OXONITINE REVISITED: ITS MECHANISM OF FORMATION FROM ACONITINE

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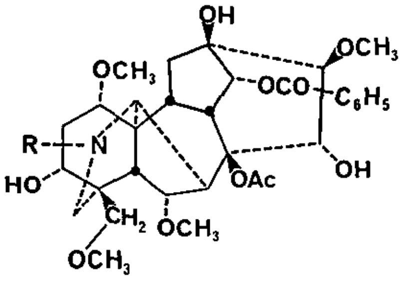
Abstract - *Oxidation of aconitine (2) to oxonitine (1) with* $KMnO_4$ *proceeds by three mechanisms, involving the* CH_3 *and* CH_2 *carbons of the N-ethyl group and the carbon of the solvent as sources of the N-CHO group of oxonitine.*

Oxonitine (1), one of the permanganate oxidation products of aconitine (2), has been a subject of study for over 50 years.[1-6] Recently two papers[7,8] have treated the mechanism of its formation. A 1982 study[7] of the oxidation of aconitine with permanganate in various solvents indicated that the source of the N-formyl group of oxonitine is the N-alkyl group of aconitine (mechanism 1) and/or the solvent (e.g. acetone, methanol or acetic acid) used for the oxidation (mechanism 2).

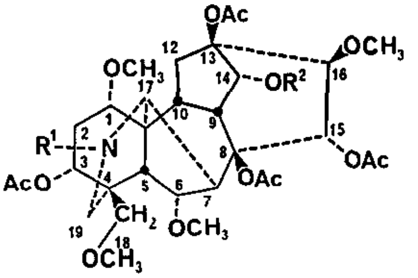


1 R = CHO

2 R = C_2H_5

3 R = Ac

4 R = H



5 R^1 = CHO; R^2 = Ac

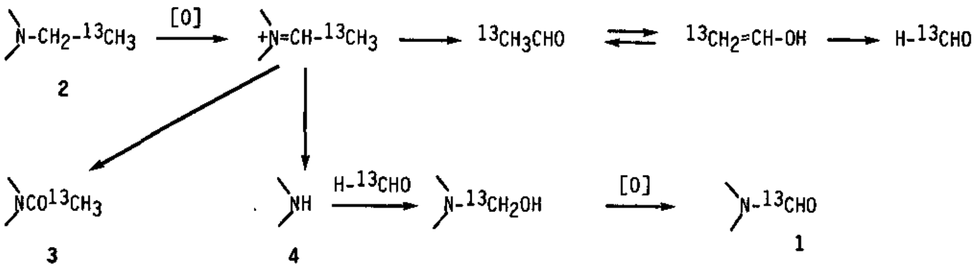
6 $R^1 = C_2H_5$; R^2 = Ac

7 $R^1 = C_2H_5$; $R^2 = COC_6H_5$

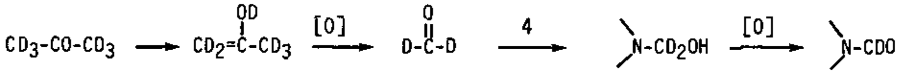
8 R^1 = CHO; $R^2 = COC_6H_5$

9 R^1 = Ac; $R^2 = COC_6H_5$

Mechanism 1[9]



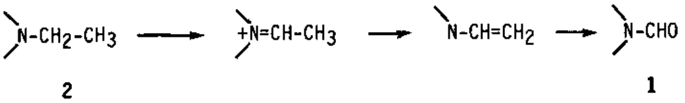
Mechanism 2[10]



$$CD_3\text{-}CO\text{-}CD_3 \longrightarrow CD_2\text{=}\overset{OD}{\overset{|}{C}}\text{-}CD_3 \xrightarrow{[O]} D\text{-}\overset{O}{\overset{\|}{C}}\text{-}D \xrightarrow{4} \rangle N\text{-}CD_2OH \xrightarrow{[O]} \rangle N\text{-}CDO$$

Subsequently, mechanism 3 was proposed[8] in which the N-formyl group of **1** and **5** is derived from the methylene of the N-ethyl group when aconitine (2)[11] and aconine pentaacetate (6)[12] are oxidized with permanganate under conditions different from those reported in reference 7. Though these investigators[8] agree with our proposal of mechanism 1 for oxidation of aconitine with aqueous $KMnO_4$, they differ with regard to mechanism 2, i.e. when aconitine is oxidized in acetone or 5% aqueous acetone.

Mechanism 3[8]

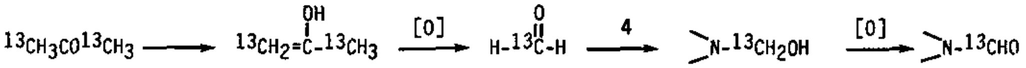


Two points are noteworthy: i) In the case of the oxidation of aconitine in acetone-d_6[8] the product was identified, it appears, exclusively by ^1H and ^{13}C nmr spectroscopy. The presence or absence of deuterium was not substantiated by more conclusive experiments, such as deuterium nmr spectroscopy, and, moreover, it is probable that the deuterium was lost during aqueous or acidic workup. ii) The results of the oxidation of aconine pentaacetate (**6**) to oxonine pentaacetate (**5**) were used to formulate a mechanism for the oxidation of aconitine (2) to oxonitine (1).[8] This transfer of results is inappropriate, since a change of substrates yielded different products (see below), and consequently, a different mechanism may operate for the oxidation of aconitine (2).

To clarify the above points aconitine was oxidized in acetone-d_6-D_2O (95:5) under the experimental conditions that were used by Amiya *et al.* However, during workup the products were collected by filtration over a column of alumina to avoid the possible exchange of deuterium that might occur during an acidic workup. Although the ^{13}C nmr spectrum of the product was essentially identical with that of oxonitine (~ 80%), it did not show the presence of an

>N-CDO group. The ^1H nmr spectrum also failed to indicate the proportions of >N-CHO and >N-CDO formed, since the formyl proton was obscured by the aromatic protons of the benzoyl group. Oxidation of aconitine furnished oxonitine in 80% yield, whereas oxidation of aconine pentaacetate (6) and aconitine triacetate (7) under identical experimental conditions furnished oxonine pentaacetate (5) and oxonitine triacetate (8) in a yield of only 50% and 60%, respectively.

Oxidation of aconitine (2) in $^{13}CH_3\text{-}CO\text{-}^{13}CH_3$ (99.5 atom % ^{13}C)-H_2O (95:5), gave a product with ^1H and ^{13}C nmr chemical shifts identical with those of oxonitine. Moreover, the ^{13}C nmr spectrum showed two intense signals at 163.1 (assigned to the formyl carbon) and 22.4 ppm (assigned to the methyl carbon of >N-CO-CH_3). Comparison of this ^{13}C nmr spectrum with that of the unlabeled oxonitine, measured under identical nmr conditions, showed that the relative intensity of the signal at 163.1 ppm is about 16 times larger than that found in the unlabeled compound (the signal at 22.4 ppm is also enhanced to the same extent), a result which demonstrates that a) intermediate **4** is formed during the oxidation and b) the solvent, acetone, is indeed a source (16%) of the >N-CHO and >N-CO-CH_3 groups.[13] Thus, mechanism 2 may be written:



$$^{13}CH_3CO^{13}CH_3 \longrightarrow {}^{13}CH_2{=}\overset{OH}{\overset{|}{C}}{-}^{13}CH_3 \xrightarrow{[O]} H{-}\overset{O}{\overset{\|}{^{13}C}}{-}H \xrightarrow{4} {>}N{-}^{13}CH_2OH \xrightarrow{[O]} {>}N{-}^{13}CHO$$

Additional support for this result was provided by the following experiments: a) oxidation of **2** in acetone for 1 h [and in acetone-water (95:5) for 30 min] furnished intermediate **4** (7.3%) [13.5%], a 61:39 [69:31] mixture of **1** and **3** (28.5%) [26.5%] and starting material (2) (47%) [48%], respectively; b) oxidation of N-desethylaconitine (4) in acetone-H_2O (95:5) furnished mainly **1** and **3** in a 2:1 ratio. Oxidation of aconitine (29 mg) in 0.5 g of $^{13}CH_3\text{-}CO\text{-}^{13}CH_3$ and 45 mg of $KMnO_4$ at room temperature for four days furnished a mixture (1:1) of oxonitine (1) and N-acetyl-N-desethylaconitine (4) (26.5 mg). The ^{13}C nmr spectrum of the mixture suggested that about 3% of the N-formyl group of oxonitine is derived from the dry acetone.

Table 1

Substrate	Solvent	1	3	8	9	unknown
		(%)	(%)	(%)	(%)	(%)
2	acetone-d_6-D_2O (95:5)	80.8	13.8	-	-	5.4
2	$^{13}CH_3\text{-}CO\text{-}^{13}CH_3\text{-}H_2O$ (95:5)	81.4	10.8	-	-	7.3
2	$^{13}CH_3\text{-}CO\text{-}^{13}CH_3$	43.5	44.8			11.7
7	acetone	-	-	19.4	62.2	18.4
7	acetone-H_2O (95:5)	-	-	56.6	17.9	25.5

The results reported here and the earlier results[7,8] demonstrate that oxidation of aconitine (2) to oxonitine (1) with $KMnO_4$ proceeds by three mechanisms, involving the CH_3 and

CH_2 carbons of the N-ethyl group and the carbon of the solvent as sources of the $\geq$N-CHO group of oxonitine. Mechanisms 1 and 3 operate to an extent of about 84%, although the proportion of oxonitine formed via each mechanism is not known. Dry acetone is inert to $KMnO_4$[14], but in aqueous acetone oxidation proceeds to furnish some formaldehyde which acylates intermediate **4** to furnish oxonitine (**1**). Table 1 illustrates the composition of the oxidation products obtained from various oxidation conditions and substrates.[15]

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9. Labeled aconitine ($\geq$N-CH_2-$^{13}CH_3$) was oxidized with aqueous $KMnO_4$ for 2 h to give a 1:1 mixture of **1** ($\geq$N-^{13}CHO) and **3** ($\geq$N-CO-$^{13}CH_3$).
10. Aconitine was oxidized with $KMnO_4$ in acetone-d_6 to afford mainly oxonitine ($\geq$N-CDO). The evidence for this mechanism is primarily by ^1H and ^{13}C NMR spectroscopy. The interpretation of the ^{13}C NMR spectrum is now uncertain. Furthermore, a close inspection of the ^1H NMR spectrum indicates that the substance is roughly a 1:1 mixture of **1** and **3**.
11. Aconitine was oxidized with $KMnO_4$ in acetone-d_6-water (95:5) for 4 days to yield 80% of **1**.[8]
12. Labeled aconine pentaacetate ($\geq$N-$^{13}CH_2$-CH_3) was oxidized in acetone-water (95:5) for 4 days to yield 79% of **5** ($\geq$N-^{13}CHO).[8]
13. That solvent acetone is also a source of the N-$COCH_3$ group is observed here for the first time. In our earlier study[7] with aqueous permanganate we showed that the ethyl of the $\geq$N-CH_2CH_3 group is the source of the $\geq$N-$COCH_3$ group.
14. A. Y. Drummond and W. A. Waters, *J. Chem. Soc.*, 1953, 435.
15. Purifying products from the oxidation of aconitine and its derivatives with $KMnO_4$ is very difficult. Compounds **1** and **3**, the major products, co-chromatograph in several solvent systems and the poor solubility of **1** in common organic solvents further hampers the separation of the two compounds by gravity and centrifugally-accelerated, radial chromatography ("Chromatotron"). Repeated crystallization from several solvents usually failed to give pure oxonitine. In this work the product composition (except for compound **5**) was determined by HPLC on a Resolve spherical C_{18}-column.

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