

acetic acid. The precipitated solid was filtered off, washed with water and suspended in a sodium bicarbonate solution to remove any free acid. The solid was filtered off, washed several times with water and air-dried. The product which weighed 15.0 g. (70%) melted at 183–184°.

E. Acid Hydrolysis of 2-(N⁴-Acetylsulfanilamido)-5-iodopyridine.—A solution of 10 g. (0.024 mole) of 2-(N⁴-acetylsulfanilamido)-5-iodopyridine in 100 cc. of 10% hydrochloric acid and 100 cc. of alcohol was refluxed for ninety minutes.⁹ The solution was treated with decolorizing carbon, filtered and the pH adjusted to about 5. The alcohol was then removed under reduced pressure and the precipitated solid filtered off, washed with water and air-dried. After crystallization from alcohol the product, which weighed 8.5 g. (94%), melted at 219–221°.

F. Alkaline Hydrolysis of 2-(N⁴-acetylsulfanilamido)-5-methylpyridine.—A solution of 74.5 g. (0.244 mole) of 2-(N⁴-acetylsulfanilamido)-5-methylpyridine in 750 cc. of a 5% aqueous sodium hydroxide solution and 25 cc. of alcohol was refluxed for thirty-five minutes.⁹ Five grams of decolorizing carbon was added, the solution refluxed for an additional ten minutes and then filtered. The pH of the filtrate was adjusted to about 5 and the precipitated solid filtered off, washed several times with water and air-dried. The crude product, weighing 61 g. (95%), melted at 184–186°. After crystallization from 95% alcohol the 2-sulfanilamido-5-methylpyridine which weighed 43 g. (67%) melted at 188–189°.

G. Reduction of Ethyl 6-*p*-Nitrobenzenesulfonylamidonicotinate.—A mixture of 72 g. (0.206 mole) of ethyl 6-*p*-nitrobenzenesulfonylamidonicotinate, 200 g. of iron powder and 650 cc. of 95% alcohol was placed in a 2-liter, 3-necked flask fitted with a mercury-sealed stirrer, reflux condenser and dropping funnel. The reaction mixture was heated to reflux and 14 cc. of 18% hydrochloric acid added dropwise with vigorous stirring. The mixture was heated for five and one-half hours after the addition of the acid was complete, and then allowed to stand overnight at

(9) In the hydrolysis of each compound, refluxing was continued until the potassium nitrite titer of an aliquot had reached a maximum. The potassium nitrite titration could not be used with derivatives of 2,6-diaminopyridine so the hydrolyses of these compounds were carried out for sixty to ninety minutes unless otherwise noted.

room temperature. The solid was filtered off, suspended in 1400 cc. of water and 5% sodium hydroxide solution added until the solution was alkaline. The mixture was filtered and the filtrate acidified with acetic acid to obtain the crude product. The extraction of the iron residue was repeated until the filtrate gave no precipitate upon acidification. The product was purified by solution in aqueous ammonia, treatment with decolorizing carbon and acidification. After crystallization from 95% alcohol the material weighing 54.9 g. (82%) melted at 201–202°.

H. Hydrolysis of Ethyl 6-Sulfanilamidonicotinate.—A mixture of 19 g. (0.06 mole) of ethyl 6-sulfanilamidonicotinate, 19 g. of barium oxide, 800 cc. of 95% alcohol and 8 cc. of water was refluxed for five and one-half hours, then cooled and the solid filtered off. The precipitate was dissolved in water, treated with decolorizing carbon, filtered and the solution acidified to pH 6 with concentrated hydrochloric acid. The solid was filtered off, washed with water and air-dried. The acid, which weighed 15.0 g. (85%), melted at 251°; crystallization from alcohol raised the melting point to 252–253°.

I. 2-Sulfanilamido-6-ureidopyridine.—A solution of 80 g. (0.238 mole) of 2-sulfanilamido-6-carbomethoxyamidopyridine in 360 cc. of absolute alcohol, containing 20 g. of ammonia, was heated at 105–110° for twelve hours. The solution was then concentrated to 120 cc. and cooled. The solid which crystallized out was filtered off and washed with a small amount of cold absolute alcohol. The crude product, which weighed 50 g. (68%) and melted at 200–205° dec., was purified by solution in dilute sodium hydroxide, treatment with decolorizing carbon and precipitation with dilute hydrochloric acid. After crystallization from absolute alcohol the product, weighing 31 g. (42%), melted at 214–216° dec.

Summary

A number of substituted sulfanilamidopyridines have been synthesized. None of the compounds synthesized showed any promise as antimalarial agents.

NEW BRUNSWICK, N. J.

RECEIVED SEPTEMBER 3, 1946

[CONTRIBUTION FROM CALCO CHEMICAL DIVISION, AMERICAN CYANAMID CO.]

Chemical Constitution and Reactivity. II. The Decomposition of *o*-Methoxybenzenediazonium Chloride

By M. L. CROSSLEY, R. H. KIENLE, C. H. BENBROOK¹ AND N. T. WOODBERRY

Introduction

The assignment of chemical structures to the molecular forms which diazo compounds may assume under various conditions of pH, dilution, etc., has occupied the attention of many chemists since the time of Peter Griess. The earlier investigators based their conclusions largely on organochemical investigations. The work of Hantzsch^{1a} on the structure of diazotates marked one of the first uses of physico-chemical methods in the accumulation of evidence in support of an organic chemical structure. More recently such workers

as Waters,² Waring,³ and ourselves⁴ have demonstrated the usefulness of *chemical kinetics* in pointing to the probable truth of one or another concept of the structure of certain diazo compounds. Among the diazo compounds whose decomposition rates we have studied is an extraordinary family of which a simple member is *o*-methoxybenzenediazonium chloride. In the present paper the behavior of this compound is discussed. Other members of the family are to be reported later.

Experimental

Unless otherwise specifically stated, the diazo solutions were studied at 0.1 molar strength and were prepared from

(1) Present address: Central Research Laboratory, General Aniline and Film Corporation, Easton, Penna.

(1a) N. V. Sidgwick, "Organic Chemistry of Nitrogen," Oxford Press, New York, N. Y., 1937, p. 414.

(2) Waters, *J. Chem. Soc.*, 113 (1937).

(3) Waring and Abrams, *THIS JOURNAL*, **63**, 2757 (1941).

(4) Crossley, Kienle and Benbrook, *ibid.*, **62**, 1400 (1940).

Eastman C. P. *o*-anisidine by use of sodium nitrite in the presence of 2.5 molar equivalents of hydrochloric acid. The temperature was kept below 5° throughout the diazotizations and until the solutions were ready for use at the various experimental temperatures. *o*-Anisidine from other sources was used in several experiments in order to demonstrate that the phenomena observed were not the result of some special property of the sample originally used. Thus, in one case a dark, old sample of technical *o*-anisidine gave a result similar to that obtained with the C. P. material.

The thermostat was controlled electrically at the different experimental temperatures to within $\pm 0.02^\circ$. The decomposition rates were followed by measurement of the rates of nitrogen evolution. The nitrogen volumes were recorded automatically by use of the recording nitrometer described in an earlier publication.⁵ This instrument records continuously rather than making periodic readings; hence points do not appear on the experimental curves shown.

Results and Discussion

In general, the decomposition of a diazonium salt in aqueous solution may be treated as a first order reaction.⁴ The marked deviation of *o*-methoxybenzenediazonium chloride from the first order law prompted this investigation.

The literature stated,^{6,7} that *o*-methoxybenzenediazonium chloride, in dilute acid solution is very stable. Our findings corroborate these qualitative statements. As shown in Fig. 1, decomposition is very slow even at 60°. When the temperature is raised to 70°, the reaction is somewhat faster, as would be expected, but during a twenty-four-hour period of observation, it is evident that the rate accelerates during decomposition. At 80° (Fig. 1) the decomposition follows a smooth "S" curve and is complete in about fifteen hours. The same "S" shaped type of curve was obtained at 60° by allowing decomposition to proceed for several days.

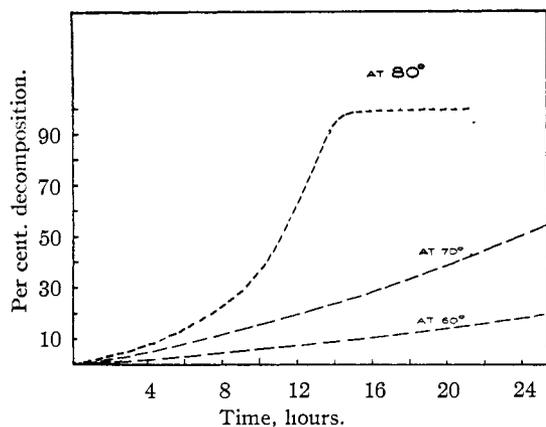


Fig. 1.—Decomposition of *o*-methoxybenzenediazonium chloride.

The decomposition of diazotized *o*-anisidine is influenced greatly by a wide variety of added ma-

(5) Crossley, Kienle and Benbrook, *Ind. Eng. Chem., Anal. Ed.*, **12**, 216 (1940).

(6) Cain, "Chemistry of Diazo Compounds," Edw. Arnold, London, 1908, p. 37.

(7) C. C. Snow, *Ind. Eng. Chem.*, **24**, 1422 (1932).

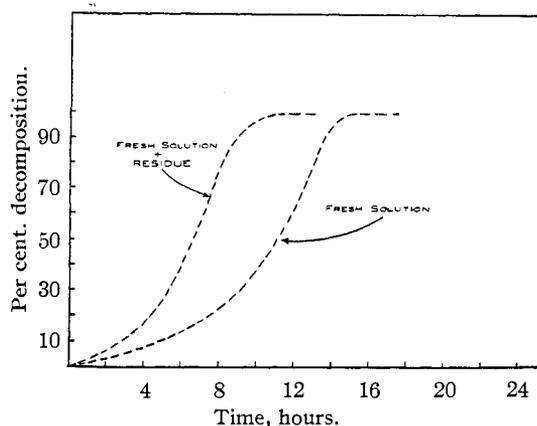


Fig. 2.—Effect of decomposition-residue upon the decomposition rate of a fresh solution of *o*-methoxybenzenediazonium chloride.

terials, although the simpler compounds such as diazotized aniline, are reported as not responding appreciably to catalysts.⁸ As shown in Fig. 2, the induction period, that period prior to the inflection of the "S" curve, is markedly shortened by addition of some residue from a completely decomposed solution of the same diazo. A similar effect may be produced by the addition of guaiacol, catechol or hydroquinone. If dioxane or

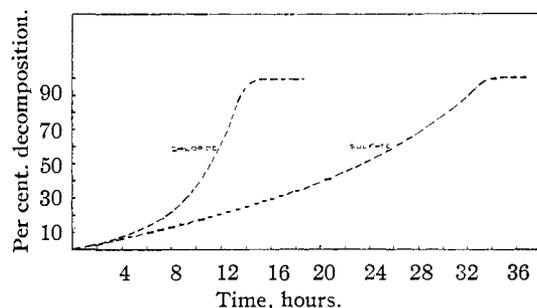


Fig. 3.—Comparison of the decomposition rates of *o*-methoxybenzenediazonium chloride and sulfate.

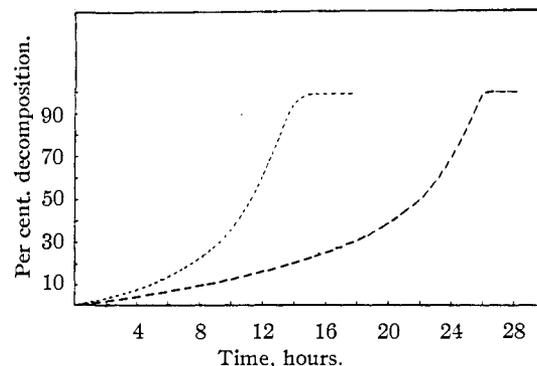


Fig. 4.—Effect of 0.1 molar equivalent of sodium dichromate upon the rate of decomposition of *o*-methoxybenzenediazonium chloride.

(8) H. A. H. Pray, *J. Phys. Chem.*, **30**, 1417 (1926).

ethanol be substituted for part of the water in the solution, the decomposition is very rapid with no suggestion of an induction period. If sulfate or nitrate ions be substituted for chloride ions, the induction period is greatly prolonged (Fig. 3), as is also the case if there is present one-tenth of one molar equivalent of sodium dichromate (Fig. 4). In the presence of a molar equivalent of hydriodic acid, the induction period is virtually eliminated.

The extent to which the induction period is shortened by the addition of decomposition residue, guaiacol, hydroquinone or catechol depends upon the amounts of these materials used. The addition of about one molar equivalent of hydroquinone or about 1.5 molar equivalent of catechol is required for complete elimination of the induction period. Under these conditions the reaction takes on the first order appearance indicated by the semi-logarithmic plot, Fig. 5. After complete decomposition of the sample to which one equivalent of hydroquinone had been added, the entire amount of this agent was recovered and no trace was found of such oxidation products of hydroquinone as might be expected if this material had functioned as a reducing agent. The rate of decomposition of benzenediazonium chloride was virtually unaffected by the presence of a molar equivalent of hydroquinone.

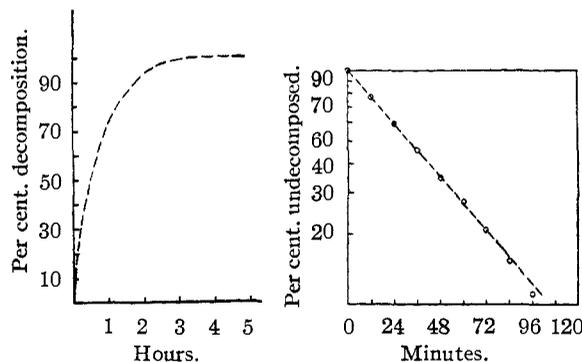


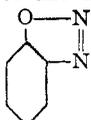
Fig. 5.—Decomposition of *o*-methoxybenzenediazonium chloride in the presence of 1.5 molar equivalents of *o*-dihydroxybenzene.

The tarry residue contains an alkali-soluble fraction, an acid-soluble fraction, and a fraction soluble in benzene. The acid- and alkali-soluble fractions could not be distilled, even at a temperature of 275° and a pressure of 18 mm. Although a small per cent. of the benzene-soluble material was distilled under reduced pressure the distillate did not boil even at 275° at atmospheric pressure. The infrared spectrum of the tar was examined. No bands characteristic of phenol, catechol or guaiacol were found.

The pronounced accelerating action shown by many compounds of the type to be expected as reaction products suggests that the "S" shaped curves may be the result of auto-catalysis. As a result of the study outlined in the following para-

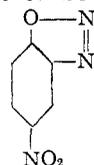
graphs we believe that the mechanism of this autocatalytic behavior may depend, in part, upon the reaction's proceeding in two consecutive steps. Consecutive reactions have been thoroughly treated mathematically^{9,10}; "S" shaped curves result when the velocities of the two or more consecutive steps are appropriately different.

It would appear that the decomposition of *o*-methoxybenzenediazonium chloride proceeds stepwise, the first step being the replacement of the methoxy group by an hydroxy group and the subsequent formation of the diazo oxide which may

be represented as  and the second step

being the decomposition of this intermediate compound. Simultaneously a small percentage of the diazo present goes directly into the formation of guaiacol. We have never succeeded in isolating the postulated intermediate product, probably because the velocity of its formation is low compared with that of its decomposition, and, therefore, the concentration of the intermediate product within the system is never permitted to rise appreciably. In the decomposition of some simple derivatives of diazotized *o*-anisidine the first step is fast compared with the second, thus at some stage during the reaction, there exists an appreciable concentration of the intermediate product. For study in this connection diazotized 4-nitro-2-aminoanisole was found useful.

Noelting¹¹ observed the formation of a red, crystalline material when a solution of diazotized 4-nitro-2-aminoanisole was heated. He isolated this material and found it to be a diazo oxide

which he represented as  (We repeat

Noelting's warning that this compound is explosive.) We have prepared this crystalline product and found that when coupled with 2-naphthol the azo dye produced is identical with that obtained by coupling diazotized 4-nitro-2-aminoanisole with 2-naphthol. The rate of decomposition of the diazo oxide, suspended in water at 80°, has been measured and the rate checks closely with the latter half of the "S" shaped decomposition curve for diazotized 4-nitro-2-aminoanisole, which in turn, as shown in Fig. 6, checks closely with the latter half of the curve for diazotized 4-nitro-2-aminophenol. It is thus reasonable to conclude that during the short induction period in the decomposition of diazotized 4-nitro-2-aminoani-

(9) Branch and Calvin, "Theory of Organic Chemistry," Prentice-Hall, New York, N. Y., 1941, p. 352.

(10) Daniels, "Chemical Kinetics," Cornell University Press, Ithaca, New York, 1938, p. 27.

(11) Noelting and Steimle, *Bull. soc. chim.*, **17**, 392 (1915).

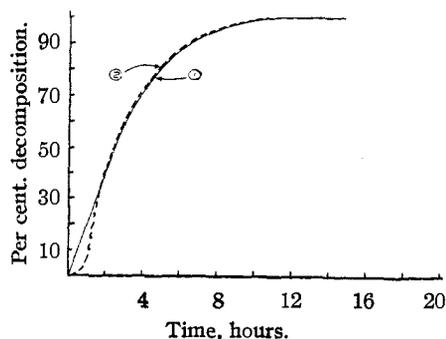


Fig. 6.—Comparison of decomposition rates of ① diazotized 4-nitro-2-aminophenol- and ② diazotized 4-aminoanisole.

sole, the major reaction occurring is the formation of the intermediate compound which Noeltling has shown to be the diazo oxide.

If the behavior of diazotized *o*-anisidine is analogous to that of its nitro derivative, the latter part of its "S" shaped decomposition curve must represent the decomposition of the diazo oxide derived from *o*-aminophenol. It has long been accepted that upon diazotization of *o*-aminophenol a diazo oxide forms almost immediately.¹² It will be observed in Fig. 7 that a curve representing the rate of decomposition of this diazo oxide at 80° coincides with the latter portion of the "S" curve obtained for diazotized *o*-anisidine. The coincidence here is less striking than in the case of the nitro derivative, but this is to be expected since the relatively slow first step masks the faster second step so that apparent coincidence does not occur until virtually complete reaction is reached.

If, by the addition of some of the agents described earlier, the first step of these two consecutive reactions could be accelerated to such a degree that it was complete in an immeasurably short time, the rate of decomposition of the intermediate compound thus formed should approach the rate for diazotized *o*-aminophenol. This is approached when 1.5 molar equiv. of catechol is added. Similarly curves of the "non-S" variety were obtained with hydroquinone, dioxane and alcohol. As we change from one to another of these agents or use varying amounts of a given agent, the rates of decomposition vary markedly, but tend to approach the rate for diazotized *o*-aminophenol.

Methoxy groups, in general, are effectively demethylated by use of hydriodic acid.¹³ In the decomposition of *o*-methoxybenzenediazamine chloride to which 1 molar equivalent of hydriodic acid had been added, the induction period was virtually eliminated. With a compound having no methoxy group, *o*-hydroxybenzenediazoniium chloride, the rate was the same in the presence of hydriodic acid as in the presence of a corresponding excess of

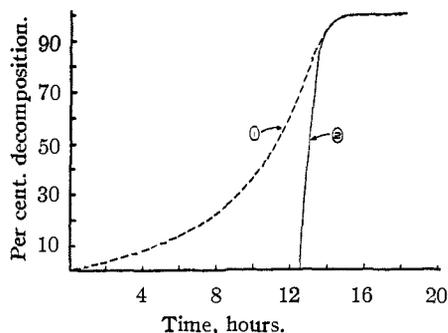
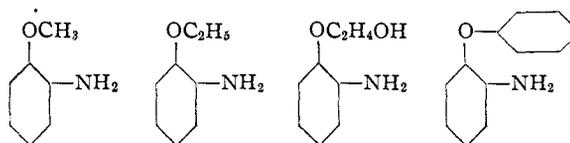


Fig. 7.—Comparison of decomposition rates of ① diazotized *o*-methoxybenzenediazoniium and ② diazotized *o*-aminophenol.

hydrochloric acid, indicating that, in the case of the *o*-methoxy compound, the attack of the hydriodic acid was upon the methoxy group and not upon the diazoniium group.

This phenomenon of the replacement of substituents by hydroxyl groups, diazo oxide formation, has received considerable attention in the past. It is interesting as well as pertinent to the present discussion to note the varying degrees of ease with which the reaction occurs with the different diazo compounds. Meldola and Hay¹⁴ have shown that an *o*- or *p*-methoxy group is eliminated in acid solution during diazotization if there is a nitro group ortho to the methoxy to act as what they call an activator. Noeltling¹¹ has found that even though the activating group is not in the ortho position, heating would bring about the elimination of the methoxy group. By alkaline treatment other investigators¹⁵ have reported the elimination of not only methoxy groups from the ortho or para position, but also alkoxy, sulfonic, nitro and halogen groups with certain other substituents present in the molecule to serve as activators. In all of our curves where we have found this "S" shaped tendency, there has been present in the ortho or para position one of the four groups which these investigators have found capable of being replaced by hydroxyl with subsequent diazo oxide formation. Conversely, we have obtained "S" curves for compounds of all four classes. But in addition we have observed the new kinetic behavior in several simpler compounds—simpler in that they have present no "activating group." Thus, pronounced inflection is to be found in the decomposition curves for the diazo derivatives of



In these cases where there is no activator present in the molecule, heating at, say, 80° for a pe-

(12) Morgan and Porter, *J. Chem. Soc.*, 107, 645 (1915).

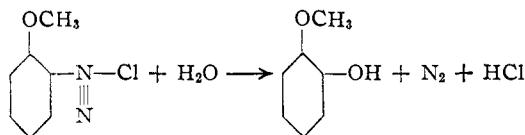
(13) Niederl and Niederl, "Organic Quantitative Microanalysis," 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1942, p. 239.

(14) Meldola and Hay, *J. Chem. Soc.*, 91, 1474 (1907).

(15) K. H. Saunders, "The Aromatic Diazo Compounds," Longmans-Green Co., New York, N. Y., 1936, p. 56.

riod of eight to twenty-four hours is necessary before inflection of the curve occurs—at which stage the presumed conversion to the diazo oxide is only partially complete. It is reasonable that a conversion which takes place easily with activators present might take place slowly during many hours of heating in the absence of activators. It is likewise reasonable that the addition of relatively large amounts of agents such as, for example, alcohol or hydroquinone, would alter the reactivity of the molecule as readily as its reactivity can be altered by substitutions within the molecule. As an example, the experience of Gaess and Ammelburg¹⁶ may be cited. They attempted to eliminate the diazonium group from diazotized 1,6-dinitro-2-naphthylamine by treatment with alcohol. They did not obtain the expected compound, but, in the presence of alcohol, the nitro group in the "1" position was replaced by hydroxyl, the diazonium group was not eliminated, and the diazo oxide was formed.

There are side reactions involved which contribute their share of evolved nitrogen and thus influence the shape of the curve produced. Doubtless some of the diazo present decomposes in the familiar manner usually represented as



We are at present unable to account for the whereabouts of the methoxy group after its postulated elimination from the ring. The identification of methyl alcohol or methyl chloride as a reaction product would have substantiated our hypothesis greatly. However, our failure to find either is not particularly distressing, since in a reaction producing a residue as complex as that obtained from *o*-methoxybenzenediazonium chloride, where not one simple reaction product was identified, it is not unlikely that the eliminated methoxy radical would take part in the formation of the complex tarry mass.

The consistent shortening of the induction period by reducing materials and the reverse effect shown by oxidizing materials is probably the key to the explanation of the widely variable results obtained when *o*-methoxybenzenediazonium chloride is decomposed in the presence of one after another of the mentioned agents. Furthermore, since most of these agents have little effect upon the decomposition rates of the simpler diazo compounds (*viz.* diazotized aniline or *o*-aminophenol), for which the postulated two-step mechanism is not possible, it must be concluded that these agents influence the velocity of the step prior to the decomposition proper—the step involving the substitution of the hydroxyl group for an ortho or

para substituent (*o*-methoxy in the case of diazotized *o*-anisidine). It is probable, as suggested by the data in Fig. 5, that the second step, the decomposition *per se* with the elimination of gaseous nitrogen, proceeds in accordance with the first order law. We know that the induction period is shortened by the presence of guaiacol, the product of direct (one step) decomposition, or by catechol, the postulated product of two-step decomposition. Hence either or both of these reaction products may be presumed to catalyze the first of the two consecutive reactions.

To summarize, the decomposition of *o*-methoxybenzenediazonium chloride can be assumed as consisting of two decomposition reactions occurring simultaneously, one, a slow single-step reaction to give guaiacol, and the other, a pair of consecutive reactions to give catechol. Both guaiacol and catechol catalyze the first of the two consecutive reactions, which step is the replacement of the methoxy group by hydroxyl to form a diazo of lowered stability (diazotized *o*-aminophenol). The decomposition of diazotized *o*-aminophenol is the second of the two consecutive reactions, the rate of which is unaffected by the presence of products of the reaction.

Summary

1. The decomposition of *o*-methoxybenzenediazonium chloride in aqueous acid solution is characterized by an induction period, giving an "S" shape to the decomposition curve.
2. The induction period is shortened by the addition of decomposition residue, guaiacol, catechol, hydroquinone, dioxane, alcohol or hydriodic acid. The induction period is lengthened by the addition of sulfuric acid, nitric acid or sodium dichromate.
3. The belief is expressed that the decomposition of *o*-methoxybenzenediazonium chloride is analogous to that of 2-methoxy-5-nitrobenzenediazonium chloride where the intermediate formation of a diazo oxide is responsible for the production of an induction period.
4. The fact that hydriodic acid, known to be active in the demethylation of methoxy groups, eliminates the induction period is considered to be additional support of the consecutive reaction hypothesis.
5. Induction periods in the decomposition of some polysubstituted alkoxy, sulfo, nitro and chloro derivative of benzenediazonium chloride are reported. It is pointed out that other investigators have found that these same types of compounds tend to eliminate the four radicals mentioned, replace them by hydroxyl groups and form diazo oxides. The connection between this behavior and the "S" shaped decomposition curves is indicated.

(16) Gaess and Ammelburg, *Ber.*, **27**, 2211 (1894).