

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

AMINE OXIDES DERIVED FROM 4-BROMODIMETHYLANILINE AND FROM 3- OR 4-NITRODIMETHYLANILINE¹

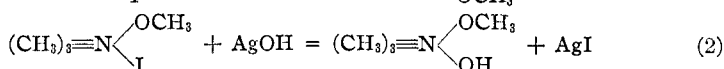
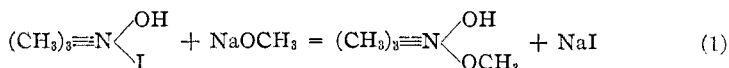
BY LAUDER W. JONES AND ELDEN B. HARTSHORN

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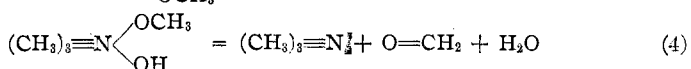
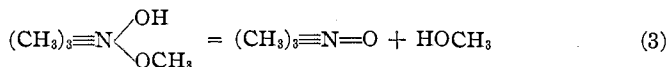
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Introduction

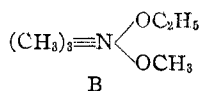
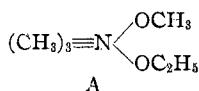
During the past decade the study of amine oxides and related compounds has raised a number of debatable questions. In 1912, Meisenheimer,² in the course of his investigations of derivatives of trimethylamine oxide, uncovered reactions of an unexpected character. The following equations illustrate two cases which he studied in detail.



Although neither of the final organic products represented in the two equations was isolated as a free compound, when solutions of them in methanol were heated totally different products were obtained from the two isomers.



The behavior of solutions of other analogous compounds prepared by Meisenheimer was similar.



The ethoxy group in A and the methoxy group in B have been introduced in place of negative ions of corresponding salts. A solution of A decomposed to give trimethylamine, formaldehyde and ethyl alcohol while a solution of B gave trimethylamine, acetaldehyde and methyl alcohol.

Not long after the publication of Meisenheimer's results, Jones³ proposed an interpretation of these reactions which employed the conception of positive and negative valences. This was based upon the assumption, first suggested by Stieglitz,⁴ that the hydroxyl group in hydroxyl-

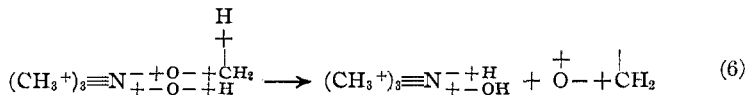
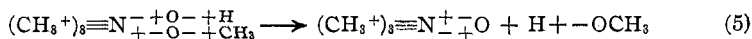
¹ This article is based upon a thesis submitted in 1922 by Elden B. Hartshorn in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in the Graduate School of the University of Minnesota.

² Meisenheimer, *Ann.*, **397**, 273 (1912); **399**, 371 (1913).

³ Jones, *THIS JOURNAL*, **36**, 1268 (1914); *Science*, **46**, 493 (1917).

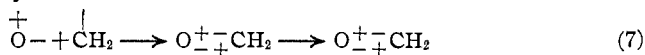
⁴ Stieglitz, *ibid.*, **36**, 272 (1914).

amine and its derivatives should be regarded as a "positive" group, $(H^+)_2=N-+OH$. The chemical changes represented in Equations 3 and 4 were formulated as follows.



In Reaction 5, a direct dissociation of "negative" methoxyl and "positive" hydrogen to give methanol is most probable. In Reaction 6, it is assumed that "positive" methoxyl is not in a condition to react with the positive hydrogen of the adjacent hydroxyl group to yield methanol.

The scheme used in Equation 6 implies that the negative valence of the nitrogen atom (which stands for a "pair of electrons") engages a positively charged hydrogen atom (now called proton) of the methyl radical. The residue, $+O-+CH_2$, in which the negative sign upon the carbon represents two electrons, readjusts itself by a migration of the two electrons from the carbon atom towards the oxygen atom or, in modern phraseology, through a "sharing of a pair of electrons" by these two atoms to give formaldehyde.



Isomers of this kind were called electromers, since the electrical condition of the two groups OH and OCH₃ attracted to N determines the isomerism. Meisenheimer's experiments indicate that two isomers of this nature are not mutually interconvertible; the compound of Formula A decomposed to give formaldehyde without a trace of acetaldehyde and, similarly, the compound of Formula B gave acetaldehyde without a trace of formaldehyde.

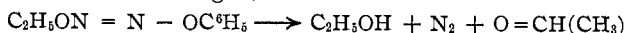
In an article published in 1920, Michael⁵ took exception to the electronic interpretation proposed above and, also, to the structural formulas assigned by Meisenheimer to some of his compounds. He admitted that the compound represented in Equations 1, 3 and 5 was correctly formulated and that it should yield methanol and trimethylamine oxide. He denied, however, that the isomer represented in Equations 2, 4 and 6 could have the formula assigned to it.⁶

Notwithstanding the positiveness of his assertion, there does seem to be some precedent for such an assumption. Thus, the diethyl ester

⁵ Michael, *THIS JOURNAL*, **42**, 1232 (1920).

⁶ Michael says, "Even if we grant that the values of valences joining the hydroxyl groups to nitrogen differ quantitatively, or in the electronic relation, there is no precedent in chemistry for the assumption that a methoxyl group, on hydrolysis, should yield formic aldehyde; on the contrary, all established facts point unmistakably to that of methyl alcohol."

of hyponitrous acid ("diazo-ethoxan") heated with water gives acetaldehyde, alcohol and nitrogen,



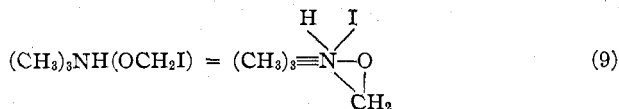
Surely, here, an ethoxyl group yields acetaldehyde.⁷ Similarly, the dibenzyl ester of hyponitrous acid gives benzyl alcohol, benzaldehyde and nitrogen.⁸

Seidel,⁹ and later Nef,¹⁰ showed that the ethyl ester of fulminuric acid (cyanisonitro-acetamide) decomposed to give acetaldehyde and desoxy-fulminuric acid. Nef observed that formaldehyde was produced when the silver salt of isodinitro-ethane was treated with methyl iodide and that methyl nitrolic acid was formed at the same time. More recently Meisenheimer¹¹ has shown that typical hydroxylamines of the general formula, $\text{R}_2\text{N}-\text{OR}'$, are hydrolyzed by acids to give an aldehyde and a secondary amine among other products. It would appear from these illustrations that the attachment of alkoxy groups to nitrogen seems to favor aldehyde formation rather than alcohol formation.

In an attempt to avoid the methoxyl group, Michael represents the addition of methyl iodide to trimethylamine oxide by the following equation,

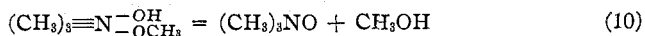


which, he says, denotes an "intermolecular reduction of the nitrogen and an oxidation of the carbon atom in the iodide." This formula, he states, would be "consistent with the formation of trimethylamine and formaldehyde by hydrolysis," but not with "the formation of a chloro-platinate and chloroaurate from the corresponding chloro derivatives; nor with the great chemical mobility of the hydrogen." So, the group, CH_2I , must be changed to satisfy these demands. It is imagined to act "intramolecularly and additively on the basic nitrogen atom" to produce a most singular result to which Michael assigns the structural formula,



This formula, he claims, "complies in every respect with the properties of the substance."

According to Michael, the reactions of decomposition represented in Equations 3 and 4, and in 5 and 6 should be expressed as follows.



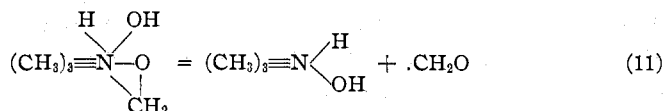
⁷ Zorn, *Ber.*, **11**, 1630 (1878).

⁸ Hantzsch and Kaufmann, *Ann.*, **292**, 317 (1896).

⁹ Seidel, *Ber.*, **25**, 431, 2756 (1892).

¹⁰ Nef, *Ann.*, **280**, 331 (1894).

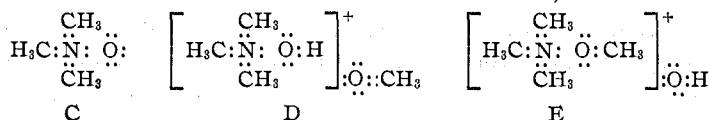
¹¹ Meisenheimer, *Ber.*, **52**, 1667 (1919).



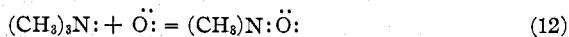
No one will gainsay the claim that if a base of this formula could be realized, its hydroxide would probably decompose to yield formaldehyde and trimethylamine. But this "condensation derivative of unstable trimethylammonium hydrate and formaldehyde," as Michael terms it, presents a most singular valence relationship for the nitrogen atom; the seven bonds with which the nitrogen atom is provided in the formula possess a strangely unfamiliar appearance¹² and find no justification in the illustration which Michael submits in a footnote on p. 1239, namely, $(\text{CH}_3)_4\text{NI}_3$ and $(\text{CH}_3)_4\text{NI}_5$.

Both Lewis and Langmuir discuss the amine oxides. Their views have in common the fundamental assumption that the maximum covalence of the nitrogen atom is four, and that a covalence bond should be regarded as consisting of a "pair of electrons" shared in common by two atoms.¹³

Translated into the symbolism of this theory, the formulas of the amine oxides and of the isomers of Meisenheimer become,



If the formula, $(\text{CH}_3^+)_3\text{N} \bar{\text{O}}$, employed above for trimethylamine oxide (see Equation 5) is considered in this connection, it will be apparent that it contains a suggestion of the idea expressed in Formula C. For, if the positive symbols are omitted, assuming that all positive unit charges reside in the nucleus of each atom, then the net result indicated in the formula by plus and minus signs consists in the displacement of one negative electron from the nitrogen atom towards the oxygen atom and the displacement of one electron from the oxygen atom towards the nitrogen atom, or in a pair of electrons shared in common by the nitrogen atom and the oxygen atom, as in Formula C. Actually, in the formation of the amine oxide by oxidation of a tertiary amine, it is probable that an oxygen atom with six electrons in its outer shell combines directly with the amine in the following fashion,¹⁴



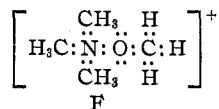
¹² See in criticism, Stieglitz, *THIS JOURNAL*, **44**, 1308 (1922).

¹³ Lewis, (a) *ibid.*, **33**, 762 (1916); (b) "Valence and the Structure of Atoms and Molecules," Chemical Catalog Co., **1923**, pp. 111, 134. Langmuir, (c) *THIS JOURNAL*, **14**, 868; (d) 1543 (1919); (e) **42**, 274 (1920).

¹⁴ In a recent article [*Trans. Faraday Soc.*, **19**, October, 1923], W. A. Noyes discusses the amine oxides. The formula which he proposes to translate the positive and negative signs into the symbols of paired electrons is $\text{R}_3\text{N}::\text{O}$; that is, he assigns a specific

Even if Formulas D and E are accepted, the question of the "positive" and "negative" character of the hydroxyl and methoxyl groups is not disposed of; for the methoxyl group in Formula D represents a negative ion, and is necessarily more negative than the methoxyl group in Formula E, which here shares a pair of electrons with the nitrogen atom. Similar reasoning applies to the hydroxyl groups in the two formulas. Relatively, therefore, these groups are respectively positive and negative. Furthermore, these groups and similar groups in pairs of isomers of this type *maintain these characteristic electronic differences*; the two isomers do not appear to be mutually interconvertible (see p. 1841). Consequently, the isomerism which they display depends upon the electronic character of these groups and, in this sense, two isomers of this kind may justly be called "electromers."

In this connection it will be interesting to consider the interpretation offered by Lewis to explain the decomposition of the ion.¹⁵ He says,



"It seems to me that we can readily form a provisional picture of the decomposition. Representing the ion by the structure (given in F) we may consider the bonding pair between nitrogen and oxygen as drawn away from the normal position of the pair in the oxygen octet. This struggle for electrons will tend to draw towards the oxygen the electrons which form the bonding pairs between carbon and hydrogen, so that the atoms of hydrogen would behave more like hydrogen of an acid than they ordinarily do in alkyl groups. So we may consider that in the presence of an alkali one of these atoms of hydrogen occasionally is drawn off as hydrogen ion. The pair of electrons left free would then form a bond with the oxygen, thus producing formaldehyde, and the nitrogen would take sole possession of the former bonding pair, giving trialkylamine."

It would seem, therefore, that the essential differences in the viewpoint of Lewis and of that involving positive and negative valences lie chiefly in a modification of the symbolism to conform to his more recent views and in the assumption that, because the nitrogen atom shows a maximum covalence of four, in compounds of the ammonium type it never manifests a "valence" of five; one radical in all such compounds is ionizable and it function to a particular pair of the six electrons which the oxygen atom is assumed to bring with it into the molecule. With electron pairs localized as this symbol suggests, scarcely a vestige of a "bond" holding the nitrogen and oxygen atoms together is left. Such a formula, in a fashion, may appear to satisfy a desire to render a "fifth valence" of the nitrogen atom visible in a symbol, but it is doubtful whether such a device actually accomplishes this result in a logical manner.

¹⁵ Ref. 13 b, p. 135.

is claimed that this "anion is not attached to the cation at all." Lewis admits, however, that it is difficult to carry this view to a strictly logical conclusion, and seeks to qualify this positive statement by assuming "that if it (the anion) is attached to the cation in a simple ammonium salt, it has a bond to the hydrogen but not to the nitrogen atom;" the hydrogen atom is said to be "bivalent." Furthermore, bases of the type illustrated in Formula E, contrary to his prediction, he finds to be very weak bases.¹⁶

The Problem Proposed

The investigations described in this article were undertaken in order to prepare isomers of the kind discussed above, which might be isolated as definite substances, possibly as solids. For this purpose several substituted-aryl alkyl amines were chosen and converted into amine oxide from which salts of the type $R_3N(OH)Cl$ were obtained. However, under the conditions chosen by us, halogen alkyls could not be caused to react with these amine oxides by addition as methyl iodide reacts with trimethylamine oxide; complicated changes occurred which will be discussed below. Consequently, the more interesting isomers, $R_3N(OCH_3)OH$, could not be obtained from these amine oxides.

Discussion of Results

In this investigation, 4-bromo-dimethylaniline, 3- and also 4-nitro-dimethylaniline were oxidized by permonosulfuric acid to the corresponding amine oxides, and the free bases and various salts of these bases were examined. In general it was found that *para* substituted-aryl dialkyl amines could be oxidized by a strongly acid solution of permonosulfuric acid, but that the other type of aryl dialkyl amines required a nearly neutral solution of this reagent in order to secure the oxide as a product. The failure to obtain the oxide under other conditions is probably due to the tendency of the oxygen atom in strongly acid solutions to migrate to the benzene nucleus to form phenolic compounds.

After the tertiary amines are oxidized, enough free sulfuric acid is ordinarily present in solution to allow the *acid sulfate* to separate in crystalline form, if such a salt is stable and of limited solubility. In the case of 4-nitro-dimethylaniline oxide this occurs; a salt of the following composition was deposited: $O_2N.C_6H_4N(CH_3)_2OH.SO_4H$. However, in the case of 4-bromo-dimethylaniline the acid sulfate is soluble in a solution containing a large excess of sulfuric acid and, later, after partial neutralization of the solutions, the acid sulfate separates as an oil which, on further neutralization, changes to a solid *normal sulfate*, $(Br.C_6H_4N(CH_3)_2OH)_2.SO_4$. The 3-nitro-dimethylaniline, which must be oxidized by nearly neutral permonosulfuric acid, is precipitated as the normal sulfate on partial neutral-

¹⁶ Noyes and Hibben, *THIS JOURNAL*, **45**, 355 (1923). Stewart and Maeser, unpublished work. See Ref. 13 b, p. 112. Hantzsch, *Ber.*, **52B**, 1544 (1919).

ization of the solution. In all cases the solubility of these salts is high, and the fair yield obtained is explained by the fact that conditions were so selected that the solution was nearly saturated with ammonium sulfate when precipitation took place.

These sulfates were readily dissolved in hot, concd. hydrochloric acid and the solution as it cooled deposited the corresponding hydrochloride in each case. The hydrochlorides were nearly purified when solutions of them in hot alcohol were precipitated by the addition of a large excess of dry ether.

The picrates formed by precipitation from solutions of the more soluble salts yielded beautiful, yellow needles on crystallization from dil. alcohol and are admirably suited to identify the respective oxides.

Except for the hydriodides, the salts prepared are quite stable at ordinary temperature. As a rule, however, they decompose when they are heated in a melting-point tube, in some cases with violence. The sensitivity to small amounts of impurities is very great and differences in the rate of heating cause considerable variation in the temperature at which they decompose.

It was noted that solutions of salts of strong acids with these amine oxides liberated free iodine from a solution of potassium iodide. Later work showed that the hydriodide is first formed and that this salt then decomposes. The addition of a concentrated solution of potassium iodide to a strong aqueous solution of the hydrochlorides of any one of these amine oxides precipitates the hydriodide which almost immediately undergoes decomposition, producing free iodine. This decomposition proceeds rapidly in the case of 4-nitro-dimethylaniline oxide hydriodide, less so for the 3-nitro derivative, and very slowly in the case of the 4-bromo-dimethylaniline oxide hydriodide. In fact, the latter salt was prepared by double decomposition of potassium iodide and the hydrochloride of this amine oxide at a temperature below zero; the iodide was isolated, analyzed for iodide ion, and its decomposition examined.

Since the other hydriodides decompose more readily, the action of potassium iodide on 4-nitro-dimethylaniline oxide hydrochloride was more thoroughly investigated. It was found that the extent of decomposition of this amine oxide hydriodide when it was warmed in aqueous solution could not be determined by titrating the free iodine with a solution of sodium thiosulfate on account of the tendency of the thiosulfate to reduce the amine oxide, itself. In experiments in which weighed amounts of 4-nitro-dimethylaniline oxide hydrochloride and potassium iodide were heated in aqueous solution to 80° for an hour, if the iodine was removed from the precipitated nitro-dimethylaniline by collecting the amine and washing it with potassium iodide to remove amine oxide not yet reduced, before washing it with thiosulfate, only approximately half of the possible

tertiary amine was obtained. Evidently *two moles* of hydriodic acid are necessary to reduce one of the amine oxide.

If the stability of the hydriodides of the amine oxides may be taken as a measure of the firmness with which the oxygen atom is held by the nitrogen, these substituted aryldialkylamine oxides would seem to be less stable than either the alkylpiperidine oxides or the simple trialkyl amine oxide. Dunstan and Goulding¹⁷ do not mention any instability on the part of alkyl amine oxides and definitely claim that the oxygen atom here is not in an "active" state as is the case in hydrogen peroxide or the alkylpiperidine bases. It is stated¹⁸ that ethylpiperidine oxide liberates iodine from potassium iodide but that its salts do not. The exact opposite is true of the amine oxides here reported; the free bases do not affect solutions of potassium iodide, while their salts with strong acids liberate iodine at once at room temperature. The hydriodides of the alkylpiperidine derivatives, however, seem to be more stable than those of the substituted aryldialkylamine oxides.

Solutions of the free amine oxides, themselves, are readily obtained by shaking the hydrochloride in methanol with moist silver oxide. In no case, however, could the solid amine oxide be satisfactorily isolated by evaporation of the methanol solution in a desiccator over phosphorus pentoxide, as had been done with trimethylamine oxide and dimethylaniline oxide. The bases could not be precipitated in any amount from strong aqueous solutions of their hydrochlorides by addition of a saturated solution of potassium acetate, a method used by Baudisch¹⁹ in preparing *p*-carboxyl-dimethylaniline oxide. In the end, a product of fair purity was obtained by removal of the methanol rapidly by distillation under diminished pressure. It was found that these solid oxides could not be sublimed in a vacuum. When this was attempted decomposition ensued. This appeared to be largely the loss of oxygen in some fashion as, in all cases examined, a large amount of the tertiary amine was recovered from the residue. When samples of these bases were heated at ordinary pressure a slight odor of formaldehyde was noted. The solid bases, 4-bromo-dimethylaniline oxide and 3-nitro-dimethylaniline oxide, are very hygroscopic crystalline solids, very soluble in water and in alcohol. The 4-nitro-dimethylaniline oxide resembles the others except that its melting point is much lower and it is not hygroscopic at all.

Perhaps the most important reaction for studying the stability of the oxides is that with methyl iodide. In the aliphatic amine oxides the oxygen atom is quite firmly bound to nitrogen. Methyl iodide addition products of amine oxides with aliphatic radicals are easily prepared, but Bamberger

¹⁷ Dunstan and Goulding, *J. Chem. Soc.*, **75**, 792 (1899).

¹⁸ Wernick and Wolfenstein, *Ber.*, **31**, 1553 (1898).

¹⁹ Baudisch, *Ber.*, **51**, 1051 (1918).

and Tschirner²⁰ failed to obtain such an addition product with dimethylaniline oxide, and Meisenheimer²¹ was unsuccessful with kairoline oxide.

In the present investigation, the action of methyl iodide in excess on 4-bromo-dimethylaniline oxide, and on 3- and 4-nitro-dimethylaniline oxides was studied. In each case the action was allowed to take place in methanol solution and was complete after the mixture had stood for about ten days. In general, the results were similar involving the reduction of the amine oxide accompanied by the liberation of iodine but *without the production of formaldehyde*. In the cases of 3-nitro-dimethylaniline oxide and of 4-bromo-dimethylaniline oxide, the tertiary amines produced by the reduction did not appear as products since, in the presence of an excess of methyl iodide, the quaternary salts, 3-nitro-phenyltrimethylammonium iodide and 4-bromo-phenyltrimethylammonium iodide, were formed. The large amount of free iodine present in each case formed, in part at least, per-iodides of these quaternary salts. The composition of these per-iodides was proved to be $3\text{-NO}_2\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_3\text{I}\cdot\text{I}_2$ and $4\text{-Br}\cdot\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_3\text{I}\cdot\text{I}_2$. In the case of 4-nitro-dimethylaniline oxide, 4-nitro-dimethylaniline and iodine were the main products.

The absence of formaldehyde as a product, makes it unnecessary to assume the formation of an intermediate addition product of the oxide and methyl iodide. In these cases it is more probable that methyl iodide was slowly hydrolyzed. The hydriodic acid, thus produced, then united with the amine oxide to yield a salt which decomposed with the formation of the corresponding tertiary amine and free iodine.

Experimental Part

Preparation of Permonosulfuric Acid

The method employed by Willstätter and Hauenstein²² for the preparation of permonosulfuric acid (Caro's acid) was used in the following experiments. Generally, 60 g. of ammonium persulfate was rubbed with 33 cc. of concd. sulfuric acid and the mixture allowed to stand at 15–20° for one hour. It was then treated with 100–150 g. of cracked ice depending on the concentration of permonosulfuric acid desired, and thereupon was employed directly for oxidations in which a strongly acid solution could be used. When a nearly neutral solution of the reagent was necessary, the diluted acid was cooled below 0° and concentrated aqueous ammonia added drop by drop, care being taken that the solution was efficiently stirred and that it was never made alkaline.

In order to determine the "available oxygen" in a solution of permonosulfuric acid, use was made of the fact that this acid in dilute acid solution releases iodine from aqueous potassium iodide instantaneously while persulfates do so very slowly.²³ Ten cc. of the oxidizing solution were diluted to 100 cc., an aliquot portion was withdrawn, treated with an excess of potassium iodide, and immediately titrated with standard thiosulfate solution

²⁰ Bamberger and Tschirner, *Ber.*, **32**, 1886 (1899).

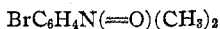
²¹ Meisenheimer, *Ann.*, **385**, 135 (1911).

²² Willstätter and Hauenstein, *Ber.*, **42**, 1842 (1909).

²³ Baeyer and Villiger, *Ber.*, **34**, 854 (1901).

whose factor was expressed in mg. of oxygen per cc. In this way it was found possible to determine rapidly the oxidizing value of a given solution of this reagent.

4-Bromo-dimethylaniline Oxide



Oxidation of 4-Bromo-dimethylaniline.—To 190 cc. of an acid solution of permono-sulfuric acid containing 2.28 g. of active oxygen, cooled below 0° , was added 25.0 g. of 4-bromo-dimethylaniline. Solution readily took place, so the mixture was kept in the ice chest until the next day, when it was partially neutralized with concd. aqueous ammonia without allowing the temperature to rise above 20° . At the start, the solution had a faint, cherry-red color and when partially neutralized, a reddish oil separated as a lower layer. Further addition of ammonia to the solution, cooled and agitated, caused this oil to solidify; this gave 34.1 g. of the crude normal sulfate of 4-bromo-dimethylaniline oxide.

This material is not very soluble in warm methanol. Recrystallization from this solvent yielded only about 60% of the initial material, even if the pure substance were used. Samples which have been recrystallized twice from methanol have the form of short, white glistening needles, which darken above 125° and explode at $132\text{--}135^\circ$. A sample kept in a vacuum desiccator over sulfuric acid for 48 hours did not lose weight.

Anal. (Carius.) Subs., 0.2255: BaSO_4 , 0.0991. Calc. for $\text{C}_{10}\text{H}_{12}\text{O}_6\text{N}_2\text{SBr}_2$: SO_3 , 15.10. Found: 15.07.

HYDROCHLORIDE, 4- $\text{BrC}_6\text{H}_4\text{N}(\text{CH}_3)_2\text{OH}\cdot\text{Cl}$.—Twenty-five g. of the pure sulfate was dissolved in 80 cc. of concd. hydrochloric acid which had been brought to the boiling point. Six days later, 19.6 g. of nearly pure white, blunt needles was collected on a filter. When 14.5 g. of the latter was dissolved in ethyl alcohol and treated with about 5 volumes of dry ether, 11.9 g. of pure white needles came down. These darkened above 160° and decomposed at $165\text{--}166^\circ$.

Anal. Subs., 0.5976, 0.6182: AgCl , 0.3363, 0.3466. Calc. for $\text{C}_8\text{H}_{11}\text{ONBrCl}$: Cl , 14.04. Found: 13.92, 13.87.

Subs., 0.3498: N_2 , 17.8 cc. (22° , 752 mm., over 30% KOH). Calc.: N , 5.55. Found: 5.70.

HYDRIODIDE, 4- $\text{BrC}_6\text{H}_4\text{N}(\text{CH}_3)_2\text{OH}\cdot\text{I}$.—When 15 cc. of saturated solution of potassium iodide was added to 5.0 g. of this hydrochloride dissolved in 60 cc. of water, both solutions being below 7° , a pure white, crystalline powder separated. This material was collected, quickly drained by suction, washed with the smallest amount of alcohol necessary to moisten it, and then shaken suspended in ether, filtered and quickly dried. This gave 5.5 g. of a nearly white, crystalline powder. In a melting-point tube it darkened rapidly above 60° , was black at 80° and decomposed completely at $92\text{--}94^\circ$. A small sample dissolved in water gave a blue color with starch and potassium iodide. Another sample dissolved in water soon gave a salmon-colored, crystalline precipitate which had the properties of *p*-bromo-dimethylaniline. After several weeks the solid was black and *p*-bromo-dimethylaniline and iodine were found to be present. When an attempt was made to hasten this decomposition by heating the solution on the water-bath, a resinous product was obtained. The solid hydriodide was a light cream color when dry, brick-red in 10–12 hours and black in 48 hours.

Anal. Subs., 0.3914, 0.3942: AgI , 0.2682, 0.2708. Calc. for $\text{C}_8\text{H}_{11}\text{NOBrI}$: I , 36.90. Found: 37.04, 37.13.

PICRATE.—When 2.0 g. of the hydrochloride was dissolved in 200 cc. of water and 3.5 g. of picric acid dissolved in 600 cc. of boiling water was added, a yellow crystalline substance separated. When the solution was cold the precipitate was collected,

washed and dried. This gave 2.9 g. which, when recrystallized once, gave 2.1 g. of beautiful, yellow needles a centimeter in length, which melted with some decomposition at 126–127°.

Anal. Subs., 0.1849: N, 21.8 cc. (28.5°, 753 mm., over 30% KOH). Calc.: N, 12.60. Found: 12.82.

Reduction of 4-Bromo-dimethylaniline Oxide Hydrochloride.—Four g. of the oxide hydrochloride was dissolved in 100 cc. of water and 20 cc. of concd. hydrochloric acid and an excess of granular zinc added. The reduction was allowed to progress for several hours and small amounts of fresh acid were added from time to time. Finally, the solution was made slightly alkaline and the white precipitate recrystallized from dil. alcohol; yield, 2.4 g. (calcd., 3.15 g.) of pure white 4-bromo-dimethylaniline; m. p., 54–55°. This reaction proved that the compound was an amine oxide and not an hydroxylamine derivative. The latter on reduction would have given a secondary amine.

4-Bromo-dimethylaniline Oxide, 4-BrC₆H₄N(CH₃)₂O.—By dissolving 10.0 g. of the hydrochloride in the smallest possible quantity of absolute methanol in a volumetric flask and shaking the solution with a little more than the required amount of moist silver oxide, a solution of the free base was obtained. After the solution was filtered, it was allowed to evaporate slowly in a desiccator over sulfuric acid. When the residue became very viscous, particles of silver oxide were noted; the residue was therefore redissolved in a small amount of absolute methanol, and the solution filtered and evaporated. The pasty sample was finally dried in a vacuum desiccator over phosphorus pentoxide. At the end of four months the material had not reached the solid state, and since some reduction to 4-bromo-dimethylaniline had taken place, it was evident that the pure oxide base could not be obtained in this manner. An unsuccessful attempt was also made to prepare it by precipitation from a solution of the hydrochloride, nearly saturated with potassium acetate.¹⁹

A methanol solution of the pure free base, prepared by the action of silver oxide on the hydrochloride as above, was then evaporated by distillation in a vacuum. At 70–80° and 20 mm., the thick material solidified to a brownish, very hygroscopic powder which melted at 167–168°. This product had a faint odor resembling that of an isocyanide, deliquesced to a liquid in air in less than half an hour, and decomposed violently when heated over a free flame. Traces of formaldehyde could be detected. The product obtained in this manner was probably not pure.

When a methanol solution of the free base prepared from 2.0 g. of the hydrochloride was evaporated in a vacuum until it solidified and the temperature was raised in an attempt to sublime the oxide, the substance melted at about 140° (thermometer in oil-bath) and 25 mm. The liquid appeared to boil. As the mass cooled it solidified to a nearly white, crystalline solid which was crystallized from alcohol; yield, 0.06 g. of white needles (m. p., 172–173°) and 0.6 g. of oily plates of *p*-bromo-dimethylaniline. The product obtained in small quantity melted at the right temperature for bi-dimethylaniline, but gave a slight qualitative test for halogen. Evidently, when the amine oxides are heated in a good vacuum the chief decomposition is abstraction of oxygen and production of *p*-bromo-dimethylaniline. When a similar experiment was performed at atmospheric pressure, a violet dye was the main product. This dye was previously observed by Wurster and Beran²⁴ who obtained it by heating *p*-bromophenyltrimethylammonium iodide.

4-Bromo-dimethylaniline Oxide and Methyl Iodide.—Twenty g. of the hydrochloride suspended in methanol was changed to the free base by shaking it with an excess of moist silver oxide. This material in 300 cc. of dry methanol was treated with two

²⁴ Wurster and Beran, *Ber.*, 12, 1820 (1879).

molecular equivalents of methyl iodide and allowed to stand in a stoppered flask for four days. A few crystals appeared, so an equal volume of dry ether was added. Thus 3.0 g. of white solid was obtained. The filtrate was allowed to evaporate to 100 cc. in air, slightly more than one molecular equivalent of methyl iodide was added and the mixture allowed to stand for one week. A large crystalline deposit had formed, and addition of dry ether augmented this somewhat. Two different types of crystals were noted immediately, pure white rhomboids and brownish-black bars. These were readily separated through the great solubility of the latter in acetone. The white solid, 11.6 g. in all, crystallized from boiling water, appeared as pearly white rhomboids which decomposed at 187–187.5° and proved to be 4-bromo-phenyltrimethylammonium iodide. The iodide ion was determined gravimetrically.

Anal. Subs., 0.5379: AgI, 0.3669. Calc. for $C_9H_{13}NBrI$: I, 37.12. Found: 36.87.

The brownish-black bars (6.1 g.) were extremely soluble in acetone. When their saturated solution in this solvent was treated with a large volume of carbon tetrachloride dark brown flakes were obtained. These melted at 165–166° and were a per-iodide of 4-bromo-phenyltrimethylammonium iodide, $Br.C_6H_4.N(CH_3)_3.I_2$. The free iodine was determined by titrating the solution of the per-iodide in acetone with standard sodium thiosulfate to the disappearance of the brown color of free iodine.

Anal. Subs., 0.2077: thiosulfate, 9.46 cc. (1 cc. = 9.359 mg. of I_2). Calc. for $C_9H_{13}NBrI_2$: I_2 , 42.61. Found: 42.63.

The mother liquor from which these two compounds were deposited still contained some unchanged amine oxide, as was shown by evaporation of the ether; addition of a hot aqueous solution of picric acid gave the picrate which melted at 126–127°. No other substances were found in the reaction mixture.

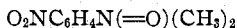
In order that there might be no question as to the exact nature of the products described above, 5.0 g. of 4-bromo-dimethylaniline was heated under a reflux condenser for four hours with 2 equivalents of methyl iodide. The product formed was crystallized from water and gave 7.0 g. of pearly white, rhombic plates. In a melting-point tube these decomposed at 187–188° and resembled completely the material obtained in the reaction of methyl iodide on 4-bromo-dimethylaniline oxide. This compound has been previously described by Wurster and Beran²⁴ who found that it decomposed at 185°.

Anal. Subs., 0.4730: AgI, 0.3240. Calc. for $C_9H_{13}NBrI$: I, 37.12. Found: 37.03.

4-Bromo-phenyltrimethylammonium iodide was found to be only slightly soluble in acetone. It readily dissolved, however, in acetone containing a little more than enough iodine to form a periodide of the constitution indicated above. Such a solution of 5.0 g. of 4-bromo-phenyltrimethylammonium iodide and iodine on treatment with carbon tetrachloride in large amount gave 7.4 g. of a periodide resembling completely the one obtained in the reaction of methyl iodide on *p*-bromo-dimethylaniline oxide; m. p., 165–166°.

Anal. Subs., 0.3078: thiosulfate, 19.8 cc. (1 cc. = 6.613 mg. of I_2). Calc. for $C_9H_{13}NBrI_2$: I_2 , 42.61. Found: 42.53.

4-Nitro-dimethylaniline Oxide



Oxidation of 4-Nitro-dimethylaniline.—When 30.0 g. (calcd., 32. g.) of 4-nitro-dimethylaniline was shaken at room temperature with 170 cc. of an acid solution of permonosulfuric acid containing 3.10 g. of active oxygen, a moderate rise in temperature took place, the amine passed into solution during the course of two or three hours, and

the next day a nearly colorless, crystalline precipitate filled the liquid. After collecting and drying this precipitate, 43.6 g. of the acid sulfate of the oxide of 4-nitro-dimethylaniline was obtained. This material, after crystallization from methanol, decomposed at 147-149° and did not lose weight in a good vacuum over sulfuric acid.

Anal. Subs., 0.5696, 0.5990: BaSO₄, 0.4746, 0.5005. Calc. for C₈H₁₂O₇N₂S: SO₃, 28.58. Found: 28.58, 28.66.

HYDROCHLORIDE, 4-NO₂C₆H₄N(CH₃)₂OH.Cl.—This salt was prepared by dissolving 25.0 g. of the acid sulfate in 70 cc. of hot, concd. hydrochloric acid. Six days later 14.9 g. (calcd., 19.5 g.) of large, nearly colorless prisms were collected. These were then purified by solution in alcohol and precipitation by the addition of a large amount of ether. They decomposed at 168-169°. A solution of the salt in water separates iodine from potassium iodide.

Anal. Subs., 0.2703, 0.6088: N₂, 32.2 cc. (27°, 755 mm.; over 30% KOH); AgCl, 0.3976. Calc. for C₈H₁₁O₃N₂Cl: N, 12.82; Cl, 16.22. Found: N, 13.1; Cl, 16.16.

HYDRIODIDE.—No attempt was made to isolate the hydriodide in this case, since qualitative tests showed that it is very unstable. Three 2.0g. samples of 4-nitro-dimethylaniline oxide were heated in aqueous solution at 75-80° for an hour under the following conditions. Each sample was dissolved in 20 cc. of distilled water in a small Erlenmeyer flask; I was heated thus alone; to II and III were added 5cc. portions of saturated potassium iodide solution immediately and before the material was heated. Soon a dark color, due to free iodine, appeared in II and III and a precipitate of *p*-nitro-dimethylaniline began to form. From time to time III was treated with known volumes of dil. thiosulfate solution and I and II were diluted with equal volumes of distilled water at the same time. At the end of an hour the three solutions were removed, allowed to stand overnight and then filtered. Enough thiosulfate solution had been added to III to reduce nearly all the free iodine present. Each filter was then washed with 70 cc. of a dilute solution of potassium iodide in five portions, the purpose being to remove all unchanged amine oxide from II. The solids on the filter paper were washed with enough dil. thiosulfate solution to remove traces of iodine adhering to the nitro-dimethylaniline and then washed with equal volumes of water. The filter papers were then dried and their contents carefully removed and weighed. The weights of *p*-nitro-dimethylaniline were: I, < 0.01 g.; II, 0.69 g.; III, 1.5 g. The calculated weight is 1.52 g. Evidently the sample to which thiosulfate was added during the period of heating decomposed to the greatest extent. Tests showed that the amine oxides are reduced by thiosulfate alone. The result in II, whereby less than half the calculated amount of tertiary amine was produced, indicates that two molecules of hydriodic acid are necessary to reduce one molecule of this amine oxide.

PICRATE.—When 4.0 g. of the hydrochloride in water was mixed with 5.0 g. of picric acid in boiling solution and the total volume made up to 500 cc., 7.3 g. of minute, yellow needles was collected on a filter. After one recrystallization from dil. alcohol these melted at 148-159°.

Reduction of 4-Nitro-dimethylaniline Oxide Acid Sulfate.—A solution of 22 g. of this salt in 300 cc. of water at 0° was slowly saturated with sulfur dioxide. A yellow solid gradually separated. This was collected on a filter, drained and washed with water; yield, 11.1 g. of 4-nitro-dimethylaniline; m. p., 159°. The filtrate contained an organic acid that was purified by changing it into the barium salt and then to the free acid by the action of sulfuric acid. This solid on recrystallization gave 0.4 g. of thick, brown needles; decomposition point, 228-229°. Among these large needles were found several blunt, cherry-red crystals. These amounted to only 0.01 g. and decomposed at 238-240°. The former substance was assumed to be 2-dimethylamino-5-

nitro-benzenesulfonic acid and was analyzed for nitrogen. The latter, perhaps, was the corresponding 2-nitro-5-dimethylamino-benzenesulfonic acid.²⁵

Anal. Subs., 0.2526: N₂, 26.0 cc. (23°, 756 mm.; over 30% KOH). Calc. for C₈H₁₀O₆N₂S: N, 11.38. Found: 11.54.

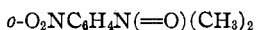
4-Nitro-dimethylaniline Oxide, 4-O₂NC₆H₄N(CH₃)₂O.—A methanol solution prepared from 3.0 g. of the hydrochloride and silver oxide was evaporated in a vacuum. At 60–70° and 20 mm., the oily product solidified and the temperature was then raised to 85° for a time. The pale yellow powder melted at 110–111°, gave off some formaldehyde when heated and showed no tendency to deliquesce. Like the solution in methanol, the solid had a pleasant odor resembling that of coumarin.

Anal. Subs., 0.2676: N₂, 36.6 cc. (27°, 755 mm.; over 30% KOH). Calc. for C₈H₁₀I₃N₂: N, 15.39. Found: 15.33.

4-Nitro-dimethylaniline Oxide and Methyl Iodide.—Twelve g. of 4-nitro-dimethylaniline oxide hydrochloride in methanol was changed into the free base by agitation with moist silver oxide, and the product evaporated in a desiccator to 30 cc. The solution was allowed to stand for three weeks in a stoppered flask with 20 g. of methyl iodide. The solution gradually darkened and within 24 hours yellow needles appeared. These increased in amount from day to day and a few black crystals appeared later. These two products were separated through the great solubility of the dark material in acetone. There were obtained 7.3 g. of 4-nitro-dimethylaniline, m. p., 160–161°, and about 0.15 g. of a per-iodide, m. p., 162–163°, which was not identified except to prove that it was not produced by the action of iodine on either 4-nitro-dimethylaniline or its oxide. Much free iodine was also found in the reaction mixture.

It was proved by a separate experiment that 4-nitro-dimethylaniline does not form a quaternary salt when warmed for eight hours with methyl iodide. The chief reaction of methyl iodide on the oxide of 4-nitro-dimethylaniline amounts to a reduction of the latter compound.

3-Nitro-dimethylaniline Oxide



Oxidation of 3-Nitro-dimethylaniline.—When this amine is oxidized with a strongly acid solution of permonosulfuric acid no amine oxide salt crystallizes on partial neutralization of the solution. When 25 g. (calcd. 28 g.) of the amine was rapidly stirred with 345 cc. of a nearly neutral solution of Caro's acid containing 2.70 g. of active oxygen, at 10° for one hour, and the mixture allowed to stand overnight in the ice chest, the color of the solution changed from red to yellow, and a cream-colored solid (38.2 g.) formed when the liquid was partially neutralized. This precipitate was assumed to be the normal sulfate and was changed into the hydrochloride.

HYDROCHLORIDE, 3-NO₂.C₆H₄N(CH₃)₂OH.Cl.—Twelve g. of the sulfate was dissolved in 50 cc. of hot, concd. hydrochloric acid and the solution allowed to stand for several days; free chlorine was present; 5.2 g. of the crystalline hydrochloride was obtained, decomposing at 150–152°. When 3.8 g. of this material was dissolved in boiling alcohol and precipitated by ether, 3.4 g. of minute, pure white crystals formed. These began to color in a melting-point tube above 140° and decomposed at 157–158°.

Anal. Subs., 0.6377, 0.6444: AgCl, 0.4161, 0.4207. Subs., 0.2122: N₂, 32.2 cc. (22°, 736 mm. over 30% KOH). Calc. for C₈H₁₁O₂N₂Cl: N, 12.82; Cl, 16.22. Found: N, 12.81; Cl, 16.14, 16.08.

HYDRIODIDE.—As in the case of the other amine oxide hydrochlorides, this one causes free iodine to separate from a solution of potassium iodide. From qualitative

²⁵ Ref. 19, p. 1049.

tests in the cold the stability of this hydriodide seemed greater than that of the 4-nitro derivative. When the solution was warmed, decomposition proceeded rapidly and 3-nitro-dimethylaniline and iodine were shown to be present in the product.

PICRATE.—The filtrate from the preparation of the hydrochloride was diluted to 800 cc. with a hot solution of 5 g. of picric acid. As the mixture cooled, precipitation was induced by scratching. The yellow solid, recrystallized from dil. alcohol, gave 5.8 g. of fluffy, yellow needles; m. p., 141–142°.

3-Nitro-dimethylaniline Oxide, $3\text{-NO}_2\text{.C}_6\text{H}_4\text{N(CH}_3)_2\text{O}$.—Two g. of the hydrochloride in methanol was changed to the free base by agitation with moist silver oxide. The filtered solution was evaporated in a vacuum at 80–100°. Near the end of the process the temperature was raised to 115° (the pressure being 20 mm.). The mass solidified to a slightly brownish, crystalline solid; m. p., 152–155°. The material had a slight odor resembling that of an isocyanide and was evidently somewhat impure. It deliquesced rapidly in air and its solution in water did not give free iodine with potassium iodide. A sample weighed immediately for analysis gave the following result.

Anal. Subs., 0.2644: N_2 , 36.4 cc. (21°, 742 mm.; over 30% KOH). Calc. for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_3$: N, 15.39. Found: 15.29.

A solution of the free base in methanol prepared from 1.9 g. of the hydrochloride was dehydrated in a vacuum and the temperature raised to about 140°. Decomposition took place, liquid was formed and this product, which solidified as it cooled, was recrystallized from alcohol and water and pressed between filter paper to remove some resinous material. There were obtained 0.7 g. of 3-nitro-dimethylaniline, m. p. 58–60°, and some resinous material. The free base evidently cannot be sublimed in a vacuum, and on heating it under reduced pressure loss of oxygen seems to occur as the chief reaction. A small sample of the oxide heated in a test-tube at ordinary pressure gave a slight odor of formaldehyde which was detected as the solid decomposed.

3-Nitro-dimethylaniline Oxide and Methyl Iodide.—When 35 cc. of a solution of this free oxide, prepared from 12.0 g. of the hydrochloride by precipitation with silver oxide and evaporation, was allowed to stand in a stoppered flask with 22 g. of methyl iodide, the solution gradually darkened and crystals appeared within 48 hours. At the end of two weeks, the solid material no longer continued to increase in amount. Extraction with acetone removed a product which was dark colored, leaving a material, 7.8 g. pure (10.9 g. crude), which crystallized from water in yellow prisms and decomposed at about 200°. This was found to be 3-nitro-phenyltrimethylammonium iodide by analysis for iodide ion. The material was also prepared by warming 3-nitro-dimethylaniline with an excess of methyl iodide under a reflux condenser for eight hours. The reaction was not complete, but 2.1 g. of the pure quaternary salt was obtained from 5.0 g. of the tertiary amine; it resembled completely the product obtained above. The decomposition of this salt is peculiarly variable and depends greatly on the method of heating.

Anal. Subs., 0.4224: AgI, 0.3222. Calc. for $\text{C}_9\text{H}_{13}\text{N}_2\text{O}_2\text{I}$: I, 41.21. Found: 41.23.

The dark colored material that was easily soluble in acetone precipitated from solution as bronze-colored plates when a large excess of carbon tetrachloride was added to the concentrated solution in acetone. In this way 3.8 g. of pure (7.0 g. of crude) periodide of 3-nitro-phenyltrimethylammonium iodide, $3\text{-NO}_2\text{.C}_6\text{H}_4\text{N(CH}_3)_3\text{I}_3$ was obtained. This periodide was quite stable at ordinary temperature and melted at 144–145°. The free iodine was determined by titrating the solution of the periodide in acetone with standard thiosulfate solution to the disappearance of the brown color.

Anal. Subs., 0.2794: thiosulfate, 18.95 cc. (1 cc. = 6.613 mg. of I_2). Calc. for $\text{C}_9\text{H}_{13}\text{N}_2\text{O}_2\text{I}_3$: I, 45.18. Found: 44.84.

This per-iodide was also prepared from 4-nitro-phenyltrimethylammonium iodide

dissolved in acetone by the addition of iodine and carbon tetrachloride. With 1.6 g. of the quaternary salt and 2 g. of iodine in 25 cc. of acetone, 2.2 g. of bronze plates, resembling completely those obtained in the above reaction, was obtained. These melted at 144–145° and were analyzed for free iodine as before.

Anal. Subs., 0.2760: thiosulfate, 18.90 cc. (1 cc. = 6.613 mg. of I₂). Calc. for C₆H₁₂N₂O₂I₃: I₂, 45.18. Found: 45.28.

Summary

1. Three new amine oxides formed from 4-bromo, and 3- and 4-nitro-dimethylaniline have been studied and various salts prepared.

2. The iodides of these amine oxides are unstable. The iodide of 4-bromo-dimethylaniline oxide was isolated, but was found to decompose rapidly. The net result of this change is the liberation of iodine and the reduction of a part of the amine oxide to the corresponding tertiary amine.

3. These amine oxides do not add methyl iodide. During the reaction, iodine is liberated and the oxides are reduced to corresponding tertiary amines without the liberation of formaldehyde.

4. The various interpretations offered to explain the isomers discovered by Meisenheimer are discussed, especially those of Jones and of Michael, and the more recent explanations of Lewis and of Langmuir.

PRINCETON, NEW JERSEY

[CONTRIBUTION FROM THE LABORATORY OF THE HENRY PHIPPS INSTITUTE OF THE UNIVERSITY OF PENNSYLVANIA]

THE PREPARATION AND PROPERTIES OF 4,4-DIPHENYL-DIARSONIC ACID

BY A. ELIZABETH HILL

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Since the discovery by Boer¹ of the partially specific disinfectant action of certain dyes, attention has been more and more frequently directed toward the specific relationships of disinfectants generally. The synthetic dyes have been shown to be variously directed in this sense. Lewis² has shown that a certain group of dyes possesses the power of inhibiting the growth of *Bacillus tuberculosis* although few of them are active against *Bacillus typhosus* in a marked degree. Among these dyes the group of the azo, and particularly the so-called tetrazo dyes presents the most striking example of differential activity. The tetrazo dyes used for the most part in Lewis' published work and since in this Laboratory for the same purpose, have been derivatives of benzidine, and it has been a working hypothesis with us that in the so-called benzidine configuration there resides some specific property directed against the tubercle bacillus. This activity does not appear to extend to the point of killing the micro-organism

¹ Behring, "Gesammelte Abhandlungen," Leipzig, 1893, p. 198.

² Lewis, *J. Exp. Med.*, 25, 441 (1917).