

## ALKYLHYDRAZINES

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In the course of our work on derivatives of 5-nitro-2-furaldehyde it became desirable to prepare some 2-alkylsubstituted semicarbazides. Since, in our opinion, the most convenient method of preparing 2-alkylsemicarbazides is the treatment of the appropriate monoalkylhydrazine with cyanic acid, it was necessary to find a suitable way to prepare the required hydrazines.

Westphal (1) has shown that higher alkylsubstituted hydrazines (hexyl and above) can be prepared in good yields from hydrazine and the appropriate alkyl halide. This method, when applied to the lower alkyl halides leads chiefly to di-, tri-, and tetra-substituted hydrazines and to quaternary ammonium salts.

The lowest member of this series, methylhydrazine, can be conveniently prepared by the action of dimethyl sulfate on benzalazine (2).

The methods for preparing the intermediate hydrazines (ethyl through amyl), however, are few. Those reported are either tedious and complicated or give poor yields. The preparation of *n*-butyl- and *n*-amyl-hydrazine could not be found in the literature.

Ethylhydrazine has been prepared by Thiele and Meyer (3) in moderate yield by the reduction of ethyl nitramine with zinc and hydrochloric acid. Fischer (4) prepared this compound in good yield by reducing *N*-nitroso-*N,N'*-diethylurea with zinc and acetic acid. Zerner (5) obtained some ethylhydrazine by the reaction of ethylmagnesium iodide with diazoacetic acid and hydrolyzing with dilute sulfuric acid. Thiele (2) mentions the preparation of ethylhydrazine from ketazine and ethyl bromide, but gives no details.

Propylhydrazine has been prepared by Stolle (6) by the treatment of potassium propyl sulfate with hydrazine. Taipale and Smirnov (7) report the preparation of this compound by the hydrolysis of azopropane.

Isopropylhydrazine has been synthesized by Lochte, Noyes, and Bailey (8) by the hydrogenation with colloidal platinum of a mixture of acetone, hydrazine hydrate, and hydrochloric acid. They also prepared it by the treatment of 2,2'-azobispropane with 18% hydrochloric acid. Neighbors and co-workers (9) obtained isopropylhydrazine by treating 1-isopropylsemicarbazide with 80% sulfuric acid. Independently, Taipale (10) prepared isopropylhydrazine by treatment of 2,2'-azobispropane with alcoholic hydrogen chloride. Also, (10) he obtained it by the distillation of *N*-nitroso-*N,N'*-diisopropylhydrazine. Klages, Nober, Kircher, and Bock (11) obtained very poor yields of crude isopropylhydrazine from the treatment of hydrazine with isopropyl bromide.

Although, as stated previously, *n*-butyl- and *n*-amyl-hydrazines are not reported, Taipale and Usachev (12) prepared *sec*-butyl- and *sec*-amyl-hydrazine by the treatment of the corresponding azo compounds with sodium hydroxide.

Sommer, Schultz, and Nassau (13, 14) reported the preparation of methyl-,

benzyl-, piperidyl- and 2-aminoethyl-hydrazines as well as several arylhydrazines in good yield by the treatment of the corresponding amines with hydroxylamine-O-sulfonic acid (called HOS in subsequent references) in the presence of alkali. The only other reference reporting the application of this method is that of Berger (15), who treated 1-amino-1-phenylacetic acid with HOS to give an unreported yield of 1-phenyl-1-hydrazinoacetic acid. His attempts to prepare the hydrazino acid from 1-amino-1,1-diethylacetic acid resulted in failure.

In view of the ready availability of the necessary amines and the apparent simplicity of the method, the synthesis utilizing HOS was adopted as the most promising for the preparation of the desired alkylhydrazines. Ethyl-, propyl-, isopropyl-, *n*-butyl- and *n*-amyl-hydrazines were prepared in good yields, as was 2-hydroxyethylhydrazine.

HOS is easily prepared by the reaction of hydroxylamine sulfate with chlorosulfonic acid or oleum (13, 16). This hydrazine synthesis is relatively simple; the appropriate amine, potassium hydroxide, and water are mixed together and the HOS, in ice-water, added. The solution is heated to reflux and acidified, concentrated, and filtered from inorganic salts. The filtrate is treated with benzaldehyde, the benzalhydrazone extracted with ether and the ether solution steam-distilled from an aqueous oxalic acid solution until all benzaldehyde is removed. Upon cooling the residue the desired oxalate separates.

Sommer (13) reported a 40% yield<sup>1</sup> of 1-hydrazino-2-aminoethane from ethylenediamine using a ratio of amine to HOS of 1:1. In repeating this work we were able to obtain a yield of only 3%. However, by raising the ratio of amine to HOS to 3:1 and reducing the amount of water, thereby increasing the concentration of amine, yields of 27% were attained. This increased ratio of amine to HOS was successfully applied to the other alkylhydrazine preparations despite Sommer's statement that equimolar ratios were desirable. Optimum conditions were not determined but a ratio of 6-7:1 gave good yields.

Some modifications were made in Sommer's method which simplified the procedure considerably. As he suggested, the HOS solution was added dropwise to the refluxing solution of amine and potassium hydroxide. By using a smaller amount of water it was found that concentration of the reaction mixture was not necessary. It was further found that the potassium hydroxide was not necessary; instead a still larger excess of the amine was used. The yields were better than in the cases in which the inorganic base was employed.

Although HOS reacts with alcohols to give the alkyl sulfates of hydroxylamine (13), the reaction is apparently slower than that with amines. It was thought, therefore, that the treatment of ethanolamine with HOS should give 2-hydroxyethylhydrazine. This was found to be the case and the latter was prepared in good yield. Again it was found that equimolar ratios of amine to HOS gave low yields (10%). Using a ratio of 6:1 a yield of 48% was obtained. Since potassium hy-

<sup>1</sup> The yield is given in both percentage and weight. The weight of product reported corresponds to a yield of 80% but this figure, too, is ambiguous because the weight of benzaldehyde used to make the intermediate hydrazone would allow a maximum yield of 57%.

dioxide is soluble in ethanolamine, one run was made in which no water was used (except enough to dissolve the HOS) and the ratio of amine to HOS was 12:1. A yield of 50% was obtained, indicating that there is a practical limit for the amine to HOS ratio as far as increase in yield is concerned. The possibility exists that the HOS reacted with both the hydroxyl and amino groups, and during the isolation procedure the hydrazinoalkyl sulfate hydrolyzed to give the desired hydrazinoalcohol.

All of the prepared alkylhydrazine oxalates were converted to the corresponding 5-nitro-2-furaldehyde 2-alkylsemicarbazones. Neutralized aqueous solutions of the former were treated with potassium cyanate. The semicarbazides themselves were not isolated; instead their acidified solutions were treated with alcoholic solutions of 5-nitro-2-furaldehyde, whereupon the slightly soluble yellow semicarbazones precipitated.

#### EXPERIMENTAL<sup>2</sup>

*Hydroxylamine-O-sulfonic acid.* The HOS was prepared, using the method of Sommer, *et al.* (13), by interaction of chlorosulfonic acid and hydroxylammonium sulfate. Commercial grade reagents were employed with satisfactory results. Yields of 90–95% of product analyzing 86–95%, by iodometric titration, were obtained. The 95% HOS was used except where otherwise indicated.

*1-Hydrazino-2-aminoethane dioxalate.* (a) Fifty cc. of 10% ethylenediamine (0.083 mole), and a solution of 9.3 g. of potassium hydroxide in 200 cc. of water were mixed. A solution of 9.8 g. (0.083 mole) of HOS in 20 cc. of ice-water was added and the solution heated to reflux in seven minutes and held there for fifteen minutes. Ten cc. of glacial acetic acid was added and 90 cc. of distillate removed at atmospheric pressure. Distillation was continued at reduced pressure (90 mm.) until 110 cc. of liquid residue remained. The latter was cooled in an ice-bath, following which the crystals of inorganic salt were filtered off. The filtrate was warmed to 50°, 5 g. (0.047 mole) of benzaldehyde added and the emulsion stirred at 50° for five minutes. It was then cooled and extracted with two 50-cc. and one 25-cc. portions of ether. The ether extracts were added to a solution of 7.5 g. of anhydrous oxalic acid in 100 cc. of water, plus Darco, and the mixture steam-distilled until no more benzaldehyde came over. Upon filtering the 250 cc. of residue and cooling, a white solid separated. Yield 0.6 g., (3%), m.p. 180–185°. <sup>3</sup> Concentration of the filtrate yielded only oxalic acid.

(b) Fifteen grams (0.25 mole) of ethylenediamine, 135 cc. of water, and 9.4 g. of potassium hydroxide were mixed and heated to reflux. Over a period of twenty minutes a solution of 9.9 g. (0.083 mole) of HOS in 25 cc. of ice-water was added with mechanical stirring. Refluxing was continued for one-half hour, the solution cooled and then acidified with 20 cc. of glacial acetic acid. The solution was concentrated to 100 cc. at atmospheric pressure, cooled, the inorganic salts filtered off and the filtrate condensed with 9 g. (0.085 mole) of benzaldehyde. It was extracted with three 50-cc. portions of ether and the ether extract added to a solution of 15 g. of oxalic acid dihydrate, plus Darco, in 100 cc. of water. Steam-distillation was carried out until no more benzaldehyde came over. Upon filtering the 200 cc. of residue and cooling, 5.6 g., (27%), of *1-hydrazino-2-aminoethane dioxalate* were obtained, m.p. 193–195°. Recrystallization from 25% alcohol gave a melting point of 206°.

*Anal.* Calc'd for  $C_8H_{13}N_3O_8$ : C, 28.24; H, 5.14.

Found: C, 28.13; H, 5.20.

<sup>2</sup> All melting points were taken on the Fisher-Johns apparatus. Microanalyses, solubilities, and ultraviolet absorption curves were done by Mr. A. Caprio.

<sup>3</sup> Sommer, *et al.* (13), report 204°.

*n*-Amylhydrazine oxalate. One hundred fifty cc. of water, 47.5 g. (0.55 mole) of *n*-amylamine, and 9.4 g. of potassium hydroxide were mixed, two layers forming. The mixture was heated to reflux with stirring and a solution of 9.9 g. (0.083 mole) of HOS in 50 cc. of ice water was added dropwise over a period of one half hour. The solution was then cooled, acidified with 70 cc. of glacial acetic acid and 50 cc. of distillate removed at atmospheric pressure. The residue was cooled and the inorganic salts filtered off. The filtrate was warmed to 50° and stirred with 9 g. of benzaldehyde for ten minutes. The emulsion was cooled and extracted with three 50-cc. portions of ether. The ether extracts were added to a solution of 20 g. of oxalic acid dihydrate in 100 cc. of water, Darco added, and the mixture steam-distilled until no more benzaldehyde distilled over. Upon filtering and cooling, a white solid separated. The precipitate was filtered off and the filtrate was concentrated to 20 cc., whereupon more solid separated. The two solids were combined and recrystallized from 150 cc. of SDA #30 alcohol.<sup>4</sup> Yield 5.0 g., (31%), m.p. 164°.

*Anal.* Calc'd for C<sub>7</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C, 43.74; H, 8.39.

Found: C, 43.16; H, 8.45.

*n*-Butylhydrazine oxalate. The same procedure used in the preparation of *n*-amylhydrazine oxalate was applied to *n*-butylamine, using 120 cc. of water, 37 g. (0.51 mole) of *n*-butylamine, 11 g. of potassium hydroxide, and 9.9 g. (0.083 mole) of HOS in 25 cc. of water. Yield 6.7 g., (45%), m.p. 165°.

*Anal.* Calc'd for C<sub>6</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>: C, 40.44; H, 7.92.

Found: C, 40.00; H, 7.99.

*n*-Propylhydrazine oxalate. The same procedure was applied to *n*-propylamine using 100 cc. of water, 25.0 g. (0.42 mole) of *n*-propylamine, 9.9 g. of potassium hydroxide, and a solution of 8.5 g. (0.072 mole) of HOS in 20 cc. of water. Yield 6.1 g., (52%), m.p. 175°.

*Anal.* Calc'd for C<sub>5</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>: C, 36.58; H, 7.37.

Found: C, 36.36; H, 7.91.

*Isopropylhydrazine oxalate.* The same procedure was applied to isopropylamine using 125 cc. of water, 36 g. (0.61 mole) of isopropylamine, 11 g. of potassium hydroxide, and a solution of 9.9 g. (0.083 mole) of HOS in 20 cc. of water. Yield 6.0 g., (44%), m.p. 172°. Taipale (10) reports the melting point 156°.

*Anal.* Calc'd for C<sub>5</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>: C, 36.58; H, 7.37.

Found: C, 36.48; H, 7.55.

*Ethylhydrazine oxalate.* Forty grams (0.49 mole) of ethylamine hydrochloride was dissolved in 50 cc. of water and cooled in an ice-bath. A solution of 51 g. of potassium hydroxide in 50 cc. of water was cautiously added so that the temperature remained below 15°. The solution was then heated to reflux and with mechanical stirring a solution of 9.9 g. (0.083 mole) of HOS in 25 cc. of water added over a period of ten minutes. The solution was cooled and neutralized with 50 cc. of glacial acetic acid. The precipitated salts were filtered off and the filtrate warmed at 50° with 9 g. of benzaldehyde. The resulting emulsion was cooled, extracted with three 50-cc. portions of ether and the ether extract added to a solution of 11 g. of oxalic acid dihydrate in 50 cc. of water. The mixture was steam-distilled until no more benzaldehyde came over. The residue was evaporated to dryness *in vacuo*, and the residual solid recrystallized from 100 cc. of SDA #30 alcohol. Yield 5.2 g., (42%), m.p. 170-171°.

*Anal.* Calc'd for C<sub>4</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>: C, 32.00; H, 6.71.

Found: C, 32.21; H, 6.77.

*2-Hydroxyethylhydrazine oxalate.* (a) Five grams (0.082 mole) of ethanolamine was dissolved in 25 cc. of water and a solution of 11 g. of potassium hydroxide in 35 cc. of water added. The solution was heated to 95° on the steam-bath and a solution of 10.8 g (0.082 mole) of HOS (86%) in 20 cc. of ice-water added over a period of thirteen minutes. The solution was heated at 95° for fifteen minutes, cooled and acidified with 35 cc. of glacial acetic acid. After filtering off the inorganic salts, the filtrate was warmed to 55° and stirred

<sup>4</sup> Denatured ethyl alcohol.

with 15 g. of benzaldehyde for ten minutes, cooled and extracted with three 50-cc. portions of ether. The ether extracts were added to a solution of 15 g. of oxalic acid dihydrate in 50 cc. of water and the mixture steam-distilled until no more benzaldehyde came over. The residue was concentrated to dryness *in vacuo* and the solid recrystallized from SDA #30 alcohol. Yield 1.3 g., (10%), m.p. 106°.

(b) Using exactly the same conditions and reagents, except that the amount of ethanolamine was raised to 31 g. (0.51 mole), the yield was 6.5 g., (48%), m.p. 106°.

(c) Using the same reagents and procedure, except that no water (other than that to dissolve the HOS) was used and the amount of amine was 61 g. (1.0 mole), the yield was 6.8 g. (50%), m.p. 106°.

*Anal.* Calc'd for  $C_4H_{10}N_2O_5$ : C, 28.92; H, 6.07.

Found: C, 28.78; H, 6.50.

A sample of 2-hydroxyethylhydrazine prepared by the method of Gabriel (17) was converted to the oxalate by dissolving equimolar amounts of oxalic acid and the 2-hydroxyethylhydrazine in absolute alcohol. The resulting precipitate was recrystallized from SDA #30 alcohol, m.p. 106°. A mixed melting point with the material prepared by the HOS method gave no depression.

#### PREPARATION OF ALKYLHYDRAZINE OXALATES WITHOUT THE USE OF INORGANIC BASE

*n-Butylhydrazine oxalate.* Thirty-seven grams (0.51 mole) of *n*-butylamine was mixed with 15 cc. of water and heated to reflux. With stirring, a solution of 5.0 g. (0.042 mole) of HOS in 15 cc. of water was added dropwise over a period of eight minutes. After completion of addition the solution was cooled, acidified with 30 cc. of glacial acetic acid and warmed to 50° with 9 g. of benzaldehyde for ten minutes. The resulting emulsion was cooled and extracted with three 50-cc. portions of ether. The ether extracts were added to a solution of 7 g. of oxalic acid dihydrate in 25 cc. of water and the mixture steam-distilled until no more benzaldehyde came over. The residue was concentrated to dryness *in vacuo* and the solid residue recrystallized from 100 cc. of SDA #30 alcohol. Yield 4.5 g., (60%), m.p. 165°.

*Isopropylhydrazine oxalate.* The same procedure was followed using 118 g. (2.0 moles) of isopropylamine, 25 cc. of water, and a solution of 20 g. (0.169 mole) of HOS in 40 cc. of water. Yield 14.3 g., (52%), m.p. 172°.

#### 5-NITRO-2-FURALDEHYDE 2-ALKYLSEMICARBAZONES

The corresponding 5-nitro-2-furaldehyde 2-alkylsemicarbazones derived from the alkylhydrazine oxalates were prepared by identical procedures. As an example, that used to prepare the *n*-amyl derivative will be presented.

*5-Nitro-2-furaldehyde 2-n-amylsemicarbazone.* Two grams of *n*-amylhydrazine oxalate was dissolved in 100 cc. of water and the pH was adjusted to 7 with dilute sodium hydroxide. A solution of 0.85 g. of potassium cyanate in 10 cc. of water was added and the resulting solution allowed to stand overnight at room temperature. It was then acidified with dilute hydrochloric acid and a solution of 1.5 g. of 5-nitro-2-furaldehyde in 10 cc. of alcohol added, whereupon a yellow solid precipitated. This was filtered off, washed with water, and dried. Yield 1.9 g., (68%). After recrystallization from dilute alcohol, the m.p. was 127–128°. Its solubility in water at 25° was 34 mg./l. Ultraviolet absorption maxima in water were observed at 2700 Å and 3900 Å,  $E_m = 12,300$  and 16,100, respectively.

*Anal.* Calc'd for  $C_{11}H_{16}N_4O_4$ : C, 49.24; H, 6.01.

Found: C, 49.01; H, 5.83.

*5-Nitro-2-furaldehyde 2-n-butylsemicarbazone.* M.p. 123°, yield 37%, water solubility 117 mg./l., ultraviolet absorption maxima at 2700 Å and 3900 Å,  $E_m = 12,900$  and 16,000, respectively.

*Anal.* Calc'd for  $C_{10}H_{14}N_4O_4$ : C, 47.24; H, 5.55.

Found: C, 47.12; H, 5.30.

*5-Nitro-2-furaldehyde 2-n-propylsemicarbazone*. M.p. 157-158°, yield 47%, water solubility 250 mg./l., ultraviolet absorption maxima at 2700 Å and 3875 Å,  $E_m = 13,200$  and 16,600, respectively.

*Anal.* Calc'd for  $C_9H_{12}N_4O_4$ : C, 45.00; H, 5.04.

Found: C, 44.94; H, 5.15.

*5-Nitro-2-furaldehyde 2-isopropylsemicarbazone*. M.p. 177°, yield 33%, water solubility 230 mg./l., ultraviolet absorption maxima at 2700 Å and 3900 Å,  $E_m = 10,400$  and 15,500, respectively.

*Anal.* Calc'd for  $C_9H_{12}N_4O_4$ : C, 45.00; H, 5.04.

Found: C, 45.19; H, 5.17.

*5-Nitro-2-furaldehyde 2-ethylsemicarbazone*. M.p. 203-204°, yield 50%, water solubility 260 mg./l., ultraviolet absorption maxima at 2700 Å and 3850 Å,  $E_m = 12,300$  and 16,100, respectively.

*Anal.* Calc'd for  $C_8H_{10}N_4O_4$ : C, 42.48; H, 4.46.

Found: C, 42.74; H, 4.44.

#### SUMMARY

Alkylhydrazines, ethyl through amyl, have been prepared in good yield by the treatment of the corresponding amine with hydroxylamine-O-sulfonic acid.

2-Hydroxyethylhydrazine has also been prepared by this method.

The corresponding 5-nitro-2-furaldehyde 2-substituted semicarbazones have been prepared from the alkylhydrazines synthesized above.

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