IMIDAZOLE DERIVATIVES BEARING POTENTIALLY LABILE GROUPS ON THE N-ATOM

III. N-(β-Aminoethyl)- and N-(β-Hydroxyethyl)benzimidazoles, and Their Behavior Toward Sodamide. The Mechanism of the Chichibabin Reaction*

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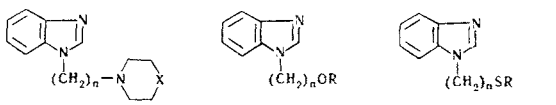
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 5, pp. 869–873, 1969

UDC 547.785.5

A number of N-aminoethyl-, N-hydroxyethyl-, and N-mercaptoethylbenzimidazoles have been synthesized, and their behavior toward sodamide investigated. The influence of the basicity of the benzimidazoles on the course of the Chichibabin reaction is discussed.

It has been shown previously [1] that N-aminomethylbenzimidazoles (I) do not undergo the Chichibabin reaction, but are smoothly cleaved by sodamide at the CH_2—NR_2 bond. The CH_2—OR bond is cleaved similarly, but to a much smaller extent, in N-alkoxy- (and aryloxy)methylbenzimidazoles (III), the greater part of these compounds remaining unchanged under the action of sodamide. This result is not obvious from the nature of the Chichibabin reaction. On the other hand, it would seem logical that the strongly electronegative CH_2—OR group [2] should reduce the electron density at the 2-carbon atom of the imidazole ring, and consequently facilitate amination.

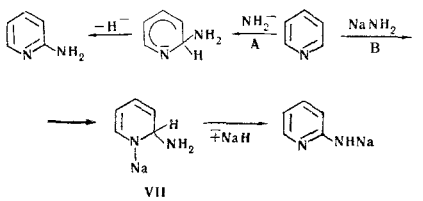


I–II: I n=1, a X=CH_2, b X=O; II n=2, a X=CH_2, b X=O

III–IV: III n=1, a R=CH_3, b R=C_6H_5; IV n=2, a R=C_6H_5

V–VI: V n=1, R=C_6H_5; VI n=2, R=p-C_4H_9

There is, at the present time, more than one view concerning the mechanism of the Chichibabin reaction. It has been suggested that the reaction proceeds either by a direct attack by the amide ion NH_2^- on the electrophilic center [3] (mechanism A), or by addition of the elements of sodamide to the C=N bond, followed by aromatization of the adduct VII (mechanism B) [4, 5] (the mechanism involving the intermediate formation of arynes [6, 7] was later repudiated [8]. The aryne mechanism would obviously be impossible in the benzimidazole series.)



VII

It is improbable that, under the usual conditions of the Chichibabin reaction in inert solvents (aromatic hydrocarbons, paraffin, dialkylanilines), the sodamide would undergo dissociation. Under these conditions, mechanism B would appear to be operative. Also, under the conditions of the Bergstrom method in liquid ammonia [9], when the sodamide is present in solution in the dissociated form [10], the reaction proceeds most rapidly by mechanism A. It thus becomes apparent why the γ-amination of quinoline is observed only under Bergstrom's conditions [9]. Assuming mechanism B, as most workers have done, we have earlier put forward the hypothesis that the progress of the Chichibabin reaction depends not only on the electrophilicity of the carbon atom of the C=N bond, but also on the basicity of the nitrogen atom [11]. In other words, amination must be related to the optimum combination of positive charge on the 2-carbon atom, and negative charge on the pyridine nitrogen. This theory has recently been given a theoretical basis in the molecular orbital method [12]. It also explains why, hitherto, no clear case of the amination of heterocycles of low basicity (pK_a < 3–4) in an inert solvent has yet been recorded.

The application of this hypothesis to benzimidazoles made it necessary to measure the basicity constants of a number of benzimidazoles (including III and IV), and to attempt to correlate their pK_a values with their behavior toward sodamide.

Table 1 shows that the nonaminated 1-methoxymethyl- and 1-phenoxymethylbenzimidazoles, as well as 1-ethyl-5-nitrobenzimidazole [13], are much less basic than the 1-alkyl- and 1-aralkylbenzimidazoles, which undergo amination. The somewhat more basic 1-phenylbenzimidazole is aminated only in xylene solution, and in ths case side-reactions also occur [14]. The lower limit of basicity at which the Chichibabin reaction will occur is apparently pK_a 4.3. Unfortunately, benzimidazoles with basicities in the region pK_a 4.3–5.0 usually contain more or less reactive groups. The reaction with sodamide, therefore, leads either to complex side reactions (for example, with 5-halobenzimidazoles [13]), or to amination accompanied by the latter. These circumstances make it extremely difficult to isolate any amine which is formed (see [14]). In this paper we describe the synthesis, and reaction with sodamide in xylene solution, of N-β-aminoethyl- (II), N-β-phenoxyethyl- (IV), and N-β-mercaptoethyl- (and -methyl-) derivatives (V, VI) (the latter are described in [20]) of benzimidazole. The pK_a values of these compounds suggest that they should undergo amination. We did not measure the basicity

*For part II, see [20].

Table 1

Ionization Constants (in 5% Aqueous Ethanol) and Behavior Toward Sodamide of Some Benzimidazoles

Compound	pK_a (25 ± 1°)	Behavior toward sodamide
Benzimidazole	5.41	Unchanged
1-Methylbenzimidazole	5.44	Aminated
1-Benzylbenzimidazole	5.05	Aminated
1-Phenylbenzimidazole	4.32	Aminated, undergoes side reactions
1-Methoxymethylbenzimidazole	4.17	Unchanged
1-Phenoxymethylbenzimidazole	4.06	Not aminated, undergoes side reactions
1-Phenoxyethylbenzimidazole	4.92	Aminated, but amine not isolated
1-Butylthioethylbenzimidazole	4.99	Aminated, but amine not isolated
1-Phenylthiomethylbenzimidazole	4.45	Not aminated, undergoes side reactions
1-Ethyl-5-bromobenzimidazole	4.78	Not aminated, undergoes side reactions
1-Ethyl-5-nitrobenzimidazole	2.98*	Not aminated, undergoes side reactions

*In 50% aqueous ethanol.

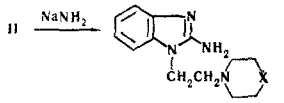
Table 2

Properties of the Compounds Prepared

Compound	Mp, °C *	Bp, °C	Molecular formula	Found, %			Calculated, %			Derivative, mp, °C	Yield, %
				C	H	N	C	H	N		
IIa	56—57[b]	209/7 mm	$C_{14}H_{19}N_3$	73.51	8.14	18.38	73.32	8.35	18.35	Dipicrate, 226	78
IIb	80—82[b]	207—210/5mm	$C_{13}H_{17}N_3O$	67.40	7.26	17.84	67.50	7.41	18.17	Dihydrochloride, 201	70
IV	96[a]	225—226/2mm	$C_{15}H_{14}N_2O$	75.88	6.06	—	75.61	5.92	—	Picrate, 193 Hydrochloride, 162-163	82
IX	89[b]	—	$C_9H_9ClN_2$	59.83	4.91	15.44	59.85	5.02	15.52	Picrate, 214 Hydrochloride, 147-148	95
VIIIa	176[c]	—	$C_{14}H_{20}N_4$	68.85	8.48	22.96	68.82	8.25	22.93	Dipicrate, 248	50
VIIIb	190[a]	—	$C_{13}H_{18}N_4O$	63.68	7.37	22.78	63.39	7.37	22.75	—	40

*Solvent for recrystallization: [a]Benzene; [b]Light petroleum; [c]Aqueous alcohol.

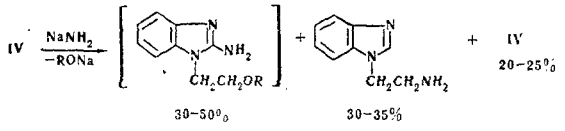
of II, since the N-atom of the β-aminoethyl group must be protonated first. The pK_a value of the pyridine nitrogen must not lie below 5. In practice, hydrogen was evolved vigorously in all cases (a sure indication that the Chichibabin reaction is occurring), but only in the case of II was the amine isolated in the pure state.



VIII a X=CH_2; b X=O

In contrast to Ia and Ib, the ethyl analogs (II) are not hydrolyzed by boiling 6 N hydrochloric acid, and they give stable picrates and dihydrochlorides. Therefore, we were unable to carry out the planned conversion of VIII into the unsubstituted 2-aminobenzimidazole [1].

Compound IV showed the same stability in acid media. However, treatment with sodamide resulted in fission of the CH_2—OR bond, with liberation of hydrogen. The former process may conveniently be followed by estimating the amount of phenol formed (by iodometry). The other product, N-β-aminoethylbenzimidazole (IX), was not isolated from the reaction mixture, but its presence was demonstrated by chromatography, by comparison with an authentic sample. In addition, the use of a large excess of sodamide led to the recovery of about 20–25% of unchanged starting material. The over-all balance of these reactions may be represented by:



30–50% 30–35% 20–25%

The action of sodamide on V gives, in addition to liberation of hydrogen, substantial amounts of thiophenol (formed by fission of the CH_2—SR bond). We succeeded in isolating from the reaction mixture, which contained a number of unidentified substances, N-aminomethylbenzimidazole, which was also obtained from I and III [1].

Sodamide reacted with VI with evolution of hydrogen, but no mercaptan was formed, which indicates the stability of the $(CH_2)_2$—SR bond. In this case, however, no pure compound could be isolated from the reaction mixture.

EXPERIMENTAL

The physical constants, yields, and elementary analyses of all the compounds prepared are given in Table 2.

1-(β-N-Piperidinoethyl)benzimidazole (IIa), and 1-(β-N-morpholinoethyl)benzimidazole (IIb). These were obtained in a similar way to N-β-diethylaminoethylbenzimidazole [15], by reaction of benzimidazole with the corresponding β-chloroethylamine hydrochloride (1 mole) in alcoholic solution in presence of caustic alkali (2 moles). The properties of the compounds differ substantially from those given in [16].

1-(β-Phenoxyethyl)benzimidazole (IVb). This was obtained by boiling equivalent amounts of benzimidazole, 2-bromoethyl phenyl ether, and caustic alkali in alcohol for 2 hr. UV spectrum (SF-4A, methanol): λ_{max}, nm; 248, 254, 264, 274, 281; lg ε 3.89; 3.87; 3.74; 3.77; 3.72.

1-(β-Chloroethyl)benzimidazole (IX). A mixture of 6.5 g of 1-(β-hydroxyethyl)benzimidazole [17] and 55 ml of thionyl chloride was boiled under reflux for 1 hr. Removal of excess thionyl chloride by distillation left 8.5 g of the hydrochloride of IX as a viscous yellow oil which crystallized on prolonged standing at −10° C. Mp 147–148° C. Found, %: N 12.77. Calculated for $C_9H_9N_2Cl \cdot HCl$, %: N 12.90. The base may be obtained from the hydrochloride by trituration with concentrated aqueous ammonia. The chlorine is extremely inert, and is not replaced by the amino group even on heating in a sealed tube with saturated alcoholic ammonia (cf [18]).

Attempts to obtain 1-(β-methoxyethyl)benzimidazole from the hydrochloride of IX by treatment with sodium methoxide resulted in the isolation of 1-vinylbenzimidazole only, in about 60% yield.

2-Amino-1-(β-piperidinoethyl)benzimidazole (VIIIa). To a suspension of 0.51 g (0.013 mole) of sodamide in 10 ml of dry xylene was added 2.29 g (0.01 mole) of IIa, and the mixture boiled with stirring for 2.5 hr, until evolution of hydrogen had ceased. After cooling, 2 ml of water was added. The amine which separated was filtered off on the following day, washed with water and light petroleum, and recrystallized.

2-Amino-1-(β-morpholinoethyl)benzimidazole (VIIIb). Obtained similarly to IIb, but isolated by decantation of the xylene from the precipitate of the sodio derivative of the amine under a stream of nitrogen. Without interrupting the nitrogen flow, water was added, and the mixture was kept at −10° C for 2 days. The crystals of the amino compound which separated were filtered off, washed with water, benzene, and light petroleum, and recrystallized.

Ionization constants. These were measured on a LPU-01 pH meter at 25 ± 1°. The solvent used was a 95 : 5 mixture of water and alcohol [19]; an 0.001 molar solution of the base was titrated with an 0.1 molar solution of HCl. The pK_a values were calculated using the Henderson equation, from 7–8 measurements. The scatter did not exceed ±0.05 pK_a.

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24 May 1967

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