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RESEARCHES ON BENZOIMIDAZOLE DERIVATIVES

XIX Nitration of N-Methyl Substituted 2-Aminobenzoimidazole and 2-Iminobenzoimidazoline*

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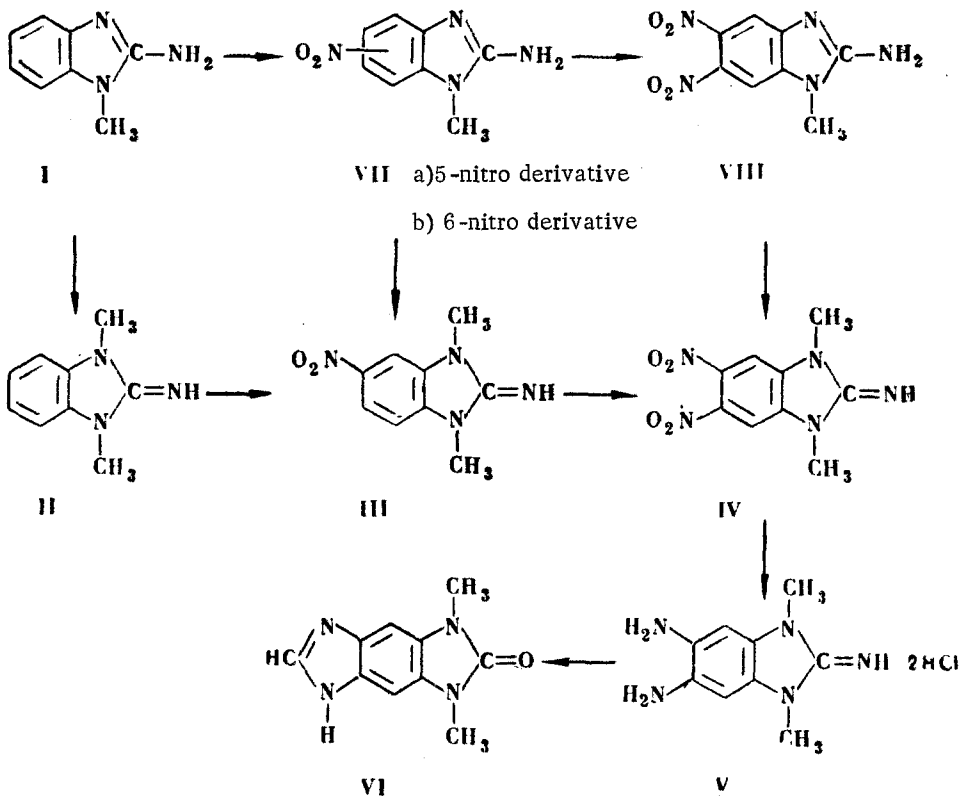
The nitration of 2-amino-1-methylbenzoimidazole and 2-imino-1, 3-dimethylbenzoimidazoline to mono and dinitro derivatives is investigated. Substitution takes place very readily a low temperature (−5° to 0°). It is shown that the nitrogroup enters at position 5 and 6.

In connection with unusual orientation results obtained when introducing the nitro group into the benzoimidazole [1-3] and benzoimidazolone [4, 5] rings, it was of interest to investigate nitration of 2-amino-1-methylbenzoimidazole (I) [6], and its methylation product 2-amino-1, 3-dimethylbenzoimidazoline (II). Experiment showed that reaction proceeded readily, to give high yields, even at low temperature. If the nitrate of 2-imino-1, 3-dimethylbenzoimidazoline is introduced into sulfuric acid (d 1.82) at −2°, a mononitro derivative III is formed; the position of the nitro group in the ring is established by alkaline hydrolysis, which gives the previously described [5] 5-nitro-1, 3-dimethylbenzoimidazolone. Dinitro derivative IV is formed by introducing 2 moles of potassium nitrate into a solution of the imine in sulfuric acid at 0-5°. Catalytic reduction using a platinum catalyst gives the diamine V, isolated as its dihydrochloride. Reaction of the diamine with formic acid, followed by alkaline hydrolysis of the reaction product makes it possible to obtain the previously described 1, 2-(1', 3'-dimethylimidazolono)-4, 5-imidazolobenzene (VI) [7]. From these reactions it can be concluded that compounds IV and V are respectively 5, 6-dinitro- and 5, 6-diamino derivatives.

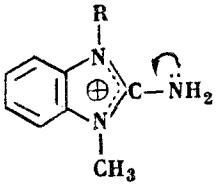
Nitration of 2-amino-1-methylbenzoimidazole (I) with an equimolecular quantity of potassium nitrate in sulfuric acid at −5° gives a mixture of mononitro derivatives melting at 260-270°. Methylation of the mixture (see [8, 9]) gives 5-nitro-2-imino-1, 3-dimethylbenzoimidazoline (III), so that the mixture can contain only 5 and 6-nitro derivatives. Recrystallization from pyridine brings the melting point down to 346°, which is identical with that of the product of reaction of 5-nitro-2-chloro-1-methylbenzoimidazole [10] with ammonia, so that it is 5-nitro-2-amino-1-methylbenzoimidazole. Addition of ether to the mother liquor leads to separation of the 6-nitro isomer, mp 272°



*For Part XVIII see [12].

Synthesis of the dinitro derivative of amine I is effected under mononitration conditions, at 0° using two molecules of potassium nitrate. Methylation of the reaction product VIII gives 5, 6-dinitro-2-imino-1, 3-dimethylbenzoimidazoline (IV), so that the nitro groups are situated at positions 5 and 6.

Similar results, obtained when the amine I and the imine II are nitrated, are explained as follows. The bases, like benzoimidazolone and its N, N'-dimethyl substitution product [5.11], react as the similarly structured cations IXa and IXb, formed by addition of a proton to I and correspondingly to II* (see also [13]).



IX a) R=H; b) R=CH_3

It is known that salts of benzoimidazole also undergo nitration [14, 15]. Nitration of amine I and imine II takes place more readily under the influence of the electron-donating amino group present in the imidazolinium ring of cations IXa and IXb.

Experimental

5-Nitro- and 6-nitro-2-amino-1-methylbenzoimidazoles (VIIa, b). A solution of 4.04 g (0.04 mole) KNO_3 in 25 ml conc. H_2SO_4 was added to a solution of 5.88 g (0.04 mole) I in 45 ml H_2SO_4 (d 1.82) over 1 hr, with the temperature held at −5°. Cooling was then stopped, and stirring continued as long as the temperature remained below room temperature. When room temperature was reached, the products were poured on to 120 g ice, aqueous ammonia added until the reaction was alkaline, the yellow precipitate formed filtered off, and washed with warm water. Yield 7.3 g. The nitration product was dissolved in pyridine (60 parts), and after 24 hr the crystalline precipitate filtered off. Yield 50%. Yellow needles mp 346° (from pyridine). The compound was soluble in dimethylformamide and dilute mineral acids, insoluble in benzene, very sparingly soluble in ethanol. It was identical with the reaction product obtained by heating 5-nitro-2-chloro-1-methylbenzoimidazole [10]. with ethanolic ammonia for 14 hr at 100-120° in a sealed tube. Found: C 49.86, 49.90; H 4.25, 4.35; N 29.26, 29.27%. Calculated for $C_8H_8N_4O_2$: C 50.00; H 4.20; N 29.16%.

The pyridine mother liquor was mixed with 3 vol ether. A precipitate formed on long standing, and was filtered off and recrystallized from ethanol. Yield 40%. Yellow plates mp 272°, unchanged by further recrystallization. The compound is considerably better than the 5-nitro derivative, dissolving in pyridine and ethanol. It must be considered to be the 6-nitro derivative as, like the compound mp 346°, it gives on methylation 5-nitro-2-imino-1, 3-dimethylbenzoimidazoline. Found: C 49.90, 49.95; H 4.25, 4.23%. Calculated for $C_8H_8N_4O_2$: C 50.00; H 4.20%.

5, 6-Dinitro-2-amino-1-methylbenzoimidazole (VIII). A solution of 8.08 g (0.08 mole) KNO_3 in 60 ml conc. H_2SO_4 was added dropwise in 2 hr to 5.88 g (0.04 mole) I dissolved in 60 ml H_2SO_4 (d 1.82) held at 0° and well-stirred, after which the reaction mixture was allowed to come to room temperature and poured on to 300 g ice. Yield 8.7 g of bright yellow long prisms, mp 334° (from dimethylformamide), soluble in pyridine, sparingly soluble in ethanol, insoluble in benzene. On standing or on heating it separated into orange crystals having the same melting point. When recrystallized from dimethylformamide the orange compound again gave yellow prisms. Found: C 40.46, 40.50; H 3.00, 3.00; N 29.43%. Calculated for $C_8H_7N_5O_4$: C 40.51; H 2.98; N 29.53%.

2-Imino-1, 3-dimethylbenzoimidazoline (II). A solution of 70 g NaOH in 80 ml water, was added to a solution of 30 g of II [8] hydriodide in 160 ml water at 70°, and the imine extracted with three lots of 200 ml hot benzene. The extract was dried over NaOH, and the benzene distilled off, to give 15.5 g colorless needles mp 117° (from heptane), readily soluble in water and ethanol. Found: N 26.07, 26.11%. Calculated for $C_6H_{11}N_3$: N 26.07%.

II nitrate (salt) was prepared from the hydriodide and $AgNO_3$ (1 mole), in H_2O-EtOH solution. Yield 98%, needles mp 220° (from alcohol). Found: N 25.12, 24.98%. Calculated for $C_9H_{11}N_3 \cdot HNO_3$: N 24.99%.

5-Nitro-2-imino-1, 3-dimethylbenzoimidazoline (III). a) 0.9 g II nitrate was added in small portions, and with vigorous stirring, to 7.5 ml sulfuric acid (d 1.82) held at −2°. Continuing the stirring, the mixture was allowed to warm up to 10°, then poured on to 40 g ice, and neutralized with ammonia solution. The precipitate was filtered

*The cation of a benzoimidazolium salt is also formed when the imino group of imine II is protonated, due to displacement of electron pairs towards the exocyclic nitrogen atom [12].

off and washed with water, yield 0.75 g, of yellow needles mp 239-240° (from aqueous ethanol), soluble in pyridine, sparingly soluble in water. Found: C 52.25, 52.55; H 4.90, 4.98; N 27.46%. Calculated for $C_9H_{10}N_4O_2$: C 52.42; H 4.89; N 27.17%.

b) 0.20 g 5- or 6-nitro-2-amino-1-methylbenzoimidazole and 0.5 ml of the methyl ester of benzenesulfonic acid were heated together for 5 min at 140°, the melt allowed to cool and then extracted with ether, after which the salt was decomposed by ammonia. The compounds prepared by methods a and b were identical.

Hydriodide mp 302°. Previously synthesized by methylating 5-nitro-2-aminobenzoimidazole, mp 304-305° [16].

Hydrolysis of III. 0.2 g compound was added to 20 ml 10% KOH solution, and the mixture boiled for 7 hr, topping up evaporated water. Ammonia was evolved. On cooling yellow needles of 5-nitro-1,3-dimethylbenzoimidazoline were formed, yield 0.1 g, mp 205° (from ethanol); mixed mp with an authentic specimen 205°.

5,6-Dinitro-2-imino-1,3-dimethylbenzoimidazoline (IV). a) 5 g KNO_3 (2 equiv) in 40 ml H_2SO_4 was dropped into 4 g II which had been dissolved with cooling in 40 ml H_2SO_4 (d 1.82), the temperature being held at −5 to 0°. The mixture was stirred, and while still below room temperature, poured on to 160 g ice, and the whole then neutralized with ammonia solution. Next day it was filtered, and the solid on the filter washed with water. Yield 5.7 g (90%), bright yellow needles (from pyridine-heptane), mp 258°, soluble in dimethylformamide, sparingly soluble in ethanol and water, insoluble in benzene and ether. Found: N 27.96, 28.20%. Calculated for $C_9H_9N_5O_4$: N 27.88%.

b) 0.5 g VIII and 2 ml methyl ester of benzenesulfonic acid was held for 10 min at 140-150°, cooled, and the melt washed with ether. The salt was decomposed with ammonia, and the base washed with water. Yield 0.4 g, mp 258°. The compound was identical with the reaction product from (a) above.

5, 6-Diamino-2-imino-1,3-dimethylbenzoimidazoline. 1.5 g IV was mixed with 70 ml ethanol, and reduced with hydrogen in the presence of platinum on carbon. The solution was filtered in a stream of hydrogen, and immediately used for the reaction below. The dihydrochloride was prepared by passing hydrogen chloride into an ethanol solution of 5, 6-diamino-2-imino-1, 3-dimethylbenzoimidazoline. Colorless needles mp about 300° (from aqueous EtOH-ether). Found: N 26.45, 26.35%. Calculated for $C_9H_{13}N_5 \cdot 2HCl$: N 26.51%.

The phenanthrazine derivative was prepared by mixing hot ethanol solutions of the diamine and 9,10-phenanthraquinone, yellow needles (ex pyridine) mp about 360° (decomp). A conc. H_2SO_4 solution was intensely crimson. Found: C 76.33, 76.32; H 4.54, 4.43%. Calculated for $C_{23}H_{17}N_5$: C 76.01; H 4.71%.

1,2-(1', 3'-Dimethylimidazolono)-4,5-imidazolobenzene (VI). An ethanol solution of 0.3 g 5,6-diamino-2-imino-1, 3-dimethylbenzoimidazoline was mixed with 3 ml 85% formic acid, the ethanol distilled off, a further 2 ml formic acid added, and the mixture refluxed for 10 hr. Excess formic acid was then distilled off under reduced pressure, and 5 ml 8% KOH added. The resultant solution was refluxed for 10 hr, then evaporated to 3-4 ml. On cooling a precipitate (0.2 g) was formed, which was dissolved in 3 ml hot water. The solution was made acid with hydrochloric acid, then neutralized with ammonia. On cooling long colorless needles separated, mp 276° (ex water) [7]. Mixed mp with an authentic specimen 276°.

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