IMIDAZOLE DERIVATIVES WITH POTENTIALLY LABILE GROUPS AT THE N-ATOM

I. N-Aminomethyl- and N-Alkoxymethylbenzimidazoles and their Behavior toward Sodamide

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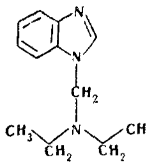
A number of N-aminomethyl and N-alkoxy(aroxy)methylbenzimidazoles are prepared. These compounds are decomposed in acid solution, giving benzimidazole. Sodamide reacts with them to give N-aminomethylbenzimidazole, and not the corresponding 2-amino derivative. The facility with which the compounds investigated decompose decreases in the order N-aminomethyl > N-aroxymethyl > N-alkoxymethylbenzimidazole. The mechanism of splitting is considered.

The Chichibabin reaction makes it possible to obtain various N-alkyl, N-aralkyl, and N-aryl derivatives of 2-aminobenzimidazole, but not 2-aminobenzimidazole itself [1, 2]. The latter is usually synthesized by treating o-phenylenediamine with the highly toxic cyanogen bromide [3]. However a theoretically possible route to 2-aminobenzimidazole is also elimination of a N_1 substituent from the proper N derivative of 2-aminobenzimidazole. With a view to checking this idea, a study has been made of the behavior toward sodamide of a series of benzimidazoles with potentially labile groups at position 1. The ones chosen in the present work were aminomethyl and alkoxy(aroxy)-methyl groups.

The literature describes N-diethylaminomethyl-(**I**), N-piperidinomethyl- (**IIa**), and N-morpholinomethylbenzimidazole (**IIb**) [4, 5]. It was found that these compounds readily decompose in acid solution to give benzimidazole: **IIa** and **IIb** on heating, I even when cold. The picrates of **IIa** and **IIb**, obtained without heating, decompose. when an attempt is made to recrystallize them, or when they are heated, forming benzimidazole picrate. Compounds I and II are rather stable in neutral and alkaline solution at room temperature, but hot water decomposes them to benzimidazole, formaldehyde, and the appropriate secondary amine.

Treatment of N-aminomethylbenzimidazoles with sodamide in liquid ammonia or xylene does not result in hydrogen evolution (characteristic of the Chichibabin reaction). A precipitate of sodium compound is formed, and decomposition of this with water gives, in the case of I benzimidazole, in the case of II N-aminomethylbenzimidazole (**III**).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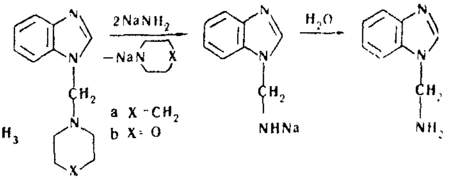


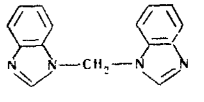
II
III

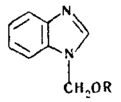
Like other derivatives of methylene diamine [6, 7], N-aminomethylbenzimidazole is quite unstable. Even on keeping, it slowly decomposes giving benzimidazole. Decomposition takes place rapidly in acid solution, and on attempting vacuum distillation. Furthermore, in alkaline medium **III** is somewhat more stable, as is shown by its formation in amination, and by its synthesis from 1-chloromethylbenzimidazole and ammonia. The NH_2 group in a freshly-prepared specimen of **III** is readily revealed by its IR spectrum, and by its giving positive carbylamine and ninhydrin reactions. **III** also forms a p-nitrobenzoate.

Di(N-benzimidazolyl)methane (**IV**) synthesized from benzimidazole and methylene bromide proved to be a stable compound, because in this methylene diamine derivative the unshared electrons of the two nitrogen atoms are drawn to the aromatic system of the imidazole rings.

1, 2-Di(N-benzimidazolyl)ethane and **IV** [8] are unchanged when treated with sodamide in xylene of dimethylaniline.

N-alkoxymethylbenzimidazoles were previously unknown.* They have now been prepared by reacting benzimidazole (2 mole) with 1 mole of the appropriate alkoxymethylchloride in boiling dry benzene or xylene (cf. [10]). The yields were 64–92%. N-phenoxymethylbenzimidazole (Vd) has now been synthesized from 1-chloromethylbenzimidazole and sodium phenoxide. All the V compounds were considerably more stable than the N-amino-methylbenzimidazoles (I–III), and the parent N-hydroxymethylbenzimidazoles (V, R = H). Unlike the latter, the picrates and hydrochlorides of V are quite stable. When they are boiled for several hours with 6 N hydrochloric or hydrobromic acid, they are gradually hydrolyzed to benzimidazole. Despite what is stated by Roe [10], it


IV


V

R = a CH_3; b C_2H_5, c n-C_4H_9; d C_6H_5

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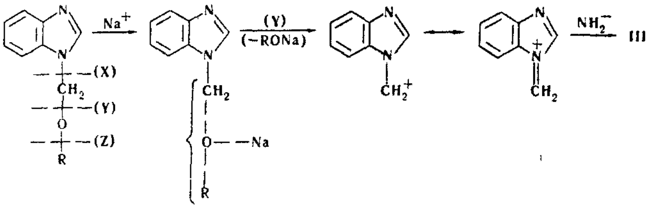
*Only two methoxymethyl derivatives in the imidazole series have been described [9, 10].

was found that this also hydrolyzes N-methoxymethylimidazole to imidazole.

As with **II**, the action of sodamide (1–3 mole, 3–7 hr) on N-alkoxymethylbenzimidazoles (**Va–c**) in xylene or dimethylaniline leads to C—O bond scission, and formation of 1-aminomethylbenzimidazole in 10–15% yield. A large proportion of the starting compound remains unchanged. With **I** under similar conditions there was 43% reaction in xylene and 48% in dimethylaniline (the extent of reaction was established from the amount of phenol formed, as determined iodometrically).

It is to be remembered that compound **V**, like **I–II**, can split in three ways (**VI**, x, y, z). In each actual case the direction and facility of splitting must be determined by the relative stability of the corresponding transition complex [11]. It is logical to assume that the first stage in the reaction is attack by a sodium cation (action of $NaNH_2$) or proton (hydrolysis) of oxygen or nitrogen p electrons to give a transition complex of the **VII** type, where diagram bracket shows the positive charge delocalization region.



Obviously the direction of the second stage, splitting of the C—O bond with simultaneous addition of a NH_2^- anion, will be determined by which group, whether R or CH_2 in **VII**, carries the larger positive charge. Mechanism Y seems more probable, as it can facilitate additional resonance stabilization of the relevant carbonium cation (**VIIIa–VIIIb**), and the experiments confirmed this. With $R = C_6H_5$ (**Vd**) the transition complex must be still more stable, due to further delocalization of the positive charge, and this, along with the enhanced acidity of the phenol, will promote strengthening of the tendency to splitting of the C—O bond by mechanism Y, which is what is actually found. The lower stability of N-aminobenzimidazoles in these reactions can be explained by the p electrons of the nitrogen being more reactive than those of the oxygen.

Splitting of compounds **II** and **V** by mechanism **X** is impeded, as the aromatic X_1 atom of the heterocyclic ring carries a formal positive charge, and so cannot readily be submitted to the action of Na^+ or a proton. The only exception is compound **I** for which, obviously, mechanism **X** is realized all the same, because of the steric hindrance that two ethyl groups create for the approach of the elements of sodamide to the aliphatic N atom (cf. [12]).

However the above review does not shed light on the cause of the unexpected deactivation of the imidazole ring in compounds **I**, **II**, and **V**, towards sodamide. We intend to investigate this question, and also to search for N substituted benzimidazoles, from which it would be possible to pass to 2-aminobenzimidazole.

EXPERIMENTAL

Compounds I and **II** were prepared by reacting benzimidazole with formaldehyde and the appropriate secondary amine [4,5]. As the mp of our 1-piperidinomethylbenzimidazole (80°, needles from hexane) was not that given in the literature (91.5–92.5°,[4]) it was analyzed. Found: C 72.59, 72.44; H 8.18, 8.18%, calculated for $C_{13}H_{17}N_3$: C 72.52; H 7.96%. UV spectrum (SF-4, in MeOH) λ_{max}, nm (lg ε): 244 (3.71); 250 (3.66); 266 (3.55); 272 (3.70); 279 (3.72).

N-Aminomethylbenzimidazole (III). a) 1.3 g 1-chloromethylbenzimidazole hydrochloride [13] was heated 80° for 7 hr with 20 ml 8 N ammonia in MeOH. To remove the ammonium chloride formed, the products were treated with ether. The solvent was removed from the filtrate under a water pump vacuum, leaving a pale yellow oil (0.9 g). When treated with $CHCl_3$ and ether, the 1-aminomethylbenzimidazole dissolved, while a trace of benzimidazole remained in the precipitate. R_f 0.55 (on paper, BuOH : AcOH : water = 4 : 1 : 5). IR spectrum (IKS-14, vaseline mull); 1495 cm^{-1} of the NH_2 group.*

b) 4.3 g (0.02 mole) N-piperidinomethylbenzimidazole, 1.95 (0.05 mole) $NaNH_2$, and 40 ml dry xylene were refluxed and stirred for 2–3 hr. The precipitate (about 5 g) of the sodium derivative of N-aminomethylbenzimidazole was filtered off, washed with dry benzene, and dried in a vacuum desiccator over KOH. On decomposition with water it gave 1-aminomethylbenzimidazole as a brown glassy mass, which was washed with water and dried over KOH. Yield 2.4 g (81.6%). The compound was identical with that prepared by method (a). Since 1-aminomethylbenzimidazole is unstable, it was analyzed as its stable p-nitrobenzoate.

N-(p-Nitrobenzoylaminomethyl)benzimidazole. A suspension of 1.69 g Na derivative, prepared by reacting 1-piperidinomethylbenzimidazole with $NaNH_2$ in 50 ml dry benzene, and 1.58 g p-nitrobenzoylchloride added to it. The mixture was stirred for 7 hr at room temperature; the precipitate was filtered off and carefully washed with water and hot benzene to remove accompanying N-(p-nitrobenzoyl)benzimidazole. It was then dissolved in dioxane and filtered on a funnel through a layer of alumina. The N-(p-nitrobenzoylaminomethyl)benzimidazole was precipitated from the solution with water. Pale yellow crystals mp 261–262° (ex dioxane-water). Found: C 60.88; H 3.90%, calculated for $C_{15}H_{12}N_4O_3$: C 60.82; H 4.08%. The same product was obtained by Schotten-Baumann benzoylation of 1-aminomethylbenzimidazole prepared by method (a).

N-(p-Nitrobenzoyl)methane (IV). Colorless plates, mp 200° (ex dioxane). Found: C 63.27; H 3.91; N 15.37%, calculated for $C_{14}H_9N_3O_3$: C 62.95; H 3.40; N 15.72%.

Di(N-benzimidazolyl)methane (IV). 11.8 g (0.1 mole) Benzimidazole was dissolved in a solution of 7 g (0.1 mole) 80% KOH in 70 ml EtOH. 8.7 g (0.05 mole) dibromomethane was added dropwise, with stirring, to this solution. After all the dibromomethane had been added, the mixture was refluxed for 3 1/2 hr, the KBr filtered off with suction, and the filtrate evaporated to dryness under a water pump vacuum. The residue was treated with water (30 ml), filtered, washed with water and then with ether, yield 8.2 g (63.5%), colorless needles mp 244.5–245.5° (ex aqueous EtOH), soluble in EtOH, acetone, insoluble in ether and benzene. Found: C 72.65, 4.97%, calculated for $C_{18}H_{12}N_4$: C 72.57; H 4.87%.

1-Methoxymethylbenzimidazole. Colorless oil, readily soluble in most organic solvents, mp 147–148° (3 mm), n_D^{20} 1.5700. Found: C 66.25, 66.16; H 6.28, 6.20%, calculated for $C_9H_{10}N_2O$: C 66.65; H 6.21%. UV spectrum (SF-4, in MeOH) λ_{max} (lg ε): 244 (3.85); 254 (3.74); 266 (3.54); 274 (3.67); 280 (3.71). Picrate. Prisms (ex acetone),

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*This band was absent from the IR spectrum of benzimidazole and compounds **II**.

mp 195°. Found: N 17.51, 17.57%, calculated for $C_9H_{10}N_2O \cdot C_6H_3N_3O_7$: N 17.64%. Hydrochloride. Colorless crystals (ex absolute EtOH-ether), mp 145-146°. Found: Cl 17.37%, calculated for $C_9H_{11}ClN_2O$: Cl 17.85%.

1-Ethoxymethylbenzimidazole. Colorless oil, bp 174-175° (10 mm); 165° (5 mm), n_d^{20} 1.5510. Found: N 16.20%, calculated for $C_{10}H_{12}N_2O$: N 15.91%. Picrate. Mp 175-176° (ex AcOH). Found: N 17.28, 17.09%, calculated for $C_{10}H_{12}N_2O \cdot C_6H_3N_3O_7$: N 17.28%. Hydrochloride. Mp 120-121° (ex EtOH-ether). Found: Cl 16.59%, calculated for $C_{10}H_{13}ClN_2O$: Cl 16.67%.

1-Butoxymethylbenzimidazole. Colorless oil bp 182-183° (8 mm). n_D^{22} 1.5446. Found: C 71.06; H 8.17%, calculated for $C_{12}H_{16}N_2O$: C 70.58; H 7.87%. Picrate. Mp 165° (ex EtOH). Found: N 15.95%, calculated for $C_{12}H_{16}N_2O \cdot C_6H_3N_3O_7$: N 16.25%.

1-Phenoxymethylbenzimidazole. A solution of 2.03 g (0.01 mole) 1-chloromethylbenzimidazole hydrochloride, 1 g (0.025 mole) NaOH, and 0.94 g (0.01 mole) phenol in 30 ml EtOH were refluxed together for 1 hr. After cooling the NaCl was filtered off, and the EtOH distilled off from the filtrate. The oily residue was crystallized from benzene-petrol ether, yield 1.5 g (65%). The compound formed colorless rhombohedra (ex benzene), mp 128°, bp 205° (5 mm). Found: C 74.87, 74.73; H 5.48, 5.44%, calculated for $C_{14}H_{12}N_2O$: C 74.96; H 5.39%. UV spectrum (SF-4, in MeOH), λ_{max}, nm (lg ϵ): 219 (3.87); 244 (3.88); 254 (3.78); 266 (3.61); 274 (3.68); 280 (3.65). Picrate. Mp 135° (ex EtOH). Found: N 15.70%, calculated for $C_{14}H_{12}N_2O \cdot C_6H_3N_3O_7$: N 15.45%.

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