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EFFECT OF N-ALKYL AND N-ARALKYL SUBSTITUENTS ON NUCLEOPHILIC SUBSTITUTION IN THE BENZIMIDAZOLE SERIES

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It is shown in the case of the Chichibabin reaction and exchange of chlorine in 2-chlorobenzimidazoles by a piperidine residue that N-alkyl and N-aralkyl groups are arranged in the following order with respect to their effect on the rate of the process (in the order of decreasing rates): $CH_3 > C_6H_5CH_2$, $C_2H_5 >$ iso-C_3H_7, $(C_6H_5)_2CH >$ n-$C_9H_{19} >$ tert-C_4H_9. The overall decrease in the rate on passing to compounds with branched N-substituents is low. It follows from this that steric hindrance to nucleophilic substitution in the 2 position is only of small significance.

In a previous study of the Chichibabin reaction in the benzimidazole series it was qualitatively concluded that α-branched N-substituents (iso-C_3H_7, $C_6H_5CH_2$, cyclohexyl, benzhydryl, and particularly tert-butyl) have a passivating effect on the course of the process; this was ascribed to steric factors [1-5]. In the present research we set out to make a quantitative study of the effect of N-alkyl and N-aralkyl groups on the two most typical nucleophilic substitution reactions in the benzimidazole series: amination with sodium amide (the Chichibabin reaction) and exchange of chlorine by a secondary amine residue (for which we selected piperidine).

Chichibabin Reaction

The results of measurements of the rate of gas evolution and the composition of the gas in the amination of 1-substituted benzimidazoles Ia-g with sodium amide in o-xylene or dimethylaniline at various temperatures are presented in Figs. 1 and 2 and Table 1. It should be noted that the composition of the gas was determined only at the end point of the reaction from the results of titration of the ammonia formed. Thus the curves in Figs. 1-3 were constructed from the results of measurements of the total volume of hydrogen and ammonia.

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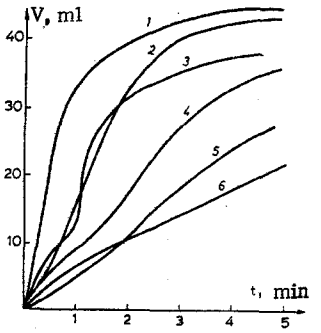


Fig. 1

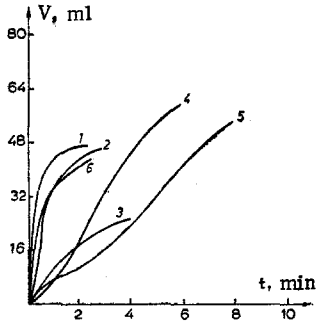


Fig. 2

Fig. 1. Dependence of the volume of the evolved gas on the time during the amination of N_1-substituted benzimidazole derivatives in dimethylaniline at 110°C: 1) 1-methylbenzimidazole; 2) 1-ethylbenzimidazole; 3) 1-benzylbenzimidazole; 4) 1-benzhydrylbenzimidazole; 5) 1-isopropylbenzimidazole; 6) 1-nonylbenzimidazole.

Fig. 2. Dependence of the volume of evolved gas on the time during the amination of N_1-substituted benzimidazole derivatives in o-xylene at 130°C: 1) 1-methylbenzimidazole; 2) 1-ethylbenzimidazole; 3) 1-nonylbenzimidazole; 4) 1-isopropylbenzimidazole; 5) 1-tert-butylbenzimidazole; 6) 1,5,6-trimethylbenzimidazole.

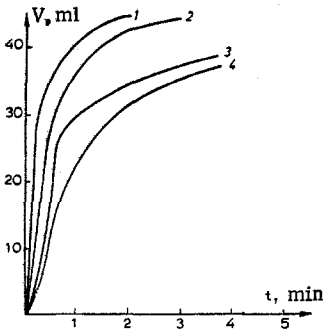
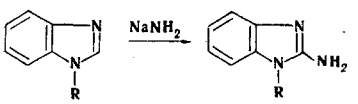


Fig. 3. Dependence of the volume of evolved gas on the time during the amination of Bz-substituted 1-methylbenzimidazoles in o-xylene at 120°C: 1) 1-methylbenzimidazole; 2) 1,5-dimethylbenzimidazole; 3) 1-methyl-5-methoxybenzimidazole; 4) 1,5,6-trimethylbenzimidazole.

This means that a reliable comparison of the reactivities of I can be made only if the ratios of ammonia and hydrogen for them are approximately the same (the reasons for the evolution of ammonia in the Chichibabin reaction are discussed in [6]). This condition is observed for most I during their amination in dimethylaniline at 110°C. 1-tert-Butylbenzimidazole is not aminated under the same conditions, on the basis of which it can be relegated to last place in the reactivity series. The amount of ammonia evolved in the amination of 1-benzhydrylbenzimidazole is considerably higher than in the case of the other compounds. This is evidently due to the formation of a carbanion as a result of ionization of the C–H bond in the benzhydryl group. The amount of ammonia evolved in the amination of 1-benzylbenzimidazole probably increases at 120°C as compared with 110°C for the same reason (experiment Nos. 10 and 11 in Table 1).* Instances of similar ionization of C–H bonds in the Chichibabin reaction are known [7].



I

I a R=CH_3; b R=C_2H_5; c R=iso-C_3H_7; d R=n-C_9H_{19}; e R=tert-C_4H_9; f R=$C_6H_5CH_2$; g R=$(C_6H_5)_2CH$

It is apparent from Fig. 1 that N-alkyl and N-aralkyl groups are arranged in the following order with respect to their effect on the ease of amination: $CH_3 > C_2H_5$, $C_6H_5CH_2 >$ iso-C_3H_7, $(C_6H_5)_2CH >$ p-$C_9H_{19} >$ tert-C_4H_9.

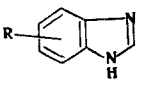
* The quality and yield of 1-benzyl-2-aminobenzimidazole are somewhat higher at 110° (84%) than at 120°C (66%).

TABLE 1. Composition of the Gas Evolved during the Amination of N_1-Substituted Benzimidazoles

No.	Compound	Solvent	Temp., °C	Reaction time, min	Gas volume, ml*		Ammonia, %
					total	hydrogen	
1	Ia	Dimethylaniline	110	9	45,0	36,8	18,2
2	Ia	o-Xylene	130	3	45,0	32,4	28,0
3	Ib	Dimethylaniline	110	9	44,9	32,3	27,9
4	Ib	o-Xylene	130	3	45,0	32,2	28,5
5	Ic	Dimethylaniline	110	9	35,6	26,0	26,9
6	Ic	o-Xylene	130	12	58,3	33,3	42,9
7	Id	Dimethylaniline	110	9	27,6	18,8	32,0
8	Id	o-Xylene	130	3	22,0	16,0	27.2
9	Ie	The same	130	12	65,1	27,3	58,0
10	If	Dimethylaniline	110	9	42,2	28,5	32,6
11	If	The same	120	9	42,5	19,3	54,6
12	Ig	" "	110	9	48,0	16,0	66,7

* Under standard conditions.

TABLE 2. Basicities of 5-Substituted Benzimidazoles [8] and Their Relationship to the Hammet σ Constants [9] of the 5-Substituents



R	pK_a (in water)	σ_p
H	5,63	0
5(6)-CH_3	5,65	−0,17
5(6)-CH_3O	5,72	−0,27
5,6-$(CH_3)_2$	5,98	−0,34*

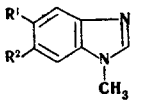
* Total constant of the two methyl groups.

Despite the fact that the curve for the amination of Ig lies above the curve for Ic (Fig. 1), their rates of amination are evidently close, since an approximately threefold greater amount of ammonia corresponds to the points on curve Ig. 1-Nonylbenzimidazole is initially aminated more rapidly than 1-isopropylbenzimidazole, but the reaction rate then slows down. This phenomenon, which is observed more distinctly when the reaction is carried out in xylene (Fig. 2), can be explained by the fact that the sodium salt of 1-nonyl-2-aminobenzimidazole, which is precipitated during the reaction, blocks the sodium amide surface because of the bulkiness of the nonyl group. This is probably also the reason that 1-benzylbenzimidazole is aminated more slowly than 1-ethylbenzimidazole in the final section of the line (Fig. 1).

1-tert-Butylbenzimidazole is aminated at an appreciable rate commencing at 130°C. The data obtained in xylene solution (Fig. 2) for it and other N-alkylbenzimidazoles lead in general to the same conclusions as the data obtained in dimethylaniline. One need only direct one's attention to the large percentage of ammonia formed in the amination of benzimidazole Ie; we explain this by the increased hygroscopicity of the compound. The reason for the increase in the amount of ammonia for derivative Ic is not at all clear.

Thus, in conformity with the earlier observations, α-branched N-substituents actually slow down the rate of the Chichibabin reaction. However, this can be explained not only by direct steric hindrance created by the N-substituent in the steps involved in the formation of a σ complex and bifunctional catalysis [6] but also by blocking of the sodium amide surface by the precipitating sodium salt of the amine because of the large volume of the N-substituent. In the case of N-alkyl groups their positive inductive effect, which should also somewhat hinder amination, also may play a decisive role.

In order to study the uncomplicated (by steric factors) effect of weak electron donors on the rate of the

TABLE 3. Composition of the Gas Evolved during the Amination of Some Bz-Substituted 1-Methylbenzimidazoles 

No.	R^1	R^2	Temp., °C	Reaction time, min	Gas volume, ml*		Ammonia, %
					total	hydrogen	
1	H	H	120	3	45,0	33,8	24,9
2	CH_3	H	120	3	44,8	32,8	26,8
3	CH_3O	H	120	9	42,5	31,0	27,0
4	CH_3	CH_3	120	6	40,6	29,8	26,6
5	CH_3	CH_3	130	3	43,6	31,0	29,9

* Under standard conditions.

TABLE 4. Rate Constants of Chlorine Exchange in 1-R-2-Chlorobenzimidazoles by a Piperidine Residue

R	$k \cdot 10^4$, sec^{-1}		
	80°	90°	100°
CH_3	0,47	0,78	1,18*
$C_6H_5CH_2$	0,23	0,33	0,62
C_2H_5	0,14	0,25	0,44
iso-C_3H_7	0,16	0,22	0,31
n-C_9H_{19}	0,10	0,15	0,22
$(C_6H_5)_2CH$	0,12	0,20	0,32

* Ricci and Vivarelli [10] give a value of $0.998 \cdot 10^{-4}$ sec^{-1}.

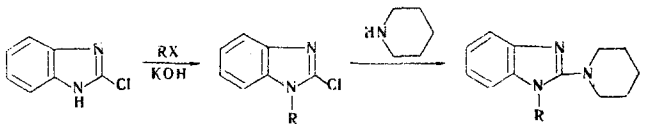
Chichibabin reaction, we investigated the amination of 1,5-dimethyl-, 1,5,6-trimethyl-, and 1-methyl-5-methoxybenzimidazoles on the rate of the Chichibabin reaction. The electron-donor effect of the corresponding substituents shows up in particular in the pK_a values (Table 2). N-Isopropyl and N-tert-butyl groups give rise to approximately the same increase in the basicity constants as compared with benzimidazole. It is apparent from the data presented in Fig. 3 and Table 3 that methyl and methoxy groups slow down amination in conformity with their relative electron-donor character: 5,6-$(CH_3)_2$ > 5-CH_3O > 5-CH_3. It is shown in Fig. 2 that the rate of amination of 1,5,6-trimethylbenzimidazole is close to the rate of amination of 1-ethylbenzimidazole, from which it can be concluded that hindrance of the reaction for Ic and Ie is due partially to the +I effect of the substituent.

Kinetics of Chlorine Exchange

The measurements of the rate of chlorine exchange in 1-R-2-chlorobenzimidazoles III, obtained by alkylation of 2-chlorobenzimidazole II, were made at three temperatures in excess piperidine, i.e., under the conditions of a pseudo-first-order reaction. The rate constants obtained are presented in Table 4.

As in the case of the Chichibabin reaction, the N-substituents are arranged in the following order with respect to their effect on the reaction rate: $CH_3 > C_6H_5CH_2 > C_2H_5 >$ iso-C_3H_7, $(C_6H_5)_2CH >$ n-C_9H_{19}. This constitutes evidence for the closeness of the mechanisms of the two reactions and for the possibility of drawing general conclusions on the basis of a study of their kinetics. In addition, one's attention is drawn to the small differences in the rate constants of the investigated compounds. The greatest decrease in the rate (by a factor of approximately three) is observed on passing from N-methyl- to N-ethyl-2-chlorobenzimidazole. The differences are small for the remaining compounds. Thus, with respect to its effect on the reaction rate, the N-benzyl group is found between methyl and ethyl, whereas the benzhydryl group is close to the isopropyl group. Unfortunately, we were unable to obtain 1-tert-butyl-2-chlorobenzimidazole; 1-tert-butylbenzimidazole does not undergo hydroxylation, and tert-butyl halide is converted to isobutylene in the case of alkylation of 2-chlorobenzimidazole II with tert-butyl halide in alkaline media. An attempt to obtain the necessary compound

starting from the accessible 1-tert-butyl-5-nitrobenzimidazolone was also unsuccessful, since treatment of it with phosphorus oxychloride leads to splitting out of the tert-butyl group to give 2-chloro-5-nitrobenzimidazole:



II IIIa-f IVa-f

III a R=CH_3; b R=C_2H_5; c R=iso-C_3H_7; d R=n-C_9H_{19}; e R=$(C_6H_5)_2CH$; f R=$C_6H_5CH_2$.

The results obtained in this research show that branched and bulky N-substituents in the benzimidazole molecule to a certain degree passivate nucleophilic substitution in the 2 position. However, considering the contribution of the inductive effect, blocking of the sodium amide surface with the amine salt (in the case of the Chichibabin reaction) and the overall relatively small decrease in the rate on passing to compounds with branched groups, it should be acknowledged that steric hindrance to nucleophilic substitution in the 2 position on the part of N-substituents is only of small significance.

EXPERIMENTAL

Starting Compounds. 1-Methyl-, 1-ethyl-, 1-isopropyl- [1], 1-nonyl- [4], 1-tert-butyl- [4], 1-benzyl- [11], 1-benzhydryl- [5], 1,5-dimethyl- [12], 1-methyl-5-methoxy- [13], 1,5,6-trimethyl- [14], 1-methyl-2-chloro- [15], and 1-benzyl-2-chlorobenzimidazoles [15] and sodium amide [6] were obtained by the indicated methods; 1-ethyl-2-chloro- [16] and 1-isopropyl-2-chlorobenzimidazoles [17] were obtained by the method proposed for 1-methyl-2-chlorobenzimidazole. The o-xylene was distilled prior to use over sodium and had bp 144-144.5°C; the dimethylaniline was distilled over anhydrous potassium hydroxide and had bp 193.5-194.5°C; the piperidine was purified by distillation over anhydrous potassium hydroxide and had bp 106.3°C.

1-Nonyl-2-chlorobenzimidazole. A 15.25-g (0.1 mole) sample of 2-chlorobenzimidazole and 31 g (0.15 mole) of nonyl bromide were added to a solution of 5.6 g (0.1 mole) of potassium hydroxide in 50 ml of alcohol, and the mixture was refluxed for 10 h. It was then cooled, and the precipitated potassium bromide was removed by filtration and washed with a small amount of alcohol. The solvent was removed from the filtrate by distillation, and the residue was subjected to chromatography (Al_2O_3, benzene) to give 20 g (72%) of 1-nonyl-2-chlorobenzimidazole as a pale-yellow oil. Found: C 68.9; H 8.8; Cl 12.3; N 10.1%. $C_{16}H_{23}ClN_2$. Calculated: C 68.9; H 8.3; Cl 12.7; N 10.1%.

1-Benzhydryl-2-chlorobenzimidazole. A 3.65-g (0.065 mole) sample of potassium hydroxide was dissolved in the minimum amount of absolute alcohol, 10 g (0.065 mole) of 2-chlorobenzimidazole was added, and the resulting solution was treated with an alcohol solution of 15 g (0.074 mole) of benzhydryl chloride. The mixture was refluxed for 2 h, after which the precipitated potassium chloride was removed by filtration, and the alcohol was removed from the filtrate by distillation. The residue was treated with a small amount of benzene, and the unconverted 2-chlorobenzimidazole (6 g) was removed by filtration. The benzene was evaporated, and the residue was subjected to chromatography (Al_2O_3), benzene). The resulting semicrystalline mass was dried over P_2O_5 and triturated with ether, and the solid was removed by filtration to give 3 g (14%) of 1-benzhydryl-2-chlorobenzimidazole, which was washed thoroughly with ether. Found: C 75.8; H 5.0; Cl 11.4; N 8.6%. $C_{20}H_{15}ClN_2$. Calculated: C 75.3; H 4.7; Cl 11.1; N 8.8%.

1-tert-Butyl-5-nitrobenzimidazolone. A mixture of 2 g (0.01 mole) of 2-amino-4-nitro-N-tert-butylaniline and 0.66 g (0.011 mole) of urea was heated slowly on an oil bath to 180°C and maintained at this temperature for 2.5 h. The mixture melted at 110°C and began to foam and immediately solidified as 180°C was reached. The cooled melt was triturated with 20% sodium hydroxide solution, and the mixture was refluxed with activated charcoal and filtered. The filtrate was acidified with concentrated hydrochloric acid, and the precipitate was removed by filtration, washed with water, and dried to give 1.6 g (75%) of pale-yellow shiny plates of 1-tert-butyl-5-nitrobenzimidazolone with mp 273-274°C (from dioxane). IR spectrum: $\nu_{C=O}$ 1705 cm^{-1}. Found: C 55.8; H 5.4; N 17.7%. $C_{11}H_{13}N_3O_3$. Calculated: C 56.1; H 5.6; N 17.9%.

Attempted Synthesis of 1-tert-Butyl-5-nitro-2-chlorobenzimidazole. A 20-g (0.085 mole) sample of 1-tert-butyl-5-nitrobenzimidazolone and 250 ml of freshly distilled phosphorus oxychloride were placed in a round-bottomed flask equipped with a reflux condenser and a gas-inlet tube projecting to the bottom of the flask, and the mixture was refluxed for 3.5 h; a stream of dry hydrogen chloride was bubbled into the mixture 15 min after the start of refluxing. The phosphorus oxychloride was removed by distillation under reduced pressure, and the residue was treated with 20% hydrochloric acid solution. The acidic mixture was filtered,

TABLE 5. 1-R-2-Piperidylbenzimidazoles

Compound	mp (from heptane), °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
IVa	82—83[8]	—	—	—	$C_{13}H_{17}N_3$	—	—	—	83
IVb	49—50	72,9	8,6	18,1	$C_{14}H_{19}N_3$	73,3	8,4	18,3	100
IVc	113—114	72,0	8,9	17,0	$C_{15}H_{21}N_3 \cdot 1/2\ H_2O$	71,4	8,8	16,7	75
IVd	—*	75,1	10,7	12,0	$C_{21}H_{33}N_3 \cdot 1/2\ H_2O$	75,0	10,2	12,5	100
IVe	165—166	80,0	6,5	11,4	$C_{25}H_{25}N_3 \cdot 1/2\ H_2O$	79,8	6,6	11,2	100
IVf	86—87	75,8	6,9	14,3	$C_{19}H_{21}N_3 \cdot 1/2\ H_2O$	76,0	7,0	14,0	83

*Oil.

and the filtrate was treated with concentrated ammonium hydroxide to give 10 g (60%) of 2-chloro-5-nitrobenzimidazole with mp 222-223°C (from aqueous alcohol) (mp 222-223°C [18]). Found: C 42.0; H 1.9; Cl 17.9; N 21.6%. $C_7H_4ClN_3O_2$. Calculated: C 42.5; H 2.0; Cl 17.9; N 21.2%.

Kinetics. The rate of amination was studied by the method in [6]. For the determination of the piperidinolysis rate constant, ~20-30-mg weighed samples of each of the N-substituted 2-chlorobenzimidazoles IIIa-e were placed in an ampul, 1 ml of absolute piperidine was poured in, and the ampul was sealed and placed in a thermostat. The reaction was stopped by rapid cooling of the ampul to room temperature and the decomposition of the contents with water. The ionic halogen in the reaction mixture was determined by potentiometric titration with an R307 potentiometer with a 0.025 N $AgNO_3$ solution. The rate constants were calculated from the formula

$$k = \frac{2.303}{\tau} \lg \frac{C_0}{C_0 - C_x},$$

where τ is the time (in seconds) from immersion of the ampul in the thermostat to the end of the reaction, C_0 is the initial concentration of the compound, and C_x is the concentration of the compound that has undergone complete conversion up to the moment of the determination.

Reaction of N-Alkyl-2-chlorobenzimidazoles with Piperidine. A 0.01-mole sample of benzimidazoles IIIa-e was dissolved in 50 ml of absolute piperidine, and the solution was heated in a sealed ampul at 100°C for 40 h. The mixture was then evaporated, and the residue was treated with water and extracted with ether. The ether was evaporated, and the residual oil was cooled with a mixture of ice and salt to bring about crystallization. The reaction products were purified by recrystallization from a small amount of heptane. 1-Nonyl-2-(1'-piperidyl)benzimidazole was purified by chromatography (Al_2O_3, elution with chloroform). The properties of all the synthesized compounds are presented in Table 5.

The melting points of all of the previously described preparations were in agreement with the literature data.

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STRUCTURE OF 3-(o-HYDROXYPHENYL) DERIVATIVES OF 2-QUINOXALONE AND 2-BENZOXAZINONE

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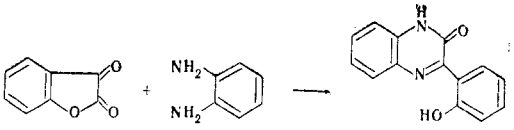
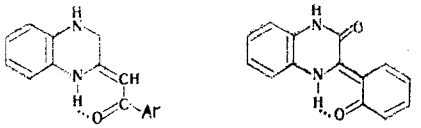
It is shown by IR and UV spectroscopy that the products of the reaction of o-hydroxybenzoylformic acid with o-phenylenediamine and o-aminophenol have the 3-(cyclohexa-3,5-dien-2-onylidene)quinoxalone structure rather than the 3-(o-hydroxyphenyl)-2-quinoxalone structure. 3-(o-Methoxyphenyl)-2-quinoxalone and 3-(o-methoxyphenyl)-3,4-dihydro-2H-benzo-1,4-oxazin-2-one were synthesized as model compounds.

In 1909, Fries [1], in an attempt to obtain coumarophenazine, carried out the condensation of coumarin-2,3-dione with o-phenylenediamine. However, the reaction product did not contain a furan ring. Fries proposed the 3-(o-hydroxyphenyl)-2-quinoxalone structure for the product.



The same compound can be obtained by reaction of o-hydroxybenzoylformic acid with o-phenylenediamine. The IR spectra of the Fries compound were investigated in 1973 [2]. It was observed that the spectrum does not contain the absorption characteristic for the stretching vibrations of the OH group. Banerji and coworkers [2] explained this by the fact that the OH line is masked by moisture in the KBr used to prepare pellets of the compound for recording of the spectra.

During a study of the products of the reaction of aroylpyruvic acids with o-phenylenediamine by PMR spectroscopy it was established that these compounds have the 3-phenacylidene-2-quinoxalone structure (I), in which there is an intramolecular hydrogen bond between the hydrogen of the NH group of the quinoxaline ring and the oxygen of the carbonyl function of the phenacylidene group.



I II

Considering the tendency of the quinoxaoline ring to form an exo ethylene bond, we assumed that the Fries compound has structure II. To prove the structure of II we investigated the IR and UV spectra of this compound, as well as the spectra of the products of the reaction of o-phenylenediamine (III) with benzoylformic (IV) and o-methoxybenzoylformic (V) acid esters.

The long-wave absorption maximum of II is found at 387 nm in the UV spectra (Fig. 1), whereas the corresponding maximum in the spectra of 3-phenyl-2-quinoxaolone (VI) and 3-(o-methoxy)phenyl-2-quinoxalone

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