

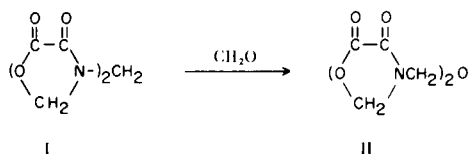
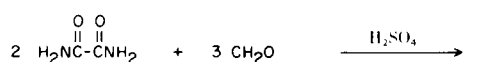
The Reaction of Oxamide with Paraformaldehyde

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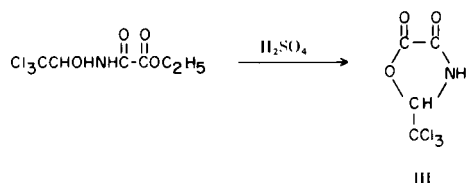
Received December 17, 1970

During the course of a study of amide-aldehyde reactions, we noted that oxamide reacts with paraformaldehyde in concentrated sulfuric acid to form *N,N'*-methylenebis(4,5-oxazolidinedione) (I).

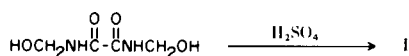


The structure of I was established by analysis, ir and nmr spectral examination, preparation of derivatives, and hydrolysis to potassium oxalate, formaldehyde and ammonia. With excess paraformaldehyde, bis[(4,5-oxazolidinedion-3-yl)methyl]oxide (II) was formed; formaldehyde insertion reactions of this general type are fairly common (1).

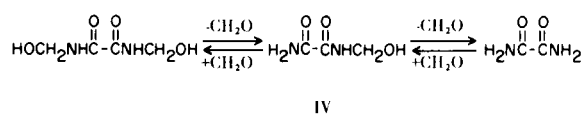
The only previous work (2,3,4) on the acid-catalyzed reaction of oxamide and formaldehyde involved the use of dilute acids, and no formation of ring compounds was noted. However, an analogous type of cyclization, also conducted in concentrated sulfuric acid, has been reported (5).



We also observed that I was formed by heating dimethyloxamide in concentrated sulfuric acid.

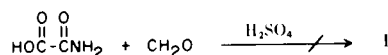


The fact that both procedures gave I in about the same yield (30-40%), and under the same conditions, suggests the existence of the following equilibrium:



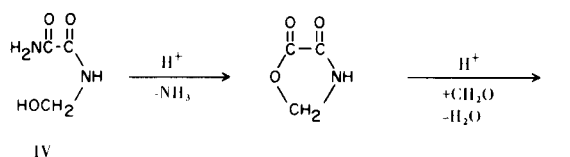
An equilibrium of this type has been proposed in the urea-formaldehyde condensation (6).

Efforts to prepare I from oxamic acid and paraformaldehyde were unsuccessful:



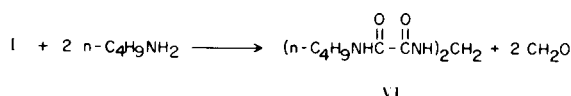
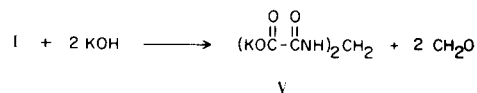
Ethyl oxamate, on the other hand, gave II as the sole product. Attempts to make a tetrathio analogue of I from dithiooxamide and paraformaldehyde were fruitless.

The above results suggest that I may be formed from IV in two steps, involving (a) intramolecular alcoholysis (of the type presumed to occur in the formation of III), and (b) reaction with formaldehyde, as follows:



Both of these types of reactions are notably acid-catalyzed. The failure of the oxamic acid system to cyclize can be explained by the comparative inferiority of the carboxyl OH moiety as a leaving group.

Compound I was found to undergo facile ring opening at room temperature with bases.



This behavior is consistent with the observation (5) that III is converted to oxamide by ammonium hydroxide.

EXPERIMENTAL (7)

N,N'-Methylenebis(4,5-oxazolidinedione) (I).

(a) From oxamide and paraformaldehyde.

Oxamide (9 g., 0.10 mole) was dissolved by stirring in 50 ml. of 96% sulfuric acid at room temperature in an open flask. Paraformaldehyde (7 g. of 90% purity, 0.21 mole) was added and the solution was heated with stirring at 70° for 1 hour. After cooling to room temperature, the solution was poured with stirring into 200 ml. ice water. The precipitate was filtered, washed with water and dried at 50°. The yield was 4.0 g. (38% based on oxamide). Two recrystallizations from dimethylformamide gave m.p. 291° dec.; ir (potassium bromide), 2930, 1800, 1725, 1450, 1360, 1260, 1160, 1060, 1025, 937, 795 and 708 cm⁻¹; nmr (DMSO-d₆): δ 5.13 (2H, s, >N-CH₂-N<); δ 5.50 (4H, s, -O-CH₂-N<).

Anal. Calcd. for C₇H₆N₂O₆: C, 39.3; H, 2.8; N, 13.1. Found: C, 39.5; H, 2.8; N, 13.2.

Compound I (2.0 g., 0.01 mole) was heated for 3 hours at 85° with 3.5 g. (0.06 mole) potassium hydroxide in 50 ml. water. The solution was evaporated to half volume and diluted with 150 ml. methanol. The precipitate was filtered, washed with methanol, and dried at 110° for 4 hours. It was identified as potassium oxalate by ir spectral comparison with an authentic sample. The yield was 2.7 g. (82%) of anhydrous potassium oxalate. The formation of formaldehyde and ammonia was detected by odor.

Attempts to improve the yield of I were unsuccessful. Reduced yields were noted upon the use of milder reaction conditions (1.5 hours at 35°), the reversed order of reagent addition, or an increase in the proportion of paraformaldehyde used. Polyphosphoric acid and 72% sulfuric acid gave no reaction; the use of concentrated hydrochloric acid at reflux resulted only in hydrolysis.

(b) From Dimethylloxamide.

Dimethylloxamide (2,3) was prepared by the following improved procedure. A suspension of 9 g. (0.10 mole) finely powdered oxamide in a mixture of 22.5 g. (0.25 mole) 40% aqueous formaldehyde and 200 ml. water was heated with stirring to 80°. Powdered potassium bicarbonate (ca. 1.0 g.) was added to raise the pH to 8.5, and stirring was continued at 80-90° until the oxamide dissolved (ca. 15 minutes). Additional potassium bicarbonate was then added if necessary to maintain a pH of 8.5, and stirring was continued for 5 additional minutes. The solution was cooled to crystallize the product, which was filtered and dried at 50°. The yield was 10.5 g. (70%); recrystallization from water gave m.p. 207° dec. (lit 204° (2); 194° (3)); ir (potassium bromide), 3230, 1650, 1520, 1455, 1400, 1285, 1223, 1087, 1035, 973, and 745 cm⁻¹.

Finely ground dimethylloxamide (4.0 g., 0.03 mole) was mixed with 25 ml. 96% sulfuric acid and the mixture was heated with stirring for 1 hour at 70°. The solution was cooled to room temperature and poured with stirring into 150 ml. ice water. The precipitate was filtered, washed with water and dried at 50°. The yield was 1.0 g. (33%) of I, as shown by the m.p. and ir spectrum.

Bis[(4,5-oxazolidinedion-3-yl)methyl]oxide (II).

A mixture of 12 g. (0.1 mole) ethyloxamate, 7 g. (.21 mole) paraformaldehyde, and concentrated sulfuric acid (50 ml.) was stirred for 6 hours at 35°. The reaction mixture was poured into 200 ml. ice water and the precipitated solid was filtered and dried. The yield was 3.0 g. (25%) of II. Recrystallization from aqueous dimethylformamide gave m.p. 215° (dec); ir (potassium bromide), 2850, 1800, 1740, 1450, 1380, 1325, 1250, 1210, 1165, 1093, 1065, 1040, 1015, 985, 960, 908, 807, and 800 cm⁻¹; nmr (DMSO-d₆): δ 5.00 (4H, s, -CH₂-O-CH₂-); δ 5.50 (4H, s, -O-CH₂-N<).

Anal. Calcd. for C₈H₈N₂O₇: C, 39.3; H, 3.3; N, 11.5. Found: C, 39.6; H, 3.5; N, 11.5.

Dipotassium Methylenebisoxamate (V).

To 2.0 g. (0.09 mole) finely ground I slurried in 10 ml. water was added with stirring 1 g. (0.19 mole) potassium hydroxide dissolved in 5 ml. water. Three drops of 20% aqueous potassium hydroxide was then added to effect a clear solution, which was evaporated to dryness at 50°. The resulting solid was dissolved in 15 ml. water, and the solution was added with stirring to 100 ml. 2-propanol. The white precipitate was filtered, washed with 2-propanol, and dried 8 hours at 85°. The yield was 2.3 g. (80%); m.p. 312° dec.; ir (potassium bromide), 3350, 3200, 1700, 1630, 1505, 1380, 1275, 1095, 1020, 773, and 742 cm⁻¹.

Anal. Calcd. for C₅H₄K₂N₂O₆·H₂O: C, 21.1; H, 2.1; N, 9.9. Found: C, 21.0; H, 2.3; N, 10.0.

Di-*n*-butyl Methylenebisoxamide (VI).

To 2.5 g. (0.034 mole) *n*-butylamine dissolved in 25 ml. water was added with stirring 1.0 g. (0.005 mole) finely ground I; a temperature rise of 3° was noted. After stirring for 2 hours at 35°, the solid was filtered, water washed, and dried at 50°. The yield was 1.2 g. (80%) of VI. After recrystallization from dimethylformamide, it melted at 266-269°; ir (potassium bromide), 3230, 2875, 1640, 1515, 1450, 1375, 1300, 1215, 1110, and 755 cm⁻¹.

Anal. Calcd. for C₁₃H₂₄N₄O₂: C, 52.0; H, 8.0; N, 18.7. Found: C, 51.9; H, 8.1; N, 18.6.

Acknowledgment.

The author is grateful to Professor B. S. Thyagarajan and Mr. V. I. Siele for helpful discussion, and to Mr. M. Warman for nmr spectral data.

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- (7) Melting points were taken in capillary tubes in a Thomas-Hoover apparatus, and are uncorrected. Infrared spectra were determined in potassium bromide pellets with a Perkin-Elmer Model 21 spectrophotometer. Nmr spectra were determined in DMSO-d₆ on a Varian T-60 spectrometer using tetramethylsilane as internal reference. Microanalyses were run by Schwarzkopf Microanalytical Laboratory.