the difficulty of studying the reaction kinetics (specificity of the conditions and occasional formation of side products). However, studies have been published recently on the reaction kinetics, based on the measurement of the rate of evolution of hydrogen[16-18].

In broad outline, the reaction involves the substitution of a hydride ion in the α- or γ-position in azaheterocycles by an amino-group. Two different mechanisms of the Chichibabin reaction have been discussed in the literature; —"addition-elimination" and "elimination-addition" (the heterocyclic aryne mechanism).

1. THE "ADDITION-ELIMINATION" MECHANISM

In 1930 Ziegler and Zeiser[19] proposed a two-stage reaction mechanism, the first stage involving the formation of an addition product I and the second its aromatisation to the 2-amino-derivative (II) as a result of the elimination of sodium hydride. It was suggested that NaH immediately reacts with the amino-group, which leads to the formation of the sodium salt of the amine (II) and the evolution of hydrogen:



(1)

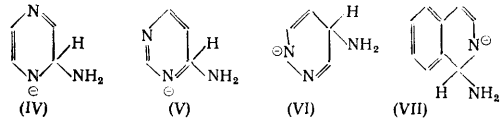
Although the main idea of this mechanism has been generally accepted[5,20,21], it has not been specified in detail and does not explain many experimental facts. Thus, as regards the addition stage, the mechanism does not provide an answer to the following questions: (1) whether sodium amide adds to the C= N bond synchronously or in stages; (2) if the addition takes place in stages, does the coordination of the $Na^{\oplus}$ ion to the pyridine nitrogen atom or the addition of $NH_2^{\ominus}$ to the carbon atom in the 2-position take place first; (3) do other intermediates, for example, radical-anions, etc., participate in the addition stage. There is similar uncertainty as regards the aromatisation stage (see below). It is not surprising that the Ziegler mechanism has no predictive power and cannot explain why some heterocycles are aminated while others, with a similar structure, are not.

Experimental facts which throw light on the mechanism of each reaction stage separately are discussed below.

(a) The Additional Stage

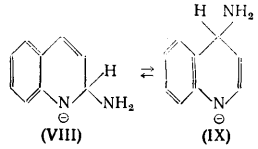
The formation of the σ-complex. For a long time the formation of anionic σ-complexes (I) was accepted without proof, although analogous adducts with sodium hydrazide[22], lithium tetrahydroaluminate[23], and phenyl-lithium[24] have been described.

Deeply coloured adducts of certain azines and diazines with sodium and potassium amides [compounds (IV)–(VII)] were detected recently in liquid ammonia by ^1H NMR:[25,26]



(IV) (V) (VI) (VII)

The σ-complexes (IV)–(VII) are formed almost instantaneously. Judging from their dissociation constants ($K \leq 10^{-5}$), the addition under these conditions is almost irreversible. It was not possible to isolate the complexes in a crystalline state[11–15,25,26]. Two σ-complexes, formed under kinetically [compound (VIII)] and thermodynamically [compound (IX)] controlled conditions, were discovered for quinoline



(VIII) (IX)

There is no doubt that σ-complexes are also formed on amination under heterogeneous conditions. Thus in the reaction involving isoquinoline the red colour characteristic of the σ-complex (VII) in liquid ammonia appears on amination in xylene and dimethylaniline. In general the appearance of a deep, frequently red, colour is a characteristic feature of the Chichibabin reaction.

Quantum-mechanical reactivity indices. Bearing in mind the nature of the Chichibabin reaction, it is logical to suppose that the carbon atom with the lowest positive charge q^+ is attacked first by the amide ion. Tables 1 and 2 present the values of q^+ for certain azines and azoles.

Quantum-mechanical calculations on the Chichibabin reaction are of dual importance. On the one hand, one can compare with their aid the reactivities of various positions within the same molecule (for example the α- and γ-positions in the pyridine and quinoline molecules) and, on the other hand, the electrophilic properties of a specific centre can be compared in different heterocycles.

Table 1. The positive charges on the carbon atoms, the basicities, and the reactivities of azines.

Compound	Position	π-Electronic charge (Ref.27) (Hückel MO method)	σ + π charge (Refs.28,29) (CNDO/2 method)	pK_a^{30}	Behaviour w.r.t. $NaNH_2$
Pyridine	2	0.077	0.102	5.23	+
	4	0.050	0.041		+–
Quinoline	2	0.104	0.090	4.94	+
	4	0.068	0.035		+–
Isoquinoline	1	0.105	0.066	5.40	+
	3	0.053	0.077		–
Benzo[*f*]quinoline	2	0.095	—	5.15	+
	4	0.059	—		–
Acridine	9	0.105	0.011	5.61	+–
Phenanthridine	6	0.133	—	4.52	+
Pyridazine	3 (6)	0.077	0.061	2.33	–
	4 (5)	0.047	0.017		–
Pyrimidine	2	0.155	0.156	1.30	+–
	4	0.126	0.115		–
Pyrazine	2,3,5,6	0.074	0.058	0.065	+–
1,3,5-Triazine	2,4,6	0.203	0.183	1.0	–
Quinazoline	2	0.073[31]	0.156	3.51	–
	4	0.064[31]	0.116		+
Quinoxaline	2	0.097	0.060	0.56	–

*The + sign means readily aminated, the +– sign means aminated with complications, and the – sign means not aminated.

Table 2. The positive charges on the α-carbon atom, the basicities, and the reactivities of azoles.

Compound	π-Electronic charge (Ref.27) (Hückel MO method)	σ + π charge (Ref.28) (CNDO/2 method)	pK_a^{30}	Behaviour w.r.t $NaNH_2^*$
Imidazole	0.094	0.110	7.33	–
4,5-Diphenylimidazole	0.107	—	5.90	–
Phenanthroimidazole	0.137	—	—	–
Benzimidazole	0.170	0.158	5.52	+
Imidazoä4,5-*b*]pyridine	0.170	—	3.95	–
Purine	0.172	0.179	2.39	–**
Naphtho[1,2-*d*]imidazole	0.152	—	5.28	+
Naphtho[2,3-*d*]imidazole	0.186	—	5.24	+
Imidazo[4,5-*b*]phenazine	0.202	—	3.62	–
Perimidine	0.256	0.198[32]	5.90	+
Indazole	0.063	—	1.27	–

*For the significance of the notation, see the footnote to Table 1.

**An attempt was made to aminate 9-ethyl-6-dimethylaminopurine ($pK_a = 3.90$)[27].

The results sometimes depend significantly on the chosen method and parameters. For example, in the calculation by the Hückel molecular orbital method the highest positive charge in the isoquinoline molecule is found in the 1-position, while calculation by the CNDO/2 method shows that it occurs in the 3-position (Table 1). Comparison of experimental data and the results of the calculations leads to the following conclusions.

1. For the successful amination of the heterocyclic compound, it is necessary that the α-carbon atom in its molecule should carry a fairly large positive charge. Thus indazole, imidazole, 4,5-diphenylimidazole, and phenanthreno[9,10-*d*] imidazole†, which do not possess a sufficiently high charge, are not aminated.

2. A high positive charge by itself does not guarantee successful amination. For example, purine, imidazo-[4,5-*b*]pyridine, and imidazo[4,5-*b*]phenazine, which are not aminated, carry a positive charge which is comparable to that in the readily aminated benzo- and naphtho-imidazoles.

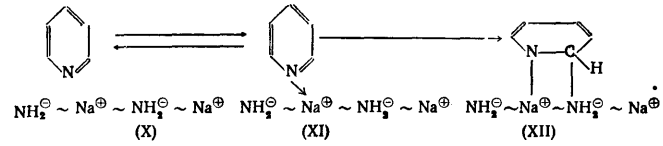
3. The site of attack by the amide ion does not always coincide with the location of the highest positive charge. For example, quinazoline is aminated in the 4-position and not the 2-position [33].

4. The employment of the energies of anionic localisation as reactivity indices is also unsatisfactory. Thus the values of L_2 and L_4 for pyridine (2.35 β and 2.37 β) and quinoline (2.24 β and 2.13 β) are non-informative and agree poorly with experiment [27,34].

The role of the basicity of the heterocycle. In principle, the Chichibabin reaction may be regarded as the interaction between the nitrogen-containing heterocycle and the amide ion, disregarding the influence of the counterion [35]. In amination in liquid ammonia, which ionises the M–NH_2 bond [10], such simplification is permissible‡, which is demonstrated, particularly, by the absence of a relation between the basicity of the heterocycle and its ability to be aminated in liquid ammonia.

On the other hand, in amination under heterogeneous conditions there is a distinct relation between the basicity of the compound and its ability to be aminated by metal amides [4,36]. Compounds whose basicity is in the range $pK_a = 5-6$ are most readily aminated; they include benzo- and naphtho-imidazoles, pyridine, isoquinoline, benzo[*f*]quinoline, and many others. Weakly basic diazines, triazines, quinoxaline, and certain imidazole systems are poorly aminated or do not react with $NaNH_2$ at all (Tables 1 and 2). The Chichibabin reaction is most sensitive to variations in basicity in the series of azoles [36-40]. Inspection of extensive experimental data shows that the lower limit of the basicity of benzimidazole derivatives which can be aminated lies in the range $pK_a = 4.2$ to 4.3. [27,36]

In order to account for the influence of basicity, it has been suggested that the pyridine nitrogen atom undergoes preliminary coordination to the sodium cation [4,36]. Such coordination not only orients the heterocycle at the $NaNH_2$ surface but also greatly increases the positive charge on the α-carbon atom, facilitating thereby the addition of the amide ion to the latter:



(X) (XI) (XII)

It has been shown by infrared spectroscopy that the sorption and coordination processes are reversible and precede the formation of the σ-complex [4,27].

If the $\geq N \rightarrow NaNH_2$ coordination is regarded as the first stage of the Chichibabin reaction, then presumably more basic heterocycles should be aminated more readily. However, this happens only up to a certain limit. The point is that, with increase of basicity, the position charge on the α-carbon atom decreases synchronously. For successful amination, the optimum combination of pK_a and q_a^+ is evidently necessary [4,36]. Heterocycles with $pK_a = 5-6$ evidently meet this requirement. Incidentally, there are also other exceptions, which will be discussed later. More basic heterocycles ($pK_a > 6-7$) do not enter into the Chichibabin reaction or are aminated with much difficulty. These include, in particular, imidazole [4] and 4- and 5-azaindoles [41]. The most basic of all the compounds which are successfully aminated is 4-dimethylaminopyridine ($pK_a = 9.37$), which reacts with $NaNH_2$ under extremely severe conditions and the yield of the 2-amino-derivative is low [41].

The hypothesis of the coordination of the pyridine nitrogen atom to the Na^+ ion helps to explain, apart from the influence of basicity, a number of other interesting features of the Chichibabin reaction, primarily the difficulty of γ-amination under heterogeneous conditions and the so-called *ortho*-dimethoxy-effect.

Characteristics of γ-amination. The possibility of γ-amination is determined mainly by two factors: the relative activities of the α- and γ-positions and the reaction conditions (homogeneous and heterogeneous). It must be emphasised that, when both positions are free, the reaction is predominantly directed to the α-atom. If the α-positions are occupied, the reaction is directed to the γ-position (the 4-position). For example, on amination in liquid ammonia, quinoline forms a mixture of 2- and 4-aminoquinolines in proportions of 6 : 1, [13] while 2-phenylquinoline [15] and quinoline-2-carboxylic acid [42] are aminated under the same conditions in the 4-position with an almost quantitative yield. Successful γ-amination under homogeneous conditions is, incidentally, not surprising, since metal amides are highly dissociated in liquid ammonia [10] and the ratio of the isomers is determined mainly by the relative reactivities of the α- and γ-carbon atoms.

On the other hand, under heterogeneous conditions, after the $\geq N \rightarrow NaNH_2$ coordination, the γ-position becomes relatively inaccessible to the amide ion for geometrical reasons and the yield of the isomer is greatly reduced. Indeed, γ-amination of quinoline under heterogeneous conditions has not been observed. 2,6-Dimethylpyridine is converted into 4-amino-2,6-dimethylpyridine with a yield of only 6%. [43]

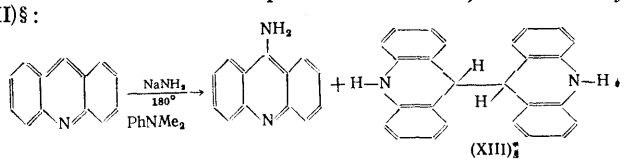
Acridine in a very convenient compounds for the study of γ-amination. In liquid ammonia 9-aminoacridine was obtained in a high yield [42], but in dimethylaniline the yield

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† Here, and henceforth in the discussion of the ability of azoles to be aminated we have in mind the behaviour of their *N*-substituted derivatives in relation to sodium amide.

‡ However, Bergstrom showed that, even under these conditions, the nature of the cation influences the reaction. Thus quinoline is more effectively aminated in liquid ammonia with the aid of $Ba(NH_2)_2$ than KNH_2. [12-15]

fell to 31% [44] and the main product became 9,9'-biacridanyl (XIII)§:

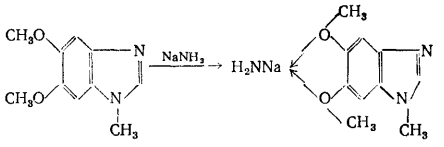


(XIII)§

Since the pK_a and q_γ^+ values for acridine favour the Chichibabin reaction (Table 1), the low yield of the amine can be accounted for only by the separation of the amide ion and the γ-position in the adsorption complex.

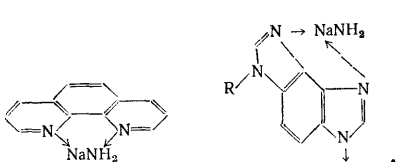
The *ortho*-dimethoxy-effect (ODE). In the study of the Chichibabin reaction involving the benzimidazole series it was observed that compounds containing methylenedioxy- or *ortho*-dimethoxy-groups cannot be aminated under a wide variety of conditions regardless of the site in the molecule containing the *ortho*-dimethoxy-group [39,46]. On the other hand, compounds with separated methoxy-groups are aminated to a satisfactory yield.

In order to account for the ODE, it has been suggested that *ortho*-dimethoxy-derivatives are sorbed on the $NaNH_2$ surface with formation of complexes of type (XIV), [39,46] which cannot be aminated further owing to their unfavourable orientation in relation to the C=N bond (ultimately one of the methoxy-groups is demethylated with formation of the corresponding phenoxide ion, which is inert with respect to $NaNH_2$ [46,47]). This explanation of the ODE has been confirmed by data for azacrown-ethers, which give rise to complexes with alkali metal ions via oxygen and not nitrogen atoms (in consequence of the ion–dipole mechanism of the interaction [48]):



(XIV)

The ODE has also been observed in the isoquinoline [46] and veratrol [47] series. The cause of the inertness of *o*-phenanthroline and benzo[1,2-*d* : 3,4-*d'*]di-imidazoles, which form complexes of types (XV) and (XVI) incapable of being aminated, is probably similar to the ODE:



(XV)

(XVI)

The polarisability of the C=N bond. Bearing in mind the role of the $\rangle N \rightarrow NaNH_2$ coordination as the first stage of the Chichibabin reaction, when the latter is considered within the framework of the LCAO-MO theory, it is necessary to take into account the results of calculation not only for neutral molecules but also for heteroaromatic cations. Conversion into cations is accompanied by a sharp increase of the positive charge on the α-carbon atom (Table 3). The difference Δq_α^+ between the charges in the base and in the cation is then not the same for different heterocycles, being a minimum for pyridine and increasing on passing to its benzologues. Δq_α^+ is particularly large for the benzo- and naphthoimidazole systems and also perimidine. The variation of Δq_α^+ on passing from one heterocyclic system to another may be attributed to the different polarisabilities of their C=N bonds in the course of the $\rangle N \rightarrow NaNH_2$ coordination (the importance of the polarisability factor in the Chichibabin reaction was first mentioned by Abramovitch et al. [49,50]). Evidently, the greater the value of Δq_α^+, the greater should be the ease, other conditions being equal, of the interaction of the heterocycle with the metal amide. Table 3 presents the Δq_α^+ calculated by the Hückel molecular orbital method for a series of heterocycles whose pK_a values lie in the region most favourable for the Chichibabin reaction. Also included are the values of $\Delta\delta_\alpha$ characterising the chemical shift of the α-CH proton in the ^1H NMR spectrum of the cation compared with the corresponding base. Overall, the variation of Δq_α^+ and $\Delta\delta_\alpha$ are the same.

Table 3. The effective positive charges q_2^+ and the chemical shift δ_2 of the protons of the α-carbon atom in certain heterocycles and their cations [27].

Compound	Neutral molecule		Cation		Δq_2^+	$\Delta\delta_2$, p.p.m.
	q_2^+	δ_2, p.p.m.	q_2^+	δ_2, p.p.m.		
Pyridine	+0.077	8.60	+0.241	8.98	+0.164	+0.38
Isoquinoline	+0.105	9.31	+0.329	10.07	+0.224	+0.76
Benzo[*f*]quinoline	+0.095	9.18	+0.276	9.95	+0.181	+0.77
Acridine*	+0.105	8.97	+0.288	10.15	+0.183	+1.18
Benzimidazole	+0.170	8.18	+0.443	9.61	+0.273	+1.43
Naphtho[1,2-*d*]imidazole	+0.152	8.15	+0.419	9.67	+0.267	+1.52
Perimidine	+0.256	7.41	+0.511	8.98	+0.255	+1.57

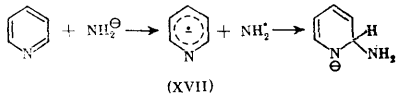
*Data for the γ-position.

On the basis of kinetic data, heterocycles can be arranged in the following series in terms of the ease with which they enter into the Chichibabin reaction: benzimidazole > isoquinoline > perimidine > benzo[*f*]quinoline > pyridine ≫ acridine [16]. If acridine is excluded (difficulty of γ-amination), this series agrees very closely with the variation of Δq_α^+, except for the fact that isoquinoline and perimidine change places. However, it is difficult to expect that a complex process such as the Chichibabin reaction should be ideally correlated in terms of a single electronic parameter. Apar from polarisability, the basicity of the compound, the positive charge on the α-carbon atom, the ease of aromatisation of the σ-complex, and possibly certain other factors play a role.

The possibility of a radical-anion stage in the Chichibabin reaction. The view that radical stages are possible in nucleophilic substitution reactions of aromatic compounds has become established in recent years [51-56]. It has also been shown in relation to the Chichibabin reaction that it is sensitive to the action of inhibitors of free radical processes [16]. It has been

§ The claim [45] that only 9-aminoacridine is formed under these conditions in 72% yield was not confirmed [44].

suggested that a one-electron transfer stage probably precedes the formation of the σ-complex and takes place immediately after the sorption of the heterocycle on the $NaNH_2$ surface:

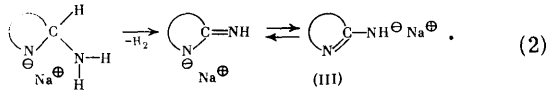


(XVII)

It must be emphasised that the introduction of the electron transfer stage does not conflict with the other considerations concerning the addition mechanism stated above and merely refines them, making it possible to explain many additional facts. In particular, certain compounds containing electron-accepting groups (NO_2, Ar–N=N, etc.) are not aminated, despite their satisfactory basicity and the large value of q_α^+. Presumably these substituents decrease with spin density in the 2-position of the radical-anion (XVII) and thereby prevent the recombination of radicals with formation of the σ-complex. On the whole, the problem of the intermediate formation of radical-anions in the Chichibabin reaction requires further study.

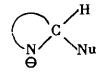
(b) The Elimination Stage

There are two main points of view concerning the mechanism of the aromatisation of the σ-complex in the Chichibabin reaction. The first, illustrated in Scheme (1), involves the loss of sodium hydride by the σ-complex. According to the Scheme (2), proposed in an early study by Bergstrom [11-15], the σ-complex is stabilised by the direct loss of an H_2 molecule as a result of the elimination of a proton from the NH_2 group and a hydride ion from the tetrahedral carbon atom:



(I) (III) (2)

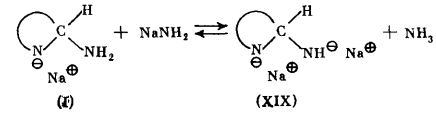
Scheme (2) is supported, in particular, by the fact that the reactions of nitrogen-containing heterocycles with anionic nucleophiles take place particularly readily when the nucleophile contains at least one hydrogen atom capable of being protonated. These include the $\overset{\ominus}{N}H_2$, $\overset{\ominus}{O}H$, and $\overset{\ominus}{N}HR$ anions. The σ-complexes (XVIII, a–c) corresponding to them



(XVIII) (a) Nu = NH_2; (b) Nu = OH;
(c) Nu = NHR;
(d) Nu = NR_2; (e) Nu = OR

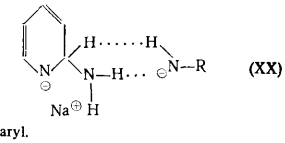
may be aromatised as a result of the loss of an H_2 molecule without preliminary elimination of sodium hydride. When the anions of secondary amines or metal alkoxides, whose σ-complexes (XVIII, d and e) cannot be stabilised in this way, are used as the nucleophiles, it is as a rule impossible to achieve the corresponding substitution reactions.

Direct elimination of hydrogen from the σ-complex is also likely to be a simplification. Clearly the mixture must contain the corresponding hydride ion and proton acceptors for this to occur. It has been suggested [12,57] that a hydride ion is eliminated from the dianionic σ-complex (XIX), formed as a result of an acid–base interaction, and not from the σ-complex (I):



(I) (XIX)

The possibility of the formation of such complexes is indirectly confirmed by ^1H NMR data [25,26] and by the finding that in liquid ammonia the amination reaction proceeds at an appreciable rate only in the presence of an excess of the metal amide [12]. In terms of this interpretation of the aromatisation stage, the evolution of hydrogen should occur as a result of the elimination of the hydride ion from the complex (XIX) with the aid of an ammonia molecule, i.e. in fact we are dealing here with bifunctional catalysis via a transition stage (XX). The decisive evidence in support of bifunctional catalysis is apparently the observation of the catalytic effect on the Chichibabin reaction of added sodium salts of amines and the presence of an autocatalytic section on the kinetic curves representing the variation of the rate of evolution of H_2. [16] Despite the presence in the mixture of an excess of more basic amide ions, the salts (III) catalyse the reaction, which shows that, in the transition complex (XX)



(XX)

(a), R=H, (b), R= heteroaryl.

the hydride ion is eliminated with greater difficulty than the proton, i.e. not only the elimination of the proton but also the elimination of the hydride ion is catalysed. This implies that the transition state in the elimination stage is close to the σ-complex (XIX) and not the Ziegler adduct (I), as has been believed hitherto.

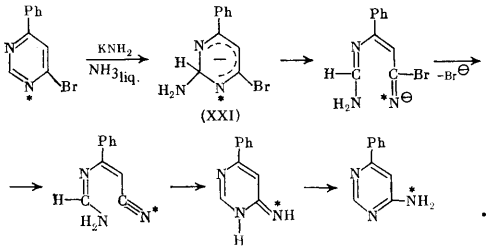
The hydride ion may be eliminated from the σ-complex also with the aid of a molecule of the initial compound, which entails the formation of dihydro-derivatives [16].

The foregoing considerations refer to heterogeneous amination. Successful amination in liquid ammonia takes place only in the presence of oxidants (KNO_3 is usually employed [11-15]), which convert the intermediate adduct (I) into an amine.

The behaviour of halogeno-derivatives of *N*-heterocycles in relation to metal amides. There has not been a single example in the literature hitherto of successful amination of halogenated *N*-heterocycles by the Chichibabin reaction, although such attempts have been made [4]. It is well known that halogeno-derivatives of heterocycles interact with metal amides, the halogen atom being substituted by an amino-group either via the S_N2Ar mechanism [5,6] or via the heteroaryne mechanism [58]. These reactions are usually carried out in liquid ammonia.

The so called *ANRORC* mechanism, proposed recently by Dutch chemists, throws some light on the characteristics of the behaviour of halogenated *N*-heterocycles in the Chichibabin reaction [59,60]. This mechanism is particularly

characteristic of compounds of the pyrimidine series, for example:

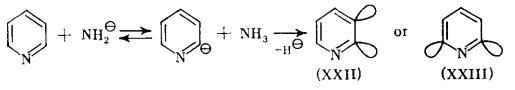


The reaction begins with the addition of an NH_2 ion to $C_{(2)}$ atom, without a halogen. The resulting σ-complexes of type (XXI) have been recently detected[61,62]. An important feature of these complexes is that they are stabilised by the elimination of a bromide ion with synchronous or stage-by-stage recyclisation and not by the loss of an $H^{\ominus}$ ion, which would constitute the Chichibabin reaction. As a result, the N atoms of the amide ion and the heterocycle change places. The *ANRORC* mechanism usually competes with the S_N2Ar or *EA* mechanism[59,60].

Yet another possible cause of the inability of halogenated heterocycles to be aminated by the Chichibabin reaction is the fact that their radical-anions (the possible reaction intermediates) are frequently fragmented with the loss of a halide ion[63]. Nevertheless it appears of interest to investigate the behaviour of halogenated *N*-heterocycles in relation to $NaNH_2$ in an aprotic medium. This applies particularly to compounds containing a relatively immobile halogen (for example, 3-bromopyridine).

(c) The "Elimination-Addition" Mechanism

The *EA* mechanism proposed for the Chichibabin reaction in 1963,[64,65] involving the intermediate formation of heteroarynes of type (XXII) or (XXIII), has been vigorously criticised[4,5,66,67]:

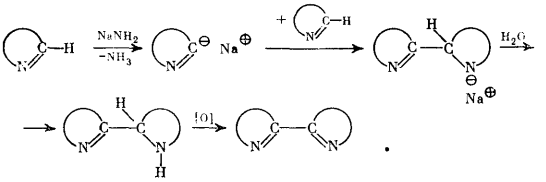


The following main evidence has been put forward:

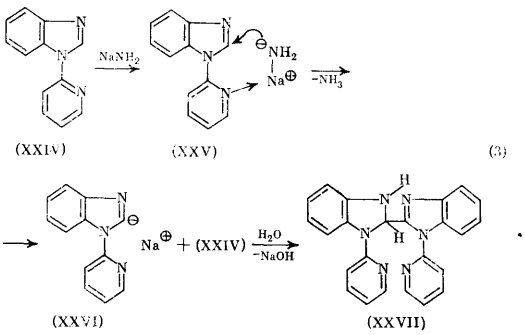
1. The absence of a kinetic isotope effect in the amination of a mixture of [2-D]pyridine and [3-D]pyridine.
2. The preferential amination of 3-substituted pyridines in the 2-position.
3. Successful amination of heterocycles which cannot form an aryne (azoles, acridine, isoquinoline). The amination of 2,5-disubstituted pyridines[68] also cannot involve the intermediate formation of 2,3- or 2,6-dihydropyridine.
4. According to calculations by the extended Hückel method, the arynes (XXII) and (XXIII) are much less stable than 3,4-dehydropyridines[69], which has been confirmed by data for the reactivities of 2- and 3-halogenopyridines[58].

2. SIDE REACTIONS

The most typical side reaction in the Chichibabin reaction amination of heterocycles is their dimerisation involving the α- or γ-positions. The formation of dimers with aromatic or hydrogenated structures has been observed for pyridine[1,3,7], quinoline[70], acridine[44], quinoxaline[71], and *N*-substituted benzimidazoles[27,38,46,72]. The yield of the dimer, which sometimes reaches 60%, depends strongly on the nature of the heterocycle and the solvent. The dimerisations mechanism is still not entirely clear. In principle, the reaction may reduce to the metallation of the α-CH bond with subsequent nucleophilic addition of the carbanion to the C=N bond of a second molecule[27]:



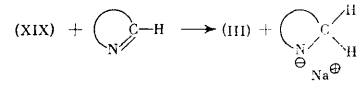
Another pathway involves the dimerisation of the intermediate radical-anion of type (XVII). According to the authors of the present review, both dimerisation pathways occur in different cases. For example, bearing in mind the ease of the polarographic reduction of acridine[73], the formation of 9,9′-biacridanyl (XIII) almost undoubtedly proceeds via a radical-anion mechanism. On the other hand, the formation of the dimer (XXVII) in 51% yield in xylene and in 10% yield in dimethylaniline when 1-α-pyridylbenzimidazole reacts with $NaNH_2$ probably involves the stage where the organosodium compound (XXVI) is formed, which may be favoured by intramolecular cooperation via type (XXV) coordination (such cooperative effects in the metallation of aromatic compounds have been described by, for example, Houghton[74] and Slocum and Stonemach[75]):



Scheme (3) is supported by the fact that 1-methyl-2-sodiobenzimidazole reacts with 1-methylbenzimidazole under the conditions of the Chichibabin reaction, giving rise to a high yield of 2,3-dihydro-1,1′-dimethyl-2,2′-bibenzimidazolyl[27]. It is noteworthy that the formation of organometallic compounds in the Chichibabin reaction should be accompanied by the evolution of gaseous ammonia. The presence of the latter in the gaseous reaction product does indeed range from 10 to 50%.[16,17] However, the main pathway leading to the formation of NH_3 is apparently the formation of the σ-complex (XIX) from the σ-complex (I). Thus up to 50% of NH_2 is evolved in the amination of 1-methylperimidine, although a dimer is not formed in the reaction at all[16].

The influence of solvents on dimerisation is indicated by the following facts. In the case of 1-alkylbenzimidazoles the formation of dimers in appreciable amounts (7–12%) is observed only in amination in dimethoxyethane or in the absence of a solvent. The amination of pyridine in hexamethylphosphoramide results in the formation of 4,4′-bipyridyl in 20% yield[7], the carbon atoms with the maximum spin density in the pyridine radical-anions being involved in the reaction[76].

The second in importance side reaction in the Chichibabin amination of heterocycles is the hydrogenation of their C=N bond, which leads to the formation of the corresponding dihydro-derivatives (XXVIII), sometimes in yields up to 25%. This reaction has been observed for phenanthridine[57], Schiff bases[20,21,77], and 1-methylperimidine. The mechanism probably involves the transfer of a hydride ion from the σ-complex (I) or, what is more likely, from the dianionic σ-complex (XIX), to the readily reduced C=N bond of the initial compound:



(XXVIII)

Other side reactions are specific to various compounds and will be considered in Section III.

3. THE INFLUENCE OF SOLVENTS

Unfortunately there are so far no quantitative data for the influence of solvents on the Chichibabin reaction. Taking into account the high polarity of the σ-complex, the ease of its formation should presumably depend on the solvating capacity and the dielectric constant of the solvent. Indeed in liquid ammonia, a solvent with proton-accepting and proton-donating activities which also has a very high dielectric constant ($\epsilon = 25.4$), the σ-complexes of many heterocycles with metal amides are formed even at −40°.[25,26] On the other hand, in inert solvents such as aromatic hydrocarbons ($\epsilon = 2-2.5$) σ-complexes are formed at 70−90°C and even higher temperatures. Dimethylaniline, dimethoxyethane, tetrahydrofuran, ($\epsilon = 7-7.5$), and other related solvents occupy an intermediate position between liquid ammonia and hydrocarbons. Amination in dimethylaniline takes place as a rule at a lower temperature and faster than in xylene or toluene although in isolated instances side products are formed in large amounts[37]. Reports have been published recently about the successful use of tetrahydrofuran and dimethoxyethane as solvents[27,57]. Thus phenanthridine is aminated in tetrahydrofuran even at room temperature[57].

Amination without a solvent has been described for 1-alkylbenzimidazoles[27], pyrazine[78], pyridine[79], anabasine[80], *N*-methylanabasine, and nicotine[80], the yields of the amino-derivative in the last two cases being even higher than in the presence of a solvent.

III. INTERACTION OF NITROGEN-CONTAINING HETEROCYCLES WITH METAL AMIDES

All the heterocycles which have been made to undergo the Chichibabin reaction hitherto contained a pyridine nitrogen atom. The role of the latter consists in the activation of the ring with respect to nucleophilic substitution by analogy with the function of the nitro-group in aromatic compounds. Indeed the σ constants of the nitro- and aza-groups are extremely similar[81]. Heterocycles with a single nitrogen atom of the pyridine type are aminated most effectively: pyridine, quinoline, isoquinoline, phenanthridine, and benzoquinolines. When several aza-groups are introduced into the molecule, the situation becomes more complex and treatment with $NaNH_2$ can lead to either amination (naphthyridines, pyrazines) or to side reactions (quinoxaline, triazine). Systems with excess π electrons, containing only a pyrrole nitrogen atom (indoles, indolizine, etc.), do not undergo the Chichibabin reaction. The only heterocycle with excess π electrons, which it has been possible to introduce into the reaction is perimidine, but its molecule contains a pyridine nitrogen atom in addition to a pyrrole nitrogen atom.

Azoles, another class of compounds with heteroatoms of both types, behave in different ways in relation to metal amides. Non-condensed azoles (imidazole, pyrazole) are usually not aminated, although there are exceptions (thiazole). The situation changes in benzazoles and naphthazoles as a result of the depletion of the heterocyclic ring in electrons and the compounds show a tendency towards amination (benzimidazole, naphthimidazoles), although this is not always the case (indazole and benzoselenazole are not aminated).

The pre-rearrangement of the N=CH group by $NaNH_2$ in a manner favouring amination is apparently so pronounced that the group is sometimes aminated even when it is not incorporated in a ring. Thus Schiff bases have been made to undergo the Chichibabin reaction[20,21,77].

The foregoing may create the impression that the presence of a pyridine nitrogen atom is a necessary condition for amination. However, such a claim must be approached with caution. In an early study Sachs showed that under severe conditions even compounds such as naphthalene, naphthylamines, and naphtholes may be aminated by sodium amide[82], hydrogen being evolved in the reaction (i.e. the latter proceeds as nucleophilic substitution). Later other non-heterocyclic compounds (mesobenzanthrone[83,84] and nitrobenzene[85]) were aminated, although the yields of amines in these instances are low. Evidently the problem of the possible amination of heterocycles without an aza-group requires further study.

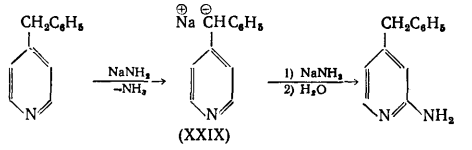
1. AZINES

(a) Pyridines

Pyridine and its 2- and 4-substituted derivatives. Despite the widely held view, pyridine is one of the most slowly aminated heterocycles. In contrast to diazines, quinoline, and isoquinoline, it does not, for example, react with KNH_2 in liquid ammonia even after prolonged treatment[25]. The amination of pyridine requires heating for many hours at 105−130°C (the yield of 2-aminopyridine is 70−85%).[1,79,86-88] Small amounts of bipyridyls, 2,2′-dipyridylamine, and 4-aminopyridine are formed as side products[1,3]. 2,6-Diaminopyridine may be obtained in 55% yield at 170−180°C [1] and 2,4,6-triaminopyridine may be formed in a low yield at 200°C and in the presence of a large excess of $NaNH_2$.[42] The relative difficulty of aminating pyridine can be accounted for by the comparatively low positive charge on the α-carbon atom and also by the low polarisability of the C=N bond (Tables 1 and 3).

2-Alkylpyridines (R = CH_3 [1,86-91] or n-C_3H_7 [3]) are aminated in the free α-position; if the latter is occupied, γ-amination takes place to a small extent[43]. 2,4,6-Trisubstituted pyridines do not enter into the Chichibabin reaction[1] and 2-t-butylpyridine is not aminated even under severe conditions[92]. The bulky t-butyl group apparently prevents, owing to steric considerations, the sorption of the compound on the $NaNH_2$ surface. The phenyl group has less stringent steric requirements and 2-phenylpyridine yields 6-amino-2-phenylpyridine (in dimethylaniline at 130−140°C) in 87% yield together with a small amount of the 4,6-diamino-derivative[93,94].

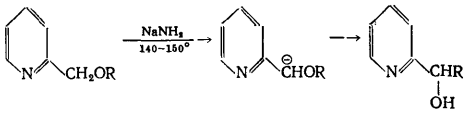
4-Alkylpyridines (R = CH_3,[95] C_2H_5,[96] n-C_3H_7,[97] or n-C_5H_{11}[98]) are converted into 2-amino-derivatives in 60 to 76% yields; 2,6-diamino-derivatives are not then formed. The high yields of amines in the amination of α- and γ-picolines show that in aprotic solvents the CH_3 group does not ionise (such ionisation takes place only in liquid ammonia[99]). On the other hand, 4-benzylpyridine initially forms the carbonium ion (XXIX), which is aminated with difficulty[98]:



(XXIX)

The difficulty of amination owing to analogous ionisation increases also for amino- and hydroxy-pyridines. Thus γ-pyridone is aminated only at 250°C in liquid paraffin, forming 2,6-diamino-4-hydroxypyridine in 69–75% yield[100]. α-Pyridone is aminated to 2-amino-6-hydroxypyridine[88]. The reaction of 2-aminopyridine with $NaNH_2$ at 120–130°C is accompanied by vigorous evolution of ammonia and the resulting salt (III) is aminated further to 2,6-diaminopyridine only at 160–180°C (in 71–79% yield)[41,87]. 4-Aminopyridine could not be introduced into the Chichibabin reaction[41]. The data for the amination of 3-aminopyridines are contradictory[41,101].

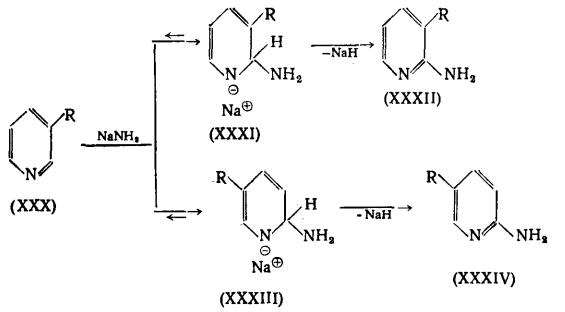
In certain cases the treatment of pyridine with $NaNH_2$ is accompanied by rearrangements or the elimination of substituents. Thus 2- and 4-alkoxymethylpyridines undergo the Wittig rearrangement[102]:



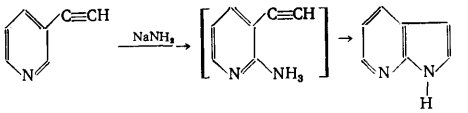
where R = C_2H_5, $C_6H_5CH_2$, etc. On treatment with $NaNH_2$, 2-dimethylaminopyridine gives a 30% yield of 2,6-diaminopyridine, the dimethylamino-group being substituted initially[41,103]. 4-Dimethylaminopyridine is aminated in the 2-position without the elimination of the substituent, but 4-diethylaminopyridine undergoes dealkylation, resulting in the formation of the sodium salt of 4-ethylaminopyridine, which is inert in relation to further treatment with $NaNH_2$.[41]

Pyridine-4-carboxylic acid and its amide are converted into 2,6-diaminopyridine on amination[104].

3-Substituted pyridines. One of the interesting features of the Chichibabin reaction is the preferential amination of 3-substituted pyridines (XXX) in the 2-position (Table 4).



As expected, 3-alkyl-groups deactivate the ring with respect to the amide ion, but the 2-position is deactivated more than the 2-position[5,50]. This feature of the amination reaction has been successfully used in the synthesis of 7-azaindole from 3-ethynylpyridine[111]:



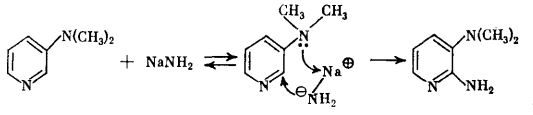
When compounds with bulky groups in the 3-position are aminated, the yield of the 6-amino-derivatives becomes equal to that of the 2-isomer or even exceeds it (Table 4).

Table 4. Amination of 3-substituted pyridines (XXX).

R	Reaction products (the ratios of the isomers are indicated in brackets)	Overall yield, %	References
CH_3	(XXXII) + (XXXIV) (10.5:1)	50	49,50,105,106
CH_3	2,6-diamino-3-methyl-pyridine	4	107
C_2H_5	(XXXII) + (XXXIV) (3.5:1)	64	108,109
n-C_4H_9	(XXXII) + (XXXIV) (4:1)	50	110
C≡CH	7-azaindole	54	111
$NHCH_3$	(XXXII)	—	112
OH	2,6-diaminopyridine	55	113
$N(CH_3)_2$	(XXXII)	62	41
COOH	2,6-diaminopyridine	12	114
$CONH_2$	2,6-diaminopyridine	44	114
$CONH_2$	(XXXII)	25	115
	(XXXII) + (XXXIV) (7.3:10)	45	116
	(XXXII) + (XXXIV) (9:11)	60—68	117–120
	(XXXII) + (XXXIV) (1:20)	40	117,121–123
	(XXXII) + (XXXIV) (1:1)	46	117,122,124

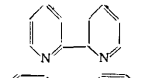
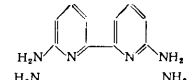
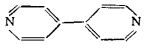
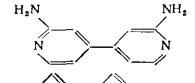
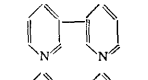
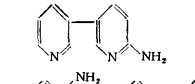
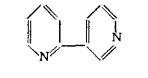
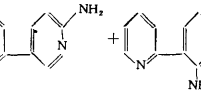
An analogous directing effect obtains in the interaction of 3-alkylpyridines with methyl-[125] and phenyl-lithium[126,127]. The nature of this phenomenon has been frequently discussed. No clear correspondence has been discovered between the position to which the nucleophile is directed and any reactivity index[128], which is not surprising, since steric and solvation effects and the possible interaction of the 3-substituent and the nucleophile in the transition state are ignored in calculations of this kind. The preferential formation of the 2-amino-derivative is believed to be associated with the fact that the corresponding σ-complex (XXXI) loses a hydride ion faster than the σ-complex (XXXIII).[5,50,126] This explanation is satisfactory if the rate of reaction is limited by the aromatisation stage. However, as already stated, a kinetic isotope effect has not been observed in the Chichibabin reaction[66].

The most attractive explanation is the hypothesis that the nucleophile is directed to the 2-position by London forces or the ion–dipole interaction of the nucleophile with the 3-substituent in the transition complex [5,50,129]. Such interaction should be particularly appreciable for 3-dimethylaminopyridine. Indeed, this compound is aminated exclusively in the 2-position [41]:



Other pyridines. The few studies on the amination of bipyridyls have shown that the latter react with $NaNH_2$ with much difficulty, forming amino-derivatives in low yields. Data for the amination of bipyridyls and disubstituted pyridines are presented in Table 5.

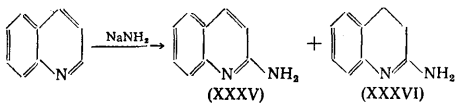
Table 5. Amination of disubstituted pyridines and bipyridyls.

Compound	Reaction product	Yield, %	References
2,5-$Me_2C_5H_3N$	2-amino-3,6-dimethylpyridine	32	130
3,5-$Me_2C_5H_3N$	2-amino-3,5-dimethylpyridine	20	130
2,6-$Me_2C_5H_3N$	4-amino-2,6-dimethylpyridine	6	43
2-Me-5-EtC_5H_3N	2-amino-3-ethyl-6-methylpyridine	70	68,96,131
2-Me-5-n-PrC_5H_3N	2-amino-3-n-propyl-6-methylpyridine	—	131
2-Me-4-HOC_5H_3N	2-amino-4-hydroxy-6-methylpyridine	—	132
3,4-$(HO)_2C_5H_3N$	2-amino-3,4-dihydroxypyridine	40	133
		—	134*
		—	96*
		—	135*
		—	136*

*There is no information about the yields.

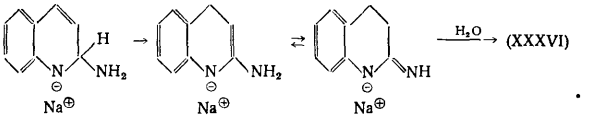
(b) Condensed Systems Containing a Pyridine Ring

In aprotic solvents quinoline is ineffectively aminated: the yield of 2-aminoquinoline (XXXV), which is difficult to purify, does not exceed 32% in toluene [1,70] and xylene [79]. In dimethylaniline the yield of (XXXV) falls to 7% and the main product becomes, somewhat unexpectedly, 2-amino-3,4-dihydroquinoline (XXXVI) (yield 24%): [137]



(XXXV) (XXXVI)

The formation of (XXXVI) can be represented schematically as follows:



This reaction occurs also for certain quinoline derivatives [138,139]. The highest yield of 2-aminoquinoline (53–69%) may be reached by amination by barium or potassium amides in liquid ammonia [13]: in the latter case 4-aminoquinoline is also formed in 10% yield.

As already mentioned, quinoline forms two σ-complexes in liquid ammonia—the 2-amino-1,2-dihydroquinolinide anion (VIII) and the 4-amino-1,4-dihydroquinolinide anion (IX). [26] Despite the fact that the latter is thermodynamically more stable, quinoline is nevertheless aminated mainly in the 2-position. A possible explanation of this finding is that (VIII) is aromatised faster (in liquid ammonia, to which the above considerations refer, the aromatisation stage is undoubtedly rate-limiting).

The results of the amination of various quinoline derivatives are presented in Table 6, which shows, in particular, that quinolines are much more readily aminated in the γ-position than pyridines.

2- and 4-Methylquinolines are not aminated in liquid ammonia owing to the ionisation of the methyl groups [14,142]. However, 4-methylquinoline is aminated in dimethylaniline (Table 6). In contrast to pyridine derivatives, quinolinecarboxylic acids and their amides are aminated without the elimination of the substituent. Hydroxy- and amino-quinolines are not aminated even under severe conditions [14].

Table 6. Amination of monosubstituted quinolines.

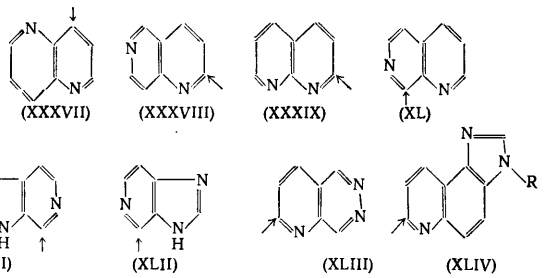
Substituent in initial compound	Substituents in reaction product	Yield, %	References
2-COOH	4-amino-2-carboxy-	81	14
2-C_6H_5	4-amino-2-phenyl-	91	15
2-OCH_3	2-amino-	51	14
2-SO_3H	2-amino-	74	14
2-$NHCH_3$	2-amino-	15	140
2-$N(CH_3)_2$	2-amino-	—	140
4-CH_3	2-amino-4-methyl-	46	3
4-COOH	2-amino-4-carboxy-	70	14
4-$CONH_2$	2-amino-4-carbamoyl-	54	141
6-CH_3	2-amino-6-methyl-	17	14
6-COOH	2-amino-6-carboxy-	60	14
6-C_6H_5	2-amino-6-phenyl-	86	15
6-$N(CH_3)_2$	2-amino-6-dimethylamino-	34	14
6-OCH_3	2-amino-6-methoxy-	27	14
6-SO_3H	2-amino-6-sulpho-	40	14
7-CH_3	2-amino-3,4-dihydro-7-methyl-	4,3	139
8-CH_3	2-amino-8-methyl-*	35	14,138
8-C_6H_5	2-amino-8-phenyl-	88	15
8-OC_2H_5	2-amino-8-ethoxy-	76	14

*2-Amino-8-methyl-3,4-dihydroquinoline was also isolated (1%). [128]

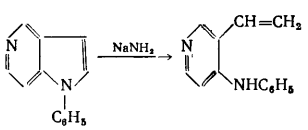
Isoquinoline is one of the most readily aminated heterocycles; the amino-group enters exclusively the 1-position. The yield of 1-aminoisoquinoline is quantitative in dimethylaniline [44], 87% in liquid ammonia [12,13], and 38% in toluene [143]. Isoquinoline-4-carboxylic acid [144], 5,6,7,8-tetrahydroisoquinoline [145], and 7-methoxyisoquinoline [146] are also satisfactorily aminated.

5,6- and 7,8-benzoquinolines give rise to high yields of 2-amino-derivatives both in liquid ammonia [15] and in dimethylaniline [147]. Phenanthridine is readily aminated in the 6-position in dimethylaniline [148,149], xylene [148], tetrahydrofuran [57], and liquid ammonia [42], but the amount of hydrogen evolved is less than the theoretical amount, which can be explained by the formation of 5,6-dihydrophenanthridine as a side product (yield 20%). [57] The amination of acridine was discussed above (Section II, 1a).

The amination of several compounds in which the pyridine ring is condensed to a further heteroatomic system has been described. These include the naphthyridines (XXXVII)–(XL), [150,151] β-carboline (XLI), [152] imidazo[4,5-*c*]-pyridine (XLII), [153] pyrido[4,5-*b*]-pyridazine (XLIII), [154] and imidazo[4,5-*f*]quinoline (XLIV) [147] (the arrow indicates the site where the amino-group enters):



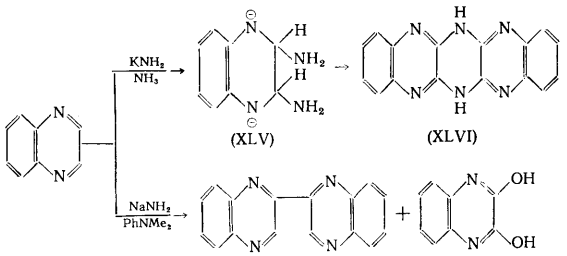
It was not possible to aminate 7-azaindolines [41], 7-azaindole [155], 1-methylimidazo[4,5-*b*]pyridine [156,157], 1-benzyl-4-azaindole, and 1-phenyl-5-azaindole [41]. It is of interest that the last compound is converted into 4-phenylamino-3-vinylpyridine on treatment with sodium amide [41], i.e. formally two-electron reductive cleavage of the C–N ring bond takes place:



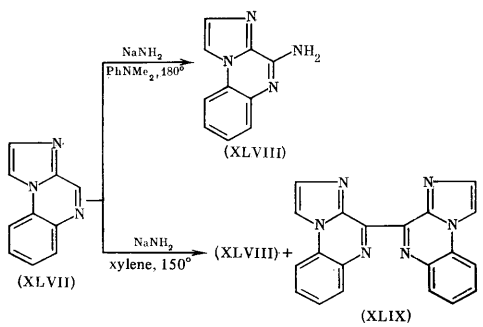
(c) Diazines and Triazines

Pyridazine does not undergo the Chichibabin reaction [154], although it does form the σ-complex (XVI) in liquid ammonia [25]. There has been only one report of the amination of pyrimidine derivatives: when 4-methylpyrimidine was treated with $NaNH_2$ in decalin, 2-amino-4-methyl- and 2,6-diamino-4-methyl-pyrimidines were isolated (the yields are not indicated) [158]. Pyrazine is aminated by sodium amide without a solvent, forming 2-aminopyrazine in a low yield (8–17%); [78] the available data on the amination of pyrazine in liquid ammonia are contradictory [159,160]. Amino-derivatives of 2,5-dimethylpyrazine are formed in 10% yield in xylene [161] and 35% yield in dimethylaniline [162]. 2,5-Di-s-butylpyrazine has been converted into an amine in 60–65% yield [163].

The reactions of quinoxaline with alkali amides take place in a complex manner and without the evolution of hydrogen. In liquid ammonia the only identified product of the reaction with two equivalents of potassium amide was fluorubine (XLVI). [160] It is apparently formed as a result of the reaction of the σ-complex (XLV) [164] with a molecule of the initial compound. In dimethylaniline the reaction of quinoxaline with sodium amide at 210–225 °C gives rise to 2,2′-biquinoxalinyl and 2,3-dihydroxyquinoxaline [71]:



The only quinoxaline derivatives aminated under the conditions of the Chichibabin reaction proved to be imidazo[1,2-*a*]quinoxaline (XLVII): the amine (XLVIII) was isolated in 44% yield in dimethylaniline, while in xylene its yield fell to 11% and the main product became the dimer (XLIX): [72]

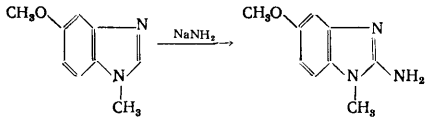


Quinazoline is aminated to 4-aminoquinazoline in dimethylaniline [33]. 4-Mercaptoquinazoline and 4-mercapto-6,7-benzoquinazoline are aminated with elimination of the mercapto-group and the formation of 2,4-diamino-derivatives [165]. Analogous results were observed also for 5,6-benzoquinazoline and its mercapto-derivatives [165].

Among triazines, the 1,3,5-isomer reacts with $NaNH_2$ and is cleaved to sodium cyanide in xylene at 160 °C. [166] Pteridine, which is soluble in liquid ammonia, combines with ammonia covalently, but decompose when acted upon by KNH_2. [167]

2. IMIDAZOLE SYSTEMS

In 1951 Simonov and Uglov [2] demonstrated the possibility of the amination of the imidazole ring in the 2-position in relation to 5-methoxy-5-methylbenzimidazole:



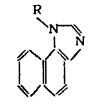
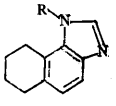
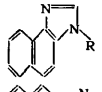
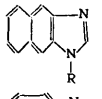
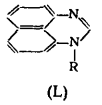
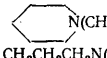
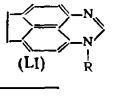
After this, the Chichibabin reaction was extended to many benzimidazole derivatives and a series of imidazole systems [4,8]. One should note that imidazoles with a free amino-group are not aminated, since they are converted into the *N*-anion, which is inert in relation to sodium amide.

The possibility of the amination of imidazole derivatives is determined mainly by three structural factors: (1) the nature of the ring condensed to the imidazole ring; (2) the

structure of the substituent at the pyrrole nitrogen atom; (3) the influence of the substituents in the aromatic ring.

The nature of the ring condensed with the imidazole ring. Whereas *N*-derivatives of benzimidazole, the isomeric naphthimidazoles, and 6,7,8,9-tetrahydronaphtho[1,2-*d*]imidazole are readily aminated in the 2-position (Table 7), *N*-substituted imidazoles, 4,5-diphenylimidazoles, and 5,6,7,8-tetrahydrobenzimidazoles do not undergo the Chichibabin reaction[168]. Thus, successful amination of the imidazole ring requires that it should be condensed to an aromatic ring. The role of the latter probably consists in creating a fairly large positive charge on the α-carbon atom as a result of the delocalisation of the π electrons (Table 2). The inability of phenanthro[9,10-*d*]imidazole to be aminated can be accounted for by the low aromaticity of the central benzene ring[168].

Table 7. Amination of naphthimidazoles, permidines, and aceperimidines.

Compound	R	Yield of amine, %	References
	C_2H_5	45	169
	CH_3	45	169
	CH_3 $C_6H_5CH_2$	75 75	169,170 171
	CH_3 $C_6H_5CH_2$	52 67	172 172
 (L)	CH_3 C_2H_5 n-C_3H_7 CH_3OCH_2 $C_6H_5CH_2$	90 (75)* 90 70 30 (75)* 75	40 40 40 40 40
		52	173
	$CH_2CH_2CH_2N(CH_3)_2$ C_6H_5	41 100	174 174
 (LI)	CH_3 C_2H_5	30 (75)* 25 (68)*	40 40

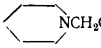
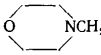
*The yield varies as a function of the solvent.

It is of interest that imidazoles which are not aminated readily undergo the azo-coupling reaction in an alkaline medium involving the μ-carbon atom, while imidazoles capable of being aminated do not react with diazonium salts; this difference served at one time as a test for ability to be aminated. This finding clearly demonstrates the differences between the charges in the μ-positions of the two types of azoles. However, there are also exceptions. *N*-derivatives of imidazo[4,5-*b*] phenazine[39], imidazo[4,5-*b*]pyridine[156], and purine[27] are inert both to diazonium salts (high q_{α}^{+}) and sodium amide (low basicity).

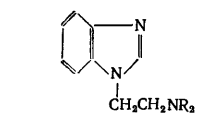
The influence of the *N*-substituent. The nature of the substituent at the nitrogen atom has a significant influence on the amination of imidazoles and in certain cases completely alters the mode of reaction.

Benzimidazoles containing straight-chain alkyl substituents are readily aminated at 105–120°C (Table 8). Secondary *N*-alkyl groups hinder the reaction only slightly[17]. 1-*t*-Butylbenzimidazole is aminated with a low yield[175].

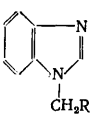
Table 8. Amination of 1-substituted benzimidazoles.

N-substituent	Yield of 2-amino-derivative, %	Refs.
CH_3	80	8,176
C_2H_5	85	26,168
n-C_3H_7	50	177
iso-C_3H_7	64	175,177
n-C_4H_9	55	177
t-C_4H_9	21	175
iso-C_9H_{19}	70	175
n-$C_{11}H_{23}$	64	175
$(C_2H_5)_2NCH_2CH_2$	50	178
	50	36
	40	36
cyclohexyl	70	37
$C_6H_5CH_2$	67	179
p-$CH_3C_6H_4CH_2$	72	180
p-iso-$C_3H_7C_6H_4CH_2$	63	180
2,5-$(CH_3)_2C_6H_3CH_2$	61	180
p-$HOC_6H_4CH_2$	29	46
p-$CH_3OC_6H_4CH_2$	61	46
$(C_6H_5)_2CH$	54	180
$(C_6H_5)(CH_3)CH$	34	181
α-Naphthylmethyl	15	181
C_6H_5	62	37
p-$CH_3C_6H_4$	47	27
p-$CH_3OC_6H_4$	74	39
o-$CH_3OC_6H_4$	82	39
p-$(CH_3)_2NC_6H_4$	71	39
2,4-$(CH_3O)_2C_6H_3$	66	46
2,5-$(CH_3O)_2C_6H_3$	60	46

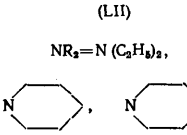
1-β-Dialkylaminoethylbenzimidazoles (LII) are aminated with greater difficulty than 1-alkylbenzimidazoles. One of the possible explanations involves competing coordination of the nitrogen atom of the substituent to the sodium cation, which should hinder the reaction. Under the conditions of the Chichibabin reaction, 1-diethylaminomethylbenzimidazole (LIIIa) gives rise to benzimidazole and 1-piperidino- and 1-morpholino-methylbenzimidazoles (LIII, b and c) are converted into 1-aminomethylbenzimidazole[182]. Compounds (LIII, d–i) do not form amino-derivatives[36,182].

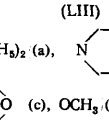
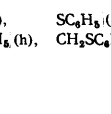


(LII)



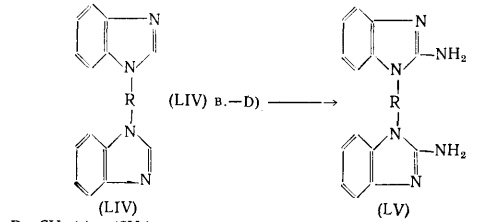
(LIII)

NR_2=N $(C_2H_5)_2$, 

R=N $(C_2H_5)_2$ (a),  (b),  (c), OCH_3 (d), OC_2H_5 (e), OC_6H_5 (f), SC_6H_5 (g), $CH_2OC_6H_5$ (h), $CH_2SC_6H_5$ (i).

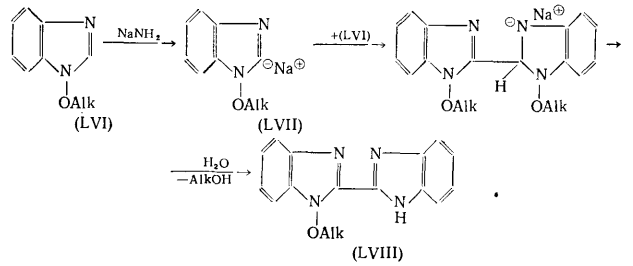
1-β-Pyridylethylbenzimidazoles do not react with $NaNH_2$ at 110–140°C, decomposing at a higher temperature with formation of benzimidazole and a tar [38].

Depending on the length of the hydrocarbon chain, di-(1-benzimidazolyl)alkanes (LIV) behave in different ways in the Chichibabin reaction. Thus compounds (LIV, a, b, and f) are not aminated even at 180°C, while compounds (LIV, c–e) form the diamines (LV).[183] The reason for the difference between the reactivities is not altogether clear.



R=CH_2 (a), $(CH_2)_2$ (b), $(CH_2)_3$ (c), $(CH_2)_4$ (d), $(CH_2)_5$ (e), $CH_2C_6H_4CH_2$ (f); R=$(CH_2)_3$, $(CH_2)_4$, or $(CH_2)_5$.

The weakly basic 1-alkoxybenzimidazoles (LVI) are converted into the "dimers" (LVIII) when acted upon by sodium amide, probably via the intermediate carbanion (LVII):[184]



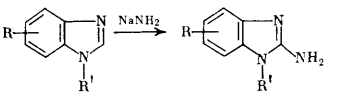
Thus the ease and mode of reaction of 1-substituted benzimidazoles with sodium amide greatly depend on the presence of a heteroatom in the substituent.

1-Benzylbenzimidazole and its derivatives with electron-donating substituents in the benzyl group are readily aminated (Table 8), with the exception of 1-*p*-hydroxybenzylbenzimidazole, which forms the less reactive *O*-anion, and 1-(3,4-dimethoxybenzyl)benzimidazole, which is converted into benzimidazole[46]. The formation of a dimer (7%) was observed in the amination of 1-*p*-methoxybenzylbenzimidazole[46]. Different 1-arylbenzimidazoles without electron-accepting substituents are also effectively aminated (Table 8). 1-γ-Pyridylbenzimidazole is inert with respect to $NaNH_2$, whereas 1-α-pyridylbenzimidazole is converted into the dimer (XXVII) under the same conditions[38] (Section II, 2).

The influence of substituents in the benzene ring of benzimidazole. When electron-accepting substituents (COOH, COOR, $CONH_2$, NO_2, N_3 PhN = N, F, Br, or Cl) are present in the benzene ring of benzimidazole, amination is impossible[8,39,185,186]. This is probably due to one of the following causes or their combination: (1) a decrease of the basicity of the nitrogen atom ($pK_a \leq 4.8$); the tendency of these groups to form non-aminated complexes with $NaNH_2$; (3) a change in the distribution of spin density in intermediate radical-anion which is unfavourable for amination.

Benzimidazoles with electron-donating groups in the benzene ring are readily aminated (Table 9), the substituents decreasing the rate of reaction in accordance with their electron-donating properties: 5,6-Me_2 < 5-MeO < 5-Me < 5-H.[17] 5-Hydroxy-, 5,6-dimethoxy-, and 5,6-methylenedioxy-benzimidazoles are not aminated[39,46] (Section I, 1a). 5-Amino-1-methylbenzimidazole is aminated under severe conditions[39].

Table 9. Amination of benzimidazoles substituted in the benzene ring



Substituents		Yield of 2-amino-derivative, %	Refs.
R	R′		
4-CH_3O	CH_3	57	39
5-CH_3	CH_3, $C_6H_5CH_2$	60–76	186
5-CH_3O	CH_3, C_2H_5, $C_6H_5CH_2$, $(C_2H_5)_2N(CH_2)_3$	55–63	2,39,176,187
5-C_6H_5O	CH_3, C_2H_5	55–60	185
5-$C_6H_5CH_2O$	CH_3	25	185
5-C_6H_5O	CH_3	70	185
5 CH_3S	CH_3	87	188
5-NH_2	CH_3	69	39
5-$N(CH_3)_2$	CH_3, C_2H_5	70–93	39
6-CH_3O	C_2H_5	52	39
7-CH_3O	$C_6H_5CH_2$	64	39
5,6-$(CH_3)_2$	CH_3, C_2H_5, C_6H_5, $C_6H_5CH_2$	38–91	189
4,7-$(CH_3O)_2$	$C_6H_5CH_2$	65	46

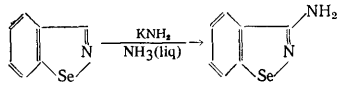
3. PERIMIDINES

Perimidines (L) are *peri*-isomeris of naphthimidazoles, but differ from the latter by the size of the heterocycle and a number of important physicochemical properties. Thus, together with a considerable deficiency of π electrons, a large excess of π electrons is also characteristic of perimidines[190], so that one may say that they are the only compounds with an excess of π electrons which enter into the Chichibabin reaction. The successful amination of perimidines is due to the strong polarisation of the C=N bond as a result of which a large positive charge is concentrated on the μ-carbon atom, where amination takes place, while a negative charge is created at the pyridine nitrogen atom (perimidines are much more basic than naphthimidazoles; see Table 2). Furthermore, the C=N bond in perimidines is highly polarisable (Table 3). *N*-Substituted aceperimidines (LI) undergo the Chichibabin reaction with much difficulty than perimidines. Data for the amination of perimidines and aceperimidines are presented in Table 7.

4. OTHER HETEROCYCLIC SYSTEMS

Thiazoles, selenazoles, and oxazoles. The Chichibabin reaction involving thiazoles and benzothiazoles proceeds in a complex manner and is of no practical importance. Sodium amide converts 4-methylthiazole into the 2-amino-derivative only after prolonged heating at 150°C.[191] Benzothiazole is aminated at 140°C but 2,2′-bibenzothiazolyl and bis-(2-aminophenyl) disulphide are formed together with 2-aminobenzothiazole[192].

When benzoselenazole was acted upon by $NaNH_2$, only bis-(2-aminophenyl) diselenide was isolated[193]. The amination of benzoisoselenazole with KNH_2 in liquid ammonia leads to the 3-amino-derivative, but its yield is low (36%):[194]



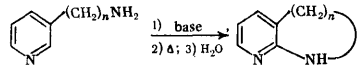
4-Methylselenazole[195] and isoxazoles[196] undergo ring opening without the formation of an amine.

Pyrazoles and indazoles. The positive charge on the α-carbon atoms of pyrazoles and indazoles are insufficient for amination. For this reason and also because of the lability of the nitrogen–nitrogen single bond, they are converted into ring-opening products and recyclisation products on being treated with methyl amides (see the relevant reviews[197,198]).

IV. REACTIONS RELATED TO THE CHICHIBABIN REACTION

Alkyl- and aryl-amination of heterocycles. The amination of nitrogen-containing heterocycles by organic derivatives of sodium amide is the closest analogue of the Chichibabin reaction. The possibility, in principle, of the phenylamination of pyridine in the 2-position by sodium anilide was demonstrated a long time ago[1]. However, owing to its low yields, the reaction is of no practical importance; furthermore, quinoline does not react with sodium anilide[22], while isoquinoline[13] and pyridine[199] do not react with sodium *N*-methylanilide. The alkylamination of heterocycles takes place successfully, but it has been little studied. Quinoline, acted upon by lithium methylamide, is known to form 2-methylaminoquinoline[200]. Alkali metal dialkylamides react only weakly with *N*-heterocycles or convert them into a tar[11,13,200].

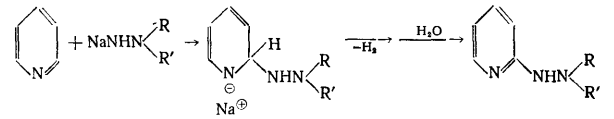
Bergstrom and coworkers achieved the alkylamination of pyridine and quinoline in the 2-position with the aid of aliphatic and alicyclic amines and the KNH_2-NaNH_2 eutectic in the presence of KNO_3.[201] The yield of reaction products reaches 60%. Kovacs and Vajda modified this method, having replaced the metal amide eutectic by metallic sodium[202–205]. Although it is natural to suppose that the aminating agent in these cases is sodium alkylamide, this is apparently not the case[204]. It has been suggested that the reaction proceeds via the intermediate formation of the pyridine radical-anion (as a result of electron transfer from sodium), which has been confirmed by the formation of 2,2′- and 4,4′-bipyridyls as side products and also by the available data on the mechanism of the interaction of sodium and pyridine[206]. An interesting variety of the reaction is intramolecular alkylamination of 3-ω-aminoalkylpyridines in the presence of strong bases (n-C_4H_9Li, Na, NaH, or $NaNH_2$) in dioxan or toluene[5,207,208]



$n = 2, 3,$ or 4.

It must be emphasised that the reaction takes place in this case exclusively in the 2-position of the pyridine ring.

Hydrazination by metal hydrazides. The sodium salts of hydrazine, *N*-methylhydrazine, and *N*,*N*-dimethylhydrazine react very readily with pyridine, quinoline, 5,6- and 7,8-benzoquinolines, and their methyl derivatives with formation of the corresponding α-hydrazino-derivatives (LX):[209,210]



(LIX) (LX)

R, R′=H, or CH_3.

The yields of products from pyridine and α-piccoline do not exceed 30%, those from quinoline do not exceed 45%, but in other cases the yields reach 70–80%.

In this reaction, which also proceeds with elimination of a hydride ion, a deeply coloured σ-complex (LIX) is formed initially[22,210], losing an H_2 molecule on heating and forming the corresponding hydrazine. A distinctive feature of the hydrazination reaction is the enhanced stability of the 1,4-adducts formed from pyridine and 2-methylquinoline: they are not aromatised even on heating[210]. It may be that their formation is the cause of the relatively low yield of 2-hydrazino-derivatives of pyridine and quinoline. Indeed, if the 4-position is occupied (γ-picoline, 4-methylquinoline, isoquinoline), α-hydrazination takes place with a satisfactory yield.

The adducts of acridine and phenanthradine with sodium hydrazide and dimethylhydrazide are anomalously stabilised. Instead of hydrogen, they split off on heating NH_3 and $(CH_3)_2NH$ molecules respectively, which results in the formation of 9-aminoacridine and 6-aminophenanthridine[22]. When quinazoline is acted upon by sodium hydrazide, hydrazination and amination take place simultaneously and 4-amino-2-hydrazinoquinazoline is formed[211]. Under these conditions, quinoxaline undergoes ring opening and pyrimidine undergoes ring contraction with formation of *o*-phenylenediamine and pyrazole respectively[211]. Yet another side reaction, which is observed, in particular, when pyridine is acted upon by sodium hydrazide, is the formation of hydrazo-compounds[210].

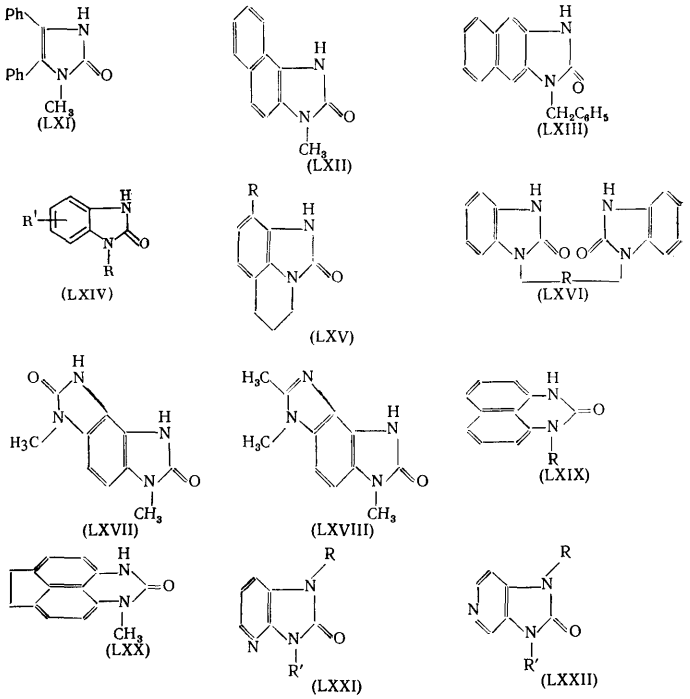
There is evidence for the possibility of direct hydrazination of benzoxazole and benzoselenazole[22]. Sodium phenylhydrazide could not be introduced into the reaction with heterocyclic compounds[209].

Hydroxylation of heterocycles. Direct hydroxylation of *N*-heterocycles is, as it were, the oxygen analogue of the Chichibabin reaction and is also accompanied by the evolution of hydrogen. The successful hydroxylation of both six- and five-membered heterocycles has now been achieved. α-Oxo-derivatives of pyridines[213–216], quinolines[215–218], benzoquinolines[218], isoquinoline[218], and phenanthridine were obtained by this method[219]. The hydroxylation of 1-substituted imidazoles and perimidines (Table 10), achieved for the first time by Pozharskii and coworkers[221], is of special preparative importance, because the *N*-monosubstituted imidazolidinones and perimidones, formed at the same time, are difficult to obtain by another procedure. It has been shown for compound (LXVI) and (LXVII) that, in the presence of two atoms active in relation to the nucleophile in the molecule of the *N*-heterocycle, both can be hydroxylated[183,220].

The hydroxylation can be carried out by fusing the heterocyclic compound with a large excess of anhydrous powdered alkali [KOH and, more rarely, NaOH and

$Ba(OH)_2$]. Owing to the weak nucleophilic properties of the $OH^{\ominus}$ ion, the process proceeds at an extremely high temperature (usually above 200°C), but is nevertheless characterised by a surprisingly high selectivity and, as a rule, high yields (particularly for imidazoles and perimidines). The only known instance of γ-hydroxylation is the formation of acridinone in 40% yield on hydroxylation of acridine with KOH at 300°C.[44] The ease of hydroxylation depends mainly on the positive charge of the α-carbon atom (Table 2).[221] Thus 1-methyl-4,5-diphenylimidazole is hydroxylated at 370–400°C, while 1-substituted perimidines are hydroxylated at a temperature as low as 200°C.

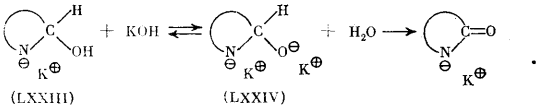
Table 10. Imidazolidinones and perimidones obtained by direct hydroxylation



Compound	Substituents R	Substituents R′	Yield, %	References
(LXI)	—	—	30	221
(LXII)	—	—	90	221
(LXIII)	—	—	80	222
(LXIV)	CH_3	H	90	221
(LXIV)	iso-C_3H_7	H	23	223
(LXIV)	n-C_9H_{19}	H	75	223
(LXIV)	$C_6H_5CH_2$	H	90	221
(LXIV)	C_6H_5	H	20	221
(LXIV)	p-$CH_3OC_6H_4$	H	70	221
(LXIV)	CH_3OCH_2	H	80	221
(LXIV)	CH_3	5-CH_3O	85	221
(LXIV)	$C_6H_5CH_2$	5,6-$(CH_3)_2$	85	221
(LXV)	H	—	58	224
(LXV)	$(C_2H_5)_2N$	—	33	224
(LXVI)	$(CH_2)_3$	—	50	183
(LXVI)	$(CH_2)_4$	—	81	183
(LXVI)	$(CH_2)_5$	—	91	183
(LXVII)	—	—	35	220
(LXVIII)	—	—	46	220
(LXIX)	CH_3	—	90	221
(LXIX)	C_2H_5	—	87	221
(LXIX)	CH_3OCH_2	—	82	221
(LXIX)	$(C_2H_5)_2NCH_2CH_2$	—	30	173
(LXX)	—	—	81	221
(LXXI)	CH_3	H	70	225
(LXXI)	H	CH_3	98	225
(LXXI)	H	$C_6H_5CH_2$	65	225
(LXXII)	CH_3	H	27	225
(LXXII)	H	CH_3	44	225

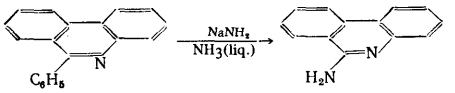
Much less is known about the side reactions in the hydroxylation process than for the Chichibabin reaction. Thus, on being fused with KOH, 1-phenylbenzimidazole gives rise to 1,1′-diphenyl-2,2′-bibenzimidazolyl together with 1-phenylbenzimidazolidinone[221]. On treatment with KOH, 1-methoxymethyl-, 1-isopropyl-, and 1-t-butylbenzimidazoles are converted into benzimidazole and other decomposition products, i.e. the elimination of the N-substituent is observed.

The hydroxylation mechanism probably resembles the mechanism of the Chichibabin reaction, although it has not been specially studied. We have reason to believe that the dianionic σ-complex (LXXIV) is formed as an intermediate: before the evolution of hydrogen, water is usually distilled off, which displaces the equilibrium (LXXIII) $\rightleftharpoons$ (LXXIV) to the right:



Direct alkoxylation of N-heterocycles by metal alkoxides could not be achieved[221].

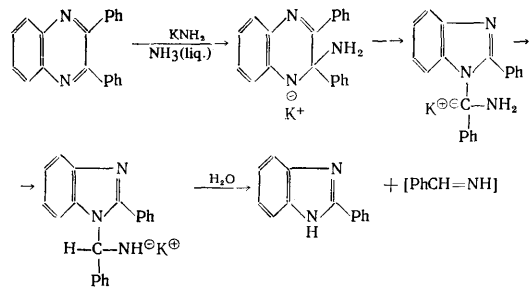
Amination and hydroxylation with elimination of a carbanion. In our discussion of the Chichibabin reaction involving pyridine and quinolines we quoted a number of reactions in which the leaving groups were NMe_2, SO_3H, a halogen, etc. and not a hydride ion. However, all the groups are readily eliminated. In this respect the reactions of N-heterocycle derivatives, in which their amination by metal amide is accompanied by the elimination of a hydrocarbon substituent, are much closer to the Chichibabin reaction. Thus it has been shown that 6-phenylphenanthridine is aminated by sodium amide in liquid ammonia with replacement of the phenyl group by the NH_2 group[226]:



Similarly, 1-methyl-2-phenylbenzimidazole is converted into 2-amino-1-methylbenzimidazole (in 55% yield) on fusion with $NaNH_2$ and into 1-methylbenzimidazolidinone (in 60% yield) on fusion with KOH. This reaction is less characteristic of 2-alkylbenzimidazoles[227,228]. There is little doubt that the phenyl group is eliminated in the form of the carbanion, since benzene is produced in the reaction. It is of interest to note that 2-phenylquinoline and 2-phenylpyridine are aminated at the vacant sites (the 4- and 6-positions respectively). An attempt should be made to discover what result is obtained when these compounds are fused with $NaNH_2$ without a solvent.

An unusual rearrangement, leading to 2-phenylbenzimidazole, was observed when 2,3-diphenylquinoxaline was acted upon by KNH_2 in liquid ammonia[229]. It has been suggested that the first stage of the process is also the formation of a σ-complex, which then undergoes ring

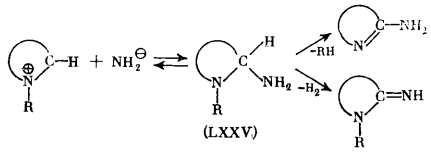
contraction with elimination of one of the phenyl groups as benzylideneamine:



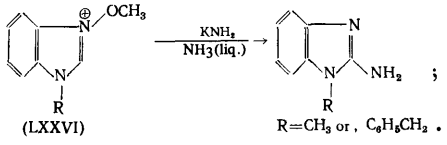
It has been shown recently that the CF_3 group in α-trifluoromethyl derivatives of pyridine, quinoline, and isoquinoline is readily substituted by an amino-group on treatment with KNH_2 in liquid ammonia [230]. The mechanism of this reaction has been studied [231].

Amination of heteroaromatic cations by metal amides. *N*-Heteroaromatic cations are known to react with nucleophiles much more readily than neutral molecules, which is frequently used for synthetic purposes. In relation to the Chichibabin reaction, this problem is of fundamental importance in connection with the hypothesis that the pyridine nitrogen atom is coordinated to the $Na^{\oplus}$ ion, as a result of which the heteroatom is partly converted into the onium state. The first data on the interaction of *N*-heterocyclic cations with metal amides were obtained only recently [232]¶.

If other possible reactions (for example, reactions involving ring opening) are disregarded, adducts of type (LXXV) can be, in principle, stabilised either by the formation of an amine (with elimination of RH) or an imine (with elimination of H_2):



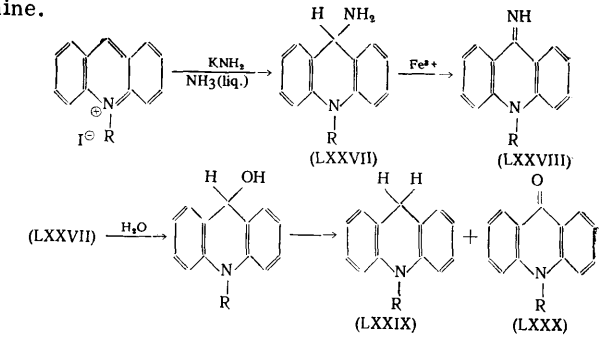
When the first pathway is followed, the *N*-substituent must be readily eliminated after the addition of the $NH_2^{\ominus}$ anion. It was shown that the *N*-methoxy-group possesses this ability. Thus, when the salt (LXXVI) is acted upon by KNH_2, 1-substituted 2-aminobenzimidazoles are formed in high yields [232]:



The problem of the action of metal amides on the *N*-oxides of nitrogen-containing heterocycles is very interesting, because the *N*-oxide group can also activate the addition of a nucleophile and then can be eliminated [184]. Surprisingly, there is so far no information in the literature about the behaviour of *N*-oxides in relation to metal amides.

¶ Certain *N*-heteroaromatic cations [164,233] and bases [167] (pteridine) undergo covalent amination in liquid ammonia even in the absence of amide ions.

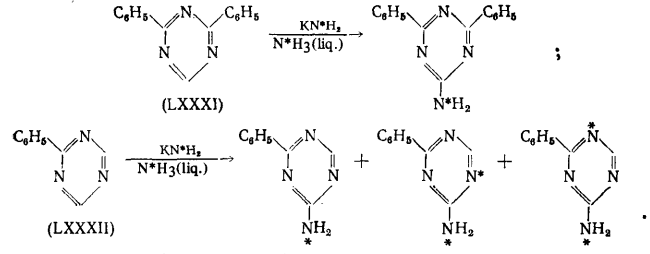
The second pathway in the aromatisation of adducts of type (LXXV) constitutes in essence the direct imination reaction. Only one example of such a reaction is known: when the *N*-methylacridinium cation is acted upon by KNH_2 in the presence of $Fe(NO_3)_3$, *N*-methyl-9-acridinone imine (LXXVIII) is formed in 35% yield with approximately the same amount of *N*-methylacridan (LXXIX) and *N*-methylacridinone (LXXX). [232] It was not possible to select more effective oxidants in order to increase the yield of the imine.



When metal amides act on 1,3-dialkylbenzimidazolium, naphthimidazolium, 4,5-diphenylimidazolium, and perimidinium salts, mainly the corresponding pseudobases or 2-oxo-derivatives are formed [232]. Thus, despite the possibility, in principle, of the amination and imination of *N*-heterocycles via their quaternary salts, synthetic methods of general importance have not in essence been developed as yet in this field. The difficulties are to a large extent associated with the selection of solvents, because metal amides are soluble only in liquid ammonia and quaternary ammonium salts are soluble in solvents in which experiments with metal amides are impossible.

Thus there have been significant advances in recent years in the study of all the aspects of the Chichibabin reaction. As regards its mechanism, the formation of σ-complexes has been demonstrated†, the phenomenon of

† Two papers by Dutch chemists, which report the successful amination in liquid ammonia of diphenyl-1,3,5-triazine (LXXXI) and phenyl-1,3-triazine (LXXXII), have been published recently [234,235]. The reaction is slow (up to 72 h) and requires a large excess of KNH_2 (by a factor of 40–50), but the yield of the amine is fairly high (72%):



The formation of hydride σ-complexes as intermediates was noted in both cases. According to the authors, (LXXXI) is aminated exclusively via the addition-elimination mechanism, while the amination of (LXXXII) takes place to an extent of 55% via the *ANRORC* mechanism and to an extent of 45% via the ***AE*** mechanism (demonstrated with the aid of tracer atoms). However, we are dealing in essence, not with a new mechanism of the Chichibabin reaction, but with an unusual behaviour of the σ-complex, capable of ring–chain tautomerism, as a result of which the label enters the ring. On the other hand, the addition and elimination stages themselves probably proceed in the usual way.

bifunctional catalysis in the aromatisation stage has been observed, a study has been made of the influence of substituents on the rate of amination, and the important role of the $\rangle N \rightarrow NaNH_2$ coordination as the initial reaction stage has been elucidated; in connection with the last item, the role of the basicity of the heterocycle, the *ortho*-dimethoxy-effect, the difficulty of γ-amination, etc. have been explained. An important factor is the determination of the relative activities of various types of heteroaromatic systems in the Chichibabin reaction. The applications of the reaction have been extended to perimidine derivatives (the first type of heterocyclic systems with an excess of π electrons which are aminated on treatment with $NaNH_2$) and quinazoline derivatives as well as condensed imidazole systems. It has been possible to introduce into the reaction *N*-heteroaromatic cations, to achieve substitutional amination with elimination of carbanions, and to extend significantly the scope of direct hydroxylation and hydrazination of heterocycles.

At the same time many problems still await solution. Thus the role of radical-anions as intermediates in the amination reaction is still not clear; the problem of the rate-limiting stage of the reaction in an aprotic medium requires elucidation. The search for new types of solvents (apart from liquid ammonia), capable of dissolving even to a slight extent sodium amide, is urgently required; the introduction of crown-ethers as additives appears to be an attractive possibility. One may expect new advances in extending the scope of the Chichibabin reaction to the *N*-oxides of nitrogen-containing heterocycles and new types of heteroaromatic systems.

REFERENCES

1. A. E. Chichibabin and O. A. Zeide, Zhur. Russ. Fiz. Khim. Obshch., 46, 1216 (1914).
2. A. M. Simonov and P. A. Uglov, Zhur. Obshch. Khim., 21, 884 (1951).
3. M. Leffler, in "Organic Reactions" (Translated into Russian), Inostr. Lit., 1948, Vol. 1, p. 115.
4. A. F. Pozharskii and A. M Simonov, "Aminirovanie Geterotsiklov po Chichibabinu" (Chichibabin Amination of Heterocycles), Izd. Rostov. Univ., Rostov-on-Don, 1971.
5. R. A. Abramovitch and J. G. Saha, Adv. Heterocylic Chem., 6, 229 (1966).
6. J. Miller, "Aromatic Nucleophilic Substitution", Elsevier Publ., New York, 1968.
7. N. Radulescu, V. Pelloni-Tamas, and J. P. Ambres, Rev. Chim. (Roumania), 23, 11 (1972).
8. A. M. Simonov, Symposium, "Ocherki po Khimii Azolov" (An Outline of the Chemistry of Azoles), Izd. Rostov. Univ., Rostov-on-Don, 1965, p. 51.
9. A. R. Surrey, "Name Reactions in Organic Chemistry" (Translated into Russian), GNTIKhL, Moscow, 1962, p. 264.
10. A. F. Pozharskii and E. A. Zvezdina, Uspekhi Khim., 42, 65 (1973) [Russ. Chem. Rev., No. 1 (1973)].
11. F. W. Bergstrom, J. Amer. Chem. Soc., 56, 1748 (1934).
12. F. W. Bergstrom, Annalen, 515, 34 (1934).
13. F. W. Bergstrom, J. Org. Chem., 2, 411 (1937).
14. F. W. Bergstrom, J. Org. Chem., 3, 233 (1938).
15. F. W. Bergstrom, J. Org. Chem., 3, 424 (1938).
16. V. N. Novikov et al., Khim. Geterotsikl. Soed., 244 (1976).
17. M. M. Medvedeva, V. N. Doron'kin, A. F. Pozharskii, and V. N. Novikov, Khim. Geterotsikl. Soed., 1120 (1977).
18. V. N. Doron'kin, Izv. Severo-Kavakaz. Nauch. Tsentra Vys. Shkoly., Estestv. Nauki, No. 2, 111 (1976).
19. K. Ziegler and H. Zeiser, Ber., 63, 1847 (1930).
20. A. V. Kirsanov and Ya. N. Ivashchenko, Zhur. Obshch. Khim., 5, 1494 (1935).
21. A. V. Kirsanov and Ya. N. Ivastchenko, Bull. Soc. chim. France, 5, 2109 (1935).
22. T. Kauffman, H. Hacker, and H. Muller, Chem. Ber., 95, 2485 (1962).
23. R. E. Lyle and P. S. Anderson, Adv. Heterocyclic Chem., 6, 45 (1966).
24. C. S. Giam and J. L. Stout, Chem. Comm., 142 (1969).
25. J. A. Zoltewicz and L. S. Helmick, J. Amer. Chem. Soc., 94, 682 (1972).
26. J. A. Zoltewicz, L. S. Helmick, T. M. Oestreich, R. W. King, and P. E. Kandetzki, J. Org. Chem., 38, 1947 (1973).
27. A. F. Pozharskii, Doctoral Thesis, Rostov University, Rostov-on-Don, 1972.
28. P. J. Pugmire, D. M. Grant, M. J. Robins, and R. K. Robins, J. Amer. Chem. Soc., 91, 6381 (1969).
29. T. Tokuhiro and G. Fracukel, J. Amer. Chem. Soc., 91, 5005 (1969).
30. A. Albert, in "Physical Methods in Heterocyclic Chemistry" (Edited by A. R. Katritzky), Acad. Press, New York–London, 1963, Vol. 1.
31. W. G. Armagero, Adv. Heterocyclic Chem., 1, 253 (1963).
32. V. I. Minkin, I. I. Zakharov, and L. L. Popova, Khim. Geterotsikl. Soed., 1552 (1971).
33. T. Higashino, Yakugaku Zasshi, 80, 245 (1960); Chem. Abs., 54, 13125 (1960).
34. O. M. Miroshnikov and L. I. Savranskii, Vestnik Kiev. Univ., Ser. Khim., 16, 22 (1975).
35. C. L. Deasy, J. Org. Chem., 10, 141 (1945).
36. A. F. Pozharskii, A. M. Simonov, E. A. Zvezdina, and V. A. Anisimova, Khim. Geterotsikl. Soed., 869 (1969).
37. A. M. Simonov and A. F. Pozharskii, Zhur. Obshch. Khim., 33, 2350 (1963).
38. A. F. Pozharskii, V. V. Kuz'menko, Yu. V. Kolodyazhniya, and A. M. Simonov, Khim. Geterotsikl. Soed., 1252 (1972).
39. A. F. Pozharskii, A. M. Simonov, V. M. Mar'yanovskii, and R. T. Zinchenko, Khim. Geterotsikl. Soed., 1060 (1970).
40. A. F. Pozharskii and I. S. Kashparov, Khim. Geterotsikl. Soed., 1129 (1970).
41. A. F. Pozharskii, V. V. Kuz'menko, V. A. Azimov, and L. N. Yakhontov, Khim. Geterosikl. Soed., 1232 (1973).
42. F. W. Bergstrom and W. C. Fernelius, Chem. Rev., 12, 43 (1933).
43. A. E. Chichibabin, Zhur. Russ. Fiz. Khim. Obshch., 47, 835 (1917).
44. A. F. Pozharskii and A. A. Konstantinchenko, Khim. Geterotsikl. Soed., 1673 (1972).
45. K. Bauer, Chem. Ber., 83, 10 (1950).
46. A. F. Pozharskii et al., Khim. Geterotsikl. Soed., 1105 (1971).
47. V. V. Kuz'menko, A. V. Pozharskii, and A. M. Simonov, Zhur. Org. Khim., 8, 1046 (1972).

48. H.K. Frensdorff, J.Amer.Chem.Soc., 93, 600 (1971).
49. R.A. Abramovitch, F. Helmer, and J.G. Saha, Chem. Ind.(London), 659 (1964).
50. R.A. Abramovitch, F. Helmer, and J.G. Saha, Tetrahedron Letters, 3445 (1964).
51. J.F. Bunnett, J.Chem.Educ., 51, 312 (1974).
52. J.K. Kim and J.F. Bunnett, J.Amer.Chem.Soc., 92, 7463 (1970).
53. J.F. Wolfe, J.C. Greene, and T. Hudlicky, J.Org. Chem., 37, 3198 (1972).
54. J.A. Zoltewicz and T.M. Oestreich, J.Amer.Chem. Soc., 95, 6863 (1973).
55. S.M. Shein, L.V. Bryukhovetskaya, A.D. Khmelinskaya, V.F. Starichenko, and T.M. Ivanova, Reakts. Sposobn. Org. Soed., 6, 1087 (1969).
56. S.M. Shein, L.V. Bryukhovetskaya, F.V. Pishchugin, V.F. Starichenko, V.N. Panfilov, and V.V. Voevodskii, Zhur. Strukt. Khim., 11, 243 (1970).
57. S.V. Kessar, U.K. Nadir, and M. Singh, Indian J. Chem., 11, 825 (1973).
58. T. Kauffmann, Angew. Chem., 77, 557 (1965).
59. J. De Volk and H.C. van der Plas, Rec. Trav. chim., 90, 1239 (1971).
60. G.M. Sanders, M. van Dijk, and H.J. Den Hertog, Rec. Trav. chim., 93, 198 (1974).
61. J.P. Geerts, H.C. van der Plas, and A. van Veldhuizen, Rec. Trav. chim., 92, 1232 (1973).
62. J.P. Geerts, H.C. van der Plas, and A. van Veldhuizen, Org. Magn. Reson., 7, 86 (1975).
63. K. Alwair and J. Grimchaw, J.Chem.Soc., Perkin Trans. II, 1811 (1973).
64. L.S. Levitt and R.W. Levitt, Chem. Ind.(London), 1621 (1963).
65. H.L. Jones and D.L. Beveridge, Tetrahedron Letters, 1577 (1964).
66. R.A. Abramovitch, F. Helmer, and J.G. Saha, Canad. J. Chem., 43, 725 (1965).
67. G.C. Barret and K. Schofield, Chem. Ind.(London), 1980 (1963).
68. A.E. Chichibabin and M.S. Vidonova, Zhur. Russ. Fiz. Khim. Obshch., 53, 238 (1921).
69. W. Adam, A. Grimison, and R. Hoffmann, J.Amer. Chem. Soc., 91, 2590 (1969).
70. A.E. Chichibabin and E.V. Zatsepina, Zhur. Russ. Fiz. Khim. Obshch., 50, 553 (1918).
71. B.C. Platt, Nature, 157, 439 (1946).
72. A.M. Simonov, I.G. Uryukina, and A.F. Pozharskii, Khim. Geterotsikl. Soed., 416 (1972).
73. S. Millefiori, J. Heterocyclic Chem., 7, 145 (1970).
74. R.P. Houghton, Chem. Ind.(London), 155 (1973).
75. D.W. Slocum and F.S. Stonemach, J.Org. Chem., 38, 1677 (1973).
76. J. Chaudhuri, S. Kume, J. Jagur-Grodzinski, and M. Szwarc, J.Amer. Chem. Soc., 90, 6421 (1968).
77. A.A.L. Challis and G.R. Clemo, J. Chem. Soc., 613 (1947).
78. R.N. Shreve and L. Berg, J.Amer. Chem. Soc., 69, 2116 (1947).
79. R.N. Shreve, E.H. Pieshers, H. Rubenkoenig, and A.H. Goodman, Ind. Eng. Chem., 32, 173 (1940).
80. I. Nenner and G.J. Schulz, J. Chem. Phys., 62, 1747 (1975).
81. H.H. Jaffe and H.L. Jones, Adv. Heterocyclic Chem., 3, 209 (1964).
82. F. Sachs, Ber., 39, 3006 (1906).
83. W. Bradley, J. Chem. Soc., 1175 (1948).
84. W. Bradley and F.K. Sutcliffe, J. Chem. Soc., 708 (1954).
85. L.S. Levitt and B.W. Levitt, Chem. Ind.(London), 520 (1975).
86. E. Schering, German P. 358 397 (1923); Chem. Abs., 17, 2118 (1923).
87. "Preparativnaya Organicheskaya Khimiya" (Preparative Organic Chemistry), Goskhimizdat, Moscow, 1959, p. 289.
88. A.E. Chichibabin, German P. 374 291 (1924); Chem. Abs., 18, 2176 (1924).
89. H.J. Schneiderwirth, US P. 2 068 353 (1937); Chem. Abs., 31, 1959 (1937).
90. E.D. Parker and W. Shive, J.Amer. Chem. Soc., 69, 63 (1947).
91. H.D. Willink and J.P. Wibaut, Rec. Trav. chim., 54, 275 (1935).
92. H.C. Brown and B. Kanner, J.Amer. Chem. Soc., 88, 986 (1966).
93. M. Goshaev, O.S. Otroshchenko, A.S. Sadykov, and M.P. Azimova, Khim. Geterotsikl. Soed., 1642 (1972).
94. M. Goshaev, M.P. Azimova, O.S. Otroshchenko, and A.S. Sadykov, Izv. Akad. Nauk Turkmen. SSR, Ser. Fiz.-Tekh., Khim. i Geol. Nauk, 108 (1973); Ref. Zhur. Khim., 16Zh321 (1974).
95. O. Seide, Ber., 57, 791 (1924).
96. H. Horsters and M. Dohrn, German P. 398 204 (1924); Chem. Zentr., 95, II, 1409 (1924).
97. W. Solomon, J. Chem. Soc., 934 (1946).
98. F.H. Case and W.A. Butte, J. Org. Chem., 26, 4415 (1961).
99. J.A. Zoltewicz and L.S. Helmick, J. Org. Chem., 38, 658 (1973).
100. H. Bojarska-Dahlig and P. Nautka-Namirski, Roczniki Chem., 30, 461 (1956); Chem. Abs., 51, 14 722 (1957).
101. A. Konopnicki and E. Placzek, Ber., 60, 2045 (1927).
102. I. Suzuki, Pharm. Bull., 4, 211 (1956); Chem. Abs., 51, 7372 (1957).
103. A.E. Chichibabin and I.L. Knunyants, Zhur. Russ. Khim. Obshch., 60, 674 (1928).
104. H. Bojarska-Dahliq and P. Nautka-Namirski, Roczniki Chem., 30, 612 (1956); Chem. Abs., 51, 4370 (1957).
105. O. Seide, Ber., 57, 1802 (1924).
106. F.E. Cislak and A.L. Kranzfelder, US P. 2 456 379 (1948); Chem. Abs., 43, 7050 (1949).
107. J. Bernstein, B. Stearns, F. Shaw, and W.A. Lott, J.Amer. Chem. Soc., 69, 1151 (1947).
108. M.M. Robison and B.L. Robison, J.Amer. Chem. Soc., 77, 457 (1955).
109. Y. Ban and T. Wakamatsu, Chem. Ind.(London), 710 (1964).
110. F. Hardegger and E. Nikles, Helv. Chim. Acta, 39, 505 (1935).
111. J. Reisch, Chem. Ber., 97, 2717 (1964).
112. E. Plazek, A. Marcinikow, and C. Stammer, Roczniki Chem., 15, 365 (1935); Chem. Abs., 30, 1377 (1936).
113. E. Plazek, Roczniki Chem., 16, 403 (1936).
114. H. Bojarska-Dahliq and R. Nautka-Namirski, Roczniki Chem., 30, 612 (1956); Chem. Abs., 51, 4370 (1957).
115. W. Caldwell, F.T. Tyson, and L. Lauer, J.Amer. Chem. Soc., 66, 1479 (1944).
116. G.R. Clemo and G.A. Swan, J. Chem. Soc., 603 (1945).

117. A.S.Sadykov, O.S.Otroshchenko, and M.K.Yusupov, Khim.Geterotsikl.Soed., 23, 980 (1953).
118. A.E.Tschitschibabin and A.V.Kirsanov, Ber., 57, 1163 (1924).
119. A.E.Chichibabin and A.V.Kirsanov, Zhur.Russ. Fiz.Khim.Obshch., 56, 157 (1924).
120. A.E.Chichibabin and L.A.Bukhol'ts, Zhur.Russ. Fiz.Khim.Obshch., 50, 548 (1918).
121. M.I.Kabachnik and M.M.Katsnel'son, Zhur.Obshch. Khim., 5, 1289 (1935).
122. G.Menschikoff, A.Grigorovitch, and A.Orechoff, Ber., 67, 289 (1934).
123. M.M.Katsnel'son and M.I.Kabachnik, Zhur.Obshch. Khim., 4, 552 (1934).
124. M.I.Kabachnik and A.I.Zitser, Zhur.Obshch. Khim., 10, 1007 (1940).
125. R.A.Abramovitch and G.A.Poulton, J.Chem.Soc.B, 901 (1969).
126. R.A.Abramovitch and C.S.Giam, Canad.J.Chem., 41, 3127 (1963).
127. R.A.Abramovitch and C.S.Giam, Canad.J.Chem., 42, 1627 (1964).
128. V.N.Drozd, V.I.Minkin, and Yu.A.Ostroumov, Zhur.Org.Khim., 4, 1501 (1969).
129. R.A.Abramovitch and A.J.Newman, J.Org.Chem., 39, 2690 (1974).
130. A.Albert and R.Willete, J.Chem.Soc., 4063 (1964).
131. R.F.Childs and A.W.Johnson, Chem.Ind.(London), 4063 (1964).
132. H.Bojarska-Dahlig and I.Gruda, Roczniki Chem., 33, 505 (1959); Chem.Abs., 54, 522 (1960).
133. I.S.Belonosov, Zhur.Prikl.Khim., 22, 1103 (1949).
134. H.D.T.Willink and J.P.Wibaut, Rec.Trav.chim., 54, 275 (1935).
135. D.A.Inoyatova, O.S.Otroshchenko, A.S.Sadykov, and A.Kh.Mamatkazina, Nauch.Trudy.Samarkand, Univ., 167, 173 (1969); Ref.Zhur.Khim., 5Zh482 (1970).
136. D.A.Inoyatova, O.S.Otroshchenko, and A.S.Sadykov, Nauch.Trudy Samarkand.Univ., 167, 123 (1969); Ref.Zhur.Khim., 5Zh491 (1970).
137. T.Kametani, K.Kigasawa, et.al., J.Heterocyclic Chem., 2, 230 (1965).
138. T.Kametani and H.Nemoto, Chem.Pharm.Bull., 15, 1910 (1967).
139. T.Kametani, H.Nemoto, and S.Takano, Chem. Pharm.Bull., 16, 367 (1968).
140. N.Goetz-Luthy, F.W.Bergstrom, and U.S.Mosher, J.Org.Chem., 14, 322 (1949).
141. H.C.White and F.W.Bergstrom, J.Org.Chem., 7, 497 (1942).
142. F.W.Bergstrom, J.Amer.Chem.Soc., 53, 3027 (1931).
143. A.E.Chichibabin and M.P.Oparina, Zhur.Russ. Fiz.Khim.Obshch., 50, 543 (1918).
144. F.W.Bergstrom and J.H.Rodda, J.Amer.Chem. Soc., 62, 3030 (1940).
145. R.Grewe, A.Mondon, and E.Nolte, Annalen, 564, 161 (1949).
146. P.K.S.Marshall, D.L.Pain, and K.R.H.Wooldridge, B.P.1 367 146 (1974).
147. B.I.Khristich, V.A.Kruchinin, A.F.Pozharskii, and A.M.Smirnov, Khim.Geterotsikl.Soed., 814 (1971).
148. G.T.Morgan and L.P.Walls, J.Chem.Soc., 2235 (1932).
149. B.L.Hollingsworth and V.Petrov, J.Chem.Soc., 1537 (1948).
150. E.V.Brown and A.C.Plasz, J.Heterocyclic Chem., 7, 593 (1970).
151. W.W.Paudler and T.J.Kress, J.Org.Chem., 33, 1384 (1968).
152. H.R.Shyder, H.G.Walker, and F.X.Werber, J.Amer.Chem.Soc., 71, 527 (1949).
153. BRD Appl.S.28 155 (1952); Houben-Weyl, "Methoden der Organischen Chemie", G. Thieme Verlag, Stuttgart, 1957, Vol.XI/1, p.16.
154. D.B.Paul and H.J.Rodds, Austral.J.Chem., 22, 1745 (1969).
155. M.M.Robison, B.L.Robison, and F.P.Butler, J.Amer.Chem.Soc., 81, 743 (1959).
156. Yu.M.Yutilov and R.M.Bystrova, Khim.Geterotsikl. Soed., 1146 (1970).
157. Y.Mizuno, M.Ikehara, T.Itoh, and K.Saito, J.Org. Chem., 28, 1637 (1963).
158. E.Ochiai and M.Yanai, J.Pharm.Soc.Japan, 59, 18 (1939); Chem.Zentr., (II), 1806 (1941).
159. M.L.Crossley and J.P.English, US P.2 394 963 (1946); Chem.Abs., 40, 3143 (1946).
160. F.W.Bergstrom and R.A.Ogg, J.Amer.Chem. Soc., 53, 245 (1931).
161. A.E.Chichibabin and M.N.Shchukina, Zhur.Russ. Khim.Obshch., 62, 1889 (1930).
162. R.R.Joiner and P.E.Spoerri, J.Amer.Chem.Soc., 63, 1929 (1941).
163. G.T.Newbold and F.S.Spring, J.Chem.Soc., 373 (1947).
164. J.A.Zoltewicz, T.M.Oestreich, J.K.O'Halloran, and L.S.Helmick, J.Org.Chem., 38, 1949 (1973).
165. A.Rosowsky et al., J.Heterocyclic Chem., 9, 1449 (1972).
166. C.Grundmann and A.Kreutzberger, J.Amer.Chem. Soc., 77, 44 (1955).
167. A.Nagel, H.C.van der Plas, and A.van Veldhuizen, Rec.Trav.chim., 94, 45 (1975).
168. A.M.Simonov and A.D.Garnovskii, Zhur.Obshch. Khim., 31, 114 (1961).
169. A.D.Garnovskii and A.M.Simonov, Zhur.Obshch. Khim., 31, 1941 (1961).
170. A.F.Pozharskii, I.S.Kashparov, Yu.P.Andreichkov, A.I.Buryak, A.A.Konstantinchenko, and A.M.Simonov, Khim.Geterotsikl.Soed., 807 (1971).
171. B.I.Khristich and A.M.Simonov, Khim.Geterotsikl. Soed., 611 (1966).
172. I.S.Kashparov, A.F.Pozharskii, and A.M.Simonov, Khim.Geterotsikl.Soed., 1147 (1970).
173. A.F.Pozharskii, L.P.Pershina, et al., Khim. Geterotsikl.Soed., 418 (1974).
174. I.V.Komissarov, A.A.Konstantinchenko, A.F.Pozharskii, I.T.Filippov, and I.S.Kashparov, Khim.-Farm.Zhur., No.7, 28 (1976).
175. A.F.Pozharskii, M.M.Medvedeva, E.A.Zvezdina, and A.M.Simonov, Khim.Geterotsikl.Soed., 665 (1971).
176. A.M.Simonov and N.D.Vitkevich, Zhur.Obshch. Khim., 30, 590 (1960).
177. A.M.Simonov and A.F.Pozharskii, Zhur.Obshch. Khim., 31, 3970 (1961).
178. A.M.Simonov, A.A.Belous, A.N.Lomakin, and V.A.Anisimova, Zhur.Vses.Khim.Obshch.im. Mendeleeva, 8, 712 (1963).
179. A.M.Simonov, N.D.Vitkevich, and B.K.Martsokha, Zhur.Obshch.Khim., 30, 3062 (1960).

180. T. P. Filipskikh, A. F. Pozharskii, V. N. Koroleva, A. M. Simonov, and E. A. Zvezdina, Khim. Geterotsikl. Soed., 809 (1972).
181. A. M. Simonov and A. F. Pozharskii, Zhur. Obshch. Khim., 34, 1572 (1964).
182. A. F. Pozharskii, A. M. Simonov, E. A. Zvezdina, and N. K. Chub, Khim. Geterotsikl. Soed., 889 (1967).
183. M. M. Medvedeva, A. F. Pozharskii, and A. M. Simonov, Khim. Geterotsikl. Soed., 1418 (1972).
184. S. Takahashi and H. Kano, Chem. Pharm. Bull. (Tokyo), 12, 282 (1964).
185. A. N. Lomakin, A. M. Simonov, and V. A. Chigrina, Zhur. Obshch. Khim., 33, 204 (1963).
186. A. M. Simonov and A. N. Lomakin, Zhur. Obshch. Khim., 32, 2228 (1962).
187. N. D. Vitkevich and A. M. Simonov, Zhur. Obshch. Khim., 29, 2614 (1959).
188. A. M. Simonov et al., Zhur. Vses. Khim. Obshch. im. Mendeleeva, 15, 232 (1970).
189. A. M. Simonov, A. F. Pozharskii, and V. M. Maryanovskii, Indian J. Chem., 5, 81 (1967).
190. A. F. Pozharskii, I. S. Kashparov, V. N. Koroleva, V. I. Sokolov, and I. V. Borovlev, "I Vsesoyuznaya Konferentsiya po Khimii Geterotsiklicheskikh Soedinenii, Tezisy" (The Ist All-Union Conference on the Chemistry of Heterocyclic Compounds. Abstracts), Chernogolovka, 1973, p. 101.
191. E. Ochiai, J. Pharm. Soc. Japan, 58, 1025 (1938); Chem. Abs., 33, 3797 (1939).
192. E. Ochiai and T. Nisizawa, J. Pharm. Soc. Japan, 60, 132 (1940); Chem. Abs., 34, 5082 (1940).
193. E. Ochiai and J. Haginiwa, J. Pharm. Soc. Japan, 67, 138 (1947); Chem. Abs., 45, 9539 (1951).
194. R. Weber and M. Renson, J. Heterocyclic Chem., 12, 1091 (1975).
195. J. Haginiwa, J. Pharm. Soc. Japan, 68, 195 (1948); Chem. Abs., 47, 8074 (1953).
196. N. K. Kochetkov and E. D. Khomutova, Zhur. Obshch. Khim., 30, 954 (1960).
197. A. M. Simonov and B. K. Martsokha, Symposium, "Ocherki po Khimii Azolov" (An Outline of the Chemistry of Azoles), Izd. Rostov. Univ., Rostov-on-Don, 1965, p. 99.
198. Yu. A. Naumov and I. I. Grandberg, Uspekhi Khim., 35, 21 (1966) [Russ. Chem. Rev., No. 1 (1966)].
199. C. R. Hauser and M. J. Weiss, J. Org. Chem., 14, 310 (1949).
200. N. G. Luthy, F. W. Bergstrom, and H. S. Mosher, J. Amer. Chem. Soc., 71, 1109 (1949).
201. F. W. Bergstrom, H. Sturz, and H. Tracy, J. Org. Chem., 11, 239 (1946).
202. K. Kovacs and T. Vajda, Acta Chim. Acad. Sci. Hung., 21, 445 (1959).
203. K. Kovacs and T. Vajda, Chem. Ind. (London), 259 (1959).
204. T. Vajda and K. Kovacs, Rec. Trav. chim., 60, 47 (1961).
205. K. Kovacs and T. Vajda, Acta Chim. Acad. Sci. Hung., 29, 245 (1961).
206. A. Palnis and M. Szwarc, J. Phys. Chem., 79, 106 (1975).
207. E. M. Hawes and D. G. Wibberley, J. Chem. Soc. C, 315 (1966).
208. E. M. Hawes and H. L. Davies, J. Heterocyclic Chem., 10, 39 (1973).
209. T. Kauffmann and W. Schoeneck, Angew. Chem., 71, 285 (1959).
210. T. Kauffmann, J. Hansen, C. Kosel, and W. Schoeneck, Annalen, 656, 103 (1962).
211. T. Kauffmann, Angew. Chem., 73, 540 (1961).
212. W. Koenigs and G. Koerner, Ber., 16, 2152 (1883).
213. R. Kudernatsch, Monatsh., 18, 613 (1897).
214. O. Schichk, A. Binz, and A. Schulz, Ber., 69, 2593 (1936).
215. A. E. Chichibabin, Zhur. Russ. Khim. Obshch., 55, 7 (1923).
216. A. E. Tschitschibabin, Ber., 56, 1879 (1923).
217. W. Koenigs, Ber., 12, 99 (1879).
218. A. E. Chichibabin and A. I. Kursanova, Zhur. Russ. Khim. Obshch., 62, 1211 (1930).
219. J. Eisch and H. Gilman, Chem. Rev., 57, 525 (1957).
220. Yu. V. Koshchienko, A. M. Simonov, and A. F. Pozharskii, Khim. Geterotsikl. Soed., 1132 (1971).
221. I. S. Kashparov and A. F. Pozharskii, Khim. Geterotsikl. Soed., 124 (1971).
222. I. S. Kashparov, A. F. Pozharskii, and A. M. Simonov, Khim. Geterotsikl. Soed., 1147 (1970).
223. A. F. Pozharskii, M. M. Medvedeva, et al., Khim. Geterotsikl. Soed., 665 (1971).
224. A. M. Simonov and V. G. Poludnenko, Khim. Geterotsikl. Soed., 242 (1972).
225. Yu. M. Yutilov and I. A. Svertilova, Khim. Geterotsikl. Soed., 1252 (1976).
226. S. S. Berg and V. Petrov, J. Chem. Soc., 3713 (1952).
227. I. I. Popov, P. V. Kachenko, A. M. Simonov, A. F. Pozharskii, and Yu. G. Bogachev, Zhur. Org. Khim., 10, 1789 (1974).
228. I. I. Popov, Yu. G. Bogachev, P. V. Tkachenko, A. M. Simonov, and B. A. Tertov, Khim. Geterotsikl. Soed., 521 (1976).
229. E. C. Taylor and A. McKillop, J. Org. Chem., 30, 2858 (1965).
230. Y. Kobayashi, I. Kumadaki, S. Taguchi, and Y. Hauzawa, Tetrahedron Letters, 3901 (1970).
231. Y. Kobayashi, I. Kumadaki, Y. Hanzawa, and M. Mimura, Chem. Pharm. Bull. (Tokyo), 23, 2044 (1975).
232. A. F. Pozharskii, V. V. Kuz'menko, I. S. Kashparov, V. I. Sokolov, and M. M. Medvedeva, Khim. Geterotsikl. Soed., 356 (1976).
233. J. A. Zoltewicz, L. S. Helmick, and J. K. O'Halloran, J. Org. Chem., 41, 1303 (1976).
234. G. Simig, H. C. van der Plas, and C. A. Landheer, Rec. Trav. chim., 95, 113 (1976).
235. G. Simig and H. C. van der Plas, Rec. Trav. Chim., 95, 125 (1976).

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