271. Permanganate Oxidation of Ambrein and the Absolute Configuration of Dihydro-γ-ionone (Supplement and Rectification)

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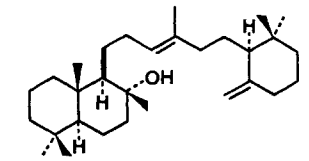
Summary

Compounds **2** to **7** were identified among the products obtained from ambrein (**1**) by potassium permanganate oxidation; (+)-dihydro-γ-ionone (**3**) was shown to have the *S*-configuration.

The application of oxidation methods constituted the basis for elucidating the structure of the triterpene (−)-ambrein (**1**), one of the main constituents of ambergris [1] [2]. (+)-Ambreinolide (**2**) [3] [4] and (+)-dihydro-γ-ionone (**3**) [1] [5] were



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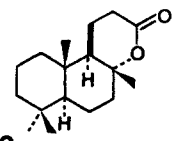

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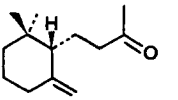

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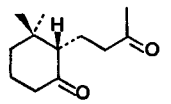
isolated on treatment of **1** with permanganate. We have now found the neutral fractions to contain further degradation products formed from the monocyclic moiety of ambrein (**1**); these are the (+)-diketone **4** [1] [5], the enol **5** of a C(9)



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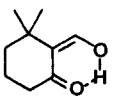

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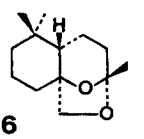

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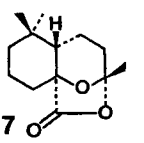

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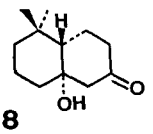
ketoaldehyde, an intramolecular (−)-acetal **6** [6] and the corresponding (−)-lactone **7**. The structure of **2**, **3** and **6** was proved by comparison with the authentic material, whereas the structure of **4**, **5** and **7** was obtained by chemical transformations.

In the presence of ethanolic sodium ethoxide solution (+)-diketone **4** yielded (−)-hydroxyketone **8** of known configuration [7]. The (+)-dihydro-γ-ionone (**3**)[1]) formed from (+)-ambrein (**1**), is related to compounds **4** and **8**, and has thus the *S*-configuration which had erroneously been attributed to its antipode [8].



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Experimental Part

General. – If not otherwise stated, the instruments and methods are as previously described [6].

(+)-Ambrein (1). – Two portions, in all 504 g, of crushed ambergris were each extracted with 3000 ml of ether for 2 h at reflux. The soluble portion (417 g, 82.7%), twice washed with 5% NaOH-solution, yielded 387.3 g (76.8%) of dark brown extract which was divided into two portions and chromatographed on 2 × 2.5 kg of silica gel in hexane/ether 95:5. Fractions 10–32 (one fraction = 1000 ml) yielded 251 g of crude ambrein (**1**) (49.8%) which was recrystallized (to constant m.p.) from hexane at −20° to give 148 g (29%) pure ambrein (**1**). M.p. 81–82° (lit.: 82.5–83.5° [2]); $[\alpha]_D^{20} = +18.42°$ ($c = 1.21$, EtOH) (lit.: +21° [2]), and +12.18° ($c = 1.28$, $CHCl_3$). – NMR. as described [9].

A solution of 145.5 g of ambrein (**1**) in 4000 ml of acetone was oxidized with 537 g of $KMnO_4$ added in portions [2]. A semi-crystalline mass (116.4 g) was obtained which was separated by washing with 5% NaOH into an acid fraction (34 g) and a neutral fraction (94.3 g).

Ambreinolide (2). – After several recrystallizations from hexane at −10°, 40.0 g of lactone **2** were obtained from the neutral fraction. M.p. 134–136° (lit.: 142° [2]); $[\alpha]_D^{20} = +33°$ ($c = 1.07$, EtOH) (lit.: +34° [2]); +28° ($c = 1.11$, $CHCl_3$) (lit.: +30° [1]). From the mother liquor (54 g) 27.3 g of a mixture were distilled from the residue (26 g) (b.p. 30–100°/0.1 Torr), chromatography of which on 1 kg of silica gel in hexane/ether 8:2, then 7:3 yielded two fractions. The first fraction (4.5 g) contained **5** (1.2%), **3** (28%), **6** (14.8%) and **7** (56%) in order of retention time on preparative GC. (Carbowax 20 M, 5%, 2.50 m, on Chromosorb W 80–100). The second fraction (19.6 g) was entirely diketone **4**.

2-Hydroxymethylene-3,3-dimethylcyclohexanone (5). – IR. (neat): 2980, 2900, 1620, 1590. – NMR. ($CDCl_3$, 90 MHz): 1.24 (*s*, 6H, $2CH_3$); 1.37–1.95 (*m*, 4H, $-CH_2-CH_2-$); 2.39 (*m*, 2H, $-CO-CH_2-$); 8.92 (*d*, $J = 3$, becomes *s* in D_2O, 1H, =CH–O–); 15.13 (*d*, $J = 3$, 1H, OH, disappears on addition of D_2O). – MS. *m/e*: 154 (M^+, 16), 139 (100), 111 (16), 97 (13), 83 (14), 69 (7), 55 (20), 41 (16), 27 (7).

Following *Näf & Decorzant* [13], 10.16 g of CH_3MgI in 40 ml abs. ether were treated at −5° first with powdered CuI and then dropwise with 5.5 g of 3-methylcyclohex-2-en-1-one. After stirring for 1 h 7.4 g of ethyl formate were added. After standing for 1 h, the mixture was worked up as usual to yield 5.1 g product consisting of 80% of 3,3-dimethylcyclohexan-1-one and 20% of ketoaldehyde **5** identical (NMR., MS.) with the degradation product **5** from ambrein.

(+)-Dihydro-γ-ionone (3). – $[\alpha]_D^{20} = +15.0°$ (neat) (lit.: +12.8° [5]); $[\alpha]_D^{20} = +17.75°$ ($c = 0.69$, $CHCl_3$). Ketone **3** obtained by the fragmentation of tertiary allylhydroperoxide of ambrein (**1**) had a rotation of $[\alpha]_D = +20.9°$ ($c = 10.4$, $CHCl_3$) [10]. The spectroscopic properties of ketone **3** correspond to those of the known racemic product [11].

Acetal 6. – $[\alpha]_D^{20} = -32°$ ($c = 0.57$, $CHCl_3$). The spectra were identical with those of the racemic product [6].

Lactone 7. – M.p. 37–39°; $[\alpha]_D^{20} = -76.30°$ ($c = 1.01$, $CHCl_3$). – IR. (liq.): 2970, 2900, 1780, 1460, 1390, 1280, 1215, 1140, 1080, 1060, 885. – NMR. ($CDCl_3$, 90 MHz): 0.90 (*s*, 6H, $2CH_3$); 1.52 (*s*,

[1]) Ketone **3** isolated from ambergris has a rotation of $\alpha_D = +12.8°$ (neat). It was reported that the direction of rotation is reversed in chloroform solution; this, however, is obviously an error [5] (see exper. part).

3H, –O–CCH$_3$–O–). – ^{13}C-NMR. ($CDCl_3$): 175.2 (*s*), 108.1 (*s*), 81.3 (*s*), 47.8 (*d*), 41.1 (*t*), 34.0 (*s*), 33.4 (*t*), 31.8 (*t*), 31.1 (*q*), 23.9 (*q*), 19.7 (*q*), 19.3 (*t*), 18.6 (*t*). – MS. *m/e*: 224 (M^+, 0), 209 (1), 191 (1), 181 (71), 165 (37), 147 (12), 139 (33), 122 (55), 111 (61), 95 (20), 81 (19), 69 (35), 55 (27), 43 (100), 27 (12).

A solution of 1.4 g of acetal **6** in 15 ml of acetone and 50 ml of *Jones*'s reagent [12], yielded 1.4 g of a lactone identical (NMR., MS. *etc.*) with compound **7**.

Diketone 4. – $[\alpha]_D^{20} = +6.19°$ ($c = 1.23$, $CHCl_3$). – IR. (neat): 2980, 2890, 1700, 1360, 1160, 1070, 930. – NMR. ($CDCl_3$): 0.77 and 1.07 (2*s*, 6H, 2CH$_3$), 2.09 (*s*, 3H, –CO–CH$_3$). – MS. *m/e*: 196 (M^+, 3), 181 (100), 163 (18), 139 (21), 121 (13), 111 (53), 95 (14), 83 (14), 69 (41), 55 (34), 43 (79), 27 (7).

A mixture of 0.5 g of diketone **4** and 40 ml of freshly prepared 0.8% NaOEt for 2 h at RT. yielded, after usual work-up and crystallization from hexane, 228 mg (45.6%) of pure ketoalcohol **8**. M.p. 159–161° (lit.: 158–160° [7]); $[\alpha]_D^{20} = -49°$ ($c = 1.08$, $CHCl_3$) (lit.: $-34°$ [7]); $-52°$ ($c = 1.05$, EtOH).

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