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I hereby recommend that the thesis prepared under my supervision by Robert Ellery Fulmer *entitled* Analogues of Cupferron

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Approved by:

Ralph E. Oesper

Alvin I. Kosak

Thomas B. Cameron

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ANALOGUES OF CUPFERRON

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in partial fulfillment of the
requirements for the degree of

DOCTOR OF PHILOSOPHY

1952

by

Robert E. Fulmer

B.S. Iowa State College 1946
M.S. University of Minnesota 1950

ProQuest LLC
789 E. Eisenhower Parkway
PO Box 1346
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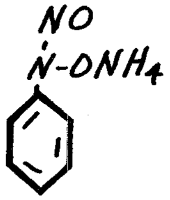
Analogues of Cupferron

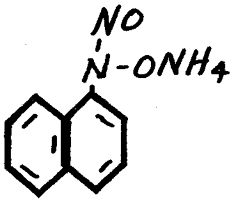
I. History and Background Material

For many years the use of organic substances for inorganic analytical procedures was limited to that of solvent, wash liquid, or other "non-reagent" capacity. The development of organic reagents for analytical use (1)(2)(3) is due to the efforts of various chemists, among whom Oskar Baudisch is notable for his introduction of cupferron and neocupferron.

Cupferron, the ammonium salt of nitrosophenylhydroxylamine (I), was first proposed as an analytical reagent by Baudisch in 1909 (4). Neocupferron, the ammonium salt of nitroso-(α)-naphthylhydroxylamine (II), was prepared by him in 1911 (5).

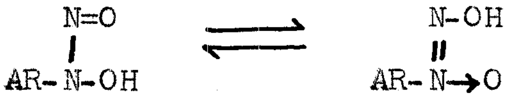


I



II

There is evidence (1) that nitrosophenylhydroxylamine and nitroso-(α)-naphthylhydroxylamine, the free acids of cupferron and of neocupferron, respectively, exist in tautomeric forms (III) (26). The fact that one of the decomposition products of nitrosophenylhydroxyl-



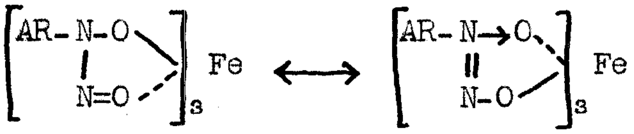
$$\overset{\overset{\displaystyle N{=}O}{|}}{AR-N-OH} \rightleftharpoons \overset{\overset{\displaystyle N-OH}{\|}}{AR-N\rightarrow O}$$

III

amine is nitrosobenzene (1) favors the possibility of two reactive forms of cupferron. Additional evidence is furnished by the differences in color between cupferron complexes of copper or iron depending on whether they are in the solid state or dissolved in an organic liquid. Such color differences are in many cases attributable to differences in constitution (1).

The value of cupferron and neocupferron as analytical reagents lies in their ability to form inner complex compounds with certain metal ions. Ley (6) coined the name "inner complex" to designate compounds (salts) in which the metal atom manifests auxiliary valences toward certain atoms of the acid radical. Inner complex compounds are, therefore, a type of chelate compound, this term having been proposed by Morgan (7) to describe metal compounds in whose molecules a metal atom, through binding, has become a member of a ring.

The two forms of the inner complexes formed with ferric ion by cupferron and neocupferron (26) are shown in IV.

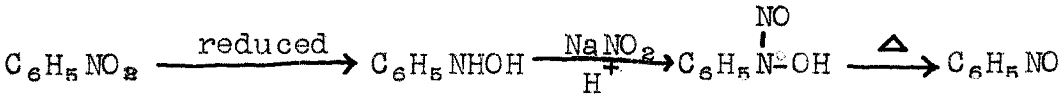

IV

Most inner complex compounds are non-electrolytes; they often are insoluble in water, but soluble in organic liquids, and many of them may be sublimed or distilled without decomposition (1). Of great importance to the analytical chemist is the fact that many of these compounds are colored.

Cupferron (4) was one of the first organic reagents used to demonstrate the value of the formation of inner complex compounds for purposes of quantitative analysis. The formation of inner complex compounds by cupferron, (and by other reagents which form such compounds), requires that the acid hydrogen atom replaced by a metal atom be "in such spatial proximity to coordinating atoms or atomic groups of the same molecule that an activation of auxiliary valences or binding forces can occur" (1). The formation of inner complex ring systems also depends on the nature of the metal atom which forms a part of the complex. Studies on the role of the metal atom in complex formation are far from complete. The stereochemistry of the complexes of the Group VIII elements has been discussed by Nyholm (8). The stability of metal complexes has received much attention. Mellor and Malley (9)(10) determined the following order of stability of bivalent metal ions in complexes with salicylaldehyde and with ethylenediamine: Pd > Cu > Ni > Pb > Co > Zn > Cd > Fe > Mn > Mg. Preliminary work with other chelating agents showed much the same order of stability, although in some cases the positions of neighbors in the series are reversed (9). A change in solvent was found to affect the stability of a metal complex (9). The order of stability may also be radically changed if the bivalency of any of the ions in the series is altered (11). No simple relation was found between complex stability and the covalent radii of bivalent metal atoms (9). However, Irving and Williams (11) found that when stability constants of several complexes formed with bivalent ions of the first transition series are plotted against their atomic numbers, it is seen that the stabilities of the complexes increase from manganese through iron, cobalt, and nickel to reach a maximum at copper. All zinc complexes are markedly less stable than those of copper (11). Pfeiffer, Thielert, and Glaser (12) studied the displacement of metal ions from a bis-salicylaldehyde-ethylenediimine complex. Assuming that a metal ion was displaced from its complex by a metal ion that would form a more stable complex, the following order of stabilities was determined: $Cu^{+2} > Ni^{+2} > Fe^{+3} > Zn^{+2} > Mg^{+2}$ (12). Displacement of iron in the series is probably due to the higher valence state. Burkin (13) gives an order of stability for bivalent ions of $Mn < Fe < Co < Ni < Cu > Zn$ for all ligands except where there is steric hindrance due to ionic size and spatial arrangement of bonds. The decrease in complex stability from Cu^{+2} to Zn^{+2} is almost certainly due to the fact that Cu^{+2} has d-orbitals available for bond formation while Zn^{+2} has no vacant d-orbitals of low energy (13). It has been observed (13) that increasing basicity of related ligands is associated with an increased stability of their complexes with a metal. If the basicity of the ligand is constant, then it would be expected that the stabilities of its metal complexes will depend on the electronegativities of the metal ions as measured by their tendencies to gain electrons. Copper has the highest ionization potential of the metals listed by Burkin (13) and has the greatest tendency to accept electrons, while manganese has the least such tendency. The electronegativity effect may be overshadowed by the availability of vacant d-orbitals of low energy which may take part in bond formation (13).

The gain in configurational entropy on forming a ring system by chelation is a very important factor in the relatively greater stabilities of complex compounds of polydentate ligands as compared to complexes of monodentate ligands (13). During dissociation of a bidentate ligand, one group is freed, but the attachment of the other group holds it in the vicinity of the metal ion so that it is readily re-attached. In the formation of a bidentate ligand complex, the first group is bound, increasing the reactivity of the second group toward the metal ion (13). It seems reasonably certain that the most stable complexes are always formed by elements terminating the transition series (11)(13), and probable that the same order of stability is preserved throughout each series. However, the acceptance of a unique order of stability operating throughout the periodic table awaits more extensive quantitative measurements with more varied ligands and a wider range of metals.

The preparation of nitrosophenylhydroxylamine was announced by Wohl and by Bamberger at about the same time in 1894. Wohl (14) reduced nitrobenzene with zinc dust and calcium chloride, and the resulting phenylhydroxylamine (V) was then nitrosated by treatment with sodium nitrite in acid solution to give the desired product.

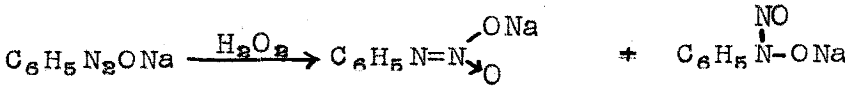


$$C_6H_5NO_2 \xrightarrow{\text{reduced}} C_6H_5NHOH \xrightarrow[H^+]{NaNO_2} C_6H_5\overset{\overset{NO}{|}}{N}-OH \xrightarrow{\Delta} C_6H_5NO$$

V

Bamberger (15) reduced nitrobenzene with zinc and sulfuric acid, and the phenylhydroxylamine (V) was then nitrosated by the action of sodium nitrite in acid solution. Wohl (14) formed the ammonium, silver, and barium derivatives of his nitrosophenylhydroxylamine and noted that on heating it decomposed to give nitrosobenzene. Wohl also ran extensive tests on his phenylhydroxylamine, including reactions with benzaldehyde, formaldehyde, and phenylisothiocyanate, and studied its behavior in the Schotten-Baumann reaction. He also obtained satisfactory analyses for nitrogen in nitrosophenylhydroxylamine and for silver in the silver derivative. Bamberger (15) formed the silver and the barium derivatives of his product, as well as noting that precipitates are formed with copper, mercury, and lead ions, but not with zinc or calcium.

Bamberger and Baudisch (16) prepared cupferron in 1909 as the result of experiments on the oxidation of benzenediazotate (VI) by dilute hydrogen peroxide in cold, alkaline solution. The resulting mixture of the sodium salts of phenylnitramine (VII) and nitrosophenylhydroxylamine was partially separated by recrystallization of the

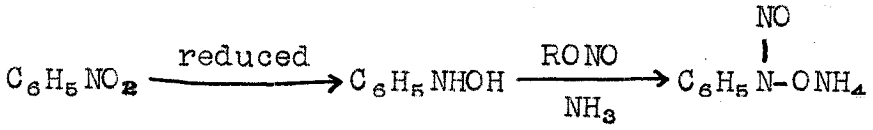


$$C_6H_5N_2ONa \xrightarrow{H_2O_2} C_6H_5N{=}N\begin{smallmatrix}\nearrow ONa\\ \searrow O\end{smallmatrix} + C_6H_5\overset{NO}{\overset{\uparrow}{N}}{-}ONa$$

VI VII

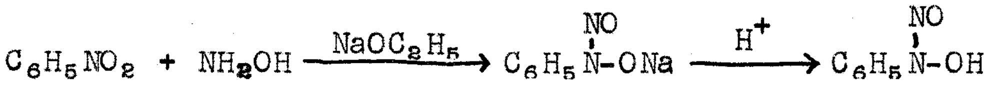
barium derivatives from pyridine. The portion enriched in nitrosophenylhydroxylamine was then further purified through formation of the ferric complex.

Other, more efficient preparations of cupferron involve the reduction of nitrobenzene by zinc dust and ammonium chloride (17) or ammonia and hydrogen sulfide (18) to give phenylhydroxylamine, which is then nitrosated, (in ammoniacal ether solution), by means of n-butyl nitrite (19), amyl nitrite (20), methyl nitrite (21), or ethyl nitrite (18).



$$C_6H_5NO_2 \xrightarrow{\text{reduced}} C_6H_5NHOH \xrightarrow[NH_3]{RONO} C_6H_5\overset{NO}{\overset{|}{N}}\text{-}ONH_4$$

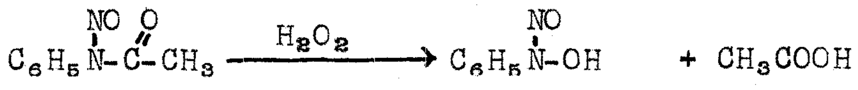
Another method for preparing nitrosophenylhydroxylamine was used by Angeli (22). He treated nitrobenzene with hydroxylamine in a solution containing sodium ethoxide, and recovered nitrosophenylhydroxylamine from the resulting sodium salt (VIII) by the action of dilute sulfuric acid.



$$C_6H_5NO_2 + NH_2OH \xrightarrow{NaOC_2H_5} C_6H_5\overset{NO}{\overset{|}{N}}\text{-}ONa \xrightarrow{H^+} C_6H_5\overset{NO}{\overset{|}{N}}\text{-}OH$$

VIII

Bamberger (23) made use of a procedure involving the oxidation of N-nitrosoacetanilide (IX) by hydrogen peroxide.

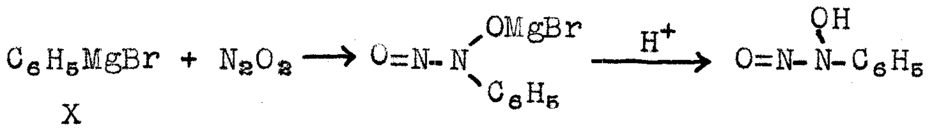


$$C_6H_5\overset{NO}{\overset{|}{N}}\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 \xrightarrow{H_2O_2} C_6H_5\overset{NO}{\overset{|}{N}}\text{-}OH + CH_3COOH$$

IX

Sand (24) prepared nitrosophenylhydroxylamine through the reaction of phenylmagnesium bromide (X) with nitric oxide, and subsequent treatment with dilute sulfuric acid. The nitric oxide appeared to react as the dimer. Sand compared his product with that of Bamberger and made the ammonium, barium, and copper derivatives.

$$2\ NO \rightleftharpoons N_2O_2$$

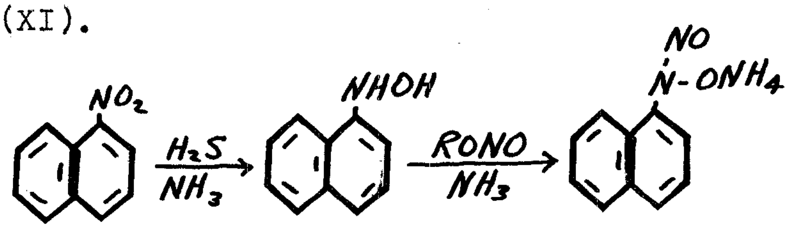


$$C_6H_5MgBr + N_2O_2 \longrightarrow O{=}N{-}N\begin{matrix}OMgBr \\ C_6H_5\end{matrix} \xrightarrow{H^+} O{=}N{-}\overset{OH}{N}{-}C_6H_5$$

X

The copper derivative gave satisfactory values for copper, carbon, hydrogen, and nitrogen content, and the nitrosophenylhydroxylamine itself was successfully analyzed for carbon and hydrogen.

Neocupferron is prepared by the action of amyl nitrite (5), ethyl nitrite (25), or n-butyl nitrite (26) on an ammoniacal ether solution of α-naphthylhydroxylamine (XI).



XI

The α-naphthylhydroxylamine is produced by the reduction of α-nitronaphthalene by ammonia and hydrogen sulfide (5)(25)(26), or by zinc dust and ammonium chloride in aqueous ethanol (27).

Cupferron is a colorless solid with a reported melting point of 163-164° (16)(26), while neocupferron is light buff and melts at 125-126° (26). These reagents are best stored in dark bottles containing solid ammonium carbonate (26). In analytical work a 6% aqueous solution of cupferron or neocupferron is used (26). The cupferron solution is colorless; the neocupferron solution is light yellow. These solutions should be made as needed, the cupferron solution for one to two week's use, but the neocupferron solution for only one day's requirements(26). Precipitations are carried out in the cold to prevent decomposition of the reagent, and usually in acid solution, varying from a pH of less than 1 in the iron determination, to just less than 7 in the case of the copper determination (26). The acidity of the solution and the acid used to adjust the pH depend on the particular metal ion to be precipitated. The ferric ion precipitation has been carried out in the presence of a quite high concentration of hydrochloric, sulfuric, perchloric, acetic, or nitric acid (28)(26).

Both cupferron and the free nitrosophenylhydroxylamine formed in acid solution are effective in forming complexes with metal ions (1). Since the free nitrosophenylhydroxylamine will be co-precipitated in acid solution, the precipitate of the metal complex will not be pure. However, the co-precipitated free acid may act as a collector for small quantities of its metal derivatives, an advantage in certain cases. When precipitations are carried out in acetic acid solution there is little decomposition of cupferron to its free acid (1). Since a metal cupferrate decomposes on heating, the complex cannot be dried and weighed directly, but must be ignited to the oxide of the metal (26). The metal oxide may be weighed directly, or converted into another form, e.g., the sulfide, prior to weighing. Oxalic acid or ammonium nitrate may be added before ignition of the metal cupferrate to reduce the volatilization loss (30). Since filtering off the metal cupferrate does not always give a quantitative recovery, Furman (29) prefers extraction with chloroform or ether when microgram or milligram quantities of a metal ion are being determined by means of cupferron.

Cupferron has been used directly for the determination of iron, copper, tin, titanium, aluminum, uranium^{IV}, niobium, tantalum, gallium, thorium, zirconium, vanadium, bismuth, molybdenum, and mercury (31)(32). Cupferron has also served in separations of groups of metal ions preparatory to the determination of the ions by other reagents(26). Many of the metals precipitated by cupferron, e.g., zirconium, niobium, molybdenum, tungsten, uranium, and the rare earths are not widespread, hence interference from these ions is not likely to be encountered in ordinary work (31). Also, non-ferrous elements, (tin, antimony, bismuth, etc.), are rarely present in the analysis of ferrous metals and alloys, just as iron may often be absent in the non-ferrous materials (31). Preliminary treatment with hydrogen sulfide, tartaric acid, oxalic acid, or boric acid may be carried out to remove or mask interfering elements, since cupferron can be used in solutions containing these acids (31).

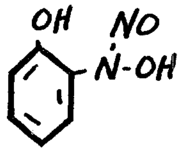
Pinkus and Martin (33) reported extensive studies on the conditions regarding precipitation, color, and solubility in water, acid, or base, of the cupferron complexes of many metal ions. Lundell and Knowles (34), Auger (35), Fresenius (28), and Lundell and Hoffman (36) have also discussed the use of cupferron in quantitative analysis.

The analytical properties of neocupferron are similar to those of cupferron (26). However, the use of neocupferron makes possible the direct determination of iron in very dilute solutions, such as mineral waters(25) (26). The use of neocupferron has not been investigated to an extent comparable to the development of cupferron as an analytical reagent.

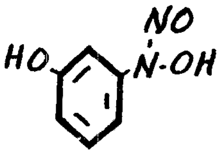
Many studies have been made of the effects of substituted groups on the characteristics of organic reagents (1)(2)(37). The investigation of the influence of substitution on the properties of cupferron has included the preparation and preliminary testing of a large number of analogues.

The =NOH group of hydroxylamine shows acidic, (salt-forming), character toward only the alkali metals. Aliphatic nitrosohydroxylamines have no precipitating action comparable to cupferron (1). However, the quantitative precipitation effect with ferric and copper ions is shown by phenyl- as well as other aryl-nitrosohydroxylamines. Therefore, it would seem that cupferron and its analogues owe their enhanced precipitating action to an increased acidic character of the =NOH group, due to the attached negative aryl and nitroso groups (1), as well as to the important ability to form an inner complex compound.

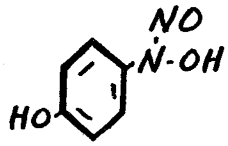
Baudisch prepared several variants of cupferron containing ring-substituted groups such as hydroxyl (XII, XIII, XIV)(38, 39, 40), methoxyl (XV, XVI)(41, 42), and toluenesulfonyl (XVII, XVIII, XIX)(43, 38, 40), and reported the complex-forming activities of these reagents toward a limited number of metal ions. Bamberger prepared and tested the formyl-substituted cupferron (XX)(44). Baudisch also made analogues containing a substituted amino group (XXI, XXII, XXIII)(43, 45). Baudisch found that the properties of cupferron are not changed by placing $-Cl$, $-Br$, $-NO_2$, $-CH_3$, or $-OCH_3$ on the ring.



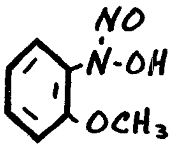
XII



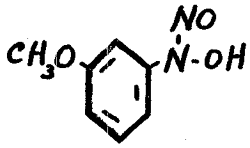
XIII



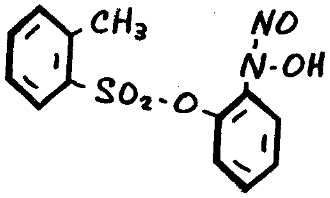
XIV



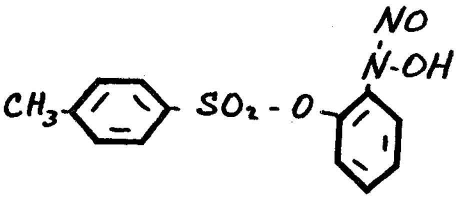
XV



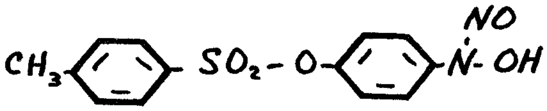
XVI



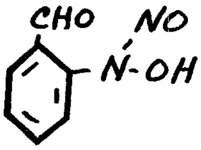
XVII



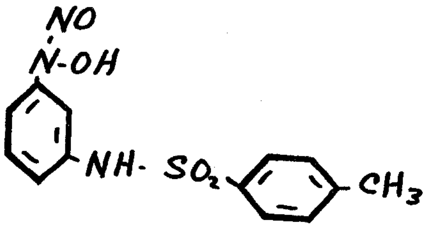
XVIII



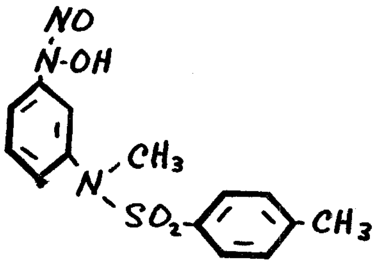
XIX



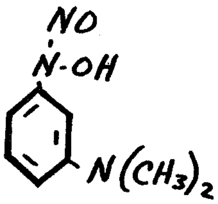
XX



XXI



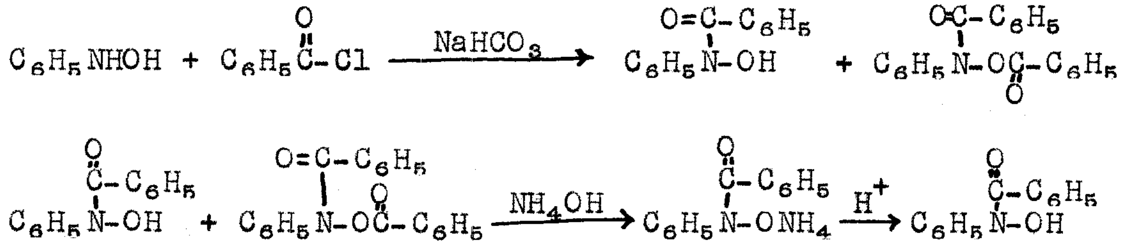
XXII



XXIII

However, the $-OSO_2-C_6H_4-CH_3$, $-OH$, $-N(CH_3)_2$, $-NHSO_2-C_6H_4-CH_3$, $-N(CH_3)SO_2-C_6H_4-CH_3$, or $-CHO$ analogues form metal complexes which vary in color from the analogous cupferron complexes and sometimes differ in ease of solution in chloroform (46)(43)(45)(47).

Shome (48) assumed that the $C_6H_5-\overset{|}{N}-OH$ portion of cupferron was effective in forming salts. He accordingly studied compounds of the general formula $C_6H_5-N(R)-OH$ in which $-R$ is $-CHO$, $-\overset{\overset{O}{\parallel}}{C}-CH_3$, $-\overset{\overset{O}{\parallel}}{C}-C_6H_5$, $-\overset{\overset{O}{\parallel}}{C}-NH_2$, $-\overset{\overset{O}{\parallel}}{C}-NH-C_6H_5$, $-\overset{\overset{S}{\parallel}}{C}-NH_2$, $-\overset{\overset{S}{\parallel}}{C}-NH-C_6H_5$, $-\overset{\overset{S}{\parallel}}{C}-NH-CH_2-CH=CH_2$, $-CH=N-C_6H_5$, or $-N=N-C_6H_5$. Of this group of compounds, the benzoyl derivative (XXIV) was the most promising.



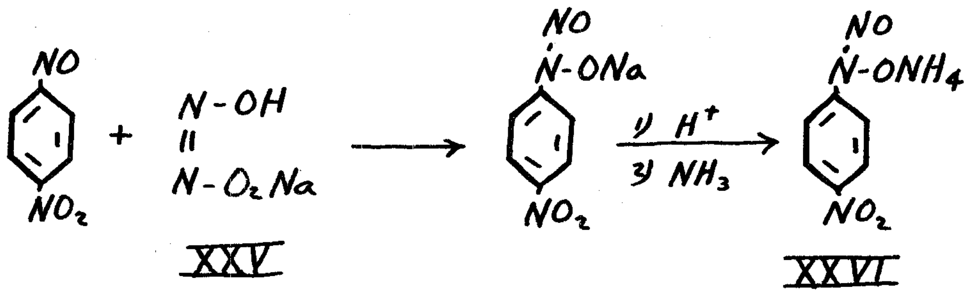
$$C_6H_5NHOH + C_6H_5\overset{\overset{O}{\parallel}}{C}-Cl \xrightarrow{NaHCO_3} C_6H_5\overset{O=\underset{|}{C}-C_6H_5}{N}-OH + C_6H_5\overset{O=\underset{|}{C}-C_6H_5}{N}-O\underset{\underset{O}{\parallel}}{C}-C_6H_5$$

$$C_6H_5\overset{\overset{\overset{O}{\parallel}}{C}-C_6H_5}{\overset{|}{N}}-OH + C_6H_5\overset{O=\underset{|}{C}-C_6H_5}{N}-O\overset{\overset{O}{\parallel}}{C}-C_6H_5 \xrightarrow{NH_4OH} C_6H_5\overset{\overset{\overset{O}{\parallel}}{C}-C_6H_5}{\overset{|}{N}}-ONH_4 \xrightarrow{H^+} C_6H_5\overset{\overset{\overset{O}{\parallel}}{C}-C_6H_5}{\overset{|}{N}}-OH$$

XXIV

This compound, previously prepared by several workers, was prepared by Shome (49) by the reaction of phenylhydroxylamine with benzoyl chloride in alkaline solution. The resulting mixture of mono- and di-benzoyl derivatives was treated with ammonium hydroxide, which dissolves only the N-benzoylphenylhydroxylamine. Neutralization of the ammonium hydroxide solution with dilute acid gives the desired product (XXIV). This reagent is said (49) to have many desirable properties, such as stability toward heat, light, and air, (it keeps indefinitely), solubility in hot water, tendency of metal precipitates to become granular upon heating, and formation of metal precipitates not contaminated with the reagent when the precipitation is carried out in hot solution. The reagent was tested and found suitable for quantitative determination of copper, iron, aluminum, or titanium (49). The copper, iron, and aluminum precipitates could be weighed directly, but the titanium precipitate had to be ignited to titanium oxide before weighing.

Bigiavi and Franceschi prepared several cupferron analogues, notably " para-nitrocupferron " (XXVI)(50), and made tests for complex formation involving several metal ions, including silver, barium, sodium, ferric, copper, nickel, and cobalt. The preparation of the

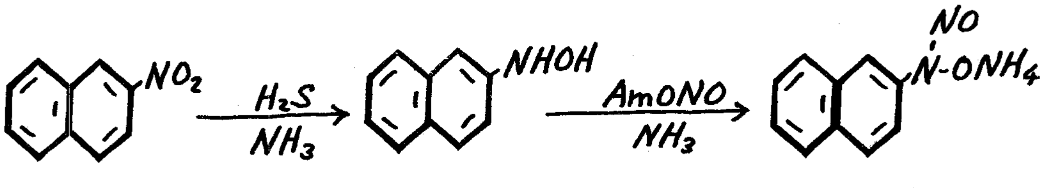


XXV

XXVI

cupferron analogues was accomplished by the action of the sodium salt of nitrohydroxylaminic acid (XXV), or hydroxylamine and sodium ethoxide, on the appropriate nitro- or nitroso-substituted benzene nucleus (50). " Para-nitro-cupferron " was found to be unstable to light.

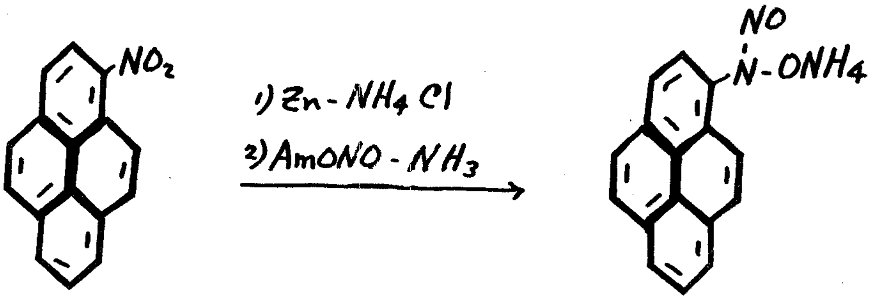
Baudisch also prepared "β-neocupferron" (XXVII) (51), the ammonium salt of nitroso-(β)-naphthylhydroxylamine, by reducing β-nitronaphthalene with ammonia and hydrogen sulfide, and treating the β-naphthylhydroxylamine so obtained with amyl nitrite in ammoniacal ether solution. He found that nitroso-(β)-naphthylhydroxylamine is more stable than the corresponding α-compound. The β-compound forms relatively stable complexes with iron, copper, and other metals (51); however, the α-compound (neocupferron) possesses greater reactivity and



XXVII

specificity (25). It was found that the β-derivatives of some metal ions differ from the cupferron derivatives in color and in ease of solubility in chloroform (51).

Lund and Berg prepared " pyrene cupferron"(XXVIII) (52) from 3-nitropyrene by reducing it in ether solution, (out of contact with air), with zinc dust and ammonium chloride, and then treating the ammoniacal filtrate with amyl nitrite. Pyrene cupferron was found to be unstable in air; it is readily oxidized to azoxypyrene (52).



XXVIII

II. Description of Experimental Work

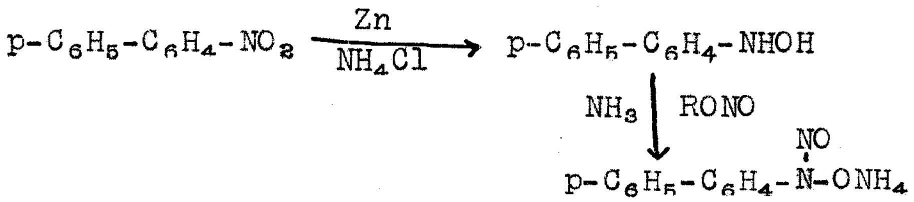
The introduction of cupferron as an analytical reagent and the subsequent development of neocupferron suggested the interesting possibilities of substituting the next larger aromatic nucleus to form a new cupferron analogue. The advantages over cupferron of neocupferron are chiefly due to the increased size and weight of the aromatic nucleus involved. A cupferron analogue containing the fluorene ring system would be expected to be a very sensitive reagent. Any differences noted in the complex compounds formed by such a new reagent add to the knowledge of the action of organic reagents.

The most logical approach to the problem was a study of the published preparation methods for cupferron, neocupferron, and cupferron analogues. The literature search revealed methods which could be useful in the preparation of the fluorenyl analogue. Laboratory evaluation of these methods was followed by the selection of a modified procedure which was used to prepare a quantity of the reagent adequate for establishing its identity and physical characteristics and investigating its possibilities as an analytical reagent.

Cupferron (26) was prepared quite easily through the reduction of nitrobenzene by zinc dust and ammonium chloride and treatment of the resulting phenylhydroxylamine with ammonia and n-butyl nitrite (55). The product, recrystallized from ethanol-ether solution, was in the form of colorless platelets. Cupferron is a salt of an organic compound, and decomposes upon heating, which characteristics make a melting point determination very difficult. The method of introducing the melting point tube into the melting point bath at a temperature just below the expected value gave a melting point for the author's preparation of cupferron of about 164-165°. A recrystallized commercial sample (Eastman Kodak) of cupferron behaved in a similar manner. The reported melting point of cupferron is 163-164° (16)(26).

The preparation of neocupferron was more difficult. Since an inadequate supply of the starting material, α-nitronaphthalene, was on hand, several methods of preparing this material were attempted, but with poor results. Finally the method of Fierz-David (53) was successfully utilized. The reduction of α-nitronaphthalene to α-naphthylhydroxylamine was attempted by the procedure of Wacker (27), using ammonium chloride and zinc dust, but the desired product could not be isolated. Reduction by ammonia and hydrogen sulfide (Willstätter)(54) gave a yellow product instead of the described "snow white" crystals of α-naphthylhydroxylamine. The yellow product was dissolved in ether and treated with ammonia and n-butyl nitrite (55), whereupon a nearly colorless precipitate of neocupferron was formed. This product in the form of a dilute (about 1%) aqueous solution was added to solutions containing the following metal ions; ferric, aluminum, copper, bismuth, cadmium, and tin. The precipitate formed by ferric ion was dark red and easily soluble in chloroform, while the precipitates given by the other ions were white or near-white.

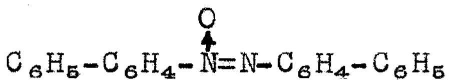
The literature search revealed that Gilman and Kirby (56) had reduced para-nitrodiphenyl to para-hydroxylaminodiphenyl, (para-xenylhydroxylamine), by zinc dust and ammonium chloride. It was thought that useful experience could be gained from carrying out this reduction and subsequently attempting to prepare a para-diphenyl analogue of cupferron (XXIX). The reduction, carried out in ethanol solution according to the method of Gilman and Kirby (56) yielded a product which reduced Fehling's solution and also gave a positive Tollen's test. This material, in ammoniacal ether solution, reacted with n-butyl nitrite to form a light yellow precipitate. Recrystallization from ethanol-ether solution gave a light yellow solid which melted, with decomposition, at 150-151° (uncorrected). The product in very dilute aqueous solution formed precipitates when added to ferric, copper, cadmium, and bismuth solutions. The ferric



$$\begin{tikzcd} p\text{-}C_6H_5\text{-}C_6H_4\text{-}NO_2 \arrow[r, "Zn", "NH_4Cl"'] & p\text{-}C_6H_5\text{-}C_6H_4\text{-}NHOH \arrow[d, "NH_3"', "RONO"] \\ & p\text{-}C_6H_5\text{-}C_6H_4\text{-}\overset{NO}{N}\text{-}ONH_4 \end{tikzcd}$$

XXIX

precipitate (brown) and the bismuth precipitate (off-white) dissolved readily in chloroform to give clear solutions, while the copper and cadmium precipitates (white) formed cloudy suspensions in chloroform. Preliminary tests using aqueous and ethanol solutions of the para-diphenyl reagent indicate that it might be used as a precipitant in the quantitative determination of iron and copper. The method of preparation of ” pyrene cupferron” used by Lund and Berg (52) suggested a new procedure that could be applied in making the para-diphenyl analogue of cupferron. The reduction of para-nitrodiphenyl was accomplished in an aqueous ether solution by means of zinc dust and ammonium chloride. The supernatant ether solution from the reduction mixture was treated with ammonia and n-butyl nitrite to give the desired product. The intermediate para-diphenylhydroxylamine is easily oxidized in air to form p,p’-azoxydiphenyl (XXX), which is described by Gilman (56) as a yellow solid melting at 207.5° (uncorrected). A by-product of the author’s



$$C_6H_5-C_6H_4-\overset{\overset{O}{\uparrow}}{N}=N-C_6H_4-C_6H_5$$

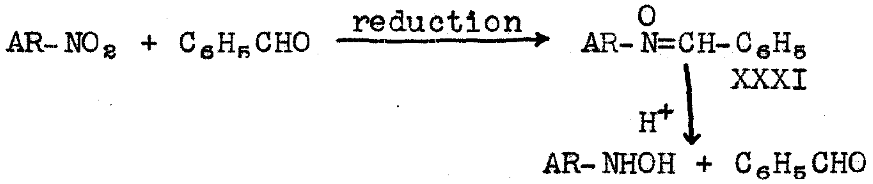
XXX

reduction of p-nitrodiphenyl, recrystallized from acetic acid, was in the form of bright yellow platelets which melted at 211-213° (uncorrected). This by-product contained 8.4% nitrogen (Dumas), while p,p'-azoxydiphenyl has a calculated nitrogen content of 8.0%.

The starting material for the preparation of the fluorenyl analogue of cupferron was 2-nitrofluorene, made by the method of Schulman (57). The attempt to reduce 2-nitrofluorene by means of ammonia and hydrogen sulfide failed; about 98% of the starting material was recovered from the reaction mixture. This result was not surprising, as Cislak (58) had found that 2-nitrofluorene is not reduced to the corresponding amine by boiling with ammonium sulfide.

A preliminary investigation of the method of Bigiavi and Franceschi (50), which involves the reaction of an aromatic nitro compound with hydroxylamine in the presence of sodium ethoxide, was unsuccessful and appeared impractical for the preparation of the fluorene analogue of cupferron.

Gilman (56) and Gatterman (59) found that an aromatic nitro compound when reduced in the presence of benzaldehyde forms a nitrone (XXXI). The nitrone can



$$AR\text{-}NO_2 + C_6H_5CHO \xrightarrow{\text{reduction}} AR\text{-}\overset{O}{N}{=}CH\text{-}C_6H_5 \quad \text{XXXI}$$

$$\xrightarrow{H^+} AR\text{-}NHOH + C_6H_5CHO$$

be decomposed by treatment with dilute acid, and the aromatic hydroxylamine compound recovered after removing the benzaldehyde through steam distillation. An acetic acid solution of 2-nitrofluorene and benzaldehyde was treated with zinc dust, and the solid reduction product was treated with dilute hydrochloric acid and steam distilled. The residue from the steam distillation was dissolved in toluene and the solution was treated with ammonia and n-butyl nitrite; only a very little, dark-colored precipitate was formed. A yellow solid was isolated from the reduction mixture, which upon recrystallization from chlorobenzene gave yellow-gold platelets which melted at 264-265° (uncorrected). The melting point and nitrogen*

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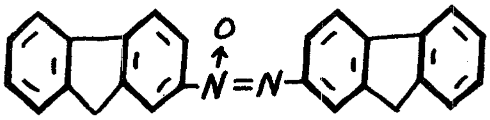
* The modified Dumas nitrogen analysis used by the author employed dry ice as the source of carbon dioxide (60). The combustion tube, nitrometer, and analytical procedure were as described in the literature (60), but the volume of carbon dioxide used was determined by timing the rate at which bubbles appeared in the nitrometer,(no gasometer was used).

analysis indicated that this yellow product was 2,2'-azoxyfluorene (XXXII)(58) instead of the expected nitrone.

It was next decided that only a determined and continued study of the application of one method at a time would bring successful results. The method of Lund and Berg, (reduction by zinc dust and ammonium chloride in ether solution)(52), was thought to be the most promising. The limited solubility of 2-nitrofluorene in ether appeared to be a great disadvantage. It was found that 2-nitrofluorene is three times as soluble in dioxane as in ether, so the reduction was attempted in dioxane solution. It was noticed that the ammonium chloride largely precipitated out of the dioxane and water solution. and this is considered a contributing factor to the poor results obtained. In an aqueous ether mixture, the ammonium chloride mostly stayed in the water layer, and thus was in a more favorable condition for reaction with the zinc dust. Since aqueous dioxane-ether mixtures did not work well, the reaction was tried in a dilute ether solution, and the partial reduction of 2-nitrofluorene to its hydroxylamine analogue was successful. The intermediate reduction product, not isolated from the ether solution, was treated with ammonia gas and n-butyl nitrite to give the fluorene analogue of cupferron (XXXIII).

A series of reactions of this type gave infor-



XXXII

XXXIII

mation as to the best conditions and amounts of reactants to be used. Most of the reactions were run in an atmosphere of nitrogen to minimize side reactions, such as formation of 2,2'-azoxyfluorene (XXXII). The details of twenty-five runs are tabulated in the experimental section. It will be noted that the use of ether recovered from previous runs resulted in practically no yield of product. Also, the substitution of calcium chloride for ammonium chloride was not successful. The initial product (fluorene analogue of cupferron) from this method of preparation is a 35% to 48% yield of a light buff solid, which melts at about 200° with much decomposition. The light buff product after recrystallization from an ammoniacal methanol-ether solution gives a colorless powder which melts with decomposition at 201-202° (uncorrected). The Dumas procedure gave erratic results for nitrogen, so the ammonia content of the product was determined by titration of the ammonia liberated from a weighed sample by treatment with alkali, and also by direct titration of the product with standard acid solution. These procedures gave acceptable values for the ammonia content, and the carbon and hydrogen analyses (*) also were satisfactory. A small quantity of the red-brown ferric complex of the new reagent was prepared and recrystallized from a chloroform-petroleum ether solution. The dark-brown powdery product was analyzed for nitrogen and for iron with satisfactory results. The ferric complex showed signs of decomposition when heated, but failed to melt below 280°.

The unrecrystallized fluorene analogue is slightly soluble in water, forming a hazy, colorless solution or suspension. Methanol or ethanol dissolves the reagent to a greater extent, forming a clear, light yellow solution. A saturated methanol solution, (containing about 0.5 gram of reagent in 100 milliliters of solvent at 15°), was used in the quantitative analytical tests (Table II). The methanol solutions will keep, in the refrigerator, for two or three days without excessive decomposition. An aqueous solution of the reagent was used in the qualitative analytical tests (Table I).

A solution containing a known amount of ferric iron (0.997 mg./ml.) was prepared for use in the quantitative precipitation tests. Aliquots of this standard solution were analyzed using the author's preparation of cupferron and gave an average value for iron of

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[*] The carbon and hydrogen analyses were made by the Clark Microanalytical Laboratory in Urbana, Illinois.

0.980 mg./ml.. Aliquots of the iron solution were also analyzed using a methanol solution of the new fluorene reagent. The results of the analyses, carried out in the presence of various acids and added metal salts, and determinations using a very dilute sample of the known iron solution are given in Table II. Since hydrochloric and sulfuric acids were used in preparing the iron solution, silver, lead, barium, and strontium ions, (which would form slightly soluble precipitates), were not tested for interference in the iron determination. About 30 ml. of a methanol solution of the new reagent was used for each 5 mg. of iron to be precipitated. Precipitation of iron from solutions containing 5% (by volume) or more of concentrated sulfuric acid was incomplete. However, the iron remaining in the filtrate from such an incomplete precipitation, (containing a little less than 4% by volume of sulfuric acid), was completely precipitated by an additional 20 ml. of reagent solution. The addition of 24 mg. or more of $CuSO_4 \cdot 5H_2O$ interfered with the iron determination, even though the precipitate was washed with 6<u>N</u> ammonium hydroxide, which procedure has been recommended to free the ferric cupferrate precipitate from copper (26). Antimony, in small amounts, caused high results in the iron determination.

Table I

Precipitates of Various Metal Ions with the Fluorene Analogue of Cupferron

Metal Ion	Solution	Precipitate
Ferric	acid (HCl)	red-brown*
Silver	neutral	white
Copper	neutral	grey-white
Copper	acid (HCl)	grey-white
Mercurous	acid (HCl)	white
Mercuric	neutral	white
Stannous	neutral	white
Stannic	neutral	white
Cobalt	neutral	red-brown *
Cobalt	basic (NH_4OH)	red-brown
Nickel	sl. acid (HCl)	yellow-green
Lead	neutral	white *
Calcium	basic (NH_4OH)	white
Barium	neutral	white
Strontium	neutral	white
Manganese	sl. acid (HCl)	grey-white
Zinc	sl. acid (HCl)	white
Chromium	sl. acid (HCl)	grey-white
Thorium	neutral	white
Bismuth	acid (HCl)	white
Cadmium	acid (HCl)	white
Antimony	acid (HCl)	light yellow*
Arsenous	neutral	--none--
Sodium	sl. acid (HCl)	--none--
Potassium	sl. acid (HCl)	--none--

* Soluble in chloroform

Table II

Ml. of Iron Solution	Acid Present	Volume %	Total Volume of Solution in ml.	Metal Salt Added	Weight in mg.	Weight of ignited Residue Expressed as mg. Iron
10	HCl	12.5	200	----	---	10.4
10	HCl	12.5	200	----	---	10.2
5	H_2SO_4	8	100	----	---	1.7
5	H_2SO_4	5	100	----	---	3.9
5	Acetic	20	100	----	---	5.3
5	Acetic	20	100	----	---	4.9
5	HCl	6	1000	----	---	5.1
5	HCl	6	1000	----	---	5.1
5	HCl	10	100	$CaCl_2$	10	4.8
5	HCl	10	100	$MnSO_4 \cdot 4H_2O$	140	4.7
5	HCl	10	100	$NiSO_4 \cdot 6H_2O$	132	4.8
5	HCl	10	100	$CoSO_4 \cdot 7H_2O$	139	5.1
5	HCl	10	100	$ZnCl_2$	226	5.0
5	HCl	11	100	$K_2Cr_2(SO_4)_4 \cdot 24H_2O$	211	5.3
5	HCl	11	100	$HgCl_2$	103	5.3
5	HCl	10	100	$Al(NO_3)_3 \cdot 9H_2O$	276	5.2
5	HCl	10	100	$Cd(NO_3)_2 \cdot 4H_2O$	245	5.2
5	HCl	10	100	----	---	4.8
5	HCl	10	100	$CuSO_4 \cdot 5H_2O$	13	5.2
* 5	HCl	10	100	$CuSO_4 \cdot 5H_2O$	24	5.4
** 5	HCl	10	100	As_2O_3	40	4.8

* Precipitate washed with cold water and finally 20 ml. 6N NH_4OH.

** As_2O_3 dissolved in the concentrated HCl used. Precipitate washed with cold 2N HCl.

III. Experimental Details

Preparation of n-Butyl Nitrite The method described in the literature (55) was employed, using one-tenth quantities of reactants. A solution of 38 g. (0.55 mole) of sodium nitrite in 150 ml. of water was cooled to 0°. To this was added, with agitation, an ice cold solution of 10 ml. of water, 13.6 ml. (0,25 mole) of concentrated sulfuric acid, and 45.7 ml. (37.0 g., 0.50 mole) of n-butyl alcohol at such a rate that the temperature remained near 0°. The light yellow upper layer (product) which separated from the cold mixture was washed twice with 10 ml. portions of 2% sodium bicarbonate-25%sodium chloride solution, dried over anhydrous sodium sulfate, and stored in the refrigerator. The average yield of undistilled n-butyl nitrite was 41 g. or 80% of theory.

Preparation of Cupferron The method given by G.F. Smith (26) was followed, using one-tenth quantities of reactants. A mixture of 25 g. (0.47 mole) of ammonium chloride, 800 ml. of water, and 41.6 ml. (50.0 g., 0.41 mole) of nitrobenzene was treated with 62 g. (0.81 mole, based on 85% purity) of zinc dust which was stirred in at a rapid rate. The temperature rose to 65°. After the suspension had cooled to about 40°, it was filtered and the residue washed with 200 ml. of boiling water, and the combined washings and filtrate then saturated by the addition of solid sodium chloride, and cooled to 0°. Light yellow needles of phenylhydroxylamine separated. They were filtered off and weighed wet, and then shaken with 460 ml. of ether. The difference between the wet weight of phenylhydroxylamine and the weight of the separated aqueous layer from the ether extraction indicated that 31.5 g. (0.29 mole) of phenylhydroxylamine had been obtained, which corresponds to a yield of 71%.

The ether solution of phenylhydroxylamine, cooled to 0°, was saturated with ammonia gas, and 33 g. (0.32 mole) of undistilled n-butyl nitrite was added slowly, with stirring. The colorless precipitate was filtered off, washed with cold ether, and dried in air. The crystalline product, (cupferron), weighed 39 g., which corresponds to a yield of 87% from phenylhydroxylamine, or a 63% over-all yield from nitrobenzene. The product was stored in an amber bottle containing a lump of ammonium carbonate (26), which helped to prevent decomposition of the cupferron. Recrystallization from ethanol gave colorless platelets which decomposed on heating. Thus the melting point was difficult to determine, but was found to be about 164-165°*, (literature melting

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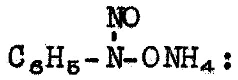
* All melting points are uncorrected unless noted.

point 163-164°)(16,26). Analysis: Calculated for  $C_6H_5\text{-}\overset{NO}{\overset{|}{N}}\text{-}ONH_4$: NH_3, 11.0%. Found: NH_3, 10.5%, 10.4%.

Preparation of α-Nitronaphthalene The method of Fierz-David (53) was used. A solution of 92 g. (1.45 moles) of concentrated nitric acid, 250 g. (4.52 moles) of concentrated sulfuric acid, and 62 ml. of water was kept between 30° and 40° during the slow addition of 132 g. (1.03 moles) of pulverized naphthalene. After the addition was complete, the mixture was kept at 50° for six hours, heated to 60° for one hour, the acid supernatant solution poured off, and the solid mass then melted with 400 ml. of water at 70°. The melting process was repeated with 300 ml. portions of 2% sodium carbonate solution until the wash solution was light yellow. After two more washings with water at 70°, the solid from the cooled mixture was dried in air and recrystallized from ethanol. The yield was 91 g. (51% of theory). The light yellow needles of α-nitronaphthalene melted at 55.5-57.0° (literature melting point, corrected, is 57.8°)(53).

Preparation of Neocupferron The reduction procedure of Willstätter (54) was followed. An ice cold solution of 20 g. (0.12 mole) of α-nitronaphthalene in 500 ml. of 95% ethanol was saturated with ammonia gas and hydrogen sulfide. The resulting mixture was kept at about 40° overnight, and then poured into 2 l. of ice water. The light yellow solid was washed with ice water, weighed wet, and then shaken with 200 ml. of ether. The difference between the wet weight of the product and the weight of the separated aqueous layer from the ether extraction indicated that a yield of 12.5 g. (0.08 mole) of α-naphthylhydroxylamine (68% of theory) had been obtained.

Nitrosation (26) was carried out by slowly adding 8.4 g. (0.08 mole) of undistilled n-butyl nitrite to the cold, ammonia-saturated ether solution of α-naphthylhydroxylamine. The resulting precipitate was filtered off, washed with cold ether, and dried in air. The light buff, unrecrystallized product melted at 115-118° with decomposition,(literature melting point 125-126°)(26). The material was stored in an amber bottle containing a lump of ammonium carbonate (26). The 14.5 g. of crude neocupferron obtained represented a yield of 88% from α-naphthylhydroxylamine or an over-all yield of 61% from α-nitronaphthalene.

Preparation of the para-Diphenyl Analogue of Cupferron

An agitated mixture of 5.0 g. (0.025 mole) of para-nitrodiphenyl, 1.0 g. (0.019 mole) of ammonium chloride and 3 ml. of water in 300 ml. of ether was kept at a temperature between 25° and 30° by means of a water bath while 5.0 g. (0.065 mole) of zinc dust was slowly added. The ether solution was decanted from the zinc residue, cooled in an ice bath, saturated with ammonia gas, and treated with 6.7 g. (0.065 mole) of undistilled n-butyl nitrite. The resulting precipitate was filtered off, washed with cold ether, and dried in air. The light yellow solid product, (1.5 g. or 26% of theory), was stored in an amber bottle containing a lump of ammonium carbonate.(26) The para-diphenyl analogue of cupferron, recrystallized from ethanol, melted at 150-151° with much decomposition.

A by-product of the reduction of para-nitrodiphenyl was thought to be p,p'-azoxydiphenyl (literature melting point 207.5°)(56). The by-product, when recrystallized from glacial acetic acid, yielded bright yellow platelets which melted at 211-213°. <u>Analysis-</u> Calculated for $C_6H_5\text{-}C_6H_4\text{-}\overset{\overset{O}{\uparrow}}{N}\text{=}N\text{-}C_6H_4\text{-}C_6H_5$: N, 8.0%. Found: N, 8.4%.

<u>Preparation of 2-Nitrofluorene</u> The method of Schulman (57) was used. A solution of 180 g. (1.08 moles) of a technical grade of fluorene in 1.5 l. of glacial acetic acid in a 3 l. beaker was heated to 60°, and 240 ml. (3.79 moles) of nitric acid (sp. gr. 1.42) was slowly added to the solution, which was stirred by a heavy duty mechanical stirrer. The solution temperature dropped slightly during the addition of the nitric acid, and a yellow precipitate formed. Then the temperature rose as the solid redissoloved to give a clear, red-brown solution, from which, in turn, a curdy, cream-colored solid separated.

The temperature of the very thick, pasty mixture was kept below 80° by rapid agitation. When the temperature had fallen to 60°, the solid was washed, (on the filter), with glacial acetic acid, sucked dry, washed twice by stirring with 1.5 l. of water and sucking dry on the filter, and then dried in air. The light buff product melted at 153-155°. It weighed 183 g., corresponding to a yield of 80% of 2-nitrofluorene. Recrystallization from glacial acetic acid gave an 88% yield of light buff, small needles which melted at 156.5-157.0° (literature melting point, 156-157°)(57).

Attempted Reduction of 2-Nitrofluorene by Ammonium Sulfide

A mixture of 24.4 g. (0.12 mole) of 2-nitrofluorene and 500 ml. of 95% ethanol was cooled in an ice bath and saturated with ammonia gas and hydrogen sulfide. After standing in the refrigerator for 12 days, the mixture was poured into 2 l. of ice water. The buff precipitate was filtered off, washed with ice water, sucked dry on the filter, and dried in air. The product, weighing 24 g., melted at 156-157°, and mixed with 2-nitrofluorene (melting point 156.5-157.0°) the melting point was 156-157°. This represented a 98% recovery of the starting material.

Reaction of Nitrobenzene with Hydroxylamine in the Presence of Sodium Ethoxide   Following the method of Bigiavi and Franceschi (50), 1.89 g. (0.08 mole) of sodium metal was dissolved in 100 ml. (78.9 g., 1.71 moles) of absolute ethanol, and 2.8 g. (0.04 mole) of hydroxylamine hydrochloride was added. The suspension was filtered, the filtrate cooled to 0°, and 2.44 g. (0.02 mole) of nitrobenzene added. The mixture was left in the refrigerator for 24 hours. A slight precipitate formed, but there was no other sign of reaction. When the mixture was carefully poured into water, heat was evolved, but no further precipitate was formed. The method was abandoned.

Reduction of 2-Nitrofluorene in the Presence of Benzaldehyde

A solution of 15.0 g. (0.07 mole) of 2-nitrofluorene and 7.6 g. (0.07 mole) of benzaldehyde in 2 l. of glacial acetic acid was slowly treated with 15.0 g. (0.195 mole) of zinc dust (85% pure). Care was taken that the temperature remained at about 30°. After standing for 45 minutes, the supernatant liquid was poured into about 3 l. of cold water. The dark colored precipitate was filtered off, washed with water, and dried in air. The dried product weighed 21.5 g., which compared fairly well with the theoretical yield of the expected nitrone (theory 20.3 g.). The dried product was added to 500 ml. of water and 1 ml. of concentrated hydrochloric acid, and the mixture was steam distilled. The odor of benzaldehyde was noted in the distillate. The distillation residue was extracted with one 300 ml. and three 75 ml. portions of toluene. The combined toluene extracts were filtered to give a clear, brown solution. The solution was treated with 4 ml. of concentrated ammonium hydroxide and about 25 ml. (23.5 g., 0.23 mole) of n-butyl nitrite, but none of the desired product, the fluorene analogue of cupferron, was isolated.

A portion of the dried product from a reduction of 5.0 g. (0.023 mole) of 2-nitrofluorene and 2.5 g. (0.024 mole) of benzaldehyde with 5.0 g. (0.065 mole) of zinc dust was extracted with 600 ml. of ether. The yellow solid recovered from the ether solution was recrystallized from toluene and then from chlorobenzene. The yellow platelets (0.5 g.) melted at 264-265°. The product may have been 2,2'-azoxyfluorene (58), which is reported to melt at 279° (corrected)(58). <u>Analysis</u>- Calculated for

$C_{13}H_9-\overset{\overset{O}{\uparrow}}{N}=N-C_{13}H_9$: N, 7.5%. Found: N, 7.8%.

Preparation of the Fluorene Analogue of Cupferron

Table III gives the details of twenty-five preparations of the fluorene analogue of cupferron. All but one of the reactions were carried out in a nitrogen atmosphere. A 500 ml. three-necked flask was fitted with a Hirsch stirrer (61), thermometer, and gas inlet and outlet tubes (61) arranged to permit sweeping the system with nitrogen, and prevent the entry of air during the reaction.

Table III

2-Nitro-fluorene used(g.)	Ether (ml.)	Temp. °C	Time (min.)	Zinc Dust (g.)	NH_4Cl Used (g.)	H_2O Added (ml.)	Yield	
							(g.)	(%)
5.3	300	25	60	5	1	3	0.5	8.2
1.0	250	26	38	1	1	3	0.1	8.7
1.0	250	25	7	1.5	1	4	0.2	17.4
1.0	250	27	81	1.5	1	4	0.1	7.8
1.0	300	20-28	45	3	1	3	0.27	23.4
2.0	350	15-20	60	5	1	6	0.16	6.9
*3.0	350	26	17	8	1	6	0.32	8.8
*2.0	350	24	9	5	1	6	0.02	0.9
*2.0	350	25	42	5	1	6	yellow needles ?	
2.0	100	27	38	5	2	10	0.25	10.9
1.5	300	23-27	22	3	2	10	0.50	28.9
1.5	300	25	18	3	3	10	0.83	48.0
**1.5	300	25-28	16	3	3	12	0.73	42.3
***4.0	700	23-28	25	8	8	35	very small	
4.0	700	22-25	20	8	4	18	1.29	28.0
4.0	700	22-24	26	10	4	18	1.42	30.8
***4.0	700	22-24	17	10	4	16	---	---
4.0	700	24	16	10	4	18	1.06	23.0
4.0	700	25-26	21	10	4	18	1.22	26.5
4.0	700	22-24	25	10	4	18	1.33	28.9
5.0	700	19-25	25	12	4	18	1.14	19.8
5.0	700	20-22	20	12	5	22	1.82	31.6
6.0	700	20-24	20	15	6	25	2.60	37.6
6.0	700	19-22	20	15	6	25	2.51	36.3
8.0	700	20-23	23	20	9	30	3.30	35.8

* (Ethyl nitrite used in nitrosation)
** (Run in presence of air)
*** (Recovered ether used)

To the agitated mixture of 2-nitrofluorene (6.0 g., 0.028 mole), 6.0 g. (0.11 mole) of ammonium chloride, and 25 ml. of water in 700 ml. of ether was slowly added, (over about 10 minutes), 15.0 g. (0.20 mole) of zinc dust, while the temperature was kept at about 20° by means of a water bath. When the reaction mixture became yellow and cloudy, the temperature was reduced to 5°, (ice bath), and when the solid matter had settled, the supernatant liquid was transferred by nitrogen pressure through a siphon tube onto a cotton filter and thence into the nitrogen-swept nitrosation flask. The cold, clear, yellow solution was saturated with ammonia gas and 8.0 ml. (7.5 g., 0.073 mole) of undistilled n-butyl nitrite was added; a practically colorless precipitate formed. The product (fluorene analogue of cupferron) was allowed to settle in the cold, filtered off, washed with cold ether, and dried in air. The light buff, crystalline product weighed 2.6 g. (38.0 % yield) and melted at about 200° with decomposition. It was stored in an amber bottle containing a lump of ammonium carbonate (26). Recrystallization from an ammoniacal methanol-ether solution gave a colorless powder which melted at 201-202° with decompostion. The melting point determination was carried out by using nitrogen-swept, sealed melting point tubes which were inserted into the melting point bath (Thiele tube) at various temperatures near 200°, so that decomposition would not interfere too much with the determination.

As the Dumas procedure failed to give a satisfactory value for total nitrogen in the product, the amount of nitrogen present as ammonia, (in the ammonium salt), was determined by two methods: a) using a micro-Kjeldahl distillation apparatus (60) the ammonia liberated by alkali from a weighed sample of the product was distilled into a 2% boric acid solution and then titrated, with standard hydrochloric acid, using a mixture of methyl red and brom-cresol green indicators b) a weighed sample of the product was crushed and mixed with 2% boric acid solution, and the mixture was titrated with standard hydrochloric acid, using methyl red and brom-cresol green as indicators. Method a) gave ammonia values of 6.3%, 6.5%, and 6.5%, while method b) gave values of 6.6% and 6.7%. Analysis- Calculated for $C_{13}H_9N(NO)ONH_4$: NH_3, 7.0%; C, 64.17%; H, 5.39%. Found- NH_3, 6.3, 6.5, 6.5, 6.6, 6.7% (average of NH_3-6.5%); C, 64.04%; H, 5.44%.

Preparation of Ethyl Nitrite The method of Slotta and Jacobi (18) was used. A solution of 5.0 g. (0.073 mole) of sodium nitrite and 8 ml. of water in 7 ml. (0.1 mole) of 95% ethanol was slowly treated with 18 ml. (0.108 mole) of 6N hydrochloric acid. The gaseous product was led through a tube into the solution to be nitrosated.

Preparation of the Ferric Complex of the Fluorene Analogue

A filtered methanolic solution of the fluorene analogue of cupferron was added to 200 ml. of a cold, acidified (HCl) 0.01 N solution of ferric chloride until no more precipitate formed. The red-brown solid was filtered off, washed with water, sucked dry, extracted with chloroform, and the chloroform solution dried over anhydrous sodium sulfate. Upon addition of ligroin (boiling point 40-60°) a very dark precipitate appeared. It was filtered off, washed with ligroin, and dried in air. The dark, red-brown powder did not melt below 280°, and gave the expected analyses for nitrogen (modified Dumas) and iron.

Analysis- Calculated for $[C_{13}H_9N(NO)O]_3Fe$: N, 11.5%; Fe, 7.64%. Found-N, 11.2, 11.1%; Fe, 7.41, 7.22%.

Determination of Iron in the Ferric Complex of the Fluorene Reagent A weighed sample was placed in a weighed porcelain crucible, treated with 4-5 drops of concentrated nitric acid, and heated very cautiously over a low flame. When the heavy brown smoke abated, the samples were carefully ignited to constant weight, and the iron content was calculated from the weight of the residue of ferric oxide.

Qualitative Tests of the Fluorene Reagent Dilute solutions of various metal ions were prepared and their pH determined (with Hydrion Paper). When adjustment of pH was desired, dilute hydrochloric acid or dilute ammonium hydroxide was used. An aqueous solution of the reagent was used, as the yellow alcohol solutions were misleading when precipitate colors were to be noted. In case of doubt as to color, the precipitate was filtered on paper and the color was then clearly evident against the white background. The ferric complex is undoubtedly very soluble in chloroform, while the cobalt, lead, and antimony complexes appear fairly soluble. The other metal ions formed precipitates with the fluorene analogue reagent which either formed suspensions in chloroform or were insoluble. Since the reagent itself is precipitated in an acid solution, tests on solutions having a low pH were avoided.

Quantitative Tests of the Fluorene Reagent A 7.0005 g. portion of recrystallized ferrous ammonium sulfate hexahydrate, $FeSO_4 \cdot (NH_4)_2SO_4 \cdot 6H_2O$, (calculated to contain 0.997 g. of iron), was dissolved in 350 ml. of water containing 70 ml. of 6N hydrochloric acid and 10 ml. of concentrated sulfuric acid. The clear solution was heated to boiling, and treated with 30% hydrogen peroxide (about 2.5 ml.) until a small drop of the solution gave no color with a freshly prepared, very dilute solution of potassium ferricyanide, showing the absence of ferrous ions.

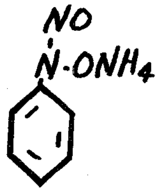
After the excess hydrogen peroxide was destroyed by boiling, the cooled solution was accurately diluted to 1,000 ml. to give a solution containing 0.997 mg./ml. of ferric iron.

A methanol solution of the fluorene reagent was prepared by crushing and grinding the solid reagent, (about a gram at a time), moistened with methanol, in a mortar and pestle, and then adding 100 ml. of methanol; the mixture was thoroughly agitated and then stored in the refrigerator until needed. Immediately before use, the mixture was filtered to give a clear, light yellow reagent solution. It was found that 100 ml. of methanol (cold) dissolves about 0.5 g. of the reagent. For the precipitation of 5.0 mg. of ferric iron, 30 ml. of this reagent was used; the theoretical volume of reagent solution required for 5.0 mg. of iron is 13 ml., (equivalent to 65 mg. of reagent), so a 130% excess of reagent was used. The iron precipitations were carried out in cold solutions containing filter pulp as filter aid (26). The iron solution, measured by pipette, was added to the filter pulp, and then the acid was added. In some cases a metal salt was also introduced. The solution was then adjusted to the final volume by the addition of distilled water. After the reagent solution was added, with stirring, the precipitate was allowed to coagulate, in the cold, for about three minutes. W. and R. Balston No. 40, 9 cm. ashless filter papers were used in the filtrations, which were carried out using cloth filter cones in glass funnels and using slight suction to facilitate filtration (26). The precipitates were washed, (usually with 100 ml. of cold water), and sucked as dry as possible on the filter. One of the precipitates formed in the iron solutions containing copper ions was washed, (on the filter), with 90 ml. of cold water and 20 ml. of 6N ammonium hydroxide, a procedure which allegedly removes copper from the cupferron precipitate of ferric iron (26). In the case of the fluorene reagent precipitate of iron, the copper apparently was not completely removed, and the appearance of a red-brown precipitate as the ammonium hydroxide wash solution mixed with the acid filtrate, (containing excess reagent), suggested that some of the iron precipitate was being dissolved by the ammonium hydroxide solution. The stirring rod and beaker used in each precipitation was wiped clean with a corner torn from the folded filter paper, and the scrap was added to the residue before careful ignition to constant weight in a weighed porcelain crucible. The weight of iron was calculated from the weight of the ignited residue of ferric oxide.

Several analyses of the known iron solution using the author's preparation of cupferron, (6% aqueous solution), gave iron values of 24.4, 24.5, 24.6, 24.6, and 24.3 mg. per 25.0 ml. of solution for an average of 24.5 mg. per 25.0 ml., or 0.98 mg./ml..

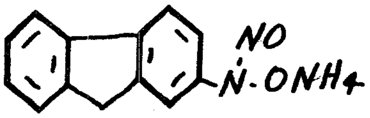
Summary

A. Two new analogues of cupferron (I) have been prepared. One, (II), containing the para-diphenyl radical, was produced through a series of known reactions and the product showed all the signs of a cupferron analogue. The other (III), containing the 2-fluorenyl radical, gave the correct analyses for nitrogen, (as ammonia given off from the ammonium salt), carbon, and hydrogen, and the ferric complex gave the correct values for iron and nitrogen (modified Dumas).



I

II



III

B. The para-diphenyl analogue (II) was used in qualitative tests with a few common ions, namely ferric, bismuth, cupric, and cadmium; precipitates were formed with all these ions.

C. The fluorene analogue (III) has been used in qualitative tests with several metal ions. This new reagent has also been used for the quantitative determination of iron (ferric) in the presence of various acids and also in the presence of several metal ions. The results have been satisfactory and indicate that further development of the use of the new fluorene analogue would be of interest. The new reagent behaves in many ways like cupferron, but is much more sensitive and exhibits a few differences in action which might well be investigated.

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