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A NEW OXIDATIVE REARRANGEMENT OF VINDOLINE[1]

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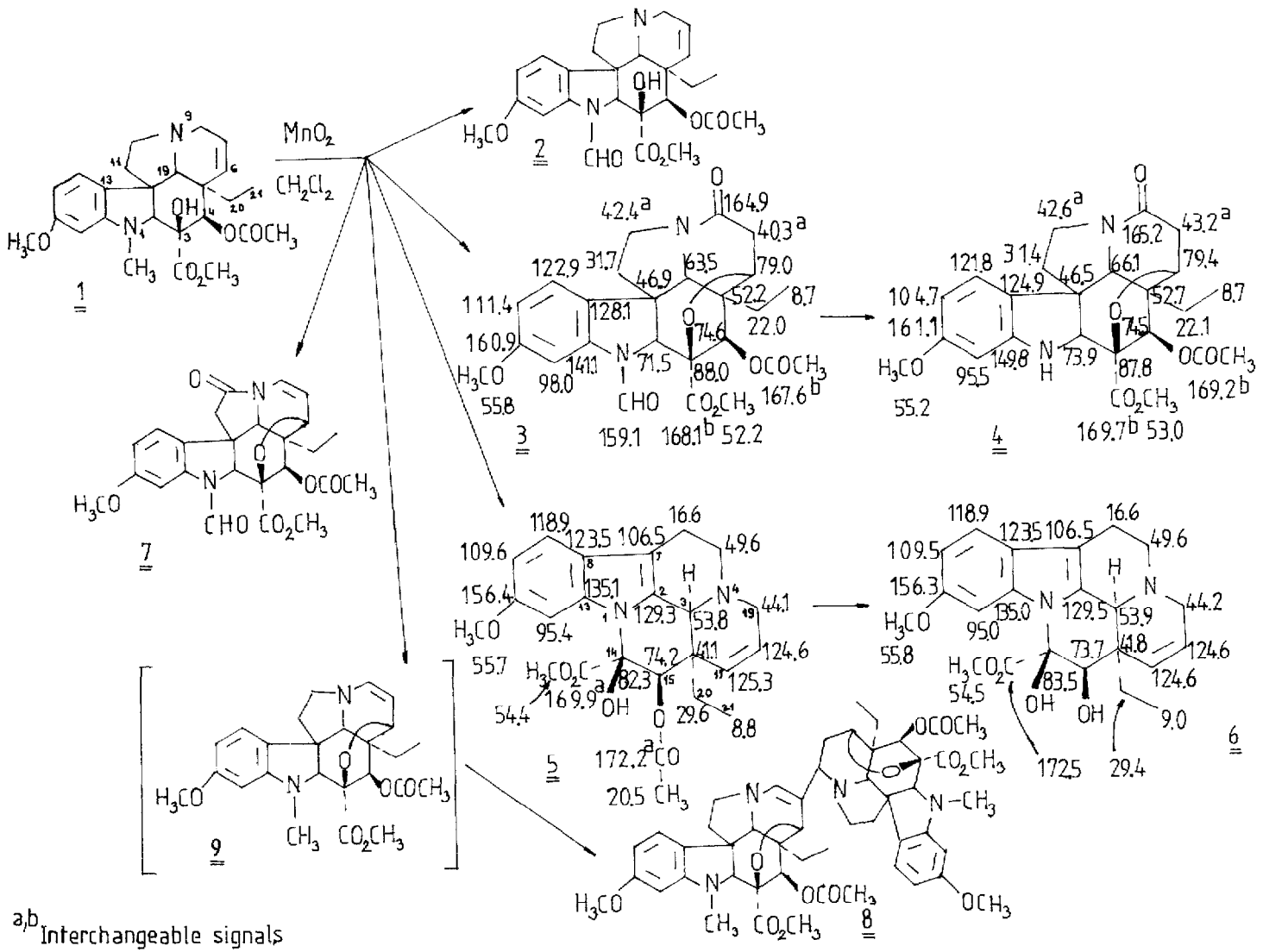
Summary: Oxidation of vindoline 1 with MnO_2 yielded a rearranged product, the vincine derivative 5, among other oxidized vindoline derivatives.

Vindoline 1 is a major alkaloid of Catharanthus roseus. Many vindoline derivatives have been synthesized and their chemical behaviour has been studied, because the coupling reaction between catharanthine type and vindoline type compounds has provided further examples of antitumor bis-indole alkaloids vincristine and vinblastine[2,5]. Kutney and his coworkers have investigated the oxidation of vindoline derivatives with mercuric acetate and potassium permanganate[3]. The iodine oxidation of 1 was studied by Le Men et al[4].

It has been reported that oxidation of vindoline with manganese dioxide in dichloromethane at room temperature gave, N-demethyl-N-formyl--vindoline 2 in 34 % yield[5]. Under slightly modified reaction conditions (longer reaction time 40 hours , MnO_2 prepared by Attenburrow's method[6]) the main product (18 %) proved to be another N-formyl-derivative, the lactam 3 containing oxygen atom at position C(8) and possessing C(3)-C(6) ether linkage. 36 % of the starting material was recovered. 3 was synthesized earlier by Kutney et al. with oxidation of the corresponding N-methyl-lactam ether[3]. The acidic treatment (HCl/methanol) of 3 gave the N-deformyl-derivative 4[11](mp. 182-185 °C, from diethylether) in 84 % yield.

In addition the rearranged product 5[11] was isolated in 7 % yield. In its mass spectrum the molecular peak was the base peak which is characteristic of the eburnane series. The ^{1}H and ^{13}C NMR spectra also confirmed the vincine skeleton. The structure of crystalline 5 (from methanol mp. 116-120 °C) was substantiated also by X-ray analysis. Treatment of 5 with acid HCl/methanol or hydrazine in water/acetic acid, EtOH gave the deacetyl-derivative 6[11] (mp. 198-201 °C, from diethylether) in 81 % yield.

The aspidospermane ⟶ eburnane skeletal rearrangement is well known starting from vincadifformine or tabersonine, but not in case of vindoline.


MnO2
CH2Cl2
1
2
3
4
5
6
7
8
9
a,b Interchangeable signals

For example: an oxidative rearrangement of (-)-vincadifformine to vincamine was observed both through a multistep procedure[7] and a onestep reaction[8,9]

A small amount (3 %) of vindoline dimer (8) was also separated from the above reaction of 1 with MnO_2. Rosazza et al. have isolated the same compound from the microbial transformation of 1[10]. Spectral data of the dimers obtained in different ways were indistinguishable. Rosazza et al.[10] supposed an enamine intermediate (9) in production of 8. A similar enamine (7)[11] but in oxidized form possessing lactam and N-formyl group was isolated (10 %) as well as a result of oxidation of 1 with MnO_2. The structure of the new compound (7)[11] (mp. 148-154 °C from diethylether) was elucidated by IR, MS and ^1H and ^{13}C NMR studies using also two dimensional HETCOR techniques.

Acknowledgement

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References and notes

1. Synthesis of Vinca Alkaloids and Related Compounds LII. For part LI see: F. Sóti, M. Peredy-Kajtár, Zs. Balogh-Kardos, M. Incze, Cs. Szántay, Synthesis of (±)-Demethoxycuanzine, in preparation.
2. a) N. Langlois, F. Guéritte, Y. Langlois, P. Potier, J. Am. Chem. Soc. 98 7017 (1976). b) J.Vukovic. A. E. Goodbody, J. P. Kutney, M. Misawa, Tetrahedron 1988 325-31.
3. J. P. Kutney, U. Bunzli-Trepp, T. Honda, J. Katsube, B. R. Worth, Helv. Chim. Acta 61 1554 (1978).
4. G. Hugel, G. Massiot, J. Levy, J. Le Men, Tetrahedron 1981 1369-75.
5. Belg. 867.255 (CA 90 P 138 081s).
6. J. Attenburrow. A.F.B. Cameron, J. H. Chapman, R. M. Evans, B.A. Hems, A.B.A. Janesen, and T. Walker, J. Chem. Soc. 1952 1094
7. G. Hugel, J. Lévy, J. Le Men, C.R., Acad. Sci. Ser. C. 1972 274 14 1350-2.
8. Hung. Pat. 185. 720
9. L. Calabi, B. Danieli, G. Lesma, G. Palmisano, J. Chem. Soc. Perkin Trans, I 1982 1371 and citations therein.
10. T. Nabih, L. Youel, J.P. Rosazza, J. Chem. Soc. Perkin I. 1978 757
11. 4 IR: (KBr) 1750 cm^{-1} (ester C=O), 1640 cm^{-1} (lactam C=O); $[\alpha]_{589}^{20}$: -66.22° (c = 1.157 $CHCl_3$); ^1H NMR δ ($CDCl_3$) 0.84 (t, 3H, C_{21}-H_3), 1.49 (q, 2H, C_{20}-H_2), 1.98 (s, 3H, -OCOCH_3), 2.45 (dd, 1H C_7-H_A), 2.82 (m, 1H,

C_7-H_B), 3.12 (m, 1H, C_{10}-H_A), 3.74 and 3.78 (2xs, 2x3H, -OCH_3), 3.86 (s, 1H, C_2-H), 4.02 (s, 1H, C_{19}-H), 4.51 (m, 1H, C_{10}-H_B) 4.62 (t, 1H, C_6 -H), 4.72 (br s, 1H, NH), 5.56 (s, 1H, C_4-H), 6.26 (d, 1H, C_{17}-H), 6.30 (dd, 1H, C_{15}-H), 6.92 (d, 1H, C_{14}-H). MS m/e 456 (M^+), 441. 425, 414, 413, 397, 381, 355, 337, 325, 309, 297, 242, 200, 186, 174, 173, 160, 159, 158, 145, 144, 143, 131, 130, 117, 108.

5 IR: (KBr) 1740 cm^{-1} (C=O); $[\alpha]_{589}^{20}$: +164.87 ^{o} (c = 1.185 $CHCl_3$); ^1H NMR δ ($CDCl_3$) 0.98 (t, 3H, C_{21}-H_3), 1.73 (q, 2H, C_{20}-H_2), 2.18 (s, 3H, -$OCOCH_3$), 3.74 and 3.81 (2xs, 2x3H, -OCH_3), 4.22 (br s, 1H, C_3-H), 5.57 (m, 1H, C_{18}-H), 5.60 (s, 1H, C_{15}-H), 5.88 (d, 1H, C_{17}-H), 6.52 (d, 1H, C_{12}-H), 6.78 (dd, 1H, C_{10}-H), 7.32 (d, 1E, C_9-H). MS m/e, 440 (M^+), 439, 425, 411, 407, 397, 381, 380, 379, 372, 363, 351, 339, 321, 293, 292, 291, 281, 280, 279, 200, 174, 146, 145.5, 122, 121.

6 IR: (KBr) 1740 cm^{-1} (C=O), $[\alpha]_{589}^{20}$ + 60.39 ^{o} (c = 1.007 $CHCl_3$); ^1H NMR δ ($CDCl_3$) 1.08 (t, 3H, C_{21}-H_3), 1.90 (q, 2H, C_{20}-H_2), 3.78 and 3.89 (2xs, 2x3H, -OCH_3), 4.16 (br s, 1H, C_3-H), 4.37 (br s, 1H, C_{15}-H), 5.57 (m, 1H, C_{18}-H), 5.68 (d, 1H, C_{17}-H), 6.64 (d, 1H, C_{12}-H), 6.80 (dd, 1H, C_{10}-H), 7.33 (d, 1H, C_9-H). MS m/e 398 (M^+), 397, 383, 381, 369, 367, 365, 351, 339, 330, 310, 281, 280, 279, 252, 200.

7 IR: (KBr) 1730 cm^{-1} (ester C=O), 1680 cm^{-1} and 1650 cm^{-1} (amide C=O); $[\alpha]_{589}^{20}$ +187.24 ^{o} (c = 1.144 $CHCl_3$); ^1H NMR δ ($CDCl_3$ + DMSO-d_6, 80 ^{o}C) 0.83 (t, 3H, C_{21}-H_3), 1.36 (q, 2H, C_{20}-H_2), 1.92 (s, 3H, -$OCOCH_3$), 2.65 (br s, 2H, C_{11}-H_2), 3.68 and 3.85 (2xs, 2x3H, -OCH_3), 4.44 (d, 1H, C_6-H), 4.48 (s, 1H, C_{19}-H), 4.55 (s, 1H, C_2-H), 5.56 (s, 1H, C_4-H), 5.67 (t, 1H, C_7-H), 6.78 (dd, 1H, C_{15}-H), 7.10 (d, 1H, C_8-H), 7.20 (br, 1H, C_{17}-H), 7.42 (d, 1H, C_{14}-H), 8.80 (br, 1H, NCHO); ^{13}C NMR δ ($CDCl_3$, rt.). Most signals exhibit splittings due to amide rotational isomerism. 8.7 + 9.3 (C21), 22.1 + 22.3 (C20), 46.8 + 46.1 (C11), 50.2 + 50.6 (C12), 53.1 + 52.9 ($COOCH_3$), 55.7 ($ArOCH_3$), 56.7 + 56.6 (C5), 59.3 + 58.8 (C19), 69.5 + 70.5 (C2), 73.0 + 72.9 (C4), 75.4 + 75.3 (C6), 87.9 + 89.0 (C3), 98.0 + 103.9 (C17), 111.1 (C15), 111.5 + 112.4 (C7), 123.2 + 121.9 (C14), 124.1 (C13), 129.3 (C8), 141.4 + 141.1 (C18), 158.4 + 159.0 (NCHO), 161.4 + 161.0 (C16), 167.7* (C10), 168.6* (OCO) 168.7* (COO) * interchangeable signals. MS m/e 482 (M^+), 453, 440, 438, 353, 323, 311, 283, 265, 238, 189, 188, 160, 145, 132, 131, 109, 108.

^{13}C NMR data of 3 ($CDCl_3$ + Me_2SO-d_6, 80 ^{o}C) and 4, 5, 6 ($CDCl_3$, rt.) can be seen on the formulas.

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