STUDIES OF BENZIMIDAZOLE DERIVATIVES

XX. Transformations During the Reaction Between Nitrosyl Sulfuric Acid and 2-Aminobenzimidazole*

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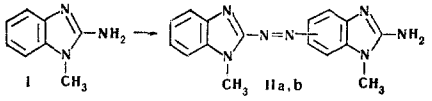
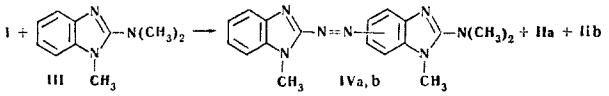
It was found that the formation of 2,5'- and 2,6'-azobenzimidazoles, formed during the action of nitrosyl sulfuric acid on 2-amino-1-alkyl (phenyl, benzyl) benzimidazoles, occurs by azo combination of the extremely active salt of benzimidazole-2-diazonium obtained at first with the original amine. The azo compound is formed from 2-aminobenzimidazole substituted in position 5 and 6 only in the presence of 2-dimethylamino-1-methylbenzimidazole or other azo constituents. In the presence of substitutes, which hinder azo combination, 2,2'-diazoaminobenzimidazoles stable also in strongly acid medium may constitute the product of the reaction.

It has recently been shown [2] that during the interaction between nitrosyl sulfuric acid (NSA) and 2-amino-methylbenzimidazole (I) in medium of sulfuric acid and phosphoric acids [3] the derivatives of 2,5'- and 2,6'-azobenzimidazole (IIa and IIb) are obtained.



IIa 2,5'-azo compound
IIb 2,6'-azo compound

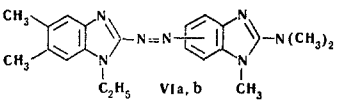
When the study of this conversion was continued, it was established that the reaction proceeds in an analogous manner if NSA reacts on a mixture of equimolecular quantities of I and 2-dimethylamino-1-methylbenzamidazole (III). The latter does not interact with the above-mentioned reagent, which eliminates the possibility that the process involves condensation of the nitrosoderivatives of I or III with the initial amine. As a result of the reaction four azo compounds are formed, IIa, IIb, IVa, and IVb.



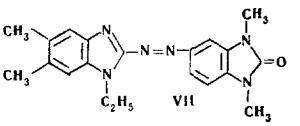
IVa, 2,5'-azo compound
IVb, 2,6'-azo compound

One might suggest that during the reaction 2-amino-1-methylbenzimidazole is converted into the diazo compound** which possesses such high activity that under the experimental conditions it rapidly participates in azo combination with the second molecule of I or III in position 5 and 6. However, the possibility that the second stage of the reaction proceeds requires confirmation, as compound III does not react with such an active diazo compound as, for example, the salt of 2,4-dinitrobenzenediazonium.

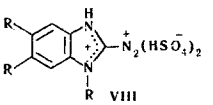
In order to provide evidence for the above-mentioned suggestion, NSA was introduced into a solution of mixture of two amines*: 2-amino-5,6-dimethyl-1-ethylbenzamidazole (V), which may participate in the conversion only as a diazo constituent, and compound III(azo constituent). Two azo compounds were obtained (VIa and VIb). The structure of compound VIa was demonstrated by reductive cleavage, and the structure of compound VIb was established by conversion of the mixture of these isomers (by methylation and hydrolysis of the product of quaternization) into the 5(6)-azo derivative of benzimidazolone (VII), also obtained by counter synthesis.



VIa, 2,5'-azo compound
VIb, 2,6'-azo compound



These data indicate that the salts of benzimidazole-2-diazonium have the ability to undergo combination, which apparently is determined by the high electrophilic nature of the radical associated with the diazo group. The latter apparently is caused by protonation of the imidazole ring of the salt in a medium of concentrated acids (see VIII).



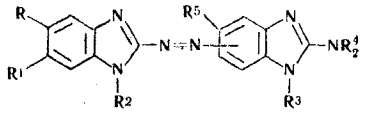
The reaction with NSA is prevalent with other 2-aminobenzimidazoles. It was found that the nature of the substitutions in position 1 and in the benzene nucleus essentially influences the course of the given transformation. In the presence of a nitro group or

*For part XIX, see [1].

**It may be found at the beginning of the experiment (before the formation of the deep color) by combination with the R-salt.

*Diazonium salt, formed from V and extremely nonstable. The yield falls if compound III is introduced into the reaction mixture a short time after the addition of NSA.

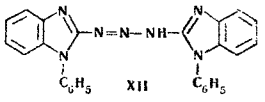
2, 5'- and 2, 6'-Azobenzimidazoles



Compound	Position of the azo group	R	R_1	R_2	R_3	R_4	R_5	Mp, °C (solvent)	Empirical formula	Found, %			Calculated, %			Yield, %
										C	H	N	C	H	N	
IVa	2.5′	H	H	CH_3	CH_3	CH_3	6′-H	195—196 (Benzene + petroleum ether)	$C_{18}H_{19}N_7$	64.37	5.86	29.39	64.85	5.74	29.41	48
IVb	2.6′	H	H	CH_3	CH_3	CH_3	5′-H	235 (Benzene)		64.45	5.49	29.54	64.85	5.74	29.41	
VIa	2.5′	CH_3	CH_3	C_2H_5	CH_3	CH_3	6′-H	212 (Benzene + petroleum ether)	$C_{21}H_{25}N_7$	67.30	6.76	26.33	67.18	6.71	26.11	93
VIb	2.6′	CH_3	CH_3	C_2H_5	CH_3	CH_3	5′-H	253—254 (Benzene)		67.21	6.96	25.97	67.18	6.71	26.11	
IX	2.6′	CH_3	H	CH_3	CH_3	H	5′-CH_3	294—295 (Pyridine)	$C_{18}H_{19}N_7$	64.93	5.75	29.04	64.85	5.74	29.41	80
Xa	2.5′*	H	H	$C_6H_5CH_2$	$C_6H_5CH_2$	H	6′-H	303—304 (Pyridine)	$C_{28}H_{23}N_7$	73.21	5.16	21.81	73.50	5.07	21.43	87
Xb	2.6′*	H	H	$C_6H_5CH_2$	$C_6H_5CH_2$	H	5′-H	306—307 (Alcohol)		73.41	5.18	21.57	73.50	5.07	21.43	
XIa	2.5′*	H	H	C_6H_5	C_6H_5	H	6′-H	256—258 (Aqueous alcohol)	$C_{26}H_{19}N_7$	72.98	4.49	22.86	72.71	4.46	22.83	36
XIb	2.6′*	H	H	C_6H_5	C_6H_5	H	5′-H	267—268 (Alcohol)		72.68	4.47	22.94	72.71	4.46	22.83	

*The given compounds are related to the series of 2,5' and 2,6'-azobenzimidazoles based on a comparison of their solubility and UV absorption spectra with analogous properties of azobenzimidazoles of known structure.

azo group in position 5 or 6 the reaction does not proceed. The action of NSA on 2-amino-1, 5-dimethylbenzimidazole leads to the formation of the 6-azo derivatives (IX), and 2-amino-1-benzylbenzimidazole is converted into a mixture of azo compounds (Xa and Xb). 2-Amino-1-phenylbenzimidazole forms a mixture of two azobenzimidazoles (XIa and XIb) and 2, 2'-diazoamino compounds (XII). A derivative of triazene (XIII) is obtained also from compound V, of only 0.5 mole NSA is introduced into the reaction mixture.



XII

As distinct from 2, 5'- and 2, 6'-azobenzimidazoles, 2, 2'-diazoamino compounds of the benzimidazole series on dissolving in concentrated H_2SO_4 do not form an intense dark-blue color which is characteristic of the former compounds*. Their stability in strongly acid medium is worthy of note. This stability is probably an account of the fact that protonation of the diazoamino group, giving rise to the possibility of cleavage [5], is hindered here the effect of the positively charged imidazole ring. During the interaction with I and III and also with β-naphthol in sulfuric acid compounds XII and XIII do not form azo compounds. Thus, participation of diazoaminocompounds as intermediate products during azo combination in this case should be considered as being exceptional.

EXPERIMENTAL

Preparation of azobenzimidazoles. a) A 0.01 mole quantity of the 2-amino derivative of benzimidazole** was dissolved on cooling with ice in 5–10 ml of conc H_2SO_4, and during vigorous shaking a solution of 0.005–0.01 mole nitrosyl sulfuric acid in conc H_2SO_4† and 10–12 ml phosphoric acid (d. 171) was added. The mixture was agitated on cooling for a further 15 min, and it was then left for 3–4 hr at 20° C, after which it was poured onto ice, and made alkaline with soda. The solution was heated almost to boiling and filtered hot. The precipitate was washed with water and dried at 60–70° C.

b) A 1 mole quantity of NSA was allowed to react with a mixture of equimolecular quantities of 2-amino- and 2-dimethylamino derivatives of benzimidazole. Subsequent procedures were similar to those described above.

Separation of isomeric azo compounds. In order to separate IVa and IVb‡ and VIa and VIb the mixture was dissolved in benzene with heating and slowly cooled. The precipitate which was almost pure 2,5'-azo compound was separated, washed with benzene, recrystallized from benzene, and the stable solvate was disrupted by heating at 130–140° C. The benzene mother liquor was diluted with petroleum ether, discarding the first normally oily fractions. In the precipitate was the 2,6'-isomer which was recrystallized from benzene with petroleum ether.

In order to separate compounds Xa and Xb the mixture was crystallized from pyridine. In order to separate XIa and XIb the mixture was crystallized from alcohol. The more soluble 2,6'isomer was extracted with ether in both cases.

The azobenzimidazoles are crystalline compounds and are dark red in color.

5-Nitro-2-dimethylamino-1-methylbenzimidazole. 5-Nitro-2-chloro-1-methylbenzimidazole was heated with dimethylamine and a small quantity of alcohol in a sealed ampul for 3 hrs at 90–95° C (see [6]). Yield, 89%. Bright yellow flakes with an mp of 149–150° C (from alcohol). Found, %: N 25.63. Calculated for $C_{10}H_{12}N_4O_2$, %: N 25.44.

5-Amino-2-dimethylamino-1-methylbenzimidazole. a) The nitro-derivatives was reduced with tin in hydrochloric acid. **Dihydrochloride.** Snow-white needles with an mp of 322–323° C (from a mixture of alcohol and ether). Found, %: Cl 26.76. Calculated for $C_{10}H_{14}N_4 \cdot 2HCl$, %: Cl 26.94. **Dipicrate**: Bright-yellow prisms with an mp of 179–180° C (from alcohol). Found, %: N 21.38. Calculated for $C_{10}H_{14}N_4 \cdot 2C_6H_3N_3O_7$, %: N 21.60.

b) Compound VIa was reduced with stannous chloride in hydrochloric acid. From the reaction mixture were isolated compound V (yield, 85%) and a diamine in the form of the dipicrate (yield, 62%), identical to the compound obtained according to method (a).

1',3',5,6-Tetramethyl-1-ethyl-benzimidazole-2-azo-5'(6')-benzimidazolone (VII). a) NSA (1 mole) in a medium of conc H_2SO_4 and phosphoric acid reacts with equimolecular quantities of compound **V** [8] and 1,3-dimethylbenzimidazolone. Yield, 79%. Dark red flakes (from benzene) with mp 245–246° C (after prolonged heating in order to disrupt the solvate). Found, %: C 65.89; H 6.34; N 23.23. Calculated for $C_{20}H_{22}N_6O$, %: C 66.28; H 6.12; N 23.19.

b) An alcoholic solution of compound VIa and VIb and methyl iodide (1 mole) were gradually heated to boiling. The residue was dissolved in water, an equal volume of 20% alkali was added, and the mixture was heated in a boiling water bath until dimethylamine ceased to be formed. Mp, 245–246° C (from benzene). Compounds, obtained according to method (a) and (b) were identical.

1,1'-Diphenyl-2,2'-diazoaminobenzimidazole (XII). 1-Phenyl-2-aminobenzimidazole reacts with nitrosyl sulfuric acid (1 mole) as described above, only the reaction proceeds at a slower rate (4–5 hr). The product of the reaction was treated with boiling alcohol and the precipitate of compound XII was removed by filtration. Yield, 31%. Shining yellow needles (from pyridine) with a mp of 312–313° C. Found, %: N 22.71. Calculated for $C_{26}H_{19}N_7$, %: N 22.83. Compounds XIa and XIb were isolated from the alcoholic solution in the form of red needles.

5,5',6,6'-Tetramethyl-1,1'-diethyl-2,2'-diazoaminobenzimidazole (XIII). The compound was obtained from V by the action of 0.5 mole NSA. Dark red flakes with an mp of 293–294° C. During vigorous reduction of the substance the original amine is formed with a yield of 68%. Found, %: C 68.20; H 7.16; N 25.26. Calculated for $C_{22}H_{27}N_7$, %: C 67.84; H 6.99; N 25.17.

*The recently obtained 2, 2'-azobenzimidazoles [4] also do not form a similar color.

**See [6] for the synthesis of 1-substitutions of 2-aminobenzimidazole.

†The solution was prepared as described in [7]. It can be used over a long period.

‡At first IVa and IVb were separated from a mixture of IIa and IIb (44% yield) formed simultaneously by extraction with benzene.

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