[CONTRIBUTION NO. 264 FROM THE INDUSTRIAL FARM PRODUCTS RESEARCH DIVISION, BUREAU OF CHEMISTRY AND SOILS UNITED STATES DEPARTMENT OF AGRICULTURE]

Some Ketonimine Dyes and Related Compounds

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In a previous investigation for the development of new bactericides the preparation of some symmetrical diamino dyes related to auramine O (the hydrochloride of 4,4′-tetramethyldiaminobenzophenonimine) and their salts was described.[1] This report concerns the preparation of the monoamino ketonimines which correspond to the diamino dyes previously reported, as well as several other new compounds prepared during the course of the investigation.

Experimental

Alkylated Diaminodiphenylmethanes.—The following new propyl and butyl derivatives of 4,4′-diaminodiphenylmethane were prepared with a view to converting them to the corresponding ketones by oxidation with chloranil as was done by Kliegl[2] with the tetramethyl derivative. However, this method of oxidation was not found applicable.

4,4′-Tetra-*n*-propyldiaminodiphenylmethane.—This compound was prepared according to the method used by Biehringer[3] for the methyl homolog.

35.9 g. of di-*n*-propylaniline was dissolved in 22 g. of 36% hydrochloric acid and diluted with 14 cc. of water. Six grams of 40% formaldehyde was added, and the mixture was held under reflux at 90° for six hours. The mixture was made alkaline with sodium carbonate and extracted with ether. The ether was dried and evaporated. The residual oil was distilled *in vacuo*, and 7 g. of di-*n*-propylaniline was recovered at 105° at 7 mm. pressure. The methane distilled as a heavy oil at 260° at 7 mm.; yield 70%; sp. gr., 0.971^{20}_{20}.

Anal. Calcd. for $C_{25}H_{38}N_2$: N, 7.65. Found: N, 7.50, 7.76.

Dipicrate of 4,4′-Tetra-*n*-propyldiaminodiphenylmethane.—The dipicrate was prepared as a solid derivative by dissolving 0.6 g. of the methane base and 0.82 g. of picric acid separately in 10-cc. portions of hot alcohol and mixing the two solutions. A gummy mass separated which solidified on cooling. It was crystallized from 40 cc. of alcohol as bright yellow needles; m. p. sinters 165°, decomposes 175°.

Anal. Calcd. for $C_{37}H_{44}N_8O_{14}$: N, 13.59. Found: N, 13.69. 13.74.

4,4′-Tetra-*n*-butyldiaminodiphenylmethane.—To 10.5 g. of di-*n*-butylaniline in 5.5 cc. of 36% hydrochloric acid plus 4 cc. of water, was added 1.5 g. of 40% formaldehyde. The mixture was treated as described above. The methane distilled as an oily liquid at 270–280° at 6 mm. pressure; yield, about 70%; sp. gr., 0.953^{20}_{20}.

Anal. Calcd. for $C_{29}H_{46}N_2$: N, 6.63. Found: N, 6.26, 6.29.

Dipicrate of 4,4′-Tetra-*n*-butyldiaminodiphenylmethane.—This was prepared as described above for the corresponding propyl compound; m. p. 156°, corr.

Anal. Calcd. for $C_{41}H_{52}O_{14}N_8$: N, 12.72. Found: N, 12.60, 12.41.

***sym*-4,4′-Di-*n*-butyldiaminodiphenylmethane.**—To 6 g. of 40% formaldehyde were added 31 g. of *n*-butylaniline in 22 g. of 36% hydrochloric acid and 14 cc. of water. It was treated as above. Four grams of butylaniline was recovered at 100° at 10 mm., and the methane distilled at 260–270° at 8 mm. After standing for one week it crystallized as colorless flat plates; m. p. 45°, corr.; yield, about 80%.

Anal. Calcd. for $C_{21}H_{30}N_2$: N, 9.03. Found: N, 8.76, 8.80.

4-Di-*n*-propylaminobenzoic Acid.—In the attempted preparation of 4,4′-tetrapropyldiaminobenzophenone by the method Michler[4] used to make first 4-dimethylaminobenzoic acid and then his ketone, the corresponding dipropyl acid was synthesized.

Four grams of phosgene was absorbed in 15 g. of di-*n*-propylaniline and allowed to stand overnight. The mass was dissolved in dilute hydrochloric acid, filtered and made alkaline with sodium hydroxide. The dipropylaniline was recovered in ether. The solution was made slightly acidic and allowed to stand overnight. The acid crystallized out. It may be extracted also with ether. It was recrystallized as long tetragonal prisms from 50% alcohol; m. p. 142°, corr.; yield, about 80% based on dipropylaniline used up.

Anal. Calcd. for $C_{13}H_{19}NO_2$: N, 6.33. Found: N, 6.14, 6.22.

4-Di-*n*-propylaminobenzophenone.—The 4-dimethyl and 4-diethylaminobenzophenones used below as well as the new 4-di-*n*-propylaminobenzophenone were prepared by the method of Meister, Lucius and Brüning, as modified by C. D. Hurd and C. N. Webb.[5]

In the preparation of the propyl ketone, 13 g. of phosphorus oxychloride was added to a mixture of 25 g. of di-*n*-propylaniline and 10 g. of benzanilide. The mixture was heated cautiously to 105–125°, at which point the temperature rose very suddenly to about 200°. It was cooled in ice water in time to keep the temperature below 200° and then heated under reflux in a boiling water-bath for four hours. It was then poured into 250 cc. of 10–15% hydro-

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(*) This work has been submitted by J. David Reid in partial fulfilment of the requirements for the degree of Doctor of Philosophy at The American University, Washington, D. C.

[1] D. F. J. Lynch and J. David Reid, THIS JOURNAL, **55**, 2515 (1933).

[2] A. Kliegl, *Ber.*, **39**, 1274 (1906).

[3] J. Biehringer, *J. prakt. Chem.*, [2] **54**, 240 (1896).

[4] W. Michler, *Ber.*, **9**, 401 (1876).

[5] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, 1928, p. 211.

chloric acid and warmed until solution took place. The intermediate hydrolyzed overnight to the ketone. The solution was filtered and diluted to 1.5 liters to get the crystalline ketone. It was recrystallized from petroleum ether (b. p. 30–65°) as hexagonal colorless prisms; yield, about 25%; m. p. 100°, corr.

Anal. Calcd. for $C_{19}H_{23}NO$: N, 4.98. Found: N, 5.00, 5.02.

4-Di-*n*-butylaminobenzophenone apparently cannot be prepared by the above method. In several trials only two had the characteristic exothermic reaction. In each case a thick resinous material insoluble in acid was obtained, which was not hydrolyzed by water or alcohol.

Hydrochloride of 4-Aminobenzophenonephenylimide.—The method devised by Madelung[6] to make 4,4′-diaminobenzophenonimine was applied to the preparation of 4-aminobenzophenonimine. The phenylimide intermediate was made by heating 13 g. (0.1 mole) of aniline hydrochloride and 19.7 g. (0.1 mole) of 4-aminobenzophenone in 50 cc. of aniline at 160–180° with occasional stirring for about an hour, or until the mass solidified. After cooling, the aniline was removed by extraction with ether, and the intermediate, 4-aminobenzophenonephenylimide hydrochloride, crystallized from alcohol; yield, about 95%; sinters about 275–280°; no melting point to 400°.

Anal. Calcd. for $C_{19}H_{17}N_2Cl$: N, 9.08. Found: N, 8.97, 8.93.

The phenylimide hydrochloride dyes silk and tannin-mordanted cotton a light yellow but is not fast to light or washing.

The base was liberated from the aqueous solution of the hydrochloride by precipitating with alkali. It was crystallized from benzene after treatment with charcoal; m. p. 154°, corr.

Anal. Calcd. for $C_{19}H_{16}N_2$: N, 10.30. Found: N, 10.22, 9.96.

3,5-Dinitrobenzoate of 4-Aminobenzophenonimine

Method I. From 4-Aminobenzophenonephenylimide Hydrochloride.—Ten grams of the phenylimide hydrochloride was suspended in 100 cc. of alcohol, and ammonia gas was bubbled into the solution until it was saturated and then the liquid was brought to boiling. As done by Madelung, this step was repeated three times to split off the aniline more effectively. The resulting liquor was cooled and the precipitate filtered off and dissolved in about 400 cc. of water, which was just faintly acid with hydrochloric acid. The solution was made alkaline and the imine base extracted with ether. The ether solution was dried over sodium sulfate, and the imine was precipitated as the 3,5-dinitrobenzoic acid salt; yield about 5%; m. p. 198°, corr. A mixed melting point taken with a sample of the same salt prepared by Method II as described below was 198°.

Method II. From 4-Aminobenzophenone.—Ten grams of 4-aminobenzophenone and 10 g. of phosphorus pentachloride, each dissolved in 30 cc. of hot toluene, were cautiously mixed in a steel bomb (100-cc. capacity), and cooled in ice, and liquid ammonia was added cautiously until the weight increased 15 g. The bomb was capped and heated for twelve hours at 100–105°. It was then cooled and opened and the solution evaporated to dryness with an air blast. The mixture of ketone and imine was dissolved in ether and the imine precipitated as a yellow salt by the slow addition of an ether solution of 3,5-dinitrobenzoic acid. The pure base was not obtained, due to the difficulty of separating the imine and the ketone by crystallization. The imine rapidly hydrolyzed to the ketone on treating the salt with alkali. Crystallized from alcohol, the salt had a melting point of 198°, corr. When it was mixed with an equal quantity of 3,5-dinitrobenzoic acid (m. p. 204°) the melting point was depressed to about 110°; yield, about 50%.

Anal. Calcd. for $C_{20}H_{16}N_4O_6$: N, 13.73. Found: N, 13.69, 13.58.

3,5-Dinitrobenzoate of 4-Dimethylaminobenzophenonimine.—Ten grams of 4-dimethylaminobenzophenone[4] was dissolved in 40 cc. of hot toluene, and 10 cc. of phosphorus oxychloride was added. It was cooled and treated with ammonia as in Method II for the preparation of 4-aminobenzophenonimine. Evaporation of the filtered toluene gave an oil from which only the ketone could be crystallized. Distillation of the oily residue *in vacuo* gave a liquid which apparently was about equal parts of ketone and ketonimine. (Calcd.: N, 12.5. Found: N, 9.5.) This material, dissolved in ether and precipitated by 3,5-dinitrobenzoic acid, crystallized from alcohol as yellow needles; yield, about 30%; m. p. 214°, corr.

Anal. Calcd. for $C_{22}H_{20}N_4O_6$: N, 12.84. Found: N, 12.67, 12.68. (Phosphorus pentachloride gave a negligible yield when used in place of the oxychloride. Phosphorus trichloride (b. p. 77°) gave a yield of 5%.)

3,5-Dinitrobenzoate of 4-Diethylaminobenzophenonimine.—This salt was prepared as above, from the 4-diethylaminobenzophenone. However, the precipitate first obtained had to be treated with very dilute alkali, shaken out with ether and reprecipitated in order to free it of ammonium 3,5-dinitrobenzoate. It crystallized from alcohol as yellow needles; yield, about 30%; m. p. 141°, corr.

Anal. Calcd. for $C_{24}H_{24}N_4O_6$: N, 12.07. Found: N, 12.22, 12.11.

An effort was made to prepare 4-di-*n*-propylaminobenzophenonimine from the corresponding ketone by the above method, but no solid product could be isolated. The only action noted was that a yellow color was produced when acid was added to the ether solution of the product.

Benzoyl - 4,4′ - tetraethyldiaminobenzophenonimine. (Benzoyl Ethyl Auramine.)—The benzoyl derivative of 4,4′-tetraethyldiaminobenzophenonimine was made by the method used by Finckh and Schwimmer[7] in preparing the benzoyl derivative of the corresponding methyl compound.

Four grams of 4,4′-tetraethyldiaminobenzophenonimine[1] was refluxed in 20 cc. of benzene with 2.9 g. of benzoic anhydride for five hours. The solution was then diluted to 80 cc. with petroleum ether (b. p. 30–65°). The thick red liquid resulting was separated, and crystallized on standing. It was recrystallized from methyl alcohol as long yellow needles; m. p. 165°, corr.; yield, about 60%.

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(6) W. Madelung, *J. prakt. Chem.*, **114,** 42 (1926).

(7) J. Finckh and M. Schwimmer, *ibid.*, [2] **50,** 434 (1894).

Although this compound is an indicator similar to Benzoyl Auramine G,[8] the color change from yellow to blue is not so sharp. The *p*H range is 4.0–5.2.

Anal. Calcd. for $C_{28}H_{33}N_3O$: N, 10.12. Found: N, 10.01, 9.95.

Solid Salts of Amines.—In working with the alkyl anilines used, it was found convenient to prepare solid derivatives by the use of 3,5-dinitrobenzoic acid. The salt of dimethylaniline has been prepared previously by the same method.[9]

0.002 mole of the dialkylaniline and 0.004 mole of the 3,5-dinitrobenzoic acid (0.002 mole with monobutylaniline) were dissolved in a few cc. of absolute alcohol and allowed to crystallize overnight. The salt was then recrystallized from absolute alcohol with char treatment. All the four salts crystallized as hexagonal prisms (see Table I).

TABLE I

3,5-Dinitrobenzoic acid salt of	M. p., °C., corr.	Nitrogen, % Calcd.	Nitrogen, % Found		Neut. equivalent Calcd.	Neut. equivalent Found
Diethylaniline	120	12.22	12.33	12.41	286.6	280
Di-*n*-propylaniline	118	11.65	11.84	11.90	300.5	294
Di-*n*-butylaniline	104	11.14	11.14	11.34	314.5	308
n-Butylaniline	98.5	11.63	11.40	11.49	361.3	352

Summary

In a study of the ketonimine dyes:

1. Di-*n*-butyldiaminodiphenylmethane, tetra-*n*-butyldiaminodiphenylmethane and tetra-*n*-propyldiaminodiphenylmethane have been synthesized. The picrates of the latter two are also given.
2. 4-Di-*n*-propylaminobenzoic acid has been made.
3. 4-Aminobenzophenonephenylimide and its hydrochloride have been prepared.
4. 4-Aminobenzophenonimine, 4-dimethylaminobenzophenonimine and 4-diethylaminobenzophenonimine have been made and characterized as their solid 3,5-dinitrobenzoic acid salts.
5. Benzoyl ethyl auramine was made, and its properties as an indicator are described.
6. The solid derivatives of diethyl-, di-*n*-propyl-, di-*n*-butyl- and *n*-butyl-aniline with 3,5-dinitrobenzoic acid have been prepared and characterized.

WASHINGTON, D. C. RECEIVED JUNE 2, 1936

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[8] J. T. Scanlan and J. D. Reid, *Ind. Eng. Chem., Anal. Ed.*, **7**, 125 (1935).

[9] C. A. Buehler, E. J. Currier and R. Lawrence, *ibid.*, **5**, 277 (1933).

[CONTRIBUTION FROM THE PEDIATRIC RESEARCH LABORATORY OF THE JEWISH HOSPITAL OF BROOKLYN]

Synthesis of Derivatives of Symmetrical Diphenylethane Related to Materials Occurring Naturally. I. Synthesis of the Ring System Proposed for Calciferol

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A general and flexible method for the synthesis of compounds related to the naturally occurring derivatives of diphenylethane, which include compounds as widely distributed in nature as alkaloids, sterols, bile acids, sex hormones, toad poisons and cardiac aglycones[1] should be of value for the synthesis of degradation products and ultimately for the synthesis of some of the naturally occurring materials themselves.

This report offers a new route to this biologically important series which is capable of wide variation. As an example of its application, a compound having the ring system proposed for calciferol was synthesized in good yield. The formulas proposed by Windaus,[2] Heilbron,[3] Lettré[4] and Müller[5] assume that the phenanthrene ring is open to give a hydrogenated diphenylethane structure to calciferol and tachysterol.

As can be seen from the accompanying flow sheet, the starting materials for this synthesis are the readily available phthalic anhydride and phenylacetic acid.

Phthalic anhydride and phenylacetic acid condense in good yield to form benzal-phthalide (I).[6] The relationship of benzal-phthalide to the naturally occurring materials was recognized and this material and its derivatives were then built up to

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[1] L. F. Fieser, "Chemistry of Natural Products Related to Phenanthrene," Reinhold Publishing Co., New York City, 1936; L. F. Small, "Chemistry of the Opium Alkaloids," U. S. Treasury Dept., Supplement No. 103, 1932. These two monographs offer an inspiring and complete review of the literature on this subject.

[2] Windaus and Thiele, *Ann.*, **521**, 160 (1935).

[3] Heilbron and Spring, *Chem. Ind.*, **54**, 795 (1935).

[4] Lettré, *Ann.*, **511**, 280 (1934).

[5] Müller, *Z. physiol. Chem.*, **233**, 223 (1935).

[6] "Organic Syntheses," Vol. XIII, 1933, p. 10; Gabriel, *Ber.*, **18**, 3470 (1885).