RESEARCH ON BENZIMIDAZOLE DERIVATIVES

XXXIX.* NUCLEOPHILIC SUBSTITUTION IN A SERIES OF 2-ARYL- AND 2-ALKYLBENZIMIDAZOLE DERIVATIVES

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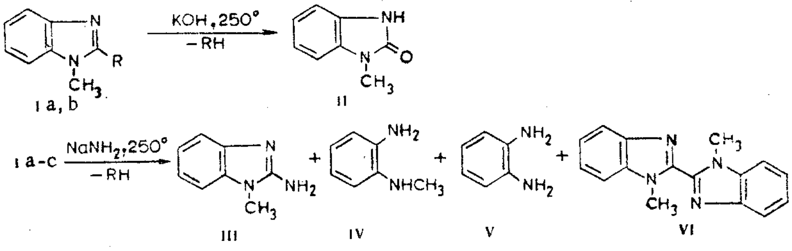
The corresponding 2-hydroxy- and 2-aminobenzimidazoles are formed when 1-methyl-2-phenyl- and 2-alkylbenzimidazoles are fused with potassium hydroxide or sodium amide. N-Dealkylation, dimerization of the benzimidazole derivatives, and cleavage of the heterocyclic ring accompany the principal trends of these transformations.

In addition to the known nucleophilic substitution reactions of halogen [2] and sulfo groups [1, 3] attached to the meso carbon atom of the benzimidazole ring, we recently showed the possibility of replacement of the phenyl group of 1-methyl-2-phenylbenzimidazole (Ia) by hydroxyl or amino groups when Ia is fused with potassium hydroxide or sodium amide [4]. Similar replacement of a phenyl group by an amino group was previously observed in the reaction of 6-phenylphenanthridine [5] and 9-phenyl-1,3-dimethyl-2,10-diazaphenanthrene [6] with potassium amide in liquid ammonia.†

A more detailed investigation of the reaction of Ia with nucleophilic reagents made it possible to establish that its reaction with potassium hydroxide leads to 1-methyl-2-benzimidazolone (II) and benzene (compare this with the hydroxylation of 1-methylbenzimidazole [7]). On the other hand, the reaction of Ia with sodium amide proceeds ambiguously: in addition to 2-amino-1-methylbenzimidazole (III), we detected products of opening of the benzimidazole ring – N-methyl-O-phenylenediamine (IV) and o-phenylenediamine (V) – and a small amount of bis(1-methyl-2-benzimidazolyl) (VI).

Continuing our study of these transformations we subjected 1-methyl-2-benzylbenzimidazole (Ib) and 1,2-dimethylbenzimidazole (Ic) to reaction with nucleophilic reagents. It was found that Ib is converted to II in good yield (70%) on reaction with potassium hydroxide. Compounds Ib and Ic react like Ia with sodium amide.



I a $R=C_6H_5$; b $R=CH_2C_6H_5$; c $R=CH_3$

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*See [1] for communication XXXVIII.

†According to our data, Ia does not react with potassium amide in liquid ammonia when potassium nitrate is either present or absent.

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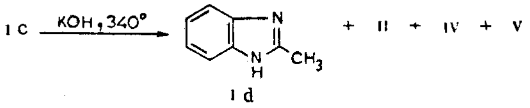
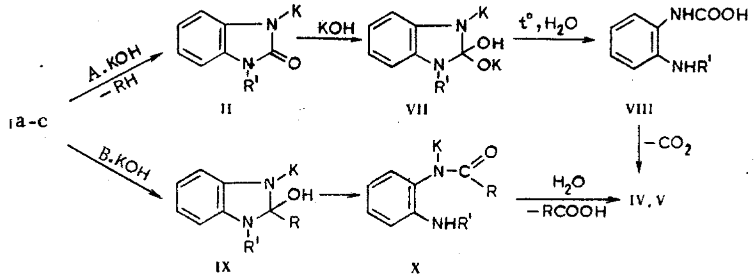
Compound Ic reacts with potassium hydroxide at higher temperature than Ia, b; in this case N-dealkylation and ring opening to give diamines IV and V accompany nucleophilic substitution of the alkyl group of Ic. 2-Methylbenzimidazole (Id) was also detected in the products of this reaction.



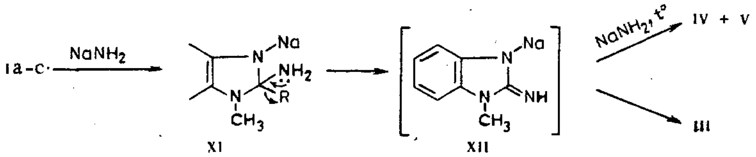
These observations provide a basis for the assumption that 2-methylbenzimidazole is an intermediate in the series of transformations of Ic to o-phenylenediamine. Benzimidazole derivatives Ia and Ib apparently also undergo similar transformations on reaction with sodium amide, and this explains the formation of diamine V.

Opening of the benzimidazole ring under the influence of nucleophiles is possible via two pathways, A and B (see [8]).



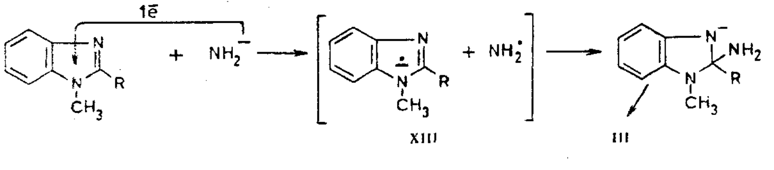
It should be noted that we did not detect the presence of carboxylic acids (acetic, phenylacetic, or benzoic) in the reaction mixture in a single case; these acids would have been formed in the case of ring cleavage via scheme B. On the other hand, detachment of the substituent attached to the meso carbon atom of benzimidazole constitutes evidence in favor of scheme A, according to which diamines IV and V are formed as a result of decarboxylation of carbamic acids (VIII). We were unable to isolate acid VIII, but after treatment of the reaction mixture with water and acidification of the alkaline filtrate and subsequent heating we observed the evolution of carbon dioxide and the formation of diamines IV and V, evidently as a result of decomposition of unstable acid VIII. Scheme A is also confirmed by the fact that the presence of diamines IV and V is detected after the action of excess potassium hydroxide on 1-methyl-2-benzimidazolone at 340°.

Diamines IV and V were not detected in the products of the reaction of amine III with excess sodium amide. It might be assumed that an intermediate (XII) is formed in the reaction of Ia-c with sodium amide and that this intermediate is subsequently primarily stabilized by conversion to the sodium salt of amine III and undergoes partial cleavage to diamines IV and V.

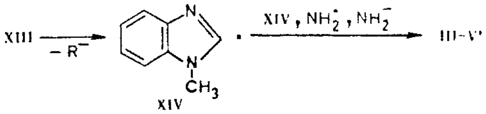


Benzimidazoles Ia, b do not react with sodium amide in the presence of solvents. Small amounts of VI and diamines IV and V are formed only on prolonged refluxing of Ia, b with sodium amide in dimethylaniline; a large amount of the starting benzimidazole (Ia or Ib) remain unchanged.

The formation of bis(benzimidazolyl) VI in the reaction of Ia, c with sodium amide can be explained by generation of free radicals during the reaction. It is known [9] that many heterolytic substitution reactions proceed with the intermediate formation of an ion radical as a result of electron transfer from the nucleophile to the substrate. According to these concepts, the reaction of Ia-c with a nucleophile may lead to the formation of radical pair XIII, the recombination of which leads to XII; the subsequent transformations of the latter proceed via a mechanism of the ionic type in accordance with the scheme presented below.



One also cannot exclude the possibility that ion radical XIII is evidently capable, on emergence from the reaction cage, of splitting out a substituent in the form of an anion and formation of free radical XIV, the transformations of which under the reaction conditions lead to bis(benzimidazolyl) VI, substitution products, N-demethylation, and ring opening.



However, our data do not provide sufficient grounds for an unambiguous conclusion in favor of ionic or radical character of the observed transformations.

EXPERIMENTAL METHOD

Reaction of 2-Substituted Benzimidazoles Ia-c with Potassium Hydroxide. A) A mixture of 1.44 g (7 mmole) of Ia and 1.4 g (25 mmole) of fused potassium hydroxide was heated to 250° and held at this temperature for 30 min. The benzene formed during the reaction was identified from its melting point, boiling point, and IR spectrum. After cooling, the fused material was dissolved in 30 ml of water, the solution was filtered, the filtrate was acidified with dilute HCl, and the precipitate was removed by filtration, dried, and crystallized from alcohol to give 0.61 g (60%) of II with mp 191-192° (mp 191-192° [7]).

B) A mixture of 1.11 g (5 mmole) of Ib and 1.4 g (25 mmole) of potassium hydroxide was fused at 250° for 40 min, after which the mixture was cooled, and the fused material was worked up by the method described above to give 0.5 g (69%) of II. The toluene generated during the reaction was identified from its boiling point and IR spectrum.

C) A mixture of 1.46 g (10 mmole) of Ic and 2.8 g (0.05 mole) of potassium hydroxide was heated to 340° and held at this temperature for 1 h. It was then cooled, and the fused material was treated with water and filtered. The filtrate was neutralized with dilute HCl and extracted with chloroform. The chloroform solution of the mixture of the reaction products was chromatographed with a column filled with activity III aluminum oxide (Brockmann classification) with elution with chloroform, and the eluate was worked up to give 0.11 g (8%) of IV, 0.14 g (10%) of Id, 0.2 g (13%) of V, and 0.7 g (46%) of II.

Reaction of 2-Substituted Benzimidazoles Ia-c with Sodium Amide. A mixture of 10 mmole of Ia-c and 2 g (50 mmole) of sodium amide was heated in a nitrogen atmosphere to 250° and maintained at this temperature for 1 h. The mixture was then cooled, and the fused material was treated with water. The precipitated I was removed by filtration, and the filtrate was extracted with chloroform. The extract was combined with precipitate I and chromatographed with a column filled with aluminum oxide (elution with chloroform). Workup of the eluate gave 2-amino-1-methylbenzimidazole (III) as well as IV, V, and VI. The yields of III were as follows: 0.84 g (56%) from Ia, 0.78 g (52%) from Ib, and 0.6 g (40%) from Ic.

Compounds IV, V, and VI were identified with known samples by means of chromatography in a thin layer of aluminum oxide. The melting points of IV, VI, and the dihydrochloride of V were in agreement with the literature values.

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