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

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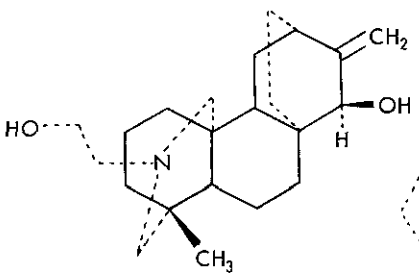
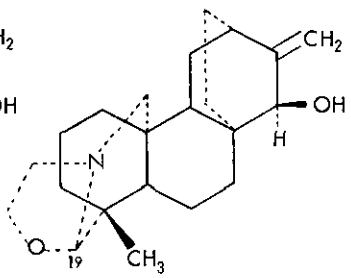
Abstract: Treatment of the N-CH_2-CH_2OH group-containing alkaloids with silver oxide in alcohol affords the "iso-type" oxazolidine ring-containing alkaloids in yields of 72 to 90% via oxidative cyclization. This method affords higher yields than earlier reported methods for this type of transformation.

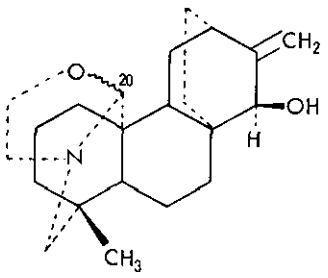
In connection with our work on C_{20}-diterpenoid alkaloids, we required a simple, high-yield method for constructing oxazolidine rings from the corresponding N-CH_2-CH_2OH group-containing compounds, e.g. conversion of dihydroatisine (1) to isoatisine (2) or atisine (3). Recently we reported[2] that 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

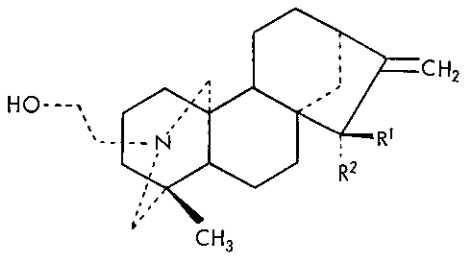


2 Isoatisine



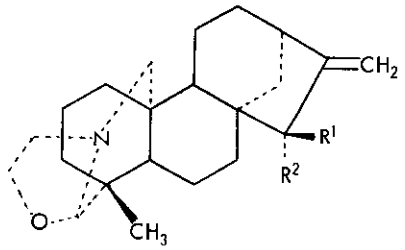
3 Atisine

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



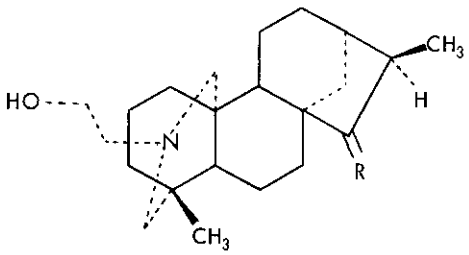
4 $R^1 = H$; $R^2 = OH$

6 $R^1 = OH$; $R^2 = H$



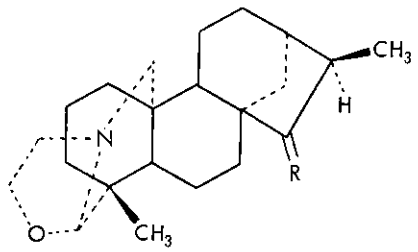
5 $R^1 = H$; $R^2 = OH$

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



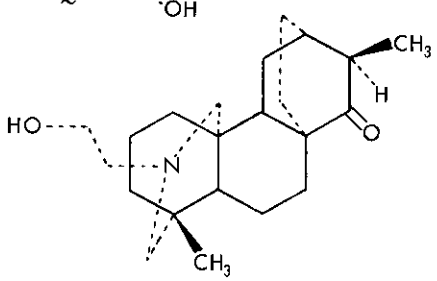
8 R = O

10 R = H, OH



9 R = O

11 R = H, OH



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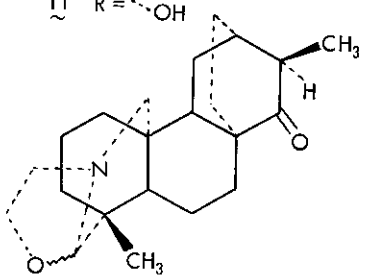

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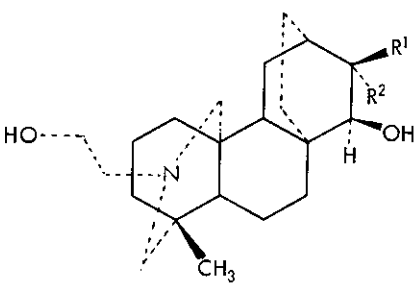
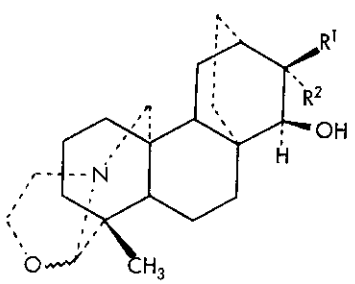


14 $R^1 = CH_3$; $R^2 = H$

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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REFERENCES AND NOTES

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3. K. Wiesner, W. I. Taylor, S. K. Figdor, M. F. Bartlett, J. R. Armstrong, and J. A. Edwards, Ber., 86, 800 (1953).
4. N. J. Leonard and W. K. Musker, J. Am. Chem. Soc., 82, 5148 (1960).
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.
7. S. W. Pelletier and P. C. Parthasarathy, J. Am. Chem. Soc., 87, 777 (1965).

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