[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

The Chemistry of Oxamidines. I[1,2]

HENRY M. WOODBURN AND WARREN E. HOFFMAN[3]

Received June 13, 1957

Salts and metal complexes of oxamidines are described, and the behavior of oxamidines toward hydrolysis, aminolysis reduction, and the action of acylating agents and bifunctional compounds such as diamines, aminomercaptans, amino-alcohols, and aminophenols is discussed.

During our study of the reactions of cyanogen with organic compounds[4] a great many oxamidines, HN NH ‖ ‖ RNHC—CNHR, have been prepared. With the emphasis on cyanogen, however, scant attention has been paid to the chemistry of the products. The presence in oxamidines of amino and imino groups favorably located for mutual as well as independent action makes it desirable to learn how to take advantage of these reactive centers.

Aliphatic oxamidines are white, crystalline solids, stable at temperatures slightly above their melting points, or colorless liquids which decompose on distillation. Their solubility in water decreases with increasing molecular weight and becomes very small at C_4. They hydrolyze slowly in moist air.

Basic properties. (a) *Salt formation.* Salts having the general formula $(RNHC(=NH)—)_2 \cdot 2HX$ were formed with hydrogen chloride,[5] hydrogen bromide, nitric,[5] nitrous, carbonic, picric, and oxalic acids. Acetic and sulfuric acids gave unsatisfactory results. Except for the carbonates all of the salts were stable.

Evidence that at least one of these salts exists as a hydrate was obtained during the preparation of dimethyloxamidine dihydrochloride which repeatedly separated first as $(CH_3NHC(=NH)—)_2 \cdot 2HCl \cdot H_2O$ and formed the anhydrous material only on redissolving in ethanol and saturating with hydrogen chloride.

(b) *Formation of metal complexes.* From the admixture of ethanol solutions of nickelous or cupric chlorides with ethanol solutions of oxamidines, excellent yields of solid complexes having the general formula $(RNHC(=NH)—)_2 \cdot MCl_2 \cdot 2H_2O$ were produced. Manganese appeared to form $(RNHC(=NH)—)_2 \cdot MnCl_2 \cdot 4H_2O$ but attempts to obtain complexes of cobalt, chromium, and iron have thus far been unsuccessful. These reactions will be described more fully in a forthcoming paper.

Hydrolysis. Earlier work has shown that cold aqueous solutions of the free base, especially if small amounts of alkyl amine are present, hydrolyze to disubstituted oxamides. Refluxing, with or without amine, causes complete breakdown to unsubstituted oxamide and alkyl amine.

Aminolysis.[6] Woodburn, Morehead, and Chen studied the reaction of oxamidine hydrochlorides with alkyl amines. When the alkyl groups are the same in the oxamidine and in the amine, substitution of the imino hydrogens occurs resulting in tetraalkyloxamidines. If the alkyl group in the amine has a greater formula weight than the alkyl group in the oxamidine and steric effects are not predominant, an exchange occurs with the formation of a new disubstituted oxamidine. This is often followed by substitution of the imino hydrogens, the tetra substituted compound being the final product. No unsymmetrical oxamidine has yet been produced although a variety of methods has been studied in an attempt to produce one.

Acylation. One of the chemical reactions which oxamidines might be expected to undergo is that of acylation:

$$(RNHC(=NH)—)_2 + 2R'COCl \longrightarrow (RNHC(=NCOR')—)_2 + 2HCl$$

Our study indicates that this occurs only when the acylating agent is aromatic, such as benzoyl chloride or benzoic anhydride. If the acylating agent is aliphatic all oxamidines give the same product, namely a diacyloxamide:

$$(RNHC(=NH)—)_2 + 2R'COCl \longrightarrow (R'CONHC(=O)—)_2 + 2RNH_2 \cdot HCl$$

(1) From the dissertation submitted by Warren E. Hoffman in partial fulfillment of the requirements for the Ph.D. degree, June 1955.

(2) Presented in part at the 50th Anniversary Celebration of the Western New York Section of the American Chemical Society, November 1955.

(3) Present address, National Aniline Division, Allied Chemical and Dye Corp., Buffalo, N. Y.

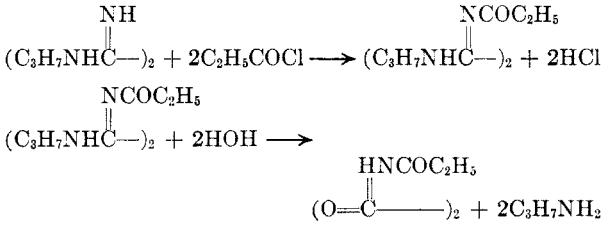
(4) Papers I–X of this series have appeared in *J. Org. Chem.* beginning with Volume 15 (1950).

(5) H. M. Woodburn, B. Morehead, and M. C. Chen, *J. Org. Chem.*, **15**, 535 (1950).

(6) H. M. Woodburn, B. Morehead, and M. C. Chen, *J. Org. Chem.*, **15**, 541 (1950).

Dipropionyloxamide, for example, resulted from the action of either propionyl chloride or propionic anhydride on dimethyl-, diethyl-, di-*n*-propyl-, diisopropyl-, di-*n*-butyl-, or di-*n*-amyloxamidine, and butyryl chloride or butyric anhydride gave di-*n*-butyryloxamide in every case from the same series.

The isolation of the aroyl derivative suggests that the mechanism of diacyloxamide formation includes the two steps of acylation and hydrolysis:



That the mechanism is not hydrolysis of the oxamidine to oxamide followed by replacement of alkyl by acyl, was demonstrated by refluxing dimethyl- and di-*n*-butyloxamides with propionic anhydride for twenty-four hours. The oxamide was recovered unchanged.

The reaction of acetyl chloride was too vigorous to control and acetic anhydride gave inconsistent results. In the two cases where crystals were obtained they corresponded in analysis to diacetyloxamide. Often, however, only red-brown or black solutions were obtained which became tars on distillation.

Reduction. Every method of reduction so far attempted has failed. O'Gee[7] used hydrogen and a catalyst at greater than atmospheric pressure and recovered the oxamidine unchanged. We have had a similar experience with lithium aluminum hydride and with sodium and acetic acid in ether. The only statement that can be made with assurance is that oxamidines are strongly resistant to reduction.

Reactions with bifunctional compounds. Study of cyanogen reactions has shown that bicyclic compounds result from properly constituted diamines[8,9] and mercaptans.[10] The same, or similar compounds result from the interaction of oxamidines with many bifunctional compounds. Table I compares the result of direct cyanogenation with the oxamidine reaction for a number of cases.

The majority of the reactions described in this paper were carried out with di-*n*-butyloxamidine because a simple change in the preparative procedure (described in the Experimental Section) resulted in an increase in yield of this compound from the original 30%[6] to 70%.

(7) R. C. O'Gee, unpublished work, University of Buffalo.

(8) H. M. Woodburn and R. C. O'Gee, *J. Org. Chem.*, **17**, 1235 (1952).

(9) H. M. Woodburn and J. R. Fisher, *J. Org. Chem.*, **22**, 895 (1957).

(10) H. M. Woodburn and B. G. Pautler, *J. Org. Chem.*, **19**, 863 (1954).

EXPERIMENTAL

sym-Dialkyloxamidines and their hydrochlorides were prepared by the method of Woodburn, Morehead, and Chen.[6] However, the existence of a hydrate of *sym*-dimethyloxamidine dihydrochloride was demonstrated for the first time and a marked improvement in the yield of di-*n*-butyloxamidine resulted from a change in procedure.

sym-Dimethyloxamidine dihydrochloride monohydrate. The free base, obtained in the prescribed manner[6] was dissolved in 95% ethanol and the solution saturated with dry hydrogen chloride. A white, curdy, non-crystalline solid separated, which was filtered, washed with ether, and recrystallized three times from ethanol. After drying in a vacuum desiccator it melted at 156–157°. The yield was 73%. The compound appeared to be perfectly stable, a two-year old sample having shown no signs of decomposition. The procedure was repeated four times with identical results.

Anal. Calcd. for $(C_4H_{10}N_4)_2 \cdot 2HCl \cdot H_2O$: C, 30.1; H, 7.5; N, 35.1; Cl, 22.3; molecular weight, 319. Found: C, 29.9; H, 8.2; N, 35.0; Cl, 22.2; molecular weight, 320.

If the monohydrate was dissolved in ethanol and the solution saturated with dry hydrogen chloride, a white, *crystalline* solid formed. After recrystallization from ethanol this melted at 289–291°C. and gave no melting point depression with a laboratory sample of *sym-dimethyloxamidine dihydrochloride.*

sym-Di-n-butyloxamidine. The following procedure gave greatly improved yields of this compound: A 33% aqueous solution of *n*-butylamine containing 73.1 g. (1.0 mole) of amine was placed in an ice bath and treated with purified cyanogen gas *until the solution started to turn milky* (slightly less than 0.5 mole). The reaction flask, still in the ice bath, was then closed with a mercury-sealed stirrer and the mixture thoroughly stirred for about one hour. During this time solid material separated and was filtered at the end of the process. Yields of 65–70% were obtained consistently. Stirring need not be commenced immediately after admission of the cyanogen but a delay of more than a few hours resulted in a decreased yield.

Effect of heat on sym-dibutyloxamidine. Three grams of di-*n*-butyloxamidine (m.p. 63°) in an open casserole was kept in an oven at 60–65° for several hours. The solid melted to a pale yellow liquid and solidified on cooling to a white solid melting at 62–63°. The recovered solid weighed 3.0 g.

Formation of salts. (*a*) *Picrates.* The hydrochloric acid salt of the oxamidine (0.1 g.) was dissolved in 10 ml. of water in an 8-inch test tube and the solution heated in a water bath to about 95°. Fifteen ml. of a saturated aqueous solution of picric acid was added, the tube shaken, and then left in the water bath for 15 min. The salt precipitated as the test tube cooled to room temperature. The product was filtered, washed several times with ether and dried in vacuo. Recrystallization was from ethanol. (The isopropyl derivative was too soluble to recrystallize well.) Table II lists the salts prepared.

The picric acid salts were soluble in hot ethanol and hot water and insoluble in ether, benzene, ligroin, and other common organic solvents.

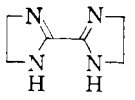
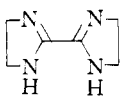
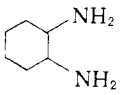
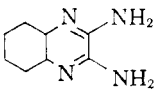
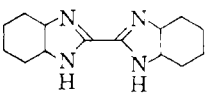
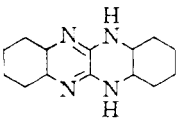
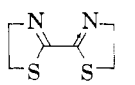
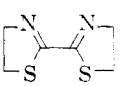
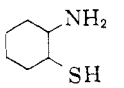
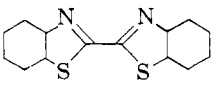
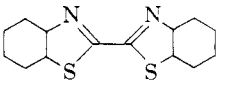
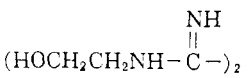
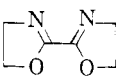
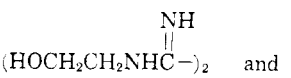
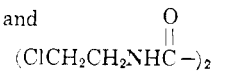
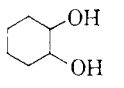
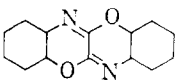
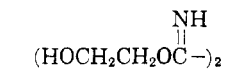
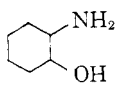
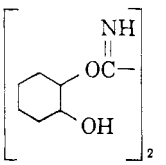
Additional salt-forming reactions were run with the purpose of proving the reaction rather than characterizing a long list of compounds. Only a few oxamidines were used and the salts were not analyzed.

Oxalates, hydrobromides, carbonates, and nitrites were formed from ether, ethanol or water solutions of the oxamidines, the precipitating agents being oxalic acid, hydrogen bromide, carbon dioxide, and sodium nitrite (followed by hydrogen chloride), respectively. All were white crystalline solids and stable in air, except for the carbonates which gradually decomposed to light brown liquids.

Several attempts with different oxamidines to produce acetates and sulfates were unsuccessful.

Reactions with acylating agents. (*a*) *With propionic anhydride.* Two grams of di-*n*-propyloxamidine dihydrochloride

TABLE I

Bifunctional Reagent	Product of Cyanogenation		Product of Oxamidine Reaction
$H_2NCH_2CH_2NH_2$		(ref.8)	
		(ref.11)	 and 
$HSCH_2CH_2NH_2$		(ref.10)	
		(ref.12)	
$HOCH_2CH_2NH_2$[a]		(ref.13)	  and 
	Unknown		 (?)[b]
$HOCH_2CH_2OH$		(ref. 14)	Unidentifiable mixture.
		(ref. 15)	Unidentifiable mixture.

[a] The bicyclic product could not be obtained from some lots of ethanolamine. We are searching for the catalyst or inhibitor which controls the process. [b] The product corresponded to a compound previously prepared by Kehrmann.[22] However, he failed to report the evidence on which he based the structure of his compound. The alternative possibility, bisbenzoxazole, has not been reported.

TABLE II

Properties of 

R	M.P., °C.	% Yield	% N Calcd.	% N Found
Methyl	226–228	73	24.5	24.3
Ethyl	210–213	71	23.3	23.1
n-Propyl	210–212	88	22.3	22.3
iso-Propyl	201–202	13	22.3	22.3
n-Butyl	208–210	70	21.3	21.3
n-Amyl	184–186	57	20.4	20.5
Phenyl	102	Very poor	—	—

was dissolved in water and neutralized with 0.1*N* sodium hydroxide. The free base was extracted by four 10-ml. portions of ether and the combined extracts placed in a flask in a hot water bath at 85–95°. An excess of propionic anhydride was added and the mixture shaken. In a few minutes the color of the liquid began to change, progressing through yellow to red, brown, and finally violet black. The flask was left in the water bath about one hour, then removed, covered, and allowed to come to room temperature. In about an hour crystals began to form. After standing overnight they were

(11) O. Hinsberg and E. Schwantes, *Ber.*, **36**, 4040 (1903).

(12) A. W. Hofmann, *Ber.*, **20**, 2251 (1887).

(13) E. L. Graminski, Ph.D. Thesis, University of Buffalo, June 1956.

(14) A. B. Whitehouse, unpublished work, University of Buffalo.

(15) G. Hahn and W. Leopold, *Ber.*, **68B**, 1976 (1935).

filtered, washed several times with ether, and recrystallized three times from ethyl acetate. They melted at 227–229° and gave no melting point depression with an authentic sample[16] of *dipropionyloxamide*. The solid was insoluble in water, ether, ethanol, benzene, ligroin, acetone, and cold ethyl acetate.

Anal. Calcd. for $C_8H_{12}N_2O_4$: C, 48.0; H, 6.0; N, 14.0; mol. wt., 200. Found: C, 48.1; H, 6.2; N, 14.0; mol. wt., 206.

The procedure was repeated for a series of oxamidines. The same product was isolated in every case. Mixed melting point determinations with the material obtained from di-*n*-propyloxamidine showed no depression nor did mixed melting points with an authentic sample of dipropionyloxamide. The product crystallized very slowly from the reaction mixtures of di-*n*-amyloxamidine (two days) and diisopropyloxamidine (one week). The yields for each oxamidine are given in Table III.

TABLE III

YIELD OF DIPROPIONYLOXAMIDE FROM VARIOUS OXAMIDINES

Oxamidine	% Yield	Oxamidine	% Yield
Dimethyl	30	Di-isopropyl	15
Diethyl	33	Di-*n*-butyl	38
Di-*n*-propyl	37	Di-*n*-amyl	34

It was also possible to obtain the product by adding propionic anhydride directly to the neutralized oxamidine salt, eliminating the ether extraction. Two layers formed. As soon as the top layer had become brownish red, it was separated and allowed to stand. Crystals of dipropionyloxamide (m.p. 227–229°) formed after an hour or two. Yields were approximately the same as those given above.

(*b*) *With propionyl chloride.* Substitution of propionyl chloride for the anhydride accelerated the reaction somewhat but gave slightly lower yields of the same product.

Mixing the reagents at a lower temperature slowed down the reaction. At 0° there was no perceptible color change and no crystals were obtained even after several days.

(*c*) *With butyric anhydride.* When butyric anhydride was reacted with di-*n*-propyloxamidine as in (*a*) above, the color change was considerably slower in coming and crystals required ten to twelve hours to appear. After two or three days the crystals were filtered and purified. They melted at 199–201° and gave no melting point depression with an authentic sample[17] of *di-n-butyryloxamide*. The yield was 25%.

Anal. Calcd. for $C_{10}H_{16}N_2O_4$: C, 52.6; H, 7.1; N, 12.3; mol. wt., 228. Found: C, 52.2; H, 7.2; N, 12.0; mol. wt., 225.

The same product was produced from the action of butyric anhydride on dimethyl-, diethyl-, and di-*n*-butyloxamidines. It was observed that in cases where the free base was used as such rather than as liberated by neutralization of the hydrochloride, a drop or two of sodium hydroxide solution was needed to bring about the reaction.

(*d*) *Butyryl chloride* gave the same product as the anhydride. The rates of reaction were similar.

(*e*) *With acetic anhydride.* Because of the vigor of this reaction it had to be carried out near 0°. The usual change in color occurred with di-*n*-propyloxamidine but from several runs crystals were obtained in only one case. These melted at 222–228° and were too few to recrystallize. No crystals were obtained from any of the other oxamidines by the method used in (*a*).

When an excess of acetic anhydride was added at room temperature to di-*n*-butyloxamidine (the free base) and the mixture allowed to stand for two days, a red color developed but no crystals. Ten ml. of water and ten ml. of ether were added and the whole mixture shaken thoroughly. The ether layer became red and the water layer light yellow. The two layers were separated. After three weeks a small amount of pink solid appeared in the ether solution. After filtration and several washings with ether it melted at 231–235°. There appeared to be no melting point depression with the crystals from (*e*). Recrystallization twice from ethyl acetate raised the melting point to 236–238°. The yield of *diacetyloxamide* was 6%.

Anal. Calcd. for $C_6H_8N_2O_4$: C, 41.9; N, 4.7; N, 16.2. Found: C, 41.7; H, 4.8; N, 16.2.

(*f*) The use of *acetyl chloride* was prohibited because the reaction proceeded at an uncontrollable rate.

(*g*) *With benzoic anhydride.* Two grams of di-*n*-butyloxamidine was dissolved in 25 ml. of ether. A solution of 9 g. of benzoic anhydride and 2 drops of aqueous sodium hydroxide in ether was added with vigorous shaking. A white, feathery solid separated. It was filtered, washed with ether and ethanol, and recrystallized from ethyl acetate. It melted at 207–209° with decomposition and represented an 87% yield of *N,N'-dibenzoyldibutyloxamidine*, $(C_4H_9NHC(=NBz)—)_2$.

Anal. Calcd. for $C_{24}H_{30}N_4O_2$: C, 70.9; H, 7.4; N, 13.8; mol. wt., 407. Found: C, 70.8; H, 7.5; N, 13.9; mol. wt., 403.

(*h*) *With benzoyl chloride.* Two grams of diethyloxamidine dihydrochloride was dissolved in water, neutralized, and extracted with ether as in (*a*). Two drops of concentrated aqueous sodium hydroxide was added, followed by an excess of benzoyl chloride. After vigorous shaking for a few minutes a white solid separated. This was filtered, washed with cold ethanol, and recrystallized from ethyl acetate. White needles, melting at 199–202° with decomposition, represented a 78% yield of *N,N'-dibenzoyldiethyloxamidine*, $(C_2H_5NHC(=NBz)—)_2$.

Anal. Calcd. for $C_{20}H_{22}N_4O_2$: C, 68.6; H, 6.3; N, 16.0; mol. wt., 350. Found: C, 68.9; H, 6.5; N, 15.7; mol. wt., 357.

With di-*n*-butyloxamidine, benzoyl chloride gave the same product as was obtained in (*g*).

Reactions with bifunctional reagents. (*a*) *Ethylenediamine.* Fifty ml. of an ethanol solution containing 5.4 g. (0.02 mole) of di-*n*-butyloxamidine dihydrochloride and 2.4 g. (0.04 mole) of ethylenediamine was heated to reflux. The solution turned yellow almost immediately and after refluxing four hours a white solid began to form. The evolution of a gas basic to litmus was also noted. The mixture was allowed to reflux thirty minutes after the evolution of gas had subsided. The white solid was filtered and washed several times with ethanol. It melted at 290° and gave no melting point depression with an authentic sample[8] of *bis*(Δ^2-*2-imidazolinyl*). The yield was almost quantitative.

The same compound was obtained from diethyloxamidine dihydrochloride and ethylenediamine[18] also in quantitative yield.

(*b*) *2-Mercaptoethylamine hydrochloride.* Fifty ml. of an ethanol solution containing 2.71 g. (0.01 mole) of di-*n*-butyloxamidine dihydrochloride and 2.27 g. (0.02 mole) of 2-mercaptoethylamine hydrochloride was refluxed for twenty-four hours. No solid had appeared, consequently water was added until a cloudiness remained. A brown solid settled out and was filtered and recrystallized from ethanol with Norite present as a decolorizer. The white product melted at 127–129° and gave no depression with an authentic sample[10] of bis(Δ^2-2-thiazolinyl). The yield was almost quantitative.

Di-*n*-butyloxamidine (the free base) gave the same prod-

(16) Th. Figee, *Rec. trav. chim.*, **34**, 294 (1915).

(17) J. Th. Bornwater, *Rec. trav. chim.*, **35**, 126 (1916).

(18) M. C. Chen, Ph.D. Thesis, University of Buffalo, February 1950.

uct in nearly quantitative yield. The yield from diethyloxamidine dihydrochloride was 81%.

(*c*) *Ethanolamine.* (1) Fifty ml. of ethanol containing 5.4 g. (0.02 mole) of di-*n*-butyloxamidine dihydrochloride and an excess of ethanolamine was refluxed for twenty-four hours and the reaction mixture allowed to stand until the next day. A light-brown solid was filtered and washed with ether, becoming almost white. It was recrystallized by dissolving in 25% ethanol and adding ether to induce crystallization. Fine white needles separated which melted at 210–212°. A mixed melting point with some independently synthesized[19] *bis*(Δ²-*2-oxazolinyl*) gave no depression.

Anal. Calcd. for $C_6H_8N_2O_2$: N, 20.0. Found: N, 20.0.

Some lots of ethanolamine did not give this reaction. We are searching for the catalyst or the inhibitor which controls the process.

(2) When an excess of ethanolamine was avoided, a white crystalline solid melting at 203° was obtained. A mixed melting point with some independently synthesized *β,β'-dichlorodiethyloxamide* gave no depression.

(3) When the equivalent amount of the free base (di-*n*-butyloxamidine) rather than the hydrochloride was used, not only was the bicyclic compound isolated, but in one week another product came out of the filtrate in small amounts. After filtration and washing with ether it melted at 120–127° and was quite soluble in water and alcohol. It gave a melting point depression with the diethanoloxamide but no depression with bis(2-hydroxyethyl) oxamidine, $(HOCH_2CH_2NC(=NH)-)_2$, recently synthesized by Graminski.[13]

(*d*) *Ethylene glycol.* A mixture of 20 ml. of ethylene glycol and 6.4 g. (0.03 mole) of di-*n*-butyloxamidine was heated cautiously on a hot plate until the oxamidine dissolved. A yellow solution resulted. No change occurred on standing for 1 hr. On heating gradually to 115° the color became orange and later brown. After standing several days at room temperature a few crystals were noted. These disappeared before they could be filtered.

Refluxing the same reagents for 24 hr. gave a viscous mixture which could not be filtered. The hydrochloride gave the same results as the free base.

(*e*) *o-Phenylenediamine.* (1) A solution of 2.0 g. (0.01 mole) of di-*n*-butyloxamidine and 3.0 g. (0.027 mole) of *o*-phenylenediamine in 45 ml. of a 2:1 mixture of nitrobenzene and ethanol was refluxed for 24 hr. and then allowed to stand one day. Distillation of the solvents left a mass of orange needles. Four recrystallizations from boiling acetic acid produced golden yellow needles which did not melt up to 541° but showed signs of decomposition at about 410°. The yield of $C_{14}H_{10}N_4$, proved by ultraviolet spectrum analysis (see Figures 1–4) to be a mixture of bisbenzimidazole and fluoflavin, was 76%.

Anal. Calcd. for $C_{14}H_{10}N_4$: C, 71.9; H, 4.3; N, 23.9; mol. wt., 234. Found: C, 71.8; H, 4.3; N, 23.8; mol. wt., 234.

(2) A solution of 1.42 g. (0.01 mole) of diethyloxamidine and 3.0 g. (0.027 mole) of *o*-phenylenediamine in 45 ml. of a 2:1 mixture of nitrobenzene and ethanol was refluxed for 24 hr. After two days at room temperature, the solvents were stripped off leaving a black residue. This was dissolved

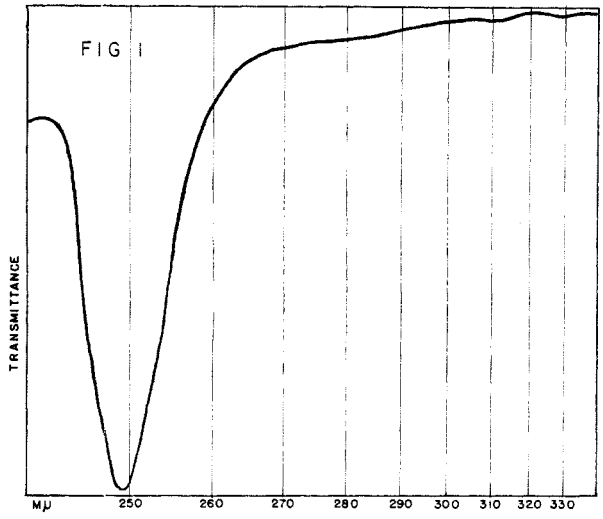


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRUM of pure fluoflavin. λ_{max} 249 mμ; ϵ_{max} 72,000.

(19) H. Wenker, *J. Am. Chem. Soc.*, 60, 2152 (1938).

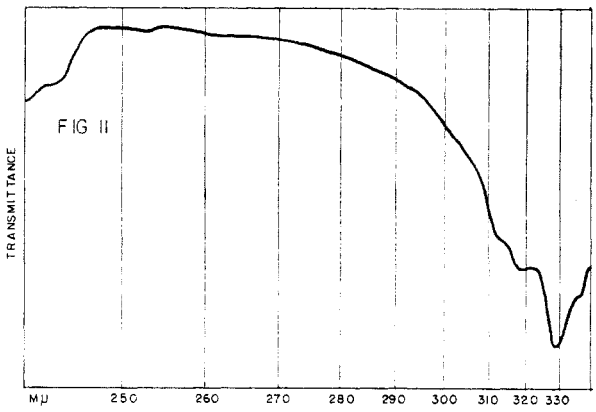


FIG. 2. ULTRAVIOLET ABSORPTION SPECTRUM of pure bisbenzimidazole. λ_{max} 329 mμ; ϵ_{max} 42,000.

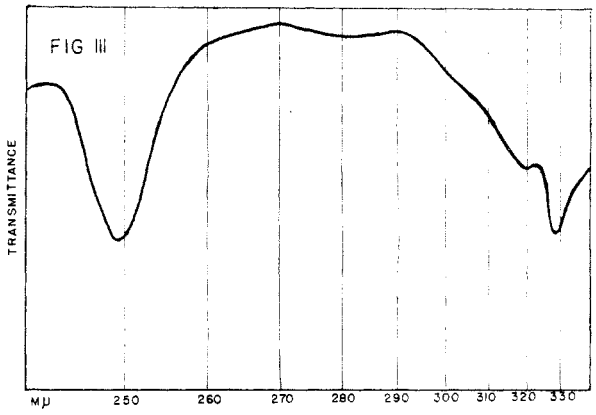


FIG. 3. ULTRAVIOLET ABSORPTION SPECTRUM of the product from the reaction of *o*-phenylenediamine and dibutyloxamidine.

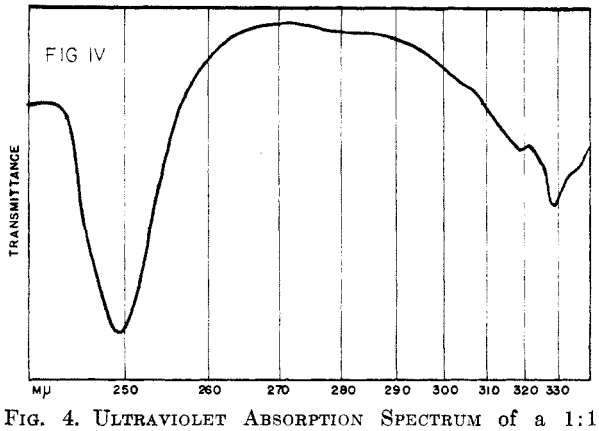


FIG. 4. ULTRAVIOLET ABSORPTION SPECTRUM of a 1:1 mixture of pure fluoflavin and pure bisbenzimidazole.

in boiling acetic acid, decolorized with Norite, and recrystallized twice from acetic acid. Golden-yellow needles of $C_{14}H_{10}N_4$ were obtained in 70% yield.

(*f*) *2-Aminobenzenethiol.* (1) A solution of 2.0 g. (0.01 mole) of di-*n*-butyloxamidine in an excess of 2-aminobenzenethiol was boiled in a covered beaker for 15 min. Shimmering crystals separated from the orange-brown solution. They were recrystallized from toluene with Norite present and melted at 303–306°. A mixed melting point with an authentic sample[12] of *bisbenzothiazole* gave no depression. The yield was 80%.

(2) The preparation was repeated using diethyloxamidine. A yield of 73% of bisbenzothiazole was obtained.

(*g*) *o-Aminophenol.* Fifty ml. of nitrobenzene containing 8.5 g. (0.042 mole) of di-*n*-butyloxamidine and 10.0 g. (0.091 mole) of *o*-aminophenol was refluxed for 24 hr. A white solid collected in the condenser. It weighed 1.7 g. and melted at 83–90°. It had the odor of butylamine but was not identified further. A mass of orange-brown crystals deposited in the reaction flask after cooling. These were filtered and washed several times with ether. The mother liquor from the reaction flask was evaporated to about one tenth its volume, producing more crystals. The combined yield was 90%. After two recrystallizations from ethanol the solid melted at 259–260°. A mixed melting point with an independently synthesized sample of Kehrmann's *diphendioxazine*[23] gave no depression.

Anal. Calcd. for $C_{14}H_8N_2O_2$: C, 71.2; H, 3.4; N, 11.9; mol. wt., 236. Found: C, 71.1; H, 3.4; N, 11.9; mol. wt., 233.

(*h*) *Catechol.* Fifty ml. of nitrobenzene containing 8.0 g. (0.04 mole) of di-*n*-butyloxamidine and 8.8 g. (0.08 mole) of catechol was refluxed for 24 hr. A very viscous mixture resulted which upon filtration (over 10 hr.), yielded a brownish solid which appeared crystalline but did not melt up to 365°. Upon standing, this solid turned black, resembling charred wood. None of the common organic solvents would dissolve it.

This experiment was repeated five times, varying the time of reflux, etc. The results were identical.

Dipropionyloxamide was prepared from propionamide and oxalyl chloride according to the method of Figee.[16] A 64% yield of white crystals melting at 226–229° was obtained. Figee recorded a melting point of 216°.

Anal. Calcd. for $C_8H_{12}N_2O_4$: N, 14.0. Found: N, 14.0.

Di-n-butyryloxamide was prepared from butyramide and oxalyl chloride according to the method of Bornwater.[17] White needles melting at 198–201° with decomposition were obtained in 57% yield.

Anal. Calcd. for $C_{10}H_{16}N_2O_4$: N, 12.3. Found: N, 12.4.

Diacetyloxamide. A solution of 4.72 g. (0.08 mole) of acetamide and 5.08 g. (0.04 mole) of oxalyl chloride in 100 ml. of pure, dry benzene was refluxed for 24 hr. No product could be isolated. The preparation was attempted three times without success.

Dibenzoyloxamide. Three attempts to prepare dibenzoyloxamide by refluxing benzamide and oxalyl chloride in benzene failed.

Bisbenzothiazole. Thirty ml. of ethanol containing 6.3 g. (0.05 mole) of 2-aminobenzenethiol was saturated with cyanogen at 0°.[12] The mixture was kept in the ice box overnight and then filtered. Two recrystallizations from toluene, using Norite for decolorization, produced shimmering white flakes which melted at 304°. The yield was 53%.

Bisbenzimidazole.[23] To a solution of 21.8 g. of *o*-nitroaniline in 200 ml. of ether was added 10 g. of oxalyl chloride. A yellow solid began to form almost immediately. The mixture was refluxed for several hours. Filtration gave a yellow solid which melted at 302–324° with decomposition compared to a literature value of 331° for 2,2′-dinitroörthooxanilide.[18] Without further purification, a mixture of 13.0 g. of this substance, 200 ml. of acetic acid, and a slight excess of finely granulated tin was refluxed for about 30 hr. Two yellow solids were isolated from the reaction mixture. Bisbenzimidazole, the main product, was recrystallized from acetic acid. Evaporation of the mother liquor from the reaction mixture gave additional solid which resulted in a final yield of 33%. The compound did not melt up to 365°. The ultraviolet spectrum of an acetic acid solution of the compound is shown in Figure 2.

The second yellow solid was identified through its picrate as *o-benzimidazole.* The picrate melted at 223° (lit. 225–226°).

Fluoflavin. A mixture of 10.8 g. of *o*-phenylenediamine and 4.5 g. of oxalic acid in 120 ml. of 4*N* HCl was refluxed for two hours.[24] The green solid which formed was filtered, washed with water, and dried *in vacuo.* It represented an almost quantitative yield of *2,3-dihydroxyquinoxaline.*

A mixture of 5.7 g. (0.036 mole) of 2,3-dihydroxyquinoxaline and an excess of phosphorus pentachloride was heated to 160° and held there for 15 min. The melt was allowed to crystallize to a brownish yellow solid. Recrystallized from ethanol, the *2,2′-dichloroquinoxaline* melted at 150°.

(1) Following the method of Hinsberg and Pollack[25] a 1:2 mole mixture of 2,2′-dichloroquinoxaline and *o*-phenylenediamine containing some rock salt as a dispersing medium was heated to about 125° and held at that temperature for about 15 min. The product was boiled in water and washed with ethanol and cold acetic acid. Recrystallization from boiling acetic acid gave golden yellow needles of *fluoflavin* in 5% yield.

(2) A second method of preparation was discovered in this work. To an ethanol solution of dichloroquinoxaline was added *o*-phenylenediamine in a 1:2 ratio. The mixture was heated to boiling for 15 min. Filtration, followed by recrystallization of the solid product gave golden yellow needles of fluoflavin.

(3) An ethanol solution of diaminoquinoxaline, prepared from *o*-phenylenediamine and cyanogen after the method of Bladin,[26] and *o*-phenylenediamine was refluxed for 24 hr. with agitation. After cooling, the mixture was filtered and the solid recrystallized from boiling acetic acid. A yield of 57% of fluoflavin resulted. The ultraviolet spectrum of an acetic acid solution of the compound is shown in Figure 1.

Diphendioxazine.[22] Kehrmann's method for the production of diphendioxazine was followed to the extent that his directions could be understood. A mixture of 6.3 g. (0.05 mole) of oxalic acid, 10.9 g. (0.10 mole) of *o*-aminophenol, and 10.0 g. of benzoic acid was heated at a maximum temperature of 200° for 15 min. The melt was poured into double its volume of ethanol, mixed thoroughly, and the solid filtered. This was washed with 0.1*N* NaOH, water, and ethanol. Recrystallization from ethanol with Nuchar gave a white solid melting at 258–260°.

Bis(Δ^2-*2-oxazolinyl*).[20] Twenty grams of diethanoloxamide, prepared from diethyloxalate and ethanolamine, was dissolved in 100 ml. of toluene and treated with 42 g. of thionyl chloride. The mixture was heated at 60° for 30 min. and at the boiling point for 90 min. more. White, crystalline β,β'-dichlorodiethyloxamide was filtered, washed with water and ethanol, and dried *in vacuo.* It melted at 200–203° (lit. 203°). The yield was 80%.

Following Wenker's method,[19] 10.6 g. (0.05 mole) of β,β'-dichlorodiethyloxamide was dissolved in 100 ml. of 1*N* methanolic KOH and boiled for 1 hr. The solution was fil-

(20) L. Knorr and P. Rössler, *Ber.*, **36**, 1278 (1903).

(21) The assistance of Mr. Richard Van Deusen in obtaining these curves is gratefully acknowledged.

(22) F. Kehrmann and C. Bener, *Helv. Chim. Acta*, **8**, 16 (1925).

(23) H. Hubner, *Ann.*, **209**, 370 (1881).

(24) M. A. Phillips, *J. Chem. Soc.*, (1928) 2393.

(25) O. Hinsberg and J. Pollack, *Ber.*, **29**, 784 (1896); O. Hinsberg, *Ann.*, **319**, 267 (1901).

(26) J. A. Bladin, *Ber.*, **18**, 672 (1885).

tered and the solid washed with cold methanol. The combined filtrates were evaporated to dryness and the residue taken up in water. Bis(Δ^2-2-oxazolinyl), melting at 210–213°, was obtained by adding sufficient alcohol to make the solution 25% and then ether to give a permanent cloudiness. An 87% yield of white needles resulted.

Ultraviolet absorption spectra were obtained with a Beckmann DK 2 Spectrophotometer. Acknowledgment is made of the gift of certain chemicals as follows:

2-Mercaptoethylamine hydrochloride from Evans Chemetics, Inc., 2-aminobenzenethiol from American Cyanamide Co., *o*-nitroaniline from National Aniline Division, Allied Chemical and Dye Corp.

BUFFALO, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE AND THE BIOMEDICAL RESEARCH GROUP, LOS ALAMOS SCIENTIFIC LABORATORY, UNIVERSITY OF CALIFORNIA]

Substituted 4,7-Phenanthrolines and Benzo[*f*]quinolines as Scintillation Solutes

RICHARD H. WILEY, C. HARRY JARBOE, JR., AND F. N. HAYES

Received June 26, 1957

A new synthesis for 4,7-phenanthroline based on *N,N'*-diacetyl-*p*-phenylenediamine has been developed. In reactions with aryllithium reagents it has been shown that 4,7-phenanthroline undergoes mono- and disubstitution reactions at positions 3 and 8. In this manner the 3,8-diphenyl, 3-phenyl, 3-(*p*-tolyl), and 3-*p*-dimethylaminophenyl derivatives of 4,7-phenanthroline have been prepared. In each case the intermediate dihydro compound was isolated. These compounds and the analogous benzo[*f*]quinolines have been evaluated as scintillation solutes. Their behavior as solutes in liquid scintillation systems is shown by calculation and actual light output to involve considerable self-quenching. The 650 cm.$^{-1}$ to 900 cm.$^{-1}$ region of the infrared spectrum has been analyzed for each of the benzo[*f*]quinolines and 4,7-phenanthrolines and is shown to be composed of vibrational frequencies due to the individual aromatic rings involved.

Those substances which have been shown to function most efficiently as solutes in liquid scintillation counting systems are structurally simple materials built up of aromatic rings in continuous conjugation. For example, *p*-terphenyl and 2-phenyl-5-(*p*-biphenylyl)oxazole are excellent solutes for liquid scintillation systems. In compounds like 4,7-phenanthroline and benzo[*f*]quinoline which possess phenanthrene-like structures there exists the possibility of building up molecules containing a similar arrangement of rings in continuous conjugation; however, such materials have thus far not been evaluated as scintillator solutes. In this report we wish to describe the preparation and discuss the relative pulse heights of a series of new mono and disubstituted 4,7-phenanthrolines and the corresponding 3-substituted benzo[*f*]quinolines.

Phenanthrolines containing the desired substituents in either or both the 3 and the 8 positions are theoretically available by a number of routes involving either the well-known ring formation reactions[1] of quinoline chemistry or by direct addition to the azomethine bond of the phenanthroline. In view of its generality of application to aromatic bromine compounds the addition of aryllithium reagents to 4,7-phenanthroline was considered to be the best synthetic approach to obtaining such structures. This necessitated a source of 4,7-phenanthroline which is reported to be available from *p*-phenylenediamine,[2] 6-nitroquinoline,[3,4] or 6-aminoquinoline[5] by the Skraup reaction. In our hands none of these methods were reproducible so the development of a synthesis was undertaken. Conditions have been devised for the use of *N,N'*-diacetyl-*p*-phenylenediamine in the Skraup reaction which give reproducible 60-75% yields of 4,7-phenanthroline. The most efficient oxidizing mixture was found to be nitrobenzene and 96% sulfuric acid with ferrous sulfate as a moderator. In the absence of ferrous sulfate, extensive decomposition of the product takes place. The crude 4,7-phenanthroline was isolated as a black, intractable solid from which the pure material could not be isolated by steam distillation or recrystallization. Purification was, however, readily effected by extracting the crude product with ligroin in a Soxhlet extractor. The procedure described in the experimental section has repeatedly given yields of 60% or over.

The addition of aryllithium reagents to 4,7-phenanthroline was found to proceed smoothly and in good yields as indicated in Table I to yield substituted phenanthrolines according to diagram 1. As in other addition reactions of aryllithium reagents[6] it was found necessary to exclude rigidly all

(1) E. H. Woodruff and Roger Adams, *J. Am. Chem. Soc.*, **54**, 1977 (1932).

(2) C. R. Smith, *J. Am. Chem. Soc.*, **52**, 397 (1930).

(3) L. Haskelberg, *J. Am. Chem. Soc.*, **69**, 1539 (1947).

(4) E. Bornemann, *Ber.*, **19**, 2377 (1886).

(5) A. Kaufmann and R. Radosevic, *Ber.*, **42**, 2613 (1909).