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SYNTHESES IN THE CINCHONA SERIES. III. AZO DYES DERIVED FROM HYDROCUPREINE AND HYDROCUPREIDINE.

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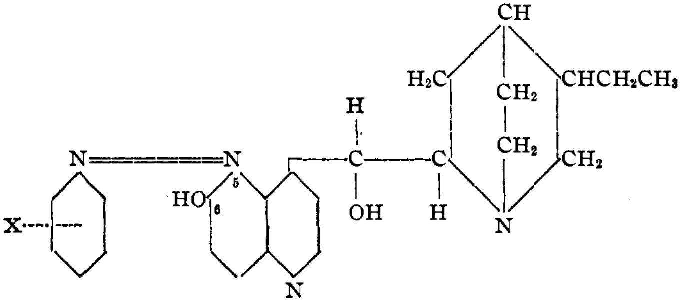
The subject matter of this and the previous paper (p. 2090) was presented at the June meeting of the New York Section of the American Chemical Society. Three months later, while the present material was being prepared for publication we received the paper of Giemsa and Halberkann[1] on "Azo-5 and Amino-5 Compounds of Cupreine, Hydrocupreine and their Methyl and Ethyl Ethers," in which the idea of azo-cinchona compounds is elaborated, although only one of the substances described in the present paper (*p*-sulfo-phenylazo-hydrocupreine) was studied. The work which we now report has been in progress for over two years and represents but a portion of the studies which we are making in the field of the cinchona alkaloids.[2] Among our objects in studying the azo derivatives of the hydroxy alkaloids was the reduction of suitable members to the amino alkaloids, which we now see has also been accomplished by the German workers. As far as 5-aminohydrocupreine is concerned, we, too, prepared this interesting compound almost two years ago, and since our work with it and analogous substances is still in progress, we shall reserve our discussion of the amino alkaloids for a future paper.

We have found that hydrocupreine and hydrocupreidine behave in a normal manner as phenolic compounds and yield well-defined azo dyes with diazotized aromatic amines.

We have assumed from the first that position 5 (*ana*) in the quinoline nucleus is the place of entrance of the azo group



since this is the only available position which would satisfy the usual rules of substitution for a 6-hydroxy-quinoline derivative, a conclusion also arrived at by Giemsa and Halberkann.

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[1] *Ber.*, 52, 906 (1919).

[2] For Paper I of this series, see THIS JOURNAL, 41, 818 (1919).

Of the dyes prepared by us from a large variety of aromatic amines the majority crystallized without difficulty or formed crystalline salts, and while others could not be made to crystallize we are convinced that methods for their crystallization could have been found in a more detailed and time-consuming study than we were able to give. In general, the phenyl and tolyl dyes, as well as those with *m*-substituents on the benzene ring gave orange to orange-red solutions in dil. acids and dyed silk various shades of orange; *o*- and *p*-alkoxy groups deepened these colors toward the red, while the dyes from the naphthylamines dyed silk a deep rose color. As a class these substances had the property of dyeing unmordanted cotton, a property also shared by 5-phenylazo-6-hydroxyquinoline,[1] which was prepared for comparison.

While the crystalline dyes which did not contain negative salt-forming groups on the aromatic amine were generally only slightly soluble in cold *N* aqueous alkali and only incompletely on boiling, solutions of the dyes in a little alcohol gave clear, deep red to purplish red solutions on dilution with *N* sodium hydroxide. All of the dyes, of course, were soluble in dil. acids.

Many of the substances described in this paper were highly bactericidal *in vitro*, a property which will be discussed in the appropriate place by our colleague, Dr. Martha Wolstein.

Experimental.

Since the azo compounds to be described in the following pages were all prepared by essentially the same technique this will be given at the start, and in cases in which modifications proved necessary these will be described under the individual compounds.

The aromatic amine was diazotized as usual in dil. hydrochloric acid solution containing 4 equivalents of the acid. The solution was then slowly added to a turbined solution of hydrocupreine in dil. sodium hydroxide, the quantity of the latter being 6 equivalents, or 2 in excess of the amount of hydrochloric acid originally employed, this having been chosen in order to hold the alkaloid in solution during the coupling. The volume of the alkaline solution was from 100 to 150 cc. for 3.1 g. (0.01 mol.) of the base and the temperature during the coupling was kept at 10–15°. As a rule the coupling proceeded rapidly, the dye in most cases separating during the reaction as a flocculent precipitate. In most instances precipitation was completed by the final addition of ammonium chloride solution. After filtering off and washing, the dye was purified by grinding under very dilute hydrochloric acid, filtering from insoluble material, and reprecipitating from the diluted filtrate with ammonia.

(A) Dyes Derived from Hydrocupreine.

Phenylazo-hydrocupreine.—On adding insufficient ammonia for neutralization to the dil. hydrochloric acid solution of the crude product

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[1] Mathëus, *Ber.*, **21**, 1642 (1888).

a tarry precipitate which separated was filtered off before making alkaline with ammonia. The dye was obtained in slightly greater yield than the amount of hydrocupreine used and forms an orange-red, amorphous powder which is readily soluble in the usual organic solvents. It gradually softens above 85°, melting completely at about 130°. It is soluble in dil. acids with an orange color and although insoluble in too dilute sodium hydroxide it dissolves in 2% alkali with a cherry-red color. It gives a deep orange-brown solution in conc. sulfuric acid.

Subs., 0.1364: 15.3 cc. N (19.0°, 754 mm.).
Calc. for $C_{25}H_{28}O_2N_4$: N, 13.46. Found: 13.02.

Phenylazo-hydrocupreine Dihydrochloride.—The purified base was dissolved in a small volume of 10% hydrochloric acid, chilled, and seeded with crystals obtained by dissolving a test portion in 1 : 1 hydrochloric acid and adding saturated salt solution. After standing in the ice box, the salt was recrystallized from a small volume of 10% hydrochloric acid and let stand at 0°, separating as dark red, felted needles containing 4 molecules of water of crystallization. When rapidly heated to 180°, then slowly, the anhydrous salt decomposes at 181–3° with preliminary darkening and sintering, and dissolves readily in the cold in water, alcohol, methyl alcohol, or chloroform. It is almost insoluble in dry ether or hot benzene and only sparingly soluble in hot dry acetone. An aqueous solution is readily decolorized by stannous chloride with the formation of aniline hydrochloride and the hydrochloride of aminohydrocupreine.

For analysis the salt was dried *in vacuo* first at room temperature over sulfuric acid and crushed alkali and finally at 80° over sulfuric acid.

Subs., air-dry, 0.5910: loss, 0.0768.
Calc. for $C_{25}H_{28}O_2N_4.2HCl.4H_2O$: H_2O, 12.84. Found: 12.99.
Subs., anhydrous, 0.1325: 13.0 cc. N (23.0°, 760 mm.). Subs., 0.1038: AgCl, 0.0578.
Calc. for $C_{25}H_{28}O_2N_4.2HCl$: N, 11.45; Cl, 14.49. Found: N, 11.32; Cl, 13.78.

***o*-Tolylazo-hydrocupreine.**—The purified amorphous dye was dissolved in a small volume of hot absolute alcohol, chilled, and seeded with crystals formed by the spontaneous evaporation of an alcoholic solution of a test portion. The dye slowly crystallized as deep red, spherular masses of microscopic crystals which darken and sinter above 100°, melting to a tar from 110 to 130°. It is readily soluble in boiling methyl or ethyl alcohol, sparingly at 0°, and dissolves very easily in chloroform or benzene, less readily in dry acetone. It dissolves in conc. sulfuric acid with an orange-red color and partially in hot 5% sodium hydroxide, yielding a cherry-red solution. In dilute acids the color is orange-red.

Subs., 0.1413: 16.2 cc. N (24.0°, 758.5 mm.).
Calc. for $C_{26}H_{30}O_2N_4$: N, 13.02. Found: 13.16.

***m*-Tolylazo-hydrocupreine.**—The purified base was obtained in good yield as an orange-red, amorphous powder which is readily soluble in the usual neutral organic solvents, and is quite soluble in cold *N* sodium hydroxide and practically completely, on boiling, forming a dull red solution. It gradually melts above 103° with preliminary sintering, becoming completely fluid at 125–30°.

Subs., 0.1119: 12.6 cc. N (27.0°, 765 mm.).
Calc. for $C_{26}H_{30}O_2N_4$: N, 13.02. Found: 12.89.

The Dihydrochloride.—The base was rubbed under sufficient conc. hydrochloric acid to give a reaction strongly acid to congo red paper and the solution diluted with dry acetone. On adding dry ether until a slight permanent turbidity formed the salt gradually separated on standing and rubbing as aggregates of red, microscopic crystals. After air-drying, the salt contained approximately 1.5 molecules of water of crystallization. When anhydrous it darkens and softens above 160° and decomposes at about 195°. It is very easily soluble in dry methyl alcohol, less easily in absolute alcohol. It dissolves with difficulty in dry acetone or chloroform but is quite soluble in the latter on boiling. It is readily soluble in water with a reddish orange color.

Subs., 0.6548: loss, 0.0373 *in vacuo* at room temp. over H_2SO_4 + NaOH.
Calc. for $C_{26}H_{30}O_2N_4.2HCl.1.5H_2O$: H_2O, 5.70. Found: 5.09.
Subs., anhydrous, 0.1034: 10.1 cc. N (26.0°, 757 mm.). Subs., 0.1442: AgCl, 0.0832.
Calc. for $C_{26}H_{30}O_2N_4.2HCl$: N, 11.14; Cl, 14.09. Found: N, 11.11; Cl, 14.27.

***p*-Tolylazo-hydrocupreine.**—The crude dye was made to crystallize by warming with 85% alcohol, the separation being completed after cooling by the cautious addition of about $^1/_3$ volume of water. Recrystallized from amyl alcohol, in which it dissolves readily at the boiling point and sparingly in the cold, it forms glistening, orange-red leaflets. When rapidly heated to 200°, then slowly, the dye melts at 202–5° with gas evolution and preliminary softening. It is rather sparingly soluble in the cold in absolute methyl or ethyl alcohol or acetone, but quite readily on warming, and also dissolves easily in chloroform or toluene. The solution in conc. sulfuric acid is bright red, and orange-red in dil. acids.

Subs., 0.1511: 17.2 cc. (N 26.5°, 752 mm.).
Calc. for $C_{26}H_{30}O_2N_4$: N, 13.02. Found: 12.84.

α-Naphthylazo-hydrocupreine.—On dissolving the purified dye in dry acetone it separated almost immediately as glistening, copper-colored, diamond-shaped platelets. It separates from alcohol as deep maroon plates with a bronzy luster, which crush to a dark, purplish red powder and melt slowly to a tar at 146–9° with preliminary sintering. It is soluble in hot alcohol or acetone, more so in the cold in methyl alcohol or benzene, very readily in chloroform, and only sparingly in dry ether and in hot dil. sodium hydroxide. It yields a bright red solution in dil. hydrochloric acid and a deep blue color in conc. sulfuric acid.

Subs., 0.1232: 13.0 cc. N (20.5°, 756 mm.).
Calc. for $C_{29}H_{30}O_2N_4$: N, 12.02. Found: 12.21.

β-Naphthylazo-hydrocupreine.—In the purification of the crude dye it was found necessary to use warm dil. hydrochloric acid, as the hydrochloride tended to separate from cold solutions in gelatinous form. Recrystallized from amyl alcohol, in which it is soluble only near the boiling point, the base separates as glistening, woolly, scarlet needles which decompose at 240–4°. The solution in dil. hydrochloric acid is bright orange-red, while that in sulfuric acid is deep violet. It is soluble in chloroform but only very difficultly soluble in alcohol, dry acetone or benzene, and is insoluble in hot dil. sodium hydroxide solution.

Subs., 0.1037: 11.0 cc. N (21.5°, 754 mm.).
Calc. for $C_{29}H_{30}O_2N_4$: N, 12.02. Found: 12.20.

Diphenyl-*p*-bisazo-hydrocupreine.—1.4 g. of benzidine were dissolved in hot water containing 13 g. of conc. hydrochloric acid, chilled, and diazotized with 1.05 g. of sodium nitrite. The solution was coupled with 4.5 g. of hydrocupreine dissolved in 180 cc. of *N* sodium hydroxide diluted to 300 cc. The resulting dye was purified in the usual manner, yielding 4.5 g. of an amorphous product. When dissolved in pyridine, filtered, and cautiously treated with water the dye precipitated as a dubiously crystalline, purplish brown powder. It melts to a tar, with preliminary sintering, above 204° and decomposes at about 220°. The dye is easily soluble in chloroform, sparingly in absolute alcohol or benzene, and very difficultly in dry ether. It dissolves in dil. acids with a deep, purplish red color and only partially in boiling *N* sodium hydroxide solution with a dull red color. The solution in conc. sulfuric acid is an intense violet-blue.

Subs., 0.1178: 13.3 cc. N (28.0°, 758 mm.).
Calc. for $C_{50}H_{54}O_4N_8$: N, 13.49. Found: 12.77.

***m*-Nitrophenylazo-hydrocupreine.**—Modification of the usual procedure was necessary in this case, as otherwise the yield was very poor. 2.1 g. of *m*-nitraniline were dissolved by heating with 12.7 g. of conc. hydrochloric acid and about an equal volume of water, rapidly chilled to form a paste of small crystals of the hydrochloride, and diazotized below 10° with a conc. sodium nitrite solution. A solution of 4.5 g. of hydrocupreine was prepared with 200 cc. of *N* sodium hydroxide, diluting to 300 cc. and cautiously adding 14.3 g. of sodium bicarbonate (enough to combine with all but 2 equivalents of the free alkali), stirring until clear, and chilling to 10–15°. After slowly adding the diazo solution and stirring for 15 minutes, the orange dye was filtered off and purified in the usual way, a relatively large amount of acid-insoluble by-products remaining on the filter. The purified product was dissolved in boiling alcohol and separated on cooling and rubbing. Recrystallized from alcohol it forms aggregates of red platelets with an orange luster, which melt at 150.5–

1.5° to a turbid liquid and yield an orange-red powder when crushed. It dissolves in conc. sulfuric acid or in dil. acids with a red-orange color and gives a deep red solution in boiling *N* sodium hydroxide. It is quite readily soluble in boiling absolute methyl or ethyl alcohol, somewhat sparingly in the cold, but dissolves more easily in cold acetone, benzene, or chloroform.

Subs., 0.1164: 15.3 cc. N (26.0°, 762 mm.).
Calc. for $C_{25}H_{27}O_4N_5$: N, 15.19. Found: 15.05.

***p*-Nitrophenylazo-hydrocupreine.**—A diazotized *p*-nitraniline solution was slowly added to a solution of hydrocupreine prepared in exactly the same way as in the preceding case. The brown-orange precipitate of the dye was washed with water, sucked as dry as possible, and added to boiling alcohol, a portion beginning to crystallize even from the boiling solution. Recrystallized from butyl alcohol it forms brown-red, glistening plates and flat prisms which appear orange under the microscope and crush to an orange-red powder. The substance gradually darkens and softens above 200° and melts and decomposes at about 220°. It dissolves in conc. sulfuric acid or in dil. acids with a red-orange color and gives a deep purple solution in boiling *N* sodium hydroxide. It is rather sparingly soluble even in boiling absolute alcohol or dry acetone, somewhat more easily in boiling methyl alcohol, and is quite soluble in boiling benzene, difficultly in the cold. Cold chloroform dissolves it very readily.

Subs., 0.1218: 16.3 cc. N (25.5°, 761 mm.).
Calc. for $C_{25}H_{27}O_4N_5$: N, 15.19. Found: 15.32.

***m*-Acetaminophenylazo-hydrocupreine.**—In the case of *m*-amino acetanilide hydrochloride[1] after coupling was complete the dye was thrown out from the deep purple solution by the addition of ammonium chloride. As it showed a tendency to run through the filter when washed with water, a little ammonia was added to the wash water, inhibiting this tendency. The purified substance forms a deep maroon, amorphous powder with a greenish reflex which slowly melts from 155 to 180° after preliminary darkening and sintering. It gives a brown solution in conc. sulfuric acid appearing red-brown by transmitted light, and a deep red color in dil. hydrochloric acid. It melts under dry methyl or ethyl alcohol and dissolves partially, forming deep red solutions. It is rather sparingly soluble in dry acetone but dissolves readily in chloroform. The color in dil. sodium hydroxide solution is a deep purplish red.

Subs., 0.1048: 13.8 cc. N (25.0°, 758 mm.).
Calc. for $C_{27}H_{31}O_3N_5$: N, 14.80. Found: 15.04.

***m*-Uraminophenylazo-hydrocupreine.**—*m*-Aminophenylurea hydrochloride[2] coupled almost at once, forming a deep purple solution from

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[1] This Journal, 39, 1448 (1917).

[2] *Ibid.*, 39, 1449 (1917).

which the dye was precipitated with ammonium chloride as orange flocks which tended to form a colloidal solution on washing with water. Addition of a few drops of ammonia to the wash water diminished this tendency. The purified dye forms an amorphous powder which darkens and sinters above 140° and gradually melts, swells, and decomposes at 165–85°. It dissolves in dil. hydrochloric acid with an orange-red color and in dil. alkali giving a cherry-red solution. The solution in conc. sulfuric acid is a deep brown-orange. The dye melts under dry methyl or ethyl alcohol and then dissolves, more easily in the former. It is less soluble in dry acetone or chloroform and only very slightly in boiling water.

Subs., 0.1077: 17.2 cc. N (25.0°, 753 mm.).
Calc. for $C_{26}H_{30}O_3N_6$: N, 17.72. Found: 18.13.

***p*-Aminophenylazo-hydrocupreine.**—The acetamino compound (see below) was boiled for one hour with 5 parts of 1 : 1 hydrochloric acid and the solution diluted, filtered, and made alkaline with ammonia. Reprecipitated with ammonia from its solution in very dil. hydrochloric acid, it separates as purplish brown, amorphous flocks which melt at 155–65° with preliminary softening. It is slightly soluble in cold water with a purplish color, more easily in boiling water with a brownish red color, and yields an orange-brown solution in conc. sulfuric acid. An aqueous suspension dissolves with a deep red color on adding a drop of acetic acid, changing to orange-brown with excess of hydrochloric acid. It dissolves readily in methyl or ethyl alcohol, acetone, or chloroform, less easily in cold benzene.

Subs., 0.1152: 15.6 cc. N (22.5°, 765 mm.).
Calc. for $C_{25}H_{29}O_2N_5$: N, 16.24. Found: 15.75.

***p*-Acetaminophenylazo-hydrocupreine.**—Precipitation of the dark red dye was completed by the addition of ammonium chloride. On diluting a methyl alcoholic solution of the purified, amorphous substance with water until the initial turbidity just redissolved, and seeding with crystals deposited on spontaneous evaporation of a test portion in methyl alcohol, the substance crystallized slowly as deep maroon, glistening, microscopic rhombs containing 1.5 molecules of water of crystallization, the separation being completed by the cautious addition from day to day of small amounts of hot water. The anhydrous substance melts to a tar at 158–62° with preliminary softening. It dissolves readily in methyl or ethyl alcohol, or acetone, less easily in benzene. In dil. sodium hydroxide it forms a purple-red solution and dissolves in conc. sulfuric acid with an orange-red color.

Subs., air-dry, 0.3677: Loss, 0.0201 *in vacuo* at 80° over H_2SO_4.
Calc. for $C_{27}H_{31}O_3N_5.1.5H_2O$: H_2O, 5.40. Found: 5.47.
Subs., anhydrous, 0.1308: 17.4 cc. N (25.5°, 747 mm.).
Calc. for $C_{27}H_{31}O_3N_5$: N, 14.80. Found: 14.95.

***p*-Uraminophenylazo-hydrocupreine.**—The purified dye from *p*-aminophenylurea[1] was dissolved in a rather large volume of 85% alcohol and cautiously diluted with water until the turbidity just redissolved. On standing and rubbing crystallization slowly started and was aided from time to time by the careful addition of water. The substance formed deep maroon, rhombic crystals accompanied by small amounts of amorphous material, but the amount obtained was too small for further purification. The anhydrous substance blackens and sinters above 170° and swells and chars at about 190°. It melts under absolute methyl or ethyl alcohol and dissolves partially, but is not very soluble even on boiling. It is sparingly soluble in hot, dry acetone or chloroform, and dissolves in conc. sulfuric acid with a deep red color. The solution in dil. alkali is purplish red and red in dil. acid.

Subs., 0.1276: 20.2 cc. N (26.0°, 756 mm.).
Calc. for $C_{25}H_{30}O_3N_6$: N, 17.72. Found: 17.99.

***p* - Hydroxyphenylazo - hydrocupreine.**—*p* - Benzoyloxy-phenylazo-hydrocupreine dihydrochloride (see below) was dissolved in hot 95% alcohol and the solution chilled and treated with 25% sodium hydroxide solution, causing precipitation of a portion of the dye as a gum. This was redissolved in hot 95% alcohol, added to the main portion, and the whole made strongly alkaline with 25% sodium hydroxide. After about 10 minutes the dark, cherry-red solution was poured into water and treated with an excess of saturated ammonium chloride solution, precipitating the hydroxy dye, which was filtered off and dried. When starting with the quantities given below, the yield was 4.0 g. The crude dye was powdered and boiled with dry acetone, crystallizing before all was dissolved. After chilling and washing with a little cold, dry acetone the substance was recrystallized by dissolving in hot commercial butyl alcohol, cooling, adding an equal volume of dry ether, and then ligroin to incipient turbidity, filtering, seeding, and letting stand in the ice box. The dye separated as spherules of deep maroon, microscopic needles which may be pulverized to a dark brown-red powder and retain $^1/_2$ molecule of butyl alcohol of crystallization on drying *in vacuo* over calcium chloride and paraffin, the solvent being given off very slowly even at 100° *in vacuo* over sulfuric acid. The solvent-free substance gradually melts, blackens and swells at 150–60° and is readily soluble in dry methyl or ethyl alcohol with a brown-red color. It is less soluble in cold dry acetone, dissolving on boiling with a bright red color. It gives an intense red color in conc. sulfuric acid, appearing purplish in thin layers, and dissolves in dil. hydrochloric acid with a bright red, in dil. sodium hydroxide with a cherry-red color. A solution in warm 10% hydrochloric acid deposits the dihydrochloride on cooling as delicate, red needles.

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[1] THIS JOURNAL, 39, 1456 (1917).

Subs., dried at room temp., 0.3740: loss, 0.0304 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{25}H_{28}O_3N_4.0.5C_4H_9OH$: 7.89. Found: 8.13.
Subs., solvent-free, 0.1265: 14.2 cc. N (24.0°, 761 mm.).
Calc. for $C_{25}H_{28}O_3N_4$: N, 12.96. Found: 12.92.

p **- Benzoyloxy - phenylazo - hydrocupreine dihydrochloride.**—3.6 g. of *p*-aminophenyl benzoate were diazotized by suspending in a little water, adding 5.5 g. of conc. hydrochloric acid, and very slowly dropping in 3.3 cc. of 5 *N* sodium nitrite solution. The filtrate was slowly added to a solution of 4.7 g. of hydrocupreine in 120 cc. of *N* aqueous sodium hydroxide, to which 50 cc. of water and 7.7 g. of sodium bicarbonate (leaving 2 mols. of uncombined alkali) had been added with vigorous stirring. The dye, which separated rapidly, was filtered off, dissolved in dil. hydrochloric acid, the solution filtered, and treated with saturated salt solution until the initial turbidity just redissolved. On seeding with crystals obtained by precipitating a portion of the solution with sodium chloride and letting stand, the dihydrochloride separated rapidly and was washed with 10% hydrochloric acid, dissolved in 50% alcohol, and treated with an equal volume of the 10% acid. On seeding and chilling the dihydrochloride separated as minute, orange needles containing 2.5 molecules of water of crystallization and dissolving quite freely in water with a red-orange color, leaving a trace of insoluble material. The anhydrous salt melts, blackens, and decomposes at about 185–95°, and dissolves readily in cold dry methyl alcohol, less easily in absolute alcohol. It is sparingly soluble in boiling dry acetone, more easily in dry chloroform. It dissolves in conc. sulfuric acid with an intense red color, appearing purplish in thin layers, the same colors being observed in the clear solution obtained by diluting an alcoholic solution with *N* aqueous sodium hydroxide.

Subs., air-dry, 0.6640: loss, 0.0483 *in vacuo* at room temp. over H_2SO_4 + NaOH.
Calc. for $C_{32}H_{32}O_4N_4.2HCl.2.5H_2O$: H_2O, 6.89. Found: 7.27.
Subs., anhydrous, 0.1239: 10.0 cc. N (28.0°, 759 mm.). Subs., 0.2259: AgCl, 0.0998.
Calc. for $C_{32}H_{32}O_4N_4.2HCl$: N, 9.20; Cl, 11.63. Found: N, 9.14; Cl, 10.93.

2-Methoxyphenylazo-hydrocupreine.—During the coupling the scarlet dye separated almost immediately. The purified substance forms a dark red, amorphous powder which darkens and softens above 105°, melts to a tar above 120° and is completely fluid at about 160°. It is easily soluble in alcohol, acetone or benzene, less readily in ether. It dissolves in conc. sulfuric acid with an intense purplish red color and in dil. acids with a redder shade than the phenyl or tolyl compounds. It is soluble in hot 5% sodium hydroxide solution with a cherry-red color.

Subs., 0.1076: 12.4 cc. N (30.0°, 752 mm.).
Calc. for $C_{26}H_{30}O_3N_4$: N, 12.55. Found: 12.85.

3-Methoxyphenylazo-hydrocupreine.—The crude dye from 2 g. of *m*-anisidine[1] was dried and ground in a mortar with about 25 cc. of commercial butyl alcohol. The substance dissolved and then quickly crystallized out in a yield of 3.9 g. Recrystallized from butyl alcohol it separates as dark red rhombs with a golden luster, crushing to an orange-red powder and melting at 188–90°, with slight gas evolution and preliminary softening. It dissolves only partially in boiling *N* sodium hydroxide solution, but if dissolved in a little alcohol and then diluted with *N* sodium hydroxide a clear, deep cherry-red solution is obtained. The dye dissolves in dil. acids with an orange-red color and in conc. sulfuric acid with a deep brown-red color. It dissolves readily in cold chloroform and rather sparingly in cold benzene but readily on boiling. It is difficultly soluble in cold dry methyl or ethyl alcohol, or dry acetone, somewhat more easily on boiling.

Subs., 0.1202: 13.2 cc. N (24.0°, 763 mm.).
Calc. for $C_{26}H_{30}O_3N_4$: N, 12.55. Found: 12.68.

4-Methoxyphenylazo-hydrocupreine.—The crude, washed dye was warmed with 85% alcohol, rapidly changing to the crystalline form. Recrystallized from amyl alcohol it forms deep red, glistening plates which decompose with gas evolution above 207°, sintering to a tar, and finally melting at 213–5° with further gas evolution. It dissolves more freely in chloroform than in the other usual solvents, and is readily soluble in hot benzene or amyl alcohol, sparingly in the cold. It yields a bright red solution in dilute acids and dissolves in conc. sulfuric acid with a deep purple color, changing to deep red, with a purple fluorescence.

Subs., 0.1409: 15.0 cc. N (21.0°, 754 mm.).
Calc. for $C_{26}H_{30}O_3N_4$: N, 12.55. Found: 12.27.

2-Ethoxyphenylazo-hydrocupreine.—The yield of the purified dye was equal to the hydrocupreine used. It forms a scarlet, amorphous powder, less easily soluble in ligroin than in the other usual neutral organic solvents. It softens at about 100°, melts gradually above 110°, and is completely fluid at 135–40°. It dissolves in dil. hydrochloric acid with a bright red color and is slightly soluble in cold *N* sodium hydroxide solution, more easily on boiling. The solution of the dye in conc. sulfuric acid is deep reddish purple by reflected light and purplish red by transmitted light.

Subs., 0.1146: 12.5 cc. N (31.0°, 758 mm.).
Calc. for $C_{27}H_{32}O_3N_4$: N, 12.17. Found: 12.22.

3-Ethoxyphenylazo-hydrocupreine.—The yield of the purified dye was slightly less than the amount of alkaloid used. It forms an orange-red powder which is less easily soluble in ligroin or ether than in the other usual neutral organic solvents. It is partly soluble in the cold in *N* sodium hydroxide solution and dissolves in dil. hydrochloric acid with a

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[1] THIS JOURNAL, 41, 1452 (1919).

deep orange-red color. It gives a deep, brown-red color in conc. sulfuric acid. The substance sinters and darkens above 75°, melts slowly above 90°, and is completely fluid at about 125°.

Subs., 0.1113: 11.7 cc. N (27.0°, 758 mm.).
Calc. for $C_{27}H_{32}O_3N_4$: N, 12.17. Found: 11.93.

4-Ethoxyphenylazo-hydrocupreine.—A ligroin solution of the purified, amorphous dye deposited the compound on standing as microscopic rhombs. However, the dye may be obtained as large, almost black rhombs by dissolving in hot 85% alcohol, cooling to 0°, diluting very cautiously with water until the initial turbidity just redissolves, seeding, and letting stand in the ice box. The crystals weathered in the air, probably owing to loss of water of crystallization. The pulverized crystals form a bright red powder, and, when anhydrous, darken and soften above 100° and melt at 156–61° when the bath is slowly heated. The substance melts when plunged into the bath at 130°. It dissolves in dil. hydrochloric acid with a bright red color, and is soluble with a purplish red color in hot, dil. sodium hydroxide solution. It dissolves quite easily in the usual neutral organic solvents with the exception of ligroin. The deep red solution in conc. sulfuric acid appears purple in thin layers and fluoresces purple.

Subs., 0.1369: 14.3 cc. N (21.5°, 755 mm.).
Calc. for $C_{27}H_{32}O_3N_4$: N, 12.17. Found: 12.03.

3,4-Methylenedioxy-phenylazo-hydrocupreine.—The dried, purified dye was dissolved in hot, dry acetone and the cooled solution filtered from a little insoluble matter and seeded with crystals obtained by allowing a test portion to stand in 70% alcohol. The substance separated on standing, the process being made more complete by the addition of small portions of water from time to time. As obtained in this way it forms deep maroon, apparently microcrystalline crusts which melt at 177–84° with slow gas evolution and slight preliminary darkening and softening. It dissolves in conc. sulfuric acid with an intense blue color and in dil. acids with a deep red shade. A suspension in boiling *N* sodium hydroxide solution dissolves only incompletely, but on diluting an alcoholic solution with *N* sodium hydroxide a clear, deep red solution is obtained. It dissolves easily in cold chloroform, less readily in the cold in dry methyl or ethyl alcohol, dry acetone, or benzene, but more freely on boiling.

Subs., 0.1255: 13.1 cc. N (24.5°, 763 mm.).
Calc. for $C_{26}H_{28}O_4N_4$: N, 12.17. Found: 12.02.

3,4-Dimethoxy-phenylazo-hydrocupreine.—Analysis showed that the usual purification process was insufficient. The dye was accordingly dissolved in acetone and treated with ligroin until about 10% had been precipitated as dark flocks. The mixture was filtered and the filtrate shaken out with water. The ligroin layer, from which most of the dye had separated, clinging to the walls of the separatory funnel, was shaken out with dil. hydrochloric acid and the solution filtered, diluted to large volume, and the dye precipitated with dil. ammonia. It forms a red, amorphous powder, which darkens above 90°, begins to melt at about 110°, and is completely fluid at about 180°. It dissolves in dil. acids with a bright red color, in dil. alkali with a cherry-red color, and is readily soluble in the usual neutral organic solvents with the exception of ligroin. The solution in conc. sulfuric acid is an intense red-violet in thick layers, and blue-violet in thin layers.

Subs., 0.1028: 10.8 cc. N (30.0°, 755).
Calc. for $C_{27}H_{32}O_4N_4$: N, 11.76. Found: 11.77.

3-Methoxy-4-ethoxyphenylazo-hydrocupreine.—Purification of the dye (from hydrocupreine and diazotized 3-methoxy-4-ethoxyaniline[1]) by the usual process failed to yield a pure product, so the dye was dissolved in a small volume of dry acetone and freed from a dark, flocculent impurity exactly as in the case of the dimethoxy compound. It forms a deep red powder which begins to darken and soften at about 80°, gradually melts above 100°, and is completely fluid at about 135°. It dissolves readily in the usual neutral organic solvents except ligroin, and is soluble in dil. sodium hydroxide with a cherry-red color and in dil. acids with a deep red color. The solution in conc. sulfuric acid is an intense violet, appearing blue in thin layers.

Subs., 0.1003: 9.8 cc. N (21.5°, 766 mm.).
Calc. for $C_{28}H_{34}O_4N_4$: N, 11.43. Found: 11.41.

4-Methoxy-5-ethoxyphenylazo-hydrocupreine.—4-Methoxy-5-ethoxyaniline[2] was diazotized, coupled with hydrocupreine, and the product purified exactly as in the case of its 3,4-isomer. The yield of dark red, amorphous product was 80% of the alkaloid taken. It was not entirely soluble in dil. sodium hydroxide solution and dissolved in dil. acids with a deep red color. It is less easily soluble in ligroin or ether than in the other usual neutral organic solvents. The dye dissolves in conc. sulfuric acid with an intense violet color, appearing redder by transmitted light than by reflected light. It softens and gradually melts above 75°, becoming completely fluid at about 120°.

Subs., 0.1308: 12.6 cc. N (23.5°, 769 mm.).
Calc. for $C_{28}H_{34}O_4N_4$: N, 11.43. Found: 11.23.

3,4-Dimethoxy-6-carboxyphenylazo-hydrocupreine.—After coupling 6-aminoveratric acid[3] with hydrocupreine in the usual way the

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[1] THIS JOURNAL, 41, 1461 (1919).

[2] *Ibid.*, 41, 1462 (1919).

[3] This substance, which does not seem to have been previously described, was prepared by nitrating methyl veratrate in acetic acid solution with fuming nitric acid, reducing to the amino ester (cf. Zincke and Francke, *Ann.*, **293**, 190 (1896)) with a solution of stannous chloride in methyl alcoholic hydrochloric acid, diluting with ice and

deep red solution was treated with ammonium chloride, precipitating the dye (not the salt in this case) as a brick-red amorphous precipitate. This was purified with the aid of dil. hydrochloric acid and the filtrate treated with sodium acetate solution. The dye forms a deep maroon powder which, when rapidly heated to 235°, then slowly, melts and decomposes at 236°. It is rather difficultly soluble in the usual solvents and dissolves in dil. hydrochloric acid with a cherry-red color and in dil. sodium hydroxide with a somewhat brighter red shade. The color in conc. sulfuric acid is an intense violet.

Subs., 0.1224: 11.4 cc. N (27.0°, 757 mm.).
Calc. for $C_{28}H_{32}O_6N_4$: N, 10.77. Found: 10.56.

O - Phenylglycollic acid - *p* - azohydrocupreine, *p* - $HO_2C.H_2C.O.C_6H_4N : NC_{19}H_{23}O_2N_2$.—The deep purplish red solution obtained on coupling *p*-aminophenoxyacetic acid[1] was acidified with a slight excess of acetic acid and the deep red precipitate filtered off and heated with 85% alcohol. The substance began to crystallize but dissolved entirely on adding sufficient boiling 85% alcohol. The solution was diluted with about $^1/_2$ volume of water, treated with a few drops of acetic acid, and seeded, and the product recrystallized from 50% alcohol, separating rapidly on seeding the cooled, supersaturated solution as brilliant, red needles containing 4 molecules of water of crystallization. An aqueous suspension dissolves only on adding a considerable excess of acetic acid, but dissolves easily on adding a drop or two of dil. sodium carbonate or hydroxide with a purplish red color, changing to orange-red on addition of hydrochloric acid. When rapidly heated to 195°, then slowly, the anhydrous acid darkens, softens, and sinters, finally melting at 199–200° with decomposition. It dissolves readily in chloroform or acetone, sparingly in dry methyl or ethyl alcohol, and gives a deep red color in conc. sulfuric acid, appearing purple in thin layers.

Subs., air-dry, 0.3940: loss, 0.0496 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{27}H_{30}O_6N_4.4H_2O$: H_2O, 12.82. Found: 12.58.
Subs., anhydrous, 0.1235: 12.6 cc. N (23.5°, 752 mm.).
Calc. for $C_{27}H_{30}O_6N_4$: N, 11.43. Found: 11.62.

m - **Carboxamido - phenylazo - hydrocupreine,** *m* - $H_2NOCC_6H_4N$:-

water, and extracting the amino ester after making alkaline. Saponified with alcoholic sodium hydroxide on the water bath and evaporated, this yielded the acid as a mass of needles after diluting with water and acidifying with acetic acid. Recrystallized from ethyl acetate, it forms almost colorless, thick plates which dissolve with difficulty in boiling water and are somewhat more readily soluble in acetone than in the other neutral organic solvents. When rapidly heated to 185°, then slowly, it effervesces at 186°. An aqueous suspension gives an indigo-blue color with ferric chloride.

Subs., 0.1439: 9.2 cc. N (24.0°, 753 mm.).
Calc. for $C_9H_{11}O_4N$: N, 7.11. Found: 7.07.

[1] THIS JOURNAL, 39, 2196 (1917).

$NC_{19}H_{23}O_2N_2$.—The dye from *m*-aminobenzamide[1] was purified in the usual way, forming an amorphous powder which sinters and darkens above 135°, begins to melt at 160°, and is completely fluid and decomposes at about 195°. It dissolves readily in alcohol, less easily in dry chloroform or acetone, or benzene, and dissolves in *N* sodium hydroxide solution with a deep cherry-red color.

Subs., 0.1077: 14.2 cc. N (24.0°, 757 mm.).
Calc. for $C_{26}H_{29}O_3N_5$: N, 15.25. Found: 15.09.

On rubbing the base with 1 : 1 hydrochloric acid it dissolves and the solution soon deposits the *dihydrochloride* as aggregates of flat, orange-red, microscopic needles.

***p*-Sulfophenylazo-hydrocupreine.**—Sulfanilic acid coupled practically instantaneously with hydrocupreine under the usual conditions. Saturated ammonium chloride solution was added at the end in order to free the hydroxyl group. The scarlet *sodium salt* precipitated immediately, the amount increasing slightly on addition of sodium chloride. After washing with saturated sodium chloride solution a portion was recrystallized from water, separating on gradual cooling as glistening, scarlet rhombs and prisms which soon lose a portion of their water of crystallization on air-drying, turning a darker red and coming to equilibrium with 3.5 molecules of water of crystallization. The salt dissolves in water with a deep brown-red color, changing to cherry-red on adding alkali. Dilute aqueous solutions give slow-forming, red rhombs of the calcium and barium salts.

Subs., air-dry, 0.5788: loss, 0.0618 *in vacuo* at 80° over H_2SO_4.
Calc. for $C_{25}H_{27}O_6N_4SNa.3.5H_2O$: H_2O, 10.85. Found: 10.68.
Subs., anhydrous, 0.1213: 11.2 cc. N (24.5°, 764 mm.).
Calc. for $C_{25}H_{27}O_5N_4SNa$: N, 10.81. Found: 10.65.

A portion of the crude salt was dissolved in much hot water and acidified slightly with acetic acid, the *free sulfonic acid* soon separating as brilliant, brown-orange leaflets. Recrystallized from 50% alcohol it separates slowly as gleaming, red prisms containing 3 molecules of water of crystallization and dissolving with difficulty in boiling water. The anhydrous acid, when rapidly heated to 250°, then slowly ,melts and decomposes at 252° with preliminary darkening and softening. It dissolves in sulfuric acid with a red-orange color, and is appreciably soluble in dry methyl alcohol, less readily in absolute alcohol or dry chloroform. An aqueous suspension dissolves readily in dil. mineral acids, but only on adding a large excess of acetic acid.

Subs., air-dry, 0.5158: loss, 0.0500 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{25}H_{28}O_5N_4S.3H_2O$: H_2O, 9.82. Found: 9.70.
Subs., anhydrous, 0.1293: 12.6 cc. N (26.0°, 762 mm.).
Calc. for $C_{25}H_{28}O_5N_4S$: N, 11.29. Found: 11.16.

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[1] THIS JOURNAL, 39, 1438 (1917).

m - Sulfonamido - phenylazo - hydrocupreine, *m* - $H_2NO_2SC_6H_4N$:$NC_{19}H_{23}O_2N_2$.—As obtained by the ordinary process of purification the dye from *m*-aminobenzene-sulfonamide[1] was still impure and it was accordingly dissolved in acetone and fractionally precipitated with ligroin, rejecting the first portions. The last fractions were dissolved in dil. hydrochloric acid and reprecipitated with ammonia, but the percentage of nitrogen was still low. The orange-brown, amorphous dye softens and sinters above 140°, gradually melts above 170°, and is completely fluid at about 190°. It dissolves in conc. sulfuric acid with an orange-red color, in dil. acids with an orange color, and in dil. sodium hydroxide with a deep cherry-red color.

Subs., 0.1018: 12.2 cc. N (30.5°, 757 mm.).
Calc. for $C_{25}H_{29}O_4N_5S$: N, 14.13. Found: 13.43.

***p*-Sulfonamido-phenylazo-hydrocupreine.**—The dye obtained from *p*-aminobenzene-sulfonamide[2] was purified in the usual way. It forms an orange-brown amorphous powder which gradually melts above 155° and is completely fluid at about 190°. It dissolves in conc. sulfuric acid with a brown-orange color, in dil. acids with a red-orange color, and gives a deep cherry-red solution in dil. sodium hydroxide. It is readily soluble in alcohol, sparingly in benzene.

Subs., 0.1321: 15.7 cc. N (21.0°, 750 mm.).
Calc. for $C_{25}H_{29}O_4N_5S$: N, 14.13. Found: 13.62.

Quinolyl-6-azohydrocupreine.—The crude dye from 6-aminoquinoline crystallized suddenly when warmed with 85% alcohol. Recrystallized from amyl alcohol it separated slowly as aggregates of bright red, glistening, lenticular platelets with a golden reflex. When rapidly heated to 230°, then slowly, the substance melts and evolves gas at 232–4°, with preliminary softening and darkening. It dissolves readily in chloroform or boiling amyl alcohol, and is rather sparingly soluble in boiling alcohol, acetone, or benzene. An aqueous suspension does not dissolve on adding dil. sodium hydroxide, but an alcoholic solution, diluted with *N* sodium hydroxide, gives a clear, cherry-red solution. The solution in conc. sulfuric acid is reddish orange, while the color in dil. acids is orange-red.

Subs., 0.1342: 17.1 cc. N (22.5°, 752 mm.).
Calc. for $C_{28}H_{29}O_2N_5$: N, 14.98. Found: 14.57.

(B) Azo Dyes Derived from Hydrocupreidine.

Phenylazo-hydrocupreidine.—13 g. of hydrocupreidine[3] were coupled with diazotized aniline in the usual way, completing the precipitation of the dye with ammonium chloride, and purifying by solution in very dilute hydrochloric acid and reprecipitation with ammonia. The yield was 13.9

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[1] THIS JOURNAL, 39, 2428 (1917).

[2] *Ibid.*, 39, 2429 (1917).

[3] *Ibid.*, 41, 827 (1919).

g. When the amorphous product is dissolved in hot acetone it soon begins to crystallize and a portion for analysis was filtered from the hot solution, as the fractions deposited on cooling were accompanied by a little amorphous material. Recrystallized from alcohol it separates slowly on seeding as a hard crust of garnet-like rhombs which melt at 183–5° with slight preliminary darkening and softening. The substance forms a scarlet powder when crushed, and is appreciably soluble at room temperature in alcohol, methyl, ethyl, or amyl alcohol, or acetone, more easily on boiling. It dissolves readily in chloroform or benzene, and gives a reddish orange-brown color in conc. sulfuric acid.

Subs., 0.1110: 12.4 cc. N (22.5°, 772 mm.).
Calc. for $C_{25}H_{28}O_2N_4$: N, 13.46. Found: 13.11.

The Dihydrochloride.—When the amorphous, purified base is dissolved in not too little dry acetone and treated with an excess of conc. hydrochloric acid the dihydrochloride is obtained as an amorphous precipitate which crystallizes almost immediately. The salt was filtered off, moistened with 1 : 1 hydrochloric acid, and treated with dry acetone, filtering again and washing the orange-red platelets with dry acetone containing a drop of conc. hydrochloric acid. The air-dry salt contains 4 molecules of water of crystallization and is readily soluble in water. After drying *in vacuo* at room temperature over sulfuric acid and crushed alkali it turns a bright red, and, when rapidly heated to 215°, then slowly, decomposes at 220–1°, with slight preliminary darkening. It is readily soluble in dry methyl alcohol, less easily in cold chloroform, and dissolves with difficulty in cold absolute alcohol, more readily on warming.

Subs., air-dry, 0.6078: loss, 0.0788.
Calc. for $C_{25}H_{28}O_2N_4.2HCl.4H_2O$: H_2O, 12.84. Found: 12.97.
Subs., anhydrous, 0.1332: 13.2 cc. N (22.0°, 760 mm.). Subs., 0.1841: AgCl, 0.1074.
Calc. for $C_{25}H_{28}O_2N_4.2HCl$: N, 11.45; Cl, 14.49. Found: N 11.48; Cl, 14.43.

α-Naphthylazo-hydrocupreidine.—The purified dye was recrystallized first from alcohol, then from a small volume of amyl alcohol, separating as tufts of deep red, hair-like needles which melt at 132–40° with preliminary darkening, softening, and sintering. It dissolves very easily in chloroform or benzene, somewhat less readily in dry acetone, and sparingly in cold methyl or ethyl alcohol, more easily on boiling. It dissolves in conc. sulfuric acid with a deep blue color, in dilute acids with a red shade, and gives a dull red color in dil. alkali.

Subs., 0.1220: 13.0 cc. N (23.5°, 761 mm.).
Calc. for $C_{29}H_{30}O_2N_4$: N, 12.02. Found: N, 12.28.

***p*-Nitrophenylazo-hydrocupreidine.**—Hydrocupreidine and diazotized *p*-nitraniline were coupled exactly as in the case of hydrocupreine (see p. 2136). The crude dye was purified in the usual manner and then crystallized readily when dissolved in boiling alcohol and allowed to cool.

Recrystallized from alcohol it separates on seeding, after cooling and filtering from a small amount of an amorphous impurity, as spherules of red microcrystals which melt to a tar at 135–9° and become completely fluid at 155–60°. It dissolves appreciably in cold methyl or ethyl alcohol, quite readily on boiling, and is very easily soluble in cold chloroform, acetone, or benzene. It dissolves in conc. sulfuric acid or dil. acids with a red-orange color, and in hot dil. *N* sodium hydroxide with a deep purplish red color. An alcoholic solution also gives a clear, deep purple solution when diluted with *N* sodium hydroxide.

Subs., 0.1192: 15.65 cc. N (27.5°, 764 mm.).
Calc. for $C_{25}H_{27}O_4N_5$: N, 15.19. Found: 15.00.

p-Sulfophenylazo-hydrocupreidine.—This substance was prepared in the same way as its hydrocupreine isomer. As the crude sodium salt showed no tendency to crystallize it was dissolved in enough hot water to give a clear solution and acidified with acetic acid, seeding with crystals obtained by strongly acidifying a conc. test portion with acetic acid. Recrystallized first from water, then from 50% alcohol, the sulfonic acid separates slowly on seeding as minute orange-red crystals containing 5.5 molecules of water of crystallization, and dissolving appreciably in cold water, more easily on heating. The anhydrous substance is a darker red and, when rapidly heated to 245°, then slowly, it decomposes at 247°, with preliminary darkening and softening. It dissolves in conc. sulfuric or dil. acids with an orange color and in dil. sodium carbonate with a brown-red color, becoming more purple on adding sodium hydroxide. It is quite soluble in dry methyl or ethyl alcohol or chloroform and appreciably in cold, dry acetone.

Subs., air-dry, 0.3397: loss, 0.0533 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{25}H_{28}O_5N_4S.5.5H_2O$: H_2O, 16.64. Found: 16.28.
Subs., anhydrous, 0.1204: 11.7 cc. N (24.5°, 762 mm.).
Calc. for $C_{25}H_{28}O_5N_4S$: N, 11.29. Found: 11.18.

(C) Derivative of 6-Hydroxyquinoline.

Phenylazo-6-hydroxyquinoline.—Aniline was coupled as in the case of the phenolic alkaloids with an alkaline solution of 6-hydroxyquinoline. Precipitation of the dye was completed with ammonium chloride and the crude product recrystallized twice from alcohol, separating as minute, narrow, red leaflets which melt at 160–1.5° with slight preliminary softening, crystallizing again on cooling. In its solubilities, color reactions, and dyeing properties it resembles the corresponding hydrocupreine and hydrocupreidine compounds. The substance was first prepared by Mathëus,[1] who, however, gives no melting point.

Subs., 0.1297: 19.2 cc. N (28.5°, 762 mm.).
Calc. for $C_{15}H_{11}ON_3$: N, 16.87. Found: 16.81.

New York, N. Y.

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[1] *Ber.*, **21**, 1642 (1888).