Phytochemistry, Vol. 33, No. 1, pp. 141–143, 1993
Printed in Great Britain.

0031-9422/93 $6.00+0.00

REVISED STRUCTURE AND STEREOCHEMISTRY OF JATAMANSIC ACID

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(*Received* 24 *August* 1992)

Key Word Index—*Nardostachys jatamansi*; Valerianaceae; jatamansic acid; guaiane derivative.

Abstract—The structure of jatamansic acid has been revised from 2D-NMR data, an INADEQUATE experiment and X-ray diffraction analysis. The stereochemistry was concluded from NOE difference spectra and H–H-couplings as well as from X-ray analysis.

INTRODUCTION

Jatamansic acid was isolated from *Nardostachys jatamansi* D.C. in 1951 and assigned **1** [1]. Subsequently, this structure was altered to **2**, on the basis of a degradation reaction which gave rise to guaiane (**3**) [2].

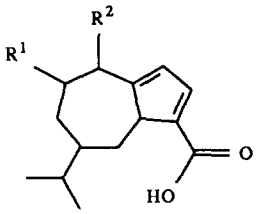
RESULTS AND DISCUSSION

The 2D-NMR spectra (H–H COSY and C–H corr., Tables 1, 2) indicated that the revised structure (**2**) for jatamansic acid was incorrect. The carbon skeleton as deduced by an INADEQUATE experiment (Table 2) suggested structure **4**, which bears the α,β-unsaturated carboxylic acid chromophore in the seven-membered ring. When applied to **4**, the chemical degradation performed earlier [2] would also lead to **3**.

The NOE difference spectra (Table 1, Fig. 1) showed that the methine protons H-3a and H-8a are synclinal, indicating a cisoid arrangement of the five- and the seven-membered ring. Since sterical interactions are observed between these two protons and H-3, the Me-12 group, which is attached to C-3, must be arranged towards the opposite side of the five-membered ring. Thus the Me-12 causes NOEs towards the methylene proton H-4_B as well as towards H-3.

From further NOEs, the conformation given in Fig. 1 results. The conjugated double bonds are arranged almost co-planarly. The UV absorbance at 282 nm also confirms a torsionless arrangement of the chromophore. In accordance with this steric arrangement, some weak, negative NOEs between H-6 and H-9 as well as between H-6 and one methylene proton at C-4, are observed. When the ^{1}H NMR spectrum is recorded in C_6D_6 or pyridine-d_5, respectively, two protons have remarkably lowered shift values compared to those observed in $CDCl_3$: 2.75 ppm, *dddd*, H-1_B (−0.30 ppm) and 7.58 ppm, *dd*, H-7 (−0.40 ppm), respectively.

The structure was further confirmed by a single crystal X-ray structure determination (Fig. 2). The asymmetric unit contains two formula units. Two molecules are linked together by hydrogen bridging of the acid groups. Both of the monomers, which are slightly different because of the packing forces, belong to the same enantiomorph. It is impossible, however, to decide which enantiomorph is the correct one.



	R^1	R^2
1	Me	H
2	H	Me

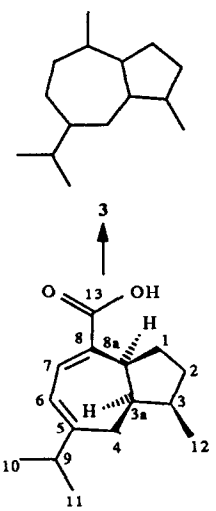


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Table 1. ^{1}H NMR spectral data of compound **4** (300 MHz, $CDCl_3$, TMS as int. standard)

H	δ	J(Hz)	H–H-COSY correlated with	NOE*
1_A	1.50 *dddd*	1_A, 1_B: 13.2; 1_A, 2_A: 12; 1_A, 8a: 10.5; 1_A, 2_B: 4.8	H-1_B; H-2_A; H-2_B; H-8a	H-1_B; H-2_A; H-4_A‖; H-8a§‖
1_B	2.45 *m*†	1_B, 8a ≈ 1_B, 2_B: *ca* 9; 1_B, 2_A: 5.5	H-2_A; H-2_B; H-8a	H-1_A; H-8a H-4_B§
2_A	1.10 *qd*	2_A, $2_B \approx 2_A$, 3: *ca* 12	H-2_B; H-3	H-1_A; H-2_B; H-1_B§
2_B	1.74 *m*†			
3	2.22 *ddqd*	3, 12: 6.8; 12; *ca* 8; *ca* 5	H-3a	H-3a; H-8a
3_a	1.71 *m*†		H-8a	
4_A	1.78 *dd*†	4_A, 4_B: 14.3; 4_A, 3a: 10.5	H-4B; H-6	
4_B	2.21 *dt*	3a, 4_B: *ca* 2	H-6	H-6‖
6	5.76 *dm*	6,7: 7.2; 6, 9: 1.2	H-7; H-9	H-7; H-9; H-10; H-11; H-4_A§‖
7	7.17 *d*	7, 8a: *ca* 1.5	H-8a	H-6; H-9§; H-10§; H-11§
8a	3.04 *td*	10.5/9/5/ *ca* 1.5/*ca* 1		H-1_B; H-3; H-3a; H-4_A‖; H-6§‖; H-7§‖
9	2.43 *sepd*†	9, 10=9, 11:6.8	H-10; H-11	H-4_A‖; H-4_B‖ H-3a§‖; H-6
10/11	1.05 *d*			H-6; H-9
12	1.07 *d*			H-4_B; H-3‖
COOH	*ca* 12 *br*‡			

*In $CDCl_3$ or C_6D_6.
†Overlapping signals.
‡Exchangeable with D_2O.
§Negative NOE.
‖Weak.

Table 2. ^{13}C NMR data of compound **4** (300 MHz, $CDCl_3$, TMS as int. standard)

C	δ*	C–H-correlation	C–H–COLOC†	INADEQUATE‡
1	33.2 *t*	H-1_A; H-1_B	—	C-2; C-8a
2	28.7 *t*	H-2_A; H-2_B	H-12	C-1; C-3
3	39.3 *d*	H-3	—	C-2; C-3a; C-12
3a	44.2 *d*	H-3a	§	C-3; C-4
4	26.7 *t*	H-4_A; H-4_B	H-6	C-3a; C-5
5	160.7 *s*	—	H-4_A; H-4_B; H-7; H-10/11	C-4; C-9
6	118.2 *d*	H-6	H-4_A; H-4_B	C-7
7	136.3 *d*	H-7	—	C-6
8	134.8 *s*	—	H-3a; H-6; H-7; H-8a	C-8a
8a	46.7 *d*	H-8a	§	C-1; C-3a; C-8
9	39.0 *d*	H-9	H-6; H-10/11;	C-5; C-10/11
10/11	21.2/21.5 *q*	H-10/11	—	C-9
12	16.1 *q*	H-12	—	C-3
13	176.4 *s*	—	H-7	—

*Multiplicity from APT experiments.
†Long-range C–H-correlation.
‡^{13}C–^{13}C-Correlation.
§Overlapping signals.

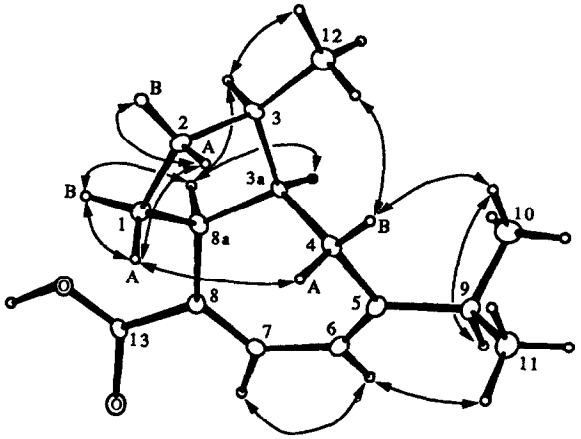

Fig. 1. A computer-generated perspective drawing of the final X-ray model of jatamansic acid (**4**). The absolute configuration shown is arbitrary. Arrows show positive NOEs.

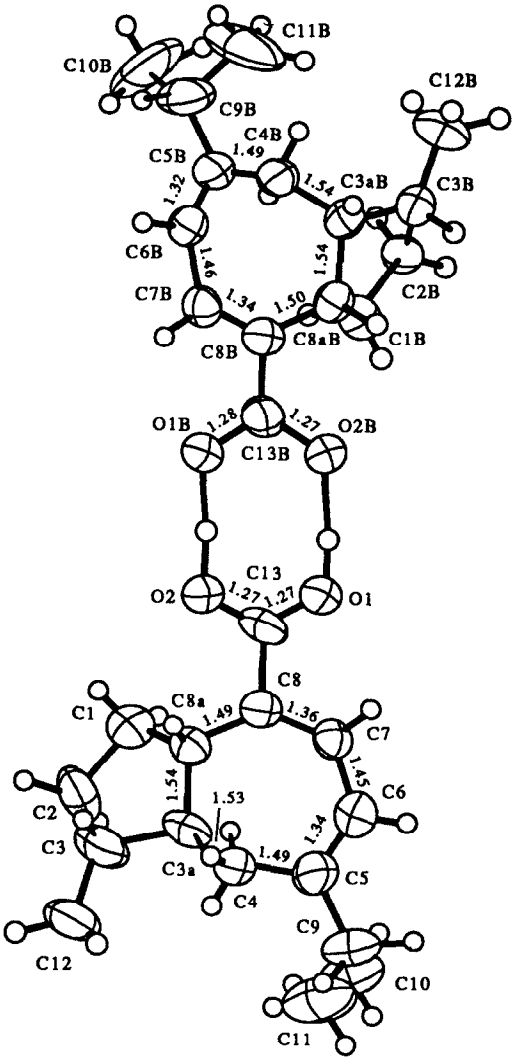

Fig. 2. ORTEP [6] plot of the dimer with 50% probability ellipsoids and the numbering scheme of the atoms. Included are the bond distances within the rings of the two inequivalent monomers.

EXPERIMENTAL

General. UV: Perkin–Elmer Lambda 2; NMR: Bruker WM 400 and AMX 500, Varian XL 300. 3-Methyl-5-isopropyl-1,2,3,3a,4,8a-hexahydroazulene-3-carboxylic acid (jatamansic acid) [2]. ^{1}H NMR: Table 1; ^{13}C NMR: Table 2.

Crystal structure determination. At 25°, on a four-circle diffractometer (AFC6R/RIGAKU, MSC) with Mo Kα radiation ($\lambda = 0.71069$ Å, graphite monochromator), using ω-2θ scans. The lattice parameters were calculated from the setting angles of 25 reflections in the θ range $12° < \theta < 17°$, resulting in $a = 13.034$ (2) Å, $b = 8.447$ (2) Å, $c = 13.271$ (2) Å, $\alpha = \gamma = 90°$, $\beta = 102.11$ (1)°, $V = 1428.6$ (4) Å^3. The space group is $P2_1$ ($Z = 4$) and the calculated density $D_x = 1.089$ gcm^{-3}. Intensity data (8440 measured reflections) were collected up to a maximum $(\sin\theta)/\lambda$ of 0.682 Å^{-1} in the range $0 \simeq h \simeq 18$, $0 \simeq k \leqslant 12$, $-18 \leqslant l \leqslant 18$ (plus Friedel pairs).

The structure was solved in spacegroup $P2_1$ by direct methods with MITHRIL [3] and subsequent electron density calculations via Fourier synthesis. Least-squares calculations were performed with F values and weights of the form $w = \{\sigma^2(F) + (\varepsilon/2)^2 F^2\}^{-1/2}$, where the relative error of intensities due to instrumental instability $\varepsilon = 0.007$ has been derived from the scattering of standard reflections about their regression curve [4].

The Friedel pairs were averaged and anomalous scattering factors were excluded. In the last cycles of refinement, all 482 parameters (non-hydrogen atoms anisotropic, hydrogens isotropic) were allowed to refine freely. The final residuals were $R = 0.034$, $R_w = 0.028$ and the goodness-of-fit, $GOF = 1.79$ for 1385 unique reflections with $I > 3\sigma(I)$. All structure calculations were performed with the program package TEXSAN [5]. Data are deposited at the Cambridge Crystallographic Data Centre.

Acknowledgements—S.K.P. is grateful to UGC, New Delhi, India and DAAD, F.R.G., for a fellowship under the Indo-German exchange program.

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