water and precipitated by the addition of more acid. The salts were filtered and washed with alcohol followed by ether.

H. **Salts of the Amines of Phenolic Ethers.**—The free amines were dissolved in alcohol, and the halogen salts were precipitated by the addition of an aqueous solution of the appropriate acid. The salts, after filtration, were washed with alcohol followed by ether.

I. **N-Methyl-N,N'-diacetyl-α,α'-bis-(4-methoxyphenyl)-ethylenediamine.**—This product was prepared by refluxing 0.050 g. of the amine with 1 cc. of acetic anhydride for one hour. After cooling, the crystalline precipitate was filtered and washed with ether. The yield was 0.050 g.

J. **N,N'-Dimethyl-N,N'-diacetyl-α,α'-bis-(4-methoxyphenyl)-ethylenediamine.**—A solution of 0.050 g. of the amine was refluxed in 1 cc. of acetic anhydride for one hour. The solvent was removed by distillation *in vacuo*, and the residue was crystallized from toluene–petroleum ether. The yield was 0.055 g.

K. **N,N'-Dichloroacetyl-α,α'-bis-(4-methoxyphenyl)-ethylenediamine.**—A mixture of 0.091 g. of α,α'-bis-(4-methoxyphenyl)-ethylenediamine, 0.114 g. of chloroacetic anhydride and 10 cc. of toluene was refluxed for two hours. The yield was 0.124 g.

L. **N,N'-Dibenzenesulfonyl-α,α'-bis-(4-methoxyphenyl)-ethylenediamine.**—Benzenesulfonyl chloride (0.14 g.), α,α'-bis-(4-methoxyphenyl)-ethylenediamine[3] (0.091 g.) and 0.5 cc. of pyridine was heated on a steam-bath for two hours. After diluting the reaction mixture with water, the product was filtered and washed with alcohol and ether. The yield was 0.161 g. The product was insoluble in dilute sodium hydroxide.

M. **N,N'-Diacetyl-α,α'-bis-(4-acetoxyphenyl)-ethylenediamine.**—A mixture of 0.150 g. of α,α'-bis-(4-hydroxyphenyl)-ethylenediamine, 15 cc. of acetic anhydride and 1 cc. of pyridine was refluxed for two hours. After cooling, the tetra-acetyl derivative was filtered and washed with ether. The yield was 0.184 g. Recrystallization from glacial acetic acid did not change the decomposition point.

N. **N,N'-Dimethyl-N,N'-diacetyl-α,α'-bis-(4-acetoxyphenyl)-ethylenediamine.**—N,N'-Dimethyl-α,α'-bis-(4-hydroxyphenyl)-ethylenediamine (0.140 g.) was refluxed with 35 cc. of acetic anhydride for one hour and fifteen minutes, during which time the solids dissolved completely. The solution was then concentrated *in vacuo* and the residue crystallized from toluene–petroleum ether. The yield was 0.180 g.

O. **N,N'-Dimethyl-N,N'-diacetyl-α,α'-bis-(4-hydroxyphenyl)-ethylenediamine.**—A suspension of 0.200 g. of N,N'-dimethyl-N,N'-diacetyl-α,α'-bis-(4-acetoxyphenyl)-ethylenediamine in 5 cc. of 1 *N* sodium hydroxide was warmed until solution of the solids was complete. The phenol was then precipitated by bubbling carbon dioxide into the alkaline solution. The crystalline phenol was then filtered and washed with water and alcohol. The yield was 0.160 g.

P. **N,N'-Dimethyl-N,N'-diacetyl-α,α'-bis-(4-methoxyphenyl)-ethylenediamine.**—A solution of the above phenol (0.06 g.) was dissolved in an excess of 10% sodium hydroxide and shaken with a few drops of methyl sulfate. The crude methyl ether was then filtered and crystallized from alcohol–water solution. The yield was 0.050 g., m. p. 218–219°. This melting point was identical with that obtained from the acetylation of N,N'-dimethyl-α,α'-bis-(4-methoxyphenyl)-ethylenediamine. The mixed melting point showed no depression. This would indicate the structure of the methyl ether remained intact save for the removal of the methyl groups during hydrolysis with hydrobromic acid.

Physiology.—The hydrochlorides of N,N'-dimethyl-α,α'-bis-(4-hydroxyphenyl)-ethylenediamine (I) and its methyl ether (II) were tested for estrogenic activity and effect on blood pressure. (I) and (II) were inactive as estrogens up to 100 γ doses. Compounds (I), (II) and ephedrine sulfate (III) were tested for effect on blood pressure by intravenous administration to dogs. The table shows some of the results:

	I	II	III
Dose[a]	4	4	0.25
B. pr.[b]	122	122	122
B. pr.[c]	−2, 13	−22, 6	18
t[d]	0.25, 8.0	0.50, 3.0	10.0

[a] In mg. per kgm. [b] Blood pressure before injection in mm. [c] Change in blood pressure in mm. [d] Duration of change in minutes.

Acknowledgment.—The authors desire to express their appreciation to Dr. F. E. Stirn, Dr. B. K. Harned and Mr. Robert Vessey of the Lederle Laboratories, Pearl River, N. Y., for the physiological results.

Summary

A series of derivatives of α,α'-bis-(4-hydroxyphenyl)-ethylenediamine has been prepared and characterized.

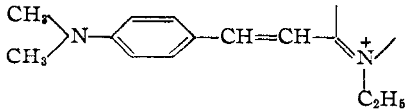
NEW YORK, N. Y. RECEIVED MARCH 15, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Bridge Substituted Hemicyanines

BY NORMAN PICUS[1] AND PAUL E. SPOERRI

One of the important types of cyanine dyes used as photographic sensitizers is the hemicyanines or *p*-dimethylaminostyryl[2] type of dye (I). Many compounds of this type have been prepared by the condensation of *p*-dimethylaminobenzaldehyde with quaternary salts of α-methyl-N-heterocyclics.[3] Hemicyanines containing longer methylidyne bridges have been prepared by the condensation of the respective aldehyde and heterocyclic salt.[4] The reaction of a heterocyclic salt



I

---

[1] From a thesis submitted in partial fulfillment of the requirements for the degree of M.S. in Chemistry.

[2] Although the term, hemicyanine, was not originated to include the *p*-dimethylaminostyryl type of dye, C. E. K. Mees in "The Theory of the Photographic Process," The Macmillan Co., New York, N. Y., 1946, p. 1034, indicates that this term may well be used to include this general type of dyestuff.

[3] L. G. S. Brooker and co-workers, THIS JOURNAL, **67**, 1875 (1945).

[4] W. König and O. Treichel, *J. prakt. Chem.*, **102**, 63 (1921).

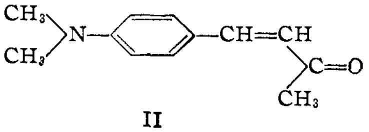
TABLE I

DERIVATIVES OF *p*-DIMETHYLAMINOBENZALACETONE

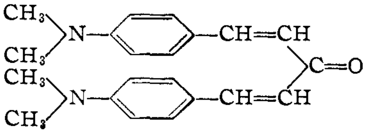
Derivative	Formula	Color	M. p. (°C. uncor.)	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Oxime	$C_{12}H_{16}ON_2$	Yellow	184–186	70.56	70.73	7.90	7.95	13.72	13.76
Phenylhydrazone	$C_{18}H_{21}N_3$	Green-yellow	166–167	77.38	77.45	7.58	7.71	15.04	14.80
p-Nitrophenylhydrazone	$C_{18}H_{20}O_2N_4$	Blue-black	200–202	66.65	66.92	6.22	6.28	17.28	17.54
2,4-Dinitrophenylhydrazone	$C_{18}H_{19}O_4N_5$	Red-brown	232–233	58.53	58.63	5.18	5.17	18.96	18.75

with ketones to form hemicyanines with substituents on the methylidyne bridge has not been investigated. McElvain and Johnson[5] have succeeded in condensing the heterocyclic bases α-picoline and quinaldine with ketones containing at least two adjacent carbonyl groups, but the condensation with monoketones has been successful only under drastic conditions.[6] This reaction has been studied only with the free base. However, the activating influence of the quaternization of the base on the α-methyl group may lead to more successful results. Brooker and White[7] succeeded in the preparation of carbocyanines having a substituent on the center carbon of the methylidyne bridge by the condensation of a quaternary α-methyl heterocyclic salt with ketones of the type 1-acetyl-methylene-2-ethylbenzothiazoline.

The type of ketone necessary to produce the structural requirements of a photographically sensitive hemicyanine was prepared by Sachs and Lewin[8] by the condensation of *p*-dimethylaminobenzaldehyde with acetone. The reaction may be carried out such that two products may be obtained: the unsymmetrical ketone, *p*-dimethylaminobenzalacetone (II), and the symmetrical ketone, bis-(*p*-dimethylaminobenzal)-acetone (III).



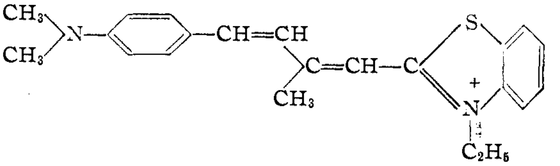
II



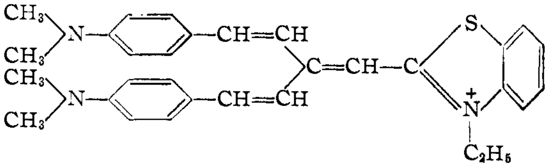
III

Our attempts to characterize these two ketones by the formation of various derivatives were successful only in the case of the unsymmetrical ketone (II) when standard procedures for the formation of the respective derivatives were used.[9] The derivatives of *p*-dimethylaminobenzalacetone are described in Table I.

The condensation of the ketones with 2-methylbenzothiazole ethiodide could not be effected by making use of a base catalyzed reaction such as is commonly used for the condensations employing the aldehyde. The reaction was successfully carried out by employing the conditions used by Brooker and White.[7] Two hemicyanine type compounds were thus obtained as highly colored crystalline materials: 2-(2′-methyl-4′-*p*-dimethylaminophenyl-1′,3′-butadiene)-benzothiazole ethiodide (IV) and 2-(2′-*p*-dimethylaminostyryl-4′-*p*-dimethylaminophenyl-1′,3′-butadiene)-benzothiazole ethiodide (V). Both dyes show a broad absorption band in the visible region, the absorption maxima being at 555 mμ and 570 mμ respectively for compounds IV and V. The absorption curves are shown in Fig. 1.



IV



V

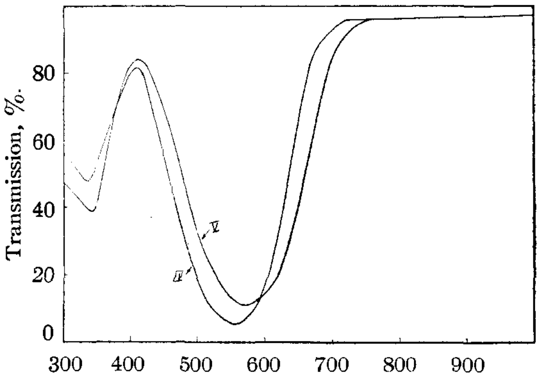


Fig. 1.—Absorption spectra.

Experimental[10,11]

***p*-Dimethylaminobenzalacetone, II.**—The procedure of Sachs and Lewin[8] was refined using the technique of Kohler and Chadwell.[12] Sixty grams (1.5 moles) of sodium

---

[5] S. M. McElvain and H. G. Johnson, THIS JOURNAL, **63**, 2213 (1941).

[6] A. E. Chichibabin, *Bull. soc. chim.*, **3**, 1607 (1936).

[7] L. G. S. Brooker and F. L. White, U. S. Patent 2,112,140 (1935).

[8] F. Sachs and W. Lewin, *Ber.*, **35**, 3575 (1902).

[9] R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 2nd ed., John Wiley and Sons, New York, N. Y., 1940, pp. 167, 64, 142 and 143.

[10] All melting points given are uncorrected.

[11] Analyses by Dr. Francine Schwarzkopf.

[12] "Organic Syntheses," Coll. Vol. I, 1941, p. 78.

hydroxide was dissolved in 490 ml. of water and added to 306 ml. of 95% ethyl alcohol contained in a 2-l. beaker. Two hundred and ninety grams (5.0 moles) of acetone was added and the mixture chilled to about 25°. One hundred and forty-nine grams (1.0 mole) of *p*-dimethylaminobenzaldehyde was added and the mixture mechanically stirred. Crystallization began in about thirty minutes and the stirring was continued for an additional two hours. The mixture was kept at 0° overnight and then filtered. The orange crystals were washed with cold water until the wash water was neutral to litmus paper. The washing was completed with about 50 ml. of cold 95% ethyl alcohol. The product was recrystallized from about 4 to 5 times its weight of 95% ethyl alcohol and yielded 149 g. (79%) of product, m. p. of 133–135°. The reported[8] m. p. of 234–235° seems to be a typographical error.

bis-(*p*-Dimethylaminobenzal)-acetone, III.—Sixty-three grams (0.3 mole) of *p*-dimethylaminobenzalacetone and 50 g. (0.3 mole) of *p*-dimethylaminobenzaldehyde were dissolved in 500 ml. of hot 95% ethyl alcohol contained in a 1-l. beaker. Twenty-five milliliters of a 10% aqueous solution of sodium hydroxide was added and the solution heated on the steam-bath while being mechanically stirred. After about fifteen minutes dark red crystals began to appear. The stirring and heating was continued for an additional two hours (adding more alcohol as needed to prevent boiling to dryness) after which time crystallization appeared to be complete. The mixture was allowed to cool, then filtered and the product washed with 95% ethyl alcohol. The dark red crystals were then boiled with 250 ml. of alcohol, filtered while hot, and washed with hot alcohol. The yield was 60 g. (55%) of product, m. p. 189.5–191°, reported[8] m. p. 191°.

2-(2′-Methyl-4′-*p*-dimethylaminophenyl-1,3′-butadiene)-benzothiazole Ethiodide, IV.—To 1.9 g. of the ketone, II, was added 3.1 g. of the quaternary salt, 2-methylbenzothiazole ethiodide, in a 200 ml. round-bottom flask fitted with a reflux condenser. Twenty-five milliliters of acetic anhydride was added and the mixture refluxed for fifteen minutes. After cooling, 150 ml. of ether was added and the supernatant liquor decanted. The tarry residue was dissolved in 200 ml. of hot methyl alcohol and 4 g. of potassium iodide added. After cooling, the greenish-black crystalline product was filtered and recrystallized several times from methyl alcohol; m. p. 229–230° (dec.); yield 0.07 g. (1.5%).

Anal. Calcd. for $C_{22}H_{25}N_2SI$: C, 55.46; H, 5.29; N, 5.88. Found: C, 55.61; H, 5.01; N, 6.02.

2-(2′-*p*-Dimethylaminostyryl-4′-*p*-dimethylaminophenyl-1′,3′-butadiene)-benzothiazole Ethiodide, V.—To 3.2 g. of the ketone, III, was added 3.1 g. of the quaternary salt, 2-methylbenzothiazole ethiodide, in a 200-ml. round-bottom flask fitted with a reflux condenser. Twenty-five milliliters of acetic anhydride was added and the mixture refluxed for twenty-five minutes. The reaction mixture was treated as above and yielded 0.33 g. (5.4%) of the greenish-black crystalline material; m. p. 242–243° (dec.).

Anal. Calcd. for $C_{31}H_{34}N_3SI$: C, 61.28; H, 5.64; N, 6.92. Found: C, 61.02; H, 5.76; N, 6.80.

Summary

Four new derivatives, the oxime, phenylhydrazone, *p*-nitrophenylhydrazone, and 2,4-dinitrophenylhydrazone, of the ketone, *p*-dimethylaminobenzalacetone, were prepared and described.

Two hemicyanines containing substituents on the methylidyne bridge were prepared by the condensation of a ketone with 2-methylbenzothiazole ethiodide in acetic anhydride solution.

BROOKLYN, N. Y. RECEIVED APRIL 6, 194

[CONTRIBUTION FROM RESEARCH LABORATORIES, THE NATIONAL DRUG COMPANY]

The Synthesis and Microbiological Properties of β-(2-Benzothienyl)-α-aminopropionic Acid[1a]

BY SOUREN AVAKIAN, JACK MOSS AND GUSTAV J. MARTIN

Fildes[1] pioneered the field of tryptophan displacement when he determined the capacity of β-indoleacrylic acid to inhibit the growth of *E. coli* and *B. typhosum*. Subsequently, many other compounds have been synthesized and studied as tryptophan displacers: 1-naphthylacrylic and styrylacetic acids,[2] 5-methyl-DL-tryptophan,[3] 3-acetylpyridine,[4] β-(cumaronyl-(3))-alanine and β-(naphthyl-(1))-alanine,[5] methylated indoles,[6] β-1-naphthylalanine and β-2-naphthylalanine.[7]

Desiring to extend knowledge of this field of displacement, the synthesis and testing of β-(2-benzothienyl)-α-aminopropionic acid was undertaken.

Experimental

2-Chloromethylbenzothiophene.—A rapid current of hydrogen chloride was passed through a vigorously stirred mixture of 20.1 g. (0.15 mole) of benzothiophene[8] and 20 cc. of 40% formaldehyde cooled in an ice-bath. The reaction temperature was kept at 20–25° for five minutes and then at 10–15°. After half an hour the mixture was diluted with ice water and extracted with ether. The ether layer was washed with aqueous sodium bicarbonate solution, and dried over sodium sulfate. Distillation gave 15.5 g. (56.3% yield) of product boiling at 129–131° (5.0 mm.). Crystallization from petroleum ether gave a white crystalline product melting at 44–45°.

Anal. Calcd. for C_9H_7ClS: Cl, 19.44. Found: Cl, 19.38.

Ethyl-α-carbethoxy-α-formylamido-β-(2-benzothienyl)-propionate.—To a solution of 1.2 g. of sodium in 100 cc. of absolute alcohol, was added 10.2 g. of ethyl formylaminomalonate[9] followed by 9.2 g. of 2-chloromethylbenzothiophene. The mixture was refluxed for three hours, poured into ice water, and the precipitate filtered; yield of the crude product, melting at 103–105° was 29 g. (83%). An analytical sample crystallized from benzene–petroleum ether melted at 106–107°. *Anal.* Calcd. for $C_{17}H_{19}O_5NS$: S, 9.15. Found: S, 8.91.

(1a) Presented in part before Organic Section, American Chemical Society Meeting in Miniature, Philadelphia Section, Jan. 22, 1948.

(1) P. Fildes, *Biochem. J.*, **32**, 1600 (1948).

(2) H. Bloch and H. Erlenmeyer, *Helv. Chim. Acta.*, **25**, 694 (1942).

(3) T. F. Anderson, *Science*, **101**, 565 (1945).

(4) D. W. Woolley, *J. Biol. Chem.*, **162**, 179 (1946).

(5) H. Erlenmeyer and W. Grubenmann, *Helv. Chim. Acta*, **30**, 297 (1947).

(6) P. Fildes and H. N. Rydon, *Brit. J. Exp. Path.*, **28**, 211 (1947).

(7) K. Dittmer, W. Herz and S. J. Cristol, *J. Biol. Chem.*, **173**, 323 (1948).

(8) C. Hansch and H. G. Lindwall, *J. Org. Chem.*, **10**, 381 (1945).

(9) A. Galat, THIS JOURNAL, **69**, 965 (1947).