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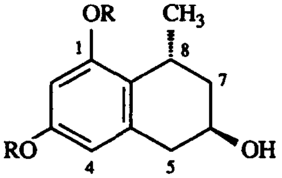
FEROXIDIN, A NOVEL 1-METHYLTETRALIN DERIVATIVE ISOLATED FROM CAPE ALOE[1]

Giovanna Speranza*, Paolo Manitto, Diego Monti, and Francesca Lianza

Dipartimento di Chimica Organica e Industriale, Università di Milano, and Centro di Studio sulle Sostanze Organiche Naturali, CNR, via Venezian 21, I-20133 Milano (Italy)

Summary : *The structure and the preferred conformation of feroxidin (1) are determined by spectroscopic methods (^{1}H-NMR, NOE, CD). The absolute configuration is deduced from chiroptical data. Feroxidin represents the first 1-methyltetralin occurring in plants.*

Cape aloe is the dried juice dripping from the cut leaves of *Aloe ferox* Mill., and is largely used for its bittering and cathartic properties.[2] All compounds so far isolated from this drug belong to the structural families of 2-acetonyl-5-methylchromones[3] (heptaketides)[4] and 1,8-dihydroxy-9-anthrones[5,6a] or 9,10-anthraquinones[6a] (octaketides).[4] We report here the structure of a new constituent of Cape aloe we named feroxidin (1). It represents the first hydroxylated 1-methyl-1,2,3,4,-tetrahydronaphthalene derivative (hexaketide)[4] occurring in *Aloe* spp.[6a] and, to our knowledge, in Nature.



1 R = H
2 R = CH$_3$

Flash chromatography[7a] of an EtOAc extract of Cape aloe,[7b] followed by DCCC separation[7c] and HPLC purification[7d] of the compound showing R_t = 7.5 min, gave a white amorphuos powder in 0.01% yield (with respect to the starting drug) : R_f 0.48;[7e] m.p. 82-84°C; $[a]_D^{20}$ - 11.30° (*c* 0.11, MeOH); UV, λ_{max} (log ϵ) : 225 sh (3.91), 277-285 nm (3.47) in MeOH; and 240 sh (3.95), 293 nm (3.51) in 0.05 N KOH-MeOH. M.w. (by high resolution MS) : found 194.09450, calcd. for $C_{11}H_{14}O_3$ 194.09429. The structure of this compound (feroxidin) was established as (6*R*,8*R*)-5,6,7,8-tetrahydro-8-methyl-1,3,6-naphthalenetriol (1) on the basis of the following chemical and spectroscopic evidence. When treated with Me_2SO_4-K_2CO_3 in anhydrous dioxane, **1** gave a dimethyl derivative **2** : R_f 0.51;[7e] $[a]_D^{20}$ - 12.14° (*c* 0.12, MeOH); UV, λ_{max} (log ϵ) : 225 sh (4.05), 275-284 nm (3.57) in MeOH; no bathochromic shift in alkaline solution. EI-MS *m/z* (%) : 222 (M^+, 80); 207 (100); 189 (82). ^{1}H NMR data of **1** and **2** (Table 1 and Fig. 1) indicated the presence of two upfield-shifted aromatic *meta*-protons and a -CH(Me)-CH$_2$-CH(OH)-CH$_2$- grouping in both molecules.

Table 1 - ^{1}H-NMR spectral data for feroxidin (1) and its dimethyl derivative (2)[a]

	2-H	4-H	5-$H_{e'}$	5-$H_{a'}$	6-H_{a}	7-H_{e}	7-H_{a}	8-$H_{e'}$	8-$Me_{a'}$
1[b]	6.10(d)	6.00(d)	2.91(ddd)	2.48(dd)	4.08(m)	1.88(dm)	1.67(ddd)	3.17(ddq)	1.18(d)
2[c]	6.30(d) (2.4)	6.21(d) (2.4)	3.00(ddd) (16.1; 5.7; 1.8)	2.54(dd) (16.1; 10.3)	4.10(m) (11.9; 10.3; 5.7; 2.5)	1.89(dm) (12.2; 2.5; 1.9; 1.8)	1.67(ddd) (12.2; 11.9; 5.9)	3.21(ddq) (5.9; 1.9; 7.0)	1.16(d) (7.0)

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[a] Registered at 300 MHz in CD_3OD at r.t.; δ(ppm) from TMS. [b] Multiplicities are given in parentheses; see Fig. 1 for coupling constants (Hz). [c] Multiplicities and coupling constants (Hz) are given in parentheses; -OMe resonances at 3.73 and 3.77 δ.

Table 2 - Proton associations based on NOE difference spectroscopy for feroxidin (1) in CD_3OD

From	to	% NOE
4-H	5-$H_{e'}$	5.3
5-$H_{a'}$	5-$H_{e'}$	32.4
	7-H_{a}	2.0
5-$H_{e'}$	5-$H_{a'}$	12.0
	6-H_{a}	3.6
	4-H	3.6
6-H_{a}	5-$H_{e'}$	4.2
	7-H_{e}	3.0
	8-$Me_{a'}$	1.9
7-H_{a}	7-H_{e}	20.4
	5-$H_{a'}$	3.7
	8-H_{e}	10.6
7-H_{e}	7-H_{a}	13.8
	8-$H_{e'}$	4.6
	8-$Me_{a'}$	0.9
	6-H_{a}	5.5
8-$Me_{a'}$	8-$H_{e'}$	11.4
	6-H_{a}	8.9
	7-H_{e}	3.3
8-$H_{e'}$	8-$Me_{a'}$	2.1
	7-H_{a}	4.3
	7-H_{e}	3.2

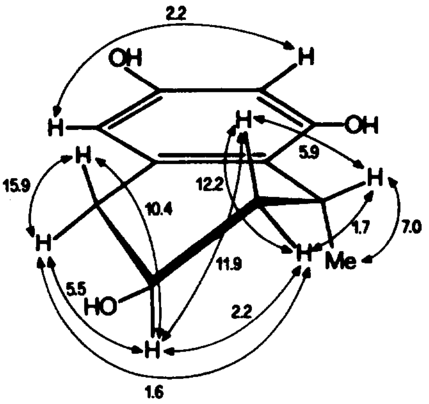
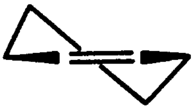


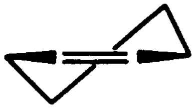
Fig. 1 - Preferred conformation of compound 1 showing proton-proton coupling constants (Hz).

Assignments of ^{1}H- and ^{13}C-resonances[8] were confirmed by homonuclear decoupling experiments, one-bond heteronuclear 2D correlations, and NOE data (Table 2). The substitution pattern of the aromatic ring of 1 with respect to the aliphatic moiety resulted from NOE experiments (Table 2) showing an intensity enhancement of each of the two proton signals at δ 6.00 (aromatic) and 2.91 (benzylic) by irradiation of the other one.

That the conformation represented in Fig. 1 for 1 (or the enantiomeric one)[9] strongly predominates in MeOH solution stems from spectral data ($^{3}J_{HH}$-values and ^{1}H NOE associations) as well as from the absence of any peak splitting in ^{1}H NMR spectra recorded at 0° to - 100° C.[10] This is understandable if one considers that one of the two alternative half-chair conformers[9] is stabilized over the other by the following factors :[11] *i)* the equatorial position of the hydroxy group at C-6 and *ii)* the preference of the methyl group to assume a pseudoaxial position,[12,13] thus relieving its steric compression with the *peri*-substituent (A$^{(1,3)}$ strain).[12a,14] Since the tetralin skeleton exists in one preferred half-chair conformation, distinction between the enantiomeric forms A and A' can be made on the basis of the CD spectra of 1 and 2.



A



A'

In fact, it has been shown that the sign of the CD band associated with the $^{1}L_b$ transition of the benzene chromophore in tetralins (at 260-290 nm)[15,16] depends neither on the substitution pattern in the aromatic ring nor on the presence of equatorial, axial, and pseudoaxial groups in the alicyclic moiety, but it is univocally related to the chirality sense of the cyclohexene ring.[13] Thus, *P* helicity[16] (as A) gives rise to a positive, and *M* helicity (as A') to a negative sign of the CD band.[17] The positive sign observed for the $^{1}L_b$ CD band in both compounds **1** ($\Delta\epsilon$ + 0.81 at 280 nm) and **2** ($\Delta\epsilon$ + 0.62 at 276 nm) was consistent with the conformation A. The absolute stereochemistry of feroxidin (*R*-configuration of C-6 and C-8 as in **1**) then follows as a consequence.

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References and Notes

1. Part 7 of the series "Studies on aloe". For part 6 see Ref.5.
2. V.E. Tyler, L.R. Brady, and J.E. Robbers, *Pharmacognosy*, Lea and Febiger, Philadelphia, 1988, p. 62.
3. G. Speranza, A. Martignoni, and P. Manitto, *J. Nat. Prod.*, 1988, **51**, 588; G. Speranza, G. Dadà, L. Lunazzi, P. Gramatica, and P. Manitto, *Phytochemistry*, 1986, **25**, 2219; G. Speranza, P. Gramatica, G. Dadà, and P. Manitto, *Phytochemistry*, 1985, **24**, 1571; P. Gramatica, D. Monti, G. Speranza, and P. Manitto, *Tetrahedron Lett.*, 1982, **23**, 2423.
4. Formally arising from a decarboxylated polyketide chain. See P. Manitto, *Biosynthesis of Natural Products*, Ellis Horwood, Chichester, 1981; U. Weiss and J.M. Edwards, *The Biosynthesis of Aromatic Compounds*, Wiley, New York, 1980.
5. P. Manitto, D. Monti, and G. Speranza, *J. Chem. Soc., Perkin Trans 1*, in press, and refs. cited therein.
6. a) T. Reynolds, *Bot. J. Linn. Soc.*, 1985, **90**, 157; b) T. Reynolds, *ibid.*, 1985, **90**, 179.
7. (a) SiO_2 using EtOAc as eluent; fractions (1-10) containing spots with R_f > 0.38 in TLC[7e] were collected and combined; (b) the origin of the commercial drug from *Aloe ferox* Mill. was ascertained by a TLC test according to ref. 6b; (c) $CHCl_3$-MeOH-H_2O (4 : 4 : 3), ascending mode; (d) column 250 x

25 mm, LiChrosorb RP 18, 7μ; CH_3CN-H_2O, linear gradient from 30 to 60 % CH_3CN in 15 min.; flow rate 15 ml/min; detector λ 280 nm; (e) silicagel plates, EtOAc-AcOH (99 : 1), visualization of spots by spraying with 0.5 % Fast Blue B salt.

8. ^{13}C NMR at 75.47 MHz in CD_3OD, δ (ppm) using the solvent signal as internal reference (δ 39.00 from TMS) : **1**, 156.87 (C-1, C-3); 137.23 (C-4a); 120.54 (C-8a); 107.52 (C-4); 101.43 (C-2); 64.83 (C-6); 40.80 (C-7); 40.39 (C-5); 29.37 (C-8); 21.98 (8-Me).
9. P. W. Rabideau (Ed.), *The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*, VCH Publishers, New York, 1989.
10. The steric energy difference between the two half-chair conformers was estimated to be *ca.* 1.51 kcal mol^{-1} by calculations (MM2 + MMP1), thus suggesting an equilibrium mixture at 300° K containing about 93 % of the conformer represented in Fig. 1.
11. a) H.-J. Schneider and P.K. Agrawal, *Org. Magn. Reson.*, 1984, **22**, 180; b) F.G. Morin, W.J. Horton, D.M. Grant, D.K. Dalling, and R.J. Pugmire, *J. Am. Chem. Soc.*, 1983, **105**, 3992 and refs. cited therein.
12. a) Y. Senda, J. Ishiyama, S. Imaizumi, and K. Hanaya, *J. Chem. Soc., Perkin Trans. 1*, 1977, 217; b) A. Schoofs, J. P. Guetté, and A. Horeau, *Bull. Soc. Chim. Fr.*, 1976, 1215; c) H. Tournier, R. Longeray, and J. Dreux, *ibid.*, 1972, 3214; e) T. Fujita, *J. Am. Chem. Soc.*, 1957, **79**, 2471.
13. J. Barry, H.B. Kagan, and G. Snatzke, *Tetrahedron*, 1971, **27**, 4737.
14. a) F. Johnson and S.K. Malhotra, *J. Am. Chem. Soc.*, 1965, **87**, 5492; b) Y. Senda and S. Imaizumi, *Tetrahedron*, 1974, **30**, 3813.
15. P. Crabbè and W. Klyne, *Tetrahedron*, 1967, **23**, 3449. See also A.I. Scott, *Interpretation of the Ultraviolet Spectra of Natural Products*, Pergamon Press, Oxford, 1964; E.S. Stern and C.J. Timmons, *Electronic Absorption Spectroscopy in Organic Chemistry*, E. Arnold, London, 1970.
16. J.C. Craig, S.-Y.C. Lee, R.P.K. Chan, and I.Y.-F. Wang, *J. Am. Chem. Soc.*, 1977, **99**, 7996.
17. This is well explained in terms of a sector rule predicting signed contributions from the chiral "second sphere" (*i.e.* the half-chair cyclohexene ring, the aromatic nucleus forming the "first sphere"), and from the "third sphere" (*i.e.* substituents attached to the second sphere).[18] Contributions of the third sphere are of the same sign as that of the second sphere except for the pseudoequatorial group. Methyl group increments, when experimentally estimated, were found to be in agreement with the above predictions.[19] A semiempirical quadrant rule (based on one-electron theory) has also been developed by Craig *et al.*[16] to rationalize chiroptical properties of 1-methyl-1,2,3,4,-tetrahydroisoquinolines of known absolute configuration. It must be pointed out that Snatzke's and Craig's rules coincide in the correlation between the sign of the ^1L_b CD band and the helicity of the half-chair ring.
18. G. Snatzke and P.C. Ho, *Tetrahedron*, 1971, **27**, 3645.
19. S. Hagishita and K. Kuriyama, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 3216.

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