Chemical Studies on Ambergris

Part II. The Thermal Decomposition and Oxidation Products of Ambrein-tetrahydropyranylether

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Ambrein (I), a major constituent of ambergris, was easily converted to ambrein-tetrahydropyranylether (II), of which thermal decomposition gave back ambrein (I). The tetrahydropyranylether (II) was oxidized to ambreinolal-tetrahydropyranylether (V) in two steps. Ambreinolal-tetrahydropyranylether (V) was synthesized from ambreinolol (VII) in four steps and converted to the C_{17}-unsaturated oxide (VI) on heating.

In 1820 Pelletier et al.\(^1\) first isolated ambrein as a major constituent of ambergris and the structure (I) of ambrein was elucidated by L. Ruzicka and E. Lederer et al.\(^2\) Ambrein could not be acetylated under normal condition, because the oxygen function is a sterically hindered tert-alcohol.

Therefore, the authors tried to prepare the ether derivatives of ambrein and found that ambrein was easily converted to ambrein-tetrahydropyranyl (THP) ether (II) on treatment with dihydropyran and the acid catalyst.

It is known that THPether was easily hydrolyzed to the original alcohols by aqueous mineral acid\(^3\) But we found that treatment of ambrein THPether as well as ambrein with acid afforded ambriatriene (III)\(^4\) and that ambrein-THPether decomposed to ambrein and ambriatriene on heating at 250°C/20 mmHg.

Oxidation of ambrein-THPether with aqueous KMnO\(_4\) solution in tert-butanol gave the ketol-THPether (IV) m.p. 200-205°C, which was cleaved by lead tetaacetate in pyridine to yield ambreinolal-THPether (V). Ambreinolal-THPether (V) was converted to the C_{17}-unsaturated oxide (VI)\(^4\) on heating.

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1) Pelletier and Caventou, *J. Pharm.*, 6, 49 (1830).
The same THPether (V) was synthesized from ambreinolol (VII) as follows.

Acetylation of ambreinolol with acetic anhydride in pyridine or acetyl chloride in the presence of magnesium in ether afforded the mono-acetate (VIII) which was converted to the THPether acetate (IX) on treatment with dihydropyran and the acid catalyst. Alkali hydrolysis of THPether acetate (IX) led to ambreinolol-9-THPether (X) which was oxidized with chromium trioxide in pyridine to yield ambreinolol-THPether (V).

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**FIG. 1. Infrared Absorption Spectra of Ambrein-THPether (II)**

**FIG. 2. Infrared Absorption Spectra of Ambreinolal-THPether (V)**
EXPERIMENTAL

1) Preparation of ambrein-THPether (II)
Ambrein (I) (10 g) m. p. 82–3°C was dissolved in dry benzene (100 ml) and dihydropyran (5 g). To this solution was added phosphorus oxychloride (50 mg) or p-toluenesulfonic acid (50 mg) under stirring at 20°C. After stirring for 6 hours at 20°C, the solution was poured into aqueous sodium bicarbonate solution and extracted with ether. The organic layer was washed with water, dried over anhydrous magnesium sulfate and evaporated. The residual oil was absorbed from benzene on alumina (250 g). Elution with benzene gave ambrein-THPether (II) as colorless oil (10.5 g) which solidified on standing and melted at 40–50°C. Ambrein-THPether (II) was distilled at 220–225°C/0.1 mmHg with decomposition. [α]D = +8.6° (benzene). Infrared absorption bands at 3080, 1650, 890 cm⁻¹ (C=CH₂), 1135, 1080, 1025, 990 cm⁻¹ (THPether).

2) Thermal decomposition of ambrein-THPether (II)
Ambrein-THPether (II) (2.5 g) was heated on an oil bath (250–270°C) under reduced pressure (15 mmHg) for 30 minutes. After cooling, the products were absorbed from pet. ether on alumina (70 g). Elution with pet. ether gave ambretriene as a colorless oil (1 g). [α]D = +28,1° (benzene) b. p. 205–210°/0.15 mmHg. Anal. Found: C, 87.54; H, 12.36. Calcd. for C30H50: C, 87.73; H, 12.27%. Further elution with benzene gave ambrein (I) as a colorless oil (1 g) which was crystallized from methanol, giving m. p. 82–83°C. Anal. Found: C, 83.85; H, 12.04. Calcd. for C30H50O: C, 84.04; H, 12.23%.

3) Acid decomposition of ambrein-THPether (II)
a) To a solution of ambrein-THPether (II) (300 mg) in 95% ethanol (50 ml) was added conc. hydrochloric acid (1 ml). The solution was stirred for 3 hours at room temperature or refluxed for 1.5 hours. The solution was poured into cold water and extracted with ether. The organic layer was washed with aqueous sodium bicarbonate solution, water and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave ambratriene (III) as an oil (250 mg) which was purified by chromatography on alumina (20 g) and was identified with the authentic sample in the infrared spectrum.
b) To a solution of ambrein-THPether (II) or ambrein (I) (300 mg) in benzene (30 ml) was added p-toluene sulfonic acid (40 mg). The solution was allowed to stand overnight and poured into aqueous sodium bicarbonate solution and extracted with ether. Evaporation of the solvents gave ambratriene (III) as an oil (250 mg). Infrared absorption band at 3080, 890 cm⁻¹ (C=CH₂).

4) The ketol-THPether (IV)
Aqueous KMnO₄ solution (KMnO₄ 25 g, water 1000 ml) was gradually added to a solution of ambrein-THPether (II) (30 g) in tert-butanol (1 kg) and pyridine (150 ml) for 4 hours at 24–25°C under stirring. After stirring for 1 hour, the mixture was filtered and the filtrate was concentrated to one-third volume under reduced pressure. Recrystallization of the collected precipitate (15 g) m. p. 170–178°C from ethanol afforded the ketol-THPether (IV) m. p. 200–205°C. Infrared absorption bands at 3480 cm⁻¹ (OH), 1710 cm⁻¹ (CO), 1140, 1080, 1025, 995 cm⁻¹ (THPether).

5) Ambreinolol-THPether (V)
Lead tetraacetate (5 g) was added to a solution of the ketol-THPether (IV) (5 g) in pyridine (50 ml) and benzene (50 ml) under stirring at room temperature. The mixture was stirred for 4 hours. After decomposition of an excess of lead tetraacetate with ethyleneglycol, the mixture was filtered and the filtrate was poured into cold water and then extracted with ether. The organic layer was washed with water, 5% cupric sulfate solution three times, water and dried over anhydrous magnesium sulfate. After removal of the solvents, the residue was absorbed from benzene on alumina (100 g). Elution with benzene afforded ambreinolal-THPether (V) as a colorless oil (1.5 g). Infrared absorption bands at 2720, 1725 cm⁻¹ (CHO), 1135, 1080, 1025, 995 cm⁻¹ (THPether).

6) The C₁₇-unsaturated oxide (VI)
Ambreinolal-THPether (V) was heated at 150–170°C and distilled at 100–110°C/0.05 mmHg. Crystallization of the distillate from ethanol gave the C₁₇-unsaturated oxide (VI) m. p. 84–85°C. Anal. Found: C, 82.10; H, 11.75. Calcd. for C₁₇H₂₈O: C, 82.20; H, 11.36%.

7) Synthesis of ambreinolal-THPether (V)
a) Ambreinolol-13-monoacetate (VIII)
To a solution of ambreinolol (VII) (5.4 g) in tetrahydrofuran (20 ml) and dry benzene (60 ml) was added pyridine (10 ml) and acetic anhydride (10 ml) at 5°C. After stirring for 4 hours at 5°C, the solution was allowed to stand overnight at room temperature. The solution was poured into cold
water and extracted with ether. The organic layer was washed with water, 5% cupric sulfate solution three times and dried over anhydrous magnesium sulfate. Evaporation of the solvents gave ambreinolol-13-monoacetate (VIII) as an oil (5.6 g). Infrared absorption bands at 3420 cm⁻¹ (OH), 1738 cm⁻¹ (COO).

Ambreinolol (VII) (5.4 g) was dissolved in tetrahydrofuran (30 ml) and dry ether (60 ml). To the solution was added magnesium (powdered 1 g) and then acetyl chloride (5 g) in dry ether (5 ml) under stirring at room temperature. After stirring for 4 hours, the mixture was poured into aqueous sodium bicarbonate solution and extracted with ether. The ether extraction gave ambreinolol-13-monoacetate (VIII) as an oil (5.6 g).

b) Ambreinolol-9-THPether-13-acetate (IX)

To a solution of the monoacetate (VIII) (5.6 g) in dry benzene (50 ml) and dihydropyran (4 g) was added p-toluenesulfonic acid (20 mg) under stirring. After stirring for 5 hours at room temperature, the solution was poured into aqueous sodium bicarbonate solution and extracted with ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvents gave the THPether acetate (IX) as an oil (5.8 g). Infrared absorption bands at 1740 cm⁻¹ (COO), 1135, 1080, 1025, 995 cm⁻¹ (THPether).

c) Ambreinolol-9-THPether (X)

The THPether acetate (IX) (5.8 g) was hydrolysed with 5% ethanolic KOH solution under refluxing for 4 hours. After removal of ethanol, the residue was poured into cold water and extracted with ether. The organic layer was washed with water, dried over anhydrous magnesium sulfate and evaporated. The residual oil was absorbed from benzene on alumina (150 g). After washing with benzene, elution with ether gave ambreinolol-9-THPether (X) as a colorless oil (5 g). Infrared absorption bands at 3480 cm⁻¹ (OH), 1135, 1080, 1025, 995 cm⁻¹ (THPether).

d) Ambreinolol-THPether (V)

Chromium trioxide (4 g) was gradually added to pyridine (50 ml) under stirring 3~5°C. To the above mixture was added ambreinolol-9-THPether (X) (5 g) in pyridine (10 ml) under stirring. After stirring for 20 hours at room temperature, the mixture was poured into cold water and extracted with ether three times. The organic layer was washed with water, 5% cupric sulfate solution, water and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was absorbed from benzene on alumina (100 g). Elution with benzene gave ambreinolol-THPether (V) as a colorless oil (1 g) which was identified with the sample (V) derived from ambrein-THPether (II) in the infrared spectrum.

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