INVESTIGATIONS OF BENZIMIDAZOLE DERIVATIVES

XXVII.* SYNTHESIS AND REACTION WITH NUCLEOPHILIC REAGENTS OF SOME N-SUBSTITUTED BENZIMIDAZOLES CONTAINING BRANCHED AND HIGH-MOLECULAR-WEIGHT SUBSTITUENTS IN THE 1-POSITION

A. F. Pozharskii, M. M. Medvedeva,
É. A. Zvezdina, and A. M. Simonov

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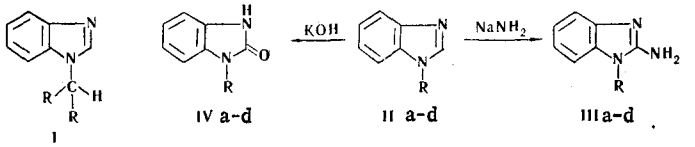
The synthesis of 1-tert-butyl-, 1-nonyl-, and 1-undecylbenzimidazoles is described. The behavior of these compounds with respect to sodium amide and dilute alkali was studied. A number of new 2-aminobenzimidazoles and benzimidazolones were synthesized.

The effect of steric factors on the Chichibabin reaction has hardly been studied. In this paper we set out to ascertain how branched substituents attached to the N atom of benzimidazole affect the amination of the imidazole ring as well as its related hydroxylation [2].

It was previously noted that α-branched substituents (isopropyl [3], α-phenylethyl [4], and cyclohexyl [5]) attached to the N_1 atom have only a small passivating effect on the occurrence of the Chichibabin reaction in the benzimidazole series. This is explained by the fact that all compounds of this type have one conformation (I) in which steric hindrance to amination should not show up. These compounds are therefore usually aminated in good yields, although more prolonged heating and a large excess of sodium amide are sometimes required for this. Thus, for example, we raised the yield of 2-amino-1-isopropylbenzimidazole (IIIa) from 39% [3] to 64% using a 2.5-fold excess of sodium amide in place of 25%.



I

II-IV a R=i-C_3H_7; b R=t-C_4H_9; c R=n-C_9H_{11}; d R=n-$C_{11}H_{23}$

In this connection, it was of interest to ascertain how 1-tert-butylbenzimidazole (IIb), in which the realization of the favorable conformation I is impossible, would behave with respect to nucleophilic agents. For this, we synthesized IIb via the scheme earlier proposed for 1-cyclohexylbenzimidazole [5] starting from tert-butylamine and 2,4-dinitrochlorobenzene. It turned out that amination of IIb in dimethylaniline with 2.5 mole of $NaNH_2$ proceeds with considerably greater difficulty than in the case of IIa, and the yield of 2-amino derivatives does not exceed 21%. (A corresponding amount of hydrogen is evolved.) About 20% of the starting compound is regenerated from the mixture, and the remainder is resinified.

The passivating effect of an N-tert-butyl group in IIb can theoretically have two causes: 1) its +I effect which, to a certain extent, reduces the positive charge on the α-carbon atom necessary for the Chichibabin reaction; and, 2) steric hindrance. The significance of the first factor is apparently low since, judging from the basicity constants, the donor effect of the tert-butyl group in IIb (pK_a 6.08) is the same as that of the dimethylamino group in 5-dimethylaminobenzimidazoles (pK_a ~ 6.1-6.2), which are readily aminated [6]. It is important, however, to note that, despite the clear manifestation of steric hindrance in IIb, even bulky groups such as the tert-butyl group cannot completely suppress the Chichibabin reaction.

*See [1] for communication XXVI.

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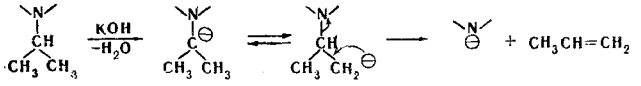
Bulky substituents attached to the N atom of the benzimidazole molecule significantly hinder hydroxylation. When IIb is melted with potassium hydroxide at 250-300°, the molecule is completely decomposed with resinification, and 1-tert-butylbenzimidazolone (IVb) cannot be obtained. The fusion of 1-isopropylbenzimidazole with KOH at 250-290° results in the formation of 23% 1-isopropylbenzimidazolone, while the major reaction product at higher temperatures (300-350°) is benzimidazolone (IV, R = H) (35% yield). The low yield of IVa and the formation of benzimidazolone are a consequence of cleavage of the N-isopropyl group as propylene under the severe reaction conditions; we recorded the evolution of propylene along with hydrogen. The cleavage reaction apparently proceeds via the following mechanism:



Benzimidazole derivatives which contain high-molecular-weight substituents (nonyl and undecyl) in the 1-position are readily aminated and hydroxylated to give good yields of the corresponding 2-amino- and 2-hydroxybenzimidazoles.

EXPERIMENTAL

N-(2,4-Dinitrophenyl)-tert-butylamine. A mixture of 46 g (0.23 mole) of 2,4-dinitrochlorobenzene, 26.3 g (0.193 mole) of crystalline sodium acetate, and 23 ml (about 0.22 mole) of tert-butylamine in 210 ml of alcohol was refluxed for 6 h. Cooling of the reaction mixture gave a yellow precipitate, which was filtered and recrystallized from alcohol to give 31 g (57%) of a product with mp 152-153° (mp 119° [7]; mp 151-153° [8]).

N-(2-Amino-4-nitrophenyl)-tert-butylamine. A mixture of 7 g (0.03 mole) of N-(2,4-dinitrophenyl)-tert-butylamine, 12.5 g (0.5 mole) of $Na_2S \cdot 9H_2O$, and 1.7 g (0.05 mole) of sulfur in 43 ml of water and 76 ml of alcohol was heated for 1 h on a water bath. The mixture was then cooled, and the dark-red oil that separated was triturated to give 4.4 g (71%) of dark-red crystals with mp 99-100° (from aqueous alcohol). Found %: C 57.0; H 7.1; N 20.1. $C_{10}H_{15}N_3O_2$. Calculated %: C 57.4; H 7.2; N 20.1.

1-tert-Butyl-5-nitrobenzimidazole. A total of 3.6 g (0.017 mole) of N-(2-amino-4-nitrophenyl)-tert-butylamine was refluxed for 4 h with 11 ml of 98% formic acid in the presence of several drops of concentrated HCl. The reaction mixture was then diluted with 60 ml of 2% hydrochloric acid and refluxed with activated charcoal. The reaction product was isolated as rose scales by adding concentrated ammonia to the filtrate to give 2.7 g (70%) of a product with mp 160-161° (from alcohol). IR spectrum (mineral oil), cm^{-1}: ν_s 1352, ν_{as} 1528 (NO_2). Found %: C 59.8; H 6.0; N 19.4. $C_{11}H_{13}N_3O_2$. Calculated %: C 60.3; H 6.0; N 19.2.

1-tert-Butyl-5-aminobenzimidazole. 1-tert-Butyl-5-nitrobenzimidazole [8.5 g (about 0.04 mole)] was added to a solution of 36.4 g (0.16 mole) of $SnCl_2 \cdot 2H_2O$ in 35 ml of concentrated HCl. The mixture was heated for 1 h on a water bath, cooled, and treated with 40% NaOH until it gave a strongly alkaline reaction. The resulting precipitate was filtered, washed with cold water, and dried. The amino derivative was isolated by repeated extraction with boiling benzene to give 6.5 g (89%) of a product with mp 153-154° (from benzene). IR spectrum (mineral oil), cm^{-1}: ν_{as} 3404, ν_s 3330; δ 1625 (NH_2). Found %: C 69.6; H 7.8; N 22.5. $C_{11}H_{15}N_3$. Calculated %: C 69.8; H 8.0; N 22.2.

1-tert-Butylbenzimidazole (IIb). A solution of 2.2 g (0.01 mole) of 1-tert-butyl-5-aminobenzimidazole in 25 ml of hydrochloric acid (1:1) was diazotized with a solution of 1.12 g (0.016 mole) of $NaNO_2$ in 3.5 ml of water at −5 to 0°. At the end of the diazotization, 6.5 ml of concentrated HCl was introduced with vigorous stirring into the mixture, followed by a solution of 7.6 g (0.073 mole) of potassium hypophosphite in 8.5 ml of water. The mixture was stirred for another hour, and the solution was then allowed to stand for 24 h in a refrigerator. The resulting KCl precipitate was filtered, and the filtrate was treated with ammonia until it gave a weakly alkaline reaction. The reaction product was then extracted with ether and purified by reprecipitation by base from hydrochloric acid solution to give 1.5 g (74%) of product with mp 59-60° and bp 162-167° (20 mm). Found %: C 72.3; H 8.2. $C_{11}H_{14}N_2 \cdot \frac{1}{2}H_2O$. Calculated %: C 72.1; H 8.3.

The alkylation of benzimidazole with nonyl chloride and undecyl chloride in alcoholic alkali with equimolecular amounts of all reagents was carried out by the method in [9].

1-Nonylbenzimidazole. This was obtained in 67% yields as colorless crystals with mp 21.5-22.5° and bp 200° (6 mm). Found %: C 78.6; H 10.3. $C_{16}H_{24}N_2$. Calculated %: C 78.6; H 9.9.

1-Undecylbenzimidazole (IId). This was obtained in 64% yield and had mp 37-38° and bp 210-211° (8 mm). Found %: C 79.9; H 10.6. $C_{18}H_{28}N_2$. Calculated %: C 79.4; H 10.3. The picrate had mp 101-101.5° (from alcohol).

2-Amino-1-tert-butylbenzimidazole (IIb). A solution of 1.5 g (0.008 mole) of 1-tert-butylbenzimidazole in 7 ml of dimethylaniline (DMA) was added dropwise, while gradually raising the temperature to 140°, to a suspension (heated to 100°) of 0.85 g (0.02 mole) of thoroughly pulverized sodium amide in 2 ml of absolute DMA. The mixture gradually became dark-brown, and hydrogen began to evolve. Hydrogen evolution ceased after 1.5 h. The mixture was cooled, 5 ml of water was added, and the mixture was allowed to stand in the refrigerator. The next day the precipitated 2-amino derivative was filtered, washed with water, benzene (2 ml), and petroleum ether to give 0.34 g (21%) of colorless crystals with mp 162-163° (from benzene). Found %: C 70.4; H 8.2; N 22.6. $C_{11}H_{15}N_3$. Calculated %: C 69.8; H 8.0; N 22.2.

A total of 0.32 g (21%) of starting 1-tert-butylbenzimidazole was isolated from the filtrate after steam distillation of the dimethylaniline. The residue was a black resin.

Amination of 1-Nonyl- and 1-Undecylbenzimidazoles. This was similarly carried out with the difference that, after addition of water to the reaction mixture, the DMA was steam distilled, and the amine was extracted from the residue with benzene and then vacuum distilled.

2-Amino-1-nonylbenzimidazole (IIIc). This was obtained as a thick, gradually crystallizing oil with bp 220-230° (6 mm) which was soluble in all organic solvents. The yield was 70%. Found %: C 74.5; H 9.9. $C_{16}H_{25}N_3$. Calculated %: C 74.1; H 9.7. The picrate had mp 188° (from alcohol).

2-Amino-1-undecylbenzimidazole (IIId). This was obtained in 78% yield as a pale-yellow oil which gradually crystallized to a product with bp 226-229° (5 mm) and mp 52°. Found %: C 74.9; H 10.2. $C_{18}H_{29}N_3$. Calculated %: C 75.3; H 10.2.

1-Isopropylbenzimidazolone (IVa). A mixture of 1 g (6.2 mmole) of IIa and 2.8 g (50 mmole) of fused powdered potassium hydroxide was heated in a Kjeldahl flask in a metal bath. The reaction commenced at 290° and then proceeded uniformly as the temperature dropped to 250°. A gas which burned with a sooty flame, and decolorized potassium permanganate solution and bromine water (apparently propylene) was evolved along with hydrogen. The reaction terminated in 30 min, and a total of 140 ml (6.2 mmole) of gas had evolved. The melt was cooled and treated with 5% hydrochloric acid until it gave an acid reaction with respect to Congo. The precipitate of IVa was filtered and washed with water to give 0.253 g (23%) of colorless crystals with mp 128-129° (from water). IR spectrum (mineral oil): 1695 cm^{-1} (C=O). Found %: C 68.0; H 6.9; N 15.9. $C_{10}H_{12}N_2O$. Calculated %: C 68.2; H 6.9; N 15.9. A mixture of benzimidazole and 1-isopropylbenzimidazole was isolated from the hydrochloric acid solution after neutralization with ammonia. When the reaction was carried out at 250-375°, 33% of benzimidazolone was formed (mp 309-310°, a sample did not depress the melting point of a genuine sample). The rest of the starting compound resinified. Much steam was evolved simultaneously, apparently as a result of metallation of the isopropyl group, and the amount of propylene increased.

Hydroxylation of 1-tert-Butylbenzimidazole. Hydroxylation at 270-300°, despite the evolution of a certain amount of hydrogen, resulted in the formation of a black resin from which a pure compound could not be isolated.

1-Nonylbenzimidazolone (IVc). This was obtained by hydroxylation of IIc, in analogy with IVa, to give 75% of colorless crystals with mp 94° (from hexane). IR spectrum (mineral oil): 1694 cm^{-1} (C=O). Found %: C 73.6; H 9.3. $C_{16}H_{24}N_2O$. Calculated %: C 73.8; H 9.3.

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