Tetrahedron Letters Vol. 21, pp 3647 - 3650 0040-4039/80/0915-3647$02.00/0

CONSTRUCTION OF "NORMAL"- AND "ISO-TYPE"OXAZOLIDINE RINGS IN C_{20}-DITERPENOID ALKALOIDS: OXIDATIVE CYCLIZATION WITH POTASSIUM FERRICYANIDE

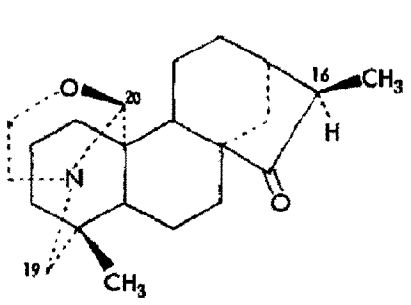
S. William Pelletier[1ab], Abdel-Monem M. Ateya[1ac], Naresh V. Mody[1a], Haridutt K. Desai[1a], and Lee C. Schramm[1ac]

Institute for Natural Products Research, the Department of Chemistry, and the School of Pharmacy

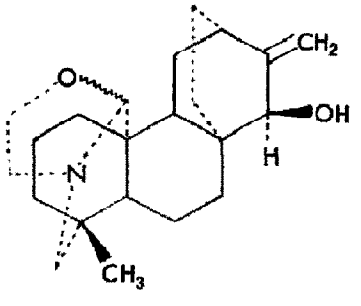
The University of Georgia, Athens, Georgia 30602, U. S. A.

An efficient and simple method using alkaline ferricyanide for converting the N-CH_2-CH_2OH group-containing alkaloid derivatives into their "normal"- and "iso-type"-oxazolidine ring-containing alkaloids has been developed. This is the first one-step oxidation method which affords both types of oxazolidine rings simultaneously.

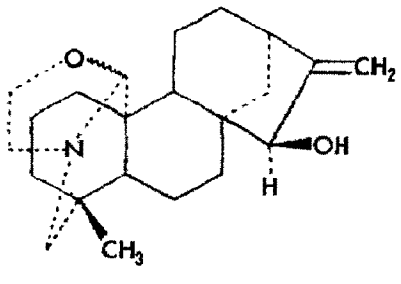
Recently we observed that cuauchichicine (1) is the only "normal-type" [C(20)-O] oxazolidine ring-containing alkaloid which exists as a single C(20) epimer, unlike alkaloids such as atisine (2), and garryfoline (3) which exist as a pair of C(20) epimers.[2] This observation prompted us to investigate the influence of the C(16) methyl group on the stereochemistry of the ring closure of N-ethanol derivatives to the "normal"- and "iso-type" [C(19)-O] oxazolidine ring-containing bases. For this study, we needed to prepare both types of oxazolidine derivatives from N-CH_2-CH_2OH group-containing precursors, e.g. cyclization of dihydroveatchine (4) to veatchine (5) and garryine (6). Cyclization methods utilizing osmium tetroxide[3], mercuric acetate[4], active manganese dioxide[5], and silver oxide[6] produce only the "iso-type" oxazolidine ring-containing alkaloids. Methods for conversion of the "iso-type" oxazolidine ring to the "normal-type" ring require several steps[7] and the yield, in some cases, is poor. Therefore, we sought an oxidizing reagent which can afford both types of oxazolidine rings from the N-CH_2-CH_2OH group-containing alkaloids.



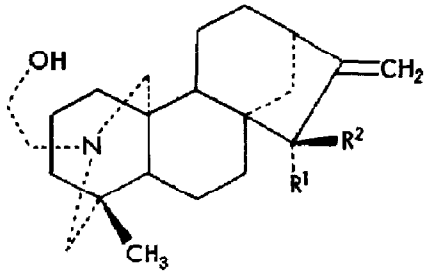
1 Cuauchichicine



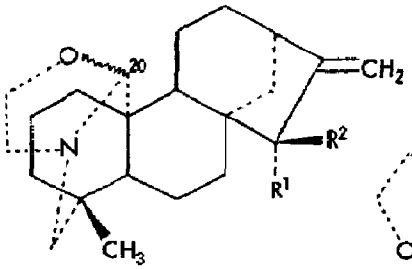
2 Atisine



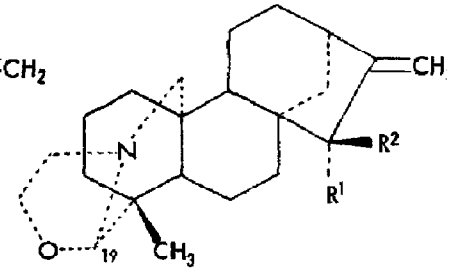
3 Garryfoline



4 $R^1 = OH$; $R^2 = H$
7 $R^1 = H$; $R^2 = OH$



5 $R^1 = OH$; $R^2 = H$
3 $R^1 = H$; $R^2 = OH$

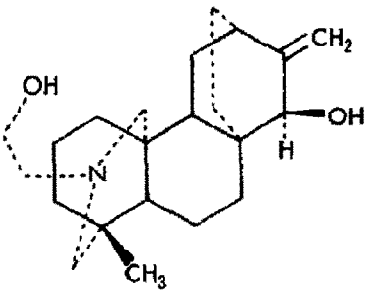


6 $R^1 = OH$; $R^2 = H$
8 $R^1 = H$; $R^2 = OH$

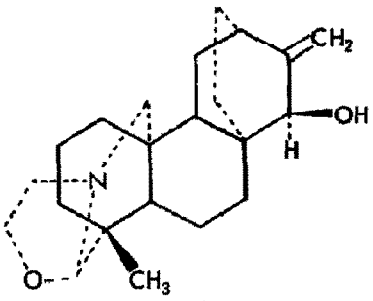
We report here an efficient method using alkaline potassium ferricyanide[8] for transforming the N-ethanol group-containing derivatives into their "normal-type" [C(20)-O] and "iso-type" [C(19)-O] oxazolidine ring-containing alkaloids. This method is simple, reliable, uses an inexpensive oxidizing reagent, and is the first one-step procedure reported which provides both types of oxazolidine derivatives simultaneously. The reaction conditions, yields, and ratio of the cyclized products are presented in Table 1. Attempts were not made to maximize yields of the cyclized products because of the limited quantities of the starting compounds.

Oxidation of the N-ethanol derivatives by a one-electron oxidant presumably occurs at the C(19) and C(20) positions to form the corresponding immonium salts ($HC=\overset{+}{N}-$), which on cyclization afford both types of oxazolidine rings. In the earlier published methods using metal oxides,[3,5,6] oxidation proceeded so as to produce only the "iso-type" oxazolidine ring. Of interest is the observation that when N-piperidineethanol was treated with alkaline ferricyanide solution, it failed to cyclize, indicating that the formation of an oxazolidine ring takes place only in a conformationally rigid system where the geometry for ring closure is favorable.

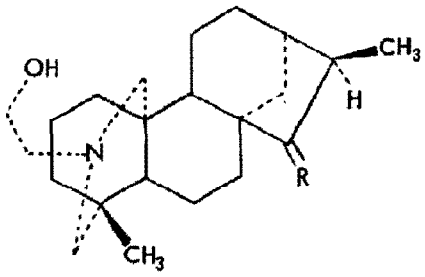
In a typical experiment, a solution of potassium ferricyanide (500 mg) in 4 ml of 8% aqueous sodium hydroxide was added to 92 mg of dihydroveatchine in 20 ml of 50% ethanol. The reaction mixture was stirred at room temperature while the progress of the reaction was monitored by thin layer chromatography on alumina. After 2.5 hours the reaction mixture was extracted with methylene chloride (4 x 20 ml). Evaporation of the dried methylene chloride extract afforded 87 mg of a mixture of veatchine and garryine, which was separated on a small column of alumina (activity III) using toluene and methanol as eluents. Alternatively, separation of a mixture of both types of oxazolidines was effected by extraction at different pH levels. The mixture was dissolved in 25 ml of ether and a slight excess of methanolic hydrochloric acid (1:1) was added to the ether solution with cooling. Water was added and the mixture was basified to pH ~ 8 with saturated potassium carbonate solution and then extracted with methylene chloride (3 x 30 ml) to give the "iso-type" oxazolidine. Further basification of the aqueous layer with 10% sodium hydroxide solution to pH ~ 12, followed by extraction with methylene chloride, afforded the strongly basic "normal-type" oxazolidine.



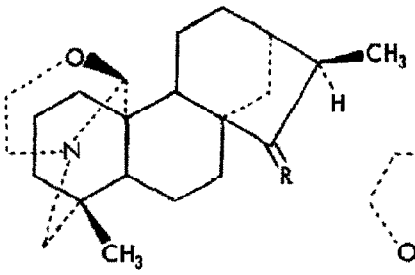
9



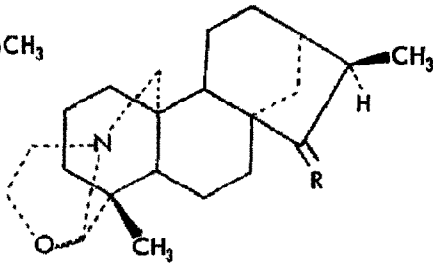
10



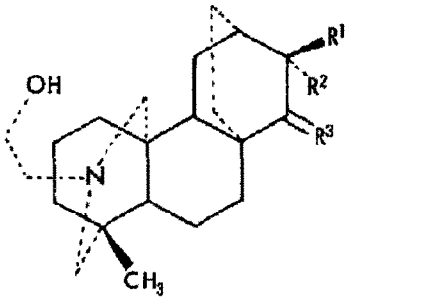
11 R = O
28 R = OH, H



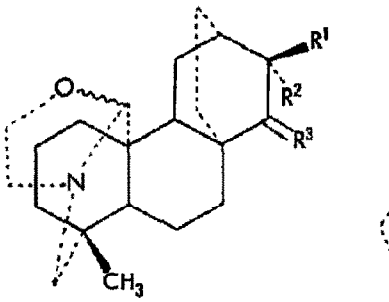
1 R = O
29 R = OH, H



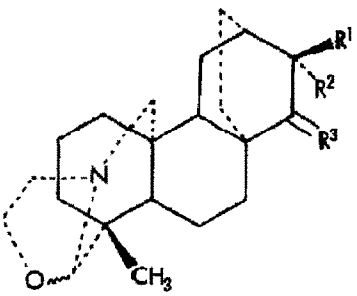
12 R = O
30 R = OH, H



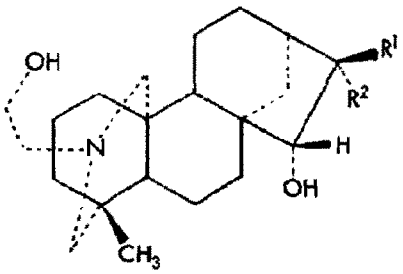
13 $R^1 = CH_3$; $R^2 = H$; R^3 = OH, H
16 $R^1 = H$; $R^2 = CH_3$; R^3 = OH, H
19 $R^1 = CH_3$; $R^2 = H$; $R^3 = O$



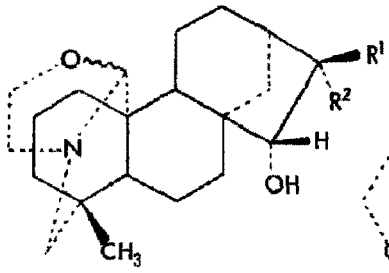
14 $R^1 = CH_3$; $R^2 = H$; R^3 = OH, H
17 $R^1 = H$; $R^2 = CH_3$; R^3 = OH, H
20 $R^1 = CH_3$; $R^2 = H$; $R^3 = O$



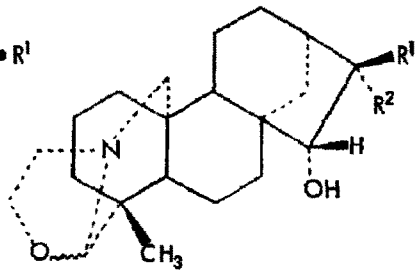
15 $R^1 = CH_3$; $R^2 = H$; R^3 = OH, H
18 $R^1 = H$; $R^2 = CH_3$; R^3 = OH, H
21 $R^1 = CH_3$; $R^2 = H$; $R^3 = O$



22 $R^1 = H$; $R^2 = CH_3$
25 $R^1 = CH_3$; $R^2 = H$



23 $R^1 = H$; $R^2 = CH_3$
26 $R^1 = CH_3$; $R^2 = H$



24 $R^1 = H$; $R^2 = CH_3$
27 $R^1 = CH_3$; $R^2 = H$

Table 1. Results of Potassium Ferricyanide Oxidation of Various N-ethanol derivatives.

Substrate	Time (hrs)	Products[a]	Ratio of normal:iso	Isolated Yield
Dihydroveatchine (4)	2.5	Veatchine (5) Garryine (6)	54:46	95%
Dihydrogarryfoline (7)	2.5	Garryfoline (3) Isogarryfoline (8)	46:53	83%
Dihydroatisine (9)	1.0	Atisine (2) Isoatisine (10)	51:49	82%
Dihydrocuauchichicine (11)[b]	1.5	Cuauchichicine (1) Isocuauchichicine (12)	35:65	60%
"α"-Tetrahydroatisine (13)	1.5	14[c] and 15[c]	45:55	72%
"β"-Tetrahydroatisine (16)	2.0	17 and 18	49:51	91%
15-Ketotetrahydroatisine (19)	1.0	20 and 21	45:55	76%
16α-Methyltetrahydroveatchine (22)	2.8	23 and 24	48:52	74%
16β-Methyltetrahydroveatchine (25)	1.0	26 and 27	56:44	72%
16β-Methyltetrahydrogarryfoline (28)	1.5	29 and 30	55:45	83%

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

[b] Oxidation of dihydrocuauchichicine was carried out at 0-5° using saturated sodium carbonate solution instead of 8% sodium hydroxide solution.

[c] Instability of these compounds in chloroform and methylene chloride results in low yields.

Acknowledgment: We thank Dr. Andrew W. Stocklinski of the School of Pharmacy, for providing the mass spectra of certain compounds needed for this work.

REFERENCES AND NOTES

1. (a) Institute for Natural Products Research, (b) Department of Chemistry, and (c) School of Pharmacy.
2. S. W. Pelletier, H. K. Desai, J. Finer-Moore, and N. V. Mody, J. Am. Chem. Soc., 101, 6741 (1979).
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. S. W. Pelletier, N. V. Mody, and J. Bhattacharyya, Tetrahedron Letters, 5187 (1978).
6. S. W. Pelletier, A. M. Ateya, N. V. Mody, and L. C. Schramm, Heterocycles, in press.
7. S. W. Pelletier, K. Kawazu, and K. W. Gopinath, J. Am. Chem. Soc., 87, 5229 (1965).
8. Several researchers have used potassium ferricyanide for formation of carbinolamine ethers, but the use of thi reagent has not been explored for construction of oxazolidine rings. [S. Sakai, Chem. Pharm. Bull., 7, 55 (1959); N. K. Hart, S. R. Johns, J. A. Lamberton, H. Suares, and R. I. Willing, Aust. J. Chem., 29, 1295 (1976)].

(Received in USA 30 June 1980)