INVESTIGATIONS OF BENZIMIDAZOLE DERIVATIVES

XXIII.* REACTION OF 2-AMINOMETHYLBENZIMIDAZOLE AND ITS 1-METHYL DERIVATIVE WITH NITROUS ACID

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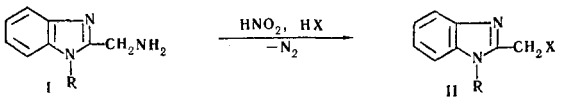
The reaction of 2-aminomethyl- and 2-aminomethyl-1-methylbenzimidazoles with nitrous acid was investigated. The reaction proceeds with nitrogen evolution with excess hydrochloric or hydrobromic acids to form 2-chloro- and 2-bromomethylbenzimidazoles, while 2-benzimidazolylmethylnitrolic acids and other products are obtained with excess nitrous acid.

It is well known that primary aliphatic amines containing electrophilic substituents (COOH, COOR) at the C_1 atom react with nitrous acid to form diazo compounds. The latter, by evolving nitrogen, are converted to carbonium ions which enter into subsequent transformations, one of the products of which is nitrolic acid [2]. The considerable electrophilicity of the benzimidazole ring makes it possible to assume that similar reactions may also occur in the 2-aminomethylbenzimidazole (Ia) series.

Compound Ia was obtained by reaction of o-phenylenediamine with glycine [3, 4]. It could not be methylated by the Roe method [5]. 2-Aminomethyl-1-methylbenzimidazole (Ib) was synthesized in low yield from N-methyl-o-phenylenediamine [6]. Compound Ib was therefore obtained by melting 2-acetamidomethylbenzimidazole with methyl benzenesulfonate and subsequent cleavage of the acetyl group with hydrochloric acid.

It was previously reported [7] that 2-chloro- and 2-bromomethylbenzimidazoles (IIa, b) are formed in high yield by the action of nitrous acid on 2-aminomethylbenzimidazole (Ia) in a medium containing excess hydrochloric or hydrobromic acids. 1-Methyl-2-aminomethylbenzimidazole (Ib) reacts similarly. When hydrofluoric acid is used, Ia is converted to 2-hydroxymethylbenzimidazole (IIc). Compounds IIa-d are identical to the compounds obtained from o-phenylenediamine and its N-methyl derivative by heating with monochloro-, monobromo-, and hydroxyacetic acids by the Phillips method [8].



I a R=H, b R=CH_3; II a R=H, X=Cl; b R=H, X=Br; c R=H, X=OH; d R=CH_3, X=Cl

The reaction in the presence of excess nitrous acid proceeds in a more complex manner [7]. Nitrogen is evolved from the reaction mixture when acid salt solutions of amines Ia and Ib which contain 3 moles of acid are introduced into a sodium nitrite solution (3 moles per mole of amine). An orange, crystalline precipitate (Va) or, respectively, a light-yellow, crystalline precipitate (Vb) are formed as the nitrogen evolves. Both compounds are hard to dissolve in the cold in water and in most organic solvents but are readily soluble in dilute alkalis with the formation of reddish-orange (Va) and orange (Vb) solutions. Heating the alkaline solutions results in decoloration with the formation of sodium nitrite. Compounds Va and Vb gradually decompose on prolonged storage with evolution of nitrogen oxides. The decomposition is accelerated on raising the temperature. On the basis of these properties the compounds obtained should be

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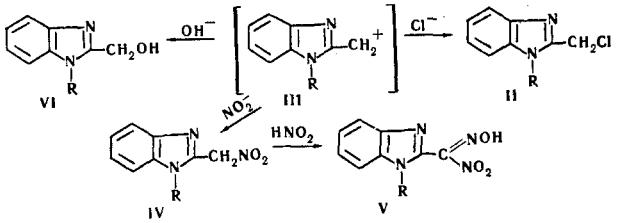
assigned nitrolic acid structures since the IR spectra indicate that they are identical to the nitrosation products of the corresponding oximes [9].

The indicated transformations apparently occur through the intermediate formation of carbonium ion III [10].



II a R=H, b R=CH$_3$; IV, V, VI a R=H, b R=CH$_3$

The filtrate after removal of Va was extracted with ether. After several hours pale-yellow needles of 1-nitroso-2-chloromethylbenzimidazole (IIe) precipitated from the extract. The compound is identical to the product of nitrosation of 2-chloromethylbenzimidazole [11].

In the case of Ib, 1-methyl-2-chloromethylbenzimidazole (IId) was isolated from the ether solution instead of IIe.

The hydrochloride of Va precipitates from the ether several hours after removal of IIe. It should be noted that nitrogen evolution does not occur during formation of the precipitates of IIe and the hydrochloride of Va. This enables one to conclude that they are obtained as the result of secondary processes. 2-Chloromethylbenzimidazole, 2-nitromethylbenzimidazole (IV), and nitrosyl chloride apparently pass into the ether; the latter apparently nitrosates IIa at the NH group and IV at the CH_2 group to form Vb and Va · HCl.

2-Hydroxymethylbenzimidazole (VIa) and 1-methyl-2-hydroxymethylbenzimidazole (VIb) were isolated and identified from the aqueous solutions after evaporation under reduced pressure.

Attempts to find 2-nitromethylbenzimidazoles (IV), which are the most probable intermediates in the formation of nitrolic acids [2], in the reaction products were unsuccessful.

2-Benzimidazolylmethylnitrolic acids manifest a capacity for nucleophilic exchange of the nitro group, as a result of which they are of interest for the synthesis of the as yet unknown or hard-to-obtain compounds of the benzimidazole series, as will be shown in our next communication.

Our results attest to the considerable influence of the benzimidazole ring on the direction of the reaction under investigation. In our case we observed an analogy to the influence of the carbonyl group manifested in the glycine molecule [2]. However, in contrast to the latter, the 2-aminomethylbenzimidazoles do not form stable diazo compounds under the influence of nitrous acid: nitrogen evolution is observed during the reaction (at −10° [12]).

EXPERIMENTAL

2-Acetamidomethylbenzimidazole. Ammonium hydroxide (22%, 29 ml) was added to a mixture of 20 g of the dihydrochloride of Ia [3] and 15 ml of water. The crystals of base which precipitated on cooling were filtered, washed with water, and suspended in 20 ml of water. Acetic anhydride (9.5 ml) was added to the suspension, the mixture was boiled for several minutes and neutralized, after cooling, with ammonium hydroxide until crystals of 2-acetamidomethylbenzamidazole began to form. Workup gave 15 g (79%) of product with mp 208-209° (water). Found %: C 62.80; H 5.80; N 21.92. $C_{10}H_{11}N_3O$. Calculated %: C 63.47; H 5.83; N 22.20. ν_{CO} 1665 cm^{-1}, ν_{NH} 3220 cm^{-1}.

1-Methyl-2-acetamidomethylbenzimidazole. This was obtained by melting a mixture of 10 g of 2-acetamidomethylbenzimidazole, 8.85 g of methyl benzenesulfonate, and 1.5 ml of alcohol with subsequent treatment of the melt with aqueous alkali. The product [8.1 g (68%)] had mp 158-160° (absolute alcohol) [16]. It was converted quantitatively into the dihydrochloride of Ib by boiling in 10% hydrochloric acid and evaporation of the solution on a steam bath.

2-Chloromethylbenzimidazole (IIa). A solution of 2.8 g (0.04 mole) of sodium nitrite in 10 ml of water was added in 30 min with stirring to a solution (cooled to −10°) of 8.8 g (0.04 mole) of the dihydrochloride

of Ia in 80 ml of 2 N hydrochloric acid. When nitrogen evolution ceased, the reaction mixture was carefully neutralized with ammonium hydroxide, and the resulting precipitate of IIa was filtered, washed with water, and dried in a desiccator to give 5.4 g (81%) of product with mp 163-164° (dioxane) [8]. When the acid-to-amine ratio was 1:1 (from −10° to +10°), a vitreous product was formed from which no individual compounds could be isolated.

1-Methyl-2-chloromethylbenzimidazole (IId). This was obtained in 60% yield by the method used to obtain IIa and had mp 95-95.5° (ether) [14].

2-Bromomethylbenzimidazole (IIb). This was obtained in the same way as IIa from 2.95 g (0.01 mole) of the dibromide of Ia, 20 ml of 2 N hydrobromic acid, 0.7 g (0.01 mole) of sodium nitrite, and 5 ml of water. The hydrobromide was filtered at the end of nitrogen evolution, and 1.53 g (90%) of the free base with mp 148-150° (dioxane) [15] was isolated with aqueous sodium acetate.

2-Hydroxymethylbenzimidazole (IIc). This was obtained in 40% yield in a manner similar to that used to obtain II in hydrofluoric acid, and had mp 170-171° (water) [13].

1-Nitroso-2-chloromethylbenzimidazole (IIe). A solution of 2 g of sodium nitrite in 3.7 ml of water was added to a solution of 3 g of 2-chloromethylbenzimidazole [8] in 7 ml of glacial acetic acid. After 24 h the resulting crystals were filtered and washed with ice water to give 2.8 g (79%) of product with mp 176° (decomp., methanol).

2-Benzimidazolylmethylnitrolic Acid (Va). A. A solution of 53 g (0.24 mole) of the dihydrochloride of Ia in 240 ml of 1 N hydrochloric acid was added in small portions in 20 min with vigorous stirring to a solution of 50.5 g (0.73 mole) of sodium nitrite in 1200 ml of water (10-15°). After an additional 15 min the crystals were filtered, washed with water, and dried in a desiccator over sodium hydroxide to give 15.7 g (32%) of product with mp 108° (decomp.). The filtrate was extracted with ether. The aqueous layer was distilled under reduced pressure to a volume of 150 ml which, on cooling, yielded 11.3 g (35%) of 2-hydroxymethylbenzimidazole (VIa) with mp 171-172° (water) [13]. Compound IIe [8 g (17%) with mp 178° (decomp., from methanol)] [7] was isolated from the ether extract after 2-3 h. After several days the filtrate, after removal of IIe, yielded 5.7 g (7%) of the hydrochloride of Va with mp 99° (decomp.). The hydrochloride was converted to Va by treatment with water.

B. 2-Formylbenzimidazole oxime [3.22 g (0.02 mole)] [17] was added to 30 ml of 70% nitric acid and the mixture was heated to 70-80°. The resulting brown solution was cooled (during which a precipitate formed), diluted with 100 ml of water, and neutralized with sodium bicarbonate. The nitrolic acid was filtered, washed thoroughly with water, and dried in a desiccator to give 2.74 g (67%) of a product with mp 107° (decomp.).

1-Methyl-2-benzimidazolylmethylnitrolic Acid (Vb). A. This was obtained in the same way as Va from 23.4 g (0.1 mole) of the dihydrochloride of Ib, 90 ml of 1 N hydrochloric acid, 21 g (0.3 mole) of sodium nitrite, and 450 ml of water. The reagents were stirred for 5 min and yielded 3.5 g (16%) of product with mp 99° (decomp.). ν_{NO_2} 1340, 1565 cm^{-1}, $\nu_{C=N}$ 1620 cm^{-1}. The methyl ester was obtained by the action of an ether solution of diazomethane on Vb and was insoluble in aqueous alkali. It formed a picrate with mp 193-194° (decomp., from alcohol). Found %: C 41.81; H 2.97; N 20.93. $C_{10}H_{10}N_4O_3 \cdot C_6H_3N_3O_7$. Calculated %: C 41.47; H 2.83; N 21.16. The precipitate from the ether extract was treated with aqueous sodium acetate to give 1.9 g (11%) of 1-methyl-2-chloromethylbenzimidazole with mp 93-94° (ether) [13]. Compound VIb [4.9 g (31%)] crystallized out from the aqueous layer after removal of a large portion of water and cooling. The reaction proceeded similarly at −10°.

B. Compound Vb [3.95 g (62%)] with mp 99° (decomp.) was obtained like Va from 5 g of 1-methyl-2-formylbenzimidazole oxime [18] by the action of 15 ml of 70% nitric acid.

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