Chemistry of Natural Compounds, Vol. 34, No. 6, 1998

MOLECULAR AND CRYSTAL STRUCTURE OF THE DIMETHYLAMIDE DERIVATIVE OF α-SANTONIN

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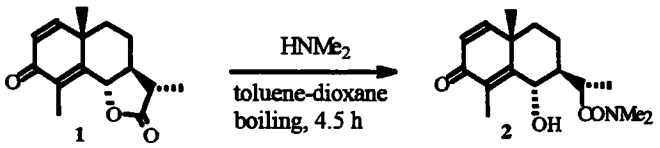
UDC 547.314:548.737

α-Santonin has been aminolyzed with dimethylamine. The spatial structure of the resulting dimethylamide has been established by the x-ray structural method.

Continuing work on the chemical modification of eudesmanolides, we have carried out the aminolysis of α-santonin (**1**) with dimethylamine, since modification at the lactone ring permits new biologically active derivatives to be obtained [1—3].



The amide (**2**) was obtained with a yield of 43% by boiling α-santonin with dimethylamine in a mixture of dioxane and toluene for 4.5 h. The structure of the dimethylamide (**2**) so obtained was established on the basis of spectral characteristics (IR and PMR) and the results of x-ray structural analysis.

The general shape of the (**2**) molecule is shown in Fig. 1. In this molecule the bond lengths and valence angles are close to the usual values within the limits of accuracy (Tables 1 and 2) [4].

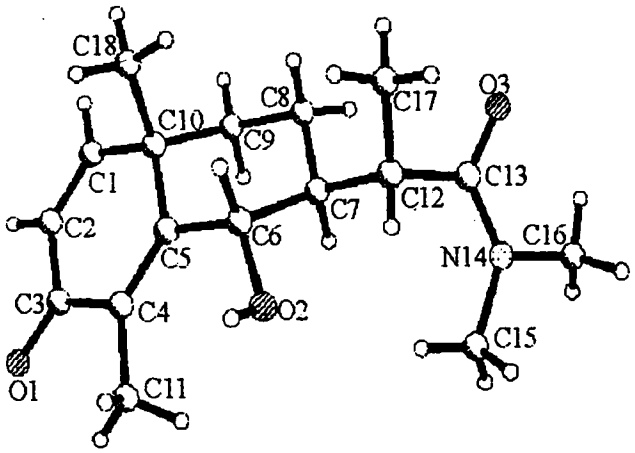


Fig. 1. Structure of the molecule of the dimethylamide derivative of α-santonin (**2**).

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0009-3130/98/3406-0683$20.00

TABLE 1. Bond Lengths *d* (Å) in the Structure of (2)

Bond	*d*	Bond	*d*
O1-C3	1.221(5)	O2-C6	1.408(5)
O3-C13	1.236(5)	C1-C2	1.314(6)
C1-C10	1.493(5)	C2-C3	1.464(6)
C3-C4	1.493(6)	C4-C5	1.350(5)
C4-C11	1.511(6)	C5-C6	1.534(5)
C5-C10	1.524(5)	C6-C7	1.550(5)
C7-C8	1.528(6)	C7-C12	1.553(5)
C8-C9	1.531(6)	C9-C10	1.556(6)
C10-C18	1.554(6)	C12-C13	1.518(6)
C12-C17	1.517(7)	C13-N14	1.330(5)
N14-C15	1.452(6)	N14-C16	1.465(7)

TABLE 2. Valence Angles ω (degrees) in the Structure of (2)

Angle	ω	Angle	ω
C2C1C10	124.5(4)	C1C2C3	121.1(4)
O1C3C2	119.8(4)	O1C3C4	122.1(4)
C2C3C4	118.1(3)	C3C4C5	120.0(3)
C3C4C11	112.8(3)	C5C4C11	127.1(4)
C4C5C6	126.0(3)	C4C5C10	122.6(3)
C6C5C10	111.4(3)	O2C6C5	115.1(3)
O2C6C7	105.3(3)	C5C6C7	111.6(3)
C6C7C8	113.5(3)	C5C7C12	109.4(3)
C8C7C12	112.4(3)	C7C8C9	111.7(3)
C8C9C10	111.8(3)	C1C10C5	113.5(3)
C1C10C9	106.9(3)	C5C10C9	108.3(3)
C1C10C18	105.7(3)	C5C10C18	111.8(3)
C9C10C18	110.5(3)	C7C12C13	110.2(3)
C7C10C17	114.1(4)	C13C12C17	110.7(4)
O3C13C12	121.0(4)	O3C13N14	119.6(4)
C12C13N14	119.4(4)	C13N14C15	119.7(4)
C13N14C16	125.2(4)	C15N14C16	114.7(4)

TABLE 3. Torsion Angles φ (degrees) in the Rings of Structure (2)

Torsion angle	φ
Ring *A*	
C1C2C3C4	-1.5
C2C3C4C5	1.1
C3C4C5C10	0.4
C4C5C10C1	-1.4
C2C1C10C5	1.0
C3C2C1C10	0.4
Ring *B*	
C5C6C7C8	49.1
C6C7C8C9	-48.6
C7C8C9C10	54.5
C8C9C10C5	-59.7
C9C10C5C6	59.8
C10C5C6C7	-55.4

The linkage of the rings C1C2C3C4C5C10 (ring *A*) and C5C6C7C8C9C10 (ring *B*) is pseudotrans (torsion angles C1C10C5C4 1.4° and C9C10C5C6 59.8°). The conformation of ring *A* is practically planar. The presence of the two double bonds C1=C2 and C4=C5 conjugated with the keto group C3=O1 leads to pronounced flattening of ring *A* (the absolute value of the intracyclic torsion angles does not exceed 1.5° (Table 3)). The atoms of the ring are coplanar to within ±0.006 Å. The O1 atom is located practically in the plane of the ring, with a deviation of 0.048 Å.

Ring *B* is symmetrical relative to a plane passing through the C7 and C10 atoms and assumes the conformation of a 7α,10β-chair ($\Delta C_s^7 = 0.6°$). The torsion angles range from 48.6 to 59.8° in absolute value (see Table 3). The O2 and C12 atoms are oriented equatorially in the α- and β-directions, respectively. The methyl group at the C10 atom has the axial β-orientation.

TABLE 4. Coordinates of the Atoms in Structure (2) ($\times 10^4$); for H ($\times 10^3$)

Atom	x	y	z	Atom	x	y	z
O1	5528(3)	8041(3)	536(2)	H2	750(4)	844(4)	90(2)
O2	5165(3)	3650(3)	949(2)	H6	619(4)	394(4)	164(2)
O3	8478(3)	758(3)	823(1)	H7	709(3)	336(3)	51(1)
C1	7972(4)	6878(4)	1207(2)	H8a	851(3)	349(3)	147(1)
C2	7299(4)	7632(4)	954(2)	H8b	893(3)	313(3)	84(2)
C3	6150(4)	7312(4)	752(2)	H9a	931(3)	509(3)	113(1)
C4	5774(3)	6089(3)	822(2)	H9b	851(3)	503(3)	58(1)
C5	6476(3)	5322(3)	1081(2)	H11a	449(4)	519(4)	38(2)
C6	6210(3)	4044(3)	1184(2)	H11b	439(4)	646(5)	34(2)
C7	7155(3)	3254(3)	928(2)	H11c	402(4)	575(4)	87(2)
C8	8379(4)	3610(4)	1092(2)	H12	614(4)	190(4)	99(2)
C9	8579(3)	4900(3)	996(2)	H15a	770(4)	26(4)	-52(2)
C10	7661(3)	5646(3)	1309(2)	H15b	25(5)	-66(5)	-18(2)
C11	4576(4)	5872(4)	594(2)	H15c	850(4)	-3(4)	-7(2)
C12	6892(4)	1979(3)	1083(2)	H16a	604(5)	139(5)	-41(2)
C13	7537(3)	1173(3)	686(2)	H16b	565(4)	193(4)	18(2)
N14	7084(3)	915(3)	182(2)	H16c	536(4)	69(4)	3(2)
C15	7651(5)	75(5)	-181(2)	H17a	685(4)	93(4)	180(2)
C16	5950(5)	1292(6)	-21(3)	H17b	669(5)	212(5)	198(2)
C17	7132(6)	1676(5)	1700(2)	H17c	784(5)	172(4)	184(2)
C18	7744(4)	5469(4)	1963(2)	H18a	764(4)	470(4)	212(2)
HO2	465(4)	383(4)	114(2)	H18b	845(4)	571(3)	211(2)
H1	873(4)	709(3)	136(2)	H18c	715(4)	589(4)	217(2)

A mesomeric effect is observed in the dimethylamide group, appearing in a shortening of the C13—N14 bond (1.330(5) Å) and a lengthening of the C13=O3 bond (1.236(5) Å) relative to the standard values [4] and also in the plane-trigonal coordination of the nitrogen atom (sum of the valence angles 359.5°).

Thus, the molecule (2) investigated may be assigned the structure [(6S,11S)-3-oxo-6-hydroxyeudesma-1,4-dien-12-oyl]dimethylamine.

EXPERIMENTAL

PMR spectra were taken in $CDCl_3$ on a Bruker WP 200 spectrometer (200 MHz, 0 — TMS), and IR spectra on a UR-20 spectrometer. Chemapol 100/250 silica gel was used for flash chromatography. The course of the reaction was monitored by TLC on Silufol plates with petroleum ether—EtOAc (1:4) as eluent.

An aqueous solution of dimethylamine (10 ml) was added to a solution of 246 mg (1 mmole) of α-santonin in 20 ml of toluene—dioxane (1:1), and the reaction mixture was boiled under reflux for 1 h. Another 10 ml of dimethylamine solution was added and boiling was continued for a further 3.5 h.

Derivative (2) was extracted with chloroform (3 × 30 ml). The chloroform layer was washed with 5% aqueous HCl, with water, and with saturated aqueous NaCl solution, dried with $MgSO_4$, filtered and distilled under vacuum. This gave 260 g of a slowly crystallizing product which was subjected to chromatographic separation on silica gel using gradient elution in EtOAc—petroleum ether and EtOAc systems. This led to 84 mg of the initial α-santonin and 125 mg (yield 43%) of the amide (2) in the form of colorless rhombic crystals with mp 210°C ($CHCl_3$—EtOAc).

IR spectrum (KBr, ν, cm^{-1}): 3720 (br., OH), 2975, 2940, 2915, 2885, 2850, 1660, 1625, 1590, 1500, 1300, 1160, 850, 840.

PMR spectrum (200 MHz, $CDCl_3$, δ, ppm, J, Hz): 1.15 (3H, d, 7 Hz, H-13), 1.21 (3H, s, H-14), 2.20 (3H, s, H-15), 2.95 (3H, s, —NMe), 3.09 (3H, s, —NMe), 4.45 (1H, dd, 10 Hz, 5 Hz, H-6), 6.18 (1H, d, 10 Hz, H-2), 6.63 (1H, d, 10 Hz, H-1).

Elementary analysis. Found, %: C 69.96, H 8.71, N 4.30. Calculated for $C_{17}H_{25}NO_3$, %: C 70.10, H 8.59, N 4.81.

X-Ray Structural Analysis. The cell parameters and the intensities of 20049 reflections of a crystal of (**2**) were measured on a Siemens SMART CDD diffractometer at a temperature of -100°C (Mo-K_α, graphite monochromator, θ/2θ scanning, 2θ < 58°). Crystals of (**2**) are tetragonal, *a*=11.601(3) Å, *b*=11.601(3) Å, *c*=23.487(3) Å, *V*=3161(7) Å^3, sp. gr. $P4_32_12$, μ=0.083 mm^{-1}, *Z*=8($C_{17}H_{25}NO_3$). The coordinates of the atoms are given in Table 4.

The structure was interpreted by the direct method. The positions of all the nonhydrogen atoms were refined anisotropically, and the H atoms were revealed by a difference synthesis and were refined isotropically. The final discrepancy factors were R = 0.052 and R_w = 0.057 for 2339 independent reflections with $I > 2\sigma$. All the calculations were made on a Pentium PC by the SHELXTL program package (PC version).

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