# Ozonation in Alkaloid Chemistry: a Mild and Selective Conversion of Vincadifformine into Vincamine

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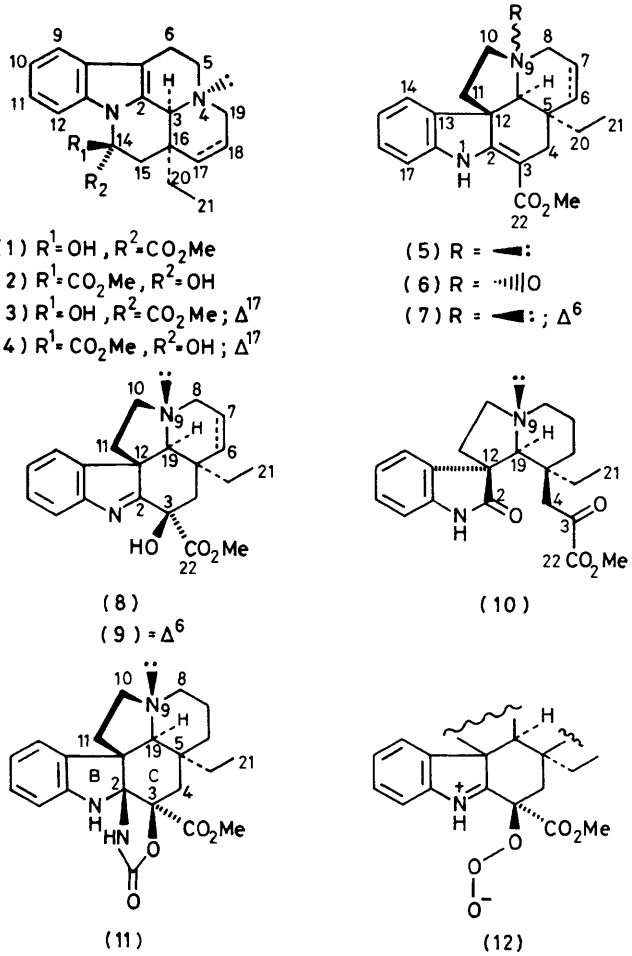
*Summary* Vincamine has been obtained in a 'one-pot' method by ozonation of vincadifformine.

ACCORDING to Wenkert's original scheme,[1] oxidation of *Aspidosperma* alkaloids to 3-hydroxy-derivatives provides a biogenetic rationalisation for eburnane alkaloids, amongst

which vincamine (**1**) deserves mention as being a useful cerebral vasodilator. Subsequently, Le Men and Levy[2] were able to emulate the biogenetic route for (**1**) starting from the appropriate precursor (−)-vincadifformine (**5**) through a multi-step procedure involving the prior oxidation to the 3-hydroxy-*N*(9)-oxide (of unknown stereochemistry), followed by $PPh_3$-reduction and acid-catalysed skeletal rearrangement to vincamine (**1**).

We report that we have obtained the key intermediate 3-hydroxyvincadifformine (**8**) by exploiting the reactivity of the highly versatile and long known oxidant, ozone.† More interestingly, this procedure provides the first efficient 'one-pot' method of converting (**5**) into (**1**). Intermediate (**8**) may be envisaged as a partial cleavage product from the ozonation of (**5**) and bubbling a stream of ozone (3·3 equiv.) into a 5% w/v solution of (**5**) in 0·87N-$H_2SO_4$–MeOH (3:1) at 20 °C, resulted in a totally stereoselective conversion into (**8**) (75% yield), m.p. 112 °C (di-isopropyl ether), $[\alpha]_D^{20}$ −151° ($CHCl_3$), $\delta_H$ ($CDCl_3$) 3·96 (3H, s, $CO_2Me$), 2·64 (1H, s, 19-H), 2·76 and 2·28 (AB system, *J* 15 Hz, 4-$H_2$), and 0·49 (3H, t, *J* 7 Hz, 21-$H_3$); $\delta_C$ ($CDCl_3$) 187·0 (C-2), 78·0 (C-19), 77·7 (C-3), 53·6 (C-10), and 52·0 (C-8) p.p.m.‡ Performing the above reaction at 60 °C we obtained directly a 7:3 mixture (74%) of known vincamine (**1**) and its 14-epimer (**2**).




The solvent polarity was crucial to the success of the reaction. On changing the solvent to AcOEt, along with (**8**) (25%), (9*S*)-vincadifformine *N*(9)-oxide (**6**) (12%), m.p. 163 °C ($Me_2CO$), $[\alpha]_D^{20}$ −266° ($CHCl_3$); $\delta_H$ ($CDCl_3$) 8·32 (1H, br d, *J* 8 Hz, 14-H), 3·76 (3H, s, $CO_2Me$), and 3·42 (1H, s, 19-H); $\delta_C$ ($CDCl_3$) 88·7 (C-19), and 66·4 and 65·3 (C-8/C-10) p.p.m., and the 2,3-seco-derivative (**10**) (45%); $M^{+\cdot}$ at *m/z* 370, $\lambda_{max}$ (MeOH) 248 (log ε 4·18) and 283 nm (log ε 3·21); $\delta_H$ ($CDCl_3$) 8·98 (1H, br s, N(1)-H), 3·84 (3H, s, $CO_2Me$), and 0·77 (3H, t, *J* 7 Hz, 21-$H_3$), were isolated.§ These two latter compounds were the only identifiable products when hexane was used as solvent. Ozonation of $\Delta^6$-vincadifformine (tabersonine) (**7**) in acetic buffer (pH 3·73; 1·5% w/v solution) at 25 °C was effected cleanly to afford the hitherto unknown (**9**) (78%); $\delta_H$ ($CDCl_3$) 5·70 (1H, dd, *J* 10 Hz, *J* 4 Hz, 7-H), 5·60 (1H, br d, *J* 10 Hz, 6-H), 3·99 (3H, s, $CO_2Me$), and 0·48 (3H, t, *J* 7 Hz, 21-$H_3$); $\delta_C$ ($CDCl_3$) 186·0 (C-2), 77·0 (C-3), 72·6 (C-19), 54·0 (C-10) and 52·0 (C-8) p.p.m. At 65 °C the known 17,18-didehydrovincamine (**3**) and its 14-epimer (**4**) as a 56:35 mixture (71%) were obtained.

The dominant interaction between the ozone LUMO[3] and the enhanced HOMO of a $\Delta^2$- *vs.* a $\Delta^6$-double bond rationalizes the observed site selectivity. This interaction, coupled with the significant steric hindrance of the β-anilinoacrylic double bond and with the appropriate polar solvents results in an electrophilic attack of ozone to give the resonance-stabilized zwitterion (**12**) which then undergoes $O_2$ disengagement.[4]

Aside from its synthetic utility in the preparation of vincamine and related eburnanes, the above reaction emphasizes the potential of ozone as a mild and selective reagent for the functionalization of indole alkaloids.

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† In principle, depending on structural features and solvent polarity, ozone usually acts either as an electrophile to give partial cleavage products (*e.g.*, epoxides, allylic alcohols) or as a 4π-electron system (1,3-dipole) yielding total-cleavage products (carbonyl compounds). For leading references, see P. S. Bailey, 'Ozonation in Organic Chemistry,' vol. I, Academic Press, London, 1978.

‡ The (3*R*)-configuration results from the ready formation (KCNO, dicyclohexyl-18-crown-6, $CH_2Cl_2$, 24 h at room temp.) of (**11**), m.p. 173 °C (AcOEt), $[\alpha]_D^{20}$ + 37·8° ($CHCl_3$); $\delta_C$ ($CDCl_3$) 156·5 ($NHCO_2$), 88·0 (C-2), 82·8 (C-3), and 37·0 (C-11) p.p.m. [*vs.* 45·0 p.p.m. in (**8**)]. The similar cyclization of the (3*S*)-epimer would result in an unacceptable *trans* B/C ring junction.

§ The stereochemical integrity of (**10**) *vs.* (**5**) is suggested by c.d. data [$\Delta\epsilon_{283}$ (+2·4), $\Delta\epsilon_{255}$ (−2·3), and $\Delta\epsilon_{225}$ (+13·0)]. However, on long standing in solution ($CHCl_3$, 12 h at room temp.), the α-keto-ester (**10**) is converted into an inseparable mixture of diastereoisomers.

[1] E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, 1965, **67**, 1580.
[2] G. Hugel, J. Levy, and J. Le Men, *C. R. Hebd. Seances Acad. Sci., Ser. C*, 1972, **274**, 1350; Belg. Pat. 761,628 (Omnium) (*Chem. Abs.*, **77**, 19866y); Ger. Offen. 2,201,795 (*Chem. Abs.*, **77**, 152430t).
[3] K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Am. Chem. Soc.*, 1973, **95**, 7301.
[4] P. S. Bailey and A. G. Lane, *J. Am. Chem. Soc.*, 1967, **89**, 4473.