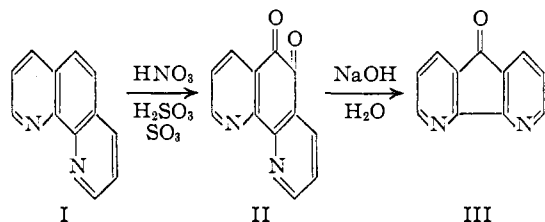


[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Formation of a New Nitrogen Heterocyclic Ring System by the Loss of Carbon Monoxide from 1,10-Phenanthroline-5,6-quinone¹

BY GEORGE E. INGLETT AND G. FREDERICK SMITH

1,10-Phenanthroline-5,6-quinone (II) has been found to lose carbon monoxide if heated with a weak aqueous sodium hydroxide solution to give 4,5-diazafluoren-9-one (III) in practically quantitative yields. The quinone² (II) can be isolated



if the nitration filtrate from 1,10-phenanthroline³ (I) is kept slightly acidic and evaporated, or 4,5-diazafluoren-9-one (III) can be obtained if the nitration filtrate is made slightly basic and evaporated to half its volume. The new compound (III) was obtained directly from the nitration filtrate in the first experiment, and in the second experiment it was prepared from II by imposing similar conditions.

This is a very surprising development because the carbon monoxide is rejected so readily and the remaining fragments combine so perfectly and completely. The reaction is reminiscent of that of ethyl oxalyl derivatives of esters and polycarbonyl compounds containing more than two carbonyl groups. This is the first reaction, however, in which carbon monoxide has been observed to be lost from a 1,2-diketone grouping. Moreover, the decarbonoxidation proceeds rather eagerly whereas some of the ethyl oxalyl derivatives of esters need to be catalyzed by cupric salts and require hours of refluxing.

1,10-Phenanthroline (I) gives a red-colored complex with the ferrous iron ion (the ferroin reaction),⁴ but 4,5-diazafluoren-9-one (III) or 1,10-phenanthroline-5,6-quinone (II) do not give a colored complex. The inability of 4,5-diazafluoren-9-one to complex ferrous iron has been attributed to the fact that the 2,2'-bipyridine nucleus which is essential for this reaction has been distorted. Infrared data have indicated a five-membered ring by giving a relatively high carbonyl value of 1718 cm^{-1} . The new ketone III belongs to a class of heterocyclic compounds previously

unknown, of which 4,5-diazafluorene, not yet synthesized, may be regarded as the parent individual. The structure of 4,5-diazafluoren-9-one has been elucidated by means of the 2,4-dinitrophenylhydrazone and picrate derivatives. Ultra-violet data have related structurally 4,5-diazafluoren-9-one and fluorenone. These compounds give experimentally identical carbonyl values in the infrared carbonyl region. 4,5-Diazafluoren-9-one is the only possible sterical structure that can be formed after carbon monoxide has been lost from 1,10-phenanthroline-5,6-quinone.

An attempt has been made to prepare 4,5-diazafluoren-9-one by heating calcium oxide and binicotinic acid. Since 2,2'-bipyridine is the only product obtained, the binicotinic acid apparently decarboxylates before it reacts with the calcium oxide.

Experimental

Separation of 4,5-Diazafluoren-9-one.—An 80-g. sample of 1,10-phenanthroline monohydrate (m. p. 100–102°) was placed in a 4-l. beaker, and one pound of 60% fuming sulfuric acid was added cautiously at such a rate as to avoid violent reaction with the monohydrate and to minimize attendant carbonization. A 215-ml. portion of concentrated nitric acid was added to the reaction mixture slowly with caution to avoid violent splattering and also to insure that the temperature did not exceed 175°. The addition of concentrated nitric acid to 60% fuming sulfuric acid brings about an exceedingly violent reaction, producing copious quantities of poisonous fumes. An efficient hood is therefore necessary. Following the addition of the concentrated nitric acid, the reaction mixture was heated at 175° on a hot-plate, with stirring, for thirty minutes. The reaction mixture was then poured slowly into a 4-l. beaker filled with crushed ice. The strongly acidic solution was then cautiously neutralized with a 30% sodium hydroxide solution. Sufficient dilute nitric acid was added to make the contents of the beaker acidic to litmus paper. The precipitate, 5-nitro-1,10-phenanthroline, was collected on a filter; yield, 90%. After the filtrate had been made slightly basic with sodium hydroxide, the solution (3.5 l.) was evaporated to half of its volume on a sand-bath. Filtration removed about a gram of black solid which was placed in a 250-ml. beaker and taken into solution with approximately 50 ml. of 95% ethyl alcohol. A small amount of Darco S51 was added and the mixture, after being heated for a short time, was filtered while hot. From the cooling alcoholic filtrate, the 4,5-diazafluoren-9-one separated in long, silver-white needles. These were recrystallized twice from water and again from 95% ethyl alcohol; m. p. 212–213°. ⁵

Anal. Calcd. for $\text{C}_{11}\text{H}_8\text{N}_2\text{O}$: C, 72.52; H, 3.30; N, 15.38. Found: C, 72.64; H, 3.43; N, 15.48.

Formation of 4,5-Diazafluoren-9-one by the Action of Sodium Hydroxide on 1,10-Phenanthroline-5,6-quinone.—In order to test the theory that the 4,5-diazafluoren-9-one was formed from 1,10-phenanthroline-5,6-quinone by the loss of carbon monoxide, a 0.021-g. sample of the quinone (m. p. 256–257°) was placed in a 100-ml. beaker and 10 ml. of 0.1 N sodium hydroxide added. A watch glass was placed over the beaker and the solution boiled

(1) This paper formed part of a thesis presented in partial fulfillment of the requirements for the B.S. degree at the University of Illinois in 1949 by George E. Inglett, present address: Department of Biochemistry, University of Wisconsin, Madison, Wisconsin.

(2) Smith and Cagle, *J. Org. Chem.*, **12**, 781 (1947).

(3) Blau, *Monatsh.*, **19**, 666 (1898).

(4) Smith and Richter, "Phenanthroline and Substituted Phenanthroline Indicators," The G. Frederick Smith Chemical Company, Columbus, Ohio, 1944.

(5) All melting points are uncorrected.

until 2-3 ml. of the solution remained in the beaker. When the solution was cooled, long, silver-white needles separated. Crystallization from 95% ethyl alcohol gave 0.017 g. of 4,5-diazafluoren-9-one, m. p. 212-213°, yield 96%.

This experiment was repeated using 1.00 g. of 1,10-phenanthroline-5,6-quinone in 50 ml. of 0.25 *N* sodium hydroxide and evaporated slowly. Crystals of 4,5-diazafluoren-9-one were collected on a filter for about every 10 ml. of solution evaporated. This procedure was repeated until no more crystals formed. The solution was successively yellow, deep red, green and brown. The yield of 4,5-diazafluoren-9-one was 97%.

Preparation of 1,10-Phenanthroline-5,6-dioxime.—A 0.20-g. sample of 1,10-phenanthroline-5,6-quinone⁶ was mixed with 0.40 g. of hydroxylamine hydrochloride and 0.40 g. of pure precipitated calcium carbonate. The mixture was placed in a 25-ml., round-bottomed flask, and 8 ml. of 95% ethyl alcohol added. A small piece of carborundum was employed as a boiling chip, the flask being attached to a reflux condenser. The mixture was heated under reflux for four hours and filtered while hot. The dioxime did not crystallize from the alcoholic filtrate; on prolonged standing the alcohol evaporated and left the 1,10-phenanthroline-5,6-dioxime as an impure residue. A 10-ml. portion of 10% sodium bisulfite was added, and the mixture heated to boiling, the solution being filtered while hot. The dioxime on the filter paper was then dissolved in 95% ethyl alcohol and the solution heated to boiling. A 2% solution of sodium bisulfite in distilled water was added until a slight turbidity was noticed. The solution was then heated until clear and, upon subsequent cooling, 1,10-phenanthroline-5,6-dioxime separated. The precipitate was collected on a filter and washed several times with water. The yield was practically quantitative; m. p. 189°. The dioxime was found to be soluble in ether, alcohol and acids and insoluble in water.

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 60.00; H, 3.34. Found: C, 60.02; H, 3.60.

2,4-Dinitrophenylhydrazone of 4,5-Diazafluoren-9-one.—Approximately 5 ml. of 2,4-dinitrophenylhydrazine reagent⁷ was added to 5 ml. of a hot, saturated, aqueous solution of 4,5-diazafluoren-9-one in a test-tube. Several milliliters of distilled water was added, and the mixture was heated in a water-bath for an hour. The orange precipitate was collected on a filter, m. p. 315-316°, with slight decomposition.

Anal. Calcd. for $C_{17}H_{10}N_6O_4$: C, 56.36; H, 2.76. Found: C, 56.04; H, 2.75.

The 2,4-dinitrophenylhydrazone was found to be insoluble in 95% ethyl alcohol and only sparingly soluble in ethyl and *n*-butyl acetates.

4,5-Diazafluoren-9-one Picrate.—A saturated, aqueous solution of picric acid was added to 5 ml. of a hot, saturated, aqueous solution of 4,5-diazafluoren-9-one. When the solution cooled, the picrate crystallized in long, pale yellow needles. It was recrystallized four times from distilled water; m. p. 142-144°.

Anal. Calcd. for $C_{17}H_9N_3O_8$: C, 49.60; H, 2.19; N, 17.03. Found: C, 49.66; H, 2.19; N, 17.06.

An Attempted Synthesis of 4,5-Diazafluoren-9-one from Binicotinic Acid.—Binicotinic acid was prepared by suspending 8 g. (0.04 mole) of 1,10-phenanthroline in 800 ml. of water, 3.2 g. (0.08 mole) of sodium hydroxide, and 19 g. (0.12 mole) of potassium permanganate in a 1 l. three-neck, round-bottomed flask. The flask was attached to a reflux condenser and a mechanical stirrer. The mixture was boiled and stirred for two hours. The excess permanganate was reduced by adding sucrose until

no further permanganate color remained as tested by applying a drop of the reaction mixture to an area of filter paper and examining the spot test fringe for a purple border. The voluminous precipitate of manganese dioxide was filtered out and the filtrate concentrated on a steam-bath. The concentrate was acidified with acetic acid, and 13.6 g. (0.08 mole) of silver nitrate, dissolved in a minimum amount of distilled water, was added with constant stirring. The resulting precipitate was filtered and transferred to a considerable volume of hot water in a precipitation flask and saturated with hydrogen sulfide. Norite decolorizing carbon was added and the solution heated to a boil. The carbon and silver sulfide were collected on a filter and the filtrate evaporated to obtain crystals of binicotinic acid. The crystals were recrystallized from a water solution; yield 85%, m. p. 260-261° with decomposition.

One gram of binicotinic acid was mixed with 0.23 g. of pure calcium oxide on a clay plate. The mixture was placed in a test-tube and heated to red heat. Five milliliters of 95% ethyl alcohol was added and the contents of the test-tube warmed to boiling on a Glas-Col heating mantle and the solid material removed by filtration. The alcoholic extract was placed in a small distilling flask and the alcohol removed. An oil remained which distilled around 270°. The distillate solidified; m. p. 68°. This compound gave a deep red coloration with ferrous iron and is in agreement with 2,2'-bipyridine (m. p. 69.5°, b. p. 272.5°).⁸

Relationship of 4,5-Diazafluoren-9-one and Fluorenone in the Ultraviolet Absorption Region.

The ultraviolet absorption spectrum of 4,5-diazafluoren-9-one in 95% ethyl alcohol solution was determined on a Beckman Spectrophotometer, Model DU. The spectrum is shown in Fig. 1 and Table I. The spectrum from 2200 to 3400 Å. is very similar to that of fluorenone shown in Table

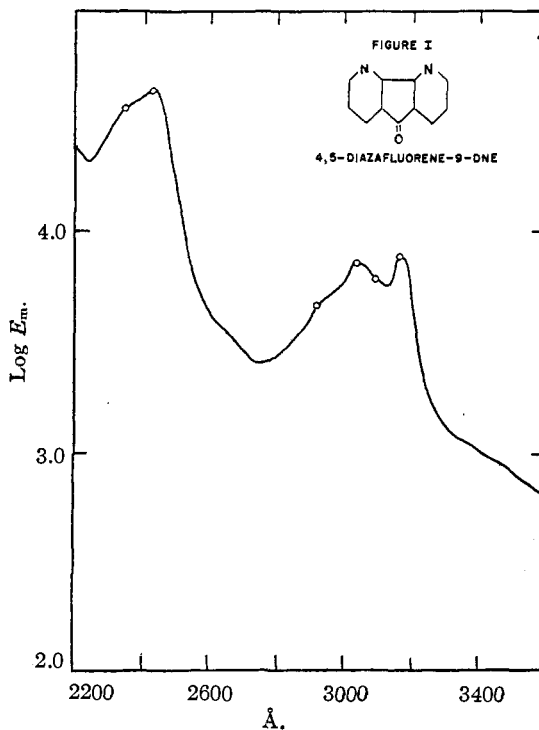


Fig. 1.

(8) Smith, *THIS JOURNAL*, **46**, 414 (1924).

(6) The 1,10-phenanthroline-5,6-quinone used in this work was generously donated by the G. Frederick Smith Chemical Company, Columbus, Ohio, and Professor Francis H. Case of Temple University, Philadelphia, Pennsylvania.

(7) Shriner and Fuson, "The Systematic Identification of Organic Compounds," third ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

2.⁹ The fine structure shown between 2800 and 3400 Å. is markedly similar to that shown by fluorenone. Because of the large bathochromic effect on the carbonyl band in fluorenone, the band is shifted well into the visible region of the spectrum. This, as well as the fine structure, is in agreement with 4,5-diazafluoren-9-one in the 2800-3400 Å. wave length region. Although the carbonyl band was not investigated for 4,5-diazafluoren-9-one in the higher ultraviolet and visible, it has been indicated in the infrared spectrum and also by a 2,4-dinitrophenylhydrazone formation.

TABLE I

Absorption wave length, Å.	Maxima intensity, log E_m	Absorption wave length, Å.	Maxima intensity, log E_m
3160	3.89	3925	2.40
(3090)	3.79	3780	2.43
3035	3.86	(3600)	2.34
(2930)	3.70	(3280)	2.97
2420	4.64	3210	3.07
2360	4.56	3150	3.19
		3060	3.28
		2930	3.54
		(2830)	3.40
		2570	5.00
		2480	4.79

The proof of structure for this new type compound has been substantiated by the use of five

(9) Jones, *THIS JOURNAL*, **67**, 2127 (1945).

separate and distinct chemical and physical observations. These are the preparation of the 2,4-dinitrophenylhydrazone, the picrate, ultraviolet absorption data, as well as infrared studies and sterical considerations. Until further structural proof if needed is made available, the structure given may be classified if not proven at least as highly probable.

Acknowledgment.—The authors are indebted to Dr. Reynold C. Fuson for many helpful suggestions and to Miss Elizabeth Peterson and Dr. J. Calvin Brantley for measuring and interpreting the infrared and ultraviolet spectra, respectively. Appreciation is expressed for helpful advice given by Drs. Elliot R. Alexander, Robert L. Frank and Nelson J. Leonard.

Summary

1. 1,10-Phenanthroline-5,6-quinone has been found to lose carbon monoxide under the influence of weak, aqueous solutions of sodium hydroxide to yield 4,5-diazafluoren-9-one, which exemplifies a nitrogen heterocyclic system hitherto unknown.

2. This is the first reaction in which carbon monoxide has been observed to be lost from a 1,2-diketone grouping.

3. An attempt has been made to synthesize 4,5-diazafluoren-9-one by heating binicotinic acid and calcium oxide.

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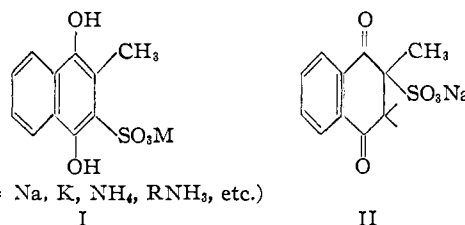
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA AND THE ORGANIC RESEARCH DEPARTMENT OF ABBOTT LABORATORIES]

The Structure of the Antihemorrhagic Sodium Bisulfite Addition Product of 2-Methyl-1,4-naphthoquinone (Menadione)¹

BY MARVIN CARMACK, M. B. MOORE AND M. EARL BALIS

2-Methyl-1,4-naphthoquinone reacts readily in aqueous solution with sodium bisulfite and other bisulfite salts to form two series of isomeric addition compounds, one having high antihemorrhagic activity equivalent to that of the parent quinone, the other having only a small fraction of the activity.² The colorless, crystalline sodium salts, $C_{11}H_9O_5SNa$, have been isolated,^{2c,d} as have also the salts of potassium, S-benzylisothiuronium, and other cations. On the basis of (1) analogy with the addition of sodium bisulfite to 1,4-naphthoquinone,³ (2) their easy oxidation to 2-methyl-1,4-naphthoquinonesulfonate salts and (3) by alternative synthesis, Baker, Davies, McElroy and

Carlson^{2d} showed that the weakly antihemorrhagic series of compounds are salts of 2-methyl-1,4-naphthohydroquinone-3-sulfonic acid (I).



The structures of the highly active isomeric salts have not heretofore been adequately explained, although the salts are of clinical importance.⁴ They cannot be naphthohydroquinone derivatives, since they resist attack by mild oxidizing agents. The resistance to oxidation also rules out simple types of loose 1,2-addition com-

(4) The U. S. Pharmacopeia lists the more physiologically active isomer as Menadione Sodium Bisulfite.

(1) Presented before the Division of Medicinal Chemistry at the meeting of the American Chemical Society in Chicago, Illinois, April 21, 1948.

(2) (a) M. B. Moore, *THIS JOURNAL*, **63**, 2049 (1941); (b) Moore and Kirchmeyer, U. S. Patent 2,367,302, C. A., **39**, 2849 (1945); British Patent 547,913, C. A., **38**, 457 (1944); (c) Baker, Davies, McElroy and Carlson, *THIS JOURNAL*, **64**, 1096 (1942); (d) Ablondi, Price, Baker and Carlson, *ibid.*, **65**, 1776 (1943).

(3) Fieser and Fieser, *ibid.*, **57**, 494 (1935).