

Glyoxal Derivatives. III. The Reaction of Glyoxal with Some Secondary Amines

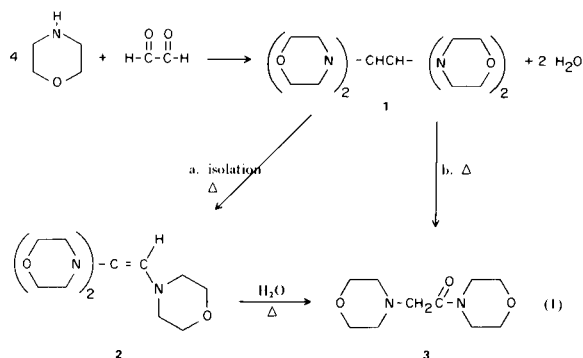
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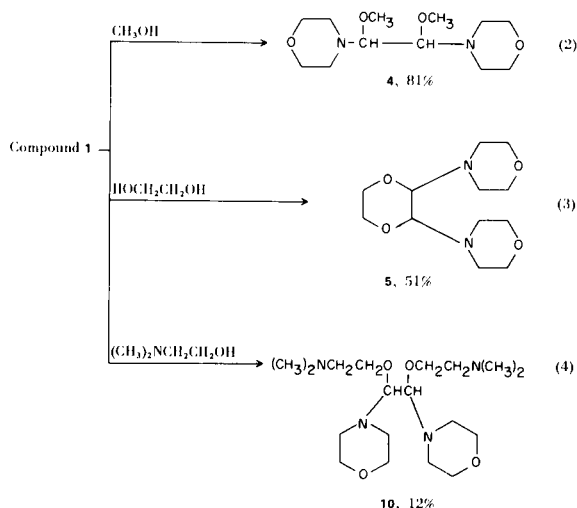
In 1938, Maurer and Waltersdorf reported that the reaction of glyoxal with the secondary amines *N,N*-diethylamine and *N,N*-dibutylamine gave the corresponding glycinamides (1). More recently, Ferruti, Segre and Fere concluded that the only products from aqueous glyoxal and secondary amines were 1,1,2,2-tetraaminoethanes, which on distillation under reduced pressure gave 1,1,2-triaminoethylenes (2). In this paper we shall report our findings on the subject.

Results.

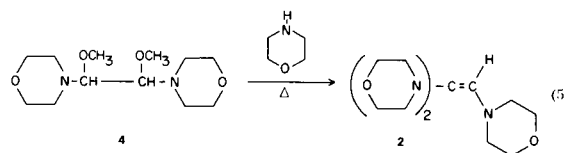
We have found that both 40% and 80% aqueous glyoxal react with morpholine in the cold to give, initially, the solid, 1,1,2,2-tetramorpholinoethane (1) in 84% yield. If this material is isolated by filtration and subjected to reduced pressure distillation, the product is 1,1,2-trimorpholinoethylene (2). However, if the 1,1,2,2-tetraaminoethane is not isolated, but is heated in the reaction mixture and distilled, the product is 4-(morpholinoacetyl)morpholine (3) in 56% yield. Compound 3 can also be isolated in 52% yield from the reaction of 1,1,2-trimorpholinoethylene with moist 2-propanol. These findings are summarized in the following set of equations:



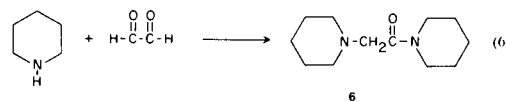
Compound 1 also reacts with organic hydroxylic compounds to give 1,2-dialkoxy-1,2-dimorpholinoethane derivatives:



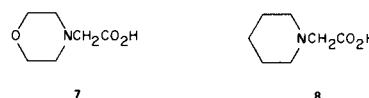
Compound 4 when heated in refluxing morpholine gives compound 2:



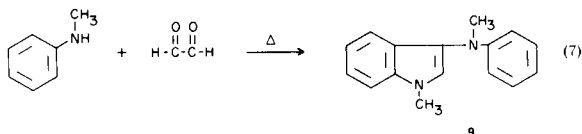
Under the conditions of reaction 1b above, piperidine gives 4-(piperidinoacetyl)piperidine, 6, in 45% yield.



In these reactions of morpholine and piperidine in which the products are glycinamides, we also isolated small amounts of morpholinoacetic acid (7) and piperidinoacetic acid (8) in 10% and 8% yields, respectively.

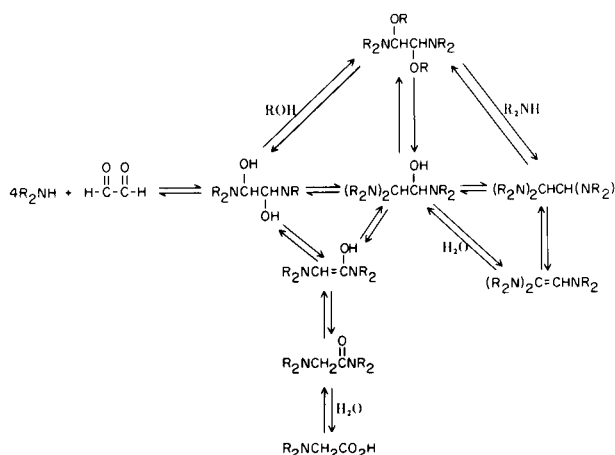


A novel cyclization reaction was observed when the secondary amine used is *N*-methylaniline. In this case the product was 1-methyl-3-(methylphenylamino)indole (**9**) in 51% yield:

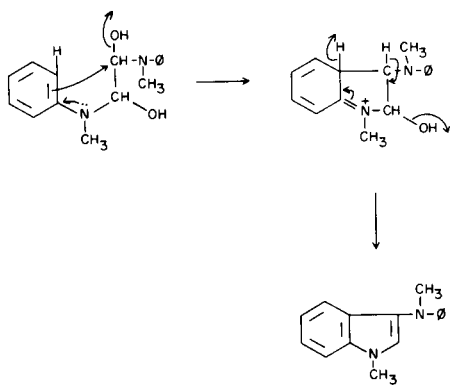


Discussion.

One set of equilibria that would explain the observed products is as follows:



A similar equilibria has been proposed for the reaction of aromatic primary amines with glyoxal (**3**). The indole derivative would be derived from at least one of the intermediates above. For example:



EXPERIMENTAL (4)

1,1,2,2-Tetramorpholinoethane (**1**).

Glyoxal (80% aqueous) (3.5 g., 0.43 mole) was added to 195

ml. of cooled morpholine (ice bath) with stirring. An exothermic reaction ensued which was controlled with an ice bath and the addition of 100 ml. of morpholine. Upon cooling a white solid precipitated. Collecting this solid on a filter, washing with hexane, and drying gave 132.0 g. of 1,1,2,2-tetramorpholinoethane, m.p. 108-112° dec. (lit. (2) 105° dec.) (84%).

Anal. Calcd. for $C_{18}H_{34}N_4O_4$: C, 58.38; H, 9.19; N, 15.14; Equiv. Wt., 91.5. Found: C, 58.09; H, 8.96; N, 15.13; Equiv. Wt., 96.3.

1,2-Dimethoxy-1,2-dimorpholinoethane (**4**).

1,1,2,2-Tetramorpholinoethane (39.0 g., 0.107 mole) was dissolved in 35 ml. of refluxing methyl alcohol. Upon cooling 22.5 g. of white crystals of 1,2-dimethoxyl-1,2-dimorpholinoethane precipitated, m.p. 146-149° (lit. (2) 134°) (81%); nmr (deuteriochloroform), δ 2.75 (m, 8.2H, CH_2N), 3.37 (s, 2.9H, CH_3O), 3.42 (s, 3.0H, CH_3O), 3.70 (m, 10.2H, CH_2O and $NCHO$).

Anal. Calcd. for $C_{12}H_{24}N_2O_4$: C, 55.35; H, 9.29; N, 10.76; Equiv. Wt., 130. Found: C, 54.96; H, 9.21; N, 10.27; Equiv. Wt., 132.

2,3-Bis(morpholino)dioxane (**5**).

Glyoxal (14.5 g., 40% aqueous, 0.10 mole) was added slowly to a mixture of morpholine (0.40 mole) and 9.3 g. of ethylene glycol (0.15 mole) in 50 ml. of isopropyl ether at 8-10°. After one hour a white solid precipitated, which upon successive recrystallization from isopropyl ether gave 13.0 g. of 2,3-bis(morpholino)dioxane, m.p. 122-123° (51%); nmr (deuteriochloroform), δ 2.83 (q, $J = 4.1$ Hz, 8.2 H, $-CH_2N-$), 3.70 (multiplet, 11.8 H, $-CH_2O$) and 4.07 (s, 1.8 H, $-NCHO-$).

Anal. Calcd. for $C_{12}H_{22}N_2O_4$: C, 55.79; H, 8.58; N, 10.84; Equiv. Wt., 129. Found: C, 56.13; H, 8.77; N, 10.86; Equiv. Wt., 129.

1,1,2-Trimorpholinoethylene (**2**).

(a) 1,1,2,2-Tetramorpholinoethane (53.4 g.) was distilled through a goose neck at 2 mm Hg (pot temperature 135-145°). The 39.2 g. of distillate thus obtained was recrystallized from heptane to give 35.4 g. of 1,1,2-trimorpholinoethylene, m.p. 96-99° (lit. (2) 100°) (95%); nmr (deuteriochloroform), δ 2.45 (m, 3.8 H, CH_2N), 2.83 (m, 4.1 H, CH_2N), 3.10 (m, 4.0 H, CH_2N), 3.63 (m, 12.2 H, CH_2O), and 4.20 (s, $C=CH$).

Anal. Calcd. for $C_{14}H_{25}N_3O_3$: C, 59.36; H, 8.83; N, 14.84; Found: C, 59.11; H, 8.89; N, 14.91.

(b) 1,2-Dimethoxy-1,2-dimorpholinoethane (13.1 g., 0.051 mole) was dissolved in 100 ml. of refluxing morpholine. Cooling and filtration gave 1.2 g. of starting material. Removal of approximately 75 ml. of morpholine *in vacuo* and cooling gave 7.4 g. of 1,1,2-trimorpholinoethylene, m.p. 90-96° (50%). Recrystallization from heptane gave 7.0 g. of solid, m.p. 96-98° undepressed with authentic material.

4-(Morpholinoacetyl)morpholine (**3**).

(a) Glyoxal (40% aqueous) (145.0 g., 1.0 mole) was added to 435.0 g. of morpholine (5.0 moles) at 10°. The white solid of 1,1,2,2-tetramorpholinoethane that soon appeared was not separated and the mixture was heated at atmospheric pressure to remove water and excess morpholine. The crude mixture that was obtained was short-path distilled at reduced pressure (2.0 mm Hg) to give 119 g. of 4-(morpholinoacetyl)morpholine, m.p. 65-68° (lit. (5) 66-68°) (56%); infrared (potassium bromide), 6.05 μ ($C=O$); nmr (deuteriochloroform), δ 2.47 (m, 4.2 H, CH_2N), 3.17 (s, 2.3 H, $-NCH_2C=O$), and 3.60 (m, 11.9 H, CH_2O and $CH_2NC=O$).

Anal. Calcd. for $C_{10}H_{18}N_2O_3$: C, 56.06; H, 8.40; N, 13.05; Molecular Wt., 214. Found: C, 55.79; H, 8.36; N, 13.06; Molecular Wt., 214 (mass spec).

A small forefraction from the above distillation solidified upon standing. Upon recrystallization from isopropyl ether 14.0 g. of 4-morpholinoacetic acid (**7**) m.p. 78-79° was isolated (10%). The infrared and mass spectrum were consistent with the substituted glycine structure.

Anal. Calcd. for $C_6H_{11}NO_3$: C, 49.64; H, 7.64; N, 9.65; Molecular Wt., 145. Found: C, 49.53; H, 7.58; N, 9.58; Molecular Wt., 145 (mass spec).

(b) 1,1,2-Trimorpholinoethylene (10.0 g., 0.035 mole) was dissolved in 25 ml. of hot 2-propanol to which a few drops of water had been added. The 2-propanol was removed *in vacuo* and the resulting oil recrystallized from heptane/ethyl acetate to give 3.9 g. of 4-(morpholinoacetyl)morpholine, m.p. 67-70° (52%). This material was identical in all respects to that obtained above.

4-(Piperidinoacetyl)piperidine (**6**).

Glyoxal (40% aqueous) (145.0 g., 1.0 mole) was added to 426.0 g. of piperidine (5.0 mole) at 10°. The reaction mixture soon solidified. This was melted and distilled giving, besides piperidine and water, a major fraction boiling at 148° @ 2.0 mm Hg. This material was redistilled to give a lower boiling fraction of piperidinoacetic acid (**8**) b.p. 103-111° @ 3.0 mm Hg, 13.0 g. of which soon solidified. Recrystallization from cyclohexane gave 12.3 g. of material, m.p. 37-39° (8%).

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.48; H, 8.94; N, 9.28.

A second fraction in the distillation, b.p. 111-128° at 3 mm Hg, 97.0 g., soon crystallized. Recrystallization from cyclohexane afforded 95.3 g. of 4-(piperidinoacetyl)piperidine, m.p. 61-63° (lit. (5) 48-50°) (45%). The infrared spectrum was consistent with that of a substituted amino acid amide.

Anal. Calcd. for $C_{12}H_{22}N_2O$: C, 68.52; H, 10.54; N, 13.32; Found: C, 68.60; H, 10.52; N, 13.04.

1-Methyl-3-(methylphenylamino)indole (**9**).

Glyoxal (40% aqueous) (145.0 g., 1.0 mole) was added to 321.0 g. of *N*-methylaniline (3.0 mole) in 600 ml. of isopropyl ether at 0-10°. After one hour at room temperature (no solid

appeared) the solution was warmed slowly and the ether and excess amine distilled up to a boiling point of 85° @ 50 mm Hg. Rapid stripping through a goose-neck gave 144.2 g. of material which was redistilled, b.p. 190-192° @ 1.5 mm, wt = 133.4 g. Recrystallization of this solid from ethanol gave 121.3 g. of pure 1-methyl-3-(*N*-methylphenylamino)indole, m.p. 77-79° (51%); ir (potassium bromide), no C=O, N-H or OH absorption; nmr (deuteriochloroform), δ 3.33 (s, 2.9 H, CH_3N), 3.58 (s, 3.1 H, CH_3N), 6.77 (m, 1.1 H, C=CH), 6.87-7.50 (m, 9.0 H, aromatic).
Anal. Calcd. for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.29; H, 6.81; N, 11.92.

1,2-Bis[2-(*N,N*-dimethylamino)ethoxy]-1,2-dimorpholinoethane (**10**).

1,1,2,2-Tetramorpholinoethane (39.0 g., 0.107 mole) was dissolved in 50 ml. of refluxing 2-(*N,N*-dimethylamino)ethanol and then cooled. The solid that precipitated was collected on a filter, 1.2 g., m.p. 108-111°, starting material. The mother liquors were stripped to 25 ml. and cooled giving 4.91 g. of product, m.p. 143-146° (12%).

Anal. Calcd. for $C_{18}H_{38}N_4O_4$: C, 57.75; H, 10.16; N, 14.97; Equiv. Wt., 93.5. Found: C, 58.11; H, 9.29; N, 14.90; Equiv. Wt., 95.0.

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- (4) All melting and boiling points are uncorrected. The nmr spectra were determined on Varian A60 and HA100 spectrometers; and the mass spectra were determined on a CEC21-130 mass spectrometer by Messrs. W. H. Joyce, C. M. Lovell, C. B. Strow, Jr. and B. E. Wilkes. Microanalyses were performed by the UCC analytical staff.
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