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ACTIVE MANGANESE DIOXIDE: A REAGENT FOR CONSTRUCTING THE OXAZOLIDINE RING OF C_{20}-DITERPENOID ALKALOIDS

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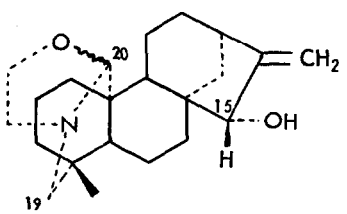
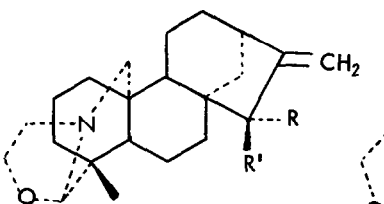
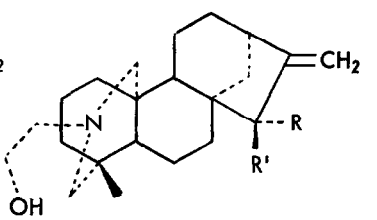
Recently we encountered difficulties in converting the known alkaloid, veatchine (1), into isogarryfoline (2), a compound in which the configuration at C(15) is inverted. To effect this transformation, we required a simple method for constructing in good yield the oxazolidine ring from the corresponding dihydro derivative. Earlier methods for effecting this transformation require the use of the very toxic and expensive osmium tetroxide[1] or of mercuric acetate.[2] In our experience with osmium tetroxide, oxazolidine ring formation, e.g., conversion of the dihydroderivative, dihydroveatchine (4), to garryine (3), takes place in yields of 16 to 26% and is accompanied by side products, e.g., glycols from the oxidation of the exocyclic double bond. This method also requires a lengthy reaction time (10 days) and a complex work up. The reaction with mercuric acetate is difficult to control, for slight over-oxidation produces an amide derivative which results in a low yield of the desired product. In several experiments using mercuric acetate, the yield of isoatisine (5) from dihydroatisine (6) did not exceed 32%.[3]



1 Veatchine



2 R = H; R' = OH
3 R = OH; R' = H



4 R = OH; R' = H
7 R = H; R' = OH

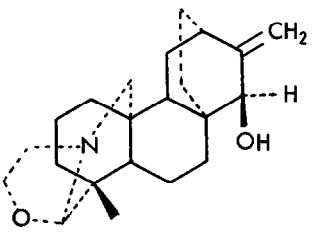
We now report a simple method using active manganese dioxide[4] for converting $-N-CH_2-CH_2-OH$ group-containing alkaloid derivatives into their iso-oxazolidine ring-containing alkaloids. This method uses an inexpensive oxidizing reagent and the reaction procedure is simple compared with earlier reported methods. Yields of iso-oxazolidines obtained from various dihydro derivatives are presented in Table 1. In a typical experiment, 180 mg of dihydroatisine in 25 ml of chloroform was treated with 540 mg of active manganese dioxide. The resulting mixture was stirred at room temperature while the progress of the reaction was monitered by alumina TLC plates. After 21 hours, the reaction was complete and the manganese dioxide was collected by filtration. Evaporation of the filtrate and separation of the product by preparative TLC plates

afforded 110 mg of isoatisine as well as some starting material. It is interesting to note that formation of the iso-oxazolidine ring occurs in preference to oxidation of the allylic hydroxy group. The severe steric hindrance at C(20) in these alkaloids restricts ring closure to the iso-position at C(19). When N-piperidine-ethanol was treated with active manganese dioxide under similar reaction conditions, it failed to cyclize to an oxazolidine. Apparently oxazolidine ring formation occurs only in a conformationally rigid system where the geometry for ring closure is favorable.

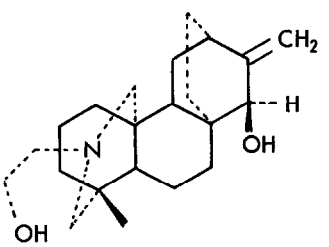
Table 1. Results of MnO_2 Oxidation of Various Dihydro Derivatives

Starting Compound	Product*	Yield
Dihydroveatchine (4)	Garryine (3)	55-60%
Dihydroatisine (6)	Isoatisine (5)	55-61%
Dihydrogarryfoline$^+$ (7)	Isogarryfoline (2)	45-50%
Dihydrocuauchichicine (8)	Isocuauchichicine (9)	60-64%

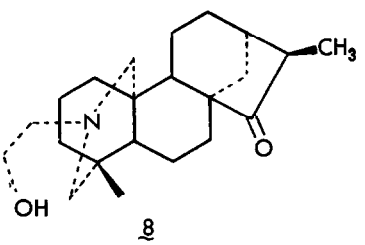
*Each product was compared with an authentic sample by ^{13}NMR spectroscopy.
$^+$The instability of this compound results in a low yield of isogarryfoline.



5 Isoatisine



6 Dihydroatisine



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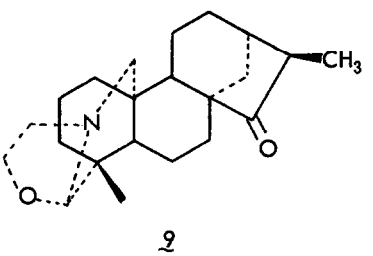

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