Amide-Glyoxal Reaction Products[1]

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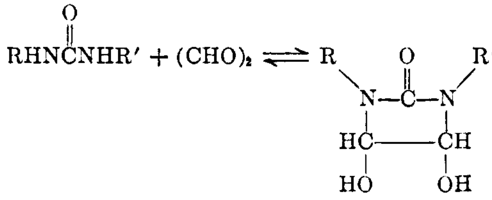
Various bisamides of the type RCONH—X—NHCOR, where R = H or CH_3 and X = alkylene or substituted alkylene, have been treated with glyoxal to produce, in some cases, the desired cyclic compounds. In addition, some reactions of these new compounds have been studied. The synthesis of four new compounds is reported.

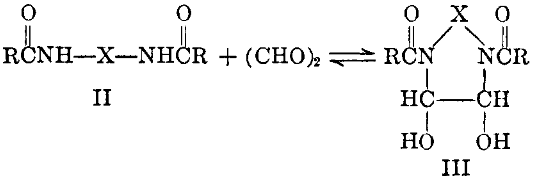
The preparation of 4,5-dihydroxy-2-imidazolidinones by addition of glyoxal to ureas has gained increasing attention since Pauly and Sauter[3] first indicated that these compounds (I) were intermediates in the synthesis of hydantoin and glyoxaldiureine.



(1)

I

The recent issuance of numerous patents is indicative of the wide use of the hydroxymethyl derivatives of I(R, R′ = CH_2OH) for imparting wrinkle resistance to cellulosic fabrics. In recent work[4,5] at this laboratory, this type of cellulose reactant has been extended to include nonhydroxymethylated compounds, I(R, R′ = CH_3). Further extension to form similar cyclic dihydroxy compounds has led to the present study, whereby bisamides of the type II(R = H or CH_3, X = alkylene, substituted alkylene, or benzylidene) were treated with glyoxal for the purpose of forming compounds of structure III. Studies[6] have also been completed in which II was treated with formaldehyde to produce the hydroxymethyl derivatives. In general, bisformamides of type II reacted with formaldehyde to produce bis(hydroxymethyl) derivatives, whereas the bisacetamides produced only the mono derivatives.

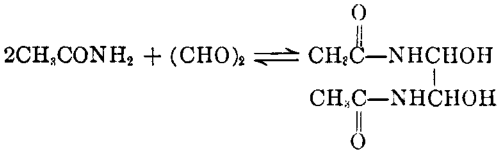


(2)

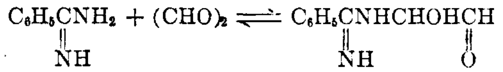
III

IIIa. X = CH_2, R = H
IIIb. X = CH_2CH_2, R = H
IIIc. X = CH_2, R = CH_3
IIId. X = CH_2CHCH_3, R = H

Examples are given of linear molecules which are reported to form from amide type-glyoxal additions. Compounds containing a 1:2[7] (equation 3) and a 1:1[8] (equation 4) molar ratio of glyoxal to amide have been reported. The products of the bisamide-glyoxal reaction isolated in this study, however, were not of these types. Elemental analyses establish the products as 1:1 addition products. Infrared spectra indicate cyclic structures containing only one type of carbonyl, the amide carbonyl (6.06–6.20 μ). Further, the amide II band, a strong band in the bisamides, is not present, thereby indicating complete addition to amido NH groups.



$$2CH_3CONH_2 + (CHO)_2 \rightleftharpoons \begin{array}{l} CH_3\overset{O}{\overset{\|}{C}}-NHCHOH \\ \qquad\qquad\quad | \\ CH_3\underset{O}{\underset{\|}{C}}-NHCHOH \end{array} \qquad (3)$$



$$C_6H_5\underset{NH}{\underset{\|}{C}}NH_2 + (CHO)_2 \rightleftharpoons C_6H_5\underset{NH}{\underset{\|}{C}}NHCHOH\underset{O}{\underset{\|}{C}}H \qquad (4)$$

Products were isolated from four of the twelve bisamides treated with glyoxal. 1,3-Diformyl-4,5-dihydroxyimidazolidine (IIIa), 1,4-diformyl-2,3-dihydroxypiperazine (IIIb), 1,3-diacetyl-4,5-dihydroxyimidazolidine (IIIc), and 1,4-diformyl-2,3-dihydroxy-5-methylpiperazine (IIId) are colorless solids which crystallized from the aqueous reaction mixture of glyoxal with methylenebisformamide, ethylenebisformamide, methylenebisacetamide, and propylenebisformamide respectively. No by-products were isolated.

None of these bisamide-glyoxal products have apparently been reported in the literature. IIIa is the least stable of the four. It partially decomposed to the starting material upon recrystal-

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(2) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Mention of trade names and firms does not imply their endorsement by the Department of Agriculture over similar products or firms not mentioned.

(3) H. Pauly and H. Sauter, *Ber.*, **63B**, 2063 (1930).

(4) S. L. Vail, P. J. Murphy, Jr., J. G. Frick, Jr., and J. D. Reid, *Am. Dyestuff Reptr.*, **50**, 550 (1961).

(5) S. L. Vail, P. J. Murphy, Jr., and R. L. Arceneaux, manuscript in preparation.

(6) S. L. Vail, C. M. Moran, and H. B. Moore, *J. Org. Chem.*, **27**, 2067 (1962).

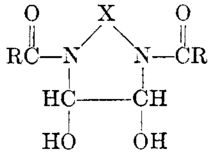
(7) Badische Anilin & Soda Fabrik Akt., French Patent 1,128,263, January 3, 1957.

(8) J. B. Ekeley and A. R. Ronzio, *J. Am. Chem. Soc.*, **57**, 1353 (1935); **59**, 1118 (1937).

lization from hot alcohol. Samples of IIIa, dried in a vacuum oven at 80°, became highly colored. A rapid melting point determination of IIIa produced a melting point close to that of the starting bisamide. IIIb, IIIc, and IIId are stable enough to be recrystallized from alcoholic solutions; however, only IIIc melts without decomposition. All four compounds are water-soluble. Further data on the properties and composition of these compounds are shown in Table I.

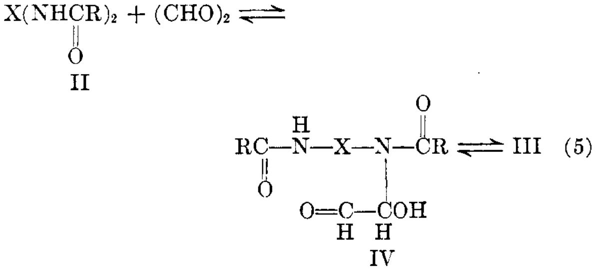
TABLE I

BISAMIDE-GLYOXAL PRODUCTS



Compound	R	X	M.P.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found
IIIa	H	CH_2	Dec.	55	17.50	17.54
IIIb	H	CH_2CH_2	Dec.	68	16.09	15.98
IIIc	CH_3	CH_2	176–177°	63	14.89	14.79
IIId	H	CH_2CHCH_3	163–164° dec.	40	14.89	14.72

The reaction is considered to be similar to urea-glyoxal additions: addition to the carbonyl carbon of the glyoxal and cyclization to the product.[5]



$$X(NH\overset{O}{\overset{\|}{C}}R)_2 + (CHO)_2 \rightleftharpoons RC(=O)-NH-X-N(-\overset{O}{\overset{\|}{C}}R)-CH(OH)-CHO \rightleftharpoons \text{III} \quad (5)$$

II

IV

Attempts were made to form a seven-membered ring by treating glyoxal with 1,3-propanebisacetamide, with 1,3-propanebisformamide and with 1,3-diformamidopropanol-2, but all attempts failed. Other bisacetamides tried in this reaction without success were ethylene-, ethylidene-, propylidene-, and benzylidenebisacetamide. *N*,*N*-Bis(3-formamidopropyl)formamide also failed to produce an isolable product with glyoxal. It is not particularly surprising that proposed compounds of other than five- and six-membered ring systems were not formed. However, it is not readily apparent why certain five- and six-membered ring compounds did not form.

Amide-formaldehyde addition mechanisms, reviewed in the accompanying paper,[6] are considered to proceed through the combination of an anion of the amide with formaldehyde. Therefore, assuming that the amide-glyoxal addition is similar, one would expect the bisformamides to be more reactive than the bisacetamides,—*i.e.*, the electron-donating effect of the methyl group would cause a decrease in proton dissociation (or anion formation). The relatively greater strain in the five-membered ring should result in slower or decreased cyclization of IV to III than for the six-membered ring. The addition of methyl groups to the alkylene portion of the bisamides can also be expected to hinder the reaction (because of steric factors) but not to block it completely.

The yields of the successful bisamide-glyoxal additions are roughly equivalent and offer no suggestions as to reactivity. However, the exceptional reactivity of ethylenebisformamide, especially when compared with the total unreactivity of ethylenebisacetamide and to the lower reactivity of propylenebisformamide, is significant. Glyoxal did not add to ethylenebisacetamide as evidenced by failure to isolate a product and by the decreasing pH of the reaction mixture. Under the reaction conditions, glyoxal is readily converted to glycolic acid. Although ethylenebisacetamide could theoretically form the favored six-membered ring, it appears that the additional methylene group, through an inductive effect, causes slight, decreased proton dissociation of the amide and thereby inhibits the addition. Electronic effects of this type have been shown[9] to affect the stability of cellulose ethers of *N*-hydroxymethyl derivatives of the bisamides mentioned in this discussion. The lower reactivity of propylenebisformamide, in comparison to that of ethylenebisformamide, is in agreement with the failure of the alkyl substituted methylenebisacetamides to form III. Benzylidenebisacetamide was insoluble in the reaction mixture and this factor also accounts for its lack of reaction.

Some Reactions of III. — The production of wrinkle-resistant cotton fabrics is generally considered to occur through crosslinking the cellulosic fibers with difunctional agents. The two hydroxy groups in I and III are theoretically capable of undergoing the well known, acid-catalyzed reaction of *N*-methylol agents. In the case of I (R,R′ = H or R,R′ = CH_3), wrinkle-resistant fabrics are efficiently formed[4]; therefore, both hydroxy groups appear to be active. III produced stable cellulosic derivatives; those prepared from IIIb, and to a minor extent from IIIc and IIId, were wrinkle-resistant. IIIa was apparently too unstable for reaction with cellulose. The cellulose ethers of IIIb and IIIc were found to resist hydrolysis under conditions which remove most *N*-methylol finishes from cotton.

In acidified 2,4-dinitrophenylhydrazine solution IIIb and IIIc were found to hydrolyze slowly. No reaction was apparent on mixing, but on standing the osazone of glyoxal was slowly formed in both solutions. In recent work[10] 1,3-diacetylimidazoli-

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(9) W. A. Reeves, S. L. Vail, and J. G. Frick, Jr., presented at the Tenth Chemical Finishing Conference, Washington, D. C., November 8–9, 1961.

(10) H. Bauer, *J. Org. Chem.*, **26**, 1649 (1961).

dine was found to resist hydrolysis more effectively under similar conditions. Upon hydrolysis a trace of formaldehyde was formed in this case. Since no formaldehyde was found in the hydrolysis of IIIc, these ring cleavages are considered to occur by different mechanisms.

Experimental[11]

Preparation of the Bisamides.—The methods used to prepare II and their properties are described in the concurrent publication.[6] Bisamides prepared were methylenebisformamide, ethylenebisformamide, 1,3-propanebisformamide, propylenebisformamide, 1,3-diformamidopropanol-2, *N*,*N*-bis(3-formamidopropyl)formamide, methylene bisacetamide, ethylenebisacetamide, 1,1-propanebisacetamide, ethylidenebisacetamide, propylidenebisacetamide, and benzylidenebisacetamide.

Preparation of III.—In general, the bisamide was added to a glyoxal solution[12] which had been adjusted to pH 7–8.5 with 20% sodium hydroxide. The bisamides generally dissolved easily with stirring. Each solution was stirred for 4 hr and then stored at 5° for several days. If no solids formed, the solution was frozen and then allowed to thaw at 5°. A seed was generally produced in the process and the desired product crystallized slowly. If this process failed, the solution was restored to room temperature for several hours or for several days and the procedure repeated. Details are presented below for those reactions which produced an isolable product and for those procedures which were altered significantly from the general procedure.

The following unchanged bisamides were isolated from the reaction mixture: ethylidenebisacetamide, propylidenebisacetamide, 1,3-propanebisacetamide, and benzylidenebisacetamide.

1,3-Diformyl-4,5-dihydroxyimidazolidine (IIIa).—To 9.8 g. (0.047 mole) of neutralized 30% glyoxal was added 7.7 g. (0.075 mole) of methylenebisformamide and 10 g. of water. More alkali was added to adjust the pH to 8. The solution was stirred for 4 hr., stored for 3–4 days at 5°, frozen at −12°, and allowed to thaw. Colorless crystals were obtained by filtration; 55% yield, m.p. 144–145° dec.

Anal. Calcd. for $C_5H_8N_2O_4$: C, 37.50; H, 5.04; N, 17.50. Found: C, 37.38; H, 5.14; N, 17.54.

A preparation which was stirred for less than 4 hr., and then stored at 5° and seeded, produced a product which was contaminated with the starting material.

1,4-Diformyl-2,3-dihydroxypiperazine (IIIb).—To 19.3 g. (0.1 mole) of neutralized 30% glyoxal was added 11.6 g. (0.1 mole) of ethylenebisformamide. The bisamide dissolved readily in the solution. More alkali was added to adjust the pH to 8.5. Within a few minutes the solution yielded a thick, white precipitate. The mixture was cooled in tap water to avoid heating above room temperature. Filtration and recrystallization from ethanol resulted in a yield of 68%. The material darkened and evolved gases at 140–150° before starting to melt at 162°.

Anal. Calcd. for $C_6H_{10}N_2O_4$: C, 41.38; H, 5.79; N, 16.09; mol. wt., 174. Found: C, 41.37; H, 5.79; N, 15.98; mol. wt. (by osmometer), 176.

1,3-Diacetyl-4,5-dihydroxyimidazolidine (IIIc).—To 19.3 g. (0.1 mole) of 30% glyoxal, adjusted to pH 8.5, was added 13.0 g. (0.1 mole) of methylenebisacetamide. To this mixture was added 5.3 g. of water. After standing for one day at room temperature, crystals appeared. After 5 days storage at room temperature, the colorless crystals obtained by filtration were recrystallized from a 1:1 ethanol–acetone mixture; 63% yield, m.p. 176–177°.

Anal. Calcd. for $C_7H_{12}N_2O_4$: C, 44.67; H, 6.43; N, 14.89; mol. wt., 188. Found: C, 44.83; H, 6.31; N, 14.79; mol. wt. (by osmometer), 190.

An attempt to synthesize this compound by allowing only 2–3 days at room temperature produced, on seeding with IIIc, only the starting bisamide.

1,4-Diformyl-2,3-dihydroxy-5-methylpiperazine (IIId).—To 3.9 g. (0.02 mole) of 30% glyoxal, adjusted to pH 8, was added 2.6 g. (0.02 mole) of propylenebisformamide. The solid readily dissolved, and the solution was allowed to stand at room temperature for four hr. Then the reaction flask was stored at −12° for 2 days; the solution did not freeze, but a precipitate began to form after 1 day. The solid was filtered and washed with cold water; the yield of dry product was 40%. The white, crystalline product melted at 163–164° dec., with a slight discoloration starting at 160°.

Anal. Calcd. for $C_7H_{12}N_2O_4$: C, 44.67; H, 6.43; N, 14.89; mol. wt., 188. Found: C, 44.78; H, 6.30; N, 14.72; mol. wt. (by osmometer), 183.

Another preparation in which the solution was allowed to stand at room temperature for 5 days and never cooled, resulted in a smaller yield (27%) of a less pure product; m.p. 156–163° dec.

Attempted Preparation of 1,4 - Diacetyl - 2,3 - dihydroxypiperazine.—Following the procedures outlined above, several unsuccessful attempts were made to isolate a product. Heating to 50° after mixing only caused the pH of the solution to decrease rapidly and alkali was consumed in attempts to maintain the pH at 7–8. Heating to 59° after the solution had remained at room temperature for 24 hr. produced the same result. Under these conditions glyoxal solutions form glycolic acid and consume alkali.

Spectral Data.—The infrared absorption spectra were obtained using a Perkin-Elmer spectrophotometer, Model 21. All samples were prepared for the instrument in potassium bromide disks. Spectral data are presented in Table II. In general, absorptivities are 0.2 or higher.

TABLE II

MAJOR INFRARED BANDS OF III (IN MICRONS)

IIIa	IIIb	IIIc	IIId
3.12	3.02[a]	3.11	3.13
6.09	3.12[a]	6.15	6.06
6.13	6.09	6.20	6.09
6.99	6.94	6.89	6.88
7.24	7.08	7.07	7.05
9.33	9.20	9.36	7.31
9.45	9.39	11.48[a]	7.67
11.19[a]	10.26	11.66	7.80
11.99[a]			9.13
13.81			9.49
			10.47[a]

[a] Absorptivities lower than 0.2.

Cellulose Reaction.—Using general pad, dry, and cure procedures described previously,[4] a 10% solution of IIIb with 2% pyridine hydrochloride as a catalyst imparted, after curing, wrinkle resistance to cotton fabric with 0.92% nitrogen content. IIIa, under similar conditions, was unreactive. IIIc [a 10% solution with 2% $Zn(BF_4)_2$] imparted wrinkle resistance to cotton fabric with 0.61% nitrogen content. IIId [a 5% solution with 2% $Zn(BF_4)_2$] imparted wrinkle resistance to cotton fabric with 0.30% nitrogen content. The wrinkle-resistance properties obtained from IIIb were superior to those obtained from IIIc and IIId. Excellent stability of the cellulose ethers of IIIb and IIIc to acid hydrolysis is indicated by the failure of a stripping solution, containing 1.5% phosphoric acid and 5% urea, to remove more than 6% of the total nitrogen content of the fabric. Stripping conditions included heating the modified cellulosic fabrics for 30 min. at 80° in the above solution.

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[11] All melting points are uncorrected. Percentages given are by weight.

[12] Glyoxal purity greatly affected the yields and rates of formation of the isolable products.

Treatment of IIIb and IIIc with 2,4-Dinitrophenylhydrazine.—IIIb and IIIc were given identical treatments with a 2,4-dinitrophenylhydrazine solution. In each case, a 0.05-g. sample of the solid was dissolved in about 25 cc. of a 0.1% solution of 2,4-dinitrophenylhydrazine, acidified with hydrochloric acid. After about 1 hr., a flocculent, yellow-orange precipitate began to appear. Precipitation was complete after 24 hr.

The 2,4-dinitrophenylosazone of glyoxal was prepared in a similar manner; the precipitate appeared immediately. This derivative melted at 300–303° dec.

The osazone formed by treatment of IIIb melted at 302–304° dec. Mixed melting point with the glyoxal derivative was 301–304° dec.

The IIIc derivative melted at 304–306° dec. Mixed melting point was 301–305° dec.

Acknowledgment.—The authors wish to thank R. T. O'Connor and co-workers for assistance in interpretation of infrared spectra and L. E. Brown and A. L. Alford for the analyses.

Oxathiane Synthesis by Mercuric Salt Ring Closure

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Treatment of allyl sulfide with aqueous mercuric salt solutions yields a pair of isomeric mercury derivatives of dimethyl-*p*-oxathiane as evidenced by the two isomers of 2,6-bis(iodomethyl)-*p*-oxathiane that are isolated after treating the mercurials with iodine. Allyl sulfone undergoes a similar sequence of reactions, but only a single isomer of 2,6-bis(iodomethyl)-*p*-oxathiane 4,4-dioxide is produced. The *cis* structure of this dioxide is proved by its oxidation to a diacid which reversibly forms a monomeric anhydride. The *cis* structure of the dominant product in the allyl sulfide-mercuric salt condensation is demonstrated by conversion to the above *cis*-dioxide. Methallyl sulfide and sulfone undergo parallel condensation reactions.

The first synthesis of a dioxane by treatment of allyl ether with an aqueous mercuric salt solution was performed by Nesmeyanov and Lutsenko.[2] The mercury derivative was precipitated as the halide and converted by iodine to a form of 2,6-bis-(iodomethyl)-*p*-dioxane. Work in our laboratory later showed[3] that two isomers rather than one were produced and established the stereochemistry of the isomers. A study of the factors affecting the proportion of the isomers[4] led to the proposal of a mechanism involving reversible reactions in the mercuration step in which the more thermodynamically stable form would predominate under equilibrium conditions of high hydrogen ion concentration or long standing. One would expect the more stable form of a 2,6-disubstituted dioxane, an analog of a *meta*-disubstituted cyclohexane, to be the *cis* form. Under equilibration conditions the *cis/trans* ratio in the dioxane case is found to be sixteen to one.[4] In the present work this type of synthesis is extended to oxathianes by substitution of allyl sulfide for allyl ether.

Discussion

Subsequent to our investigation of the general reaction of terminal diolefins with aqueous mercuric salts,[5] allyl sulfide was treated with aqueous mercuric acetate solution. A mercurial precipitated from solution which is probably identical with the 2,6-bis(acetoxymercurimethyl)-*p*-oxathiane (Ia) reported by Baker and co-workers.[6] Our yield of the acetoxy mercurial, m.p. 166–182°, was 50%. Several recrystallizations from acetone rendered crystals, m.p. 197–199° dec. An additional 32% yield of 2,6-bis(iodomercurimethyl)-*p*-oxathiane (Ib) was obtained from the filtrate of the reaction mixture by adding potassium iodide.

Iodine replaced the mercuries of both mercurials to give a product which after crystallizations from large volumes of ethanol, could be separated into two compounds which were later shown to be the *cis* isomer II, and a small amount of the *trans* isomer III, of 2,6-bis(iodomethyl)-*p*-oxathiane. The reaction with iodine was complicated by formation of large amounts of tarry materials, probably sulfonium iodide polymers. The diiodide II could not be oxidized directly to the diacid with nitric acid, nor could it be oxidized to a sulfone with hydrogen peroxide; but alcoholic sodium sulfide gave the bicyclic compound, 9-oxa-3,7-dithiobicyclo[3.3.1.]-nonane (IV), evidence of a *cis* configuration.

Further proof of the *cis* configuration of II was obtained by oxidation to a 2,6-bis(iodomethyl)-*p*-oxathiane 4,4-dioxide (V), by peracetic acid. This

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[1] This research was supported by N.S.F. Grant 7335.

[2] A. N. Nesmeyanov and I. F. Lutsenko, *Bull. acad. sci. U.R.S.S., Classe sci. chim.* 296 (1943).

[3] R. K. Summerbell and J. R. Stephens, *J. Am. Chem. Soc.*, **76**, 731 (1954).

[4] R. K. Summerbell, G. J. Lestina, and H. Waite, *J. Am. Chem. Soc.*, **79**, 234 (1957).

[5] R. K. Summerbell, Erwin S. Poklacki, and Sherri R. Forrester, to be published.

[6] L. Goodman, L. O. Ross, M. O. Greene, J. Greenberg, and B. R. Baker, *J. Med. and Pharm. Chem.*, **3**, 65 (1961). These authors isolated a 25–37% yield of the acetoxy mercurial and tentatively assigned a *trans* structure to their supposedly isomerically pure sample, m.p. 191–193° dec. The experimental basis for the assignment of a *trans* configuration is not stated, as the paper is primarily concerned with the therapeutic value of a series of related mercury compounds in cancer treatment. No yield of the *cis* isomer is mentioned, although, on the basis of our experience with the closely related dioxanes, the *cis* isomer would be expected as the dominant product.