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The Ketonimine Dyestuffs and their Derivatives

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Auramine, the hydrochloride of 4,4′-tetramethyldiaminobenzophenonimine, was first patented in 1884 by Caro and Kern.[1] At present, approximately a million pounds per year are produced in the United States for the dyeing of paper, cotton and silk.

The attention of the authors was attracted to auramine because of its use as an antiseptic under the name of Pyoktanium Aureum, for the treatment of infections. Fairbrother and Renshaw[2] chose auramine as the most powerful bactericide in a large number of dyes tested. Dyson[3] states—"Auramine is probably the most potent antiseptic dyestuff known (with the exception of the cyanine dyes), and one which is, moreover, very general in its action. It inhibits the growth of all tested organisms at a dilution of 1 in 5000, and even at 1:250,000 it inhibits the growth of *Micrococcus ureae* to a considerable extent." Marchard[4] states that auramine is efficacious in the treatment of mildew at a dilution of 1:3000.

In the hope of producing an improved bactericide, work was instituted to investigate the synthesis of certain homologs of auramine and their acid salts.

The two commercial methods of making auramine were investigated: (1) from Michler's ketone, zinc chloride and ammonium chloride;[1] and (2) from 4,4′-tetramethyldiaminodiphenylmethane, sulfur, ammonium chloride and gaseous ammonia.[5] The latter process, although patented in the name of Adolph Feer, is credited to Traugott Sandmeyer.[6] The method of Ewer and Pick,[7] in which the condensation of dimethylaniline and urea in the presence of zinc chloride gives first the ketone and then the ketonimine, was also studied. The yield was very small and in adapting this method to the preparation of 4,4′-diaminobenzophenonimine according to patent directions, the desired compound was not formed, but instead the zinc chloride salt of an unidentified compound.

For the production of auramine of that degree of purity necessary for medicinal use, all these methods have the disadvantage of producing a considerable amount of residue, and in two methods zinc chloride is intro-

(1) H. Caro and A. Kern, U. S. Patent 301,802 (July 8, 1884); German Patent 29,060 (March 11, 1884).

(2) T. H. Fairbrother and A. Renshaw, *J. Soc. Chem. Ind.*, **41**, 134T (1922).

(3) Malcolm G. Dyson, "The Chemistry of Chemotherapy," Ernest Benn, Ltd., London, England, 1928, p. 78.

(4) R. Marchard, *Chimie & industrie*, **27**, 15–17 (1932).

(5) Adolph Feer, German Patent 53,614 (Aug., 1889).

(6) H. E. Fierz-David, "The Fundamental Processes of Dye Chemistry," translated by F. E. Mason, J. and A. Churchill, London, England, 1st ed., 1921, pp. 159–161.

(7) Ewer and Pick, German Patent 31,936 (May 9, 1884).

duced. Furthermore, the authors were unable to adapt these methods to the preparation of the homologs of auramine.

Four new or modified methods of producing auramine in solution were accordingly developed, and the most suitable applied to the production of the new 4,4′-tetraethyldiaminobenzophenonimine, as well as to the preparation of benzophenonimine. New organic acid salts of these compounds and of 4,4′-diaminobenzophenonimine were prepared. The new oxime of 4,4′-tetraethyldiaminobenzophenone was synthesized from the phenone and also from 4,4′-tetraethyldiaminothiobenzophenone. The latter, though patented,[8] had not been previously described.

The bactericidal properties of these compounds are now being investigated.

Experimental

Preparation of Auramine in Solution. Method I.—Good yields of 4,4′-tetramethyldiaminothiobenzophenone were obtained in a high boiling organic solvent (above 190°) by dissolving 25 g. of 4,4′-tetramethyldiaminodiphenylmethane and 6.4 g. of sulfur in 100 g. of naphthalene, and refluxing for five hours. The thio ketone had been previously prepared from the methane: (1) by the Kranz[9] method with 50% sodium hydroxide and sulfur; and (2) according to German Patent 289,108[10] with crystallized sodium sulfide and sulfur. The formation of the thio ketone is indicated by the evolution of the by-product, hydrogen sulfide, which may be measured by the production of lead sulfide. To ascertain the best medium for this reaction, a number of solvents were tested over a considerable range of temperature. These solvents are listed in Table I. Blank runs were, of course, made in each case. As indicated, the higher boiling inactive hydrocarbons proved more successful and of these naphthalene the most desirable.

TABLE I

DATA ON REACTION MEDIA FOR THE PREPARATION OF THIO KETONE

Solvent	Approximate temp., °C.	Results
Benzene	80	Negative
Toluene	111	Negative
Xylene	137	Negative
p-Cymene	177	Some H_2S from sulfur and cymene alone
Diethylbenzene	181	Negative
Triethylbenzene	217	Very little H_2S from blank. More H_2S with methane base
Tetraethylbenzene	248	Results same as triethylbenzene
Pentaethylbenzene	276	Results same as triethylbenzene. Pungent odor
1,2-Dichlorobenzene	181	Negative
Nitrobenzene	204	Slightly positive
Naphthalene	210–218	Copious evolution of H_2S
Diphenyl	210–250	Copious evolution of H_2S
Phenanthrene	340	Copious evolution of H_2S
Ethyleneglycol	197	Some H_2S by vigorous boiling
Propyleneglycol	188	Small amount of H_2S by vigorous boiling
Ethyl benzoate	210	Negative

(8) Badische Aniline und Soda-Fabrik, German Patent 40,374 (Oct. 22, 1886).

(9) F. H. Kranz, U. S. Patent 1,661,293 (Mar. 6, 1928).

(10) Badische Aniline und Soda-Fabrik, German Patent 289,108 (Dec. 17, 1913).

To the reaction mixture of naphthalene and thio ketone, 14 g. of ammonium chloride was added, and during three hours heating a stream of ammonia gas was bubbled through the solution. It was then cooled to 90° and dry hydrogen chloride run in to convert all the base into auramine. The mass was poured out, pulverized, and extracted with water at 60°. The dye was salted out, recrystallized from alcohol, and identified by mixed melting points of the anthranilic acid salts; yield, approximately 10%.

Method II.—Auramine base was prepared as follows. To a suspension of 10 g. of 4,4′-tetramethyldiaminothiobenzophenone in 40 cc. of absolute alcohol, in a steel bomb, anhydrous ammonia was added cautiously from a dropping funnel until there was an increase of 15 g. in weight. The bomb was then capped and heated to 100° for five hours on a steam-bath. The bomb was opened cautiously and the alcohol solution filtered off. About 20% of the thio ketone is converted to Michler's ketone. Most of the unchanged thio ketone was recovered by extracting the residue with toluene. The auramine base was obtained either by fractional crystallization from alcohol, or by precipitating the auramine as an organic acid salt from an ether solution. It was identified as above; yield, approximately 17%. *Note:* Due to the stability of 4,4′-diaminothiobenzophenone, this method proved ineffective with this series.

Method III.—To 50 cc. of a 4% phenylauramine absolute alcohol solution in a steel bomb, 15 g. of liquid ammonia was added, as described above. The bomb was closed and heated on the steam-bath. When opened the alcohol was evaporated off and the residue extracted with ether. The auramine formed was recovered, weighed and identified as the anthranilate; yield, 50%. *Note:* The ease with which some phenylimines are prepared recommends this procedure.

Method IV.—Ten grams of Michler's ketone was dissolved in 50 cc. of toluene and 4 cc. of fresh phosphorus oxychloride added to the hot solution. (*Note:* A smaller yield is obtained when phosphorus pentachloride is substituted for the oxychloride.) The hot toluene mixture is put immediately into a bomb and the blue α,α-dichloro-4,4′-tetramethyldiaminodiphenylmethane precipitates in the bomb. After one-half hour the bomb was cooled and 15 g. of anhydrous ammonia added as above. The capped bomb was heated for five hours on the steam-bath. Upon opening, the toluene solution was evaporated with an air blast, giving a gum from which the free auramine base may be obtained by fractional crystallization from ligroin. Or it may be obtained as a salt by dissolving the gum in ether and precipitating the base free of the ketone with an organic acid. This method is a modification of Caro and Kern's original method[1] as described in their German patent where ammonium hydroxide was used. The yield was raised to approximately 75% by use of anhydrous ammonia.

Preparation of 4,4′-Tetraethyldiaminobenzophenonimine.—This was prepared exactly as above, using the same relative amounts of reagents. This imine has not been described previously, although the preparation is patented. Fierz-David[6] states that it is impossible to purify this substance from the reaction mixture. Experiments in this Laboratory with the commercial methods of preparation from ketone and methane tended to confirm this statement, although after becoming familiar with the properties of the substance, it was found possible to separate it in very small yields as the organic acid salt.

The pure ketonimine base crystallized from ligroin in white needles, m. p. 67–68°. It turns yellow rapidly, as does auramine base, when exposed to the atmosphere. *Anal.* Calcd. for $C_{21}H_{29}N_3$: N, 13.02. Found: N, 12.88. Yield approximately 50%.

Preparation of Benzophenonimine.—This compound was prepared by refluxing one-twentieth mole of benzophenone and one-twentieth mole of phosphorus pentachloride for one hour, and treating the resulting compound in toluene with 15 g. of anhydrous ammonia in a bomb, as above. F. J. Moore[11] prepared this substance by the action of

(11) F. J. Moore, *Ber.*, **43**, 564 (1910).

ammonia on α,α-dibromodiphenylmethane in chloroform. Hantzsch and Kraft[12] stated: "the experiment to make the benzophenonimine directly from benzophenone chloride and ammonia was futile."

Preparation of Salts.—The general procedure in making salts consisted of dissolving the ketonimine base and the acid separately in a solvent and mixing the two solutions. In the case of a fairly soluble salt, the solvent was generally ether. The precipitated salt was then recrystallized from a suitable solvent.

The base of auramine was prepared from the commercial hydrochloride, the 4,4'-tetraethyldiaminobenzophenonimine and benzophenonimine as above. The 4,4'-diaminobenzophenonimine was prepared by the method of Madelung[13] from 4,4'-diaminobenzophenone which was synthesized from diphenylmethane according to Staedel's method.[14]

For Staedel's acid reduction of 4,4'-dinitrobenzophenone to 4,4'-diaminobenzophenone, an alkaline reduction with sodium sulfide was substituted, with better results. The product was purified by dissolving in dilute acid and precipitating with sodium hydroxide.

The salts of auramine base are described in Table II, those of 4,4'-tetraethyldiaminobenzophenonimine in Table III, and those of 4,4'-diaminobenzophenonimine in Table IV.

Other New Compounds.—In the search for new methods of making ketonimines, the following new compounds were prepared:

Benzophenonimine Benzoate.—This new compound was prepared by mixing equivalent amounts of benzophenonimine base and benzoic acid in ether. After some time white needles crystallized out. These were filtered and washed with ether. They were purified by vacuum sublimation and again washed with ether. Unlike the hydrochloride, the benzoate does not instantly decompose when dissolved in water; white needles, m. p. 182°.

Anal. Calcd. for $C_{20}H_{17}NO_2$: N, 4.62. Found: N, 4.75, 4.71.

4,4'-Tetraethyldiaminobenzophenonoxime. Method I.—Twenty-four grams of hydroxylamine hydrochloride and 75 g. of 4,4'-tetraethyldiaminobenzophenone were refluxed in 300 cc. of alcohol for four hours. The alcohol was evaporated, giving a thick oil which was dissolved in dilute hydrochloric acid and precipitated as a wax-like mass with ammonium hydroxide. This material gave light yellow needles from benzene. Recrystallization gave needles melting at 135°; yield, 85%.

Method II.—Five grams of 4,4'-tetraethyldiaminothiobenzophenone (preparation described below) was added to a solution of 2 g. of hydroxylamine hydrochloride in 100 cc. of absolute alcohol and the mixture refluxed for three hours. An odor of hydrogen sulfide was observed. The alcohol solution was evaporated and the residue, treated as above, gave fine, light yellow needles; m. p. 135°. The mixed melting point with the ketoxime, obtained above, was 135°; yield, 85%.

Anal. Calcd. for $C_{21}H_{29}N_3O$: N, 12.39. Found: N, 12.44.

4,4'-Tetraethyldiaminothiobenzophenone.—Ten grams of 4,4'-tetraethyldiaminobenzophenone was dissolved in 40 cc. of toluene, and 4 cc. of phosphorus oxychloride was added with stirring. Hydrogen sulfide was passed in immediately in the cold for one hour. The toluene solution was shaken with sodium carbonate solution until there was no further reaction, then washed with water and evaporated to dryness with an air blast. The resulting gummy mass was washed with cold absolute alcohol. The crystals remaining were treated with activated charcoal in benzene, the benzene solution

(12) A. Hantzsch and F. Kraft, *Ber.*, **24**, 3517 (1891).
(13) W. Madelung, *J. prakt. Chem.*, **114**, 42 (1926).
(14) W. Staedel, *Ann.*, **194**, 370 (1878); **218**, 344 (1883); **283**, 151 (1894).

TABLE II

SALTS OF 4,4′-TETRAMETHYLDIAMINOBENZOPHENONIMINE

Salt	M. p., °C.	Crystal structure	Crystallized from	Solubility in water	Formula	Nitrogen, % Calcd.	Found	
Anthranilate	172	Yellow plates	Benzene	>(1:1000)	$C_{24}H_{28}N_4O_2$	13.86	13.75	13.72
p-Toluate	147	Yellow plates	Benzene	>(2:3000)	$C_{25}H_{29}N_3O_2$	10.42	10.26	10.31
Salicylate	205	Yellow plates	Benzene	<(1:1000)	$C_{24}H_{27}N_3O_3$	10.37	10.17	10.23
3,5-Dinitrobenzoate	198	Yellow needles	Bz and acetone	<(1:1000)	$C_{24}H_{25}N_5O_6$	14.62	14.41	14.50
p-Hydroxybenzoate	184	Yellow plates	Acetone	<(1:1000)	$C_{24}H_{27}N_3O_3$	10.37	10.20	10.25
Benzoate	156	Yellow plates	Acetone	>(1:1000)	$C_{24}H_{27}N_3O_2$	10.80	10.60	10.65

TABLE III

SALTS OF 4,4′-DIAMINOBENZOPHENONIMINE

Salt	M. p., °C.	Crystal structure, plates	Crystallized from	Solubility in water	Formula	Nitrogen, % Calcd.	Found	
Benzoate	191	Flat yellow	Benzene	>(2:1000)	$C_{20}H_{19}N_3O_2$	12.61	12.42	12.45
p-Toluate	175	Irregular yellow	Benzene	>(2:1000)	$C_{21}H_{21}N_3O_2$	12.11	11.91	11.98
Anthranilate	168	Irregular yellow	Benzene	>(2:1000)	$C_{20}H_{20}N_4O_2$	16.09	15.94	16.02

TABLE IV

SALTS OF 4,4′-TETRAETHYLDIAMINOBENZOPHENONIMINE

Salt	M. p., °C.	Crystal structure	Crystallized from	Solubility in water	Formula	Nitrogen, % Calcd.	Found	
Hydrochloride	262	Yellow needles	Benzene	>(1:1000)	$C_{21}H_{30}N_3Cl$	11.68	11.57	11.48
Benzoate	155	Yellow flat plates	Benzene	>(1:1000)	$C_{28}H_{35}N_3O_2$	9.44	9.38	9.42
Anthranilate	157	Yellow flat plates	Benzene	<(1:1000)	$C_{28}H_{36}N_4O_2$	12.17	11.96	11.95
Salicylate	170	Yellow flat plates	Benzene	<(1:1000)	$C_{28}H_{35}N_3O_3$	9.11	8.99	8.96
p-Toluate	158	Yellow flat plates	Benzene	<(1:1000)	$C_{29}H_{37}N_3O_2$	9.15	8.98	9.06

evaporated, and the substance recrystallized from absolute ethyl alcohol or amyl alcohol; m. p. 158°; yield, 35%.

Anal. Subs., 0.5039, 0.5057: $BaSO_4$, 0.3375, 0.3389. Calcd. for $C_{21}H_{28}N_2S$: S, 9.421. Found: S, 9.199, 9.204.

Solubility. Absolute ethyl alcohol, 0.04 g./100 cc. at 0°, 0.13 g./100 cc. at 29.7°, 1.32 g./100 cc. at boiling point. Amyl alcohol, 0.12 g./100 cc. at 0°, 0.24 g./100 cc. at 30°, 2.20 g./100 cc. at boiling point.

The substance is quite soluble in all the ordinary organic solvents, such as toluene, benzene, chloroform, acetone and ether. A very dilute solution is green. A concentrated solution is red. It gives a green color with methyl iodide, and crystallizes from ethyl or amyl alcohol in beautiful cylindrical rods which are brilliant purple by reflected light, or a deep wine-red by transmitted light. It can be hydrolyzed with water. Litharge, in alcoholic-alkali solution, transforms it nearly quantitatively to the ketone in a short time. With hydroxylamine hydrochloride in alcohol it gives the ketoxime (see above).

Summary

In a study of auramine (4,4′-tetramethyldiaminobenzophenonimine hydrochloride) and related compounds, with a view to developing improved bactericides, three new methods of preparing auramine or its base in solution were devised.

Five new organic acid salts of auramine base, a synthesis of benzophenonimine and its new benzoic acid salt, and three new salts of 4,4′-diaminobenzophenonimine are described.

The new oxime of 4,4′-tetraethyldiaminobenzophenone was prepared both from the ketone and the thio ketone. The new 4,4′-tetraethyldiaminothiobenzophenone is described.

The synthesis of the new compound, 4,4′-tetraethyldiaminobenzophenonimine, and five salts of it, are described.

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