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

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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 (3*S*,3a*R*,7a*R*)-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/$HClO_4$, 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, $^1H,^{13}C$-HSQC, and HMBC data, allowed us to secure the entire hydrocarbon framework of structure **2** as well as the ^1H- and ^{13}C-NMR assignments (*Table*).

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

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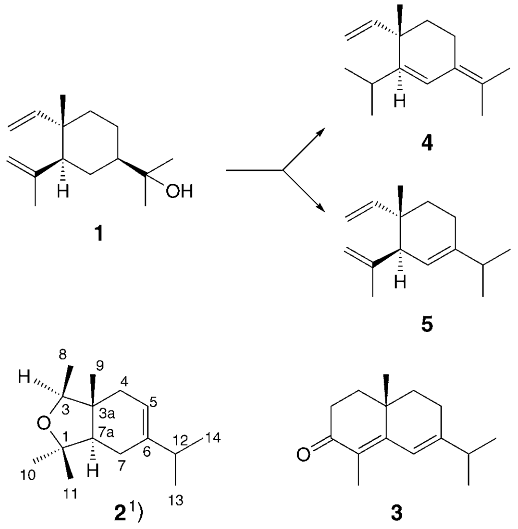
Scheme 1



1

4

5

2¹)

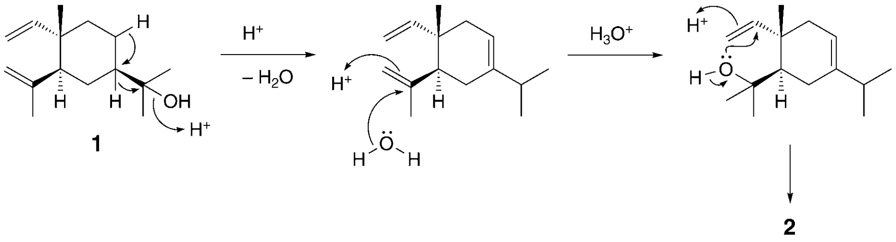
3

Table. *^{1}H- and ^{13}C-NMR, and COSY Data of Elemoxide* (**2**) *in $CDCl_3$*. 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 (*d*)	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 (*t*)	1.89 (*d*, *J*=3.3)	H–C(7a)	C(5), C(3a)	H–C(12), H–C(7a)
H–C(7a)	54.3 (*d*)	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 (*d*)	2.18–2.29 (*m*)	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 (3*S*,3a*R*,7a*R*)-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*.

Scheme 2. *Formation of Elemoxide* (**2**) *from Elemol* (**1**)



The ^{1}H-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 ^{13}C-NMR spectrum (*Table*) revealed signals for 15 C-atoms that, on the basis of DEPT experiments, were indicative of 6 Me, 2 CH_2, 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 ^{1}H,^{1}H-COSY spectrum, the correlations of H–C(5) at δ 5.36 with CH_2(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 CH_2(7) at δ 1.89 were clearly observed[1]). The 2- or 3-bond ^{1}H,^{13}C-HMBC correlations of the olefinic H–C(5) at δ 5.36 with C(7), C(12), and C(3a) and of CH_2(4) with C(6), C(7a), and C(9) established the presence of a pentahydro-isopropyl-methylbenzene moiety. The ^{1}H,^{13}C-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 ^{1}H,^{1}H-COSY data established the gross structure of **2** to be 1,3,3a,4,7,7a-hexahydro-6-isopropyl-1,1,3,3a-tetramethylisobenzofuran. 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.

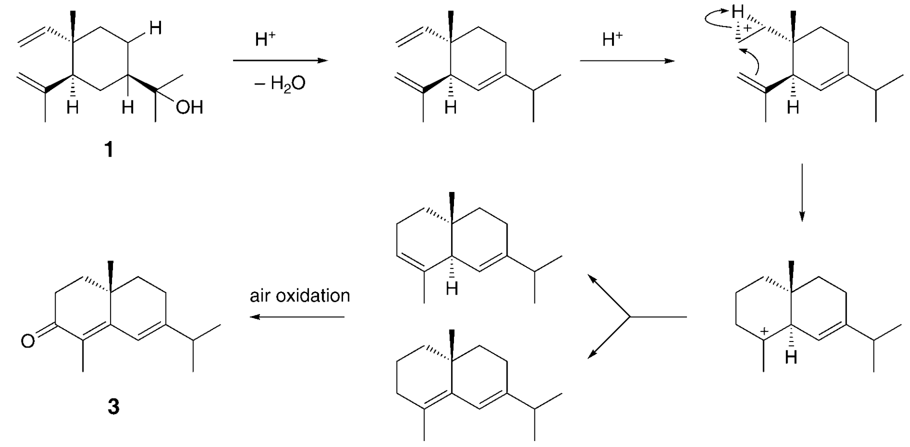
The more polar compound **3** of molecular formula $C_{15}H_{22}O$ showed in its IR spectrum the presence of an α,β unsaturated ketone moiety (1658, 1618 cm^{-1}). Comparison of all spectral data of **3** with published data for (+)-β-cyperone [6–12] showed an excellent agreement. The spectral data of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

The ^{13}C- and DEPT-NMR data of **3** indicated the presence of 4 Me, 4 CH_2, and 2 CH groups, of which one was an olefinic CH, and 5 quartenary C-atoms. Thus, **3** must be bicyclic. The ^{1}H-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*).

Scheme 3. *Formation of (+)-β-Cyperone* (**3**) *from Elemol* (**1**)



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.

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Experimental Part

1. *General.* Anal. TLC: precoated 0.25 mm *Merck* silica gel *G60 F_{254}* aluminium sheets; visualization by spraying with 5% H_2SO_4/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 $CHCl_3$. IR Spectra: *Shimadzu FT-IR-8201-PC* spectrometer; KBr pellets. NMR Spectra (^1H, ^{13}C, COSY, HMQC, and HMBC): 300-MHz *Bruker Avance-300* spectrometer. $CDCl_3$ soln. containing $SiMe_4$ 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 (SiO_2, gradient petroleum ether/AcOEt). The fraction eluted with petroleum ether/AcOEt 95:5 furnished **1**. Colorless crystals (MeOH). M.p. 52° ([1]: 53°). R_f (AcOEt/light petroleum ether 8:92) 0.5. $[\alpha]_D = -4.73$ ($c = 2.3$, $CHCl_3$).

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° for 72 h with stirring. The dark brown soln. was diluted with H_2O and extracted with Et_2O, the Et_2O 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 (=*(3*S*,4a*R*,7a*R*)-1,3,3a,4,7,7a-hexahydro-6-isopropyl-1,1,3,3a-tetramethylisobenzofuran*; **2**): R_f (AcOEt/light petroleum ether 4:96) 0.6. $[\alpha]_D = -57.2$ ($c = 1.1$, EtOH). IR (KBr): 2964, 1640, 1377, 1365, 1184, 1068, 950, 808, 777. ^{1}H- and ^{13}C-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 (=*(4a*S*)-4,4a,5,6-Tetrahydro-7-isopropyl-1,4a-dimethylnaphthalen-2(3*H*)-one*; **3**): R_f (AcOEt/light-petroleum ether 6:94) 0.4. $[\alpha]_D = +365$ ($c = 1.5$, $CHCl_3$). IR (neat): 2925, 1658, 1618, 1323, 1288. ^{1}H-NMR: 6.29 (*d*, $J = 2.1$, H–C(8)); 2.7–2.1 (*m*, CH_2(3), CH_2(6), Me_2CH); 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_2CH). ^{13}C-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*, Me_2CH); 33.8 (*t*, C(3)); 33.2 (*s*, C(4a)); 23.7 (*t*, C(6)); 21.5 (*q*, *Me*CHMe); 21.0 (*q*, MeCH*Me*, *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°). $[\alpha]_D = +721$ ($c = 0.6$, $CHCl_3$). R_f (AcOEt/light petroleum ether 1:9) 0.6. IR (KBr): 3311, 2927, 1618, 1591, 1500, 1336, 1309. ^{1}H-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). ^{13}C-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).

REFERENCES

[1] S. K. Paknikar, S. C. Bhattacharya, *Tetrahedron* **1962**, *18*, 1509.
[2] N. Akira, M. Michio, T. Haruki, Y. Toshio, JP 54084551, 1979.
[3] G. Mehta, P. V. R. Acharyulu, *J. Ind. Chem. Soc.* **1998**, *75*, 601.
[4] T. G. Halsall, D. W. Theobold, K. B. Walshaw, *J. Chem. Soc.* **1964**, 1029.
[5] A. D. Wagh, S. K. Paknikar, S. C. Bhattacharya, *Tetrahedron* **1964**, *20*, 2647.
[6] P. S. Adamson, F. J. McQuillin, R. Robinson, J. L. Simonsen, *J. Chem. Soc.* **1937**, 1576.
[7] H. Bruderer, D. Arigoni, O. Jeger, *Helv. Chim. Acta* **1956**, *39*, 858.
[8] D. H. R. Barton, E. J. Tarlton, *J. Chem. Soc.* **1954**, 3492.
[9] R. Howe, F. J. McQuillin, *J. Chem. Soc.* **1955**, 2423.
[10] R. B. Gammil, T. A. Bryson, *Synth. Commun.* **1976**, *6*, 209.
[11] B. Gonzalo, L. Cardona, B. Garcia, L. G. Cristina, J. R. Pedro, *Tetrahedron* **1996**, *52*, 10507.
[12] G. Z. Z. Xiong, Y. Chen, Y. Li, *J. Chem. Res. (S)* **1998**, 650.
[13] A. E. Bradfield, B. H. Hedge, B. Sanjiva Rao, J. L. Simonsen, A. E. Gillam, *J. Chem. Soc.* **1936**, 667.

[14] J. P. Kutney, J. Balsevich, P. Grice, *Can. J. Chem.* **1980**, *58*, 2641.
[15] D. P. Piet, A. J. Minnard, K. A. Van der Heyden, C. R. Fransen Maurice, J. B. P. A. Wijinberg, A. De Groot, *Tetrahedron* **1995**, *51*, 243.

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