Aliphatic Hydroxylamines. Part I. Preparation.

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Methods for the preparation of *NN*-dialkylhydroxylamines from the corresponding amine are reviewed. The pyrolysis of tertiary amine oxides bearing at least one ethyl or propyl radical is a satisfactory, if occasionally ambiguous, method. *N*-Oxides of β-dialkylaminopropionic esters or nitrile, or of Mannich bases, decompose very readily to give the desired compound unambiguously.

In this series of papers we shall be primarily concerned with *NN*-dialkylhydroxylamines, $(R{\cdot}CH_2)_2N{\cdot}OH$. No new methods for the preparation of the monoalkylhydroxylamines are reported, but in later papers some of the properties of the monoalkylhydroxylamines will be compared with those of the dialkyl series. The cyclic hydroxylamines, *e.g.*, *N*-hydroxypiperidine, are regarded as dialkyl derivatives of hydroxylamine. Methods of preparation which use as starting material any substance other than the corresponding amine have not been considered, because they are not applicable to cyclic hydroxylamines. In fact, methods using, *e.g.*, nitroparaffins, although convenient for some monoalkylhydroxylamines, are not particularly convenient for the dialkyl series.

A number of methods for preparation of dialkylhydroxylamines from the corresponding amines has been reported; broadly, these fall into three groups.

(1) Direct oxidation of the secondary amine by hydrogen peroxide (Mamlock and Wolffenstein, *Ber.*, 1900, **33**, 159; Henry and Dehn, *J. Amer. Chem. Soc.*, 1950, **72**, 2780). This has been found to be quite unreliable, not surprisingly in view of the strong reducing properties of the hydroxylamines which are formed in the presence of hydrogen peroxide.

(2) Decomposition of certain types of amine oxides. In the simplest examples, Mamlock and Wolffenstein (*loc. cit.*) made dipropylhydroxylamine by liquid-phase pyrolysis of tripropylamine oxide, and Wenick and Wolffenstein (*Ber.*, 1898, **31**, 1560; cf. Haase and Wolffenstein, *Ber.*, 1904, **37**, 3228) prepared *N*-hydroxypiperidine by the pyrolysis of *N*-ethylpiperidine oxide. These results, which appear to have been overlooked by later workers (but cf. Hurd, " The Pyrolysis of Carbon Compounds," The Chemical Catalog Co., 1929, p. 671), are fully confirmed and extended in this paper.

Cope, Foster, and Towle (*J. Amer. Chem. Soc.*, 1949, **71**, 3929, 3423) have studied the vapour-phase pyrolysis of 1- and 2-phenylethyl-*tert.*-amine oxides, and claim good yields in certain cases. The intermediates are not particularly easy to make, however, and the process has no particular advantage as a preparative method. Cope, Pike, and Spencer recently (*ibid.*, 1953, **75**, 3212) have made oxides of dimethylamino-*cyclo*octane, -*cyclo*heptane, and -*cyclo*hexane. These are degraded smoothly, giving high yields of the olefin and of dimethylhydroxylamine.

(3) Gambarjan and Kazaryan (*J. Gen. Chem. U.S.S.R.*, 1933, **3**, 222) and Gambarjan (*Ber.*, 1925, **58**, 1775) treated benzoyl peroxide with secondary amines and obtained *O*-benzoyldialkylhydroxylamines. The yields claimed could not be substantiated.

Pyrolysis of the amine oxides with loss of ethylene or propylene, now studied in some detail, is of general application and is the method of choice, but a limitation is the ambiguity of the elimination; it cannot be predicted with certainty that, *e.g.*, $Et_2PrN{\rightarrow}O$ will give $EtPrN{\cdot}OH + C_2H_4$ and not $Et_2N{\cdot}OH + CH_3{\cdot}CH{:}CH_2$ or both. By analogy with the Hofmann degradation of quaternary ammonium compounds, ethylene should be eliminated preferentially (Hanhart and Ingold, *J.*, 1929, 998). Cope, Foster, and Towle (*loc. cit.*), however, present evidence that an intra-molecular, cyclic process is involved, and that on occasion the stereochemistry of the olefin differs from that obtained by Hofmann degradation, so that the analogy is not good.

An alternative and unambiguous method has been developed for the preparation of secondary hydroxylamines from the corresponding amines under mild conditions. Compounds of the type $R_2N{\cdot}CH_2{\cdot}CH_2X$ ($X = CO_2R'$, CN, or COPh) react with monoperphthalic acid in ether, precipitating the phthalate of the *N*-oxide, $R_2N({\rightarrow}O){\cdot}CH_2{\cdot}CH_2X,C_6H_4(CO_2H)_2$ (cf. Witkop and Kissman, *J. Amer. Chem. Soc.*, 1953, **75**, 1977, footnote, for evidence of the competing deoxygenation of the oxide by the per-acid). Most of the products are oily, but one was crystalline and gave a satisfactory analysis. They are unstable under alkaline conditions, and undergo a reverse Michael addition, the activation by the *N*-oxide being reminiscent of the well-known effect of quaternisation on Mannich bases. In a single experiment using perbenzoic acid in chloroform in place of perphthalic acid in ether, the secondary amine used being piperidine, the *N*-oxide benzoate was not precipitated, and the successful isolation of *N*-hydroxypiperidine shows that the reverse Michael reaction proceeded even more readily and without added alkali; possibly the alkalinity of the reaction mixture before 1 mol. of perbenzoic acid had been added was sufficient, but if free hydroxylamine was present at this stage it is remarkable that it should have survived admixture with further per-acid.

Extensions of both these methods are under investigation.

EXPERIMENTAL

A valuable spot test for hydroxylamines unsubstituted on the oxygen is provided by triphenyltetrazolium chloride which, in the presence of alkali, gives the characteristic purple-red colour of the reduction product. Snow (*J.*, 1954, 2588) has commented on the specificity of the reaction, and by its means the presence or absence of hydroxylamines can usually be safely deduced. The progress of ether-extractions, steam-distillation, and so on can be followed in this way.

Tertiary Amine Oxides.—The tertiary amine (1 mol.), hydrogen peroxide (1·1 mols.), and sufficient water, alcohol, or acetone to give a homogeneous mixture are mixed and heated under reflux (bath) at 50—60° until the starch–iodide test for hydrogen peroxide is negative (overnight). Lower homologues may react violently with hydrogen peroxide; the mixing should then be carried out with ice-cooling, and the mixture be kept for some hours in ice before being heated. Occasionally, the temperature requires to be raised to 70° for a further 24 hr. The solvent is removed under reduced pressure, and the thermal degradation is carried out without further purification of the oxide, which is usually obtained as a syrup. Methods for following the disappearance of amine and for decomposing the excess of hydrogen peroxide have been described by Cope, Foster, and Towle (*loc. cit.*).

Pyrolysis: General Method.—The syrup from the oxidation is heated, usually under reduced pressure, in an apparatus set up for distillation, with an efficient condenser and, for the lower homologues, ice-cooling of the receiver. The oil-bath temperature is raised slowly to about 130°; there is always a little dark residue. The distillate may be (*a*) treated with excess of oxalic acid, and the oxalate isolated, or (*b*) dried (KOH) and redistilled. Yields are rather variable, and those quoted are not necessarily maximal; for example, Cope, Foster, and Towle (*loc. cit.*), using a liquid-air trap and conducting the pyrolyses at low pressures, obtained over 90% yields of dimethylhydroxylamine from *NN*-dimethyl*cyclo*hexylamine oxide. There is usually a little tar remaining from the pyrolysis. It is often convenient, when working on a large scale, to conduct the pyrolysis under reflux, with adequate precautions for disposal of the large volumes of ethylene or propylene evolved, at atmospheric pressure, and then to distil the product under reduced pressure.

NN-Dimethylhydroxylamine is most conveniently made by pyrolysing the concentrated aqueous solution of the *N*-oxide of *NN*-dimethyl*cyclo*hexylamine in a glass tube packed with glass or porcelain rings, heated electrically to 200—220°, in a slow stream of nitrogen. Molar quantities can be handled very well in this way with satisfactory yield. The batchwise pyrolysis of the *N*-oxide of dimethyl*cyclo*hexylamine is liable to be violent, and the anhydrous *N*-oxide sublimes into the condenser.

β-*Dimethylaminopropiophenone Oxide Phthalate*.—The base made from β-dimethylaminopropiophenone hydrochloride (90 g.) in ether (about 200 c.c.) was stirred, with external ice-cooling. Monoperphthalic acid (*Org. Synth.*, 1948, **20**, 70 *) (750 c.c., 1 mol. in 2·2 l.) was run in at such a rate that the temperature remained below 15°. A transient pale blue colour appeared during the addition, and a mobile oil separated. Addition of the acid solution was stopped when the ethereal layer showed a permanent positive starch–iodide reaction (5 min.). The ether was removed by decantation, and the oil rinsed with ether two or three times. To the residue was added 2N-sodium hydroxide (300 c.c.), and the whole was distilled under reduced pressure with use of an efficient condenser system and ice-cooled receiver, until the distillate no longer showed reducing properties. Excess of aqueous oxalic acid was added to the distillate, which was then evaporated to dryness, and the hydrogen oxalate crystallised from methanol; it had m. p. 146—148° (12·73 g., 21·5%).

Pyrolysis of amine oxides.

Amine oxide	Hydroxylamine produced	B. p.	Yield (%)	Notes
$PrMe_2NO$	$Me_2N{\cdot}OH$	—	20	$Me_2N{\cdot}OH$ is very volatile. The pyrolysis was conducted at atmospheric pressure, and the receiver, which was cooled in ice, contained water.
$C_6H_{11}{\cdot}NMe_2O$ ...	$Me_2N{\cdot}OH$	—	61	Pyrolysed through hot tube. See above.
Et_3NO	$Et_2N{\cdot}OH$	50°/17 mm.	67	
$Pr^n{}_3NO$	$Pr^n{}_2N{\cdot}OH$	70°/17 mm.	50—79	
$Pr^n{}_2MeNO$	$Pr^nMeN{\cdot}OH$	98—99° (*ca.*)	—	Some material was lost. Isolated as *hydrogen oxalate*,[a] m. p. 112—113° from acetone.
Et_2MeNO	$EtMeN{\cdot}OH$	26—30°/10 mm.	82	*Hydrogen oxalate*,[b] m. p. 112—113° from acetone.
$[CH_2]_5{>}NEtO$	$[CH_2]_5{>}N{\cdot}OH$	89°/23 mm.	42	Yield based on *hydrogen oxalate*[c] (m. p. 112°, from methanol), isolated from primary distillate by evaporation with aqueous oxalic acid.

[a] Found: C, 40·4; H, 7·2; N, 8·0. $C_6H_{13}O_5N$ requires C, 40·2; H, 7·3; N, 7·8%. [b] Found: C, 36·4; H, 6·9; N, 8·6. $C_5H_{11}O_5N$ requires C, 36·35; H, 6·7; N, 8·5%. [c] Found: N, 7·2. $C_7H_{13}O_5N$ requires N, 7·3%.

Ethyl β-*Dialkylaminopropionate* N-*Oxide Phthalates*.—β-Disubstituted aminopropionic esters (Whitmore, Masher, Adams, Taylor, Chaplin, Weisel, and Yanke, *J. Amer. Chem. Soc.*, 1944, **66**, 725), dissolved in a little ether, were treated with monoperphthalic acid. (Cooling is convenient, as the ether is liable to boil, but has little effect on the yield.) The phthalates of the following oxides were obtained as oils, and not isolated or characterised: ethyl β-diethylaminopropionate *N*-oxide; ethyl β-di-*n*-propylaminopropionate *N*-oxide; ethyl β-di-*n*-butylaminopropionate *N*-oxide; ethyl β-piperidinopropionate *N*-oxide. *Ethyl* β-*morpholinopropionate* N-*oxide phthalate* crystallised, and was isolated as white needles (83%), m. p. 129—130°, from alcohol (Found: C, 54·9; H, 6·0; N, 4·1. $C_{17}H_{23}O_8N$ requires C, 55·3; H, 6·3; N, 3·8%).

Ethyl β-piperidinopropionate *N*-oxide benzoate was made (also as an oil) by the use of perbenzoic in place of monoperphthalic acid (see below).

Decomposition of the N-*Oxide Salts*.—No standard procedure could be devised. The hydroxylamines were prepared in the following ways:

NN-*Diethylhydroxylamine*. The *N*-oxide phthalate from 61 g. of ethyl β-diethylamino-

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* The process as described was liable to lead to vigorous decomposition during the preparation. Addition of 0·5% of quinol to the phthalic anhydride prevented this.

propionate was dissolved in acetone (200 c.c.) and stirred with solid anhydrous potassium carbonate until effervescence ceased and was not resumed on addition of more potassium carbonate. The solution was filtered and made acid (Congo-red) with an acetone solution of anhydrous oxalic acid. There was no precipitate, so the solution was evaporated to dryness and the gummy residue was extracted with ethyl acetate repeatedly until the residue was no longer reducing. The *hydrogen oxalate* (30 g.) separated as slightly sticky crystals, which, recrystallised from acetone, had m. p. 106—107° (Found: C, 40·6; H, 7·5; N, 7·8. $C_6H_{13}O_5N$ requires C, 40·2; H, 7·3; N, 7·8%). The yield is 50% based on the crude material. The neutral oxalate is recorded (Wieland, *Ber.*, 1903, **36**, 3216) as having m. p. 138°.

NN-*Dipropylhydroxylamine.* The *N*-oxide phthalate from ethyl β-dipropylaminopropionate (95 g.) was dissolved in acetone (250 c.c.) and stirred with excess of anhydrous potassium carbonate. The filtered solution was treated with excess of a solution of anhydrous oxalic acid in acetone. The hydrogen oxalate, m. p. 137—138°, was precipitated in 56% yield and could be recrystallised from acetone. In some preparations the material was contaminated with the oxalate of the starting material and careful fractionation was required. Alternatively, the *N*-oxide could be dissolved in aqueous alkali, and the hydroxylamine extracted with ether.

NN-*Dibutylhydroxylamine.* The oily *N*-oxide phthalate was dissolved in water and basified with potassium hydroxide. On cooling in ice the hydroxylamine solidified and was collected. The hydrogen oxalate, crystallised from water, had m. p. 140—141° (Dermer and Dermer, *J. Amer. Chem. Soc.*, 1942, **64**, 3057, give m. p. 144—144·5°).

N-*Hydroxymorpholine.* The *N*-oxide phthalate (59 g.) was heated with aqueous ammonia under reflux for 2 hr. The solution was evaporated to dryness, and the gummy residue extracted with hot acetone. The acetone was distilled, leaving an oil, which was distilled (7·76 g.; b. p. 66—66·9°/5 mm., n_D^{25} 1·4690) (Found: C, 46·4; H, 9·1; N, 13·4. Calc. for $C_4H_9O_2N$: C, 46·6; H, 8·8; N, 13·6%). It solidified in ice, and had m. p. 19—19·5°; it gave a *hydrochloride*, colourless prisms (from acetone), m. p. 103—105° (Found: C, 34·45; H, 8·05; N, 10·5. $C_4H_{10}O_2NCl$ requires C, 34·45; H, 7·15; N, 10·05%), and a *picrate*, needles (from toluene), m. p. 136° (Found: N, 16·8. $C_{10}H_{12}O_9N_4$ requires N, 16·9%).

N-*Hydroxypiperidine.*—Ethyl β-piperidinopropionate (26 g.) in chloroform (25 c.c.) was treated with a chloroform solution of perbenzoic acid until the mixture was peroxidic to starch–iodide paper. The *N*-oxide benzoate did not separate. The solution was evaporated to dryness, and the residue, dissolved in ether, gave, with anhydrous oxalic acid in acetone, a white precipitate, m. p. 104—106°, of the hydrogen oxalate of *N*-hydroxypiperidine.

2-*Cyanoethyldimethylamine.*—Into aqueous dimethylamine (24·8%; 1300 c.c.) was run acrylonitrile (212 g.) with external cooling to below 30° and stirring. The mixture was stirred for 1 hr. at room temperature, then for 1 hr. at 100°. Saturation of the cooled solution with sodium carbonate and extraction with ether gave the *base* (251·5 g.; b.-p. 170°) (Found: N, 29·4%; *M*, by titration, 98. $C_5H_{10}N_2$ requires N, 28·6%; *M*, 98). The *picrate*, needles (from methanol–acetone), had m. p. 154—155° (Found: C, 40·7; H, 4·25. $C_{11}H_{13}O_9N_5$ requires C, 40·4; H, 4·0%).

2-*Cyanoethyldimethylamine Oxide Phthalate.*—To 2-cyanoethyldimethylamine (33 g.) in ether (100 c.c.) was added monoperphthalic acid in ether until the mixture showed a permanent positive starch–iodide reaction; a transparent oil separated, and this was collected by decantation and washed with ether. No solid derivative could be made. To decompose this *N*-oxide salt, the gum was dissolved in 2N-sodium hydroxide, and the mixture steam-distilled until the distillate was no longer reducing; the distillate was made slightly acid with aqueous oxalic acid, and the water removed under reduced pressure. The crystalline residue was extracted with methanol from considerable amounts of insoluble material, and from the extract on concentration there was obtained *NN*-dimethylhydroxylamine hydrogen oxalate (11·07 g., 22%), m. p. 148—149°.

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