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DECOMPOSITION OF PROP-2-YNYLIC N-OXIDES TO ACROLEIN AND SCHIFF BASES *VIA* O-ALLENYL HYDROXYLAMINES

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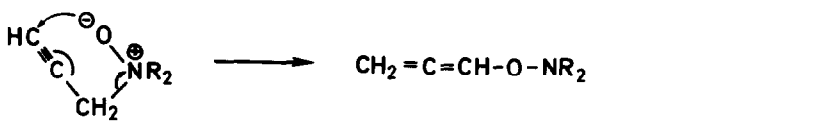
Summary: Prop-2-ynylic N-oxides rearrange thermally *via* O-allenyl hydroxylamines to acrolein and an imine. The second rearrangement step, falling in the class of thermal *cis*-eliminations, is shown with variously ^{2}H-substituted pargyline N-oxides.

Previous studies[1] on the N-oxides of some N,N-dialkylprop-2-ynylamines showed that they undergo an intramolecular, Meisenheimer-type rearrangement (Scheme 1) when refluxed in aprotic solvents, to generate O-allenyl hydroxylamines. The same reaction also occurred when the N-oxides were injected on a gas chromatograph.

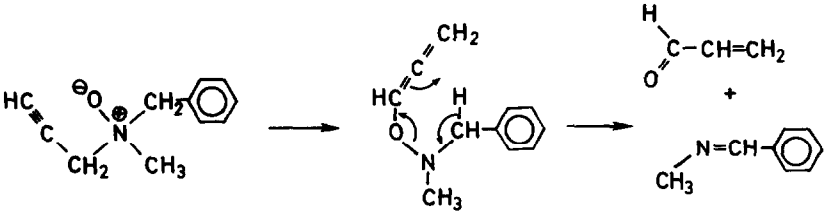


R = CH_3, $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$ *Scheme 1*

The antidepressive drug pargyline (N-benzyl-N-methylprop-2-ynylamine) is converted to the corresponding N-oxide by biooxidation in mammal liver microsomal preparations. When investigating this metabolic reaction[2], it became evident that pargyline N-oxide decomposes on analysis by GC-MS, generating

N-benzylidenemethylamine. These results prompted us to extend our studies[1] on 2-alkynylamine N-oxides.

Contrary to our results with other prop-2-ynylic N-oxides, no allenyl hydroxylamine was found when pargyline N-oxide[3] was refluxed in Et_2O, THF or CCl_4, but instead substantial amounts of N-benzylidenemethylamine, as evidenced by direct inlet mass spectrometry[4]. Similarly, GC-MS showed the imine but no allenic product. Referring to Scheme 1, a possible mechanism for the formation of N-benzylidenemethylamine can be rationalized, which involves two consecutive rearrangements (Scheme 2). The second rearrangement yields the imine and propenal (acrolein).



Scheme 2

To prove the formation of propenal, pargyline N-oxide was refluxed in THF in a system where any vapour leaving the condensor passed through an aqueous 2,4-dinitrophenylhydrazine (DNPH) reagent solution. An orange precipitate was formed constituting the propenal DNPH-derivative as proved by MS-analysis[5].

To obtain evidence for the suggested intramolecular mechanism, ($^2H_2$)-pargyline N-oxide[6], labelled in the benzylic position, was rearranged. Both $^2H_1$- and unsubstituted propenal DNPH-derivatives (ratio ^2H : ^1H, 6 : 10) were found. The presence of the deuteriodeficient propenal could be due to either tautomeric equilibration in the (^2H)aldehyde in the aqueous DNPH reagent solution prior to derivatization or to an alternative direction in the rearrangement, involving hydrogens from the methyl group. Support for the latter possibility was obtained when the N-oxides[1] of prop-2-ynylpiperidine and prop-2-ynyldimethylamine were reinvestigated as also these compounds generated propenal on *prolonged* reflux in THF or Et_2O[7]. The involvement of hydrogens from either α-carbon in the propenal formation from pargyline N-oxide was confirmed with N-benzyl-N-($^2H_3$)methylprop-2-ynylamine N-oxide[8]. In this case the ^2H : ^1H ratio (1:10) again showed the presence of two isotopic variants of the propenal DNPH-derivative, but with a pronounced preference

for hydrogen migration from the benzylic position. The results from experiments with the two labelled substrates thus indicate that the regioselectivity of the hydrogen migration is influenced by a ^{2}H : ^{1}H isotope effect as well as the directive effect of the phenyl group. These effects can either work in the same (($^{2}H_3$)N-oxide) or opposing directions (($^{2}H_2$)N-oxide).

The N-benzylidenemethylamines, formed in the two cases, contained as expected only the $^{2}H_1$- and $^{2}H_3$-congener, respectively, which was proved by GC-MS. N-Methylidenebenzylamine, the Schiff base corresponding to hydrogen migration from the methyl group, was not detected by direct GC-MS but acid hydrolysis of the rearrangement products yielded benzylamine in addition to benzaldehyde.

Prop-2-ynylic N-oxides are thus shown to undergo two consecutive rearrangements (Scheme 2), the first being a [2,3]sigmatropic migration[9] while the second is analogous to the electrocyclic thermal elimination of esters or xanthates[10] and related to the |1,5|hydrogen shifts. The stability of the intermediary O-allenyl hydroxylamine and its ability to form different types of imines will depend on the type of substituents on the nitrogen.

As prop-2-ynylic N-oxides can be expected as metabolites to various prop-2-ynylamines used as drugs and pesticides a knowledge of the chemical properties of the N-oxides can help explain some of the diverse pharmacological effects seen with these amines[11]. The ease with which the N-oxides generate propenal might be of utmost importance in evaluating their toxicity[12].

References and Notes

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3. Treatment of pargyline with *m*-chloroperbenzoic acid in $CHCl_3$ yielded 94 % of the N-oxide which was isolated as its HCl salt, m.p. 124-126°C. Alternative oxidation with H_2O_2 in H_2O-MeOH was also used with good results.

4. The 70 eV mass spectrum: m/z (% relative intensity) 119 (60) 118 (100) 91 (20) 77 (26) 55 (14) 51 (16) 42 (40), was identical to that of a reference sample.

5. The 20 eV mass spectrum: m/z (% relative intensity) 236 (100) 219 (12) 201 (8) 189 (36) 159 (24) 142 (18) 79 (21) 69 (23) 42 (37), was identical to that of a propenal DNPH-derivative.

6. $LiAl^2H_4$-reduction of N-methyl-N-prop-2-ynylbenzamide yielded 70 % ($^2H_2$)pargyline. Isotopic purity >97 %. Subsequent H_2O_2-oxidation afforded the N-oxide.

7. Substantial amounts of the acetaldehyde-DNPH derivative were also formed when Et_2O was used as solvent. Control experiments showed that the acetaldehyde was formed from Et_2O, presumably through an N-oxide supported cleavage.

8. Deuteriomethylation of N-benzylprop-2-ynylamine with $^2HC^2HO$ and $^2HCOO^2H$ according to the Eschweiler-Clarke reaction yielded 74 % $^2H_3$-substituted amine. Isotopic purity >98 % (c.f. B. Lindeke, E. Anderson and D.J. Jenden, Biomed. Mass. Spec. 3, 257 (1976)). Subsequent H_2O_2-oxidation afforded the N-oxide.

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