benzenesulfonyl chloride and 60.6% cyanuric chloride, m.p. 142° (lit.[45] m.p. 145°).

Chlorinolysis of S-Benzylthiouronium Chloride. A. In Acetic Acid.—A quantity (5.0 g.) was chlorinolyzed to yield 39.5% benzylsulfonyl chloride and 44.1% sulfate ion.

B. In Water.—A quantity (5.0 g.) was chlorinolyzed to yield 93.2% benzylsulfonyl chloride. No sulfate ion was detected.

Chlorinolysis of S-*p*-Methylbenzylthiouronium Chloride.—The sulfide (6.6 g.) was chlorinolyzed in 50 ml. of glacial acetic acid containing 4.0 ml. of water to yield 99.3% sulfate ion.

Chlorinolysis of S-*p*-Nitrobenzylthiouronium Chloride.—A solution containing 5.0 g. of sulfide in 50 ml. of glacial acetic acid containing 2.0 ml. of water was chlorinolyzed to yield 90.5% *p*-nitrobenzylsulfonyl chloride, m.p. 92° (lit.[50] m.p. 90°). No sulfate ion was detected.

Chlorinolysis of Benzyl *p*-Nitrobenzyl Sulfide.—The sulfide (15.0 g.) dissolved in 50 ml. of glacial acetic acid containing 12.0 ml. of water was chlorinolyzed to yield 90.5% *p*-nitrobenzylsulfonyl chloride, 45.7% benzyl chloride, and 37.4% benzyl acetate.

Radioactive Interchange of $^{36}Cl^-$ with 4,7-Dichloroquinoline.—The $^{36}Cl^-$ was procured from the Oak Ridge National Laboratory as an aqueous HCl solution with the following analysis: 145.6 mg./ml. of chloride, 4.1 *N* acid, 0.05 ± 10% mc./ml., and specific activity of 0.343 mc./g.

A solution (22 ml.) of 4,7-dichloroquinoline (0.0084 g./ml.) in 1:1 acetic acid–water was placed in a flask and 100 λ of the isotope solution was added. This was stirred at room temperature for 5 min. and then 2.0 ml. of this solution was withdrawn, neutralized with aqueous sodium hydroxide, and diluted to 5.0 ml. with water; 0.17 ml. of this solution was withdrawn, dried, and counted to give 3644 c.p.m.

The remainder of the original solution was allowed to stir for 30 min. and then 10.0 ml. was withdrawn and neutralized. The precipitated solid was filtered, dried, weighed, and counted; weight 59.1 mg., count 43 c.p.m.

A quantity of 1.0 ml. of 0.040 *M* chlorine in glacial acetic acid was added to the remaining 10 ml. and the solution was stirred for 30 min. The entire solution was neutralized and the precipitated solid was filtered, dried, weighed, and counted; weight 37.9 mg., count 1150 c.p.m.

A second experiment was made in which 10.0 ml. of the 4,7-dichloroquinoline solution, 50 λ of the isotope solution, and 1.0 ml. of the chlorine solution were mixed and allowed to stand for 16 hr. This was worked up as before to yield 61.5 mg.; count 1640 c.p.m.

(50) C. K. Ingold, E. H. Ingold, and F. R. Shaw, *J. Chem. Soc.*, **130**, 827 (1927).

Acknowledgment.—The support of the Petroleum Research Fund of the American Chemical Society is gratefully acknowledged.

The Formation of N,N'-Dihydroxyethylenebisamides from Glyoxal and Selected Amides

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Received December 8, 1964

The addition of carboxylic acid amides and carbamates to glyoxal to form N,N'-dihydroxyethylenebisamides (I) is favored by basic conditions. In general, linear derivatives of I are formed by the addition of unsubstituted amides, such as acetamide, benzamide, or isopropyl carbamate, to glyoxal. However, the addition of formamide to glyoxal produced a low yield of N,N'-dihydroxyethylenebisformamide, the major reaction product being 1,4-diformyl-2,3,5,6-tetrahydroxypiperazine. Formation of linear derivatives of I has also been extended to include the N-substituted amides, N-methylformamide and 2-pyrrolidone. N,N'-Methylenebis(methyl carbamate) was added to glyoxal to form 1,3-dicarbomethoxy-4,5-dihydroxyimidazolidine. Attempts to form a dihydroxydiazetidine were unsuccessful. The formation of some methyl ethers and the acetates of I is reported.

Based on extensive studies of the addition reactions of amides to formaldehyde,[2] it has been proposed that under alkaline conditions the amido nitrogen may attack an aldehyde carbonyl as a nucleophile to produce I. On examination of eq. 1 and 2, it is evident that

$$>NH + OH^- \rightleftharpoons >N^- + H_2O \qquad (1)$$

$$>N^- + \underset{H}{\overset{O}{\overset{\|}{C}}} + H_2O \rightleftharpoons >N-\underset{H}{\overset{OH}{C}}- + OH^- \qquad (2)$$

I

electronic factors which increase the electron density on the amido nitrogen should reduce the deprotonation of the amide and inhibit the addition to glyoxal.[3]

The base-catalyzed additions of acetamide and methyl and ethyl carbamate to glyoxal have been reported[4] to form linear N,N'-dihydroxyethylenebisamides (II). However, of the examples provided in these patents,[4] apparently only one compound was purified to the extent that it was accurately characterized (Table I). It has been possible to extend this base-catalyzed reaction to produce compounds of the general structure II from formamide, acrylamide, isopropyl carbamate, benzamide, N-methylformamide, and 2-pyrrolidone. Formamide, acrylamide, benzamide, and 2-pyrrolidone reacted readily, whereas N-methylformamide and isopropyl carbamate were slower.

$$2RCONHR' + (CHO)_2 \rightleftharpoons \begin{matrix} O \\ \| \\ RC-NR'-CH-OH \\ \quad\quad\quad | \\ RC-NR'-CH-OH \\ \| \\ O \end{matrix} \qquad (3)$$

IIa, R = CH_3; R' = H
b, R = OCH_3; R' = H
c, R = OC_2H_5; R' = H

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

(2) (a) M. Okano and Y. Ogata, *J. Am. Chem. Soc.*, **74**, 5728 (1952); (b) J. I. DeJong and J. DeJonge, *Rec. trav. chim.*, **71**, 643 (1952); (c) J. Ugelstad and J. DeJonge, *ibid.*, **76**, 919 (1957).

(3) G. A. Crowe, Jr., and C. C. Lynch, *J. Am. Chem. Soc.*, **72**, 3622 (1950).

(4) (a) Badische-Anilin and Soda Fabrik Akt., French Patent 1,128,263 (Jan. 3, 1957); (b) R. K. Madison and W. J. Van Loo, Jr. (to American Cyanamid Co.), Belgian Patent 615,320 (Sept. 20, 1962). These authors claim to have prepared over ten glyoxal–amide adducts of type II, but identification and characterization of the adducts in almost all cases was not reported.

TABLE I
AMIDE–GLYOXAL ADDUCTS

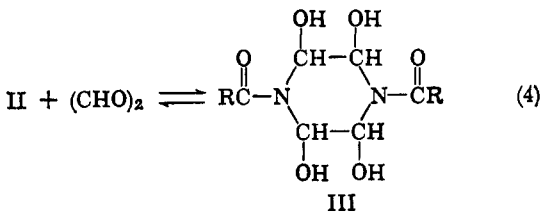
Compd.	M.p., °C.[a]	Lit. m.p., °C.	Ref.	Calcd. C, %	Calcd. H, %	Calcd. N, %	Calcd. Mol. wt.	Found C, %	Found H, %	Found N, %	Found Mol. wt.
II, R, R′ = H	148–150 dec.[b]	...	...	32.43	5.44	18.92	148	32.63	5.20	19.20	139
II, R = CH_3; R′ = H	166–167 dec.[c]	136 dec.	*d*								
		156–157.5[e]	*f*	40.90	6.87	15.90	176	40.85	6.84	16.00	172
II, R = CH_2=CH, R′ = H	153–157 dec.[g]	...	*f*	47.99	6.04	13.99	...	47.89	6.26	13.64	...
II, R = C_6H_5; R′ = H	167–169 dec.	...	...	63.99	5.37	9.33	...	63.88	5.50	9.59	...
II, R = OCH_3; R′ = H	174–175[h]	150[c]	*d*	34.62	5.81	13.46	...	34.43	5.63	13.50	...
II, R = OC_2H_5; R′ = H	140–142[c]	139–140[c]	*d*	40.67	6.82	11.86	...	40.90	6.71	11.77	...
II, R = $OCH(CH_3)_2$; R′ = H	175–176[i]	...	...	45.45	7.63	10.60	...	45.47	7.54	10.37	...
II, R = H; R′ = CH_3	156–158 dec.[j]	...	...	40.91	6.87	15.90	...	41.05	6.80	15.73	...
II, from 2-pyrrolidone	190–192 dec.[j]	...	...	52.62	7.07	12.27	...	52.90	7.27	12.15	...
III, R = H	*Ca.* 225 dec.	...	...	34.94	4.89	13.59	206	34.59	5.04	13.49	201
Vb	192–193 dec.[e]	162 dec.	*k*	...	...	...	...	...	...	...	...
Ve	149–151 dec.[h]	...	...	38.18	5.49	12.72	...	38.21	5.42	12.67	...
Formylosazone	283–284 dec.[l]	...	...	33.80	4.26	39.42	...	34.01	4.45	38.96	...

[a] Compound generally discolored below the melting point range. [b] Recrystallized from water–methanol–acetone. [c] Recrystallized from water. [d] Ref. 3. [e] Recrystallized from methanol–water. [f] Ref. 4. [g] Appears to polymerize on melting. [h] Recrystallized twice from methanol. [i] Recrystallized from 2-propanol. [j] Recrystallized from ethanol–water. [k] Ref. 7. [l] Adduct was prepared from *s*-diformylhydrazine and glyoxal and recrystallized from dimethylformamide–water.

II was isolated from the reaction mixture as the sole product except in reactions with formamide. No reaction was obtained with N-methylacetamide, N-methylurethan, and N-isopropylacrylamide. The linear N,N′-dihydroxyethylenebisamides were found to have surprisingly low solubilities in water, *i.e.*, about 10% with that of some compounds considerably lower.

These data represent the first published report of the successful addition of an N-substituted amide to glyoxal to form linear adducts of type II. Presumably the N-alkyl group hinders the addition because of both steric and electronic effects. On the other hand, the addition reaction of unsubstituted amides to glyoxal to produce I appears to be generally applicable.

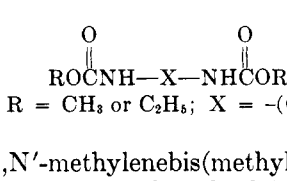
Theoretically, 2 moles each of an amide and glyoxal (or 1 mole of glyoxal and II) can produce a series of heterocyclic tetrahydroxy derivatives of structure III.



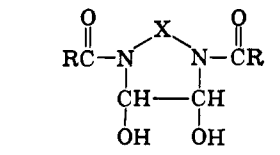
III

Although IIa and IIc have been found to add to formaldehyde to form N-methylol derivatives,[5] the desired tetrahydroxypiperazine derivatives were not isolated from glyoxal solutions containing these bisamides. However, the formamide–glyoxal reaction produced a 60% yield of a material which was an equimolar adduct of formamide and glyoxal. The material precipitated as an insoluble, high-melting, white solid which discolored on standing. The infrared spectrum of the material indicated that it was a polyhydroxyamide with all nitrogens fully substituted. Molecular weight determinations and elemental analyses of the material and its tetraacetate established the structure as the diformyl derivative of III (R = H) rather than a 1:1 formamide–glyoxal polymer. A similar cyclic tetrahydroxy compound has been obtained by the addition of nitromethane to glyoxal.[6] 1,4-Diformyl-2,3,5,6-tetrahydroxypiperazine (III, R = H) was formed in preference to N,N′-dihydroxyethylenebisformamide over a wide range of reaction conditions.

An attempt to prepare a series of cyclic N,N′-dicarboalkoxy cyclic derivatives from six N,N′-alkylenebiscarbamates (IV) and glyoxal was unsuccessful. Only N,N′-methylenebis(methyl carbamate) was found to add (relatively slowly) to glyoxal to form 1,3-dicarbomethoxy-4,5-dihydroxyimidazolidine, whereas similar biscarbamates, such as N,N′-ethylenebis(methyl carbamate) and N,N′-methylenebisurethan, were found to be unreactive in the presence of alkaline, aqueous glyoxal. Although surprising, these results agree with prior work[7] in which a similar series of bisformamide- and bisacetamide–glyoxal additions were attempted. Thus, formation of these five- to seven-membered cyclic derivatives from bisamides and glyoxal is, at present, limited to the compounds Va–e.



IV, R = CH_3 or C_2H_5; X = $-(CH_2)_{1-3}-$



Va, R = H; X = CH_2
b, R = H; X = CH_2CH_2
c, R = H; X = CH_2CHCH_3
d, R = CH_3; X = CH_2
e, R = OCH_3; X = CH_2

The formation of a four-membered heterocyclic compound (a diazetidine) was attempted by the addition of the hydrazides, *s*-diformylhydrazine and *s*-diacetylhydrazine, to alkaline, aqueous glyoxal. Although these hydrazides methylolate partially with

(5) S. L. Vail and C. M. Moran, *Am. Dyestuff Reptr.*, **53**, 282 (1964).

(6) F. W. Lichtenthaler and H. O. L. Fischer, *J. Am. Chem. Soc.*, **83**, 2005 (1961).

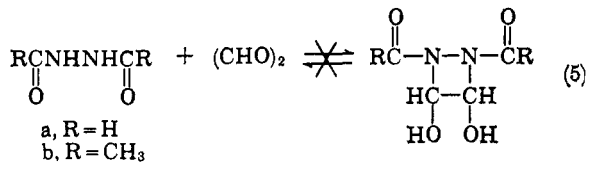
(7) S. L. Vail, C. M. Moran, H. B. Moore, and R. M. H. Kullman, *J. Org. Chem.*, **27**, 2071 (1962).

TABLE II

ETHERS AND ACETATES OF AMIDE–GLYOXAL ADDUCTS

Compd.	Derivative[a]	M.p. °C.	Lit. m.p., °C.	Ref.	Calcd. C, %	Calcd. H, %	Calcd. N, %	Calcd. Mol. wt.	Found C, %	Found H, %	Found N, %	Found Mol. wt.
II, R = CH_3; R' = H	Ether	225–226[b]	212 dec.[b]	c	47.04	7.90	13.72	...	47.01	7.79	13.69	...
II, R = CH_2=CH; R' = H	Ether	d	...	...	52.62	7.07	12.28	228	52.56	7.22	12.18	202
II, R = OC_2H_5; R' = H	Ether	161–164[b]	162–163[b]	c	45.44	7.63	10.60	264	45.53	7.54	10.57	246
II, from 2-pyrrolidone	Ether	199–202[b]	...	...	56.23	7.87	10.93	...	56.35	7.74	10.90	...
III, R = H	Acetate	255–256 dec.[e]	...	...	44.92	4.84	7.48	374	45.04	4.86	7.37	370
Va, R = H; X = CH_2	Acetate	158–159[e]	...	...	44.26	4.95	11.47	...	44.46	4.78	11.42	...
Vb, R = H; X = CH_2CH_2	Acetate	139–140[g]	...	...	46.51	5.46	10.85	258	46.78	5.61	11.01	264
Vd, R = CH_3; X = CH_2	Ether	Oil	...	...	...	...	...	...	...	...	...	...
Ve, R = OCH_3; X = CH_2	Ether	100–101	...	...	43.55	6.50	11.29	...	43.48	6.48	11.29	...

[a] Ethers are fully methylated; acetates are fully acetylated. [b] Recrystallized from methanol. [c] Ref. 13. [d] Softens, but does not melt, at about 230°. [e] Recrystallized from benzene. [f] Recrystallized from ethyl acetate. [g] Recrystallized from ethyl acetate and then from water.

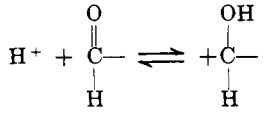


(5)

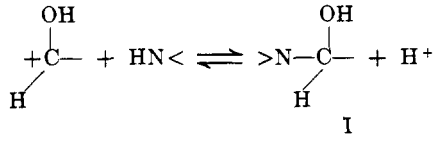
formaldehyde,[8] no dihydroxydiazetidines were isolated. The formylosazone of glyoxal was the only product identified from these reaction mixtures.

These base-catalyzed additions proceeded best using fresh glyoxal solutions in the pH range 8–10. However, in those additions which were relatively slow, the competing Cannizzaro reaction consumed the alkali and the solution became acidic. In such cases sodium bicarbonate was superior to sodium hydroxide for maintaining the solution at an alkaline pH. Presumably, some of the base-catalyzed amide–glyoxal addition reactions occur at such very slow rates that it is impractical to synthesize the adducts in this manner. Additional data to substantiate these comments were provided by an n.m.r. study of selected amide–glyoxal reactions to form I.[9]

The complications introduced by the competing Cannizzaro reaction and pH control can theoretically be avoided in acid-catalyzed systems. Equations 6 and 7 represent a mechanism suggested for the acid-



(6)

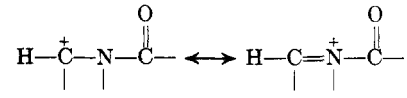


(7)

I

catalyzed addition of amides to formaldehyde[2] involving nucleophilic attack by the neutral amido nitrogen on the previously protonated carbonyl function. However, protonation of the N-methylolamide occurs readily and generally leads to the formation of methylenebisamides as the sole product.[10] Similarly, amides are expected to add to glyoxal to produce I or those products formed subsequent to protonation of I. Ureas have been previously found[11] to add readily to glyoxal under acidic conditions; however, in sharp contrast, selected carboxylic acid amides and carbamates were found to add slowly at room temperature or not at all. For example, Vb formed rapidly after alkaline glyoxal and N,N'-ethylenebisformamide were mixed. However, 2–3 weeks were required for formation of a significant amount of Vb when the glyoxal was adjusted to an acidic pH. The reaction appears to be inhibited by acid rather than enhanced. An attempt to isolate I by forcing the reaction was unsuccessful; only a thick, black residue was obtained from heating a solution of glyoxal and formamide at pH 4.

Etherification of I (Table II) using acidic conditions (a trace of HCl in refluxing methanol) is considered to proceed by a series of reversible reactions involving a resonance-stabilized carbonium ion[10b] intermediate.



(8)

Prior work[12] has demonstrated that only relatively mild acidic conditions are required to methylate the acetamide and urethan derivatives of II (R = CH_3 or OC_2H_5). Etherification of the acrylamide and 2-pyrrolidone derivatives of II proceeded under similar conditions. However, the N-methylformamide derivative required stronger conditions, *i.e.*, additional acid and longer heating, which resulted in some decomposition. On the other hand, N,N'-dihydroxyethylenebisformamide and 1,4-diformyl-2,3,5,6-tetrahydroxypiperazine did not etherify. Etherification of V proceeded in a manner analogous to II except that the diformyl derivatives of V did not etherify even on extended refluxing in acidified methanol. In general, etherification of II and V occurred under acidic conditions that were predictable from considerations of electronic effects of the substituents on the intermediate (eq. 8). These conditions are milder than those used for etherification of aliphatic alcohols and are similar to or stronger than conditions used in acetal formation.

(8) C. M. Moran, S. L. Vail, and J. D. Reid, *Ind. Eng. Chem., Prod. Res. Develop.*, **2**, 178 (1963).

(9) Unpublished results. For example, a series of n.m.r. spectra of an alkaline, aqueous solution of glyoxal and N,N,-ethylenebisacetamide taken during a period of over 24 hr. demonstrated that this bisamide was relatively inert to glyoxal.

(10) (a) J. F. Walker, "Formaldehyde," 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1964, p. 373; (b) H. Hellman, "Newer Methods of Preparative Organic Chemistry," Vol. II, W. Foerst, Ed., Academic Press Inc., New York, N. Y., 1963, p. 277.

(11) (a) W. A. Burris (to American Cyanamid Co.), U. S. Patent 3,091,617 (May 28, 1963); (b) S. L. Vail, R. H. Barker, and P. G. Mennitt, manuscript in preparation.

(12) Badische Anilin and Soda Fabrik Akt., British Patent 779,849 (July 24, 1957).

Some N,N′-diformyl derivatives of III and V which resisted etherification or were highly unstable were found to acetylate readily when the reaction was catalyzed with a trace of sulfuric acid. The acetates were isolated as stable, crystalline derivatives, those from Va and Vb melted sharply without decomposition (Table II). Therefore, the formation of acetate and ethers of I provides derivatives which are, generally, though not always, more thermally stable than the parent N-methylolamides.

Experimental[13]

General Procedure for Addition of Monoamides to Glyoxal.—To 0.5 mole of glyoxal was added 1 mole of the amide, neat or dissolved in 50–100 ml. of water. The mixture was adjusted to pH 8–9 with solid sodium bicarbonate or 20% sodium hydroxide and allowed to stand at room temperature for varying times up to several days. During this time base had to be added to maintain the alkaline pH for those additions which were relatively slow. In successful syntheses white crystals generally formed and were filtered from the mother liquor. The crude products were generally recrystallized from alcohol and water (Table I). Chilling of the filtrate generally produced further crops of the desired product. In unsuccessful syntheses chilling and repeated evaporations of the reaction solution produced no solid material or only the starting amide. If no crystals were obtained on chilling, the solution was evaporated *in vacuo* to semi-dryness. The mass which resulted was then examined by infrared spectroscopy. Generally, the spectra were sharp enough to establish that little or no reaction had occurred.

Using this general procedure, acetamide, methyl carbamate, urethan, isopropyl carbamate, benzamide, acrylamide, 2-pyrrolidone, and N-methylformamide were added to aqueous glyoxal to produce three known and five unknown linear adducts of type II. Pertinent experimental data on these adducts are given in Table I. Stability of these compounds was good; only the formyl derivatives of II darkened on storage for 6 months. Repeated recrystallizations raised the melting point of the compounds significantly and reduced or eliminated the decomposition prior to melting. Two syntheses are presented in detail to illustrate a facile and a difficult addition.

N,N′-Dihydroxyethylenebis(2-pyrrolidone).—To 85 g. (1 mole) of 2-pyrrolidone was added 72.5 g. (0.5 mole) of 40% glyoxal. On adjusting the solution to an alkaline pH of about 8 with 20% sodium hydroxide, the solution heated to 65° and a precipitate formed. The solution was filtered while still warm to produce 74 g. of a dry, crude product. The residue was worked up to yield 10 g. more (74% yield).

N,N′-Dihydroxyethylenebis(methylformamide).—To 59 g. (1 mole) of methylformamide was added 73 g. (0.5 mole) of 40% glyoxal. The solution was adjusted to a pH of 8 with 20% sodium hydroxide. After standing at room temperature for 48 hr., with sodium bicarbonate added to maintain an alkaline pH of 8–9, the darkened solution was stored at about −15°. In 2–4 weeks, two small batches of crystals were obtained. Recrystallization from ethanol–water and washing with ethanol produced a white crystalline material (14% yield) which melted at 156–158° with decomposition starting at 140–150°. On standing the product darkened. Evaporation of the residue using vacuum increased the yield to 20%.

Unsuccessful Additions of N-Substituted Monoamides to Glyoxal.—No reaction was obtained with N-methylacetamide, N-methylurethan, and N-isopropylacrylamide. With the latter amide a portion of the reaction mixture was evaporated to dryness, examined by infrared, and found to contain only the starting materials. Unsuccessful attempts were made to isolate a product from the reaction mixtures of the other N-substituted amides. Residues from these reactions containing glyoxal were quite thick and difficult to work with.

Addition of Formamide to Glyoxal. 1,4-Diformyl-2,3,5,6-tetrahydroxypiperazine (III, R = H) and N,N′-Dihydroxyethylenebisformamide.—One mole of formamide was dissolved in 0.5 mole of glyoxal, 40% solution. The pH of the mixture was varied from 4.5 to 10. The reaction temperatures were varied from 0 to 25°. Generally, after about 1 or 2 hr. at 25°, there was found a white precipitate which was filtered and washed with water (60% yield). The compound was insoluble in alcohols, acetic acid, tetrahydrofuran, and CCl_4, but was slightly soluble in dimethylformamide and dimethyl sulfoxide. The compound (III, R = H) eventually dissolved in boiling water, apparently with decomposition. Major spectral bands (less than 50% transmittance) in the infrared spectrum were found at 2.97, 3.07, 5.96, 6.76, 6.93, 7.09, 7.34, 7.51, 7.69, 7.88, 8.35, 9.30, 9.50, 9.89, 10.18, and 12.55 μ.

In addition, the reaction was run at room temperature at a pH of 8–9 and with 3:1 excess of formamide. There was an additional product formed. This new compound, N,N′-dihydroxyethylenebisformamide, precipitated as the second crop. The white product was recrystallized from a water–methanol–acetone mixture (20% yield).

When 1 mole of formamide was dissolved in 0.5 mole of 40% glyoxal (no adjustment of pH made, pH 4) and heated at 50° for 14 hr., no precipitate formed. On evaporation to dryness using vacuum and heat, a thick black mass resulted. After standing 5 months, no solids were obtained. No attempt was made to identify this product.

Attempted Addition of N,N′-Dihydroxyethylenebisurethan and N,N′-Dihydroxyethylenebisacetamide to Glyoxal.—Both of these amides had limited solubility in alkaline aqueous glyoxal, with or without added methanol. However, even after standing for several weeks at room temperature only the starting amides were recovered after working up the mixture by evaporation and cooling.

Addition of N,N′-Alkylene Biscarbamates (IV) to Glyoxal.—The general procedures for reactions of monoamides and glyoxal were followed except that additional solvent was generally required because of the relatively low solubility of IV in aqueous glyoxal. Variations in this procedure and pertinent observations are described below.

1,3-Dicarbomethoxy-4,5-dihydroxyimidazolidine (Ve).—To 48.6 g. (0.3 mole) of N,N′-methylenebis(methyl carbamate) (IVa) was added 58 g. of 30% glyoxal (0.3 mole). After mixing the materials the pH was increased to 9 by the addition of 20% aqueous sodium hydroxide. The mixture (a paste) was dissolved in methanol and allowed to stand at room temperature for 1 day. During this period the pH of the mixture was checked occasionally and readjusted, when necessary, to about 9 with dilute sodium hydroxide. The thickened mass was dissolved in warm methanol and then chilled to aid precipitation. Several fractions of N,N′-methylenebis(methyl carbamate) precipitated before 21 g. of the desired product, 1,3-dicarbomethoxy-4,5-dihydroxyimidazolidine, precipitated. Recrystallizations from methanol removed the unreacted biscarbamate.

In a similar manner unsuccessful attempts were made to add N,N′-alkylene biscarbamates to glyoxal. In syntheses with N,N′-ethylenebis(methyl carbamate), N,N′-methylenebisurethan, and N,N′-ethylenebisurethan the identities of the precipitates and the residues were determined by melting points and examination of the residues by infrared spectroscopy. In many attempted preparations recovery of the starting carbamate was essentially quantitative. N,N′-Ethylidenebisurethan and N,N′-(1,3-propyl)bisurethan were highly insoluble in the glyoxal solutions and no evidence for reaction was encountered.

1,4-Diformyl-2,3-dihydroxypiperazine (Vb).—Equimolar quantities of N,N′-ethylenebisformamide and glyoxal were mixed to form solutions of pH 4 and 2. Hydrochloric acid was used to adjust the pH to 2. A portion of the solution of pH 4 was withdrawn and adjusted to a pH of 9. Vb crystallized from the alkaline reaction solution within minutes while 2–3 weeks were required for Vb to crystallize from the acidic solutions. Yields from the acidified solutions were 40%.

Reaction of Symmetrically Disubstituted Hydrazines with Glyoxal.—Equimolar quantities of *s*-diformylhydrazine and 40% glyoxal solution, adjusted to pH 9 with aqueous NaOH, were mixed and allowed to stand at room temperature for 24 hr. The flocculent, light yellow precipitate was filtered, washed with water, and dried. The compound was recrystallized from a N,N-dimethylformamide–water mixture and was identical with the osazone formed from formylhydrazine and glyoxal; m.p. 283–284° dec. (no depression of the mixture melting point).

(13) All melting points are uncorrected and were determined on a Thomas–Hoover melting point apparatus. Room temperature was 20–25°. Glyoxal used in this work was the 30 and 40% "pure" grades supplied by these commercial firms: BASF Colors and Chemicals, Inc., Dr. F. Jonas Co., and Union Carbide Corp.

Similar treatment of *s*-diacetylhydrazine yielded no isolable product.

General Procedure for Etherification of I.—To 0.05 mole of I was added 0.5–1.0 mole of methanol and 1–2 drops of 6 *N* hydrochloric acid. The solution was refluxed for a predetermined period of time or until most of the solid had dissolved. Solutions were then neutralized with dilute sodium hydroxide and the products were obtained by crystallization from the excess methanol. Oils were obtained after evaporation of the methanol at room temperature. The conversion to the diether appeared to be quantitative in the examples which were checked for conversion. Yields reported refer to isolable recrystallized product. Pertinent experimental data are summarized below. Comparisons to literature melting points are given in Table II.

N,N′-(1,2-Dimethoxyethylene)bisacetamide, N,N′-(1,2-dimethoxyethylene)bisurethan, and **N,N′-(1,2-dimethoxyethylene)-bisacrylamide** were synthesized in about 40% yield using the general procedure outlined above.

N,N′-(1,2-Dimethoxyethylene)bis(2-pyrrolidone).—The reactants were refluxed for 1 hr.; the infrared spectrum of an aliquot evaporated to dryness indicated 100% conversion to the ether.

1,3-Diacetyl-4,5-dimethoxyimidazolidine.—To 3 g. of Vd was added 100 ml. of methanol and 3 drops of concentrated hydrochloric acid. The solution was refluxed for 16 hr. with an aliquot removed after 8 hr. Evaporation of the solvent in both cases produced oils which, on comparison of their infrared spectra, were found to be identical. Also, the hydroxyl band in the 3-μ region was absent. The n.m.r. spectrum of the oil in chloroform and the infrared spectrum established the oil as the dimethyl ether of Vd. Repeated recrystallization attempts from various solvents failed to produce a solid material.

1,3-Dicarbomethoxy-4,5-dimethoxyimidazolidine.—To 0.016 mole of Ve was added 1.0 mole of methanol and 1 drop of 6 *N* hydrochloric acid. The solution was refluxed for 6 hr. with aliquots removed after 1 and 2 hr. Infrared spectra of the residues indicated that less than 10% Ve remained in the 1-hr. aliquot, a trace in the 2-hr. aliquot, and none after refluxing 6 hr. No other products were formed as determined by these spectra.

A Methyl Ether of N,N′-(1,2-Dihydroxyethylene)bis(methylformamide).—Excess methanol and hydrochloric acid, in addition to those quantities given in the general procedures and an 8-hr. reflux period, were used to produce an oil which on examination of the n.m.r. spectrum (D_2O solvent) appeared to be a mixture of the ether, the dihydroxy compound, N-methylformamide, and glyoxal. The peak from the methoxy protons at 3.32 p.p.m. was significant but only one-fifth of the integrated value of the peaks from the N-methyl protons. Repeated crystallization attempts failed to produce a solid product.

Unsuccessful Etherifications.—N,N′-Dihydroxyethylenebisformamide, 1,4-diformyl-2,3,5,6-tetrahydroxypiperazine, 1,4-diformyl-2,3-dihydroxypiperazine (Vb), and 1,4-diformyl-2,3-dihydroxy-5-methylpiperazine (Vc) were all, except for the tetrahydroxypiperazine, recovered essentially unchanged from refluxing solutions of hydrogen chloride and methanol. The conditions used were stronger than those described in the general procedures, *i.e.*, increased methanol and hydrogen chloride with refluxing from 6 to 16 hr. The tetrahydroxypiperazine was only partially soluble in the methanol and was slightly decomposed by the procedure. No attempt was made to etherify Va since this material has been reported[7] to be unstable in hot alcohol.

Acetylation of 1,3-Diformyl-5,6-dihydroxyimidazolidine (Va).—To 1.8 g. of Va was added 40 ml. of acetic anhydride and 1 drop of concentrated sulfuric acid. After 1 hr. at room temperature the acetic anhydride was evaporated at 40° under vacuum. The residue was crystallized from ethyl acetate producing 1 g. of crystals.

Acetylation of 1,4-Diformyl-2,3-dihydroxypiperazine (Vb).—To 45 ml. of acetic anhydride was added 3.0 g. of Vb (m.p. 192–193° with decomposition starting at about 185°). The mixture was stirred for 1 hr. with little or no reaction occurring. On the addition of 1 drop of concentrated sulfuric acid, Vb rapidly went into solution. After 0.5 hr. the solution was chilled and a precipitate was obtained. The filtrate was evaporated to dryness. The precipitate and the residue had identical infrared spectra and were combined and recrystallized from ethyl acetate and then from water. The purified product and the crude precipitate and residue had essentially the same infrared spectra. The yield was quantitative.

Acetylation of 1:1 Formamide–Glyoxal Adduct.—A mixture of 4 g. of adduct (III, R = H), 90 ml. of acetic anhydride, and 0.5 ml. of concentrated sulfuric acid was heated at 60° for 2 hr. A small quantity of the adduct usually remained undissolved. The mixture was filtered while hot and then it was cooled in ice. There was formed a white crystalline product which was filtered and washed with cold water. The product can be recrystallized from acetic acid or benzene. The infrared spectrum had two carbonyl absorptions, and there was no hydroxyl absorption. The acetylated product is 2,3,5,6-tetraacetoxy-1,4-diformylpiperazine.

Acknowledgment.—The authors wish to express their appreciation to E. R. McCall and G. J. Boudreaux of Southern Regional Research Laboratory for assistance in obtaining the spectral data. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

Synthesis of Cyclopropanetricarboxamides

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Received November 17, 1964

Attempts to prepare carboxamidocarbenes by the action of potassium *t*-butoxide on α-chloroacetamides led to *trans*-1,2,3-cyclopropanetricarboxamides. Evidence for an anionic rather than a carbene mechanism is presented. Hydrolysis of the cyclopropanetricarboxamide yields the triacid. The sequence α-chloroamide to cyclopropanetricarboxamide to *trans*-1,2,3-cyclopropanetricarboxylic acid in a 56% over-all yield appears to be the best synthesis of the latter compound.

Although the existence of carbonylcarbenes I, prepared by the decomposition of diazo compounds II, has been well substantiated,[1] the preparation of these entities by the treatment of α-halocarbonyl compounds with strong base has not been reported. An attempted utilization of an α-halo ester[2] [III, R = $-OC(CH_3)_3$] for the preparation of I produced tar, probably by an acetoacetic ester type condensation. Evidently the loss of chloride ion from IV did not compete favorably with the condensation of IV with III. It appeared that the use of a less reactive carbonyl compound, *i.e.*, an amide,[3] would decrease the condensation and perhaps favor carbene formation.

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