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THE MECHANISM OF THE FORMATION OF OXONITINE BY PERMANGANATE OXIDATION OF ACONITINE

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An isotopic labeling study has shown that the N-formyl group of oxonitine, a product of permanganate oxidation of aconitine in a 95:5 acetone-water, originates from the methylene group of the N-ethyl of aconitine.

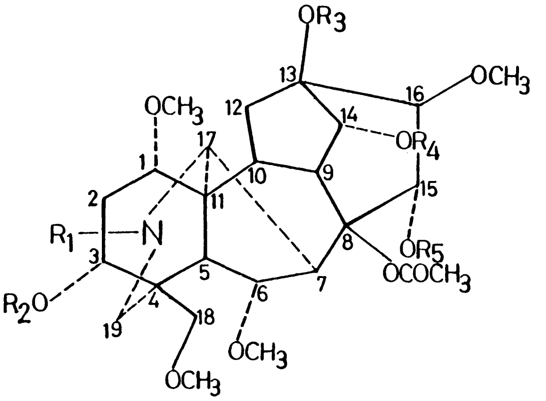
Since oxonitine (1), a permanganate oxidation product of aconitine (2), was first reported by Carr in 1912,1) its structure and the mechanism of the formation have been studied by many investigators.2) Its structure as an N-formyl-N-desethylaconitine was suggested by Turner et al.2b) and Jacobs et al.3) but the mechanism of its formation from 2 has remained unsettled despite study by several groups2b,2c) of investigators. Pelletier et al.4) recently published their results on the mechanism of the formation of 1 from 2 and showed that the N-formyl group of 1 was derived from acetone as solvent as well as from the methyl group of the N-ethyl group of 2, when 2 was oxidized with permanganate in several aqueous systems.

The present authors wish to report that, <u>contra</u> Pelletier et al., the N-formyl group of 1 originates from the methylene group of the N-ethyl of 2 when 2 is oxidized with permanganate in a 95:5 acetone-water. The present results therefore confirm that a different mechanism operates when the oxidation is carried out in a solvent containing a smaller amount of water.

For this study we prepared aconine pentaacetate (3), mp (decomp) 222-223 °C, with a labeled N-ethyl group ($N\text{-}^{13}CH_2CH_3$) from N-desethylaconitine 3-acetate5) in three steps.6) ^{13}C NMR spectrum ($CDCl_3$) of 3 clearly indicated the labeled methylene of the N-ethyl group at δ 48.8 ppm.

Oxidation of 3 for 4 days at room temperature in acetone-water (95:5 v/v) with potassium permanganate gave N-formyl-N-desethylaconine pentaacetate (4), mp (decomp) 239-241 °C, in 79% yield. The ^{13}C NMR spectrum ($CDCl_3$) of 4 showed a labeled formyl carbon at δ 162.4 ppm and 75% of ^{13}C labeled carbon of 3 was proved to be remained in 4. The oxidation of aconitine (2) for 4 days in acetone-d_6-water (95:5 v/v), on the other hand, gave 1 in 80% yield and its ^1H and ^{13}C NMR spectra ($CDCl_3$) exhibited both the proton and the carbon of the formyl group at δ 8.10 (1H,s) and 163.0 ppm (d) respectively and showed no incorporation of deuterium from acetone-d_6.

These results unambiguously indicate that the N-formyl group of 4 is derived from the methylene group of the N-ethyl of 3. A probable mechanism of the formation of 1 from 2 under the conditions mentioned above is depicted in Scheme 1.[5] The oxidation first generates an enamine (B) and its oxidation cleavage may give 1. On the other hand, hydrolysis of an immonium salt (A) to form the N-desethyl compound might be a preferred reaction when a greater amount of water is present.[4]

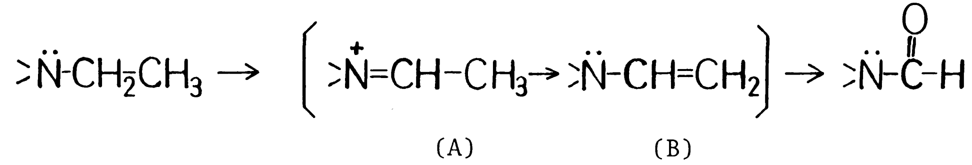


1) R_1=CHO, R_2=R_3=R_5=H, R_4=COC_6H_5

2) R_1=CH_2CH_3, R_2=R_3=R_5=H, R_4=COC_6H_5

3) R_1=$^{13}CH_2CH_3$, R_2=R_3=R_4=R_5=$COCH_3$

4) R_1=^{13}CHO, R_2=R_3=R_4=R_5=$COCH_3$



Scheme 1.

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6) Acetylation of N-desethylaconitine 3-acetate with [1-^{13}C]-acetic anhydride gave N-acetyl-N-desethylaconitine 3-acetate, mp (decomp) 213-215 °C, with a labeled N-acetyl group (N-$^{13}COCH_3$). The labeled N-acetyl derivative was reduced with lithium aluminium hydride to N-ethyl derivative (aconine with the labeled N-ethyl group), mp (decomp) 123-125 °C, and its acetylation with acetyl chloride afforded the labeled aconine pentaacetate (3). An overall yield of 3 from N-desethylaconitine 3-acetate was 50%.

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