Reaction of Elemol with Acetic Acid/Perchloric Acid: Characterization of a Novel Oxide and (+)- β -Cyperone

by Solimabi Wahidulla*, Mangala Babu Govenkar, and Sashikumar Keshav Paknikar

National Institute of Oceanography, Dona Paula-403004, Goa, India (fax: +91-(0) 832-2450603, 2450604; e-mail: solima@darya.nio.org)

The minor unidentified compounds of the acetic acid/perchloric acid dehydration of elemol (1) were fully characterized. The structure and relative configuration of the less polar fragrant compound 2, named elemoxide, was deduced by 1D- and 2D-NMR data including C,C-connectivity, NOE, and NOESY experiments. The absolute configuration was established as (3S,3aR,7aR)-1,3,3a,4,7,7a-hexahydro-6-isopropyl-1,1,3,3a-tetramethylisobenzofuran (2) on the basis of its preparation from elemol (1). (+)- β -cyperone (3), a known sesquiterpene, was also identified as a minor product of the reaction. A plausible mechanistic explanation for the formation of elemoxide (2) and (+)- β -cyperone (3) is presented.

Introduction. – The structure of the major product α -elemene (4) [1][2], obtained by reaction of elemol (1) with AcOH/HClO₄, was established beyond doubt by chemical correlation studies [1]. The assigned structure recently received further confirmation by *Mehta* and *Acharyulu* [3]. Besides the α - and δ -elemenes (4 and 5, resp.) [2], the reaction mixture contained an uncharacterized fragrant substance 2 (*Scheme 1*)¹). We report herein the structure of this component, now called elemoxide (2), and the identification of a more polar product as (+)- β -cyperone (3).

GC/CI-MS Analysis of the reaction product obtained from **1** revealed the presence of four stereoisomers, including **2**, with the retention time t_R 19.6, 20.5, 26.1, and 27.2 min and a % area of 6.48, 8.26, 15.19, and 21.56, respectively. Identification was based on the molecular ion $[M + H]^+$ and the fragmentation pattern observed in the MS. NMR did not show the presence of regioisomers.

Results and Discussion. – Elemoxide (**2**), obtained as an optically active light yellow oil, displayed a molecular ion M^+ at m/z 222 in its EI-MS confirming the molecular formula $C_{15}H_{26}O$. The IR spectrum displayed an absorption at 1068 cm⁻¹ due to an ether linkage; the absorptions at 1640 and 808 cm⁻¹ were attributed to a trisubstituted C=C bond, and a geminal dimethyl moiety was evident from a doublet at 1365 and 1377 cm⁻¹. Detailed analysis of the NMR data, in particular the ¹H,¹H-COSY, ¹H,¹³C-HSQC, and HMBC data, allowed us to secure the entire hydrocarbon framework of structure **2** as well as the ¹H- and ¹³C-NMR assignments (*Table*).

¹) For convenience, the side chains are arbitrarily numbered.

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Table. ¹*H*- and ¹³*C*-*NMR*, and COSY Data of Elemoxide (2) in CDCl₃. δ in ppm, J in Hz.

	¹³ C-NMR	¹ H-NMR	¹ H, ¹ H-COSY	¹ H, ¹³ C-HMBC	NOESY
C(1)	78.7 (s)	_	_	-	-
H–C(3)	81.2 <i>(d)</i>	3.55 (q, J=6.3)	Me(8)	C(9), C(4), C(7a)	Me(11), Me(8), CH ₂ (4), H–C(7a)
C(3a)	42.7 (s)	_	_	-	_
$CH_{2}(4)$	37.7 (t)	1.9 (s)	H–C(5)	C(6), C(9), C(7a)	H–C(5), H–C(3)
	-	1.72 (d, J=5.1)	H–C(5)	C(6), C(9), C(7a)	H–C(5), Me(9)
H–C(5)	117.7 (d)	5.36(d, J=4.5)	CH ₂ (4)	C(3a), C(7), C(12)	$H-C(12), CH_2(4), Me(13)$
C(6)	143.4 (s)	-	_	-	_
CH ₂ (7)	23.9 (<i>t</i>)	1.89(d, J=3.3)	H–C(7a)	C(5), C(3a)	H–C(12), H–C(7a)
H–C(7a)	54.3 (<i>d</i>)	1.75(t, J=5.4)	CH ₂ (7)	C(4), C(10), C(9), C(11), C(6)	Me(11), CH ₂ (7), H–C(3)
$Me(8)^{1}$)	14.4 (q)	1.13 (d, J=6.3)	H–C(3)	C(3a)	$CH_2(4), Me(9)$
$Me(9)^{1}$)	12.6(q)	0.77(s)	_	C(4), C(7a), C(3)	$CH_2(7), CH_2(4), Me(8)$
$Me(10)^{1}$)	24.8(q)	1.16(s)	-	C(11), C(7a)	_
$Me(11)^{1}$)	30.6(q)	1.24(s)		C(10), C(7a)	H–C(7a)
$H-C(12)^{1}$	35.2 (<i>d</i>)	2.18–2.29 (<i>m</i>)	Me(13)	C(5)	CH ₂ (7), Me(13), H–C(5)
Me(13) ¹)	21.4 (q)	1.02 (d, J=7.92)	H–C(12)	C(6), C(14)	H–C(12), CH ₂ (7)
Me(14) ¹)	21.9 (q)	1.04 (d , $J=7.92$)	H–C(12)	C(6), C(14)	H–C(12), CH ₂ (7)

The relative configuration of **2** was inferred on the basis of NOESY and NOE difference spectra. Since the absolute configuration of elemol (**1**) is known [4][5], the absolute configuration of the oxide was established as (3S,3aR,7aR)-1,3,3a,4,7,7a-hexahydro-6-isopropyl-1,1,3,3a-tetramethylisobenzofuran (**2**). The probable pathway for the formation of elemoxide (**2**) from elemol (**1**) is shown in *Scheme 2*.



The ¹H-NMR spectrum of **2** showed signals for an olefinic H-atom at δ 5.36 (d, J=4.5 Hz), a OCH moiety at δ 3.55 (q, J=6.3 Hz) and a CH group centered at δ 2.26 (m). In the upfield region appeared signals for three tertiary Me groups centered at δ 1.24 (s), 1.16 (s), and 0.77 (s), for isopropyl Me groups centered at δ 1.03 (d, J=7.92 Hz, 6 H) and for a secondary Me group at δ 1.13 (d, J=7.2 Hz).

The ¹³C-NMR spectrum (*Table*) revealed signals for 15 C-atoms that, on the basis of DEPT experiments, were indicative of 6 Me, 2 CH₂, and 4 CH groups (including an olefinic and a O-bearing CH), and 3 quarternary C-atoms. The low-field signals revealed the trisubstituted nature of the C=C bond at δ 143.4 and 117.7.

In the ¹H,¹H-COSY spectrum, the correlations of H–C(5) at δ 5.36 with CH₂(4) at δ 1.9 and 1.72, of H–C(3) at δ 3.55 with Me(8) at 1.13, of H–C(12) at δ 2.26 with Me(13) and Me(14) at δ 1.03, and of H–C(7a) at δ 1.75 with CH₂(7) at δ 1.89 were clearly observed¹). The 2- or 3-bond ¹H,¹³C-HMBC correlations of the olefinic H–C(5) at δ 5.36 with C(7), C(12), and C(3a) and of CH₂(4) with C(6), C(7a), and C(9) established the presence of a pentahydro-isopropyl-methylbenzene moiety. The ¹H,¹³C-HMBC correlations H–C(3)/C(7a), H–C(9)/C(7a), Me(10)/C(7a), and Me(11)/C(7a) suggested the inclusion of the benzene system in a isobenzofuran moiety. These correlations in conjunction with the ¹H,¹⁴C-OSY data established the gross structure of **2** to be 1,3,3a,4,7,7a-hexahydro-6-isopropyl-1,1,3,3a-tetramethyl-isobenzofuran. The position of the C=C bond was confirmed by decoupling experiments: on selective irradiation of the olefinic signal at δ 5.36, the signal at δ 1.72 collapsed to a broad *s*. A NOESY relationship between H–C(3) at δ 3.55 and H–C(7a) at δ 1.75 suggested *trans* configuration at the fusion site C(3a)–C(7a) and a *trans* relationship of Me–C(3a) and H–C(3). The NOESY correlation observed between Me(8) (=Me–C(3a)) and Me(9) indicated that they are *cis* to each other. Thus the β configuration of Me–C(3a) and the α -configuration of H–C(7a) present in natural elemol (**1**) has remained unchanged during the conversion to the tetrahydrofuran derivative.

The more polar compound **3** of molecular formula $C_{15}H_{22}O$ showed in its IR spectrum the presence of an α,β unsaturated ketone moiety (1658, 1618 cm⁻¹). Comparison of all spectral data of **3** with published data for (+)- β -cyperone [6–12] showed an excellent agreement. The spectral data of the (2,4-dinitrophenyl)hydrazone derivative of **3** was also in accordance with the literature values [13][14].

The ¹³C- and DEPT-NMR data of **3** indicated the presence of 4 Me, 4 CH₂, and 2 CH groups, of which one was an olefinic CH, and 5 quartenary C-atoms. Thus, **3** must be bicyclic. The ¹H-NMR spectrum confirmed the above conclusion. Two 3-H *s* at δ 1.11 and 1.87 were assigned to the angular Me group and a

Me group in α position to a carbonyl group as a part of the conjugated ketone system. The presence of an isopropyl group and an olefinic proton was evident from the *d* at δ 1.084 (*J*=2.1 Hz) and a *s* at δ 6.29, respectively.

The formation of (+)- β -cyperone (3) from elemol (1) can be explained by acid catalyzed dehydration of 1 to δ -elemene (5) which in turn is transformed to the eudesmane hydrocarbon δ -selinene (=2,3,4,4a,5,6-hexahydro-7-isopropyl-1,4a-dimethylnaphthalene) [15]. While carrying out the reaction, oxygen was not excluded from the mixture. An oxidation of these hydrocarbons would finally afford (+)- β -cyperone (3) as outlined in (*Scheme 3*).



Conclusions. – In summary, we have described the novel fragrant sesquiterpene oxide **2** and the known (+)- β -cyperone (**3**) as minor products of the dehydration of elemol (**1**). The novel oxide is multiodorant being a combination of rhubarb, laurel, thyme, and florex. Both compounds were identified on the basis of their extensive NMR spectroscopic data. A mechanism for their formation from **1** is also discussed.

The authors wish to thank Dr. S. R. Shetye, Director NIO for his keen interest in the work and constant encouragement. Our special thanks are due to Dr. B. Maurer of Firmenich SA, Geneva, for some of the spectra and valuable comments. We are also grateful to Mr. Ramakant Harlalkar, for the generous gift of an elemol-rich fraction of Java citronella oil. One of the authors (M. G.) wishes to thank CSIR for the award of JRF. NIO contribution number is 4058.

Experimental Part

1. General. Anal. TLC: precoated 0.25 mm Merck silica gel G60 F_{254} aluminium sheets; visualization by spraying with 5% H₂SO₄/MeOH. Column chromatography (CC): silica gel (60–120 mesh; Qualigens). Melting points (m.p.): Electrothermal 91. Optical rotations: optical polarimeter ADP 220 (Bellingham Stanley Ltd.); in CHCl₃. IR Spectra: Shimadzu FT-IR-8201-PC spectrometer; KBr pellets. NMR Spectra (¹H, ¹³C, COSY, HMQC, and HMBC): 300-MHz Bruker Avance-300 spectrometer. CDCl₃ soln. containing SiMe₄ as the internal standard. EI-MS: at 70 eV. GC/MS: Shimadzu 2010 gas chromatograph fitted with a *XTI-5* (bonded, 5% phenyl) capillary column (30 m×0.32 mm; film thickness 0.25 µm) and coupled to a *Shimadzu 2010* mass selective detector; oven temp. was programmed from 60° at 5°/min; He as carrier gas at a flow rate of 1.8 ml/min; ion-source temp. 200°, interface temp. 220°, solvent cut time 2 min, and detector voltage 1 kV; scanning from m/z 60 to 400 for 85 min; PCI mode for analysis with isobutane as the reagent gas.

2. *Purification of Elemol* (1). The higher boiling fraction of Java citronella oil (supplied by *Nishant Aromas*, Mumbai) was subjected to CC (SiO₂, gradient petroleum ether/AcOEt). The fraction eluted with petroleum ether/AcOEt 95:5 furnished 1. Colorless crystals (MeOH). M.p. 52° ([1]: 53°). $R_{\rm f}$ (AcOEt/light petroleum ether 8:92) 0.5. $[\alpha]_{\rm D} = -4.73$ (c = 2.3, CHCl₃).

3. Dehydration of Elemol (1). To a soln. of 1 (3.5 g) in AcOH (42 ml), 60% perchloric acid (0.7 ml) was added dropwise, and the mixture was left at $25-27^{\circ}$ for 72 h with stirring. The dark brown soln. was diluted with H₂O and extracted with Et₂O, the Et₂O layer washed free from acid, dried, and evaporated, and the residue subjected to careful CC (silica gel). Besides α -elemene (4) and δ -elemene (5), 0.28 g (8%) of 2 was obtained (with AcOEt/light petroleum ether 4:96) and 0.12 g (3.4%) of 3 (with AcOEt/light petroleum ether 5:95; after purification by repeated CC (silica gel)).

Data of Elemoxide (= (3S,4aR,7aR)-1,3,3a,4,7,7a-hexahydro-6-isopropyl-1,1,3,3a-tetramethylisobenzofuran; **2**): $R_{\rm f}$ (AcOEt/light petroleum ether 4 :96) 0.6. $[a]_{\rm D} = -57.2$ (c = 1.1, EtOH). IR (KBr): 2964, 1640, 1377, 1365, 1184, 1068, 950, 808, 777. ¹H- and ¹³C-NMR: *Table*. EI-MS: 222(14.4), 207(30.2), 178(14.4), 163(32.4), 149(10.8), 135(74.8), 121(46), 107(44), 93(100), 79(18), 43(43).

Data of (+)-β-Cyperone (=(4aS)-4,4a,5,6-Tetrahydro-7-isopropyl-1,4a-dimethylnaphthalen-2(3H)one; **3**): $R_{\rm f}$ (AcOEt/light-petroleum ether 6:94) 0.4. [a]_D=+365 (c=1.5, CHCl₃). IR (neat): 2925, 1658, 1618, 1323, 1288. ¹H-NMR: 6.29 (d, J=2.1, H–C(8)); 2.7–2.1 (m, CH₂(3), CH₂(6), Me₂CH); 1.87 (br. s, Me-C(1)); 1.78–1.5 (m, 4 H); 1.11 (s, Me–C(4a)); 1.084 (d, J=2.1, Me_2 CH). ¹³C-NMR: 199.2 (s, C(2)); 156.2 (s, C(1)); 156.0 (s, C(8a)); 126.35 (s, C(7)); 118.2 (d, C(8)); 37.1 (t, C(4)); 36.4 (t, C(5)); 36.1 (d, Me₂CH); 33.8 (t, C(3)); 33.2 (s, C(4a)); 23.7 (t, C(6)); 21.5 (q, MeCHMe); 21.0 (q, MeCHMe, Me-C(4a)); 10.1 (q, Me-C(1)). EI-MS: 218 (25, M⁺), 203 (43), 175 (47), 147 (21), 119 (32), 91 (100).

5. 2,4-Dinitrophenylhydrazone of **3**. To a soln. of 2,4-nitrophenylhydrazine (50 mg) in MeOH (5 ml), 3 drops of conc. HCl soln. were added, followed by **3** (120 mg) in MeOH. The mixture was allowed to stand for a few minutes. Then, the formed red precipitate was filtered and purified by CC (silica gel, AcOEt/light petroleum ether 1:9): bright red needles. M.p. 216–218° ([13]: 218°). $[a]_D = +721$ (c=0.6, CHCl₃). R_f (AcOEt/light petroleum ether 1:9) 0.6. IR (KBr): 3311, 2927, 1618, 1591, 1500, 1336, 1309. ¹H-NMR: 11.3 (s, 1 H); 9.13 (d, J=3, 1 H); 8.05 (d, J=7.5, 1 H); 8.3 (dd, J=7.5, 3, 1 H); 6.4 (s, 1 H); 1.0 (s, 3 H); 1.118 (d, J=6.9, 6 H); 2.08 (s, 3 H). ¹³C-NMR: 155.8 (s); 144.7 (s); 147.8 (s); 152.2 (s); 129.9 (d); 129.5 (s); 123.6 (d); 117.9 (d); 32.7 (s); 23.5 (t); 21.6 (t); 21.6 (q); 21.2 (q). EI-MS: 398 (100, M^+), 383 (22), 364 (5), 349 (6), 321 (6), 307 (1), 216 (5), 200 (8), 186 (3), 172 (5), 157 (10), 131 (12), 105 (15), 91 (21).

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Received October 6, 2005