DIAZO COMPOUNDS OF THE HETEROCYCLIC SERIES.

4.* SOME PECULIARITIES OF THE DIAZO COUPLING OF BENZIMIDAZOLE-2-DIAZONIUM SALTS WITH PHENOLS AND THEIR ETHERS

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The corresponding hydroxy (methoxy)-substituted azobenzimidazoles were obtained by diazo coupling of benzimidazole-2-diazonium salts with phenols and their complete and incomplete ethers in strongly acidic media; in the case of phenol ethers the process is complicated by dealkylation of the methoxy group in the ortho position relative to the azo bridge.

It is known that the diazo coupling of some heterocyclic diazonium salts with a number of substrates is possible only in strongly acidic media [2]. Included among such salts are benzimidazole-2-diazonium phosphates, which are obtained by diazotization of 2-amino-1-alkylbenzimidazoles I in concentrated phosphoric acid [3]; the addition of water to the diazo solution shifts the diazo equilibrium to favor the highly stable N-nitrosoamines [1], which are then readily converted to symmetrical triazenes III, which are not cleaved by acids [4]. At the same time, when phenols and their ethers are used as the azo component, the reaction is usually carried out in close-to-neutral media to avoid protonation of the azo component, which decreases its activity significantly [5]. In this connection the present research was devoted to working out the optimum conditions for the synthesis of and methods for the identification of hydroxy(alkoxy)-arylazobenzimidazoles, which are potential ligands and intermediates in the synthesis of deeply colored dyes.

We have shown that in strongly acidic media the reaction of benzimidazole-2-diazonium salts II with phenols and their ethers frequently leads to the formation of mixtures of substances, the isolation of the desired product from which is difficult. A rather long time (up to 18 h) is required for completion of the diazo coupling of diazonium salt IIa with p-substituted phenols (p-cresol, hydroquinone) and their methyl ethers in a mixture (1:1) of concentrated H_3PO_4 and CH_3COOH (acid medium A); in the case of p-cresol and its ether one observes an ambiguous orientation of the diazonium cation, which leads to the formation of m-hydroxy(methoxy)-substituted products Va, b in addition to "normal" products IVa, b. This reaction pathway is explained by the high activity of diazonium salts II, which permits activation of the ring in the protonated phenol by only one methyl group (see [6]).

As the reaction mass is diluted with water, the amount of the protonated phenol in the mixture decreases, and the yield of the product of "anomalous" orientation of the diazonium cation decreases simultaneously. Thus, Va is isolated in 4% yield from H_3PO_4–CH_3COOH–H_2O (1:1:2.5), while the yield is close to 20% in the diazo coupling of p-cresol without the addition of water. A mixture composition ranging from 1:1:2 to 1:1:2.2 is optimal for obtaining products IV with a normal orientation of the diazonium cation. Further dilution appreciably intensifies the competitive (with diazo coupling) conversion of diazonium salt IIa to symmetrical triazene III.

In the case of hydroquinone and its ethers one must also be limited to 2.5 volumes of added water. Hydroquinone monomethyl ether at any permissible dilution forms only one isomer (VIb). Since the orienting effects of hydroxy and methoxy groups in an acidic medium are close, the preferableness of attack by the diazonium cation in the ortho position relative to the hydroxy group in this case may be associated with the possibility of stabilization of the transition state due to the formation of an intramolecular hydrogen bond (IMHB).

*See [1] for Communication 3.

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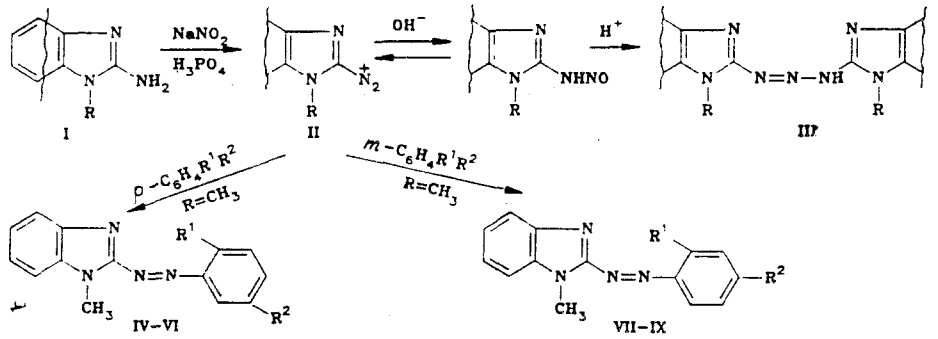

I, II a $R=CH_3$, б $R=C_2H_5$; IV a,b $R^1=CH_3$, a $R^2=OH$, b $R^2=OCH_3$; V a $R^1=OH$, b $R^1=OCH_3$, a,b $R^2=CH_3$; VI a,b $R^1=OH$, c $R^1=OCH_3$, a $R^2=OH$, b,c $R^2=OCH_3$; VII a,b $R^1=CH_3$, a $R^2=OH$, b $R^2=OCH_3$; VIII a,b $R^1=OH$, c,d $R^1=OCH_3$, a,c $R^2=OH$, b,d $R^2=OCH_3$; IX $R^1=H$, $R^2=OCH_3$

In contrast to p-substituted phenols, a dilution of up to 1:1:4 is permissible for m-substituted azo compounds, and they react two to three times faster. The formation of isomeric azo compounds VIIIb, c is observed only for resorcinol monomethyl ether; the o-hydroxy azo isomer is formed in an amount that is almost twice the amount of the corresponding p-hydroxy azo-substituted VIIIc only in acidic medium A. When the reaction mixture is diluted with water, the yields of isomeric VIIIb and VIIIc are equalized. These observations can be explained by processes that are similar to those described for hydroquinone monomethyl ether; however, the kinetic factor plays an appreciable role here only under the condition of protonation of the phenol. The high activities of free diphenols level out the differences in the energies of the activated complexes in the formation of isomers VIIIb, c.

In addition to the complications associated with the formation of mixtures of isomeric azo compounds in a number of cases, partial dealkylation of the ether groups is observed when phenol ethers are used as the azo components. Individual cases of this sort of dealkylation, which takes place during diazo coupling with phenol ethers, have been described; primary cleavage of the methoxy groups in the para position relative to the azo bridge is noted [7]. In contrast to the literature data, in the diazo coupling of diazonium salt IIa with phenol ethers one observes primary cleavage of the o-methoxy group, chiefly in reactions with less active azo components. Thus, 23% o-hydroxy azo compound VIb was isolated in the diazo coupling of IIa with hydroquinone dimethyl ether in acidic medium A, whereas up to 50% dealkylation product IVa was isolated in the diazo coupling of IIa with p-cresol methyl ether. At the same time, the yields of dealkylation products VIIa and VIIId do not exceed 6% when p-cresol and resorcinol methyl ethers are used as the azo components. Note that in the reaction with the less active azo component – anisole – only traces of p-hydroxy-substituted products are formed.

In the opinion of Bunnett and Hoey [8], dealkylation in the diazo coupling of phenol ethers is a consequence of hydrolytic cleavage of the ether groups in the resulting azo compounds. To verify this assumption, we studied the behavior with respect to hydrolysis of azo compounds IVb, VIb, c, VIIb, VIIIb, c, d, and IX in acidic medium A at room temperature. The azo compounds based on the complete and incomplete ethers VIb, c of hydroquinone are the least stable: disappearance of the starting substance is observed here after the reaction mixtures have stood for 4 and 7 days, respectively. Azo compound VIIId is hydrolyzed with the primary formation of monomethoxy-substituted VIIIc after 12 days. Cleavage of the ether bond in azo compounds based on monophenol ethers proceeds with greater difficulty: after 38, 43, and 48 days, respectively, for the p-cresol (IVb), m-cresol (VIb), and anisole (IX) azo compounds. Thus, a direct relationship is observed between the rate of cleavage in the azo compounds and the basicity of the corresponding azo component. Only the azo compounds based on resorcinol monoethers VIIIb, c, the hydrolysis of which occurs after 1.5 months, constitute an exception. The degree of dealkylation in the diazo coupling of diazonium salt IIa with phenol ethers does not display a similar dependence: it is maximal in the case of p-cresol methyl ether and minimal for resorcinol ethers. Hence, it follows that dealkylation is not a consequence of cleavage of the ether groups in the products of diazo coupling but rather probably occurs in the step involving the formation of the σ complex and is associated with the possibility of a decrease in the energy of the transition state due to the formation of an IMHB. This explanation is in good agreement with the smaller degree of dealkylation in the diazo coupling of m-substituted phenols, for which a decrease in the height of the activation barrier as a consequence of the formation of an IMHB does not play an appreciable role.

Dilution of the reaction mass with water during the diazo coupling decreases dealkylation: in the case of an H_3PO_4–CH_3COOH–H_2O ratio of 1:1:2 the amount of o-hydroxy-substituted compound in the reaction with hydroquinone methyl ether and p-cresol methyl ether decreases to 5% and 18%, respectively. Thus, the addition of water to acidic medium A during

TABLE 1. Characteristics of 2-Hydroxy(methoxy)phenylazobenzimidazoles IV–IX

Compound	Empirical formula	mp,* °C	PMR spectrum (in $CDCl_3$), ppm, **			Yield,*** %	
			$ArCH_3$	NCH_3	OCH_3	A	B
IV a	$C_{15}H_{14}N_4O$	196 ... 197	2,25	3,93	—	18	70
IV b	$C_{16}H_{16}N_4O$	127 ... 128	2,16	3,95	3,82	7	23
V a	$C_{15}H_{14}N_4O$	239 ... 240	2,53	4,17	4,17	20	4
V b	$C_{16}H_{16}N_4O$	136 ... 137	2,58	3,96	3,73	16	—
VI a	$C_{14}H_{12}N_4O_2$	293 ... 294	—	3,98	—	56	60
VI b	$C_{15}H_{14}N_4O_2$	178 ... 179	—	3,80	3,71	67	79
VI c	$C_{16}H_{16}N_4O_2$	164 ... 165	—	3,95	3,65; 3,84	34	59
VII a	$C_{15}H_{14}N_4O$	239 ... 240	2,38	3,94	—	73	78
VII b	$C_{16}H_{16}N_4O$	135 ... 137	2,70	3,90	3,72	74	83
VIII a	$C_{14}H_{12}N_4O_2$	247 ... 248	—	3,83	—	—	72
VIII b	$C_{15}H_{14}N_4O_2$	178 ... 179	—	3,82	3,75	38	39
VIII c	$C_{15}H_{14}N_4O_2$	228 ... 229	—	3,95	3,90	20	30
VIII d	$C_{16}H_{16}N_4O_2$	132 ... 134	—	3,90	3,72; 3,85	75	78
IX	$C_{15}H_{14}N_4O$	154 ... 155	—	3,95	3,75	76	81

*The compounds were recrystallized: IVa, VIb, VIIb, VIIIb, and IX from benzene; IVb and Vb from hexane; Va from pyridine; and VIa, c and VIIIa, c from alcohol.
**The solvent for IVa, Va, and VIIa was CF_3COOH.
***The diazo coupling was carried out in acidic medium A or in H_3PO_4–CH_3COOH–H_2O (1:1:2) (B).

the diazo coupling of diazonium salt IIa with phenols and their ethers acts positively under the condition that its amount does not exceed 2.5 volumes for p-substituted phenols and 4 volumes for m-substituted azo components.

We were able to separate the products by fractional precipitation, recrystallization, and column chromatography; preparative TLC was used in the separation of Vb and IVb. The PMR and IR spectra, in which some principles of the interrelationship between the structures and the positions of the bands were revealed (see Table 1), were found to be applicable for the identification. Thus, in the PMR spectra of azo compounds IV, V, and VII, as in the spectra of 2-arylazobenzimidazoles [9], the signal of the protons of the methyl group in the benzene ring in the ortho position relative to the azo bridge is shifted to weak field. A smaller weak-field shift is also characteristic for the o-methoxy group. In addition, when a hydroxy group is present in the ortho position relative to the azo bridge, the band of the $N–CH_3$ group is shifted somewhat to strong field.*

The IR spectra make it possible to distinguish the o-hydroxy-substituted compounds from the corresponding meta and para isomers from the absorption in the region of the stretching vibrations of the OH group. The o-hydroxy-substituted compounds give a broad band at 3140–3390 cm^{-1}, which is due to vibrations of an OH group that participates in the formation of an IMHB, while the meta and para isomers give a distinct signal at 3360–3440 cm^{-1}. The absorption has medium intensity for the spectra of solutions of the azo compounds in chloroform and weak intensity for the spectra of suspensions in mineral oil.

A region at ~1600 cm^{-1} is characteristic for azobenzimidazoles IV–IX: a sharp band at 1610–1630 cm^{-1} with an intensity from medium to strong on passing from suspensions to solutions is observed here for the o-hydroxy azo compounds, while the meta and para isomers do not give appreciable absorption in this region.

All of the hydroxy (alkoxy) azo compounds absorb intensely in the region of the deformation and stretching vibrations of the –C–O bond of the phenol and ether groups at 1100–1280 cm^{-1}. The ether groups also give a medium-intensity band of symmetrical stretching vibrations (–C–O–Ar) at 1040–1110 cm^{-1}. However, we could not ascertain distinct principles of a relationship between the positions of the bands in this region and the structures of the azo compounds. A correlation between the character of the substitution in the ring of the azo component and the position of the bands of the out-of-plane deformation vibrations of the ring C–H bonds at 600–900 cm^{-1} is not observed, although this sort of correlation was observed in the spectra of 2-arylazobenzimidazoles that do not contain polar substituents [9].

*This principle is violated in solution in CF_3COOH (see Table 1).

All of the assignments of the structures made on the basis of the above-indicated principles in the spectra are also confirmed by other properties of the azo compounds: the higher solubilities and chromatographic mobilities of the o-hydroxy azo compounds, the ease of formation for them of deeply colored complexes with heavy-metal salts, and the higher melting points of the p(m)-hydroxyphenylazo-substituted compounds as compared with the corresponding ortho isomers. The structures of the azo compounds based on phenol ethers are confirmed by their conversion via hydrolysis in concentrated H_3PO_4 at 50°C to hydroxy azo compounds; primarily the methoxy group in the ortho position relative to the azo grouping is cleaved.

Thus, the chief reasons for the complications that arise in the synthesis of hydroxy(methoxy)-substituted azobenzimidazoles via diazo coupling of diazonium salts II with phenols and their ethers in strongly acidic media are dealkylation of the ether groups and the ambiguous orientation of the diazonium cation, which leads to the formation of a mixture of isomeric azo compounds.

EXPERIMENTAL

The IR spectra of suspensions in mineral oil and solutions in chloroform were recorded with a Specord IR-75 spectrometer. The PMR spectra [with hexamethyldisiloxane (HMDS) as the internal standard] of solutions in $CDCl_3$ and CF_3COOH were recorded with a Tesla BS-487C spectrometer (80 MHz). The course of the reactions and the individuality of the substances were monitored by TLC on Al_2O_3 in chloroform. The mixtures of substances were separated on activity I and II Al_2O_3 by means of column chromatography in an ascending solvent.

The starting 1-alkyl-substituted 2-aminobenzimidazoles I were obtained by alkylation of 2-aminobenzimidazole with alkyl iodides by the method in [10].

The characteristics of IV–IX are presented in Table 1. Satisfactory results of elementary analysis for the C, H, and N content were obtained for them.

General Method for Obtaining Hydroxy(methoxy)arylazobenzimidazoles. A 1.73-g (25 mmoles) sample of finely ground $NaNO_2$ was added in the course of 10 min at –10°C with vigorous stirring to a solution of 10 mmoles of amine I in 15 ml of concentrated H_3PO_4. In the course of 0.5 h the temperature rose to 0°C, after which it rose to 10°C in the course of ~1 h. After the granules of $NaNO_2$ had vanished, urea was added to the solution, and the mixture was stirred until foaming ceased. The dark-red diazo solution was subjected to diazo coupling by adding it to a solution of 10 mmoles of the azo component in 15 ml of glacial CH_3COOH. When the reaction was carried out without dilution with water, the mixture was stirred for ~1 h as the temperature was raised to 20°C, and it was then allowed to stand for 18 h in the case of p-substituted phenols or for 6 h when m-substituted phenols were used as the azo components. If dilution was necessary, water was added dropwise at the rate of 1 volume every 0.5 h with stirring of the mixture. The reaction time decreased to 12 h or 3 h, depending on the activity of the azo component. After the reaction mixture was maintained at room temperature, it was usually diluted with water and neutralized with sodium carbonate to pH 5–6.

If a salt of the azo compound precipitated at the end of diazo coupling, it was removed by filtration and triturated with 5% $NaHCO_3$ solution. The mixture of reaction products was separated as described in each specific case. The yields in Table 1 are given for the individual substances obtained after separation.

2-(4-Methoxyphenylazo)-1-methylbenzimidazole (IX). This compound was obtained by diazo coupling with anisole in H_3PO_4:CH_3COOH:H_2O in a ratio of 1:1:0.1 (method A) or in a ratio of 1:1:2 or 1:1:3 (method B).

2-(2-Methyl-4-methoxyphenylazo)-1-methylbenzimidazole (VIIa). This compound was synthesized by method A or B in the same way as anisole derivative IX.

2-(2-Hydroxy-5-methoxyphenylazo)-1-methylbenzimidazole (VIb). The crude product obtained in the diazo coupling of salt IIa with hydroquinone monomethyl ether was heated with 200 ml of boiling CCl_4 for 10 min, after which the mixture was filtered and cooled, and the precipitated VIb was separated. An additional amount of VIb was obtained from the filtrate by evaporating it to 50 ml.

2-(2,4-Dihydroxyphenylazo)-1-methylbenzimidazole (VIIIa). The precipitated salt of azo compound VIIIa obtained in the reaction of diazonium salt IIa with resorcinol in H_3PO_4:CH_3COOH:H_2O (1:1:3) was treated with 35 ml of 4% ammonium hydroxide and filtered, and the precipitate on the filter was treated repeatedly with 20 ml of ammonium hydroxide solution. A 20% solution of CH_3COOH was added dropwise to the ammoniacal filtrate until a colorless sample was obtained, after which the precipitate was filtered and dried at 100°C.

2-(2-Methyl-4-hydroxyphenylazo)-1-methylbenzimidazole (VIIa). This compound was obtained by coupling salt IIa with m-cresol via the above-described method, but the precipitated salt of the azo compound was dissolved in a mixture of alcohol with ammonium hydroxide by heating.

2-(2,5-Dihydroxy)-1-methylbenzimidazole (VIa). This compound was obtained by coupling salt IIa with hydroquinone by method A or B but without diluting the mixture by more than a composition of up to 1:1:1.5.* The precipitate after neutralization of the reaction mixture was recrystallized from DMF or pyridine.

Separation of Isomeric 2-(2-Methyl-5-hydroxyphenylazo)-1-methylbenzimidazole (IVa) and 2-(2-Hydroxy-5-methylphenylazo)-1-methylbenzimidazole (Va). The precipitate of the products of diazo coupling of salt IIa with p-cresol formed after trituration of the salts of the azo compounds with $NaHCO_3$ solution was treated with 30 ml of boiling benzene, and the residue was treated repeatedly with 10 ml of boiling alcohol. The undissolved part was isomer Va, while pure IVa precipitated from the benzene and alcohol solutions. An additional amount of IVa could be obtained by chromatographic purification of the contents of the benzene and alcohol filtrates with a column packed with Al_2O_3 in chloroform.

Separation of the Products of Diazo Coupling of Salt IIa with p-Cresol Methyl Ether (IVb and Vb). The oily precipitate obtained after neutralization of the reaction mixture in the coupling of salt IIa with p-cresol methyl ether was chromatographed with a column packed with Al_2O_3 in $CHCl_3$–CCl_4 (3:1) with elution of the first yellow fraction. After removal of the solvents by distillation, the residue was chromatographed repeatedly on plates with a thin layer of Al_2O_3 in CCl_4–$CH_3C(O)CH_3$ (10:1). The poorly moving dark-colored zone (R_f 0.5) corresponded to o-methoxy-substituted IVb, while the front-running light-yellow zone (R_f 0.7) contained a mixture of IVb and Vb. The poorly soluble IVb was separated by heating this mixture with hexane, while Vb, which was crystallized repeatedly from pentane, precipitated from the hexane filtrate on standing.

Separation of 2-(2-Hydroxy-5-methoxyphenylazo)-1-methylbenzimidazole (VIb) and 2-(2,5-Dimethoxyphenylazo)-1-methylbenzimidazole (VIc). The mixture of products of the diazo coupling of diazonium salt IIa with hydroquinone dimethyl ether in a concentrated solution of acids was refluxed for 7 min with 25 ml of benzene, after which the hot solution was filtered, 10 ml of petroleum ether was added to the filtrate, and the mixture was allowed to stand for a few hours. The precipitated VIb was crystallized from alcohol and dried at 90°C until the solvate decomposed. The benzene–petroleum ether filtrate and the alcoholic solution were evaporated, and the residue was chromatographed with a column in $CHCl_3$–CCl_4 (1:1) with elution of the dark-orange fraction containing VIc. The column of Al_2O_3 was then extruded, the reddish-brown fragment emerging after the principal fraction was cut out, and the VIb was extracted with acetone. The yield of dealkylation product VIb was 23%.

In the case of an H_3PO_4–CH_3COOH–H_2O composition of 1:1:2.5 the precipitate of salts of azo compounds VIb and VIc that formed at the end of the reaction was removed by filtration, dried, and treated successively with warm carbon tetrachloride and sodium bicarbonate solution. The precipitate was crystallized from aqueous alcohol (1:2) to isolate the bulk of VIc. From the acidic filtrate we isolated a precipitate which, after chromatography with a column, gave an additional amount of VIc and VIb (~5%).

Separation of 2-(2-Hydroxy-4-methoxyphenylazo)-1-methyl benzimidazole (VIIIb) and 2-(2-Methoxy-4-hydroxyphenylazo)-1-methylbenzimidazole (VIIIc). The precipitated mixture of isomers VIIIb and VIIIc obtained after diazo coupling of diazonium salt IIa with resorcinol monomethyl ether was treated with 40 ml of boiling benzene, after which the undissolved part was removed by filtration and crystallized from chloroform with the addition of a small amount of petroleum ether for the complete isolation of p-hydroxy isomer VIIIc. The combined benzene and chloroform mother liquors were evaporated, and the residue was chromatographed with a column in chloroform–benzene (4:1). The first brown-violet fraction corresponded to o-hydroxy isomer VIIIb, while the following red fraction corresponded to p-hydroxy isomer VIIIc.

Separation of 2-(2-Hydroxy-4-methoxyphenylazo)-1-methylbenzimidazole (VIIIb) and 2-(2,4-Dimethoxyphenylazo)-1-methylbenzimidazole (VIIId). The mixture of products of diazo coupling of diazonium salt IIa with resorcinol dimethyl ether (the diazo coupling was carried out by method A or B) was treated with boiling benzene (two 25-ml portions) to extract dimethoxy derivative VIIId; its dealkylation product VIIIc (in 6% yield) remained in the residue. Azo compound VIIId was purified by column chromatography of the benzene extract after it was evaporated to the minimum volume. The front-running orange-red fraction was collected.

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*In the case of greater dilution, processes involving the oxidation of hydroquinone are intensified, evidently due to the effect of the N-nitrosoaminobenzimidazole formed from salt IIa upon dilution.

Study of the Hydrolysis of Azo Compounds IVb, VIb, c, VIIb, VIIIb, c, d, and IX. A solution of 4 mmoles of the azo compound in 10 ml of the acidic medium was maintained at room temperature. Samples (0.05 ml) were diluted to twice their original volumes with water, made alkaline with sodium carbonate, and extracted with chloroform to remove the azo compound. The extract was chromatographed on a plate with a thin layer of Al_2O_3 in chloroform or $CHCl_3$–C_2H_5OH (10:1). The complete disappearance of the starting substance in the chromatographic sample constituted evidence for the completion of the reaction.

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