EFFECT OF BENZO ANNELATION ON THE CHICHIBABIN REACTION

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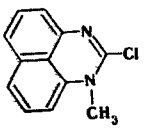
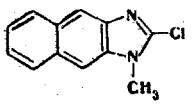
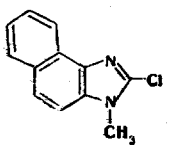
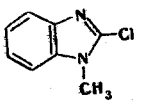
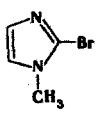
The kinetics of amination with sodium amide (the Chichibabin reaction) for six azines and five azoles and the kinetics of the piperidinolysis of 2-chloro-substituted azole systems were studied. The following orders of reactivities were established for the Chichibabin reaction: isoquinoline > phenanthridine > benzo[h]quinoline > benzo[f]-quinoline > pyridine ≫ acridine and 1-methylbenzimidazole > 1-methylnaphth[2,3-d]-imidazole > 1-methylperimidine > 1-methylnaphth[1,2-d]imidazole > 3-methylnaphth-[1,2-d]imidazole. The changes in the reactivities are explained by the changes in the hydride labilities of the corresponding σ complexes.

It is well known that benzo annelation causes acceleration (by one to three orders of magnitude) of the nucleophilic substitution reactions of halogen and other groups that leave easily in azines [1, 2]. The transition to dibenzo derivatives is accompanied by a further increase in the rate of transformation [1-4]. It is apparent from our data, which are presented in Table 1, that a similar principle is observed in the azole series. However, the literature does not contain quantitative data on the effect of benzo annelation on the ease

TABLE 1. Rate Constants for Piperidinolysis under Pseudo-First-Order Conditions at 40°C

Compound	k_1, sec^{-1}	k_{rel}
	$2{,}56 \cdot 10^{-3}$	4876
	$2{,}01 \cdot 10^{-4}$	383
	$6{,}05 \cdot 10^{-6}$	12
	$5{,}25 \cdot 10^{-7}$	1[5]
	Does not react [6]	

Rostov State University, Rostov-on-Don 344006. Novocherkassk Polytechnic Institute, Novocherkassk 346400. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 257-261, February, 1979. Original article submitted February 13, 1978.

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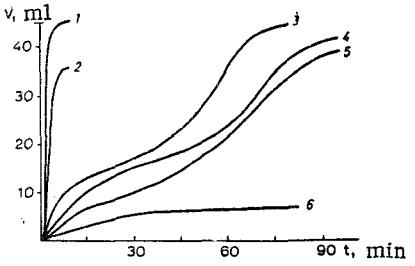


Fig. 1. Dependence of the volume of evolved gas on the time in the amination of azines in o-xylene at 140°C: 1) isoquinoline; 2) phenanthridine; 3) benzo[h]quinoline; 4) benzo[f]quinoline; 5) pyridine; 6) acridine.

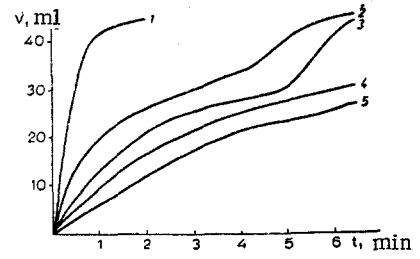


Fig. 2. Dependence of the volume of evolved gas on the time in the amination of azoles and perimidine in dimethylaniline at 110°C; 1) 1-methylbenzimidazole; 2) 1-methylnaphth-[2,3-d]imidazole; 3) 1-methylperimidine; 4) 1-methylnaphth[1,2-d]imidazole; 5) 3-methylnaphth[1,2-d]-imidazole.

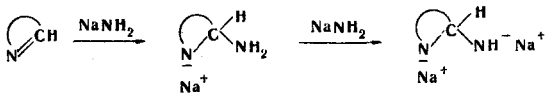
TABLE 2. Composition of the Gas Evolved during Amination in Dimethylaniline (A, 110°C) and in o-Xylene (B, 140°C)

Compound	Experimental conditions	Time, min	Gas volume, ml*			Ammonia, % of the total gas volume
			total	hydrogen	ammonia	
1-Methylbenzimidazole	A	5	45,0	36,8	8,2	18,2
1-Methylnaphth[1,2-d]imidazole	A	30	42,0	29,4	12,6	30,0
3-Methylnaphth[1,2-d]imidazole	A	30	42,5	33,1	9,4	22,0
1-Methylnaphth[2,3-d]imidazole	A	9	44,9	27,4	17,5	39,0
1-Methylperimidine	A	9	46,0	34,2	11,8	25,7
Pyridine	B	90	39,1	34,1	5,0	12,7
Isoquinoline	B	30	45,0	30,0	15,0	33,4
Phenanthridine	B	5	35,8	24,7	11,1	31,0
Benzo[f]quinoline	B	90	41,8	29,2	12,6	30,1
Benzo[h]quinoline	B	75	44,5	35,8	8,7	19,5

*The theoretical amount of hydrogen is 44.8 ml; all the volumes are corrected to standard conditions.

of replacement of the hydride ion, which is known to be a group that leaves with difficulty. The most typical reaction of this sort is the Chichibabin reaction. In the present research by measuring the rate of gas (hydrogen plus ammonia) evolution by the method developed in [7] we attempted to evaluate the effect of benzo annelation on the ease of the Chichibabin reaction in the azine and azole series. We studied the following azines: pyridine, isoquinoline, phenanthridine, acridine, benzo[f]quinoline, benzo[h]quinoline. In the imidazole series we selected benzimidazole and the three possible naphthimidazoles — one linear and two angular. In addition, we studied the amination of perimidine, which can be regarded as perinaphthimidazole.

Curves that show the dependence of the amount of gas evolved on the time are presented in Figs. 1 and 2, and data on the composition of the gas are presented in Table 2. The composition of the gas was determined only at the end of the reaction. This is explained by the fact that, as established in [7], virtually all of the ammonia is evolved at the beginning of the reaction (the initial gently sloping section of the S-shaped curve). The chief complication in the processing of the results consists in allowance for the amount of ammonia, which varies extremely markedly on passing from one heterocycle to another. We have already presented evidence that the ammonia in the Chichibabin reaction is evolved as a result of conversion of σ complex I to dianionic σ complex II, which, however, does not even come close to going to completion [7].



I II

Hydrogen evolution is a consequence of aromatization of σ complex I, which in this case is converted to the sodium salt of an amine (see [7] for a discussion of the mechanism of this step). Insofar as the dianionic σ complex is concerned, it is difficult to imagine how it can undergo aromatization with splitting out of a molecule of H_2. Considering the undoubtedly increased hydride activity of σ complex II, it is logical to assume that the principal pathways of its aromatization should be thermal splitting out of sodium hydride and hydrogenation of the C=N bond of the starting heterocyclic compound. The dehydro derivatives formed in the latter case (e.g., phenanthridine [9] and 1-methylperimidine [8] were actually isolated as side products in up to 25% yields. It follows from this that the amount of evolved ammonia should correspond to the amount of unevolved hydrogen and that the total amount of gas should thus characterize the rate of amination. If this is so, the investigated heterocycles can be arranged in the following orders with respect to their activity in the Chichibabin reaction on the basis of the data obtained: isoquinoline > phenanthridine benzo[h]quinoline > benzo[f]quinoline > pyridine ≫ acridine and 1-methylbenzimidazole > 1-methylnaphth[2,3-d]imidazole > 1-methylperimidine > 1-methylnaphth[1,2-d]imidazole > 3-methylnaphth[1,2-d]imidazole >>> 1-methylimidazole.

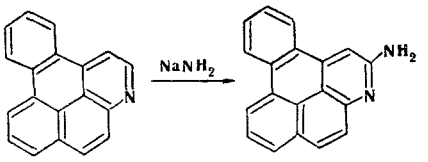
The principal conclusion that can be drawn from a comparison of the series obtained is that the most active compounds for both azines and imidazoles are the two-ring compounds, viz., isoquinoline and 1-methylbenzimidazole; they are much more active than pyridine and imidazole (the latter is not aminated at all) and appreciably more active than the corresponding dibenzo derivatives.

Thus the effect of benzo annelation on the replacement of groups that leave easily and with difficulty differs in the heteroaromatic series. In our opinion, this is due to the interaction of two chief factors: the ease of addition of a nucleophile and the ease of splitting out of the leaving group. The combination of these factors takes on different forms for the two types of reactions. The addition step should be the rate-determining step in the replacement of halogen for all of the systems. In fact, the increase in the reaction rate on passing from noncondensed systems to monobenzo and then to dibenzo derivatives reflects the well-known fact of the decrease in the localization energy, i.e., the increase in the ease of addition. Thus, for example, the anionic localization energies [10] decrease on passing from imidazole to benzimidazole, naphth[2,3-d]imidazole, and then to perimidine in the following way: 3.29, 1.93, 1.88, and 1.71 β. This sequence is in good agreement with the relative activities of 2-halo derivatives of the indicated compounds in nucleophilic substitution reactions (Table 1).

In the case of the Chichibabin reaction, the ease of detachment of a hydride ion from σ complexes I and II takes on great significance in addition to the ease of addition of sodium amide to the C=N bond. There is no doubt that the inability of 1-alkylimidazoles and 1-alkylphenanthroimidazoles to undergo amination is due to the high L_2^- value and the low positive charge on their μ-carbon atoms [8, 10]. If adducts of these compounds with sodium amide were formed, their subsequent aromatization to 2-aminoimidazoles would proceed readily in view of the high hydride activity of Δ^4-imidazolines [11]. On the other hand, in the case of naphthimidazoles and perimidine the addition of $NaNH_2$ proceeds extremely easily at 100-110°C, as indicated by the formation of a copious precipitate prior to hydrogen evolution. The aromatization of the corresponding σ complexes proceeds vigorously beginning at 110-120°C. Benzimidazole occupies a special position. Conditions that ensure the ease of the addition step with sufficiently high hydride lability of the σ complex are evidently optimally combined in this compound (see the data on the hydride activity of Δ^4-benzimidazolines [11]). This is precisely the factor that ensures the increased ease of amination of 1-alkylbenzimidazoles, which takes place at 60-80°C. Similar principles also obtain in the azine series. It should be noted that, upon the whole, imidazole systems are aminated somewhat more easily than azines.

The literature does not contain information regarding the amination of heterocyclic systems that contain more than two condensed benzene rings. An attempt to carry out the amination of 1-methylphenanthreno[9,10-d]imidazole was unsuccessful [12]. We were able to

accomplish the Chichibabin reaction with phenanthreno[9,10,11-d,e,f]quinoline (III), which contains four condensed benzene rings; the yield of amine IV in dimethylaniline at 150-155°C is 88%:



III IV

Amination does not take place at low temperatures, probably because of the reduced hydride activity of the corresponding σ complex, as one should expect for such systems.

EXPERIMENTAL

The method for the study of the rate of the Chichibabin reaction is described in [7]. For the determination of the piperidinolysis rate constants 10-15-mg samples of the chlorides were placed in thermostated test tubes, and 1 ml of piperidine, maintained at 40 ± 0.1°C, was added. The reaction was stopped by the rapid addition of 25-30 ml of ice water. The ionic halogen was determined by potentiometric titration with $AgNO_3$ solution with an R37-1 potentiometer. The rate constants were calculated from the formula $k = (2.303/t)\log (c_0/c_X)$, where t is the reaction time (in seconds), c_0 is the initial concentration of the compound, and c_X is the concentration of the compound at time t.

Amination of Phenanthreno[9,10,11-d,e,f]quinoline. Dimethylaniline (10 ml) was added in a stream of nitrogen to a mixture of 0.75 g (3 mmole) of phenanthreno[9,10,11-d,e,f]quinoline [13] and 1.15 g (0.03 mole) of sodium amide, and the mixture was heated to 150-155°C with stirring and maintained at this temperature for 2 h. It was then cooled in a stream of nitrogen, 10 ml of water and 15 ml of petroleum ether were added, and the resulting precipitate was removed by filtration, washed with water and petroleum ether, and dried to give 0.7 g (88%) of 2-aminophenanthreno[9,10,11-d,e,f]quinoline (IV) as a yellow substance with mp 241-242°C (from dimethylaniline—petroleum ether). IR spectrum (mineral oil): 3460 and 3290 cm^{-1} (N—H). Found: C 85.3; H 4.6; N 10.2%. $C_{19}H_{12}N_2$. Calculated: C 85.1; H 4.5; N 10.4%.

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