141. Ring-opened Analogues of *Ambrox*®: Synthesis and Structure-Odour Relationships

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Dedicated to Dr. *G. Ohloff* on the occasion of his 65th birthday

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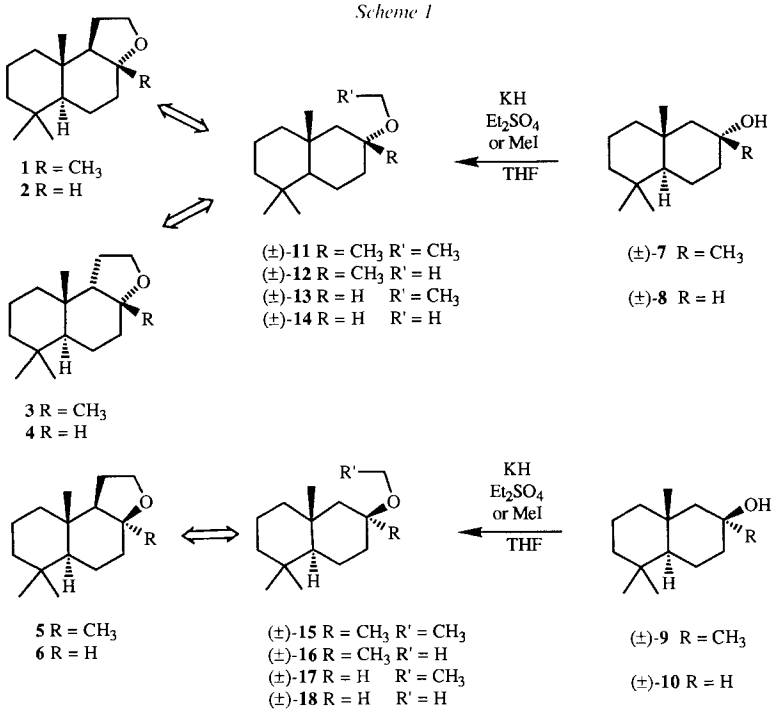
Eight bicyclic ether derivatives **11**–**18**, related to the tricyclic odorant *Ambrox*® (**1**) and its analogues **2**–**6** by formal heteroring-opening, have been prepared; their odoriferous activity/inactivity is correlated with the steric accessibility of the ether O-atom, calculated by computer-aided molecular modeling.

Introduction. – *(−)-Ambrox*®[1]) (**1**), first synthesized in 1950 [1] and later detected in tincture of ambergris [2], is a key compound in perfumery, being one of the principal sources of the persistent amber odour and of the associated exalting effect [3] *(Scheme 1)*.

Scheme 1



[1]) *Ambrox*® is a registered trade name of *Firmenich SA*. CA name of *Ambrox*®: [3a*R*-(3aα,5aβ,9aα,9bβ)]-dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan.

Its diastereoisomers (−)-**3** [4] and (+)-**5** [5] as well as the demethyl analogues (−)-**2** [6], **4** [7] and (+)-**6** [6] differ from (−)-**1** somewhat in their odour quality and mainly in their reduced odour strength, except for (−)-**3** [8]. On the other hand, numerous bicyclic compounds are known with odoriferous properties reminiscent of one or several ambergris tonalities, a biological activity which is highly dependent on configuration [3]. For example, among the racemic bicyclic alcohols **7**–**10** [9], only **7** develops an amber-like scent [10]. The initial goal of preparing **11** (from **7**) as a heteroring-opened analogue to both **1** and **3** was expanded to include derivatives **12**–**18**[2]) and to examine structure-odour relationships in this series of compounds[3]).

Results and Discussion. – Ethers **11**–**18**, in racemic form, were prepared from the corresponding alcohols **7**–**10** [9] by standard procedures [12] *(Scheme 1)*. Together with **18**[2]), the new compounds **12**, **13**, and **14** possess typical woody-ambergris-type odours; all the other compounds were devoid of such activity *(Table 1)*.

Regarding structure-odour correlations, careful studies of a large number of ambergris-type compounds, typified by **1**, have led to the formulation of the 'triaxial rule of odour sensation' [13] [3], and, more recently, to the postulate of an 'ambergris triangle' [14]. Although all known ambergris-type odorants fulfil the generalized structural conditions found necessary for ambergris-type activity, this is also true for several inactive analogues. A recent study on this topic[4]) has focussed on a particular aspect of the structures under consideration, namely the steric accessibility of the functional group [15]. The assumption is that the polar (hydrophilic) part of simple monofunctional compounds acts as one important element that the receptive system should recognize, for example by formation of a H-bond with donor groups belonging to various entities present at the receptive sites (*e.g.* water, proteins, glyco-proteins, *etc.*) [16]. However, it should be kept in mind that this aspect is only a part of the complementary interactions which an odorant molecule may undergo with the receptive system; for example, for three series of ambergris-type compounds with an identical polar subunit, it has already been demonstrated that the activities are also highly dependent on variations in the apolar (lipophilic) part of the molecule [8]. Nevertheless, for a given compound, the steric accessibility of the functional group, which depends on its close molecular environment, is amenable to a quantitative evaluation with the help of computer-aided molecular modeling (programme MODEL [17]). Thus, the structures are first optimized to their lowest energy conformations by molecular mechanics (MM2) calculations [18]; then, with a programme developed by *Lee* and *Richards* [19], the accessible polar surface area is computed for each optimized structure, *i.e.* in the present study, the surface of the ether O-atom that would be accessible to a sphere of chosen radius (in this case 1.4 Å, a value which approximates the size of an H_2O molecule). For a series of rigid ambergris-type compounds related to **1**, the results of these calculations indicate that activity is highly correlated with the accessibility of the functional group [20].

The same calculations were carried out for compounds **11**–**18** and, as an illustrative example, the results for compound **12** are presented below *(cf. Scheme 2)*.

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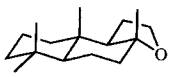
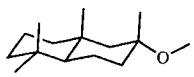
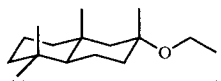
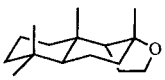
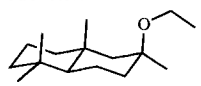
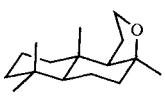
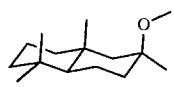
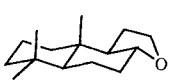
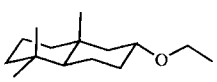
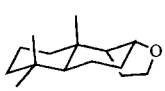
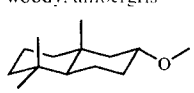
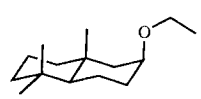
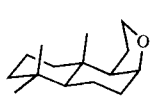
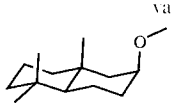
[2]) The odour of **18** has already been described as being dominated by a woody tonality [3].

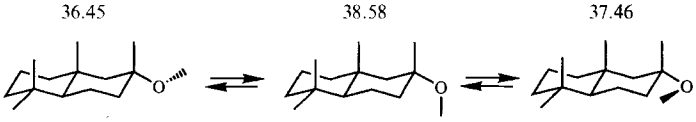
[3]) For a study of another type of heteroring opened analogues of **1**–**6**, see [11].

[4]) Methods and preliminary results were presented at the *Firmenich* symposium on 'Chemical Communication', Geneva, December 19th, 1986, and at the '8th International Congress of the Chemoreception Research Organisation', Coventry, July 19th, 1988.

Table 1. *Calculated Oxygen Accessibility Ranges, Using a Probe Radius of 1.4 Å, and Activity Data for Compounds* **11–18**

Active Reference compounds		Active		Inactive	
 **1**	12.8 Å^2	 **12** woody, ambergris	6.7–9.3 Å^2	 **11** odourless	1.1–2.4 Å^2
 **3**	11.6 Å^2			 **15** weak anis. medicinal	0.1–0.8 Å^2
 **5**	9.1 Å^2			 **16** weak woody, eucalyptus	2.0–4.4 Å^2
 **2**	16.6 Å^2	 **13** woody, ambergris	2.3–8.6 Å^2		
 **4**	17.7 Å^2	 **14** woody, ambergris	9.1–16.0 Å^2	 **17** vague	0.2–0.3 Å^2
 **6**	11.5 Å^2			 **18** weak, woody	1.7–4.9 Å^2

Scheme 2

MM_2 Energy [kcal/mol]	36.45	38.58	37.46
Lowest-energy rotamers of **12**			
Van der Waals polar surface area	9.8 Å^2	9.8 Å^2	7.7 Å^2
Accessible polar surface area[a])	9.1 Å^2	9.3 Å^2	6.7 Å^2
O-Bonds angle	115°	117°	116°

[a]) Calculated for a probe radius of 1.4 Å.

As expected, the accessibility of the ether oxygen atom is highly dependent on the conformation of the relatively flexible ether side chain and ranges, for compound **12**, from 6.7 to 9.3 Å^2. For the methyl ethers, these values encompass the three optimised staggered rotamers; in the case of the ethyl ethers, only the three lowest energy conformers out of the nine possible staggered rotamers were used to calculate the accessibility ranges. The results for the whole series and for the corresponding reference compounds, together with the activity data[5]), are summarised in *Table 1*.

The numerical values in *Table 1* indicate that the active ring-opened analogues have upper limit values of their accessibility ranges which are notably larger than their inactive analogues, but also consistently smaller than the corresponding tricyclic compounds. From the data available at present, it is not possible to define an optimum value of accessibility for optimum activity, nor to set an upper limit; however, a lower limit for activity seems to appear around 5–6 Å^2. The results reported here tend to support the hypothesis that, in this series of analogues, activity correlates with steric accessibility of the functional group.

I wish to thank *W. Thommen* and *R. Brauchli* for recording and assistance in interpretation of the ^{13}C-NMR spectra, Dr. *D. Kastner* and Dr. *P.A. Blanc* for the sensory evaluations, and Dr. *A. Boschung* for the computer software implementation and up-keeping.

Experimental Part

(With the valuable collaboration of *M. Schmid*)

General. GLC: *Hewlett Packard 5890* instrument equipped with a flame ionization detector coupled to a *Hewlett Packard 3392A* integrator; capillary columns *Chrompack CP-Wax-52 CB* (10 m) and *CP-Sil-5 CB* (10 m). TLC: silica gel 60 (*Merck F 254*, layer thickness 0.25 mm). Preparative CC: silica gel 60 (*Merck*, 0.063–0.2 mm, 70–230 mesh, ASTM). Bulb-to-bulb distillation: *Büchi GKR-50* oven; b.p. correspond to the air temp. IR spectra (liquid film): *Perkin-Elmer 297* spectrometer; cm^{-1}. ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$): *Bruker WH 360* (360 and 90 MHz, resp.); δ [ppm] rel. to TMS (= 0 ppm); coupling constants J in Hz. MS: *Varian MAT 112* spectrometer (*ca.* 70 eV); intensities in % relative to the base peak (100%).

Computer-aided Molecular Modeling. The software *MODEL* (Version 1.5) [18] was used. Calculations were carried out on a *Digital Equipment Corporation VAX 11/750* computer, visualisation of the molecular structures was performed with a *Pericom GP-A* terminal. All surface area calculations were performed using a probe radius of 1.4 Å and spacing increments of 0.1 Å.

General Procedure for the Preparation of Ethyl Ethers **11**, **13**, **15**, *and* **17**. To a suspension of KH (3.6 ml of a 22% dispersion in oil, 20 mmol) in THF (40 ml), at r.t., a soln. of the corresponding alcohol (7 mmol) in THF (10 ml) was added. Et_2SO_4 (2 ml, 2.36 g, 15 mmol) was added dropwise, and the temp. rose to 40°. The mixture was stirred at r.t., until no more starting alcohol was detected by TLC or GLC (*ca.* 15 h). The mixture was diluted with Et_2O (50 ml), washed successively with sat. aq. $NaHCO_3$ soln., H_2O, and brine, dried (Na_2SO_4), and evaporated. Bulb-to-bulb distillation *i.v.* (followed for **13**, **15**, and **17** by CC) afforded the ethers **11**, **13**, **15**, and **17** as colorless oils.

(±)-6α-Ethoxy-1,2,3,4,4a,5,6,7,8,8aα-decahydro-1,1,4aβ,6β-tetramethylnaphthalene (**11**; 99% yield from **7**). B.p. 130°/0.1 Torr. IR: 2800–3000, 1450, 1380, 1365, 1120, 1110, 1080, 1060. ^{1}H-NMR: 0.78 (*s*, 3 H); 0.86 (*s*, 3 H); 0.96 (*s*, 3 H); 1.14 (*t*, J = 7, 3 H); 1.28 (*s*, 3 H); 3.41 (*m*, 2 H). ^{13}C-NMR: *Table 2*. MS: 238 (1, M^+), 223 (2), 192 (3), 177 (3), 149 (1), 137 (4), 123 (3), 109 (4), 99 (100), 71 (25).

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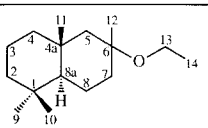
[5]) These results have been presented in a preliminary form during a conference at the '7th European Symposium on QSAR', Interlaken, September 5th–9th, 1988.

Table 2. *^{13}C-NMR Chemical Shifts and Assignments for Compounds* **11**–**18**[a])

C-Atom	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
C(1)	33.0	33.0	33.0	33.0	33.0	33.1	33.3	33.2
C(2)	42.4	42.4	42.5	42.5	42.6	42.6	42.6	42.6
C(3)	18.6	18.5	18.7	18.6	18.5	18.6	18.5	18.4
C(4)	42.9	42.8	42.2	42.1	42.9	42.9	42.8	42.7
C(4a)	34.7	34.6	35.1	35.0	34.9	34.9	34.6	34.6
C(5)	55.4	55.6	51.2	50.6	52.8	52.0	46.8	46.5
C(6)	74.6	74.7	74.3	76.0	74.1	74.5	74.6	76.9
C(7)	39.9	39.5	33.9	33.3	39.4	39.1	33.2	32.4
C(8)	20.2	20.1	21.0	20.8	18.6	18.6	17.8	17.6
C(8a)	54.3	54.3	53.4	53.4	54.9	54.8	54.8	54.7
C(9)	33.2	33.1	33.2	33.1	33.4	33.5	33.3	33.2
C(10)	21.2	21.1	21.3	21.2	21.5	21.6	21.5	21.4
C(11)	21.2	21.1	20.7	20.1	20.1	19.9	20.5	20.4
C(12)	24.8	24.1	–	–	27.0	26.4	–	–
C(13)	56.3	48.2	63.1	55.6	56.0	48.8	61.1	55.9
C(14)	16.5	–	15.8	–	15.9	–	15.7	–

[a]) C-Atom numbering:



(±)-6α-Ethoxy-1,2,3,4,4a,5,6,7,8,8aα-decahydro-1,1,4aβ-trimethylnaphthalene (**13**; 78% from **8**). B.p. 110–115°/0.1 Torr. IR ($CHCl_3$): 2820–3000, 1455, 1375, 1165, 1080. ^{1}H-NMR: 0.78 (*s*, 3 H); 0.86 (*s*, 3 H); 0.92 (*s*, 3 H); 1.18 (*t*, *J* = 7, 3 H); 3.42 (*m*, 1 H); 3.50 (*m*, 2 H). ^{13}C-NMR: *Table 2*. MS: 224 (0.5, $M^{+\cdot}$), 209 (1), 178 (26), 163 (46), 149 (3), 137 (100), 122 (20) 109 (23), 95 (34), 81 (49), 69 (42), 55 (38), 41 (33).

(±)-6β-Ethoxy-1,2,3,4,4a,5,6,7,8,8aα-decahydro-1,1,4aβ,6α-tetramethylnaphthalene (**15**; 69% yield from **9**). B.p. 120–125°/0.1 Torr. IR: 2800–3000, 1450, 1380, 1360, 1195, 1120, 1060. ^{1}H-NMR: 0.82 (*s*, 3 H); 0.86 (*s*, 3 H); 1.06 (*s*, 3 H); 1.09 (*s*, 3 H); 1.15 (*t*, *J* = 7, 3 H); 3.35 (*m*, 2 H). ^{13}C-NMR: *Table 2*. MS: 238 (1, $M^{+\cdot}$), 223 (11), 192 (3), 177 (10), 149 (1), 137 (9), 121 (5), 109 (9), 99 (100), 95 (16), 81 (17), 71 (25), 55 (20), 43 (25).

(±)-6β-Ethoxy-1,2,3,4,4a,5,6,7,8,8aα-decahydro-1,1,4aβ-trimethylnaphthalene (**17**; 67% yield from **10**). B.p. 115°/0.1 Torr. IR: 2800–3000, 1455, 1440, 1380, 1360, 1340, 1115, 1075. ^{1}H-NMR: 0.82 (*s*, 3 H); 0.85 (*s*, 3 H); 1.08 (*s*, 3 H); 1.17 (*t*, *J* = 7, 3 H); 3.34 (*dq*, *J* = 9, 7, 1 H); 3.50 (*dq*, *J* = 9, 7, 1 H); 3.54 (*m*, 1 H). ^{13}C-NMR: *Table 2*. MS: 224 (30, $M^{+\cdot}$), 209 (4), 178 (26), 163 (84), 149 (7), 137 (61), 122 (24), 109 (52), 95 (54), 85 (90), 81 (100), 69 (88), 55 (74), 41 (61).

General Procedure for the Preparation of Methyl Ethers **12**, **14**, **16**, *and* **18**. To a suspension of KH (3.6 ml of a 22% dispersion in oil, 20 mmol) in THF (20 ml) at r.t., a soln. of the corresponding alcohol (7 mmol) and MeI (2.5 ml, 5.7 g, 40 mmol) in THF (10 ml) was added dropwise; during the addition, the temp. of the mixture rose to 40°. The mixture was stirred at r.t., until no more starting alcohol was detected by TLC or GLC (*ca.* 2 h). The mixture was diluted with Et_2O (50 ml), washed successively with sat. aq. $NaHCO_3$ soln., H_2O, and brine, dried (Na_2SO_4), and evaporated. Bulb-to-bulb distillation *i.v.* afforded **12**, **14**, **16**, and **17** as colorless oils.

(±)-1,2,3,4,4a,5,6,7,8,8aα-Decahydro-6α-methoxy-1,1,4aβ,6β-tetramethylnaphthalene (**12**; 98% yield from **7**). B.p. 150°/0.1 Torr. IR: 2800–3000, 1450, 1370, 1180, 1120, 1100, 1060, 850. ^{1}H-NMR: 0.78 (*s*, 3 H); 0.86 (*s*, 3 H); 0.95 (*s*, 3 H); 1.27 (*s*, 3 H); 3.20 (*s*, 3 H). ^{13}C-NMR: *Table 2*. MS: 224 (5, $M^{+\cdot}$), 209 (17), 192 (37), 177 (59), 163 (4), 149 (8), 137 (31), 123 (17), 109 (29), 95 (17), 85 (100), 71 (11), 67 (15), 55 (21), 41 (29).

(±)-1,2,3,4,4a,5,6,7,8,8aα-Decahydro-6α-methoxy-1,1,4aβ-trimethylnaphthalene (**14**; 84% yield from **8**). B.p. 110°/0.02 Torr. IR: 2800–3000, 1455, 1375, 1360, 1195, 1180, 1115, 1090. ^{1}H-NMR: 0.78 (*s*, 3 H); 0.86 (*s*, 3 H); 0.92 (*s*, 3 H); 3.32 (*s*, 3 H); 3.32 (*m*, 1 H). ^{13}C-NMR: *Table 2*. MS: 210 (0, $M^{+\cdot}$), 195 (0.5), 178 (25), 163 (47), 149 (3), 137 (100), 122 (18), 107 (24), 95 (38), 81 (55), 69 (41), 55 (37), 41 (40).

(±)-1,2,3,4,4a,5,6,7,8,8aα-Decahydro-6β-methoxy-1,1,4aβ,6α-tetramethylnaphthalene (**16**; 99% from **9**). B.p. 150–155°/0.5 Torr. IR: 2800–3000, 1450, 1380, 1360, 1190, 1120, 1060, 860. ^{1}H-NMR: 0.82 (*s*, 3 H); 0.86 (*s*, 3 H);

1.05 (*s*, 3 H); 1.07 (*s*, 3 H); 3.15 (*s*, 3 H). ^{13}C-NMR: *Table 2*. MS: 224 (1, $M^{+\cdot}$), 209 (10), 192 (3), 177 (11), 149 (2), 137 (12), 125 (7), 109 (14), 95 (16), 85 (100), 81 (20), 69 (18), 55 (21), 41 (22).

(±)-1,2,3,4,4a,5,6,7,8,8aα-Decahydro-6β-methoxy-1,1,4aβ-trimethylnaphthalene (**18**; 71% yield from **10**). B.p. 170°/4 Torr. IR ($CHCl_3$): 2800–3000, 1455, 1360, 1095, 1080. ^{1}H-NMR: 0.82 (*s*, 3 H); 0.86 (*s*, 3 H); 1.07 (*s*, 3 H); 3.29 (*s*, 3 H); 3.44 (*m*, 1 H). ^{13}C-NMR: *Table 2*. MS: 210 (17, $M^{+\cdot}$), 195 (8), 178 (9), 163 (77), 149 (5), 137 (29), 121 (24), 107 (45), 95 (48), 81 (100), 72 (34), 69 (60), 55 (53), 41 (51).

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