Secondary Amines via Reductive Cleavage Reactions of N-Oxides

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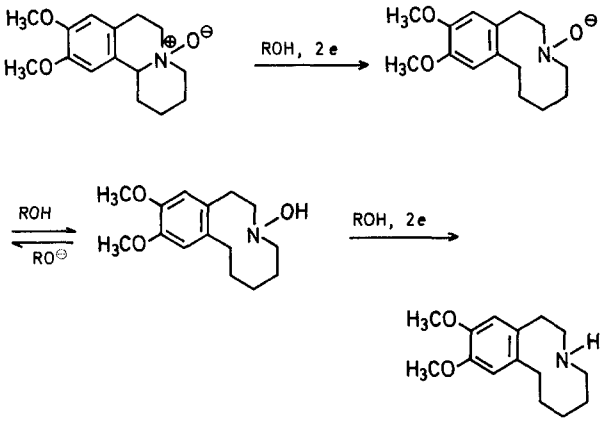
Carbon-nitrogen bonds in benzylic and allylic tertiary amines do not undergo fission in alkali metal-ammonia reducing systems. Their quaternary salts, however, are readily cleaved to tertiary amines[1]. An adaption of this method to the synthesis of secondary amines using a potentially labile quaternizing agent has been published[2]. We find that the corresponding amine oxides are readily cleaved to secondary amines using lithium in liquid ammonia containing an alcohol as a proton source and buffering agent[3]. The following reaction scheme is suggested.



The hydroxylamine intermediate, admixed with product, was obtained from a reaction using a limited amount of lithium and omitting a proton donor.

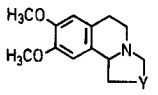
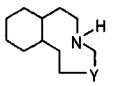
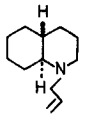
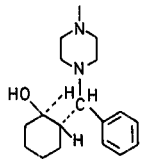
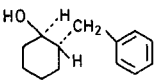
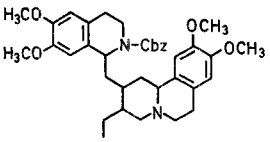
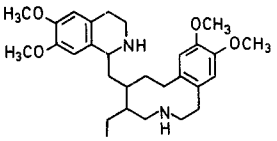
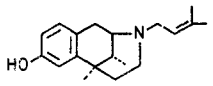
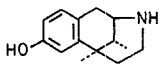
Amine oxides are weak bases; their conjugate acids have a pK_a of approximately 5[4], and since the pK_a of alcohols is in the 16–18 range[5] the initial cleavage is presumably mediated via the amine oxide itself. The cleavage product is therefore a dialkylhydroxylamine anion, the conjugate base of a weak acid with an expected pK_a in the 12–13 range[6], sufficiently close to that of the proton donor to allow further reduction to proceed via free dialkylhydroxylamine produced in the equilibrium.

1-Methoxy-2-propanol was satisfactory as a proton donor for the amine oxides of **1**, **2** and **3**. In the case of **4**, the crude bis N-oxide (mass spectrum: m/e = 321, $[M+1]^{\oplus}$) was cleaved using lithium alone to avoid reduction of the phenyl nucleus, the fate of the amine component being secondary in interest to the stereochemistry of the neutral fragment. An early attempt to determine the stereochemistry of **4** by catalytic hydrogenolysis was unsuccessful[7].

Application of the cleavage reaction to **5** afforded, via its oily N-oxide, a crystalline mixture of secondary amine and its hydroxylamine intermediate, even using an extended reaction time and in the presence of excess 1-methoxy-2-propanol. This is presumably due to the insolubility of the hydroxylamine lithio-salt in the reaction medium, since re-reduction of the isolated product using identical conditions afforded pure secondary amine in 90% yield, for an overall yield of 45%. It is relevant that phenylhydroxylamine is smoothly reduced by sodium in liquid ammonia alone, indicating that N—O bond cleavage is preferred to salt formation[8]. The isolation and re-reduction procedure was avoided by the addition of sufficient acetic acid at the first apparent end point to exactly neutralize all lithium added to that point, converting all hydroxylamine salts to the $\geq$N—OH form; readdition of lithium to a second end-point afforded pure secoemetine in 57% overall yield.

Insoluble intermediates are presumably a factor in the case of **6**, since the yield of secondary amine using 1-methoxy-2-propanol alone was 35%, while sequential treatment with acetic acid, followed by readdition of lithium as described for the emetine case, afforded a 55% yield of secondary amine.

Table. Secondary Amines from N-Oxides of Tertiary Amines

Tertiary Amine	Ref.	Product[a]	Yield (%)[b]	Ref.
				
1 Y = $-CH_2-$	13		60	2
2 Y = $-(CH_2)_2-$	13		60	2
 **3**			65	16
 **4**	7		70	14
 **5**	2		57	2
 **6**	15		55	12

[a] All compounds were identified either by direct comparison with authentic samples (**1**,**2**,**3**,**5**) or by comparison with published physical constants (**4**,**6**).

[b] Overall isolated yields based on the tertiary amine.

Compound **3** was prepared from *trans*-decahydroquinoline and allyl chloride in acetonitrile containing one equivalent of triethylamine. The hydrochloride of **3** had m.p. 133–135°.

The method may be regarded as complementary to the catalytic hydrogenation method[9] for the debenzylation of tertiary amines where this method fails, as for the bridgehead carbon-nitrogen benzylic bonds found in **1**, **2**, and **3**. The method provides an alternative to catalytic hydrogenation of allylic tertiary amines which is less satisfactory than the benzylic case, since even under preferred conditions the competing hydrogenation reaction is significant[10].

Amine oxides were prepared either by monoperphthalic acid oxidation in ether-methanol or preferably by the method of Craig and Purushothaman[11] using *m*-chloroperbenzoic acid in tetrahydrofuran. N-oxidation of allylic amines was highly selective by either method. The amine oxides were used crude and identified only by T.L.C., N.M.R. and mass spectrometry techniques. Some representative cleavage reactions are described below.

1,2,3,4,5,6,7,8-Octahydro-10,11-dimethoxy-3-benzazecine Hydrochloride:

The crude N-oxide (2 g, 7.6 mmol) obtained from **2** in tetrahydrofuran (20 ml) was added to liquid ammonia (500 ml) containing 1-methoxy-2-propanol (3 ml, 30 mmol). Lithium (260 mg, 37 mg-atom) was added portionwise to the vigorously stirred solution. The deep blue solution was stirred for a further 6 min, the excess lithium was decomposed by water, and the reaction mixture was diluted cautiously with warm water. The product, isolated by chloroform extraction, was purified by filtration in ether through a short column of Woelm Alumina (Grade I basic). It was converted to the hydrochloride by addition of isopropanolic hydrogen chloride directly to the column eluate and was recrystallized from acetone-hexane; yield: 1.2 g, m.p. 125–126°, identical with an authentic sample[2].

1',2'-Secoemetine:

Benzyloxycarbonylemetine (**5**, 14.3 g, 23.2 mmol) in methanol (60 ml) was treated, dropwise, at −10° with ethereal monoperphthalic acid (58.5 ml, 0.58 *M*, 34 mmol). The mixture was kept at 0–5° overnight and was then basified with 10% sodium hydroxide solution and extracted with chloroform (five times). The chloroform extracts were washed with brine, dried (K_2CO_3), and evaporated, giving the crude oily N-oxide; yield: 12 g.

The N-oxide (5 g, 7.7 mmol) in tetrahydrofuran (25 ml) was added to liquid ammonia (1.5 l) containing 1-methoxy-2-propanol (4.8 ml, 48 mmol). Lithium (260 mg, 37 mg-atom) was added portion-

wise until a permanent deep blue coloration appeared, indicating the presence of lithium despite the addition of only 4.8 of the 6 equivalents theoretically required (fission reactions require 4; carbobenzyloxy group require 2 equivalents). Acetic acid (2.22 g, 37 mmol) added to neutralize all lithium added up to that point, afforded a colorless solution. Readdition of lithium (200 mg) in one portion afforded a persistent deep blue solution which, after 6 min, was diluted with hot water and extracted with chloroform. The chloroform extracts were washed with brine and dried (Na_2SO_4). The residue was dissolved in ether and, after a brief treatment with charcoal, converted to the bis-hydrochloride using a slight excess of isopropanolic hydrogen chloride. The precipitate was crystallized from acetone as a partial acetone solvate; yield: 3 g; m.p. 234–237°. The identity of the product was confirmed by conversion of a portion to the bis-hydroiodide and comparison with an authentic sample[2].

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