FORMATION OF A BENZIMIDAZOLE RING ACCOMPANIED BY THE CLEAVAGE OF A NITROGEN-CARBON BOND

A. S. Petrov, I. N. Somin, and S. G. Kuznetsov

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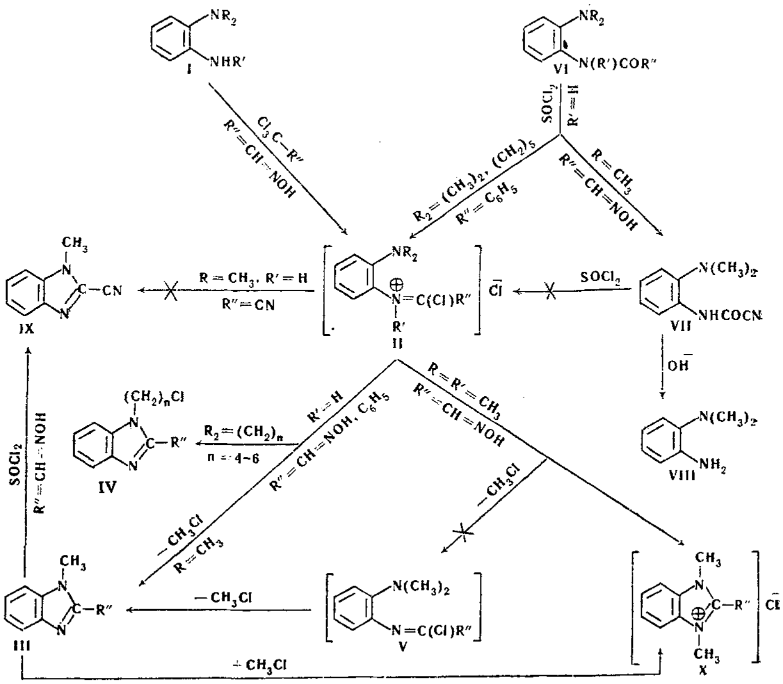
The reaction of thionyl chloride with arylamides of aromatic acids, which usually gives rise to stable imidoyl chlorides, leads in the case of N-(o-dimethylaminophenyl)benzimide and N-(o-piperidinophenyl)-benzimide to the formation of a benzimidazole ring, which is accompanied by the cleavage of the nitrogen-carbon bond. This reaction and the reaction of chloral oxime with o-dialkylaminoanilines studied previously, which also leads to the formation of a benzimidazole ring, are compared with the Braun reaction. It has been shown that when thionyl chloride reacts with N-(o-dimethylaminophenyl)isonitrosoacetamide, no formation of a benzimidazole ring takes place and only N-(o-dimethylaminophenyl)carbamoyl cyanide is formed.

We have recently found that the reaction between chloral oxime and N,N-di- and N,N,N'-trisubstituted o-phenylenediamines leads to the formation of a benzimidazole ring, which is accompanied by the cleavage of a nitrogen-carbon bond and the formation of a carbon-chlorine bond. It was assumed that the conversion of I into III or IV (see scheme) takes place through intermediate imidoyl chlorides of type II or V [1–3].



Imidoyl chlorides are generally obtained from amides by the action of phosphorus pentachloride, thionyl chloride, or phosgene [4, 7]. Our hypothesis relating to the mechanism of ring-closure could thus be confirmed by the independent synthesis of the benzimidazole ring from the corresponding amides under

isonitrosoacetamide (VI, R" = CH=NOH) complications connected with the high sensitivity of the hydroxyimino group to this reagent might be expected. In fact, the action of thionyl chloride on N-(o-dimethylaminophenyl) isonitrosoacetamide (VI, R = CH_3, R' = H, R" = = CH=NOH) gave only the dehydration product—N-(o-dimethylaminophenyl)carbamoyl cyanide (VII)—in almost quantitative yield. The structure of the latter was confirmed by its ready hydrolysis to o-dimethylaminoaniline (VIII). The analogous cyanide is formed by the action of thionyl chloride on isonitrosoacetanilide [8]. It must be stressed that this reaction forms neither the oxime of 2-formyl-1-methylbenzimidazole (III, R" = CH=NOH) nor the product of its transformation—2-cyano-1-methylbenzimidazole (IX) [9]. The formation of the latter could be expected not only from the oxime (III → IX) but also as a result of the further conversion of the cyanide VII via the corresponding imidoyl chloride II. Performing the reaction under conditions leading to the formation of the imidoyl chlorides (VI → II → III or IV). However, in the case of more severe conditions leads, however, to resinification of the mixture, although 2-cyano-1-methylbenzimidazole is stable under these conditions [9].

In view of this, to solve the problem presented we used model compounds—benzanilide derivatives containing tertiary amino groups in the ortho position of the N-phenyl nucleus (VI, R' = H; R" = C_6H_5 ; R_2 = = $(CH_3)_2$, $(CH_2)_5$). Although, like other purely aromatic imidoyl chlorides, N-phenylbenzimidoyl chloride is thermally stable [4, 5], its o-amino analogs proved to be unstable, as was expected. The action of thionyl chloride on N-(o-dimethylaminophenyl)- and N-(o-piperidinophenyl)benzamides and subsequent treatment with water yielded 1-methyl- and 1-(5'-chloropentyl)-2-phenylbenzimidazoles with yields of 64 and 58%, respectively, (VI → II → III and IV, R" = = C_6H_5). We detected no appreciable amounts of the initial amides, which could have been formed by the hydrolysis of the imidoyl chlorides if the latter were stable under the conditions of the process.

The production of a benzimidazole ring taking place with the intermediate formation of imidoyl chlorides and accompanied by the cleavage of a N–C and the formation of a C–Cl bond is a peculiar variant of the Braun reaction [4, 5, 7, 10].

$$R{-}NHCOR' \xrightarrow{PCl_5, SOCl_2} R{-}N{=}CCl{-}R' \xrightarrow{t^\circ} RCl + R'CN$$

$$(R{=}Alk,\ R'{=}Ar)$$

Since the cleavage of imidoyl chlorides by the Braun reaction is carried out under more severe conditions than those which we used in the present and previous investigations [1–3], it is obvious that the closure of the ring takes place considerably more rapidly. This conclusion is strikingly confirmed by the results of an investigation of the reaction of chloral oxime with N,N,N'-trimethyl-o-phenylenediamine [2]. In this case, only the oxime of 2-formyl-1,3-dimethylbenzimidazolium chloride was isolated (I → II → X) and no 1-formyl-1-methylbenzimidazole oxime was detected. The latter could be formed (I → II → V → → III) only if Braun cleavage (II → V) took place more rapidly or at a rate comparable with that of the direct closure of the ring (II → X). There is no doubt, however, that the formation of a stable aromatic ring is considerably more favorable energetically than Braun linear fragmentation. The possibility of the formation of a benzimidazolium salt by the quaternization of a tertiary benzimidazole (III → X) with methyl chloride must be excluded. In actual fact, in the reaction of chloral oxime with o-dimethylaminoaniline (I → II → III) [1, 2], where a tertiary benzimidazole and methyl chloride are formed, no quaternization takes place under the conditions of the process.

EXPERIMENTAL

Reaction of N-(o-dimethylaminophenyl)isonitrosoacetamide (VI, R = CH_3, R' = H, R" = CH=NOH) with thionyl chloride. In small portions, 0.17 g (0.0007 mole) of the hydrochloride of VI [11] was added to 0.5 ml of thionyl chloride. The hydrochloride dissolved at first, but a precipitate rapidly formed. The mixture was heated at 60° C for 15 min, the excess of thionyl chloride was distilled off in vacuum, and the residue was treated with ether and filtered. The yield of the hydrochloride of N-(o-dimethylaminophenyl)carbamoyl cyanide (**VII**) was 0.15 g (96%); mp 135° C (decomp., from ethanol). The substance is readily soluble in water, moderately soluble in acetone, and insoluble in benzene and ether. Found, %: N 18.48, 18.60; Cl 15.80, 15.85. Calculated for $C_{10}H_{11}N_3 \cdot HCl$, %: N 18.67; Cl 15.76. When the reaction mixture was heated for a long time (80° C, 3 hr), a dark resinous mass was formed from which no individual products could be isolated.

Compound **VII** (0.15 g) was treated with 10 ml of 5% caustic soda solution and extracted with ether; the ethereal solution was dried and an ethereal solution of picric acid was added to it. The picrate, with mp 138° C, was shown by a mixed melting point test to be identical with an authentic sample of the picrate of **VIII**.

Reaction of N-(o-dimethylaminophenyl)benzamide and of N-(o-piperidinophenyl)benzamide (VI, R' = H, R" = C_6H_5, R_2 = $(CH_3)_2$, $(CH_2)_5$) with thionyl chloride. The hydrochloride of compound **VI** (R = CH_3) was obtained from the base [12] by the action of hydrogen chloride in ether. Mp 168–169° C (from acetone). Found, %: Cl 12.81, 12.95. Calculated for $C_{15}H_{16}N_2O \cdot HCl$, %: Cl 12.82.

The hydrochloride of compound **VI** (R_2 = $(CH_2)_5$) was obtained by heating the free amide [13, 14] in 1N HCl. Mp 191–192° C (from a mixture of ethanol and ether). Readily soluble in chloroform, benzene and ethanol; insoluble in ether. It crystallizes from dilute hydrochloric acid. Found, %: Cl 11.17, 11.20. Calculated for $C_{18}H_{20}N_2O \cdot HCl$, %: Cl 11.23.

A mixture of 1.8 g (0.0065 mole) of the hydrochloride of **VI** (R = = CH_3) and 2 ml of thionyl chloride was heated at 60–65° C for 3 hr. The residue obtained after the distillation of the thionyl chloride in vacuum was dissolved in water, and the solution was neutralized with potassium carbonate to a weakly alkaline reaction, after which the precipitate was filtered off and washed with water. The yield of 1-methyl-2-phenylbenzimidazole (**III**, R" = C_6H_5) was 0.87 g (64%); mp 97° C (from ether). A mixture with an authentic sample [15] gave no depression of the melting point. The hydrochloride was isolated from a similar experiment by the dilution with dichloroethane of the residue obtained after the distillation of the thionyl chloride. After 2 hr, the precipitate was filtered off and washed with dichloroethane. Yield was 63%; mp 200° C (from dichloroethane). Similarly, 1-(5'-chloropentyl)-2-phenylbenzimidazole (**IV**, R" = C_6H_5, n = 5) was obtained in 58% yield from the hydrochloride of **VI** (R_2 = $(CH_2)_5$). Mp 72° C (from petroleum ether). Found, %: N 9.53, 9.62. Calculated for $C_{18}H_{19}ClN_2$, %: N 9.36. Hydrochloride mp 89° C (from 1N HCl). Found, %: Cl 10.47, 10.51. Calculated for $C_{18}H_{19}ClN_2 \cdot HCl$, %: Cl 10.59.

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Institute of Toxicology
Ministry of Health of the
USSR, Leningrad