HETEROCYCLIC DIAZO COMPOUNDS. 5.*REACTION OF BENZIMIDAZOLE-2-DIAZONIUM SALTS WITH NAPHTHOLS AND THEIR ETHERS

S. N. Kolodyazhnaya, L. N. Divaeva, V. A. Polenov, and A. M. Simonov

The principal pathways for the reaction of benzimidazole-2-diazonium ion salts with naphthols and their methyl ethers in a mixture of phosphoric acid annd acetic acid have been elucidated. In concentrated acidic media, in addition to substitution at the 4-position in naphthol and its ether, azo coupling at the 8-positin is also possible. It has been found that a 2-methoxy group in naphtylazobenzimidazole exhibits anomalously high reactivity with respect to hydrolytic cleavage, which explains the observed ease of dealkylation of the azo compound during the course of the azo coupling sequence.

A distinguishing characteristic of salt I, prepared by diazotization of 2-amino-1-methylbenzimidazole (II) in concentrated phosphoric acid, is the unusual ease with which the diazo equilibrium is shifted in favor of the primary N-nitrosamine, which undergoes further condensation to give the symmetric triazene III [2]. For this reason, in the case of azo compound synthesis reactions based on amine II the azo coupling sequence is generally carried out in strongly acidic media, and the principles of this reaction sequence remain largely unstudied [3]. We have previously reported in the literature concerning coupling reactions of diazonium salt I with phenols and their ethers [1]. Continuing these studies, we have now examined the reactivity of salt I with 1- and 2-naphthols (IV, V) and their methyl ethers (VI, VII). The product composition and their yields, as in the case of azo coupling involving I and phenols and their ethers [1], depend on the amount of water in the reaction mixture. We discuss below the results obtained for reactions in concentrated acid solution, a mixture of H_3PO_4:CH_3COOH:H_2O (1.0:1.5:2.0) (method A), and in a 1.0:2.0:3.0-3.5 ratio mixture (method B). If the water concentration is further increased conversion of salt I to triazene III is strongly accelerated and favored.

Reaction of salt I with 1-naphthol (IV) using method A leads to the formation of a mixture of azo compounds VIII and IX. Azo coupling reactions of 1-naphthol generally take place at the 4-position, although in the case of less active diazo components reaction also occurs at the 2-position [4]. Substitution at the 8-position, which is observed in this case, is probably the result of attack by the active cation in compound I at the protonated site in molecule IV in strongly acidic solution. For the deactivated naphthol ring, of the two relatively accessible sites for electrophiles, position 8 is probably favored for diazo coupling due to the appearance of intramolecular hydrogen bonding in the transition state complex.

When azo coupling of salt I with naphthol IV is carried out using method B the yield of the "normal" orientation product VIII is increased more than threefold relative to the yield of the 8′-substituted product IX (cf. Table 1). In contrast to the behavior of compound IV, however, 2-naphthol V reacts with salt I in both concentrated and dilute acid solutions to form azo compound X exclusively.

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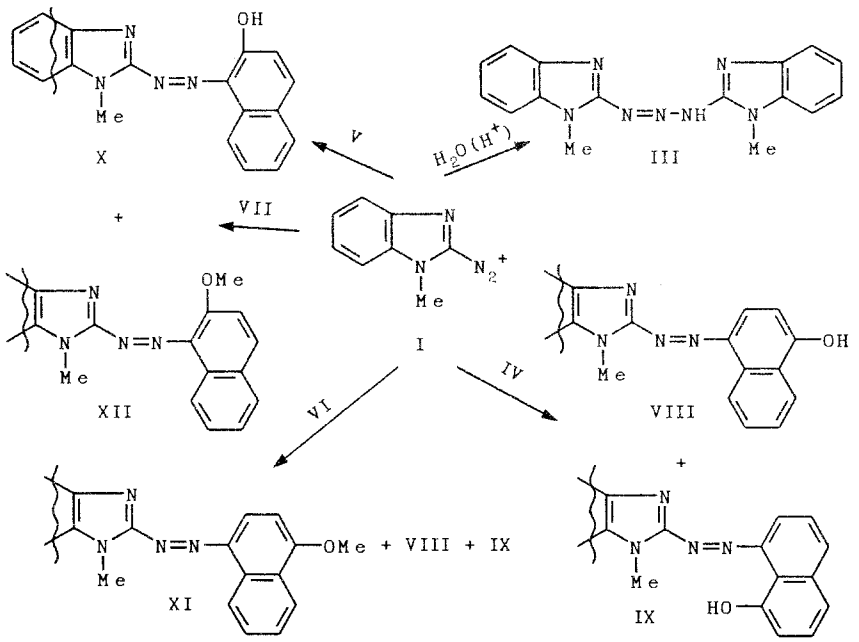
TABLE 1. Physical Properties of 2-Naphthylazobenzimidazoles VIII-XII

Compound	Molecular formula	T_{mp}, °C*	IR spectrum, ν, cm^{-1}**	Yield, %	
				A	B
VIII	$C_{18}H_{14}N_4O$	238...240	870 m, 830 s, 745 s, 730 s, 710 s,	62	80
IX	$C_{18}H_{14}N_4O$	289...290	870 m, 790 s, 730 s, 675 s,	9,5	3
X	$C_{18}H_{14}N_4O$	181...182	870 m, 760 s, 740 s, 700 s,	76	74
XI	$C_{19}H_{16}N_4O$	186...187	870 m, 805 s, 760 s, 730 s, 710 s,	56	78
XII	$C_{19}H_{16}N_4O$	158...159	865 m, 835 s, 760 s, 748 s, 730 s, 715 m	8	53

*Compound VIII was recrystallized from butanol, compound IX from a mixture of CCl_4 and hexane, and compound X from $CHCl_3$–hexane, compounds XI and XII from benzene.

**Vaseline mulls, 900-675 cm^{-1} region.

The orientation of the diazo cation in salt I observed for attack at naphthols IV and V is also retained in the case of their ethers VI and VII, but the azo coupling reaction is more complex for these substrates due to dealkylation of the methoxy group. The main reaction product obtained from diazo salt I with 1-methoxynaphthalene (VI) using method A is compound XI; however, in addition to XI, a mixture of isomers VIII and IX is also produced in 16% yield, with the latter isomer predominating. Since compound VIII does not undergo isomerization to its isomer IX under the reaction conditions, we conclude that the 8′-hydroxy-substituted derivative IX is the dealkylation product of its corresponding ether, which was not isolated. When the reaction



of salt I with naphthalene VI is carried out using method B, the dealkylation process is almost completely suppressed; although azo compounds VIII and IX are identified chromatographically in this reaction, their total yield is less than 2%.

Dealkylation of the methoxy group occurs to a significantly greater extent in the case of azo coupling of salt I with 2-methoxynaphthalene VII: using method A the yield of product X exceeds 70%, while using method B the yield is 20%; the desired product XII is formed in only 8 and 53% yield, respectively, under these reaction conditions (Table 1). The dealkylation process cannot be completely suppressed even upon greater dilution of the reaction mixture than in method B. Such extremely high dealkylation rates accompanying azo coupling have been observed previously, in the case of reaction of diazonium salt I with p-cresol methyl ether, although the desired product in this case, namely, 1-methyl-2-(2-methoxy-5-methylphenylazo)benzimidazole (XIII), was found to be relatively stable with respect to hydrolytic cleavage of the ether group. In this example, therefore, dealkylation apparently proceeds in the transition state complex stage for the azo coupling reaction of compound I.

TABLE 2. PMR Spectra of 2-Naphthylazobenzimidazoles VIII-XII

Compound	σ, ppm* (J, Hz)			
	NCH_3, s	OCH_3, s	aromatic protons	8'-H, br.d
VIII	3,75	—	6,46 (d,1H, 3'-H, *J*=9,8); 7,01...8,40 (m,8H)	8,75 (*J*=7,8)
IX	3,92	—	6,79 (d,1H, 7'-H, *J*=9,6); 7,00...8,28 (m,9H)	—
X	4,08	—	6,72 (d,1H, 3'-H, *J*=9,9); 7,08...8,14 (m,8H)	9,18 (*J*=7,6)
XI	3,80	3,82	6,55 (d,1H, 3'-H, *J*=9,8); 7,01...8,15 (m,8H)	8,84 (*J*=7,8)
XII	3,81	3,85	7,08...7,87 (m,9H)	8,88 (*J*=7,8)

*The spectra of compounds XI, XII were recorded in $CDCl_3$ solution, compounds VIII, IX, X in DMF-D_7.

Studying the hydrolysis reactions of ether groups in compounds XI and XII, we have found that the 2'-methoxy substituted derivative XII exhibits the lowest stability with respect to hydrolytic cleavage, at least within the class of known alkoxy substituted azobenzimidazoles. Thus, the hydrolysis half-life times ($\tau_{1/2}$) at 20°C in the solvent mixture A are 2, 33, and 198 h, respectively, for compounds XII, XI, and benzimidazole XIII, which was used as a reference compound.

The hydrolysis data for compounds XI and XII, along with the observed degree of dealkylation in the case of reaction of salt I with ethers VI and VII, lead us to conclude that there exists a second possible pathway for dealkylation accompanying azo coupling, namely, ether group cleavage in the final products. The dealkylation pathway discussed above (where ether group cleavage occurs during the course of azo coupling itself) is apparently realized only in the case of relatively unreactive (low-activity) azo components, and only when substitution occurs ortho to the ether group; this pathway leads to a reduction in the activation barrier due to the existence or appearance of hydrogen bonding in the transition state. For example, reaction of I with 1-naphthol according to this pathway leads to the formation of the 8'-hydroxy substituted product IX, which is confirmed by the fact that there is no evidence for the presence of even traces of the 8-alkoxy substituted azo compound in the reaction mixture. Dealkylation in the final product stage can affect ether groups in any position, and does not lead to a substantial decrease in the yield of methoxy substituted azo compounds (cf. [1]). The exception to this trend is reaction of salt I with 2-naphthol; the product of this reaction, namely, compound XII, undergoes anomalously easy hydrolysis. The factor responsible for this behavior of compound XII is probably a favorable conformation in the azo compound, suggesting that an ortho-orientation of methoxy group relative to the azo bridge is not a necessary condition for the ease of hydrolysis (cf. XIII).

The structures of azo compounds VIII-XII were verified based on the results of elemental analysis, their PMR and IR spectral data, and the hydrolysis of compounds XI and XII. The PMR spectra of compounds VIII and X-XII (Table 2) contain signals for the 8'-H proton in the range 9.18-8.74 ppm, in the form of a broad doublet (due to spin–spin coupling with the protons in the unsubstituted naphthalene ring [5]). The observed downfield shift for the α-proton in the naphthalene ring indicates that the azo compound exists in an S,Z-conformation, in which the 8'-H proton falls within the deshielding cone of the azo group. The position of the 8'-H proton signals also leads us to conclude that the potential tautomeric compounds VIII and X exist predominantly in the azo form (cf. [6, 7]), since in the case of quinoid forms for azo substituted naphthalenes the 8'-H signal should appear significantly more upfield [8]. In the spectrum of compound IX there is not weak field doublet which appears isolated from the multiplet due to the other aromatic protons, and this is consistent with its assigned structure.

The upfield portion of the aromatic proton resonance region in the spectra of compounds VIII-XI is characterized by the presence of one more isolated doublet at 6.79-6.46 ppm. In the case of compounds VIII, X, XI this sharp signal represents the proton in the 3'-position which is split due to coupling with the 4'-H proton. Compound IX, on the other hand, exhibits a broad doublet at 6.79 ppm, which is assigned to the 7'-H proton which is split by the 6'-H proton and broadened due to further interaction with the 5'-H proton. The presence of this upfield doublet in the spectrum of isomer IX excludes the otherwise possible 1,2-substituted azo compound structure for the side product of the azo coupling reaction of diazo cation I with compound VI, since in the case of that putative isomer the proton in the 4'-H position cannot appear so high upfield, representing as it does both a para- and α-proton. The absence of an isolated upfield doublet in this region in the spectrum of compound XII is probably due to a weakened shielding effect of the methoxy group, which is deviated from conjugative interaction for steric reasons.

The IR spectra of these products exhibit characteristic absorption bands which provide suitable structural evidence or identification for azo compounds in this benzimidazole series containing naphthalene azo components (Table 2). In the case of compounds VIII-XI the most characteristic region of their spectra if the range of out-of-plane bending vibrations (deformations) for the aromatic C–H bonds. Compounds VIII, X-XII contain three intense bands in this region, two of which at 740-730 and 760-745 cm^{-1} correspond to vibrations of four adjacent C–H bonds in the benzimidazole and naphthalene fragments of the molecules. The third band, which is less intense, at 840-805 cm^{-1}, arises due to two neighboring C–H bonds in a 1,4- or 1,2-disubstituted naphthalene ring. Also, in accord with literature data [9], this peak is accompanied by a weaker absorption band at 715-700 cm^{-1}.

In contrast to the spectra of azo compounds VIII, X-XII, containing substituents in only one ring of the naphthalene fragment, in the spectrum of the 8′-hydroxy substituted derivative IX one of the bands due to 1–H absorption has disappeared, and a new intense peak is present at 790 cm^{-1}, which is characteristic of three adjacent C–H bonds in a naphthalene derivative with substituents in both rings.

Compounds IX and X do not contain any significant absorption in the OH stretching vibration region, which has been noted often in the spectra of azo compounds with possible intramolecular hydrogen bonding [5]. The 4′-hydroxy substituted derivative VIII exhibits a broad band with a maximum at 3290 cm^{-1}, which is shifted to 3340 cm^{-1} in chloroform solution. Although the positions of the remaining peaks in the IR spectra of these compounds do not contradict their assigned structures, neither have we been able to discern any correlations with the positions of the substituents in the naphthalene rings.

In conclusion, azo coupling of diazonium ion I with naphthols IV and V and their ethers VI and VII in acidic media results, in addition to the normal orientation of diazo cation to 1-naphthol, in substitution at the 8-position as well; this occurs apparently, only in the case of active diazonium salts of type I. During the course of azo coupling of salt I with 2-naphthol methyl ether an unusually high degree of dealkylation is observed, due to the anomalously high reactivity of the ether group in the final azo coupling product XII with respect to hydrolytic cleavage.

EXPERIMENTAL

IR spectra were obtained on a Specord IR-75 spectrophotometer using Vaseline mulls of chloroform solutions. PMR spectra (versus HMDS as internal standard) were measured in $CDCl_3$ or DMF-D_7 solution using a Varian XL (100 MHz) spectrometer. The course of reactions and the purity of reaction materials were monitored by TLC on Brockman activity II-grade Al_2O_3 using chloroform or a mixture of chloroform–alcohol (9:1) as eluent. Column chromatography was also carried out on activity II grade Al_2O_3.

The results of C, H, N elemental analysis for the newly synthesized compounds agreed with calculations.

2-Amino-1-methylbenzimidazole was prepared by alkylation of 2-aminobenzimidazole with methyl iodide according to [10]. 2-(2-Methoxy-5-methylphenylazo)-1-methylbenzimidazole (XIII) was prepared according to a literature procedure [1].

2-Amino-1-methylbenzimidazole II was dissolved in 85% phosphoric acid using sodium nitrite, according to [1].

2-(4-Hydroxynaphthylazo)-1-methylbenzimidazole (VIII) and 2-(8-Hydroxy-naphthylazo)-1-methylbenzimidazole (IX). A. To a solution of 3 g (21 mmoles) compound IV in 60 ml glacial acetic acid, which was stirred and cooled to 10°C, was added a solution of diazonium salt I, which had been prepared from 2.94 g (20 mmoles) amine II in 32 ml conc. H_3PO_4. The flask used to add the diazo solution was rinsed with a mixture of 5 ml CH_3COOH and 3 ml H_2O. After 1 h the stirring and cooling was discontinued and the mixture was allowed to stand for 13-14 h at 20°C. The mixture was then poured into 300 ml water, and the precipitate was removed by filtration, dried at 50°C, and washed with 30 ml ether. The precipitate was then triturated with 50 ml of 1% ammonia solution, filtered, and washed with 0.5 liter of hot water. The total yield of isomers VIII and IX was 73%. The mother liquor also contained about 4% of contaminated isomer VIII. The isomers were separated by treating the mixture with 80 ml boiling benzene for 10-15 min; 3.7 g (62%) of pure 4′-hydroxy isomer VIII was removed by filtration after this treatment process. The benzene extract was evaporated and subjected to further fractional precipitation with petroleum ether from a hot saturated solution in $CClD_4$. Loss of isomer IX is significant in this procedure, and so its yield was determined in a separated experiment the following way. A solution of 1 g of material, namely, the azo coupling mixture VIII and IX, in 5 ml chloroform, was passed through an Al_2O_3 column (l = 25 cm, d = 2.2 cm) with CCl_4–$CHCl_3$ (1:2) eluent, and the first violet fraction was collected, corresponding to isomer IX. Yield 0.095 g (9.5%).

B. To a 10°C-cooled solution of 3 g (21 mmoles) compound IV in 90 ml aqueous acetic acid (1:2) was added a solution of diazonium salt I, which had been prepared from 2.94 g (20 mmoles) amine II in 30 ml conc. H_3PO_4. Over the course of 1 h and 30 min the reaction mixture was further diluted by the addition in portions of 70 ml water, and the reaction mixture

was then maintained for 5-6 h at 20°C; an additional 200 ml water was added, and the precipitate was removed by filtration and dissolved (triturated) in 50 ml 1% ammonia solution, then dried at 50°C. The isomers were separated by treating the precipitate with 10-15 ml boiling benzene. After evaporation of the benzene extract and chromatography of the residue on an Al_2O_3 column (l = 35 cm, d = 2.5 cm) with $CHCl_3-CCl_4$ (2:1), the yield of azo compound IX was 0.18 g (3%). The residue remaining after extraction with benzene (4.8 g, 80%) consisted of the 4′-hydroxy isomer VIII.

2-(4-Methoxynaphtylazo)-1-methylbenzimidazole (XI). Prepared by azo coupling reaction of diazonium salt I, synthesized from 2.94 g (20 mmoles) amine II, with 3 g (21 mmoles) of 1-methoxynaphthalene IV, storing the reaction mixture for 15 h (method A) or 7-8 h (method B). The mixture was neutralized with 5% ammonia to pH 7-8, and the precipitate was removed by filtration and dried at 50°C, then treated with 100 ml boiling acetone for 10 min. Isolation of azo compound XI from the reaction mixtures for A and B was accomplished in the following manner.

A. The hot acetone solution was filtered, yielding 0.4 g of methoxy substituted product XI, and after 13-15 h another 2 g of azo compound XI was separated; the acetone extract was then evaporated and the residue subjected to column chromatography on Al_2O_3 (l = 25 cm, d = 2.5 cm) via elution with $CHCl_3-CCl_4$ (2:1), yielding a dark orange fraction containing XI. The overall yield of compound XI was 3.54 g (56%).

The adsorbent material was extruded from the column and the violet fraction was cut out, extracted with alcohol, and the solution evaporated to give 0.96 g (16%) of a mixture of hydroxy substituted products VIII and IX. These were separated according to the procedure discussed above to yield 0.36 g (6%) 4′-hydroxy isomer VIII and 0.60 g (10%) 8′-hydroxy isomer IX.

B. After treatment of the reaction products with boiling acetone a precipitate consisting of 0.30 g of a mixture of methoxy substituted derivative XI and triazene III was removed by filtration. The precipitate was treated with 20 ml chloroform, and the insoluble portion containing triazene III was filtered off; the chloroform mother liquor was combined with the acetone filtrate was evaporated. The residue was purified chromatographically, as described above in experiment A, yielding 4.93 g (78%) of compound XI and 0.12 g (2%) of a mixture of hydroxy-substituted derivatives VIII and IX.

2-(2-Hydroxynaphthylazo)-1-methylbenzimidazole (X). Prepared by azo coupling of diazonium salt I, itself prepared from 2.94 g (20 mmoles) amine II, with 3 g (21 mmoles) 2-naphthol, dissolved in a mixture of 45 ml CH_3COOH and 30 ml H_2O. After 18 h (as in method A above) or 6-7 h (method B) the reaction mixture was neutralized with sodium hydroxide solution to pH 7. The resulting precipitate was removed by filtration, dried, and triturated with 60 ml of benzene–petroleum ether (1:2). In order to purify the product from triazene III contamination the material was dissolved in 50 ml chloroform, the insoluble yellow portion corresponding to triazene III was filtered off, and the chloroform solution was evaporated to give azo compound X.

2-(2-Methoxynaphthylazo)-1-methylbenzimidazole (XII). Prepared from diazonium salt I and 2-methoxynaphthalene VII, in the same proportions as in the experiment for compound XI. The reaction products were isolated from their respective reaction mixtures from methods A and B using the following procedures.

A. After completion of the azo coupling reaction step the reaction mixture was neutralized with soda to pH 7, the oily precipitate was separated and treated with 25 ml boiling ethanol for 10 min; hydroxy derivative X was insoluble under these conditions and was removed by filtration. The alcohol mother liquor was evaporated and then purified by column chromatography (l = 40 cm, d = 2.2 cm) using $CHCl_3-CCl_4$ (1:1) eluent mixture; the orange fraction corresponding to compound XII was collected. Yield 0.51 g (8%). The adsorbent column was extruded and the violet fraction excised and extracted with acetone to give the dealkylation product X. The overall yield of compound X was 4.35 g (72%).

B. The reaction mixture remaining after neutralization contained an oily residue which was refluxed with 50 ml ethanol; the mixture was then filtered to separate 0.35 g of a mixture of triazene III and azo compound XII. This solid mixture was further triturated with 20 ml chloroform, and the insoluble portion corresponding to triazene III was removed by filtration; the chloroform mother liquor was combined with the alcohol filtrate and evaporated. The residue was purified by column chromatography as describedin part A above, to give 3.34 g (53%) of methoxy derivative XII and 1.40 g (22%) of its dealkylation product X.

Hydrolysis of Methoxy Substituted Azobenzimidazole Derivatives XI, XII, and XIII. A solution containing 1 mmole of azo compound XI, XII, or XIII was prepared in 10 ml of the acidic solvent mixture corresponding in composition to that used in experiments A and B, respectively, and the solution was stored at 20°C. At appropriate intervals after reaction onset (1 h, 1 h 30 min, 2 h, and 2h 30 min for compound XII; 5, 21, 33, 47 h for compound XI in experiment A, etc.) the reaction mixture was poured into 25 ml water, neutralized with soda solution to pH 7, and extracted with chloroform (2 × 15 ml) to give a mixture of azo compounds. The chloroform extract was evaporated and the residue separated by column chromatography

(l = 20 cm, d = 2 cm) using $CHCl_3-CCl_4$ (1:1) as eluent; the orange fraction corresponding to the initial methoxybenzimidazole derivative was eluted first, followed by the violet fraction corresponding to the hydroxy-substituted product. The weights of methoxybenzimidazole fractions XI, XII, XIII were compared against the weights of control samples, which were subjected to the same experimental procedures, but dissolved initially in 0.1 N H_2SO_4 and neutralized almost immediately after mixing. The time needed to achieve hydrolysis of half the original starting material was noted ($1_{1/2}$). The half-life times are only approximate, since the degree of hydrolysis at the indicated intervals was between 47 and 57%.

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