INVESTIGATIONS IN THE FIELD OF IMIDAZO[1,2-a]BENZIMIDAZOLE

III.* REACTIONS OF THE 3-NITROSO DERIVATIVES

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The nitrosation and azo coupling reactions in the imidazo[1,2-a]benzimidazole series have been studied. Position 3 of the system undergoes attack. The nitroso compounds readily undergo hydrolysis in acid and alkaline media at the 1-2 bond with the formation of derivatives of benzimidazolone or 2-iminobenzimidazoline.

Continuing a study of transformations in the imidazo[1,2-a]benzimidazole series, we have found that its 2-phenyl derivative (Ia) readily reacts with nitrous acid. As in bromination [2], substitution takes place at position 3 and leads to the nitroso compound (II), which undergoes the reactions usual for these substances: with benzyl cyanide it forms an anil and with arylamines areneazo derivatives (III); the latter are also obtained by the reaction of I with diazonium compounds. Consequently, nitrosation and azo coupling take place at the same position of the nucleus.

When electrophilic groups are included in an imidazole ring adjacent to a benzimidazole nucleus, it becomes unstable and readily opens. Thus, on being heated in aqueous alkaline solution the methiodide of compound I is converted into 1-methyl-3-phenacylbenzimidazolone [2], and the methiodide of Ib is converted into a derivative of 2-iminobenzimidazoline (VIIb).† The nitroso compound II was subjected to a similar conversion in boiling ethanolic alkali; here, also, the ring opened at the 1-2 bond, the nitroso group being converted into an isonitroso group and the imino group being split off hydrolytically.

When the reaction solution was acidified to pH 5-6, 3-hydroxyimonophenacyl-1-methylbenzimidazolone (V) precipitated from it as a colorless compound with mp 227-228°C (α-monooxime). This conclusion is in harmony with the IR spectrum, in which the absorption of two CO groups appears in the form of a broad band with two closely adjacent maxima (1677 and 1700 cm^{-1}), and the $C=N$ stretching vibrations are represented by a band at 1623 cm^{-1}. The unambiguity of the assignment of the carbonyl absorption bands of compound V is confirmed by the IR spectrum of 3-phenacyl-1-methylbenzimidazolone, in which the analogous vibrations are present at 1687 and 1694 cm^{-1}.

When the mother liquor after the precipitation of V was acidified to pH 1, a compound precipitated with mp 184-185°C – the salt of the imino compound VIIa formed by the incomplete hydrolysis of the nitroso compound. The base – 3-hydroxyiminophenacyl-2-imino-1-methylbenzimidazoline (VIIa) – which was isolated from the salt by the action of ammonia, was converted on fusion or on long storage into the initial nitroso compound. (See scheme, page 640.) The structure of VIIa was confirmed by its IR spectrum. It contained very strong bands in the $\nu_{C=N}$ (1645 cm^{-1}) and ν_{CO} (1680-1690 cm^{-1}) regions and one in the ν_{OH} and ν_{NH} regions appearing in the form of a continuous broad band with maxima at 3090 and 3250 cm^{-1}, respectively. Analogous bands are observed in the IR spectrum of the hydrochloride of this compound (VIIa · HCl): ν_{CO} 1689, $\nu_{C=N}$ 1628, ν_{OH} 3040, and ν_{NH} 3230 cm^{-1}.

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*For Communication II, see [1].

† These facts permit the conclusion that in the methiodide of I it is the 1-2 bond which is cleaved and not that at the guanidine C atom, as was assumed previously [1].

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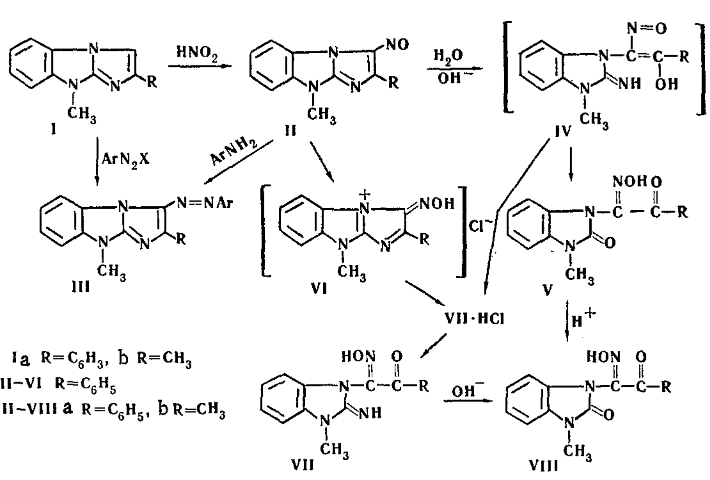

Ia R=C_6H_3, b R=CH_3
II–VI R=C_6H_5
VII–VIII a R=C_6H_5, b R=CH_3

The formation of the hydrochloride (VIIa • HCl) also takes place when an ethanolic solution of the salt of the isonitroso compound VI is heated. When an aqueous alkaline solution of VIIa was boiled, the imino group was saponified and the β-monooxime VIIIa with mp 216°C was isolated in quantitative yield; this, unlike the α-monooxime, forms a complex copper salt [3]. The latter is converted into the β form in boiling ethanolic hydrochloric acid or on prolonged storage in the light.

The formation of compounds V and VIIa convincingly shows that the nitroso group in the nucleus of II is present at position 3.

It was impossible to obtain a nitroso compound from Ib. The action of nitrous acid on Ib in ethanolic solution in the presence of hydrochloric acid led to simultaneous nitrosation and the opening of the imidazo ring, with the formation of 3-hydroxyiminoacetonyl-2-imino-1-methylbenzimidazoline (VIIb • HCl). On saponification of the NH group, the base VIIb isolated from the salt was converted into compound VIIIb, which is the β-monooxime, since it readily forms a copper salt.

EXPERIMENTAL

2,9-Dimethylimidazo[1,2-a]benzimidazole Methiodide. A solution of 1 g (5.4 mmoles) of 2,9-dimethylimidazo[1,2-a]benzimidazole [1] and 1.02 ml (16 mmoles) of methyl iodide in 10 ml of absolute ethanol was boiled for 6 h. Yield of snow-white needles with mp 249°C (ethanol), 1.5 g (78%). Found %: C 43.86; H 4.46; I 38.34; N 12.73. $C_{12}H_{14}N_3I$. Calculated %: C 44.05; H 4.31; I 38.79; N 12.85.

3-Acetonyl-1-methyl-2-methyliminobenzimidazoline. a. A mixture of 1 g of the methiodide of Ib and 15 ml of 10% caustic potash solution was heated in the boiling water bath for 2 h. The oil that separated out crystallized on standing in the refrigerator. Yield 0.53 g (80%). Colorless needles with mp 136–137°C (water), soluble in ethanol and benzene. Found %: C 66.45; H 7.41; N 19.31, 19.51. $C_{12}H_{14}N_3O$. Calculated %: C 66.34; H 6.96; N 19.34.

b. The same substance was obtained by boiling an ethanolic solution of 0.5 g of 1-methyl-2-methylaminobenzimidazole [4] with 33 ml of bromoacetone. The hydrobromide that deposited (0.3 g) was separated off and was then heated with 10% caustic potash for 1 h. After cooling, the oil that had separated out crystallized in the form of colorless needles with mp 136°C (water). A mixture with the product of experiment a gave no depression of the melting point.

9-Methyl-3-nitroso-2-phenylimidazo[1,2-a]benzimidazole (II). A solution of 1.24 g (5 mmoles) of Ia in 10 ml of glacial acetic acid was treated dropwise with vigorous stirring at 20°C with a solution of 0.35 g (5 mmoles) of sodium nitrite in 2 ml of water, and then 30 ml of water was added gradually. The precipitate was filtered off and washed with water. Yield 1.18 g (92%). Bright green, strongly electrifying needles with mp 247°C (ethanol), soluble in ether and acetone, and sparingly soluble in ethanol. Found %: C 69.25; H 4.42; N 20.29. $C_{16}H_{12}N_4O$. Calculated %: C 69.55; H 4.38; N 20.28.

When an acetone solution of II was mixed with conc. HCl, a precipitate of hydrochloride of the isonitroso compound VI was formed. Bright red needles with mp 208–209°C, soluble in ethanol, hydrolyzing under the action of water to the initial nitroso compound. Found %: C 61.50; H 4.14; N 17.97; Cl 11.85. $C_{16}H_{13}ClN_4O$. Calculated %: C 61.44; H 4.19; N 17.91; Cl 11.34.

3-Hydroxyiminophenacyl-1-methylbenzimidazolone (the α-monooxime, V). A suspension of 1 g of II in 15 ml of ethanolic caustic soda (0.2-0.3 g) was boiled for 10-15 min. After cooling, the yellow solution was acidified with conc. HCl to pH 5-6, and the monooxime was precipitated by dilution with water. Yield 0.5 g (47%). Lustrous snow-white prisms with mp 227-228°C (decomp., ethanol), insoluble in water and acids, soluble in dilute alkalies with the formation of a yellow solution [5]. Found %: C 65.23; H 4.35; N 14.24; mol. wt. 297 (Rast). $C_{16}H_{13}N_3O_3$. Calculated: C 65.08; H 4.44; N 14.23; mol. wt. 295. 2,4-Dinitrophenylhydrazone. Lustrous yellow needles, mp 150-251°C (from glacial acetic acid). Found %: C 55.47; H 3.64; N 20.79. $C_{22}H_{17}N_7O_6$. Calculated %: C 55.58; H 3.60; N 20.62. From aqueous acetic acid or from ethanol the hydrate of the hydrazone deposited, and this did not lose water even at 150°C. Bright orange needles, yellowing at 185°C and melting at 250-251°C. Found %: C 54.02; H 4.02; N 19.88. $C_{22}H_{17}N_7O_6 \cdot H_2O$. Calculated %: C 53.55; H 3.88; N 19.87.

3-Hydroxyiminophenacyl-2-imino-1-methylbenzimidazoline (VIIa). a. Acidification to pH 1 of the mother solution after the separation of compound V led to the precipitation of 0.45 g of the hydrochloride of VIIa. mp 85°C (ethanol containing ether). Yield 37.5%.

b. A suspension of II in ethanol was treated with a few drops of conc. HCl, and the resulting solution was boiled for 5-10 min, whereupon VIIa • HCl precipitated from it in almost quantitative yield. Snow-white needles, mp 184-185°C (ethanol containing ether). Found %: C 58.24; H 4.70; N 17.06; Cl 10.55. $C_{16}H_{14}N_4O_2 \cdot HCl$. Calculated %: C 58.10; H 4.57; N 16.94; Cl 10.72.

On the addition of concentrated ammonia, an ethanolic solution of the hydrochloride deposited light yellow plates of VIIa. It melted at 105°C; the green melt immediately recrystallized and then melted again at 247°C. When VIIa was recrystallized from ethanol, a dark green solution was formed which, on rapid cooling, deposited light yellow crystals with the above-given melting point (on slow heating) – the nitroso compound II. They were dried in a vacuum desiccator at 20°C (drying at 100°C or prolonged storage likewise converts VIIa into the green nitroso compound II). The substance is soluble in dilute ammonia and alkalies. Found %: C 63.69; H 5.09; N 18.61. $C_{16}H_{14}N_4O_2 \cdot \frac{1}{2}H_2O$. Calculated %: C 63.36; H 4.98; N 18.47.

3-Hydroxyiminophenacyl-1-methylbenzimidazolone (the β-monooxime, VIIIa). A solution of 0.2 g of VIIa in 5 ml of 10% aqueous potash was boiled for 2 h 30 min and, after cooling, was acidified with concentrated hydrochloric acid, and the precipitate was filtered off. Yield 0.19 g (almost quantitative). mp 212-214°C (decomp.). Lustrous colorless cubic crystals, mp 216°C (ethanol), sparingly soluble in the usual solvents and readily soluble in alkalies forming yellow solutions. Found %: C 65.00; H 4.51; N 14.43. $C_{16}H_{13}N_3O_3$. Calculated %: C 65.08; H 4.44; N 14.23. A mixture with V gave a depression of the melting point (209°C).

The copper complex salt of the β-monooxime VIIIa was formed by boiling an ethanolic solution of VIIIa with copper acetate. The mixture was filtered hot, and the dark green microcrystalline precipitate was washed on the filter with hot ethanol, acetone, chloroform, and ether. mp 204-205°C (violent decomposition). Found %: N 9.72. $C_{16}H_{12}N_3O_3 \cdot Cu(CH_3COO)$. Calculated %: N 10.08.

3-(1'-Hydroxyiminoacetonyl)-2-imino-1-methylbenzimidazoline (VIIb). An ethanolic solution of 0.74 g (4 mmoles) of Ib was treated with 2 ml of concentrated hydrochloric acid and, with ice cooling, a solution of 0.41 g (6 mmoles) of sodium nitrite in 2 ml of water was slowly added. The white precipitate gradually deposited from the solution. After 30 min, it was filtered off and washed with acetone. Yield 0.85 g (80%). When the mother solution was diluted with water, another 0.2 g of the hydrochloride deposited. The total yield was almost quantitative. Colorless needles, mp 196-197°C (ethanol containing ether). Soluble on heating in ethanol and water. Found %: C 48.90; H 5.18; N 20.55; Cl 13.26. $C_{11}H_{12}N_4O_2 \cdot HCl$. Calculated %: C 49.17; H 4.88; N 20.85; Cl 13.20.

0.7 g of the hydrochloride of VIIb was triturated with an excess of 22% ammonia, and the precipitate of the base was filtered off and washed with water. Yield 0.58 g (89%). Fine yellow needles with mp 137-138°C (decomp., from ethanol). Found %: C 52.52; H 6.00; N 22.66. $C_{11}H_{12}N_4O_2 \cdot H_2O$. Calculated %: C 52.79; H 5.64; N 22.39.

3-(1'-Hydroxyiminoacetonyl)-1-methylbenzimidazolone (the β-monooxime, VIIIb). Obtained in quantitative yield in the same way as VIIIa by boiling VIIb in 10% caustic potash for 5 h. Large colorless crystals with mp 207-208°C (decomp., from ethanol). Found %: C 56.80; H 5.03; N 18.33. $C_{11}H_{11}N_3O_3$. Calculated %: C 56.65; H 4.75; N 18.02. 2,4-Dinitrophenylhydrazone. Dark yellow needles with mp 235-237°C (from ethanol). Found %: C 49.46; H 3.73; N 23.69. $C_{17}H_{15}N_7O_6$. Calculated %: C 49.40; H 3.66; N 23.72.

Copper Complex Salt of the β-Monooxime VIIIb. Brownish green microcrystalline precipitate with mp 212°C (decomp.). Found %: N 11.57. $C_{11}H_{10}N_3O_3 \cdot Cu[CH_3COO]$. Calculated %: N 11.84.

3-α-Cyanobenzylideneamino-9-methyl-2-phenylimidazo[1,2-a]benzimidazole. A suspension of 0.28 g of II in 5 ml of ethanol was treated with 0.25 ml of benzyl cyanide and three drops of a 5% solution of caustic soda, and the mixture was boiled for 25-30 min. The nitroso compound gradually dissolved and then the red solution deposited the reaction product. Yield 0.19 g (50%). Colorless needles with mp 183-184°C (decomp., from dioxane containing ether), sparingly soluble in ethanol, benzene, and chloroform; readily soluble in dioxane. Found %: C 73.30; H 5.15; N 17.78. $C_{24}H_{17}N_5 \cdot H_2O$. Calculated %: C 73.26; H 4.87; N 17.80.

9-Methyl-2-phenylimidazo[1,2-a]benzimidazole-3-azo-1-p-benzoic Acid (III, Ar = C_6H_4COOH-p). a. A solution of 0.5 g (2 mmoles) of II and 0.26 g (2 mmoles) of p-aminobenzoic acid in 4 ml of glacial acetic acid was boiled for 2 h. On the following day, the solution was diluted with water, and the precipitate was filtered off. Yield 0.43 g (57%). mp 305-306°C (dimethylformamide). Found %: C 69.93; H 4.38; N 17.87. $C_{23}H_{17}N_5O_2$. Calculated %: C 69.86; H 4.33; N 17.71.

b. To a solution of 0.14 g of anhydrous sodium carbonate in 5 ml of water were added 0.34 g (2.5 mmoles) of p-aminobenzoic acid and 0.18 g of sodium nitrite in 2 ml of water. The solution was poured into a mixture of 2.5 g of ice and 0.5 ml of concentrated hydrochloric acid, and an ethanolic solution of 0.62 g (2.5 mmoles) of Ia was added. After half an hour, the precipitate that had deposited was filtered off and washed with water, with dilute ammonia solution, and with methanol. Yield 76.5%. Lustrous red needles, mp 306°C (dimethylformamide). The substance was identical with the product obtained from II by method a.

4-Bromobenzene-1-azo-3-(9-methyl-2-phenylimidazo[1,2-a]benzimidazole). At 0-5°C, a solution of 0.18 g (2.5 mmoles) of sodium nitrite in 1.5 ml of water was added to a solution of 0.43 g of p-bromoaniline (2.5 mmoles) in 1.5 ml of water and 1 ml of concentrated hydrochloric acid. Then 0.62 g (2.5 mmoles) of Ia in 2.5 ml of glacial acetic acid was added and the mixture was heated in the water bath for 5-10 min (see [6]). After cooling, the precipitate was filtered off and was washed with water and 10% ammonia solution. Yield 0.91 g (84%). Lustrous bright red needles with mp 295°C (benzene). Found %: C 61.75; H 3.99; Br 18.10; N 16.37. $C_{22}H_{16}BrN_5$. Calculated %: C 61.40; H 3.75; Br 18.57; N 16.28.

2-Phenyl-substituted imidazo[1,2-a]benzimidazoles react similarly with the diazonium salts obtained from sulfanilic acid and from o-, p-, and m-nitroanilines.

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