270. Formation of Ambergris Odorants from Ambrein under Simulated Natural Conditions

by **Günther Ohloff, Karl H. Schulte-Elte** and **Bernard L. Müller**

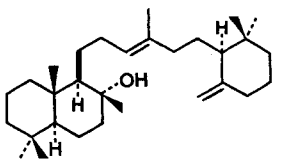
Firmenich SA, Research Laboratories, CH-1211 Geneva 8

(7. XI. 77)

Summary

Singlet oxygen oxygenation of ambrein (**1**) and subsequent degradation of the primarily formed allyl hydroperoxides led to the naturally occurring ambergris odorants **2** to **5**. The results allowed the postulate that $^1O_2$ is an active reagent in the biodegradation of the tricyclic triterpene alcohol **1** in ambergris.

Ambergris, a precious ingredient for fine perfumery, is a pathological intestinal secretion of the blue sperm whale [1] [2]. The sensorily important components are present in the fractions obtained by steam distillation and amount to less than 0.3% of the crude material [3]. One hypothesis assumes these components to be formed by autoxidative degradation of the tricyclic triterpene alcohol ambrein (**1**) [1], composed

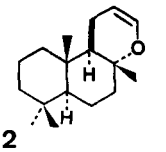


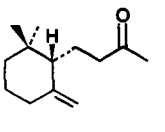
1

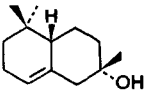
of a bicyclo-nerolidyl moiety and a γ-monofarnesyl moiety. Copper ions originating from haemocyanin [4] might function as catalyst in this degradation [1].

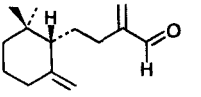
Dihydro-γ-ionone (**3**) [3] had already been identified, and besides the tricyclic enol ether (**2**) [6], and α-ambrinol (**4**) [7] [8] recently the hitherto unknown ambra aldehyde (**5**) [5] were found to be typical ambergris odorants. Bicyclic and tricyclic derivatives of this series, under conditions of equal molecular parameters, possess similar odoriferous properties and are related to each other by the 'triaxial rule of odour sensation' [9–11].

Singlet oxygen may be regarded as an active agent in the degradation of ambrein, especially since porphyrins, known to be efficient photosensitizers, have been identified in ambergris [12] [13], and we wished to carry out this process *in vitro*. We now find that ambrein (**1**) [3] [14] in toluene solution easily takes up 1 mol equiv. of molecular oxygen in the presence of dinaphthylenethiophen as a photosensitizer and

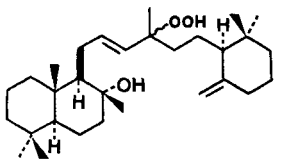

2

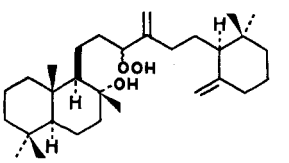

3


4

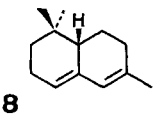

5

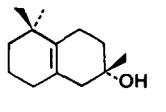
light of a high pressure mercury lamp. In order to simulate natural conditions [15], the allyl hydroperoxides **6** and **7** formed in the photooxygenation[1]) were subjected


6


7

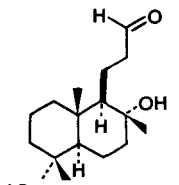
to a thermal or an acid-catalysed treatment. Gas chromatography (GC.) enabled 75% of the distillable reaction products to be isolated, their structure being determined by comparison with authentic samples. Thermal fragmentation of the photooxygenation mixture, at 110° in toluene, yielded 55% of volatile products, in which was present a small amount of the tricyclic oxide **2**, the remainer mainly being products formed from the γ-monocyclofarnesyl moiety of ambrein: 30% (−)-α-ambrinol **4**, 25% (+)-dihydro-γ-ionone **3**, 12% (−)-hexahydronaphthalene derivative **8**, 4% β-ambrinol (**9**) and about 0.5% ambra aldehyde (**5**). Nearly the same mixture in different propor-


8

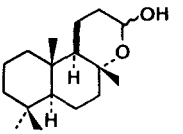

9

tions with more aldehyde **5**, was obtained by the BF_3-catalysed decomposition of allyl hydroperoxides **6** and **7**: 34,5% **4**, 17% **8**, 16% **2**, 2% **9**, 1.5% **5**, and less than 1% **3**. The fragments **10** and **11** which, like ambra aldehyde (**5**), should be formed as a result of the fragmentation of the allyl hydroperoxide **7** were not among the products obtained by distillation. The hemiacetal **11**, which can be regarded as the intermediate of enol ether **2**, had been found as an odourless component in ambergris [5]. Both the bicyclic compound **10** and dihydro-γ-ionone **3** are fomed from the two allyl hydroperoxides **6** and **7** by a *Hock-Criegee* fission [17] [18]. The course of this

[1]) M^me^ *Elise Jégou*, Institute de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France, has identified compound **7** *via* its reduction product and the same amount of compound **6** must be considered present [16].



10



11

reaction has been investigated on related systems [19]. Ambrinols **4** and **9**, and diene **8** result from the acid-catalysed cyclization of dihydro-γ-ionone **3** [7]. The absolute configurations of (−)-ambrinol (**4**) and (−)-diene **8** are determined by the relationship with (+)-7,8-dihydro-γ-ionone (**3**)[2]).

Experimental Part

General. – Our (+)-ambrein (**1**) had the following physical constants: $[\alpha]_D = +12.18°$ ($CHCl_3$), m.p. 81–82° (uncorr.) [21] (lit. [1] [14]: $[\alpha]_D^{16} = +21°$ (ethanol), m.p. 83.5°). The photooxygenations were carried out at 18–20° in a conventional *Pyrex* irradiation apparatus [22] equipped with a centrally arranged water-cooled lamp. The oxygen (> 99% pure) was delivered from a volumetric storage flask, and its consumption was recorded automatically. Light source: *Philips* HPK 125 W.

For the gas chromatographs and spectrophotometers used see [11].

1. Photooxygenation of ambrein (1). – A solution of 2.1 g of **1** in 50 ml of toluene absorbed 110 ml of O_2 (1 equiv.) within 1.5 h when irradiated in the presence of 60 mg dinaphthylenethiophen (*Columbia Chem. Inc.*, USA) under the above conditions. (The maximum rate of O_2 absorption at the beginning of the conversion was 8 ml/min). The oxygenation was then interrupted, and the oxygenation mixture was treated as follows.

a) *Thermal decomposition of the oxygenation products from* **1**. Half of the irradiated solution (25 ml) was added dropwise under N_2 to stirred toluene (10 ml) at 110°, and the mixture was further refluxed for *ca.* 1.5 h, when conversion was complete (peroxide test with KI/glacial acetic acid negative). The reaction mixture was concentrated *in vacuo*, and the residue (1 g) was distilled in a bulb tube ($\leqslant 120°/10^{-2}$ Torr), when 0.55 g of an oily liquid was collected. This liquid was analysed by GC./MS. coupling[3]) (*Carbowax*, 50 m). The following main constituents were identified (in order of elution): diene **8** (12%), ketone **3** (25%), alcohol **4** (30%), aldehyde **5** (0.5%), alcohol **9** (4%) and oxide **2** (3%). Non-identified products: 25.5%.

b) *BF_3-catalysed decomposition of the oxygenation products from* **1**. To the other half of the irradiated solution (25 ml) at 0–5° was added 1 ml BF_3-etherate (*Fluka*, freshly distilled). The mixture was allowed to stand for 24 h at the same temperature. The peroxide test (KI/glacial acetic acid) was then negative. The solution was washed to neutrality (water, $NaHCO_3$, water), dried (Na_2SO_4), and concentrated *in vacuo*, to obtain 1.1 g of residue which, on distillation in a bulb tube at $\leqslant 120°/10^{-2}$ Torr, yielded 0.45 g of an oil. This mixture had the following composition (GC./MS.): **8** (17%), **3** (1%), **4** (34.5%), **5** (1.5%), **9** (2%), **2** (16%) and non-identified products (28%).

2. Isolation and identification of compounds 2 to 9. – The mixtures of compounds **2** to **9** obtained as described above were combined (850 mg) and separated by chromatography on silica gel (500 g, activity 2, in petroleum ether/ether ~9:1). The following compounds were obtained in order of elution: a) (−)-(S)-*2,5,5-Trimethyl-3,4,5,6,7,10-hexahydronaphthalene* (**8**): $[\alpha]_D = -1.8°$ ($c = 10.5$, $CHCl_3$). – ^{1}H-NMR. (CCl_4) (δ ppm): 0.76 and 0.98 (1 *s* each, $C(CH_3)_2$); 1.74 (*s*, $C{=}CCH_3$); 5.37 and 5.82 (1 *m* each, CH=CCH=C). – MS.: M^+ 176 (85); *m/e*: 161 (60), 120 (100), 105 (95), 41 (35), identified with known spectra [7]. – b) (+)-(S)-*7,8-Dihydro-γ-ionone* (**3**): $[\alpha]_D = +20.9°$ ($c = 10.4$, $CHCl_3$). –

[2]) The absolute configuration of (+)-7,8-dihydro-γ-ionone [20] has been revised [21].

[3]) We are indebted to Dr. *B. Willhalm* and Mr. *W. Thommen* for the recording and aid in interpretation of the spectra.

IR. (film): λ=1710 (C=O), 1640 (C=C). – ^{1}H-NMR. ($CDCl_3$): 0.9 and 1.0 (1 *s* each, $C(CH_3)_2$); 2.1 (*s*, $COCH_3$); 4.5 and 4.7 (1 *m* each, $C=CH_2$). – MS.: M^+ 194 (10); *m/e*: 177 (4), identified with known spectra [3] [5]. – c) (−)-(*2* R,*10* S)-*α-Ambrinol* (**4**): $[\alpha]_D = -67.6°$ (*c*=10.2, $CHCl_3$). – IR. (film): λ=3450 (OH). – ^{1}H-NMR. (CCl_4): 0.87 and 0.92 (1 *s* each, $C(CH_3)_2$); 1.13 (1 *s*, $HOCCH_3$), 5.4 (*m*, C=CH). – MS.: M^+ 194 (2); *m/e*: 176 (33), 161 (30), 136 (48), 120 (68), 105 (98), 43 (100), 41 (95), identified with known spectra [7]. – d) (±)-*4-(2,2-Dimethyl-6-methylenecyclohexyl)-2-methylenebutanal* (**5**): $[\alpha]_D = +2.5°$ (±1°; *c*=1.2, $CHCl_3$, not clear). – IR. (film): λ=3080, 1640 and 885 ($C=CH_2$), 1625 and 940 (conj. $C=CH_2$), 2700 and 1690 (CHO conj.). – ^{1}H-NMR. (CCl_4): 0.8 and 0.9 (1 *s* each, $C(CH_3)_2$); 4.53 and 4.75 (1 *m* each, $C=CH_2$); 5.86, 6.14 and 9.48 (1 *s* each, CH_2=C–CHO). – MS.: M^+ 206 (6); *m/e*: 151 (8), 173 (32), 95 (42), 81 (64), 69 (91), 41 (100), identified by comparison of spectra [5]. – e) *β-Ambrinol* (**9**) [7]: identified by GC. retention times and mass spectrum: M^+ 194 (3); *m/e*: 176 (48), 161 (100), 133 (18), 121 (50), 105 (68), 91 (46), 77 (28), 55 (26), 43 (56). – f) *Tricyclic enol ether* **2** [1] [5]: identified by comparison of mass spectrum with that of authentic material: M^+ 248 (10); *m/e*: 233 (5), 215 (4), 191 (30), 177 (10), 137 (12), 121 (22), 109 (40), 95 (82), 81 (73), 69 (69), 55 (54), 41 (100).

Added after having finished the manuscript: It is interesting to note that an analogous biomimetic approach has been independently followed by *B. D. Mookherjee* and *R. R. Patel* who confirmed some of our own results and mentioned their investigation at the 7th International Congress of Essential Oil, in Kyoto, Japan (October 1977).

REFERENCES

[1] *E. Lederer*, in «Fortschritte der Chemie Organischer Naturstoffe», Vol. VI, ed. L. Zechmeister, Springer Verlag, Vienna 1950, p. 97.
[2] *G. Ohloff*, in «Fortschr. chem. Forsch.», Vol. 12, Springer Verlag, Berlin–Heidelberg–New York 1969, p. 185.
[3] *L. Ruzicka, C. F. Seidel & M. Pfeiffer*, Helv. *31*, 827 (1948).
[4] *E. Lederer*, J. chem. Soc. *1949*, 2115.
[5] *E. Jégou, J. Polonsky, E. Lederer, K. H. Schulte-Elte, B. Egger & G. Ohloff*, Nouveau Journal de Chimie, in print.
[6] *L. Ruzicka & C. F. Seidel*, Helv. *33*, 1285 (1950).
[7] *M. Stoll & M. Hinder*, Helv. *38*, 1593 (1955); *M. Stoll, C. F. Seidel, B. Willhalm & M. Hinder*, ibid. *39*, 183 (1956).
[8] *A. C. Armour, G. Büchi, A. Eschenmoser & A. Storni*, Helv. *42*, 2233 (1959).
[9] *G. Ohloff*, 'Relationship between Odor Sensation and Stereochemistry of Decalin Ring Compounds', Gustation and Olfaction, an International Symposium, Geneva, June 1970, Academic Press, London–New York 1971, p. 178.
[10] *G. Ohloff, F. Näf, R. Decorzant, W. Thommen & E. Sundt*, Helv. *56*, 1414 (1973).
[11] *G. Ohloff, W. Giersch, K. H. Schulte-Elte & Ch. Vial*, Helv. *59*, 1140 (1976).
[12] *Y. Okahara*, Jap. J. med. Sci., Sect. II, *1*, 247 (1927).
[13] *E. Lederer & R. Tixier*, C.r. hebd. scéances Acad. Sci. *224*, 531 (1947).
[14] *E. Lederer, F. Marx, D. Mercier & G. Pérot*, Helv. *29*, 1354 (1946).
[15] *G. Ohloff*, Pure appl. Chemistry *43*, 481 (1975).
[16] *K. Gollnick*, Adv. Photochem. *6*, 1 (1968); *R. W. Denny & A. Nickon*, Org. Reactions *22*, 133 (1973).
[17] *H. Hock & S. Lang*, Ber. deutsch. chem. Ges. *77*, 257 (1944); *H. Hock & H. Kropf*, Angew. Chem. *69*, 313 (1957); *R. Criegee*, Liebigs Ann. Chem. *560*, 127 (1948).
[18] *C. Rüchardt*, in «Fortschr. chem. Forsch.», Vol. 6, Springer Verlag, Berlin–Heidelberg–New York 1966, p. 251.
[19] *G. O. Schenck & K. H. Schulte-Elte*, Liebigs Ann. Chem. *618*, 185 (1958); *G. Ohloff, H. Strickler, B. Willhalm* et al., Helv. *53*, 623 (1970).
[20] *C. H. Eugster, R. Buchecker, Ch. Tscharner, G. Uhde & G. Ohloff*, Helv. *52*, 1729 (1969).
[21] *G. Ohloff & Ch. Vial*, Helv. *60*, 2767 (1977).
[22] *G. O. Schenck*, in «Präparative Organische Photochemie», ed. A. Schönberg, Springer Verlag, Berlin 1958, p. 210.