

INVESTIGATION OF BENZIMIDAZOLE DERIVATIVES

XXX.* TRANSFORMATIONS OF BROMO-SUBSTITUTED 2-AMINO-BENZIMIDAZOLES ON REACTION WITH NITROSYLSULFURIC ACID

S. N. Kolodyazhnaya, A. M. Simonov,
and I. G. Uryukina

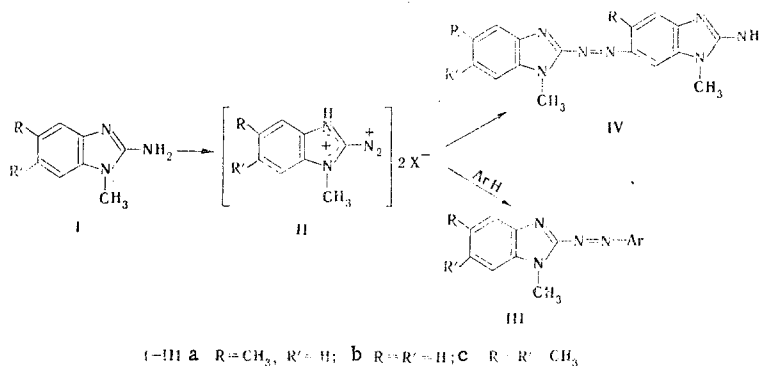
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Under the influence of nitrosylsulfuric acid, 5- and 6-bromo-substituted 2-amino-1-methylbenzimidazoles are converted, as a result of self-coupling, to, respectively, 2',5- and 2',6-azobenzimidazoles, which are resistant to reductive cleavage. 5,6-Dibromo-2-amino-1-methylbenzimidazole forms similarly constructed azo compounds by splitting out of one of the bromine atoms. The behavior of bromo-substituted 2-aminobenzimidazoles toward nitrosylsulfuric acid in the presence of arenes was studied.

It has been shown that unstable highly active benzimidazole-2-diazonium salts (II) are formed during the action of nitrosylsulfuric acid (NSA) on 2-amino-1-alkylbenzimidazoles (I) in concentrated sulfuric acid. If $R = R' = H$, or $R = CH_3$ and $R' = H$, self-coupling [2,3] may then occur to give derivatives of 2',5- or 2',6-azobenzimidazoles (IV, for example); when $R = R' = CH_3$, II can undergo azo coupling with arenes, previously introduced into the reaction mixture [4], to give 2-areneazobenzimidazoles (III). Moreover, the activity of II proved to be so high that they could be introduced into reaction with toluene and benzene, which, up until now, could not be used as azo components (see [5,6]).

During a further study of these transformations, it was found that the possibility of the preparation of III in the case of 5- or 6-unsubstituted I ($R = R' = H$; $R = CH_3$, $R' = H$) is determined by the ratio of the rates of two competitive reactions: self-coupling and coupling with the arene. It turned out that benzene and toluene give only traces of III, while the reaction gives appreciable yields of III with both xylene and mesitylene (Table 1).

The data presented in the table demonstrate that the activities of the 5 and 6 positions in the 2-aminobenzimidazolium cation are comparable to that of mesitylene, while a methyl group in the 5 position lowers the yield of areneazobenzimidazole by facilitating self-coupling.



*See [1] for communication XXIX.

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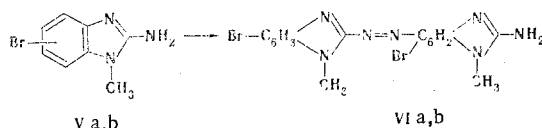
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TABLE 1. 2-Areneazo-5-R-6-R'-benzimidazoles (III)*

| R | R' | Ar | Mp, °C (from petroleum ether) | Empirical formula | Found, % | | | Calc., % | | | Yield, % | |
|-----------------|-----------------|---|----------------------------------|--|----------|-----|------|----------|-----|------|----------|----|
| | | | | | C | H | N | C | H | N | III | IV |
| H | H | 2,4,6-(CH ₃) ₃ C ₆ H ₂ | 139—140 | C ₁₇ H ₁₈ N ₄ | 73,6 | 6,3 | 20,2 | 73,4 | 6,5 | 20,1 | 40 | 43 |
| H | H | 2,4-(CH ₃) ₂ C ₆ H ₃ | 130—131 | C ₁₆ H ₁₆ N ₄ | 73,2 | 6,2 | 21,5 | 72,7 | 6,1 | 21,2 | 21 | 49 |
| CH ₃ | H | 2,4,6-(CH ₃) ₃ C ₆ H ₂ | 144 | C ₁₈ H ₂₀ N ₄ | 74,2 | 7,3 | 19,3 | 73,9 | 6,9 | 19,2 | 18 | 57 |
| CH ₃ | H | 2,4-(CH ₃) ₂ C ₆ H ₃ | 136—137 | C ₁₇ H ₁₈ N ₄ | 73,3 | 6,5 | 20,4 | 73,4 | 6,5 | 20,1 | 12 | 60 |
| CH ₃ | CH ₃ | 2,4,6-(CH ₃) ₃ C ₆ H ₂ | 157—158 | C ₁₉ H ₂₂ N ₄ | 74,8 | 7,6 | 18,1 | 74,5 | 7,2 | 18,3 | 73 | — |

*The compounds were obtained via the method in [4]. After extraction of the azo compound (III) with benzene, the insoluble IV was washed with alcohol; the benzene extract was chromatographed with a column filled with Al₂O₃.

It seemed of interest to ascertain how the reaction with NSA would proceed with amines containing a ring-deactivating substituent, for example, a bromine atom in the 5 or 6 position (V) [7]. It was found that, in this case, the reaction proceeds more slowly and that it is necessary to increase the experimental time to 8-10 h. In the absence of other azo components, the reaction products are brightly colored substances, to which the azo compound structure VI (i.e., self-coupling products) should be assigned on the basis of the results of analysis and UV spectroscopy.



Va 5-bromo derivative VIa 5,5'-dibromo-2',6'-azo derivative
 Vb 6-bromo derivative VIb 6,6'-dibromo-2',5'-azo derivative

Although VI do not give the characteristic blue coloration when they are dissolved in concentrated sulfuric acid,* the form of the absorption curves and, particularly, the position and character of the long-wave band are in agreement with the spectral data of previously studied azo compounds [3] (Fig. 1). We note that the position of the long-wave maximum of azobenzimidazoles is relatively slightly dependent on the nature of the substituents in the benzene ring and those attached to the N atom of the imidazole ring and is determined principally by the position of the azo group (405-420 nm for 5-azo- and 440-470 nm for 6-azo-substituted compounds).

Resistance of the azo group to reductive cleavage is characteristic for azo compounds VI. Refluxing of VI with stannous chloride in hydrochloric acid solution for many hours gives a hydrazo derivative, which is rapidly oxidized in air to the starting azo compound. The starting amine (Vb) and a difficult-to-separate mixture of diamines VII and VIII (with predominance of the latter) could be obtained only by vigorous reduction of Vb with tin in hydrochloric acid. Numerous crystallizations of the mixture gave VIII as the dihydrobromide; the formation of VII was proved by conversion of the mixture of diamines to the previously described mono- (Va) and, respectively, dibromo-substituted (IX) compounds by the Sandmeyer reaction. These observations demonstrate that the reductive cleavage of azo compounds VI with tin metal proceeds primarily with splitting out of the bromine atom in the o position relative to the azo group (see [9]). Similar results are also obtained in the reduction of VI with sodium hydrosulfite, except that the final products of the reduction are markedly contaminated, probably because of the side processes sometimes observed when sodium hydrosulfite is used.

Thus the data on the reduction of the azo compounds also confirm the structure of VI. The entrance of the azo group into the o position relative to the bromine atom is somewhat unexpected and, although it has not been observed previously, is in agreement with the known cases of electrophilic substitution in 2-aminobenzimidazoles [7, 10, 11].

*The azonium form produced by protonation of the azo group [8], which for azo compounds of the III or IV type is possible only in concentrated sulfuric acid, is apparently responsible for the appearance of the blue color. It might be assumed that protonation of VI is hindered by the effect of the bromine atom, as a consequence of which no coloration is observed.

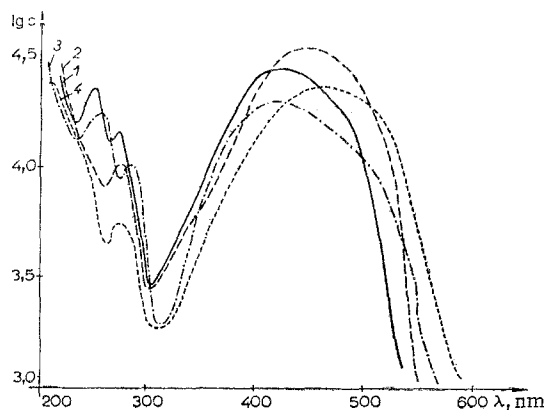
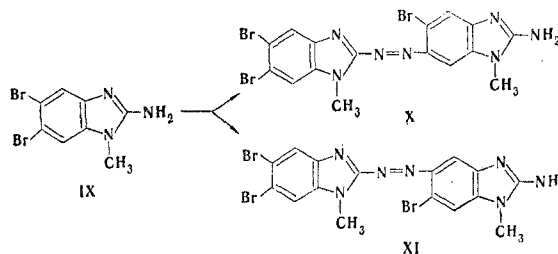


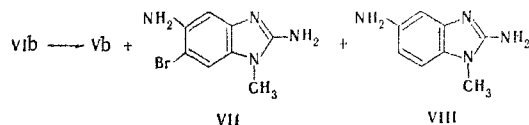
Fig. 1. UV spectra: 1) 1,1'-dimethyl-2-amino-2',5'-azobenzimidazole [2]; 2) 1,1'-dimethyl-2-amino-2',6'-azobenzimidazole [2]; 3) 6,6'-dibromo-1,1'-dimethyl-2-amino-2',5'-azobenzimidazole; 4) 5,5'-dibromo-1,1'-dimethyl-2-amino-2',6'-azobenzimidazole.

[13] series and have been studied somewhat more extensively for α -bromo(chloro)- β -naphthols [14, 15]. In the latter case, it was shown that the highly active bromine cation that is split out undergoes side reactions (for example, it is reduced to the bromide ion). However, we were unable to detect either bromide ions or appreciable amounts of side products in our experiments. Considering the possibility of the formation of complexes of Br^+ with tertiary bases of the pyridine type [16], it might be assumed that the bromine cation is tied up with the starting amine (IX). Decomposition of the complex with freeing of the starting amine (IX) probably occurs when the reaction mass is poured over ice and the reaction products are subsequently treated with alcohol. In fact, about 30% of amine IX is recovered in all of the experiments, and the yield of IX does not decrease as the experimental time is increased. In addition, if the step involving treatment of the reaction products with alcohol (the role of which apparently reduces to reduction of Br^+ [12, 13]) is omitted, a markedly contaminated and hard-to-separate mixture of substances is formed; this is probably associated with secondary processes induced by the bromine cation during thermal treatment of the reaction products (drying and recrystallization).



The presence of one or two bromine atoms in the 5 and 6 positions of 2-aminobenzimidazoles, contrary to expectations, does not promote azo coupling with arenes. In the case of more active arenes - mesitylene and m-xylene - interaction of the hydrocarbons themselves with NSA apparently predominates [17] because of the difficulty in diazotization of bromo-substituted amines V and IX; as a result, areneazo-benzimidazoles are formed in low yields and are markedly contaminated. In addition, the rate of decomposition (probably under the influence of the arene introduced into the reaction mixture) of the unstable bromo-substituted benzimidazole-2-diazonium salts apparently exceeds the rate of azo coupling (see [18]). An areneazo compound of the III type therefore could not be obtained even in the case of toluene and benzene, which are passive to the action of NSA; repeated purification leads only to substances with a nitrogen content that is 6-7% too low (for the time being these were not subjected to closer study).

* We note that 4(?),5,6-tribromo-2-amino-1-methylbenzimidazole does not react with NSA under the conditions used.



Continuing our search among 2-aminobenzimidazoles for compounds that are capable of reacting with NSA only as diazo components, we subjected 5,6-dibromo-2-amino-1-methylbenzimidazole (IX) to this transformation. In this case, the reaction time was increased to 80-90 h.* Although both the 5 and 6 positions are substituted, in this case one also observes the self-coupling and the formation of isomeric tribromoazo derivatives (X and XI), which are similar in properties to azo compounds VI.

The formation of X and XI is a result of "displacement" self-coupling and should be accompanied by splitting out of a positively charged bromine atom. Relatively little study has been devoted to reactions involving replacement of halogen by an azo group: they have been noted in the thiophene [12] and thiazole

It should be noted that 5-bromo-1,3-dimethyl-2-iminobenzimidazoline, in contrast to the unsubstituted imine [19], does not undergo reaction with NSA even in the course of 3-4 days; this is in complete agreement with the passivating action of a bromine atom on the 2-amino group, which is also observed for amines.

EXPERIMENTAL

The UV spectra of methanol solutions of the azo compounds were recorded with an SF-4a spectrophotometer.

Reaction of Bromo-Substituted 2-Aminobenzimidazoles with NSA. This reaction was carried out in concentrated H_2SO_4 via the method in [1], except that the amount of concentrated H_3PO_4 added was reduced to 4-5 ml per 0.01 mole of amine, 1.5 moles of NSA were used per mole of amine V, 3 moles of NSA were used per mole of amine IX, and the reaction time was increased to 8-10 h for V and to 80 h for IX.

6,6'-Dibromo-1,1'-dimethyl-2-amino-2',5'-azobenzimidazole (VIb). The precipitate that formed when the reaction mixture was poured over ice and treated with alkali was dried and treated with 30 ml of boiling alcohol.* The mixture was cooled, and the precipitated azo compound was removed by filtration to give 67% of bright orange plates with mp 314° (dec., from pyridine) that were only slightly soluble in alcohol, benzene, and ether; λ_{max} , nm (log ϵ): 255 (4.20), 282 (4.02), 405-420 (4.28). Found, %: C 41.6; H 2.6; Br 34.4; N 21.1. $C_{16}H_{13}Br_2N_7$. Calculated, %: C 41.5; H 2.8; Br 34.5; N 21.2.

5,5'-Dibromo-1,1'-dimethyl-2-amino-2',6'-azobenzimidazole (VIa). The solid that precipitated from the reaction mixture was treated with 150 ml of boiling water and washed on the filter with 10 ml of hot alcohol to give 62% of dark-claret-colored prisms with mp 328° (dec., from pyridine or dimethylformamide); λ_{max} , nm (log ϵ): 272 (3.73), 440-465 (4.32). Found, %: C 41.4; H 2.9; Br 34.0; N 21.3. $C_{16}H_{13}Br_2N_7$. Calculated, %: C 41.5; H 2.8; Br 34.5; N 21.2.

6,6'-Dibromo-1,1'-diethyl-2-amino-2',5'-azobenzimidazole. This compound was obtained in 51% yield by the procedure used to prepare VIb, except that the precipitate was treated with 20 ml of cold alcohol. The bright orange plates had mp $282-283^\circ$ (from alcohol or pyridine); λ_{max} , nm (log ϵ): 252 (4.25), 282 (4.00), 408-420 (4.32). Found, %: C 44.0; H 3.7; Br 32.3; N 19.9. $C_{18}H_{17}Br_2N_7$. Calculated, %: C 44.0; H 3.5; Br 32.5; N 20.0.

5',6,6'-Tribromo-1,1'-dimethyl-2-amino-2',5'-azobenzimidazole (XI). The precipitate obtained as a result of the reaction of amine IX with NSA was dried slightly in air and treated with 30 ml of boiling alcohol for 30-40 min. The hot mixture was filtered, and isomeric azo compounds X and XI (59% yield) were isolated and separated as described below. The alcohol was removed from the filtrate by distillation, and the residue was crystallized from aqueous alcohol (1:1) to give starting amine IX in about 30% yield. The dried and powdered mixture of azo compounds was heated for 10-15 min in 40 ml of boiling pyridine, and the mixture was cooled to 50° and filtered. The insoluble residue was recrystallized successively from glacial acetic acid and from a large volume of pyridine to give bright orange plates with mp $324-326^\circ$ (dec., $330-332^\circ$ on rapid heating.)† According to the UV spectrum, the product was 5-azo-substituted XI; λ_{max} , nm (log ϵ): 255 (4.30), 282 (inflection), 408-420 (4.32). Found, %: C 35.0; H 2.4; Br 44.3; N 18.6. $C_{16}H_{12}Br_3N_7$. Calculated, %: C 35.5; H 2.2; Br 44.2; N 18.1.

5,5',6'-Tribromo-1,1'-dimethyl-2-amino-2',6'-azobenzimidazole (X). The pyridine solution from the separation of the 5-isomer (XI) was allowed to stand for 24 h, and the resulting precipitate was removed by filtration. A triple volume of ether was added to the filtrate, and the precipitate that formed after 8-10 h was separated, crystallized from a small volume of pyridine, and combined with the major amount of precipitate to give dark red crystals with mp $333-336^\circ$ (dec., from pyridine, glacial acetic acid); λ_{max} , nm (log ϵ): 272-274 (inflection), 440-465 (4.44). Found, %: C 35.2; H 2.6; Br 44.6; N 18.7. $C_{16}H_{12}Br_3N_7$. Calculated, %: C 35.5; H 2.2; Br 44.2; N 18.1.

Reduction of Azo Compound VIb. A. A 1-mmole sample of VIb was heated for 3-4 h with 0.4 g of powdered tin and 15-20 ml of hydrochloric acid (1:1) on a boiling-water bath. The reaction was considered to be complete when a red coloration was no longer observed upon the addition of sodium nitrite to a sample.

*Here and in what follows, the numerical values given are based on 0.01 mole of the starting amine.

† The melting points (decomposition) of X and XI cannot be used to prove the completeness of the separation of the isomers, since they depend only relatively little on this factor. The individuality of the isomers was established on the basis of a comparison of the UV spectra of these compounds and "standard" VIa and VIb.

The mixture was evaporated to half its original volume and cooled, and the precipitated complex was treated with 8 ml of boiling alcohol. The insoluble precipitate was triturated with 40% sodium hydroxide solution, the mixture was filtered, and the solid was crystallized from aqueous alcohol (1 : 1) to give a product identical to amine Vb in 66% yield. The hydrochloric acid solution remaining after separation of the complex was combined with the residue from the removal of the solvent from the alcohol extract, and the mixture was diluted with water and treated with hydrogen sulfide to precipitate the tin. The tin sulfides were separated, and the filtrate was evaporated to 2-3 ml, treated with 3-4 ml of concentrated HBr, and allowed to stand overnight in an open beaker. The resulting precipitate was removed by filtration and washed with acetone to give 0.22 g of product. Chromatography in a thin layer of Al₂O₃ with acetone-chloroform-alcohol (1 : 1 : 0.2) indicated the presence of two substances: a major product that was chromatographically identical to the dihydrobromide of VIII, and a second component, the nature of which as the dihydrobromide of VII was established by means of conversion of the indicated mixture of dihydrobromides to IX and Va via the Sandmeyer reaction. The mixture of VII and VIII could not be separated; two crystallizations from alcohol gave only the quantitatively prevailing dihydrobromide of VIII in the pure state with mp 318-319° [2].

B. The reduction of VIb with sodium hydrosulfite was carried out by heating a mixture of the reagents (1.5 g of the reducing agent per millimole of VIb) in aqueous alcohol (2 : 1) for 4 h. The oily precipitate that formed after the mixture was cooled was treated with 15 ml of 2 N H₂SO₄, and the mixture was filtered after 3-4 h. The filtrate was evaporated to half its original volume and cooled with ice. The precipitate was washed with 5 ml of hot acetone and made alkaline to isolate a base identical to amine Vb (58% yield). The sulfuric acid mother liquor was evaporated to dryness, and the residue was treated (while heating) with three portions of acetone. The solvent was removed from the acetone extracts by distillation, 7 ml of concentrated HBr was added, and the mixture was cooled. The precipitate was crystallized from alcohol to give a product identical to the dihydrobromide of VIII.

Attempts to Obtain Bromo-Substituted 2-Areneazobenzimidazoles. A. A 2-mmole sample of amine V or IX was dissolved in 10 ml of concentrated H₂SO₄, 0.3-0.4 ml of mesitylene or m-xylene and 3 mmole of NSA were added, and the mixture was shaken at 20° for 6-10 h. After the usual workup of the reaction mixture [4], the benzene extract was chromatographed with a column filled with Al₂O₃; the fraction closest in chromatographic behavior to the known 2-areneazobenzimidazoles was separated. The azo compounds could not be isolated in analytically pure form by repeated chromatography and crystallization from hexane or benzene-petroleum ether.

B. The reaction of amines V or IX with NSA in the presence of toluene or benzene was carried out as described in part A, except that chloroform was used for the extraction. The chloroform-insoluble residue was washed with hot alcohol to give azo compound VI (26-28%) or, respectively, a mixture of X and XI (17-20%). The chloroform extract was chromatographed with a column filled with Al₂O₃; the colored fraction that emerged first was collected. The solvent was removed by distillation, and the residue was crystallized from benzene-petroleum ether to give yellow substances containing 6-7% less nitrogen than in the corresponding bromo-substituted 2-areneazobenzimidazoles.

LITERATURE CITED

1. M. M. Medvedeva, A. F. Pozharskii, and A. M. Simonov, *Khim. Geterotsikl. Soedin.*, 1418 (1972).
2. S. N. Kolodyazhnaya and A. M. Simonov, *Khim. Geterotsikl. Soedin.*, 187 (1967).
3. A. M. Simonov and S. N. Kolodyazhnaya, *Khim. Geterotsikl. Soedin.*, 513 (1969).
4. A. M. Simonov and S. N. Kolodyazhnaya, *Zh. Organ. Khim.*, 3, 1146 (1967).
5. J. Goerdeler and H. Haubrich, *Ber.*, 93, 397 (1960).
6. J. Houben and T. Weyl, *Methoden der Organischen Chemie*, Volume 10/3, Stuttgart (1965), p. 53.
7. S. N. Kolodyazhnaya and A. M. Simonov, *Khim. Geterotsikl. Soedin.*, 714 (1969).
8. E. Gesson and E. Heilbronner, *Helv. Chim. Acta*, 45, 42 (1962).
9. J. Houben and T. Weyl, *Methoden der Organischen Chemie*, Vol. 5/4, Stuttgart (1960), p. 769.
10. A. M. Simonov, Yu. M. Yutilov, and V. A. Anisimova, *Khim. Geterotsikl. Soedin.*, 913 (1965).
11. A. G. Leonard, D. J. Curtin, and K. M. Beck, *J. Am. Chem. Soc.*, 69, 2459 (1947).
12. C. D. Hurd and H. M. Priestley, *J. Am. Chem. Soc.*, 69, 859 (1947).
13. R. Walther and H. Roch, *J. Prakt. Chem.*, 87, 27 (1913).
14. I. S. Ioffe, *Zh. Obsheh. Khim.*, 6, 1074 (1936).
15. I. S. Ioffe, *Zh. Obsheh. Khim.*, 7, 2637 (1937).
16. F. Cotton and G. Wilkinson, *Advanced Inorganic Chemistry*, Wiley (1966).
17. Z. Z. Allan, J. Podstata, D. Snobl, and J. Jarkovsky, *Coll. Czech. Chem. Commun.*, 32, 1449 (1967).

18. J. Goerdeler and P. Mertens, *Ber.*, 103, 1805 (1970).
19. A. M. Simonov and S. N. Kolodyazhnaya, *Khim. Geterotsykl. Soedin.*, 1562 (1970).