

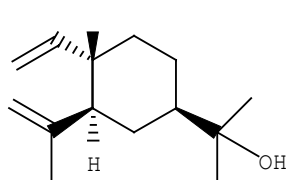
**Reaction of Elemol with Acetic acid –Perchloric acid: Characterization of a novel oxide and (+)- $\beta$ -cyperone**

**Solimabi Wahidulla,\* Mangala Babu Govenkar and**

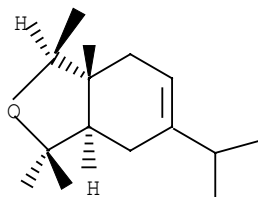
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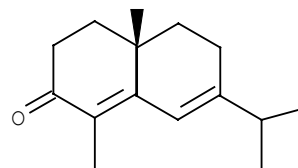
**Graphical abstract:**



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**Reaction of Elemol with Acetic acid –Perchloric acid: Characterization of a novel oxide and (+)- $\beta$ -cyperone**

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The minor unidentified compounds of acetic acid- perchloric acid dehydration of elemol (**1**) have been fully characterized. The structure and relative stereochemistry as shown in (**2**) of the less polar fragrant compound named as elemoxide was deduced by 1D and 2D NMR data including carbon-carbon connectivity, NOE and NOESY experiments. The absolute stereochemistry was established as 3S,3aR,7aR-6-isopropyl-1,1,3,3a-tetramethyl 1,3,3a,4,7,7a hexahydro isobenzofuran (**2**) on the basis of its preparation from elemol **1**.

(+)- $\beta$ -cyperone (**3**), a known sesquiterpene, has also been identified as a minor product of the reaction. Plausible mechanistic explanation for the formation of elemoxide (**2**) and (+)- $\beta$ -cyperone (**3**) presented.

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**Key words:** elemol, elemoxide/ dehydration/ perchloric acid/ (+)-  $\beta$ -cyperone/ elemenes

**Introduction.** - The structure of the major product [1- 2],  $\alpha$ -elemene **4** obtained by reaction of elemol **1** with AcOH/HClO<sub>4</sub> was established beyond doubt by chemical correlation studies [1]. The assigned structure recently received further confirmation by Mehta and Acharyulu [3]. Besides  $\alpha$ - and  $\delta$ - elemenes (**4 & 5** respectively) [2] the reaction mixture contained an uncharacterized fragrant substance **2**. We report herein, the structure of this component, now called elemoxide **2** and identification of a polar product as (+)- $\beta$ -cyperone **3**.

GC-CIMS analysis of reaction product indicated it to be a mixture of four stereoisomers, including **2**, with the retention time of 19.6, 20.5, 26.1 and 27.2 mins. and % area of 6.48, 8.26, 15.19 and 21.56 respectively. Identification was based on the molecular ion (M+H)<sup>+</sup> and the fragmentation pattern observed in the mass spectra. NMR did not show the presence of regioisomers.

**Results and Discussion.** - Elemoxide **2**, obtained as a light yellow oil, [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -57.2° (c1.1%, EtOH) displayed a molecular ion M<sup>+</sup> at m/z 222 in its EI-MS confirming the molecular formula C<sub>15</sub> H<sub>26</sub> O. The IR spectrum displayed absorption at 1068 cm<sup>-1</sup> due to an ether linkage; absorption at 1640 and 808cm<sup>-1</sup> were attributed to a trisubstituted double bond and a gem dimethyl group was evident from a doublet at 1365 and 1377 cm<sup>-1</sup>. The <sup>1</sup>HNMR spectrum showed signals for a vinylic hydrogen at  $\delta$  5.36 (1H,d, J=6.12Hz), a quartet at  $\delta$  3.55 (1H, J=7.2 Hz) due to an oxymethine and a multiplet integrated for one proton at  $\delta$  2.26. In the upfield region

appeared signals for three tertiary methyls at  $\delta$  1.24 (3H,s);  $\delta$  1.16 (3H,s);  $\delta$  0.77 (3H,s), isopropyl methyls at  $\delta$  1.03 (6H,d,  $J=7.92$  Hz) and a secondary methyl at  $\delta$  1.13 (3H,d,  $J=7.2$ Hz).

The  $^{13}\text{C}$  NMR spectrum (*Table 1*) revealed signals for 15 carbons that on the basis of DEPT experiments were indicative of six methyls, two methylenes, four methines (including one olefinic and one bearing oxygen) and three quaternary carbons. The low field signals revealed the trisubstituted nature of the double bond at  $\delta$  143.4 and 117.7.

Detailed analysis of NMR data, in particular, the  $^1\text{H}$ - $^1\text{H}$  COSY,  $^1\text{H}$ - $^{13}\text{C}$  HSQC and HMBC data, allowed us to secure the whole hydrocarbon framework of structure **2** as well as the  $^1\text{H}$  and  $^{13}\text{C}$  NMR assignments. In the  $^1\text{H}$ - $^1\text{H}$  COSY spectrum, the correlation in the spin system from H-5 at  $\delta$  5.36 to H-4 at  $\delta$  1.9 and 1.72; from H-3 at  $\delta$  3.55 to H-8 at 1.13; H-12 at  $\delta$  2.26 to H-13, 14 at  $\delta$  1.03 and  $^1\text{H}$ - $^1\text{H}$  coupling of C-7a methine proton at  $\delta$  1.75 with the C-7 methylene protons at  $\delta$  1.89 were clearly observed. The 2 or 3 bond  $^1\text{H}$ - $^{13}\text{C}$  correlation in the HMBC spectrum, originating from the vinylic H-5 proton at  $\delta$  5.36,  $^3\text{J}_{\text{C-7,H-5}}$ ;  $^3\text{J}_{\text{C-12,H-5}}$ ;  $^3\text{J}_{\text{C-3a,H-5}}$  and from H-4 allylic methylene protons  $^3\text{J}_{\text{C-6,H-4}}$ ;  $^3\text{J}_{\text{C-7a,H-4}}$  and  $^3\text{J}_{\text{C-9,H-4}}$  established the presence of methyl, isopropyl pentahydro cyclohexane ring system. The HMBC correlation  $^3\text{J}_{\text{C-7a,H-3}}$ ;  $^3\text{J}_{\text{C-7a,H-9}}$ ;  $^3\text{J}_{\text{C-7a,H-10, 11}}$  established fusion of pentahydrocyclohexane ring system with isobenzofuran moiety. These correlations in conjunction with the  $^1\text{H}$ - $^1\text{H}$  COSY data established the gross structure of **2** to be 6-isopropyl-1, 1, 3, 3a tetramethyl- 1, 3, 3a, 4, 7, 7a hexahydro isobenzofuran.

The position of the  $\Delta^5$  double bond was confirmed by decoupling experiments where the olefinic signal at  $\delta$  5.36 when selectively irradiated, the signal at  $\delta$  1.72 collapsed to a broad singlet. The relative stereochemistry of **2** was inferred on the basis of NOESY and NOE difference spectra. NOESY relationship between H-3 at  $\delta$  3.55 and H-7a at  $\delta$  1.75 suggested a trans relationship between junctions C3a- C7a and C3a-C3. The NOESY correlation observed between 8-H3 and 9-H3 indicated they are *cis* to each other. Thus the  $\beta$  configuration of C(3a)-H3 and C(7a)-H present in natural elemol has remained unchanged during the conversion to the tetrahydrofuran derivative. Since the absolute configuration of elemol is known [4-5], the absolute stereostructure of the oxide was established as 3S, 3aR, 7aR -6-isopropyl -1,1,3,3a tetramethyl -1, 3, 3a, 4, 7, 7a hexahydro isobenzofuran **2**.

The probable pathway for the formation of **2** from elemol is as shown in (*Scheme-1*). The more polar compound, C<sub>15</sub>H<sub>22</sub>O in its IR spectrum showed the presence of  $\alpha,\beta$  unsaturated ketonic moiety (1658,1618 cm<sup>-1</sup>). The <sup>13</sup>C and DEPT NMR indicated that the more polar compound contained four methyl groups, four methylenes, two methines of which one was olefinic hydrogen and five quaternary carbons and therefore must be bicyclic. The <sup>1</sup>H NMR spectrum confirmed the above conclusion. Two three proton singlets at  $\delta$  1.11 and 1.87 were assigned to the angular methyl group and a methyl  $\alpha$  to carbonyl group as a part of conjugated ketonic system. The presence of an isopropyl group and one vinyl proton was evident from the doublet at  $\delta$  1.0845 (J=2.1Hz) and a singlet at  $\delta$  6.29 respectively. Comparisons of all spectral data on polar substance were in excellent agreement

with published data for (+)- $\beta$ -cyperone [6-12]. The spectral data of its 2:4 dinitrophenyl hydrazone is also in accordance with the literature values [13-14].

The formation of (+)- $\beta$ -cyperone can be explained by acid catalysed dehydration of elemol to  $\delta$ -elemene **5** which in turn gets transformed into the eudesmane hydrocarbon /  $\delta$ -selinene [15]. While carrying out the reaction, oxygen was not excluded from the mixture. An oxidation of these hydrocarbons would finally afford (+)- $\beta$ -cyperone as outlined in (*Scheme 2*).

**Conclusion.** - In summary, we have described a novel fragrant sesquiterpene oxide and the known  $\beta$ -cyperone as minor products of dehydration of elemol. The novel oxide is multiodorant being a combination of rubarb, laurel, thyme and florex. Both the compounds were identified on the basis of their extensive NMR spectroscopic data. Mechanism for their formation from elemol has also been discussed.

### Experimental Part

1. *General.* Column chromatography (CC): silica gel (60-120 mesh; Qualigens).  
Anal. TLC: precoated 0.25 mm Merck silica gel G60 F<sub>254</sub> aluminium sheets, with visualization using MeOH-H<sub>2</sub>SO<sub>4</sub> (5%) as spraying agent. Melting points (m.p.): Electrothermal 91  
IR spectra: Shimadzu FT-IR 8201PC Spectrometer; KBr Optical rotations were recorded in CHCl<sub>3</sub> using Optical Polarimeter ADP 220 (Bellingham Stanley Ltd.).  
Mass spectra were obtained on a EIMS operating at 70 eV. NMR (1H, 13C, COSY,

HMQC & HMBC) experiments were recorded in CDCl<sub>3</sub> solution, containing TMS as the internal standard, on a 300 MHz Bruker Avance 300 spectrometer. GC-MS was carried out in a Shimadzu GC-2010

2. *Purification of elemol.* Higher boiling fraction of Java Citronella oil (supplied by Nishant Aromas, Mumbai) was subjected to CC (SiO<sub>2</sub>, petroleum ether/AcOEt, gradient elution). Fraction eluted with petrol: ethyl acetate (95:5) furnished elemol **1** as colourless crystals (methanol), m.p.52° [lit.<sup>1</sup> 53°], [ $\alpha$ ]<sub>D</sub> -4.73 (c=2.3, CHCl<sub>3</sub>). TLC- ethyl acetate: light petrol (8:92), R<sub>f</sub>= 0.5.

3. *Dehydration of elemol.* To a solution of elemol (3.5g) in acetic acid (42 ml), perchloric acid (60%, 0.7 ml) was added dropwise and the mixture left at room temperature (25-27°C) for 72 hrs with stirring. The dark brown solution was diluted with water, extracted with ether, the ether layer washed free from acid, and dried. Removal of the solvent yielded a residue that on careful chromatography over silica gel gave besides  $\alpha$ -elemene (**4**) and  $\delta$ - elemene (**5**), elemoxide (**2**) (0.28g, yield-8%). R<sub>f</sub>=0.6 in ethylacetate: light petrol (4:96). IR (KBr): 2964, 1377, 1184, 950, 808, 777. EIMS: m/z (rel.int.): 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). <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>) and <sup>13</sup>CNMR (360 MHz, CDCl<sub>3</sub>): see *Table I*.

4. *Purification of  $\beta$ -cyperone.* Elution with ethyl acetate: light petrol (5:95) yielded a fraction rich in **3** purified by repeated chromatography over silica gel. Yield (0.12g, 3.4%); R<sub>f</sub>= 0.4 (light petrol: ethyl acetate; 94:6). [ $\alpha$ ]<sub>D</sub> +365°(c=1.5, CHCl<sub>3</sub>). IR (neat): 2925, 1658, 1618,1323, and 1288. <sup>13</sup>C NMR (300MHz, CDCl<sub>3</sub>) 199.2 (s, C(3)), 156.2 (s, C(4)), 156.0 (s, C(5)), 126.35 (s, C(7)), 118.2 (d, C(6)),

37.1 (t,C(1)), 36.4 (t,C(9)), 36.1 (t,C(11)), 33.8 (t,C(2)), 33.2 (t,C(10)), 23.7 (q,C(8)), 21.5 (q,C(12)), 21.0 (q,C(13),C(14)), 10.1(q,C(15)). <sup>1</sup>H NMR (300MHz, (D)CHCl<sub>3</sub>): 6.28 (1H d, J=2.1, H-C(6)), 2.7-2.1 (5H,m, H-C(2), H-C(8), H-C(11)), 1.87 (3H, bs, H-C(15)), 1.78-1.5 (4H,m), 1.11(3H,s, H-14), 1.084 (6H, d, J=2.1,H-C(12), H-C(13)).EI-MS: m/z (rel.int.): 218 (M<sup>+</sup>,25), 203 (43), 175 (47),147 (21), 119 (32), 91 (100).

5. *2:4- Dinitrophenyl hydrazone of (3)*. To a solution of 2:4 dinitrophenylhydrazine (50mg) in 5 ml methanol, 3 drops of concentrated HCl were added. The carbonyl compound (120 mg) in methanol was added to the above solution and allowed to stand for few minutes. The red precipitate obtained was filtered and purified on silica gel using ethyl acetate: light petrol (1:9) to yield bright red needles m.p. 216-218° (lit 218°); [ $\alpha$ ]<sub>D</sub> +721(c=0.6, CHCl<sub>3</sub>). TLC, R<sub>f</sub>=0.6, ethyl acetate: petrol (1:9). IR (KBr): 3311, 2927, 1618, 1591, 1500, 1336, 1309. <sup>1</sup>HNMR (300MHz, (D)CHCl<sub>3</sub>) 11.3 (1H, s), 9.13 (1H,d, J=3), 8.05 (1H,d, J=7.5), 8.3(1H,dd, J=7.5,3), 6.4 (1H,s), 1.0 (3H, s), 1.118 (6H,d, J=6.9), 2.08 (3H,s); <sup>13</sup>C NMR (CDCl<sub>3</sub>), 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: m/z (rel.int.): 398 (M<sup>+</sup>,100), 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).

*GC-MS Analysis:* GC/MS analysis was carried out on a Shimadzu-2010 gas chromatographfitted with a XTI-5 (bonded, 5% phenyl) capillary column (30mx0.32mm; film thickness 0.25  $\mu$ m). The oven temperature was programmed from 60°C at 5°C/min. Helium was used as carrier gasat a flow rate 1.8 ml/min. The



gas chromatograph was coupled to a Shimadzu-2010 mass selective detector. The MS system was operated with ion source temperature at 200°C, interface temperature 220°C, solvent cut time, 2 minutes and detector voltage 1 KV. The scan ranging from m/z 60 to m/z 400 was run for 85 minutes. PCI mode was used for analysis with iso-butane as the reagent gas.

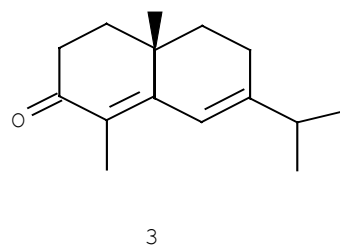
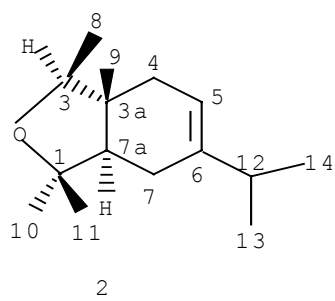
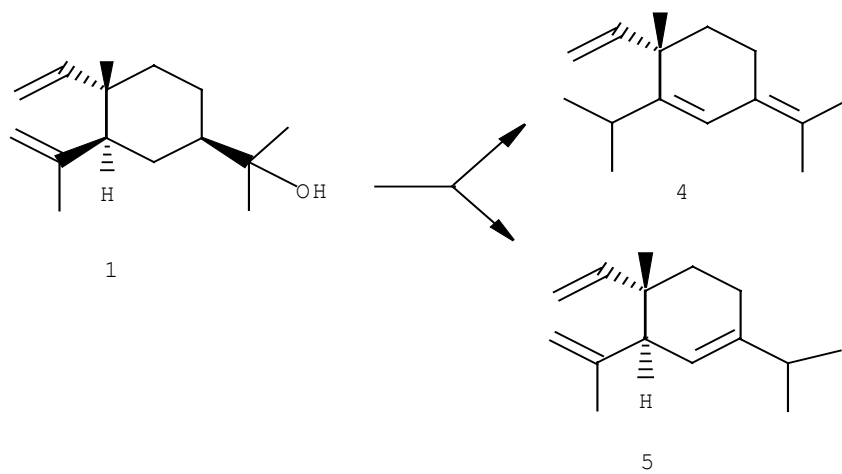
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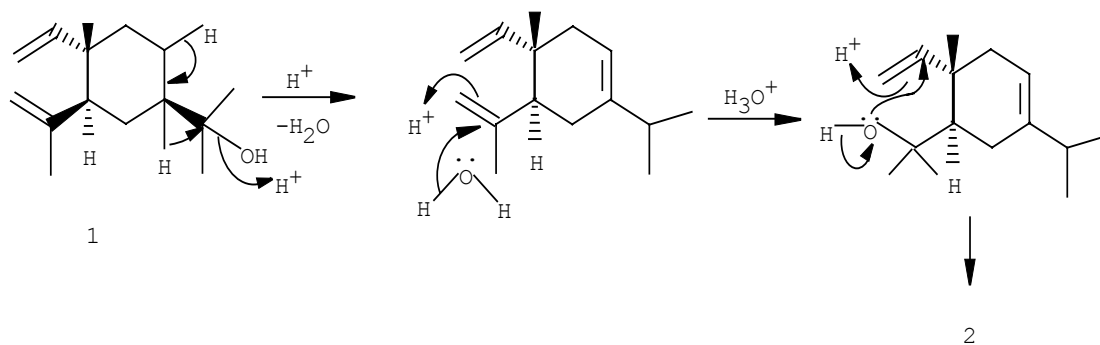
**REFERENCES**

- [1] S. K. Paknikar, S. C. Bhattacharya, *Tetrahedron* **1962**, *18*, 1509.
- [2] Nagakura Akira, Moroe Michio, Tsuruta Haruki, Yoshida Toshio. JP 54084551, **1979**.
- [3] G. Mehta, P. V. R. Acharyulu, *J. Ind. Chem. Soc.* **1998**, *75*, 601.
- [4] T. G. Halsall, D. W. Theobald, 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. Chem. 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. Wijnberg, A. De Groot, *Tetrahedron* **1995**, *51*, 243.

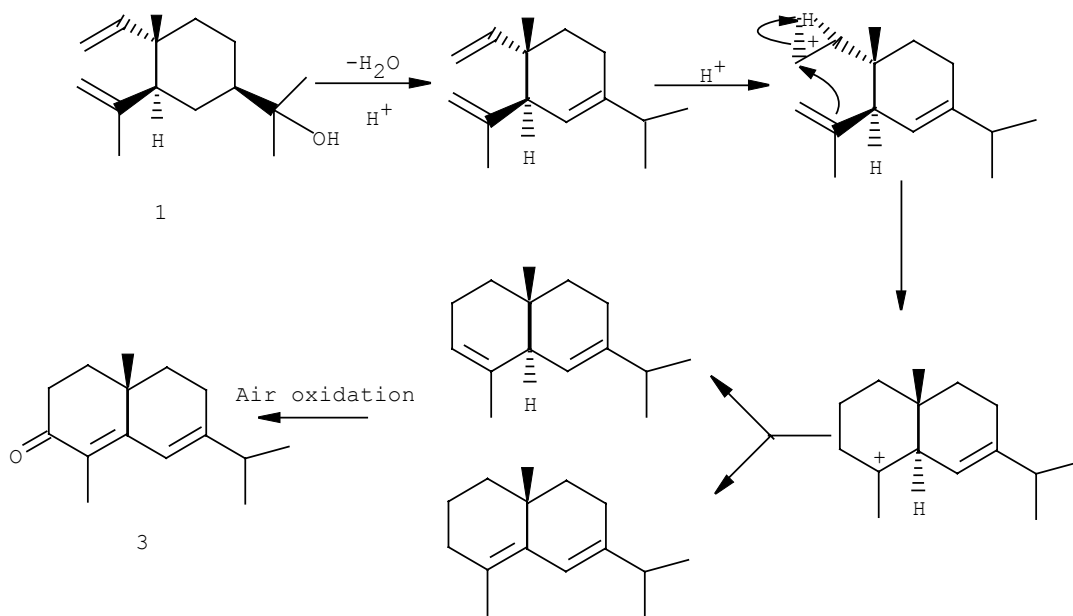
Table 1.  $^1\text{H}$ ,  $^{13}\text{C}$  and COSY of Elemoxide (**2**) in  $\text{CDCl}_3$ 

Carbon Nos.	$^{13}\text{C}$ NMR	$^1\text{H}$ NMR	COSY	HMBC	NOESY
			$^1\text{H}$ - $^1\text{H}$	$^1\text{H}$ - $^{13}\text{C}$	
1	78.7 s	-	-	-	-
2	-	-	-	-	-
3	81.2 d	3.55(1H,q,18.9,12.6,6.3)	H8	C9,C4,C7a	H11,H8 ,H4 ,H7a
3a	42.7 s	-	-	-	-
4	37.7 t	1.9(s)	H5	C6,C9,C7a	H5,H3
	-	1.72(d,5.1)	H5	C6,C9,C7a	H5, H9
5	117.7 d	5.36(1H,d, 4.5)	H4	C3a,C7,C12	H12,H4 ,H13
6	143.4 s	-	-	-	-
7	23.9 t	1.89(d,3.3)	H7a	C5, C3a	H12,H7a
7a	54.3 d	1.75(1H,t,5.4,5.7)	H7	C4,C10 ,C9 C11, C6	H11,H7,H3
8	14.4 q	1.13 (3H,d, 6.3)	H3	C3a	H4, H9
9	12.6 q	0.77 (s)	-	C4,C7a,C3	H7,H4 ,H8
10	24.8 q	1.16 (s)	-	C11, C7a	-
11	30.6 q	1.24 (s)	-	C10, C7a	H7a
12	35.2 d	2.18- 2.29(1H,m)	H13	C5	H7,H13,H5
13	21.4 q	1.02(3H, d, 1.8)	H12	C6, C14	H12, H7
14	21.9 q	1.04(3H, d,1.5)	H12	C6, C14	H12, H7





**Scheme 1.** Formation of elemoxide (2) from elemol (1).



**Scheme 2.** Formation of  $\beta$ -cyperone (3) from elemol (1).

**Figure legends. –**

**Scheme 1.** *Formation of elemoxide (2) from elemol (1).*

**Scheme 2.** *Formation of  $\beta$ -cyperone (3) from elemol (1).*