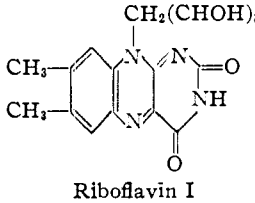
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

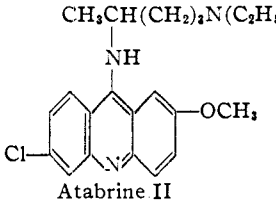
Heterocyclic Basic Compounds. VII. Basically-substituted Isoalloxazine Derivatives[1]

BY ROBERT R. ADAMS,[2] CHARLES A. WEISEL AND HARRY S. MOSHER

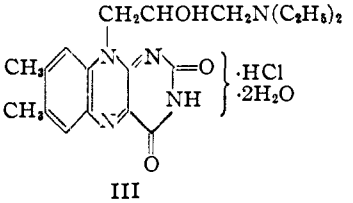
As an extension of our previous work in this Laboratory on various basically-substituted heterocyclic compounds,[3] we have prepared a number of basically-substituted isoalloxazine derivatives. These compounds are of very special interest because of their structural relationship to both riboflavin (I) and atabrine (II).



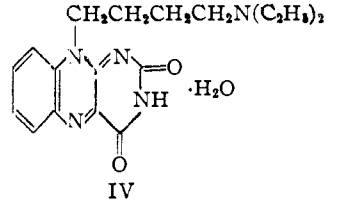
Riboflavin I



Atabrine II



III



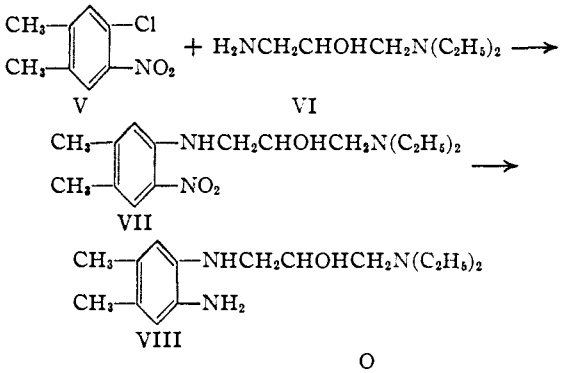
IV

Basically-substituted isoalloxazines

The therapeutic activity of certain compounds composed of a heterocyclic nucleus and a basic side-chain has already been well established. Additional incentive for making these products is found in the report of Silverman and Evans[4] that Atabrine exhibits a marginal reversal of the metabolic activity of riboflavin when tested on *L. casei*. It was considered possible that a greater degree of antagonism toward riboflavin might result if the basic side-chain were on the isoalloxazine nucleus instead of the acridine nucleus. This, however, did not prove to be the case, since the basically-substituted isoalloxazines as represented by III showed no bacteriostatic activity and hence no antagonistic action toward riboflavin when tested[5] on *L. casei* and *E. coli* at concentrations of 100 mg. per cent.

Riboflavin antagonists have been investigated by Kuhn and co-workers,[6] Emerson and Tishler[7] and Wooley.[8] These investigators found that by either altering the ring system or substituents of the riboflavin nucleus they were able to produce riboflavin antagonists. The inactivity of III and similar compounds substantiates the findings of Euler and co-workers[9] concerning the essentiality of the *d*-ribityl side-chain. In spite of their relationship to Atabrine, these compounds showed no antimalarial activity.

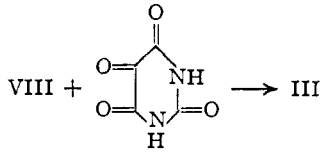
The synthesis of compounds of type III was achieved by the reaction of an *o*-chloro-nitrobenzene or 4-chloro-5-nitro-*o*-xylene (V) with a basically-substituted primary aliphatic amine (VI) to give a basically-substituted *o*-nitroaniline or xylidine (VII).



V VI

VII

VIII



IX

Other intermediates of this type have been made by Kipnis, Weiner and Spoerri[10] by another

(1) Presented before the Division of Organic Chemistry at the 108th meeting of the American Chemical Society, New York, N. Y., September 13, 1944.

(2) Parke, Davis and Co., Postdoctorate Research Fellow 1943-1944. Present address: Parke, Davis and Company, Detroit, Michigan.

(3) For the previous paper in this series, see Adams and Whitmore, THIS JOURNAL, **67**, 1271 (1945).

(4) Silverman and Evans, *J. Biol. Chem.*, **150**, 265 (1943).

(5) We are greatly indebted to Dr. O. S. Bird of Parke, Davis and Co. for the anti-metabolite tests on these compounds.

(6) Kuhn, Weygand and Möller, *Ber.*, **76**, 1044 (1943).

(7) Emerson and Tishler, *Proc. Soc. Exptl. Biol. Med.*, **55**, 184 (1944).

(8) Wooley, *J. Biol. Chem.*, **154**, 31 (1944).

(9) Euler, Karrer *et al.*, *Helv. Chim. Acta*, **18**, 522 (1935).

(10) Kipnis, Weiner and Spoerri, THIS JOURNAL, **66**, 1446 (1944).

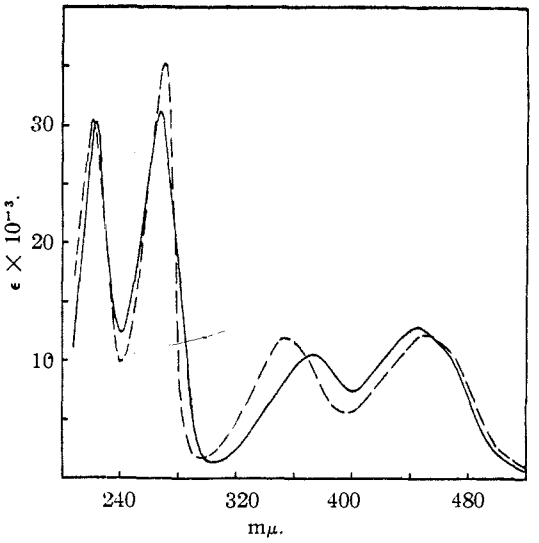


Fig. 1.—Ultraviolet absorption spectra[12] of basically-substituted 7,8-dimethylisoalloxazine III: —, in 0.1 *N* HCl; ---, in 0.1 *N* NaOH.

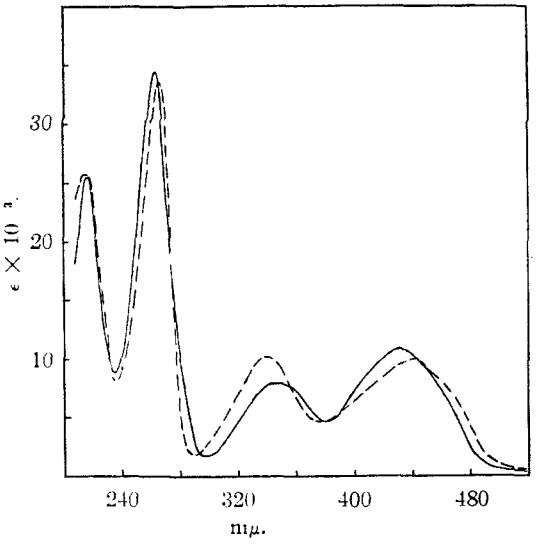


Fig. 2.—Ultraviolet absorption spectra (ref. 12) of the basically-substituted isoalloxazine IV: —, in 0.1 *N* HCl; ---, in 0.1 *N* NaOH.

method. In our work these intermediate nitroanilines were not isolated but were reduced directly to the corresponding substituted *o*-phenylenediamines (VIII), which were purified by vacuum distillation. Since they were very sensitive to air oxidation, they were not analyzed but utilized immediately in the coupling reaction with alloxan (IX) to give the basically-substituted isoalloxazines. This method is essentially the same as that first reported by Karrer, *et al.*[11] The first attempts to analyze these compounds, after drying to constant weight, gave very erratic results due to their rapid rate of hydration. However, the hydrated compounds, which were isolated from alcoholic solutions, were stable and gave consistent analytical results.

The structural identity of the final products was verified by a comparison of the ultraviolet absorption spectra[12] of III and IV (Fig. 1 and 2) with that of riboflavin (Fig. 3).

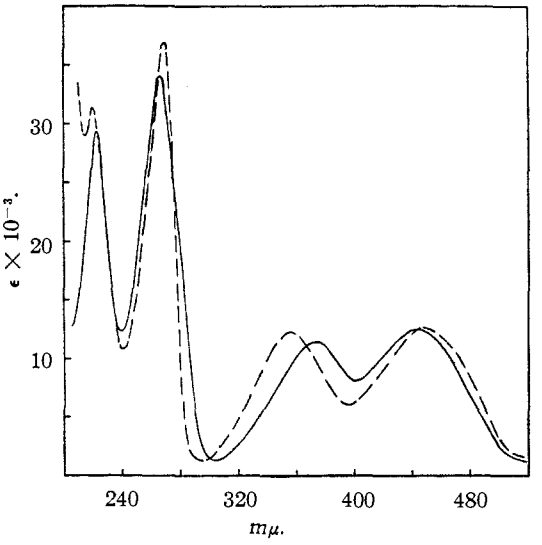


Fig. 3.—Ultraviolet absorption spectra (ref. 12) of riboflavin: —, in 0.1 *N* HCl; ---, in 0.1 *N* NaOH.

It is evident from the position of the maxima and minima, as well as the great similarity in changes with *p*H, that the ultraviolet absorption of these compounds differs only in minor details from that of riboflavin.

Since the completion of this work, Hall and Turner[13] have reported on their unsuccessful attempts to obtain compounds of the above type.

Experimental

o-(γ-Aminopropylamino)-aniline.—*o*-Chloronitrobenzene 8 g. (0.05 mole), was added dropwise to 18.4 g. (0.25 mole) of refluxing trimethylenediamine.[14] After the addition was completed, the solution was refluxed for one hour. The cool reaction mixture was treated with 100 ml. of water, saturated with potassium carbonate and extracted with three 75-ml. portions of chloroform. The chloroform was distilled, the residue taken up in 300 ml. of methanol and reduced catalytically under three atmospheres of hydrogen in the presence of Adams catalyst. When reduction was complete, the catalyst was removed by filtration, the methanol distilled and the fraction boiling at 150–153° (3 mm.) collected; yield 6.4 g. (77%).

10-(γ-Aminopropyl)-isoalloxazine Monohydrochloride Dihydrate.—*o*-(γ-Aminopropylamino)-aniline, 5.0 g. (0.0306 mole), was dissolved in 30 ml. of anhydrous methanol and the resulting solution treated with excess dry hydrogen chloride. A solution of 4.73 g. (0.0295 mole) of alloxan monohydrate, dissolved in 25 ml. of anhydrous methanol, was added to the solution of the amine hydrochloride at the boiling point with rapid agitation. In about

(11) (a) Karrer, Salomon, Schöpp and Schlitter, *Helv. Chim. Acta*, **17**, 1165 (1934); (b) Karrer, Schlitter, Pfaehler and Benz, *ibid.*, **17**, 1516 (1934).

(12) We are greatly indebted to Dr. J. M. Vandenbelt of Parke, Davis and Co. for these absorption data.

(13) Hall and Turner, *J. Chem. Soc.*, 699 (1945).

(14) Furnished through the courtesy of Sharples Chemical Co.

thirty seconds the orange crystalline product started to separate. The solution was cooled, the product removed by filtration and washed with methanol; 4.8 g., m. p. 202°. Concentration of the filtrate yielded an additional 1.8 g. of the product; total yield 65%.

Anal. Calcd. for $C_{13}H_{13}N_5O_2 \cdot HCl \cdot 2H_2O$: C, 45.43; H, 5.28; N, 20.37; Cl, 10.31. Found: C, 45.54; H, 5.46; N, 20.88; Cl, 10.29.

The first time this compound was prepared, the sample was dried to constant weight *in vacuo* at 110° before analysis.

Anal. Calcd. for $C_{13}H_{13}N_5O_2 \cdot HCl \cdot H_2O$: C, 47.93; H, 4.95; N, 21.50. Found: C, 48.90; H, 5.05; N, 21.69.

The sample was first analyzed for carbon and hydrogen and apparently was not completely anhydrous. But by the time the nitrogen analysis was performed, enough water had been absorbed so that the data agreed with that calculated for the monohydrate. This difficulty was experienced throughout the work until attempts to dry the compounds for analysis were abandoned.

o-(γ-Piperidinopropylamino)-nitrobenzene Hydrochloride.—A mixture consisting of 60 g. (0.295 mole) of *o*-nitrobromobenzene, 45 g. of fused sodium acetate and 30 g. (0.21 mole) of γ-piperidinopropylamine[15] was heated at 130° for five hours. The reaction mixture was cooled, acidified and steam distilled. The residue was cooled and the orange crystalline hydrochloride of the product removed by filtration and recrystallized from ethanol; m. p. 193–195°; yield 43 g. (68%).

o-(γ-Piperidinopropylamino)-aniline.—*o*-(γ-Piperidinopropylamino)-nitrobenzene hydrochloride, 42 g. (0.14 mole), in 400 ml. of ethanol was reduced with hydrogen under three atmospheres pressure in the presence of 30 mg. of platinum oxide. The alcohol was distilled, the residue taken up in anhydrous ether and dry hydrogen chloride bubbled into the solution. Since no solid precipitated, the solution was shaken with a saturated solution of potassium carbonate, the ether layer separated and dried over anhydrous potassium carbonate. The drying agent was filtered, the ether evaporated, and the residue distilled; b. p. 176–178° (3 mm.); yield 21.7 g. (67%). The hydrochloride was prepared in anhydrous ether and after recrystallization from ethanol melted at 203–204°.

10-(γ-Piperidinopropyl)-isoalloxazine Monohydrochloride Hydrate.—A solution of 2.9 g. (0.018 mole) of alloxan monohydrate dissolved in 20 ml. of dilute hydrochloric acid was added to 6 g. (0.026 mole) of *o*-(γ-piperidinopropylamino)-aniline in 15 ml. of water and was then acidified with dilute hydrochloric acid. The solution was heated on the steam-bath, cooled and placed in the refrigerator for two days. At the end of this time a sludge had formed which was separated and taken up in hot ethanol. On cooling, gray-green crystals of the product separated which were collected and recrystallized from ethanol; yield 4.4 g. (59.5%); m. p. 274–277° dec. This was one of the earlier samples which was dried to constant weight at 110° before analysis.

Anal. Calcd. for $C_{18}H_{21}N_5O_2 \cdot HCl \cdot H_2O$: C, 54.89; H, 6.14; N, 17.78. Found: C, 54.59; H, 6.77; N, 19.24.

o-(γ-Morpholinopropylamino)-aniline.—A mixture consisting of 20 g. (0.0127 mole) of *o*-chloronitrobenzene and 43 g. (0.3 mole) of γ-morpholinopropylamine was heated at 150° for two hours, cooled, stirred with 200 ml. of saturated potassium carbonate solution and extracted with four 50-ml. portions of chloroform. The chloroform was removed by distillation, the residue taken up in 200 ml. of methanol and reduced catalytically under three atmospheres of hydrogen in the presence of Adams catalyst. After reduction was complete, the catalyst was removed by filtration and the methanol distilled; yield 22.8 g. (76.4%) of the desired *o*-(γ-morpholinopropylamino)-aniline, b. p. 185–195° (2 mm.). The light yellow colored product gradually solidified.

(15) Whitmore, Mosher, Adams, Taylor, Chapin, Weisel and Yanko, THIS JOURNAL, **66**, 725 (1944).

10-(γ-Morpholinopropyl)-isoalloxazine Monohydrochloride Hydrate.—A boiling solution of 7.6 g. (0.032 mole) of *o*-(γ-morpholinopropylamino)-aniline in 40 ml. of methanol, saturated with hydrogen chloride, was treated with a solution of 5.05 g. (0.032 mole) of alloxan monohydrate in 30 ml. of methanol and the resulting mixture heated for thirty minutes on a steam-bath. After twelve hours, the solution was decanted from the black sludge which had separated and evaporated to dryness. The residue was crystallized from methanol; yield 9.1 g. (70%) of greenish-yellow 10-(γ-morpholinopropyl)-isoalloxazine hydrochloride dihydrate; m. p. 223° dec. The product was dried at 110°.

Anal. Calcd. for $C_{17}H_{19}N_5O_3 \cdot HCl \cdot 1^1/_2H_2O$: C, 50.48; H, 5.72; N, 17.30. Found: C, 50.38; H, 5.74; N, 17.59.

o-(δ-Diethylaminobutylamino)-aniline.—A mixture consisting of 20 g. (0.14 mole) of δ-diethylaminobutylamine[15] and 10.9 g. (0.069 mole) of *o*-chloronitrobenzene was heated at 160° for five and one-half hours. The reaction mixture was treated with 150 ml. of water and the resulting red oily mixture saturated with potassium carbonate. The solution was extracted with four 75-ml. portions of ether and the combined ether extracts dried over potassium carbonate, filtered, and the ether distilled. The dark residue was taken up in 150 ml. of methanol and reduced catalytically under three atmospheres pressure of hydrogen in the presence of Adams catalyst. The catalyst was removed, the methanol distilled, and the residue fractionated; yield 16.0 g. (99.3%) of the pure product; b. p. 156–158° (3 mm.). The product was very sensitive to oxidation and rapidly turned a dark red color.

10-(δ-Diethylaminobutyl)-isoalloxazine Monohydrate IV).—*o*-(δ-Diethylaminobutylamino)-aniline, 15.0 g. (0.0638 mole), was dissolved in a mixture of 45 ml. of water and 16.0 ml. of concentrated hydrochloric acid (6.65 g. or 0.183 mole of hydrogen chloride). The resulting orange solution was treated with 9.4 g. (0.059 mole) of alloxan monohydrate dissolved in 25 ml. of water. The solution immediately turned a yellowish black color. The mixture was heated on a steam-bath for one-half hour, cooled and made alkaline with solid potassium carbonate. The colloidal blue precipitate, which was not investigated, was removed by filtration and the aqueous solution extracted with eight 75-ml. portions of chloroform. The chloroform extracts were dried and the chloroform removed by distillation. The black, tarry residue was treated with 50 ml. of anhydrous ether and the brown colored crude product removed by filtration. An attempt to recrystallize the product from benzene–petroleum ether mixture was unsuccessful but by decantation of the solvent and stirring the oily residue with 25 ml. of anhydrous ether a bright yellow crystalline product was obtained. The product was removed by filtration, washed with ether and recrystallized from benzene; 7.1 g. (33.8%); m. p. 180–181°. A sample was treated with Norit and crystallized twice from a methanol–acetone mixture; m. p. 207–208°. The ultraviolet absorption measurements reported in Fig. 2 were made on this sample.

Anal. Calcd. for $C_{18}H_{23}O_2N_5 \cdot H_2O$: C, 60.16; H, 7.01; N, 19.49. Found: C, 60.41; H, 7.08; N, 19.69.

γ-Diethylamino-β-hydroxypropyl Chloride.[16]—Diethylamine, 36.5 g. (0.5 mole), was added to 46.8 g. (0.5 mole) of rapidly stirred epichlorohydrin over a period of one-half hour keeping the temperature between 30 and 35°. After the addition was completed the reaction mixture was stirred at 35° for three hours and distilled; 42.7 g. (51.3%) of the desired product, b. p. 110–113° (25 mm.), was obtained.

The picrate was prepared in ethanol and after recrystallization melted at 192–193°.

γ-Diethylamino-β-hydroxypropylamine[17] (VI).—To one liter of concentrated ammonia solution containing 20 g. (0.5 mole) of sodium hydroxide, 42 g. (0.25 mole) of γ-

(16) Drozdov and Chentzov, *J. Gen. Chem. U.S.S.R.*, **4**, 969–974 (1934).

(17) Jensch, U. S. Patent 1,790,096, Jan. 27, 1931.

diethylamino-β-hydroxypropyl chloride was added with rapid stirring. The reaction mixture was stirred for two hours at room temperature, 500 g. of potassium carbonate added, and the mixture heated on the steam-bath for twelve hours to expel the ammonia. The solution was cooled, saturated with potassium carbonate and extracted with chloroform. The chloroform extracts were combined, distilled and the product boiling at 116–118° (25 mm.) collected; yield 18.4 g. (50%). The picrate was prepared in ethanol and after recrystallization melted at 199.0–199.5°.

o-(γ-Diethylamino-β-hydroxypropylamino)-aniline.—A mixture of 40 g. (0.275 mole) of γ-diethylamino-β-hydroxypropylamine and 21.8 g. (0.138 mole) of o-chloronitrobenzene was heated at 150° for two hours. The cool reaction mixture was treated with 200 ml. of water saturated with potassium carbonate, extracted with three 75-ml. portions of chloroform, the chloroform distilled, and the residue taken up in 250 ml. of methanol. The crude o-(γ-diethylamino-β-hydroxypropylamino)-nitrobenzene was reduced catalytically under three atmospheres pressure of hydrogen in the presence of Adams catalyst. The methanol was evaporated and the residue distilled; yield 12 g. (36.6%); b. p. 160–165° (3 mm.).

10-(γ-Diethylamino-β-hydroxypropyl)-isoalloxazine Monohydrochloride Dihydrate.—Freshly distilled o-(γ-diethylamino-β-hydroxypropylamino)-aniline, 3.4 g. (0.0143 mole), was dissolved in 30 ml. of absolute ethanol and the base converted to the hydrochloride by the addition of 3 ml. of methanol saturated with dry hydrogen chloride. A solution of 2.35 g. (0.0147 mole) of alloxan monohydrate in 15 ml. of absolute ethanol was added and the mixture heated on the steam-bath for five minutes, cooled, and the yellow crystalline product removed by filtration and washed with ethanol; yield 2.0 g.

The filtrate was evaporated to about two-thirds of the original volume, cooled and the dark colored hygroscopic product filtered, and recrystallized from absolute ethanol to give 1.9 g.; total yield 65%; m. p. 256°.

Anal. Calcd. for $C_{17}H_{21}N_5O_3 \cdot HCl \cdot 2H_2O$: N, 16.84. Found: N, 16.99, 16.75.

o-(β-Ethanolaminoethylamino)-aniline.—A mixture consisting of 15 g. (0.095 mole) of o-chloronitrobenzene and 30 g. (0.288 mole) of aminoethylethanolamine[18] was heated at 150° in an oil-bath for two and one-half hours. The reaction mixture was cooled and 100 ml. of water added. The oily orange mixture was treated with 20 g. of potassium carbonate and the mixture extracted with four 50-ml. portions of chloroform. The dark residue from the chloroform extracts was taken up in 200 ml. of methanol and reduced catalytically with hydrogen in the presence of Adams catalyst. The catalyst was removed by filtration, the methanol evaporated and the residue distilled; b. p. 195° (3 mm.); yield 13.8 g. (74.3%). Two recrystallizations from benzene yielded the pure white product, m. p. 108.5–109.0, which rapidly turned pink on exposure to air.

10-(β-Ethanolaminoethyl)-isoalloxazine Monohydrochloride Dihydrate.—o-(β-Ethanolaminoethylamino)-aniline, 3.0 g. (0.0154 mole), was dissolved in 30 ml. of anhydrous methanol and a slight excess of methanolic hydrogen chloride added. A solution of 2.2 g. (0.0138 mole) of alloxan monohydrate in 20 ml. of methanol was added to the amine hydrochloride and the mixture heated on a steam-bath; after two minutes, the characteristic isoalloxazine color appeared and after heating for fifteen minutes, crystals separated from the boiling solution. The solution was cooled and the crystalline product removed by filtration and washed with a small amount of methanol; 2.65 g., m. p. 252–253°. On concentration of the filtrate an additional 0.85 g. of bright yellow crystalline product was obtained; total yield 3.5 g. (68.2%). Although the product separated from an alcoholic solution, it could not be redissolved in boiling absolute ethanol. It was extremely soluble in water and aqueous alcohol, but it could not be crystallized from either of these two solvents.

(18) Furnished by Carbide and Carbon Chemical Corporation.

Anal. Calcd. for $C_{14}H_{15}O_3N_5 \cdot HCl \cdot 2H_2O$: C, 44.98; H, 5.39; N, 18.73. Found: C, 45.10; H, 5.45; N, 18.17.

4-Chloro-5-nitro-o-xylene (V).[19]—4-Amino-5-nitro-o-xylene,[20] 10 g. (0.06 mole), was dissolved in 150 ml. of concentrated hydrochloric acid and the solution cooled to 5° by the addition of a small amount of ice. A solution of 4.57 g. of sodium nitrite in 15 ml. of water was introduced below the surface of the acid solution over a period of ten minutes with rapid stirring. The mixture was stirred for about one-half hour, keeping the temperature below 5° by the addition of ice, diluted with 200 ml. of ice water, and filtered to give a clear red solution of the diazonium salt.

A solution of cuprous chloride (freshly prepared from 16.6 g. of cupric sulfate pentahydrate) in 50 ml. of concentrated hydrochloric acid was cooled to about 0° by the addition of 100 g. of ice. The cold diazonium salt solution was added to the cuprous chloride solution with stirring, keeping the temperature below 5°. This caused the immediate separation of a bright yellow precipitate. The reaction mixture was stirred for an additional one-half hour and then allowed to stand at room temperature for twelve hours. The mixture was steam distilled until about 2.5 liters of distillate was collected, the distillate cooled, the bright yellow crystalline product filtered, washed with water and dried; yield 8.67 g. (77.5%); m. p. 61–62°. An additional 0.78 g. of the product (m. p. 61°) was obtained by extracting the filtrate with ether; total yield 85%.

4-(γ-Diethylamino-β-hydroxypropylamino)-5-amino-o-xylene (VIII).—A mixture consisting of 8.6 g. (0.046 mole) of 4-chloro-5-nitro-o-xylene (V) and 15 g. (0.091 mole) of γ-diethylamino-β-hydroxypropylamine (VI) was heated at 145° for three and one-half hours. A small sample of the mixture was withdrawn and found to give a positive silver nitrate test, but it was not completely soluble in dilute hydrochloric acid. When the temperature of the mixture had reached 195°, a violent reaction occurred. After ten minutes the mixture was cooled and dissolved in 200 ml. of 3 *N* hydrochloric acid; the resultant red solution was made alkaline with 10 *N* sodium hydroxide and saturated with potassium carbonate. The oil layer was diluted with 50 ml. of ether, separated, the aqueous solution extracted with three 50-ml. portions of ether, and the combined ether extracts dried over potassium carbonate. These extracts were filtered and the 4-(γ-diethylamino-β-hydroxypropylamino)-5-nitro-o-xylene (VII) in methanol solution was reduced under three atmospheres pressure of hydrogen in the presence of Adams catalyst. The catalyst was removed, the ether evaporated, and the residue distilled; b. p. 195° (3 mm.); yield 8 g. (65.6%). The light yellow product gradually crystallized to a yellow white solid, m. p. 70–71°.

7,8-Dimethyl-10-(γ-diethylamino-β-hydroxypropyl)-isoalloxazine Monohydrochloride Dihydrate (III).—4-(γ-Diethylamino-β-hydroxypropylamino)-5-amino-o-xylene (VIII), 2.5 g. (0.0094 mole), was dissolved in 50 ml. of dry ether and the resulting solution treated with an excess of dry hydrogen chloride. The ether was evaporated from the white powdery hydrochloride and the residue taken up in 20 ml. of absolute ethanol. A solution of 1.75 g. (0.011 mole) of alloxan monohydrate in 12 ml. of absolute ethanol was added and the resulting mixture heated for ten minutes on a steam-bath. Since the product did not separate on cooling, it was precipitated with dry ether and the ether solution decanted from the bright yellow solid. The precipitated product (III) was recrystallized from a small amount of absolute ethanol, in which it was very soluble; yield, 2.0 g. (48%) of bright orange crystals; m. p. 247–248°. Recrystallization from a mixture of methanol–acetone raised the melting point to 249–250°.

Anal. Calcd. for $C_{19}H_{25}N_5O_3 \cdot HCl \cdot 2H_2O$; C, 51.41; H, 6.81. Found: C, 51.69; H, 6.81.

(19) Hinkel, Ayling and Walters, *J. Chem. Soc.*, 287 (1934).

(20) Noelting, Braun and Thesmar, *Ber.*, **34**, 2248 (1901).

Summary

The preparation of seven new basically-substituted isoalloxazine compounds and the intermediates used in their preparation has been described.

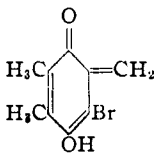
STATE COLLEGE, PENNSYLVANIA
RECEIVED JANUARY 26, 1946

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

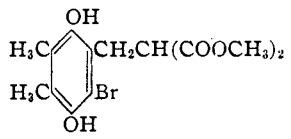
The Reaction between Quinones and Metallic Enolates. XX.[1] Second Paper on Bromotrimethylquinone and Sodio Malonic Esters

BY LEE IRVIN SMITH AND PAUL F. WILEY[2]

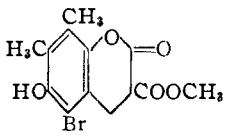
The reaction between methylated quinones and metallic enolates, leading to coumarins, has been pictured as involving four steps: (a) a "pentadenolization" of the quinone to give a methylene quinone, such as I; (b) a Michael reaction, involving addition of the metallic enolate (or of its ions) to the new conjugated system in I, producing the hydroquinone II; (c) cyclization of II to a hydrocoumarin III; and (d) dehydrogenation of the hydrocoumarin to the coumarin V. The end result of this series of reactions will depend upon a number of factors such as the relative velocities of competitive (or consecutive) reactions, solubilities of the intermediates, oxidizing power of the quinone (or its tautomer), presence or absence of air or other oxidizing agent, etc. Theoretically it is possible, therefore, for the reaction between a methylated quinone and a metallic enolate to produce either a coumarin or a hydrocoumarin. Although the products have been coumarins in all cases heretofore observed, it has now been found that the reaction between bromotrimethylquinone and methyl malonate in the presence of magnesium methoxide produced not the coumarin V, but the hydrocoumarin III.



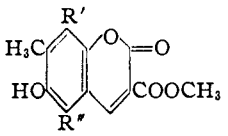
I



II

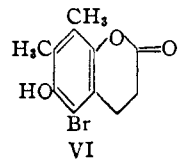


III

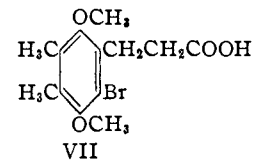


IV, R′ = Br, R″ = CH_3
V, R′ = CH_3, R″ = Br

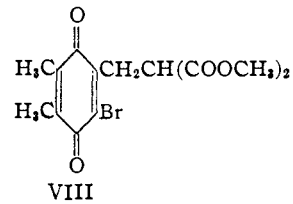
The product of this reaction (obtained in a yield of 69%) formed a diacetate and gave a dimethyl ether by reaction with diazomethane, which eliminated structure V for it. The presence of an ester grouping in III was shown by hydrolysis of the substance to carbon dioxide and a non-acidic substance VI, although the properties of VI were somewhat peculiar for a compound of this structure. It was not possible to convert III into VII by action of potassium hydroxide and methyl sulfate according to the method of Smith and Denyes.[3] Since the condensation between



VI



VII



VIII

alkylated quinones and metallic enolates, leading to coumarins, involves dehydrogenation at some step, it appeared possible that III could be dehydrogenated to V. This reaction was achieved. When III was refluxed with trimethylbromoquinone in methanol or dioxane, V was formed in a yield of 20%; in the first case, trimethylbromohydroquinone was isolated from the reaction mixture. The product V, as well as its acetate, was identified by comparison with authentic samples.

In previous papers[4] reports have been made of successful dehydrogenations of dihydrocoumarins by action of ferric chloride. When the hydrocoumarin III was subjected to the action of ferric chloride in methanol, the quinone VIII was formed in a yield of 90%. This quinone was reduced readily to the hydroquinone II, which on oxidation regenerated VIII. The hydroquinone II, when hydrolyzed by action of hydrochloric acid, gave the same substance VI as was obtained by similar hydrolysis of the hydrocoumarin III. This indirect conversion of III to VI *via* VIII and II afforded added evidence that the substance was not a coumarin, V, and it also eliminated II as a possible structure for this product (the com-

(1) Paper XIX, THIS JOURNAL, **66**, 1320 (1944).

(2) Abstracted from a thesis by Paul F. Wiley, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree, July, 1944.

(3) Smith and Denyes, THIS JOURNAL, **58**, 304 (1936).

(4) (a) Smith and Horner, THIS JOURNAL, **60**, 676 (1938); (b) Smith and Johnson, *ibid.*, **59**, 673 (1937).