[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI, CINCINNATI 21, OHIO]

The Wallach Rearrangement. I. The Behavior of 4-Substituted Azoxybenzenes in Strongly Acidic Solution[1]

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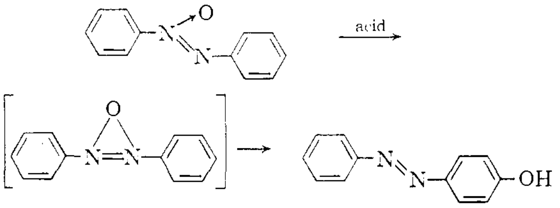
The rearrangement of 4-substituted azoxybenzenes into hydroxyazobenzenes has been studied by an ultraviolet spectrophotometric method and by isolation of the rearranged compounds. The oxygen atom in the azoxy group migrated to the unsubstituted ring, depending neither on the substituent already present in the other ring, nor on the distance between the oxygen atom and the available position. The position in the open ring, *ortho* or *para*, to which the oxygen migrates depends on the substituent already present in the other ring.

Wallach[3] has reported that azoxybenzene is rearranged into 4-hydroxyazobenzene in the presence of acid, and Bandish and Fürst,[4] and Cumming and Steel[5] have reported that both 1,1′- and 2,2′-azoxynaphthalenes rearrange under irradiation by sunlight or ultraviolet light to hydroxyazonaphthalenes, in which the hydroxy group is *ortho* to the azo group. Badger and Buttery[6] have supported Cumming's work and proposed that the mechanism of the rearrangement is intermolecular in nature. Shemyakin, Maimind and Vaichunaite[7] have recently reported results on the rearrangement of azoxybenzene labeled with N^{15}. They found that, at room temperature, the two benzene rings were attacked by the oxygen atom with equal ease and concluded that the initial step is probably the formation of an intermediate containing a 3-membered NNO ring



They believe that, subsequently, the oxygen may migrate equally to either benzene ring, since the intermediate is symmetric.

At elevated temperature (90°), they found preponderance of migration to the far ring, and proposed an alternate mechanism in which the oxygen atom migrates directly without involvement of the 3-membered cyclic oxide. To date, none of the mechanisms of the rearrangement have been demonstrated conclusively.

In connection with a study of the basicities of azoxy compounds in this Laboratory,[8] the Wallach rearrangement was observed to occur when dilute solutions of azoxybenzene were treated with sulfuric acid. Preliminary experiments showed that this reaction, which was observed as a disturbing side reaction, led rapidly to a quantitative yield of 4-hydroxyazobenzene. These observations aroused our curiosity about the mechanism of this reaction. Since the basicity studies particularly involved compounds substituted in the *p*-position of one ring only, the behavior of such compounds under rearrangement conditions was investigated.

Experimental

Compounds.—**4-Hydroxyazobenzene, 4-hydroxy-4′-bromoazobenzene and 4-hydroxy-4′-methoxyazobenzene,** which were previously prepared in this Laboratory,[9] were recrystallized 2 to 3 times until each of the known constant melting point was obtained.

4-Hydroxy-4′methylazobenzene was prepared by the coupling of the diazonium salt (chloride) of toluidine[10] with phenol in alkaline solution; m.p. 151° (lit. 151°).

2-Hydroxy-4′-methylazobenzene[11] was obtained in a very small yield as a side product in the preparation of the isomer 4-hydroxy-4′-methylazobenzene. The separation of the *o*-isomer, 2-hydroxy-4′-methylazobenzene, from the *p*-isomer was achieved by steam distillation. The 2-hydroxy compound was isolated from the distillate by precipitation with about 50% alcoholic copper acetate solution. The copper salt was destroyed with HCl, the solution extracted with ether, and the compound recrystallized from boiling EtOH; m.p. 100° (lit.[11] 100–100.5°).

2-Hydroxy-4-methylazobenzene was prepared by coupling of nitrosobenzene with 2-hydroxy-*p*-toluidine (4-amino-*m*-cresol[12]) which was prepared by nitration of *m*-cresol.[13] In the nitration, the 2- and 6-nitro isomers are formed, together with the desired 4-nitro-*m*-cresol. Steam distillation separated the non-volatile 6-nitro compound from the other two. The 4-nitro isomer crystallized from the distillate, and was purified by recrystallization from benzene; m.p. 56° (lit.[11] 56°). Any 2-nitro isomer formed remained in the steam distillate. The 4-nitro compound was reduced with iron and HCl to 2-hydroxy-*p*-toluidine, which was coupled with nitrosobenzene by the usual procedure,[9] yielding 2-hydroxy-4-methylazobenzene, which was purified by chromatography on alumina from ligroin (60–90° fraction); m.p. 122° (lit.[12] 121–122°).

Anal. Calcd. for $C_{13}H_{12}ON_2$: C, 73.56 H, 5.69; N, 13.21. Found: C, 72.93; H, 5.53; N, 13.44.

The compound could also be prepared by coupling of nitrosobenzene with 2-acetyl-*p*-toluidine, which was prepared by acetylation of 4-nitro-*m*-cresol and reduction with iron and HCl. The hydroxyazo compound prepared in this way could, however, not be obtained in a completely pure form, although its ultraviolet spectrum was identical with that of a sample obtained by the first method.

Azoxybenzenes.—The preparation of the azoxybenzenes used was described in a previous paper.[8]

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[1] This work was supported jointly by a Grant in Aid from the American Cancer Society, and by the Office of Ordnance Research, U. S. Army.

[2] Abstracted from the University of Cincinnati Ph.D. Thesis of C. S. H.

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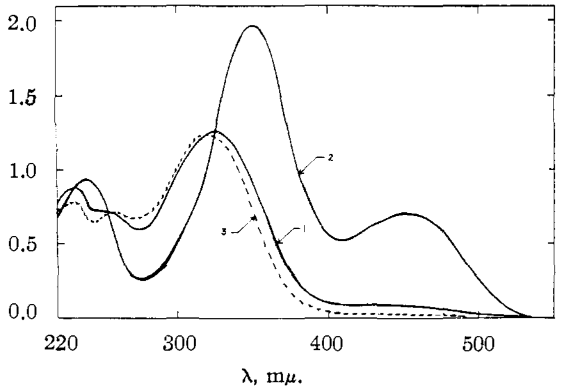


Fig. 1.—The spectrum of azoxybenzene in: 1, "9% H_2SO_4" diluted from "90% H_2SO_4"; 2, "10% H_2SO_4" diluted from "100% H_2SO_4"; 3, "9% H_2SO_4" prepared directly.

Rearrangement and Measurement.—All stock solutions of azoxybenzenes and hydroxyazobenzenes were prepared in the manner described in the previous paper.[8] The Wallach rearrangement was produced in the last step of serial dilution, when the final stock solution (5×10^{-4} M) was diluted to 5 times its volume with 100% sulfuric acid; during this step the solutions were not cooled and this was sufficient to produce complete rearrangement. The rearranged solutions were then further diluted to 10 times their volume with 20% EtOH, so that the final solvent consists of 20% EtOH and 80% of 10 vol. % aqueous H_2SO_4. The final concentration of rearranged azoxybenzenes was then 10^{-5} M. Solutions of hydroxyazobenzenes were also prepared in the same manner, and a final stock solution (5×10^{-4} M) of hydroxyazobenzene was diluted to five times its volume with 10% H_2SO_4, yielding a solution in the same medium as the rearranged azoxy compound, but only one-tenth as concentrated. The spectral measurements of the compounds under investigation were made using a Cary model 11 recording spectrophotometer; 10-cm. silica cells were used for the 10^{-5} M solutions, 1-cm. cells for 10^{-4} M solutions.

Isolation of the Rearranged Azoxybenzenes.—Isolation of the rearranged azoxybenzenes was carried out by two methods. In the first method, the strongly acidic solution in which the azoxy compound had rearranged was neutralized very slowly with concentrated (*ca.* 35–36 N) NaOH solution until the pH of the solution was about 9; the solution was kept cold throughout the neutralization in an acetone–Dry Ice-bath. The precipitate formed was removed by filtration, and the filtrate was extracted with ether. By this method, 4-hydroxyazobenzene and 4-hydroxy-4′-bromoazobenzene were isolated from the corresponding rearranged azoxy compounds. In the second method, the reaction mixture in acidic solution was refluxed and then was poured into an ice–water-bath. A precipitate appeared, which was removed by filtration and washed several times with ice–water. The crude product was recrystallized from 95% EtOH. By this method 2-hydroxy-4′-methylazobenzene was isolated. The products were characterized by spectra, melting points and mixed melting points with authentic samples.

Discussion

Azoxybenzene.—The nature of the Wallach rearrangement was first examined with azoxybenzene. The spectra of solutions of this compound in a solvent consisting of 20 vol. % ethanol and 80 vol. % of aqueous sulfuric acid containing x vol. % H_2SO_4 were obtained for $x = 9$, 90 and 100%. Such solutions will be referred to below as "9% H_2SO_4," "90% H_2SO_4," etc., for convenience. The spectrum in "90% H_2SO_4" is ascribed to the conjugate acid of azoxybenzene. When such a solution is diluted to 10 times its volume with 20% ethanol, the spectrum of the resulting solution, shown in Fig. 1, is virtually superimposable with a "9% H_2SO_4" solution made directly with 9% H_2SO_4. This indicates that in "90% H_2SO_4" almost no rearrangement has occurred, and that the species present in this medium is formed by a readily reversible reaction, presumably the acid–base reaction postulated. Azoxybenzene, however, has distinctly different spectrum in "100% H_2SO_4" from that in "90% H_2SO_4," and 10-fold dilution does not reverse the spectrum to that of azoxybenzene. Figure 2 compares the spectra of the "100% H_2SO_4" solution and of the solution obtained by 10-fold dilution therefrom with the spectra of corresponding solutions of 4-hydroxyazobenzene. The spectra of the corresponding solutions are seen to be superimposable, indicating that the azoxy compound was rearranged quantitatively to 4-hydroxyazobenzene. The identity of the rearranged product was further verified by isolation.

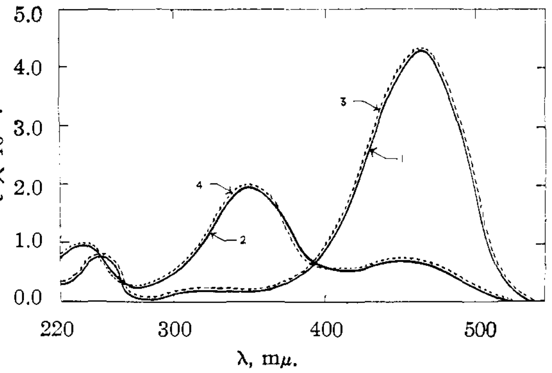


Fig. 2.—The spectra of azoxybenzene in: 1, "100% H_2SO_4" and, 2, "10% H_2SO_4" diluted from "100% H_2SO_4"; and 4-hydroxyazobenzene in 3, "100% H_2SO_4" and, 4, "10% H_2SO_4" diluted from "100% H_2SO_4."

4-Substituted Azoxybenzenes.—Barring tracer experiments, it is not possible to determine whether the oxygen atom of azoxybenzene or of 4,4′-disubstituted azoxybenzenes migrates to the near or far ring during the Wallach rearrangement. In monosubstituted azoxybenzenes, however, it should be readily possible to determine the direction of migration. To investigate this problem, α- and β-4-bromo-, methyl- and methoxyazoxybenzenes were investigated by ultraviolet spectrophotometry in the same way as azoxybenzene, and the rearranged compounds were isolated and identified.

The spectra of the α- and β-isomers of 4-bromoazoxybenzene solution in "10% H_2SO_4" which were obtained by dilution of solutions in "100% H_2SO_4" are shown in Fig. 3 and compared with the spectrum of 4-hydroxy-4′-bromoazobenzene in "10% H_2SO_4." These spectra are superimposable. This fact indicates that both α- and β-4-bromoazoxybenzene in 100% H_2SO_4 solution quantitatively rearrange to 4-hydroxy-4′-bromoazobenzene, independent of the position of the bromine atom already present in the starting material. These findings were confirmed by isolation of 4-hydroxy-4′-bromoazobenzene from the solution of α-4-bromoazoxybenzene treated with 100% H_2SO_4. In other words, the oxygen atom of the azoxy group of the compound migrates to the p-position

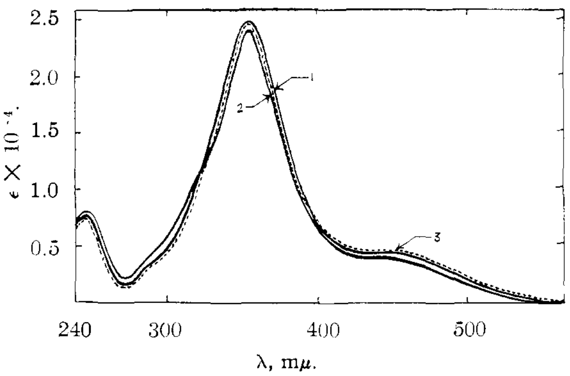


Fig. 3.—The spectra of rearranged (1), α-, (2) β-4-bromoazoxybenzene in "10% H_2SO_4," diluted from "100% H_2SO_4," and (3) of 4-hydroxy-4′-bromoazobenzene in "10% H_2SO_4."

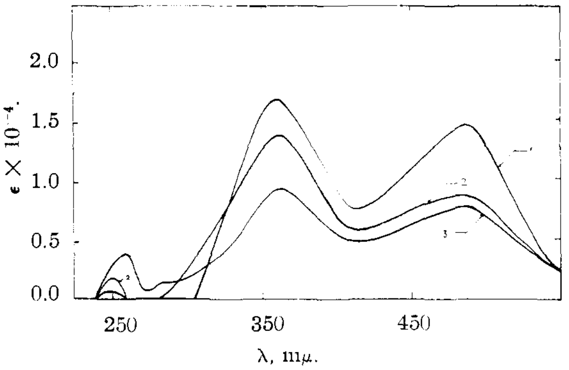


Fig. 4.—The spectra of (1) 4-hydroxy-4′-methoxyazobenzene in "10% H_2SO_4" and of (2) α-, and (3) β-4-methoxyazoxybenzene in "10% H_2SO_4" diluted from "100% H_2SO_4."

of the unsubstituted ring. It seems that the migration of the oxygen atom does not depend on its distance from the available position. There is no evidence that the oxygen atom migrates to the *o*-position of either of the rings, whether substituted or not.

The spectra of α- and β-4-methoxyazoxybenzene in "10% H_2SO_4" diluted from "100% H_2SO_4" solutions are shown in Fig. 4 together with the spectrum of 4-hydroxy-4′-methoxyazobenzene in the same medium. Comparison of these spectra strongly suggests that most of the α- and β-4-methoxybenzene had rearranged to 4-hydroxy-4′-methoxyazobenzene, but it appears that the rearrangement of the methoxy compounds does not proceed as cleanly as those of azoxybenzene and the isomeric 4-bromoazoxybenzenes. Although the fate of the portion of azoxy compound not forming 4-hydroxy-4′-methoxyazobenzene has not been investigated, the spectroscopic results suggest that a side reaction occurs, forming products absorbing at shorter wave lengths, rather than an incomplete rearrangement. Furthermore, the yield of hydroxyazo compound from α-4-methoxyazoxybenzene seems to be larger than from the β-isomer under the same condition. However, no comparison of rates of the rearrangements has been made so far. Thus the Wallach rearrangement of the isomeric 4-methoxyazoxybenzenes proceeds in the same way as their bromo analogs, although with lower yields.

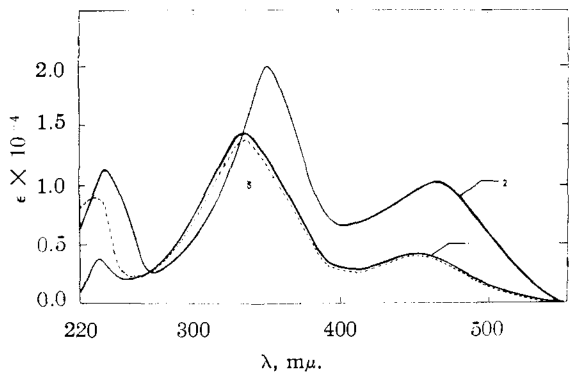
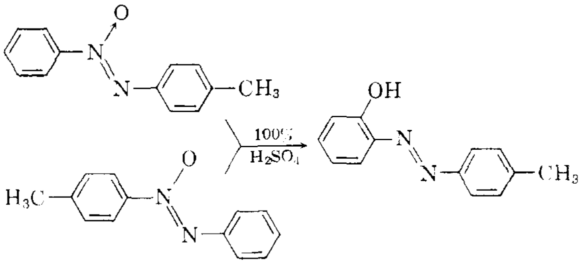


Fig. 5.—The spectra of (1) α- and β-4-methylazoxybenzene in "10% H_2SO_4" diluted from "100% H_2SO_4"; (2) 4′-, (3) 2′-hydroxy-4-methylazobenzene in "10% H_2SO_4."

The products of the rearrangement of α- and β-4-methylazoxybenzene differ markedly from those of the other compounds described above. The spectra of α- and β-4-methylazoxybenzene, 2- and 4-hydroxy-4′-methylazobenzene treated in the same manner as the other compounds are shown in Fig. 5. It appears obvious that both α- and β-isomer of 4-methylazoxybenzene rearrange to the same product, and that this is 2-hydroxy-4′-methylazobenzene. Thus, the oxygen atom of the azoxy group of both α- and β-4-methylazoxybenzene migrates to the *o*-position of the unsubstituted ring under the same conditions, not to the *p*-position as in the compounds discussed above.



Although the intensities of the 243 mμ band of authentic 2-hydroxy-4′-methylazobenzene and rearranged α- and β-4-methylazoxybenzene differ slightly, the 336 mμ and 450 mμ bands are cleanly superimposable.

In order to confirm that the rearrangement of 4-methylazoxybenzenes leads to the *o*-substituted product, the rearranged product was isolated from the solution in which β-4-methylazoxybenzene was diluted with 100% H_2SO_4. The spectrum of the isolated compound is superimposable with the spectrum of the isolated compound is superimposable with the spectrum of the authentic compound.

There can, thus, be no doubt that α- and β-4-methylazoxybenzene in strongly acid solution completely rearranged to 2-hydroxy-4′-methylazobenzene.

Thus, it is found that the oxygen atom of 4-mono substituted azoxybenzenes migrates to the unsubstituted ring, independent of the substituent already present in the other ring, independent of the substituent already present in the other ring. In the 4-bromo and 4-methyl compounds, the α- and

β-isomers give identically quantitative yields of the same compound. In the 4-methoxy compounds, the yields are neither quantitative nor equal, but apparently, judging from the spectra obtained, the other products are not hydroxymethoxyazobenzenes. Probably side reactions occurring at different rates complicate the reaction. The findings thus seem to confirm the Russian workers proposed mechanism involving a three-membered ring intermediate.[7]

The most unexpected finding is that, whereas the oxygen atom migrates to the free *p*-position in both the 4-bromo- and 4-methoxy compounds, it migrates to an *o*-position (in the unsubstituted ring) in the 4-methyl compound. This is even more surprising since the electronic effect of the methyl group is generally considered intermediate between the bromo and methoxy groups. No explanation for this surprising finding can be offered at this time. It is conceivable that minor differences in reaction conditions give rise to the observed differences in behavior. This possibility, however, is extremely unlikely because the reactions are so clean, giving no indication that mixtures are obtained. The question is being investigated further.

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The Basicities of Substituted Azoxybenzenes[1]

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The basicities of sixteen 4-, 4'- and 4,4'-substituted azoxybenzenes were determined. The effect of substituents on the basicities of these compounds and the structure of the conjugate acid of azoxybenzenes are discussed.

Although a tremendous amount of work has been concerned with the structure and stereochemistry of the azoxy group,[3] particularly in azoxybenzene and its derivatives, little is known about the physico-chemical behavior of this group. In connection with studies in this Laboratory of the base strengths of azobenzene derivatives[4] and of other weak nitrogen bases and their N-oxides,[5] we have now undertaken an investigation of the base strengths of azoxybenzene and substituted azoxybenzenes, about which no previous work has been reported. The pK_a's of the conjugate acids of the parent compound, four symmetrically disubstituted, nine monosubstituted and two unsymmetrically disubstituted derivatives were determined by a standard spectrophotometric method[6] in 20% ethanolic solution of sulfuric acid.[4]

Experimental

Compounds.—All the azoxybenzenes under investigation are 4-, 4'-mono- and 4,4'-disubstituted compounds, which were prepared by oxidation of the appropriate azobenzene derivatives.[7] The azobenzenes, in turn, were prepared by condensation of anilines and nitrosobenzenes.[8] The anilines were commercially available; the nitroso compounds were prepared by reduction and oxidation from nitro compounds.[9] Oxidation of the azo compounds, in general, produces mixtures of α- and β-azoxybenzenes, which were separated by chromatography on columns of alumina. The compounds were repeatedly recrystallized, usually from aqueous alcohol, until melting points were unchanged and agreed with literature values. The compounds and their melting points are listed in Table I.

Spectrophotometric and Acidity Measurements.—The methods used were substantially the same as those previously described.[4] The spectra of the various compounds, in neutral and acid solution, were recorded using a Cary model 11 spectrophotometer. Titration curves at selected wave lengths (ϵ *vs.* Ho) were determined using a Beckman model DU quartz spectrophotometer. Although at the wave lengths used in the work on azo compounds,[4] water was found to be adequate as material in reference cells, at the wave lengths used in the present work, particularly below 250 $m\mu$, preliminary work showed that it was essential to have solutions having the same water–sulfuric acid–ethanol ratio in the reference cell as in the sample compartment. Consequently, reference solutions were prepared just like sample solutions, omitting the azoxy compound.

Preparation of Solutions.—Solutions (5×10^{-5} *M*) of the azoxy compounds in a solvent consisting of 20% ethanol and 80% sulfuric acid-water mixture of various composition were required for the determination of the titration curves. In the preparation of such solutions, considerable heat is obviously evolved. In our previous work with azo compounds we had found that reproducible results could be obtained by mixing precooled 10^{-4} *M* stock solutions of the substrate with precooled and premixed water–sulfuric acid mixtures in an ice-bath, provided the process was performed slowly. Similar mixing of azoxybenzene stock solutions with sulfuric acid–water mixtures invariably led to solutions containing various amounts of hydroxyazo compounds, formed by the Wallach rearrangement,[10] when the sulfuric acid in the aqueous component exceeded about 50%. Thus occurrence of the Wallach rearrangement could not be prevented by cooling to lower temperatures or by slowing down additions, and is believed to be due to local heating at the point where a drop of one solution first comes in contact with the other. The technique of using a single stock solution was considered highly desirable because it ensures constant

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[1] This work was supported jointly by a Grant in Aid from the American Cancer Society, and by the Office of Ordnance Research, U. S. Army.

[2] Abstracted from the University of Cincinnati Ph.D. thesis of C.S.H.

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