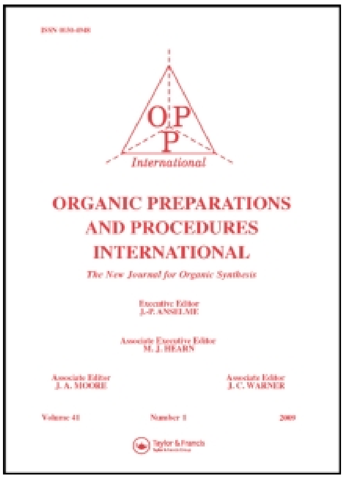

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ETHYLHYDRAZINE. THE FISCHER SYNTHESIS REVISITED

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ETHYLHYDRAZINE. THE FISCHER SYNTHESIS REVISITED

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Ethylhydrazine was first prepared by Emil Fischer from N,N'-diethylurea as shown below;[1] and Weygand gives a

$$C_2H_5NHCONHC_2H_5 \xrightarrow[H_2SO_4]{NaNO_2} C_2H_5N(NO)CONHC_2H_5 \xrightarrow[HOAc]{Zn}$$

$$C_2H_5N(NH_2)CONHC_2H_5 \xrightarrow[HCl]{H_2O} C_2H_5NHNH_2\cdot 2HCl \xrightarrow{NaOH} C_2H_5NHNH_2$$

detailed procedure based on the Fischer synthesis.[2] It has also been obtained by reduction of ethyl nitramine with zinc and hydrochloric acid,[3] by reaction of ethylmagnesium iodide with ethyl diazoacetate,[4] by alkylation of hydrazine with diethyl sulfate,[5] and by amination of ethylamine with chloramine[6] or with hydroxylamine-O-sulfonic acid.[7]

Although alkylation of hydrazine with diethyl sulfate[5] would appear to be the simplest route, it failed to give any ethylhydrazine in our hands. Only hydrazine, as the dihydrochloride, was recovered upon workup of the reaction mixture as directed.[5] The other methods do not appear to offer any advantages over the Fischer route. (See ref. 2.)

The Fischer-Weygand route, with modifications introduced here, is not as tedious as it may appear, because intermediates are used without purification. All things considered -- ease and safety of operation, cost and availability of starting materials, and yield and purity of the product -- it appears to us to be the most satisfactory route for preparation of moderately large quantities (of the order of one mole) of ethylhydrazine. Because of this, and because the Fischer and Weygand references are becoming increasingly inaccessible, we present our procedure in detail.

EXPERIMENTAL

N-Nitroso-N,N'-diethylurea.- One hundred grams (0.86 mole) of N,N'-diethylurea (Aldrich Chemical Co. No. D10,108) and 300 ml of ether were placed in a 1-l. three-necked flask fitted with a stirrer, thermometer, and a dropping funnel extending beneath the surface of the liquid. Concentrated hydrochloric acid (83 ml, 1.0 mole) was added slowly with stirring and cooling to maintain the temperature below 25°. A slurry of 70 gm (1.0 mole) of sodium nitrite in 70 ml of water was then added from the funnel in the course of two hours with stirring and cooling so as to maintain the temperature at 10-20°. After one-half hour, the layers were separated; and the lower, aqueous layer was extracted with two 40-ml portions of ether. The ethereal solutions were combined and washed with three 20-ml portions of cold saturated sodium chloride solution, and then dried overnite with anhydrous magnesium sulfate. The ether was removed by distillation under reduced pressure at room temperature and left 131 gm (105%) of

N-nitroso-N,N'-diethylurea as an orange-red oil.

2,4-Diethylsemicarbazide.- In a 2-l. three-necked flask equipped with a stirrer, thermometer, and dropping funnel were placed 800 ml of water, 160 gm of 30-mesh granular zinc, and the 131 gm of crude N-nitroso-N,N'-diethylurea. The flask was cooled in an ice-water bath; and 250 ml of glacial acetic acid was added dropwise with stirring and cooling at 25-35° in the course of $2^1/2$ hr. Stirring was continued one-half hour. The solution was then filtered with suction from unreacted zinc; and the filtrate was returned to the 2-l. flask. Concentrated aqueous ammonia (450 ml of 15N NH_3) was added and was followed by 400 gm of solid sodium hydroxide, added in portions with stirring and cooling to below 30°. The mixture (1500 ml in volume) was separated into two portions for extraction with ether in two 1-l. separatory funnels. At this point and during the subsequent extraction with ether, needle-like crystals of sodium acetate trihydrate separated and were removed by filtration with suction as necessary. Oily product that separated from each portion of the solution was withdrawn before extraction with ether. Five 30-ml portions of ether were used, each portion being used to extract each half of the aqueous solution in turn. The ether extracts were combined with the oily product first separated; and the whole was dried overnight with anhydrous potassium carbonate. The ether was removed by aspiration and warming to 40°. There remained 88 gm (0.67 mole) crude 2,4-diethylsemicarbazide (78% from N,N'-diethylurea) as a light yellow syrup.[8]

Ethylhydrazine Dihydrochloride.- The crude 2,4-diethylsemicarbazide obtained above was added in small portions to 125 ml of concentrated hydrochloric acid contained in a 500-ml round-bottomed flask. (The amount of acid is 10% more than needed to convert the liberated bases to their monohydrochlorides.) A hydrochloride salt of the semicarbazide precipitated. A reflux condenser was attached and the mixture was heated under reflux 2.5 hr. Evolution of gas (CO_2) had ceased after 1.5 hr.[9] The solution was cooled; 50 ml of concentrated hydrochloric acid was added; and the mixture was heated under reflux again for one hour. It was then cooled; 100 ml of concentrated hydrochloric acid was added; and the resulting mixture was cooled thoroughly in an ice bath with agitation to induce crystallization.[10] The crystals were collected by filtration with suction and weighed 83 gm. The filtrate was reduced to about half its volume by distillation under reduced pressure (aspirator) and yielded a second crop of 17 gm. A third crop of 6 gm was obtained by further concentration to about 75 ml, followed by addition of an equal volume of 12N HCl and thorough cooling.

In order to ensure freedom from ethylamine hydrochloride, the crude product was purified by recrystallization from 90 ml of 6N HCl. A first crop of 60 gm was obtained -- and a second crop of 17 gm by addition of 90 ml of 12N HCl to the mother liquor, followed by thorough cooling.[10] The total yield of 77 gm of recrystallized product is 86% of theory from 2,4-diethylsemicarbazide and 67% from N,N'-diethylurea.

<u>Ethylhydrazine</u>.- A mixture of 80 gm of sodium hydroxide and 50 ml of water was prepared in a 250-ml distilling flask and cooled thoroughly in an ice-water bath. The 77 gm of recrystallized ethylhydrazine dihydrochloride was added to

it in small portions with good mixing and cooling over a period of 1.5 hr. The mixture was distilled. To avoid bumping, the flask was heated carefully by playing a Bunsen burner flame over its bottom. The distillate was collected in a 125-ml. distilling flask attached to the side arm of the 250-ml flask by means of a cork or rubber stopper and cooled with running water collected in a funnel draining to the sink. About 50 ml of an azeotrope with water, distilling at 105-108°, and weighing 46 gm, was collected. The distillate contains 30-35 gm (86-100% from the dihydrochloride) of ethylhydrazine, and is suitable for many purposes.

> CAUTION: AS THE TOXICITY OF ETHYLHYDRAZINE IS NOT KNOWN, SUITABLE PRECAUTIONS SHOULD BE TAKEN TO AVOID BREATHING ITS VAPORS OR HAVING IT CONTACT THE SKIN.

For drying, 10 gm of solid sodium hydroxide is added, the distilling flask is stoppered (the side arm loosely) and left several hours with occasional agitation, if possible, and then overnight. A lower aqueous layer is withdrawn with a pipet, 4-5 gm of solid sodium hydroxide is added, and the material is distilled as before into a second 125-ml distilling flask. A few grams of calcium hydride is added carefully to the distillate, the flask is stoppered (the side arm loosely to permit escape of hydrogen) and allowed to stand several hours or overnight. The liquid is then decanted into an oven-dried 125-ml distilling flask, a little calcium hydride is added (there should be little or no effervescence), and the material is distilled as before into a second oven-dried distilling flask. A boiling range of 99-103° may be observed, depending on the amount of superheating of vapors near the end. Lit. bp. 99.5°/709 torr.[1] The yield is 26-30 gm (75-86% from the dihydrochloride). The residual calcium hydride should effervesce strongly when added to water.[11]

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8. Preliminary tests indicated additional product could be recovered from the aqueous solution as an oily acetone derivative, $(CH_3)_2C{=}NNEtCONHEt$, which could be hydrolyzed to ethylhydrazine dihydrochloride like the 2,4-diethylsemicarbazide itself; but these experiments were not carried to conclusion.
9. The 15 hr. of heating used by Fischer[1] and Weygand[2] was unnecessary.
10. Alternatively, the solution may be saturated with HCl gas at this point.[2]
11. Ethylhydrazine may also be dried by distillation from barium oxide.[1,5]

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