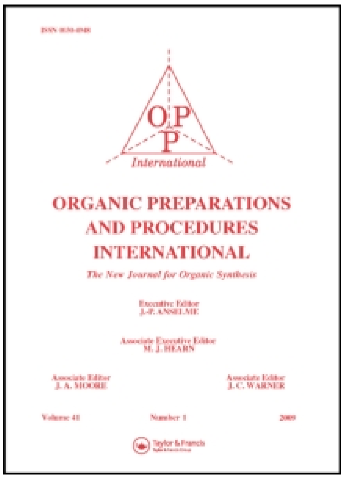

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ETHYLMETHYLAMINE, ETHYLMETHYLNITROSAMINE AND 1-ETHYL-1-METHYLHYDRAZINE

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ETHYLMETHYLAMINE, ETHYLMETHYLNITROSAMINE AND 1-ETHYL-1-METHYLHYDRAZINE

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CHART I

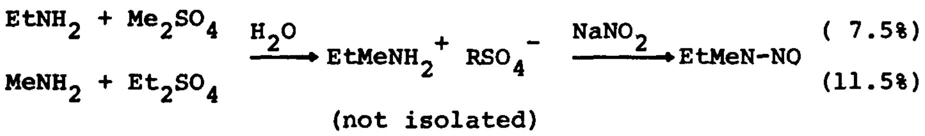
$$\mathrm{EtNH_2} \xrightarrow{\mathrm{C_6H_5CHO}} \mathrm{PhCH{=}NEt} \xrightarrow{\mathrm{Me_2SO_4}} \mathrm{PhCH{=}N(Me)Et^+\ MeSO_4^-} \xrightarrow{\mathrm{H_2O}}$$

$$\mathrm{EtMeNH_2^+\ MeSO_4^-} \xrightarrow{\mathrm{NaNO_2}} \mathrm{EtMeNNO} \xrightarrow{\mathrm{Zn,\ HOAc}} \mathrm{EtMeNNH_2}$$

A procedure has been developed for synthesis of 1-ethyl-1-methylhydrazine from ethylamine by way of N-benzylideneethylamine, $C_6H_5CH{=}NEt$, without isolation of the other intermediates shown in Chart I. The procedure incorporates the following improvements in the synthesis of ethylmethylamine to be found in Organic Syntheses:[1] (i) the use of 70% aqueous, rather than anhydrous, ethylamine for the preparation of N-benzylideneethylamine; (ii) elimination of codistillation with benzene for removal of water in that step; and (iii) use of benzaldehyde as a solvent for methylation of N-benzylideneethylamine with dimethyl sulfate, which eliminates tar formation and obviates the use of high pressure equipment, needed with methyl iodide. The overall yield is 51% from ethylamine; and more than 92% of the benzaldehyde is recovered.

Our success here prompted us to investigate, as routes to ethylmethylnitrosamine, the direct methylation of ethylamine with dimethyl sulfate, and the direct ethylation of methylamine with diethyl sulfate, each followed by nitrosation without isolation of the intermediate ethylmethylamine (Chart II). The yields were 7.5% and 11.5%, respectively. The difference in yields is believed to be significant and to be a consequence of a lesser amount of further alkylation of the intermediate ethylmethylamine with diethyl sulfate than with dimethyl sulfate, because of steric factors. These routes do not compare favorably with the one by way of N-benzylideneethylamine, however, because of the much larger volume of reagents needed to achieve the same end.

CHART II



$$\begin{array}{l}EtNH_2 + Me_2SO_4\\ MeNH_2 + Et_2SO_4\end{array} \xrightarrow{H_2O} \underset{\text{(not isolated)}}{EtMeNH_2^+\ RSO_4^-} \xrightarrow{NaNO_2} EtMeN\text{-}NO \quad \begin{array}{l}(\ 7.5\%)\\ (11.5\%)\end{array}$$

EXPERIMENTAL

N-Benzylideneethylamine.[1,2] Benzaldehyde (244 gm, 2.30 moles) was placed in a three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a thermometer reaching into the liquid. The flask was cooled in an ice-water bath; and 150 gm (189 ml, 2.33 moles) of 70% aqueous ethylamine was added dropwise with stirring and cooling so as to maintain the temperature at 20-30°. Within an hour from the start of addition of the ethylamine, the mixture was poured into a separatory funnel. The lower layer was drawn off and discarded; and the upper layer was dried with anhydrous sodium carbonate and distilled under reduced pressure. After a small wet forerun (4-5 gm, recyclable), there was obtained 293 gm (2.20 moles, 95.7%) of N-benzylideneethylamine boiling at 60-64° at 3.2 torr, and a small after-run to 68°, which was recyclable.

Methylation of N-Benzylideneethylamine; Hydrolysis to Ethylmethylammonium Methosulfate. N-Benzylideneethylamine (133 gm, 1.00 mole) and 100 gm of benzaldehyde as solvent were placed in a 500-ml Erlenmeyer flask. A thermometer was inserted; and 50 ml (66 gm, 0.52 mole) of dimethyl sulfate (Matheson, Coleman, and Bell research grade) was added. In 10 minutes, the temperature reached 50°. The flask was cooled in an ice-water bath; and the temperature was maintained at 45-55° until the need for cooling abated. The temperature was then brought to 40° by external cooling of the flask; and another 50 ml of dimethyl sulfate was added. The temperature was maintained at 45-55° as before, until the reaction subsided (about 30 min.). The flask was then heated on a steam bath at 55° for 15 min. The contents of the flask were then poured into 200 ml of cold water, contained in a 500 ml separatory funnel, and mixed thoroughly with the water.

The mixture was cooled to room temperature. The lower, aqueous layer was drawn off; and the upper, benzaldehyde layer was poured into a flask. The aqueous layer was extracted with three 15-ml portions of ether. The ether extracts were combined with the benzaldehyde and the whole was dried with anhydrous sodium carbonate preparatory to recovery of the benzaldehyde.

The aqueous layer was used directly in the next step.[3]

The benzaldehyde and ether extracts were distilled under reduced pressure (aspirator). After a small forerun, which was recyclable, the benzaldehyde (190 gm, 92%) was collected at 79° at 25 torr.

Ethylmethylnitrosamine.[2,4,5] To the aqueous solution from the preceding step, 69 gm (1.00 mole) of sodium nitrite was added; and most of it was brought into solution by swirling. A drop of concentrated sulfuric acid was added and mixed in by swirling. When the effervescence subsided, a second drop of acid was mixed in as before; and this slow, dropwise addition of sulfuric acid was continued until 1-2 ml had been added, whereupon the effervescence accompanying addition ceased; and the solution had become permanently acidic. During the acidification, the temperature of the mixture rose to about 35°. The temperature was then brought to 60° by 20 minutes of heating on a steam bath.

The mixture was then distilled under reduced pressure (aspirator, about 25 torr) until the residue in the distilling flask became thick with solid. An ice-cooled trap was used to limit losses. About 225 ml of distillate was obtained, including ice-trapped material.

This distillate can be used directly in the next step. For isolation of ethylmethylnitrosamine, however, the distillate is saturated with potassium carbonate, the oily layer is separated, the aqueous layer is extracted with two 25-ml portions of ether, the combined extracts are dried with anhydrous potassium carbonate and distilled under reduced pressure. The yield of ethylmethylnitrosamine boiling at 66-68° at 21 torr is about 60 gm (68%).[6]

CAUTION: SUITABLE PRECAUTIONS SHOULD BE TAKEN AGAINST SKIN CONTACT AND INHALATION OF VAPORS OF ETHYLMETHYLNITROSAMINE AND HYDRAZINES.

1-Ethyl-1-methylhydrazine.[2,4,5,7] The aqueous distillate from the preceding step was made up to 800 ml with water and was placed in a 2-l. three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a thermometer reaching into the liquid. Zinc, 30-mesh granular, or dust, 130 gm pure weight (2.0 moles), was added. The stirrer was started; and 285 ml (300 gm, 5.0 moles) of glacial acetic acid was added dropwise in the course of one hour, with cooling of the flask in an ice-water bath so as to maintain the temperature at 25-30°. After all the acetic acid had been added, the cooling bath was removed and the temperature was allowed to rise to 60-70°. It was maintained at 70° by external heating, with continued stirring, for one hour. The mixture was then allowed to cool to room temperature.

The mixture was filtered with suction from unreacted zinc. The filtrate was divided into two portions and one portion was placed in a 2-l. flask for steam distillation. A cold solution of 180 gm of sodium hydroxide in 200 ml of water was added rapidly with swirling.[8] The hot mixture was subjected immediately to steam distillation. To the first 250 ml of distillate was added 180 gm of solid sodium hydroxide, with cooling. The hydrazine layer was separated and placed over solid sodium hydroxide for further drying. The aqueous sodium hydroxide solution from this separation was used to basify the second half of the filtrate from the reduction. An additional 150 ml of distillate was collected from steam distillation of the first half of the filtrate and was added to the second half prior to its steam distillation. The second half was then subjected to steam distillation as was the first. The first 250 ml of distillate contained most of the hydrazine and was treated with 180-200 gm of solid sodium hydroxide for its recovery.[9]

The 1-ethyl-1-methylhydrazine, after further drying with solid sodium hydroxide, was purified by distillation through a 20 x 1-cm column packed with glass helices. The product, bp 81-83°, lit.[2] bp. 83-84°, weighed 40 gm (54% from benzylideneethylamine.)

Ethylmethylnitrosamine via Methylation of Ethylamine and Ethylation of Methylamine.- The conditions in these experiments were designed to duplicate those in the successful preparation from N-benzylideneethylamine described above.

A. Via Methylation of Ethylamine.- To 32 gm (40 ml, 0.50 mole) of 70% aqueous ethylamine and 90 ml of water in a 500-ml three-necked flask fitted with a stirrer, dropping funnel, and a thermometer reaching into the liquid, and cooled in an ice-water bath, was added 48 ml (63 gm, 0.50 mole) of dimethyl sulfate with stirring and cooling so as to maintain the temperature at 25-30°. After one hour, 36 gm (0.52 mole) of sodium nitrite was added. This was followed by dropwise addition of conc. sulfuric acid with stirring and cooling, until reaction ceased; about 3 ml was required. The solution was transferred to a 500-ml Erlenmeyer flask and heated to 60°. Another 2 ml of sulfuric acid was added.

The mixture was distilled under reduced pressure (aspirator) with an ice-cooled trap to minimize losses, until the pot residue became thick with solid. About 100 ml of distillate was obtained. It was saturated with anhydrous potassium carbonate and extracted with ether. The ethereal extracts were dried with anhydrous potassium carbonate and then distilled under reduced pressure to give 3.3 gm (7.5%) of ethylmethylnitrosamine, bp. 68°/25 torr.

B. Via Ethylation of Methylamine.- To 39 gm (0.50 mole) of 40% aqueous methylamine and 77 ml of water in a 500-ml three-necked flask equipped with a mechanical stirrer, thermometer, and dropping funnel was added 77 gm (65 ml, 0.50 mole) of diethyl sulfate, with stirring while the temperature was maintained at 30-35°. The reaction was slow and the diethyl sulfate remained as a separate layer until it reacted. The mixture was heated briefly to 50° to complete the reaction. It was then cooled to 25° and 36 gm (0.52 mole) of sodium nitrite was added, followed by the dropwise addition of conc. sulfuric acid; NO_2 was evolved. The mixture was then distilled and worked up as before to give 5.1 gm (11.5%) of ethylmethylnitrosamine.

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1. S. Wawzonek, W. McKillip, and C. J. Peterson, in "Organic Syntheses", Vol. 44, W. E. Parham, ed., Wiley, New York, N. Y., 1964, p. 75.

2. K. A. Jensen, H. R. Baccaro, O. Buchardt, G. E. Olsen, G. Pederson and J. Toft, Acta Chem. Scand., <u>15</u>, 1109 (1961).

3. For isolation of ethylmethylamine, one would proceed as in Ref. 1.

4. N. N. Ogimachi and H. W. Kruse, J. Org. Chem., <u>26</u>, 1642 (1961).

5. K. Klages, U. S. Patent 3,214,474 (10/26/65); Chem. Abstr., <u>64</u>, 1958 (1966).

6. It may be noted that the direct nitrosation without isolation of ethylmethylamine would not be possible if methyl iodide, instead of dimethyl sulfate, were used to methylate N-benzylideneethylamine, because of complicating redox reactions between iodide ion and nitrous acid.

7. H. H. Stroh and H. G. Scharnow, Chem. Ber., <u>98</u>, 1588 (1965).

8. The amounts of reagents are in accordance with the stoichiometry of the reactions involved (continuing from Chart I):

   3. $PhCH{=}N(Me)Et^{+}\ MeSO_4^{-} + H_2O \rightarrow PhCHO + EtMeNH_2^{+}\ MeSO_4^{-}$

   4. $EtMeNH_2^{+}\ MeSO_4^{-} + NaNO_2 \rightarrow EtMeNNO + H_2O + NaMeSO_4$

   5. $EtMeNNO + 2Zn + 5HOAc \rightarrow EtMeNHNH_2^{+}\ OAc^{-} + 2Zn(OAc)_2 + H_2O$

   6. $EtMeNHNH_2^{+}\ OAc^{-} + 2Zn(OAc)_2 + 9NaOH \rightarrow EtMeNNH_2 + EtMeNNH_2 + 9Na^{+} + 2Zn(OH)_4^{=} + 5AcO^{-} + H_2O$

9. If the procedure is to be repeated many times for production of a large quantity of the hydrazine, the steam distillation should be continued and a second fraction, 150-250 ml, collected. This fraction would contain 3-5 gm of the hydrazine and could be used as part of the water in the zinc reduction of another batch of ethylmethylnitrosamine, with a consequent slight improvement in yield.

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