202. *Hydroxyamino-derivatives from Formaldehyde. Their Reaction with Acyl Halides.*

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The reaction of *N*-methylhydroxylamine with formaldehyde in the presence of a secondary amine has been reinvestigated, and, contrary to previous reports, good yields have been obtained of the Mannich bases. On treatment with acyl halides these gave mixtures of monoacylated *N*-methylhydroxylamines and the corresponding chloromethylamine. A mixture of *O*- and *N*-acetyl-*N*-methylhydroxylamine underwent transacetylation on heating, with the formation of *NO*-diacetyl-*N*-methylhydroxylamine, the *O*-acetyl derivative being the acetylating agent. In the reaction of *NN'*-dimethyl-*NN'*-methylenebishydroxylamine with *p*-nitrobenzoyl chloride, both monoacylated derivatives were isolated, the ratio of *O*- to *N*-acylation being about 6 : 1.

The instability of certain hydroxyamino-derivatives, due to their ready transformation into the isomeric oximes or nitrones, is reflected in the existence of such derivatives of formaldehyde [1,2] and 5-hydroxypentanal [3] as the only known members of the class. In their investigation of the Mannich reaction, using *N*-monosubstituted hydroxylamines as the active hydrogen component, Hellmann and Teichmann [2] obtained the Mannich bases from *N*-phenylhydroxylamine, formaldehyde, and secondary amines, but found that the operation of recrystallization was enough to cause their transformation into *NN*-diphenylglyoxalnitrone, with the loss of the secondary amine. When they used *N*-methylhydroxylamine, the product was *NN'*-dimethyl-*NN'*-methylenebishydroxylamine (I), rather than the Mannich base. This result is compatible with the finding by Thesing *et al.*[4] that *N*-methylhydroxylamine could also function as the amine component in the Mannich reaction. However, when we repeated the reaction of *N*-methylhydroxylamine with formaldehyde and morpholine or piperidine, the Mannich bases (II) and (III) were obtained in good yield. Small amounts of *NN'*-dimethyl-*NN'*-methylenebishydroxylamine (I) were also isolated.

$$\mathrm{Me{\cdot}NH{\cdot}OH + CH_2O + NHR_2 \longrightarrow HO{\cdot}NMe{\cdot}CH_2R}$$

(I) R = NMe·OH. (II) R = Morpholino. (III) R = Piperidino.

Elementary and infrared spectral analyses of the products (II) and (III) are in good agreement with the proposed structures, and both compounds gave the characteristic hydroxylamine test with triphenyltetrazolium chloride.[5] They distilled under reduced pressure without decomposition and were unchanged after being kept for several months, thus being surprisingly more stable than the Mannich bases of *N*-phenylhydroxylamine, formaldehyde, and the same secondary amines.

The ready cleavage of the bisamino-derivatives from formaldehyde by acyl halides to give a tertiary chloromethylamine and a substituted amide, recently reported by Böhme and Hartke,[6] was also found to take place when the mixed amino-hydroxyamino-compound (III) was treated in ether with one equivalent of acetyl chloride. There was immediate precipitation of 1-chloromethylpiperidine (IV), identified by its conversion into dipiperidinomethane (V) in aqueous base. From the ether was obtained a mixture of two compounds, to which the structures *O*- (VI) and *N*-acetyl-*N*-methylhydroxylamine (VII) were assigned on the basis of infrared absorption. The spectrum of the mixture

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[1] Bamberger, *Ber.*, 1900, **33**, 941.

[2] Hellmann and Teichmann, *Chem. Ber.*, 1956, **89**, 1134.

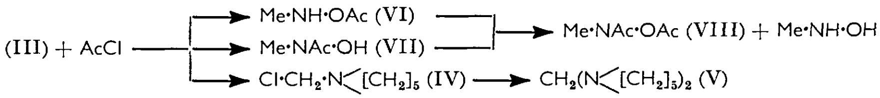
[3] Ulrich and Sayigh, *Angew. Chem.*, 1962, **74**, 468.

[4] Thesing, Uhrig, and Muller, *Angew. Chem.*, 1955, **67**, 31.

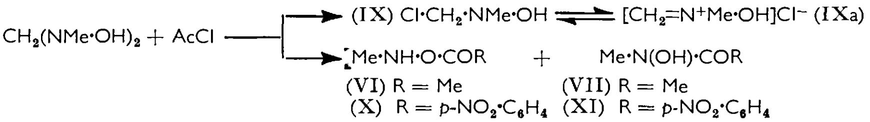
[5] Snow, *J.*, 1954, 2588.

[6] Böhme and Hartke, *Chem. Ber.*, 1960, **93**, 1305.

included hydroxyl absorption at 3·23 μ and carbonyl absorption at 5·68 and 6·15 μ. The hydroxyl and the second carbonyl band correspond to those in compound (VII), synthesized from acetyl chloride and *N*-methylhydroxylamine. The 5·68 μ band is also seen in the spectra of other *O*-acetylhydroxylamines.[7] When the ether-soluble material was distilled *in vacuo*, transacetylation took place to produce *NO*-diacetyl-*N*-methylhydroxylamine (VIII), the formation of which could be demonstrated by the appearance of two new carbonyl absorption bands in the infrared spectrum, at 5·56 and 6·00 μ. The disappearance of the bands at 5·68 and 3·23 μ shows that the acetylating agent is the *O*-acetyl component (VI).

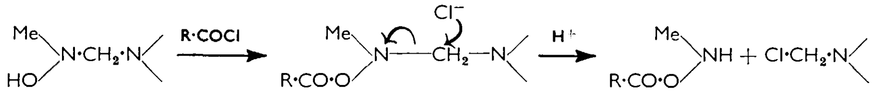


When the bishydroxylamino-derivative (I) was treated with acetyl chloride in ether, a similar reaction occurred, with the separation of an ether-insoluble product, (IX). Neutralization of an aqueous solution of this material with sodium carbonate gave the starting material (I). The ethereal solution contained a mixture of compounds (VI), (VII), and (VIII). The insolubility of the *N*-chloromethyl-*N*-methylhydroxylamine (IX) is apparently due to its existence in its tautomeric salt form (IXa).



The ratio of *O*- to *N*-acylation in this reaction with acetyl chloride could not be determined since the *O*-acetyl-*N*-methylhydroxylamine could not be separated without decomposition. However, the reaction with *p*-nitrobenzoyl chloride was shown to result in an *O* : *N*-acylation ratio of 6 : 1 by extraction of the products with dilute sodium hydroxide solution, in which the *N*-acylated product (XI) dissolves and the *O*-acylated product (X) does not.

It is probable that the mechanism of the cleavage of the hydroxylamino-derivatives by acyl halides is acylation of the hydroxyl group, followed by attack of the acylated acetal by the chloride ion in a typical S_N2 reaction, with elimination of the less basic substituent.



EXPERIMENTAL

Infrared spectra were measured with a Perkin-Elmer model 21 spectrophotometer. Microanalyses were by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

NN′-*Dimethyl*-NN′-*methylenebishydroxylamine* (I).—(*a*) *Preparation.* To a solution of methylhydroxylamine hydrochloride[8] (8·35 g., 0·1 mole) in methanol (20 ml.) was added anhydrous sodium carbonate (5·3 g., 0·05 mole), with stirring and ice-cooling, followed by 37% aqueous formaldehyde (4·3 g., 0·05 mole). The mixture was stirred for 15 min., then to it was added methylene chloride (100 ml.). The organic layer was separated, dried, and evaporated to yield *NN*′-dimethyl-*NN*′-methylenebishydroxylamine (6 g., 56·5%), m. p. 115—116° (lit.,[2] 111—112°); after recrystallization from methanol, the m. p. was 119—120°.

(*b*) *Reaction with acetyl chloride.* Acetyl chloride (1·7 g., 0·022 mole) in anhydrous ether

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[7] Exner and Horak, *Coll. Czech. Chem. Comm.*, 1959, **24**, 2992; Exner and Kakac, *ibid.*, 1960, **25**, 2530.

[8] Beckmann, *Annalen*, 1909, **365**, 201.

(30 ml.) was added dropwise, with stirring and ice-cooling, to a solution of the bishydroxylamine (2·3 g., 0·022 mole) in anhydrous ether (60 ml.). Immediately, a reaction took place and a white semi-solid material separated. Decantation and evaporation *in vacuo* of the ethereal solution gave a residue (1·4 g., 72·5% calc. on monoacetyl-methylhydroxylamine) consisting of *O*-acetyl-*N*-methylhydroxylamine (VI), $\nu_{max.}$ (in $CHCl_3$) 5·68 μ (C=O), and a very small amount of *NO*-diacetyl-*N*-methylhydroxylamine (VIII), $\nu_{max.}$ (in $CHCl_3$) 5·56 and 6·00 μ (C=O). The solid, ether-insoluble material was dissolved in water and this solution neutralized with sodium carbonate and extracted with chloroform. Evaporation of the dried extract gave starting material (0·9 g., 78%), m. p. 113—114°.

(*c*) *Reaction with* p-*nitrobenzoyl chloride*. *p*-Nitrobenzoyl chloride (9·25 g., 0·05 mole) in anhydrous ether (50 ml.) was added dropwise, with stirring and ice-cooling, to a solution of the bishydroxylamine (5·3 g., 0·05 mole) in anhydrous ether (100 ml.). At once, a light yellow oil separated, which solidified during 20 hours' stirring at room temperature. Treatment of this solid with a small amount of water gave a mixture of solids (7·1 g., 72·3% calc. on *N*-methyl-mono-*p*-nitrobenzoylhydroxylamine) from which N-*methyl*-N-p-*nitrobenzoylhydroxylamine* (XI) was isolated by extraction with 5% sodium hydroxide solution and acidification with dilute hydrochloric acid. The precipitated derivative (0·9 g., 9·15%), m. p. 191°, when recrystallized from xylene or water, had m. p. 197—197·5° (Found: N, 14·55. $C_8H_8N_2O_4$ requires N, 14·3%) and $\nu_{max.}$ (in KBr) 3·26, 3·52, 6·10, 6·27, 6·60, 7·37, 8·23, 8·48, 11·55, 11·70, and 13·87 μ. An emulsion in water gave the violet colour with ferric chloride, characteristic of hydroxamic acids.

The alkali-insoluble component of the crude product mixture crystallized from ethyl acetate, to give pure N-*methyl*-O-p-*nitrobenzoylhydroxylamine* (X), m. p. 157—159° (Found: N, 14·3%), $\nu_{max.}$ (in KBr) 2·98, 3·27, 3·50, 5·73, 6·22, 6·57, 7·42, 8·05, 9·35, 9·90, 11·43, 11·80, and 13·95 μ.

N-*Methyl*-N-*morpholinomethylhydroxylamine* (II).—A mixture of *N*-methylhydroxylamine hydrochloride (15·5 g., 0·185 mole) and 37% aqueous formaldehyde (15 g., 0·185 mole) was added gradually, with stirring and ice-cooling to morpholine (34·8 g., 0·4 mole). Stirring was continued for 30 min. and then the upper oily layer was separated and distilled under reduced pressure, to give N-*methyl*-N-*morpholinomethylhydroxylamine* (15·5 g., 58·5%), b. p. 60—65°/1 mm., n_D^{24} 1·5010, $\nu_{max.}$ (in $CHCl_3$) 3·18, 3·45—3·65, 6·85, 7·03, 7·33, 7·78, 8·65, 8·95, 9·30, 9·63, 9·80, 11·00, and 11·53 μ (Found: N, 19·0. $C_6H_{14}N_2O_2$ requires N, 19·2%). *NN'*-Dimethyl-*NN'*-methylenebishydroxylamine (I) (0·5 g., 5%), m. p. 115—116°, separated from the aqueous layer on cooling.

N-*Methyl*-N-*piperidinomethylhydroxylamine* (III).—(*a*) *Preparation*. Piperidine (34 g., 0·4 mole) was added with stirring and ice-cooling to *N*-methylhydroxylamine hydrochloride (16·7 g., 0·2 mole). Then 37% aqueous formaldehyde (16·5 g., 0·2 mole) was added dropwise and stirring continued for 30 min. The solid which separated (7·1 g.), consisting of a mixture of the compound (I) and piperidine hydrochloride, was filtered off and the filtrate extracted with chloroform. The extract was dried, evaporated, and distilled under reduced pressure, to give N-*methyl*-N-*piperidinomethylhydroxylamine* (15·75 g., 54·5%), b. p. 56°/0·4 mm., n_D^{23} 1·4768, $\nu_{max.}$ (in $CHCl_3$) 3·22, 3·45—3·65, 6·92, 7·30, 7·40, 7·73, 7·92, 8·60, 8·85, 9·62, 9·95, and 11·58 μ (Found: N, 19·3. $C_7H_{16}N_2O$ requires N, 19·4%). The solid product mixture was fractionally crystallized from methanol, giving compound (I) (2·5 g., 23·6%), m. p. 117—118°, and piperidine hydrochloride (4·3 g., 8·8%), m. p. 250—252°.

(*b*) *Reaction with acetyl chloride*. Acetyl chloride (3·9 g., 0·05 mole) in anhydrous ether (50 ml.) was added dropwise with stirring and ice-cooling to a solution of the piperidino-compound (7·1 g., 0·05 mole) in anhydrous ether (100 ml.). Immediate separation of a solid was seen, and after 30 min. 1-chloromethylpiperidine (IV) (6·4 g., 96·5%) was filtered off. An aqueous solution of this material was neutralized with 5% sodium hydroxide solution and extracted with ether. The dried extract was evaporated and distilled, to give 1,1-methylenedipiperidine (V) (2·6 g., 60%), b. p. 101—102°/13 mm. (lit.,[9] b. p. 103—104°/13 mm.). Evaporation of the original ethereal solution gave a mixture of *O*- (VI) and *N*-acetyl-*N*-methylhydroxylamine (VII) (3 g., 69% calc. on acetyl-*N*-methylhydroxylamine). Distillation under reduced pressure gave impure *NO*-diacetyl-*N*-methylhydroxylamine (VIII) (1·8 g.), b. p. 110—116°/20 mm., $\nu_{max.}$ 5·56 and 6·00 μ (C=O), no hydroxyl absorption at 3·23 μ or carbonyl absorption at 5·68 μ. Attempted purification of these materials by gas–liquid chromatography failed as a result of their thermal instability.

N-*Acetyl*-N-*methylhydroxylamine* (VII).—Acetyl chloride (7·85 g., 0·1 mole) was added

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[9] G.P. 287,802; *Chem. Zentr.*, 1915, II, 1033.

dropwise with stirring and ice-cooling to a mixture of sodium carbonate (10·6 g., 0·1 mole) and *N*-methylhydroxylamine hydrochloride (8·35 g., 0·1 mole) in methanol (60 ml.). After it had been stirred for 30 min., the mixture was filtered and evaporated and the residue distilled under reduced pressure. This yielded *N*-acetyl-*N*-methylhydroxylamine (5·1 g., 57·7%), b. p. 74—76°/0·8 mm., n_D^{23} 1·4512 (lit.,[10] b. p. 80°/2 mm., n_D^{20} 1·4523), $\nu_{max.}$ (in $CHCl_3$) 3·23 (OH) and 6·15 μ (C=O).

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[10] Exner, *Coll. Czech. Chem. Comm.*, 1951, **16**, 258.