FORMATION OF THE OXAZOLIDINE RING IN C_{20}-DITERPENOID ALKALOIDS BY OXIDATIVE CYCLIZATION WITH SILVER OXIDE

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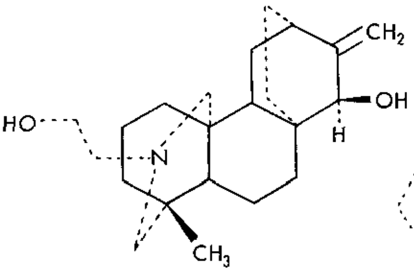
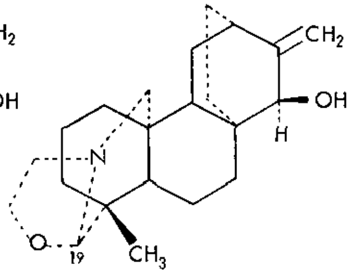
Abstract: Treatment of the $N-CH_2-CH_2OH$ group-containing alkaloids with silver oxide in alcohol affords the "iso-type" oxazolidine ring-containing alkaloids in yields of 72 to 90% via oxidative cyclization. This method affords higher yields than earlier reported methods for this type of transformation.

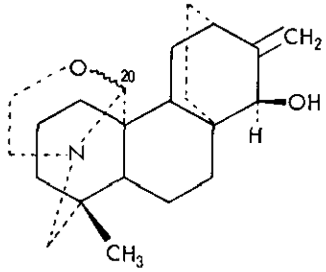
In connection with our work on C_{20}-diterpenoid alkaloids, we required a simple, high-yield method for constructing oxazolidine rings from the corresponding $N-CH_2-CH_2OH$ group-containing compounds, e.g. conversion of dihydroatisine (**1**) to isoatisine (**2**) or atisine (**3**). Recently we reported[2] that the use of active manganese dioxide affords better yields (50 - 60%) of cyclized products than the earlier reported methods using the very toxic and expensive osmium tetroxide[3] or mercuric acetate.[4] We report here the use of silver oxide[5] for converting the $N-CH_2-CH_2OH$ group-containing alkaloid derivatives into their "iso-type" [C(19) — O —] oxazolidine ring-containing alkaloids. This method is very simple, gives higher yields of iso-oxazolidine derivatives than any of the reported methods,[2-4] and involves easy workup. The reaction conditions and yields of the cyclized products are presented in Table 1.



1 Dihydroatisine

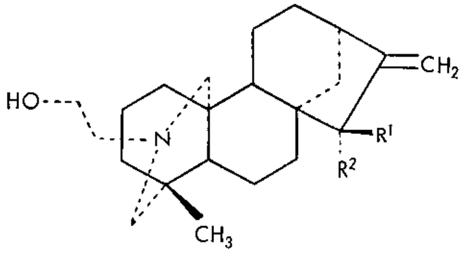


2 Isoatisine



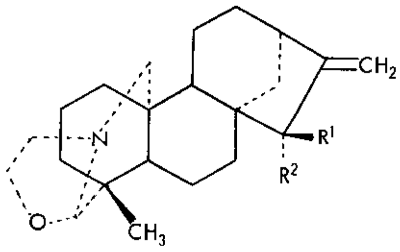
3 Atisine

In a typical experiment, 20 mg of dihydroatisine in 15 ml of 75% ethanol was treated with 60 mg of silver oxide.[6] The resulting mixture was heated at 96° with stirring for 2.5 hours. During this time, a silver mirror appeared on the surface of the reaction flask. The reaction mixture was filtered, evaporated to dryness and the product was chromatographed over a short alumina (activity III) column to yield 18 mg of isoatisine.[7] This reaction may be carried out in methanol or 75% ethanol. It is worth noting that N-piperidineethanol



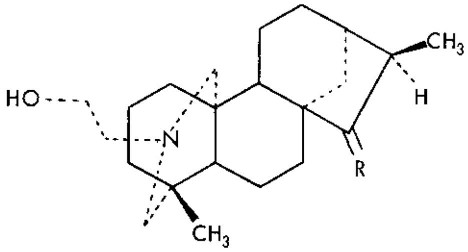
4 $R^1 = H$; $R^2 = OH$

6 $R^1 = OH$· $R^2 = H$



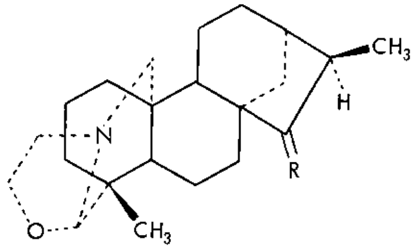
5 $R^1 = H$; $R^2 = OH$

7 $R^1 = OH$; $R^2 = H$



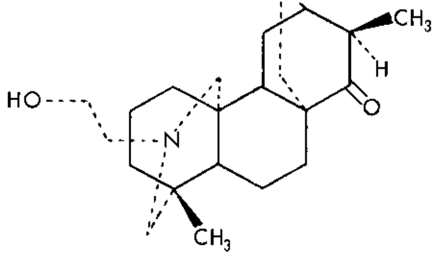
8 $R = O$

10 $R = \langle^{H}_{OH}$



9 $R = O$

11 $R = \langle^{H}_{OH}$



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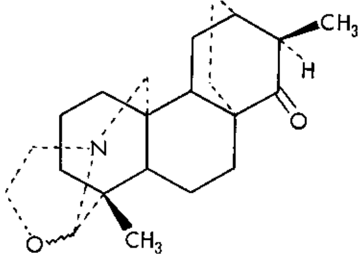

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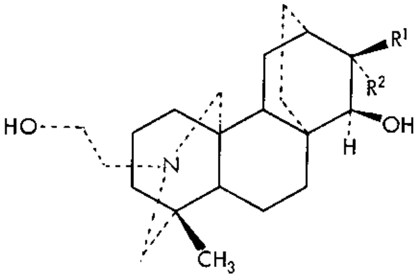
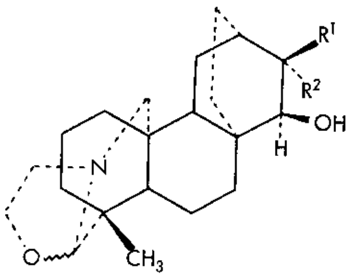


14 $R^1 = CH_3$; $R^2 = H$

16 $R^1 = H$; $R^2 = CH_3$



15 $R^1 = CH_3$; $R^2 = H$

17 $R^1 = H$; $R^2 = CH_3$

failed to cyclize to an oxazolidine, when it was treated with silver oxide under similar reaction conditions. This observation suggests that oxazolidine ring formation occurs only in a conformationally rigid system where the geometry for ring closure is favorable. Formation of the oxazolidine ring in these alkaloids occurs at C(19) *(e.g. isoatisine) in preference to the C(20) position (e.g. atisine). We did not detect any "normal-type"* [C(20)-O-] oxazolidines as cyclization products.

Table 1. Silver Oxide Cyclization of Various Alkaloid Derivatives

Substrate	Temp.	Time, hrs.	Product[†]	Isolated Yield
Dihydroatisine (1)	96°	2.5	Isoatisine (2)	90%
Dihydroveatchine (4)	96°	2.5	Garryine (5)	78%
Dihydrogarryfoline (6)	64°	3.0	Isogarryfoline (7)	76%
Dihydrocuauchichicine (8)	96°	2.5	Isocuauchichicine (9)	76%
Tetrahydroveatchine (10)	80°	1.0	Compound 11	79%
15-Ketotetrahydroatisine (12)	24°	5.0	Compound 13	83%
α-Tetrahydroatisine (14)	24°	5.5	Compound 15	72%
β-Tetrahydroatisine (16)	24°	4.5	Compound 17	72%

[†] Each product was characterized by ^{1}H, ^{13}C NMR, and mass spectral analysis or by comparison with an authentic sample

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5. Several investigators have used silver oxide for formation of carbinolamine ethers, but the use of this reagent has not been explored for construction of oxazolidine rings. [R. Anet, D. W. Clayton, and L. Marion, Can. J. Chem., 35, 397 (1957); K. Wiesner, S. Itô, and Z. Valenta, Experientia, 14, 167 (1958); S. Sakai, Chem. Pharm. Bull., 7, 55 (1959)].
6. Silver oxide, either freshly prepared or as old as three months, was used in this reaction.
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