[Contribution from the Chemical Laboratory of Princeton University]

O,N,N-TRIALKYLHYDROXYLAMINES

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Received June 21, 1928 Published October 6, 1928

A number of trialkyl substituted hydroxylamines of the amine oxide type, R_3NO, have been described, but information concerning the isomeric compounds of the form R_2NOR is very limited. With the exception of Lossen's[1] O,N,N-triethylhydroxylamine, the description of which was so meager as to make the evidence for its existence quite doubtful, and the substituted hydroxylamino alcohols, $R(RO)NCH_2CH_2OH$, described by Jones and Burns[2] and by Jones and Major,[3] no O,N,N-trialkylhydroxylamines have been prepared.

Dunstan and Goulding[4] isolated trimethylamine oxide, $(CH_3)_3NO$, from the products obtained by the action of methyl iodide upon hydroxylamine. To account for the amine oxide, they suggested that O,N,N-trimethylhydroxylamine, $(CH_3)_2NOCH_3$, or its salt, was probably an intermediate product and that, by rearrangement, it passed to the amine oxide.[5]

$$(CH_3)_2NOCH_3 \longrightarrow (CH_3)_3N{=}O$$

Since O,N,N-trimethylhydroxylamine had not been prepared, it was not possible to reach a decision concerning the correctness of this assumption. However, certain other O,N,N-trisubstituted hydroxylamines were found to be comparatively stable compounds[1,2,3,6] which showed no tendency to rearrange to amine oxides. This made the explanation of the reaction proposed by Dunstan and Goulding rather unlikely. It is interesting to note, also, that Meisenheimer and his co-workers have observed that certain amine oxides, when heated in alkaline solution, suffer the reverse change and pass to O,N,N-trisubstituted hydroxylamines.[6b,c]

In the course of these investigations, O,N,N-trimethylhydroxylamine was obtained by the action of methyl iodide upon O,N-dimethylhydroxylamine in ether according to the equation

$$CH_3I + 2CH_3ONH(CH_3) \longrightarrow CH_3ONH_2(CH_3)I + CH_3ON(CH_3)_2$$

The ether solution, separated from the iodide, was treated with phenyl isocyanate to eliminate any O,N-dimethylhydroxylamine as α-phenyl-

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[1] Lossen, *Ann.*, **252**, 233 (1889).

[2] Jones and Burns, This Journal, **47**, 2972 (1925).

[3] Jones and Major, *ibid.*, **49**, 1532 (1927).

[4] Dunstan and Goulding, *J. Chem. Soc.*, **75**, 794 (1899).

[5] Dunstan and Goulding, *ibid.*, **75**, 1004 (1899).

[6] (a) Behrend and Leuchs, *Ann.*, **257**, 225, 237 (1890); (b) Meisenheimer, *Ber.*, **52**, 1667 (1919); (c) Meisenheimer, Greeske and Willmersdorf, *Ber.*, **55**, 513 (1922); (d) ref. 3, pp. 1535, 1536.

β,β'-methylmethoxyurea. Ether and the trimethyl compound were then distilled from the urea and the O,N,N-trimethylhydroxylamine hydrochloride was precipitated from the ether by hydrogen chloride gas. The free base, liberated from the salt in the usual manner, was a liquid boiling at 30°. It did not reduce ammoniacal silver nitrate. It showed no tendency to rearrange to trimethylamine oxide. Obviously it cannot be regarded as the intermediate in the preparation of trimethylamine oxide as Lossen supposed. Undoubtedly methyl iodide reacts with hydroxylamine in such a fashion that methyl groups become attached to the nitrogen atom until the compound $(CH_3)_3NOHI$ is formed, which is responsible for the amine oxide.

When O,N,N-trimethylhydroxylamine was heated with concentrated hydrochloric acid at 190°, methylamine and formaldehyde were produced. Behrend and Leuchs[7] found that O,N,N-tribenzylhydroxylamine was decomposed by concentrated hydrochloric acid to give dibenzylhydroxylamine and benzyl chloride according to the equation

$$(C_6H_5CH_2)_2NOCH_2C_6H_5 + HCl \longrightarrow (C_6H_5CH_2)_2NOH + ClCH_2C_6H_5$$

If O,N,N-trimethylhydroxylamine decomposed in a similar manner, we should expect dimethylhydroxylamine and methyl chloride as products of the reaction. It is well known that N,N-dialkylhydroxylamines are quite readily decomposed to give aldehydes and alkylamines.[8] Therefore, if one disregards salt formation, the action of hydrochloric acid on O,N,N-trimethylhydroxylamine may be represented schematically as follows

$$\begin{aligned}&(CH_3)_2NOCH_3 + HCl \longrightarrow (CH_3)_2NOH + CH_3Cl\\&(CH_3)_2NOH \longrightarrow CH_3N{=}CH_2 + H_2O\\&CH_3N{=}CH_2 + H_2O \longrightarrow CH_2O + CH_3NH_2\end{aligned}$$

The possibility that the production of formaldehyde depended upon the initial elimination of the methoxy group as formaldehyde according to the equation

$$(CH_3)_2NOCH_3 \longrightarrow (CH_3)_2NH + CH_2O$$

followed by decomposition of dimethylamine by the acid to yield methylamine, was excluded because of the fact that at the temperature of the experiment, namely, 190°, dimethylamine was not decomposed by concentrated hydrochloric acid.

By similar reaction, O,N-diethyl-N-methylhydroxylamine was formed from methyl iodide and O,N-diethylhydroxylamine. Ethyl iodide, however, reacted with O,N-diethylhydroxylamine very slowly; even when the reaction was allowed to continue three times as long, scarcely any addition was observed.

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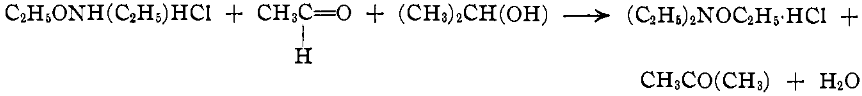
[7] Behrend and Leuchs, *Ann.*, **257**, 231 (1890).

[8] (a) Walder, *Ber.*, **219**, 1629, 3287 (1886); (b) Behrend and Leuchs, *Ann.*, **257**, 233 (1890); (c) Dunstan and Goulding, *J. Chem. Soc.*, **75**, 793 (1899); (d) Bewad, *J. prakt. Chem.*, **63**, 193 (1901).

An unsuccessful attempt was made to prepare O,N,N-triethylhydroxylamine by the action of acetaldehyde on O,N-diethylhydroxylammonium chloride in the presence of *iso*propyl alcohol, according to the equation



$$C_2H_5ONH(C_2H_5)HCl + \underset{\displaystyle H}{CH_3\overset{}{C}}{=}O + (CH_3)_2CH(OH) \longrightarrow (C_2H_5)_2NOC_2H_5{\cdot}HCl + CH_3CO(CH_3) + H_2O$$

Ethyl piperidine has been made in a similar manner by the action of acetaldehyde on piperidine hydrochloride in the presence of *iso*propyl alcohol.[9] Since acetone was observed among the products of the reaction, it was thought possible that *iso*propyl alcohol reduced O,N-diethylhydroxylammonium chloride. This was found to be the case; a mixture of O,N-diethylhydroxylammonium chloride, heated with *iso*propyl alcohol at 150°, gave acetone, ethylammonium chloride and probably ethyl alcohol according to the equation

$$C_2H_5ONH(C_2H_5)HCl + (CH_3)_2CH(OH) \longrightarrow C_2H_5NH_2{\cdot}HCl + CH_3CO(CH_3) + C_2H_5OH$$

When trimethylamine oxide is treated with methyl iodide, trimethylmethoxyammonium iodide is formed according to the equation[10]

$$(CH_3)_3N{=}O + CH_3I \longrightarrow [(CH_3)_3NOCH_3]I$$

The question arose whether the same compound would be formed by the action of methyl iodide on O,N,N-trimethylhydroxylamine, as follows

$$(CH_3)_2NOCH_3 + CH_3I \longrightarrow [(CH_3)_3NOCH_3]I$$

This was found to be the case; the compound formed in this way corresponded in every respect to the substance described by Dunstan and Goulding and by Meisenheimer.

Experimental Part

1. O,N,N-Trimethylhydroxylamine, $(CH_3)_2NOCH_3$

Preparation of O,N,N-Trimethylhydroxylammonium Chloride.—Two-tenths mole of O,N-dimethylhydroxylamine, prepared by Major and Fleck's modification of Jones' method,[11] was added to a solution of 0.1 mole of methyl iodide in dry ether. A white solid soon began to form. After the mixture had stood in a closed vessel for four days, the white precipitate was removed by filtration. It melted at 134° and weighed 13 g. It was dissolved in alcohol and shaken with sufficient silver oxide to combine with all of the iodide ion present. The free base was then distilled at room temperature under reduced pressure and collected in dilute hydrochloric acid. The small oily residue left in the distilling flask was probably trimethylmethoxyammonium hydroxide. The hydrochloric acid solution, evaporated to dryness, gave a white, crystalline solid which, after one crystallization from absolute alcohol, melted at 115–116°. A mixture of this compound with pure O,N-dimethylhydroxylammonium chloride, m. p. 115–116°, also melted at 115–116°.

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[9] D. R. P. 291,222; Friedländer, **12**, 803 (1914–16).

[10] (a) Dunstan and Goulding, *J. Chem. Soc.*, **75**, 797 (1899); (b) Meisenheimer, *Ann.*, **397**, 288 (1913).

[11] (a) Jones, *Am. Chem. J.*, **20**, 44 (1898); (b) Major and Fleck, THIS JOURNAL, **50**, 1480 (1928).

A little dry potassium carbonate, to combine with any hydrogen iodide, and 0.17 of a mole of phenyl isocyanate were added to the cooled ethereal filtrate from the above mentioned solid (m. p. 134°). The isocyanate removed any O,N-dimethylhydroxylamine by combining with it to give a urea derivative. The mixture was allowed to stand in a closed container at room temperature for fifteen hours. Ether and free O,N,N-trimethylhydroxylamine were then distilled into a receiver surrounded by an ice-bath. Dry hydrogen chloride passed into the ether solution caused a white precipitate which was recrystallized from absolute alcohol; m. p. 123°; yield, 46%.

Anal. Subs., 0.2691: AgCl, 0.3416. Calcd. for $C_3H_{10}ONCl$: Cl, 31.81. Found: 31.66.

Chloroplatinate.—To 0.2 g. of O,N,N-trimethylhydroxylammonium chloride dissolved in absolute alcohol a solution of 0.5 g. of chloroplatinic acid in absolute alcohol was added. Orange-colored crystals precipitated. They were recrystallized from hot absolute alcohol; m. p. 159°, with decomposition.

Anal. Subs., 0.2356: Pt, 0.0819. Calcd. for $C_6H_{20}O_2N_2PtCl_6$: Pt, 34.85. Found: 34.79.

Isolation of the Free Base.—To prepare O,N,N-trimethylhydroxylamine, the hydrochloride was treated with an excess of a concentrated solution of potassium hydroxide. This solution was distilled and the vapors were passed over solid pieces of potassium hydroxide heated to 95° before they were condensed. Pure O,N,N-trimethylhydroxylamine distilled at 30°. The hydrochloride, regenerated from base by passing dry hydrogen chloride into an ether solution of it, melted at 123° and corresponded in every way with the hydrochloride from which the free base had been made. This excluded the possibility of rearrangement. Free O,N,N-trimethylhydroxylamine possessed a fishy odor somewhat like that of other alkyl substituted hydroxylamines. It did not reduce ammoniacal silver nitrate.

Decomposition of O,N,N-Trimethylhydroxylamine by Treatment with Hydrochloric Acid.—A solution of 0.7 g. of O,N,N-trimethylhydroxylamine in 5 cc. of concentrated hydrochloric acid was heated in a sealed tube at 190° for eight hours. Considerable gas, undoubtedly methyl chloride, escaped when the tube was opened. The contents of the tube was dark in color. About half of it was distilled. The distillate had a pronounced odor of formaldehyde and gave a distinct color test for this substance with a solution of guaiacol in concentrated sulfuric acid.[12] The portion that remained in the distilling flask was evaporated to dryness on a water-bath. A rather dark colored solid was obtained, which, after recrystallization twice from absolute ethyl alcohol, was colorless and melted at 231°. A mixture of this compound with methylammonium chloride, m. p. 231°, also melted at 231°.

Action of Hydrochloric Acid on Dimethylamine.—A solution of 1 g. of dimethylammonium chloride, m. p. 171°, in 5 cc. of concentrated hydrochloric acid was heated at 190° for nine hours. The tube was cooled and opened and its contents evaporated to dryness on a water-bath. Unchanged dimethylammonium chloride, melting at 171°, was recovered.

2. O,N-Diethyl-N-methylhydroxylamine, $C_2H_5ON(C_2H_5)CH_3$

One-tenth mole of O,N-diethylhydroxylamine, prepared by the method of Major and Fleck,[11b] was added to a solution of 0.05 mole of methyl iodide in dry ether. The mixture was allowed to stand in a closed container at room temperature for four days. A heavy, pink oil gradually formed. It was separated from the ether solution by decantation. After washing it thoroughly with dry ether, it was made alkaline with

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[12] "Deutsches Arzneibuch," R. v. Decker's Verlag, Berlin, 1926, p. LIV.

potassium hydroxide and the free base recovered in the usual manner. Four g. of the free base, b. p. 78–84°, was recovered. It had the characteristic odor of O,N-diethylhydroxylamine. The major fraction, b. p. 83°, was added to a solution of phenyl isocyanate in benzene. Evaporation of the benzene, after the mixture had stood for a day, left a white solid which melted at 63°, after it had been recrystallized once from ligroin. Pure α-phenyl-β,β'-ethylethoxyurea melts at 63°.[13]

The ether solution, from which the pink oil was separated, was shaken with a little mercury in order to remove a trace of dissolved iodine. A little potassium carbonate and 0.9 of a mole of phenyl isocyanate were then added to remove any O,N-diethylhydroxylamine by the formation of a substituted urea. The mixture was allowed to stand in a closed container at room temperature for two days. Ether and free O,N-diethyl-N-methylhydroxylamine were then distilled and collected in a receiver surrounded by an ice-bath. Dry hydrogen chloride was passed into the ether solution. A heavy oil precipitated. The ether was decanted but since the oil was somewhat soluble in ether, probably due to a partial splitting into hydrogen chloride and O,N-diethyl-N-methylhydroxylamine, it was not washed with pure ether but with a little ether which had been saturated with hydrogen chloride. The oil failed to solidify.

Free O,N-diethyl-N-methylhydroxylamine was obtained from this hydrochloride in the manner described above in the preparation of O,N,N-trimethylhydroxylamine from its hydrochloride. It boiled at 79°. It had an odor somewhat like that of the other alkyl substituted hydroxylamines but slightly more ethereal; yield, 20%. Dry hydrogen chloride precipitated an oily hydrochloride from an ether solution of a portion of the free base.

Chloroplatinate.—A solution of 0.25 g. of O,N-diethyl-N-methylhydroxylamine in absolute alcohol was saturated with dry hydrogen chloride. The calculated amount of a solution of chloroplatinic acid in absolute alcohol was added. Orange needles soon precipitated. The amount of these was increased by adding dry ether. They were recrystallized from hot 95% alcohol; m. p. 158°. The compound was very soluble in water, readily soluble in hot 95% alcohol, but soluble only with difficulty in hot or cold absolute alcohol and insoluble in ether.

Anal. Subs., 0.2055: Pt, 0.0651. Calcd. for $C_{10}H_{28}O_2N_2PtCl_6$: Pt, 31.68. Found: 31.68.

3. Action of Isopropyl Alcohol on O,N-Diethylhydroxylammonium Chloride

To a solution of 0.56 g. of O,N-diethylhydroxylammonium chloride in 1 cc. of water was added 1 cc. of acetone-free *iso*propyl alcohol. This mixture was heated at 150° for two hours. When the tube was cooled and opened, a brownish solution was found. A portion of this solution was distilled and the distillate tested for acetone with vanillin according to the method of Kolthoff.[14] It gave a very pronounced test for acetone.

The rest of the solution was evaporated to dryness on the water-bath. The dark, solid residue was recrystallized several times by dissolving it in absolute alcohol and reprecipitating it by the addition of dry ether; m. p. 98°. A mixture of this hydrochloride with ethylammonium chloride (m. p. 98°) also melted at 98°.

4. Trimethylmethoxyammonium Iodide, $[(CH_3)_3NOCH_3]I$

To 1 g. of O,N,N-trimethylhydroxylamine was added an equivalent molecular portion of methyl iodide. The mixture became turbid at once and in four hours had

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[13] Jones and Major, THIS JOURNAL, **49**, 1538 (1927).

[14] Kolthoff, *Pharm. Weekblad*, **55**, 1021 (1918); *C. A.*, **12**, 2180 (1918).

changed entirely to a solid, white, crystalline mass. This was recrystallized from dry methanol. It did not have a definite melting point but, as described by Meisenheimer for the trimethylmethoxyammonium iodide prepared from trimethylamine oxide and methyl iodide, gradually darkened and decomposed at about 162°.[10b] It formed narrow, plate-like crystals which were readily soluble in water, less so in alcohol and insoluble in ether.

Anal. Subs., 0.2271: AgI, 0.2451. Calcd. for $C_4H_{12}ONI$: I, 58.48. Found: 58.34.

Decomposition of Trimethylmethoxyammonium Hydroxide by Heat.—When a solution of trimethylmethoxyammonium hydroxide, obtained from the iodide made by the action of trimethylamine oxide on methyl iodide, was heated, formaldehyde was formed.[15] In order to find out whether or not the same change would take place with the trimethylmethoxyammonium hydroxide obtained from O,N,N-trimethylhydroxylamine and methyl iodide, 1 g. of trimethylmethoxyammonium iodide was made alkaline with a concentrated solution of sodium hydroxide. The volatile portions of this solution were distilled into an aqueous solution of *p*-nitrophenylhydrazine hydrochloride. An orange-colored precipitate formed which was recrystallized from dilute alcohol; m. p. 181°. Formaldehyde *p*-nitrophenylhydrazone melts at 181–182°.[16] The odor of formaldehyde was also very marked when trimethylmethoxyammonium iodide was warmed with sodium hydroxide.

Summary

1. O,N,N-trimethylhydroxylamine and O,N-diethyl-N-methylhydroxylamine have been prepared by the action of methyl iodide on O,N-dimethylhydroxylamine and O,N-diethylhydroxylamine, respectively.

2. It has been shown that O,N,N-trimethylhydroxylamine is a comparatively stable compound which shows no tendency to rearrange to trimethylamine oxide. The probable course of the action of methyl iodide on hydroxylamine has been outlined in harmony with this fact.

3. The decomposition of O,N,N-trimethylhydroxylamine when heated with hydrochloric acid has been studied and the probable course of the reaction discussed.

4. The action of *iso*propyl alcohol on O,N-diethylhydroxylammonium chloride has been investigated.

5. It has been found that the trimethylmethoxyammonium iodide obtained by the action of methyl iodide on O,N,N-trimethylhydroxylamine is the same as that obtained by the action of methyl iodide on trimethylamine oxide.

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[15] Ref. 10 b, p. 292.

[16] Bamberger, *Ber.*, **32**, 1807 (1899).