Pergamon

Tetrahedron Letters, Vol. 35, No. 37, pp. 6869-6872, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01443-4

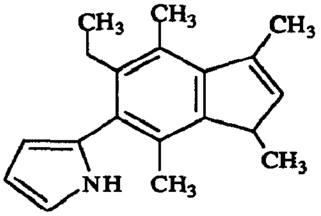
Trikendiol, an Unusual Red Pigment from the Sponge *Trikentrion loeve*, Anti-HIV-1 Metabolite

Ali Loukaci and Michèle Guyot*

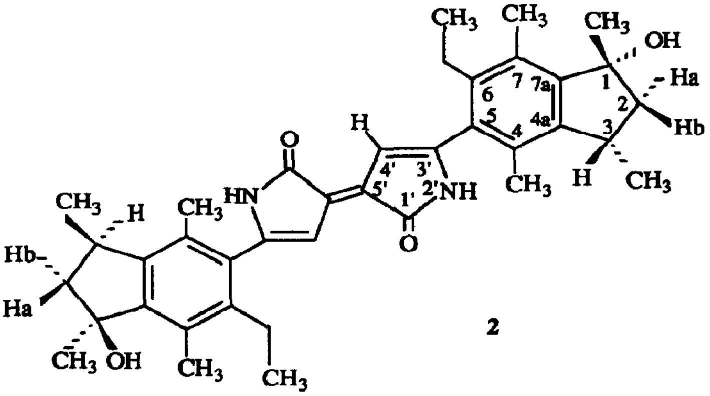
Laboratoire de Chimie, associé au C.N.R.S., Muséum National d'Histoire Naturelle,
63 rue Buffon, 75005 Paris, France.

Abstract. Trikendiol **2**, an unusual red pigment, has been isolated from the sponge *Trikentrion loeve*. The structure was determined by the interpretation of spectral data. Trikendiol was shown to be anti-HIV-I.

Chemical studies of sponges belonging to the genus *Trikentrion* (Axinellide, family Euryponidae) have previously led to the isolation of original compounds : *T. helium* furnished a carotenoid trikentriorhodin [1], *T. flabelliforme*, contained the trikentrins, a series of cyclopentanoindoles [2,3]. From *T. loeve*, trikentramine **1**, an unusual pyrrole derivative [4] and a new glycolipid [5] were previously isolated. Here, we report the structure of a deep red pigment, trikendiol **2** from the same species.



1



2

Trikentrion loeve Carter was collected along the coast of Senegal. The dichloromethane extract of air-dried sponges was bright red and TLC analysis ($CHCl_3$/MeOH 95/5) revealed the presence of several red pigments. Successive chromatographic separations on a silicagel column using CH_2Cl_2-acetone (9/1) and LH 20 (MeOH-CH_2Cl_2 6/4) followed by another silicagel column (CH_2Cl_2-acetone 9/1) furnished trikendiol

2 as the major pigment, 0.025 % dry weight. Trikendiol 2 crystallized from acetone, m.p. 160-162°C, $[\alpha]_D$ +102 (c; 0.02, $CHCl_3$), U.V. λ_{max} (ε): 210 (37390), 265 (8047), 337 (sh.), 510 (8360), I.R. ν_{max} : 1677, 3400 cm^{-1}.

The molecular formula was established as $C_{38}H_{46}N_2O_4$ by HR-FABMS : $[M+H]^+$ peak at m/z 595.3436 (calculated for $C_{38}H_{47}N_2O_4$: 595.3534, Δ 0.01mu).

The ^{13}C NMR spectrum (table 1) displayed signals for 19 carbon atoms which conjugated with the MS data suggested a dimeric structure.

Analysis of ^1H and ^{13}C (table I) and 2D NMR (COSY, HMQC) data together with long-range ^1H-^{13}C NMR correlations (HMBC) enabled us to propose structure 2 for trikendiol and unambiguously assign all protons and carbons. ^1H and ^{13}C signals corresponding to an aromatic ring (C-4a-C-7a) with the same substitution pattern as that found in trikentramin 1were corroborated by HMBC experiments. A deshielded signal at δ 1.61 ppm (s, 3H) suggested the presence of a methyl group attached to a carbon bearing an hydroxyl group. The methyl group at δ 1.30 ppm as a doublet was coupled to a proton itself coupled with the two protons of a methylene group (δ_C 52.2 ppm). These two methyl groups showed long range correlations (HMBC) with the carbon at δ 52.2 and respectively with the carbons at δ 146.3 (C-7a) and 144.3 (C-4a) ppm, which gave good evidence for an indanol structure derived from trikentramine 1.

Table - ^1H (300 MHz) and ^{13}C (75.5 MHz) NMR data of trikendiol 2 in $CDCl_3$

Position	δ^1 H, ppm (m, *J* Hz)	δ ^{13}C (ppm)	HMBC (^{13}C)
1		82	
2a	1.82 (dd, *J* = 13.5, 5), 1H	52.2	9, 8, 3, 1, 4a
2b	2.48 (dd, *J* = 13.2, 8.3), 1H		9, 8, 3
3	3.13 (ddq, *J*=8, 7, 3), 1H	35.4	
4		130.9	
4a		144.3	
5		130.5	
6		141.4	
7		131.4	
7a		146.3	
8	1.61 (s), 3H	28.2	2, 1, 7a
9	1.3 (d, *J* = 7), 1H	22.1	3, 2, 4a
10	2.23 (s), 3H	16.7	4a, 4, 5
11	2.65 (q, *J* = 7.5), 2H)	24.1	13
12	1.11 (t,*J* = 7.5), 3H	15.6	11, 6
13	2.47 (s), 3H	14.0	6, 7a, 7
1'		170.7	
2'	6.78 (s, br)*, 1H		
3'		129.3	
4'	6.72 (d, *J* =2), 1H	104.1	3', 1', 5'
5'		148.9	

* Exchangeable D_2O

The remaining ^{13}C signals were assigned as followes: the occurrence of a signal at δ 170.7 ppm, together with an IR band at 1677 cm^{-1} favoured the presence of an amide fonction. The proton at δ 6.72 ppm displayed a weak coupling constant with the D_2O exchangeable proton at δ 6.78 and long-range correlations with the carbon signals at δ 148.9, 170.7, 129.3 ppm. Only structure 2 including a bis-pyrrole-2-one-yliden is compatible with these observations.

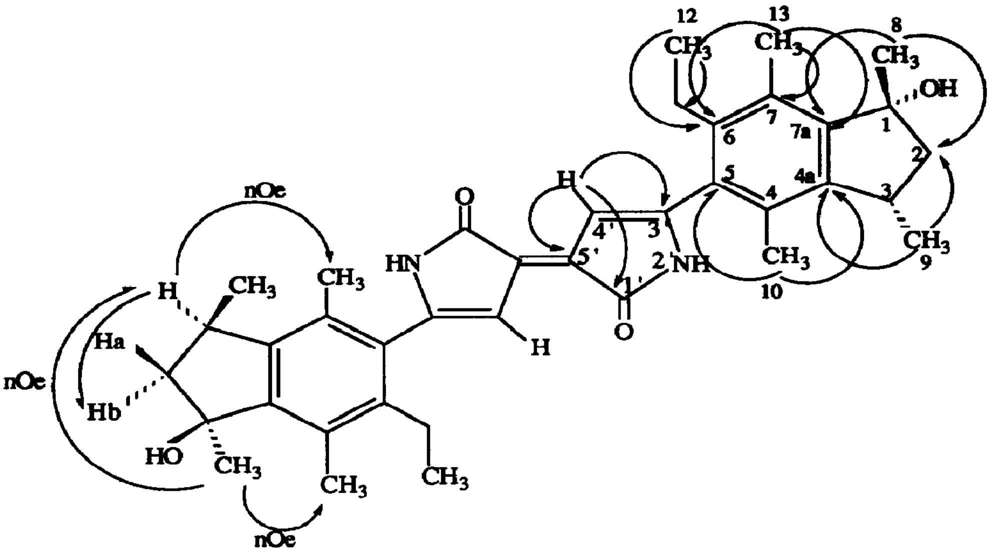
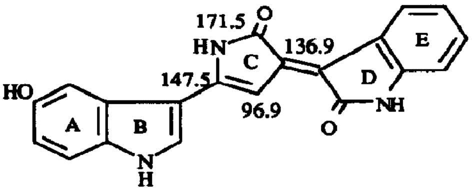
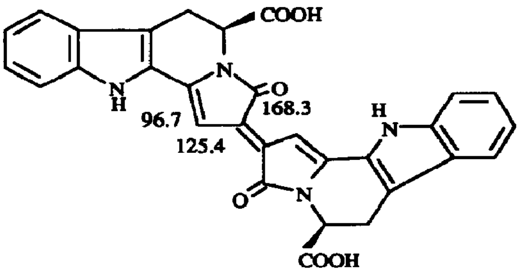


Fig. Long range ^1H-^{13}C correlations (HMBC) and nOe for trikendiol 2.

Literature data provided only few examples of such structures. We found that ^{13}C NMR data of the natural pigments violacein 3 [6] and trichotomine I 4 [7] showed good similarities with the values observed for trikendiol 2.



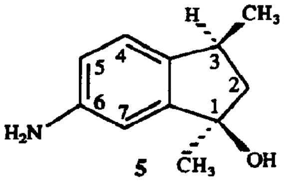
Violacein 3



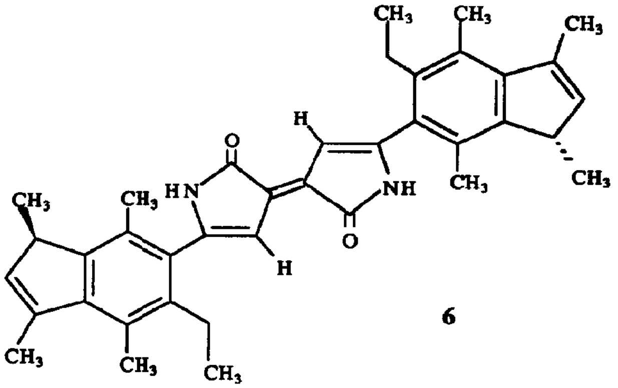
Trichotomine 4

In an attempt to establish the relative configuration of substituents of the indanol ring, nOe difference experiments were performed. Irradiation of CH_3-8 causes enhancement of the H-3 signal (and Me-13), but irradiation of the H-3 causes enhancement of CH_3-9, CH_3-10 and Hb only. NMR data of 2 were compared to those given for the synthetic *cis*- 6-amino-1,3-dimethylindan-1-ol 5 [7]. The values described : 3.0 (H-3), 2.45 and 1.66 (H-2) were similar to those observed for 2, however NMR data of the *trans* isomer were not available. Hence the relative stereochemistry of the methyl groups at 1 and 3 positions was tentatively assigned to be *trans* . Work is in progress to establish the absolute configuration of the indanol moiety, so the enantiomer shown represents an arbitrary choice.

When stored (some hours) in CDCl$_3$, trikendiol **2** led to **6**, another red pigment ; EIMS : m/z : 558 (M$^+$). ^{1}H NMR data of **6** differs from those of **2** by the presence of an additional ethylenic proton at δ 6.18 ppm, disappearance of the methyl doublet (1.3 ppm) and presence of a methyl (s) at δ 2.35 ppm[8]. Such an easy dehydration of an indanol to the corresponding indene was previously reported in a recently published synthesis of trikentrin A [9]. In our case we attributed the transformation of **2** into **6** to the slight acidity of CDCl$_3$.



5



6

In our continuous effort to detect bioactive molecules, trikendiol **2** was found to be active in a CEM-4 HIV-1 infection assay (IC$_{50}$ 2µg/ml) as measured by inhibition of the cytopathogenic effect of the virus, but caused no inhibition of the HIV-1 aspartyl protease at 10^{-5} M.

Acknowledgments.

We thank Drs A. Mousseau and Y.Lelièvre for the bioassays toward HIV-1 and HIV-1 protease, A. Couté and J.M. Kornprobst for collections of the sponge, N.Boury-Esnault for sponge identification, M.T. Martin for helpful advices, The Service de spectrométrie de masse du CNRS for FAB-MS spectra.

References.

1 Agilar-Martinez, M.; Liaaen-Jensen, S. *Acta Chem. Scand.*, **1974**, 1247-1248.
2 Capon, R.J.; J.K. Macleod, J.K.; Scammells, P.J. *Tetrahedron*, **1986**, *42*, 6545-6550.
3 Muratake, H.; Natsume, M. *Tetrahedron Lett.*, **1989**, *30*, 5771-5772.
4 Aknin, M.; Miralles, J.; Kornprobst, J.M.; Faure, R.; Gaydou, E.M.; Boury-Esnault, N., Kato, Y.; Clardy, J. *Tetrahedron Lett.*, **1990**, *31*, 2979-2982.
5 Constantino, V.; Fatorusso, E.; Mangoni, A.; Aknin, M.; Fall, A.; Samb, A.; Miralles, J. *Tetrahedron*, **1993**, *49*, 2711-2716.
6 Hoshino, T.; Uchiyama, T.; Ogasawara, N. *Niigata Daigaku Nogakubu Kenkyu Hokoku*, **1988**, *40*, 17-32.
7 Ashraf, C.M.; Jackson, W.R. *Aust. J. Chem.*, **1978**, 1845-1849.
8 ^{13}C NMR data of **6**: (CDCl$_3$, 75 MHz, δ ppm): 170.8, 149.2, 146.8, 144.2, 140.6, 140.1, 139.1, 131.5, 130.5, 129.1, 127.7, 104.3, 42.3, 29.8, 24.3, 18.6, 16.6, 15.9, 14.7.
9 Macleod, J.K.; Monahan, L.C. *Tetrahedron Lett.*, **1994**, *35*, 391-392.

(*Received in France* 29 *June* 1994; *accepted* 22 *July* 1994)