Absolute Configuration of (+)-Occidol

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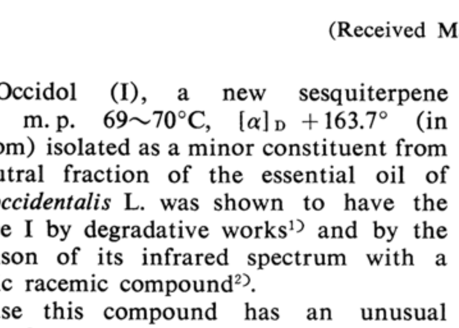
(Received March 30, 1962)

(+)-Occidol (I), a new sesquiterpene alcohol, m. p. 69∼70°C, $[\alpha]_D$ +163.7° (in chlorofom) isolated as a minor constituent from the neutral fraction of the essential oil of *Thuja occidentalis* L. was shown to have the structure I by degradative works[1] and by the comparison of its infrared spectrum with a synthetic racemic compound[2].

Because this compound has an unusual structure feature, which is apparently derived from eudesmane sesquiterpene precursor by the dienol-benzene rearrangement or similar mechanism[3], determination of the absolute configuration of this alcohol is interesting from a biogenetic point of view.

This paper is concerned with the correlation of C_7 absolute configuration with (−)-santonin (II)[4].



II

III $R=CO_2H$
IV $R=COCl$
V $R=COMe$
VI $R=OAc$
VII $R=OH$

VIII

I

Hyposantonous acid (III), prepared from (−)-santonin (II) via the oxime and hyposantonin, was converted by thionyl chloride into acid chloride IV, which afforded the ketone V with dimethycadmium. Baeyer-Villiger oxidation of V with perbenzoic acid in chloroform gave the acetate VI, which was separated from the unchanged ketone V using Girard P reagent. The crude acetate VI was hydrolyzed directly with methanolic potassium hydroxide to alcohol VII. Chromatography on Florisil gave a viscous oil, b. p. 140∼180°C/0.5 mmHg. The alcohol VII was oxidized with chromic anhydride-pyridine complex to ketone VIII. Grignard reaction of ketone VIII with methylmagnesium iodide afforded a tertiary alcohol which was purified by chromatography on Florisil. Recrystallization from petroleum ether gave crystals, m. p. 69∼70°C, $[\alpha]_D$ +76.7° (in chloroform), the identity of which with (+)-occidol[5] was established by the mixed melting point determination and comparison of infrared spectra in chloroform.

These findings show that (+)-occidol has the *R* configuration at C_7, typical of the natural eudesmane type sesquiterpenes and this fact suggests the close relationship of (+)-occidol with eudesmane type compounds[4]. In the steroid field, compounds which have an aromatic A ring are common, especially among female hormones, where the biological passway involving the splitting of the angular methyl group at C_{10}, has been worked out thoroughly.

However, there had not been reported a steroid with an aromatic ring containing the methyl group originally attached to C_{10}. Recently the sapogenins, meteogenine and luvigenin, isolated from *Metanarthecium luteo-virid* Maxim. were shown to have the structures IX and X, respectively[6], and as possible

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1) Y. Hirose and T. Nakatsuka, *Bull. Agri. Chem. Soc. Japan*, **23**, 143 (1959).

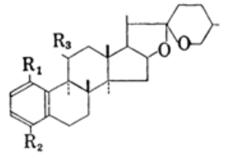
2) Y. Hirose and T. Nakatsuka, ibid., **23**, 253 (1959).

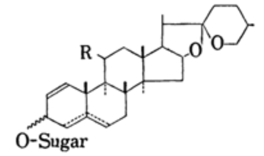
3) M. J. Gentles, J. B. Moss, H. L. Herzog and E. B. Hershberg, *J. Am. Chem. Soc.*, **80**, 3702 (1958); H. Dannenberg and Ch. H. Doering, *Z. physiol. Chem.*, **311**, 84 (1958); H. Dannenberg, Ch. H. Doering and D. Dannenberg-von Dresler, ibid., **317**, 174 (1959); H. Dannenberg and Hans-Günter Neumann, *Ann.*, **646**, 148 (1961).

4) W. Cocker and T. B. H. McMurry, *Tetrahedron*, **8**, 181 (1960).

5) Generously supplied by Dr. Hirose, Department of Agriculture, Tokyo University.

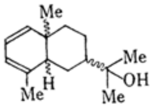
6) K. Takeda, T. Okanishi, K. Igarashi and A. Shimaoka, *Tetrahedron*, in the press; K. Igarashi, *Chem. Pharm. Bull.*, **9**, 722, 729 (1961).





IX R_1=Me, R_2=H, R_3=OH
X R_1=H, R_2=Me, R_3=H

XI



XII

precursors the dienol-glycosides (XI) were suggested.

Although its absolute configuration is still to be elucidated, (+)-occidentalol (XII)[7], isolated as the major constituent of the essential oil of *Thuja occidentalis* L., might be a precursor of (+)-occidol (I). It is suggested that a careful examination of the mother liquor of the extract of the sapogenins IX and X might reveal the existence of the $\Delta^{1,3}$-sapogenins.

Experimental*

Hyposantonin[8].—To a solution of 26 g. of (−)-santonin oxime in 1 l. of 90% ethanol, 50 cc. of concentrated sulfuric acid was added, and was chilled to 20°C. After a solution of 1 g. of copper sulfate in 5 cc. of water was added, 150 g. of zinc powder was added slowly and the reaction temperature was kept below 40°C with vigorous stirring (with Vibro-Mischer) and cooling. After the initial exothermic reaction had subsided (50 g. of zinc powder), the remainder of zinc powder could be added rapidly. The stirring was continued for 10 hr. and during this time the temperature was kept at 31∼35°C.

The zinc powder was filtered and washed repeatedly with warm ethanol (40°C), and the filtrate and washings were combined. After evaporation of the solvent at 40°C, the viscous residue was extracted twice with 350 cc. of warm water (40°C). The combined extracts were freed from polymeric viscous mass by filtration through a layer of Hyflo super cell, and was boiled to precipitate hyposantonin, which weighed 14 g., m. p. 142∼149°C. Recrystallization from aqueous ethanol gave cystals, m. p. 151∼152°C, $[\alpha]_D^{23}$ +36.1° (*c* 1.05, in benzene) (literature[9]; m. p. 152∼153°C, $[\alpha]_D$ +32.75° (*c* 2.4), in benzene).

Hyposantonous Acid (III)[8].—Three hundred grams of zinc powder was adedd in two portions to a boiling solution of 24.3 g. of hyposantonin in 1.5 l. of acetic acid with vigorous stirring (Vibro-Mischer). After heating under reflux with stirring for 16 hr., the zinc powder was removed by filtration, and washed with hot acetic acid. The combined acetic acid solutions were concentrated under reduced pressure, and the viscous residue was diluted with water to precipitate crystals, which were recrystallized from aqueous acetic acid to give colorless prisms, 16 g., m. p. 92∼94°C. The mother liquor was evaporated and the residue was distilled to afford a viscous oil, b. p. 155°C/0.01 mmHg (bath temp. 200∼210°C), which solidified by scratching, 5.6 g., m. p. 91°C, and made total yield 93%. $[\alpha]_D^{12}$ +85.0° (*c* 0.31, in 95% ethanol) (literature[10]; m. p. 95.5°C, $[\alpha]_D^{28}$ +75.95° in ethanol).

Hyposantonous Acid Chloride (IV).—A mixture of 11.6 g. of hyposantonous acid, 13 g. of thionyl chloride and 15 cc. of benzene was refluxed for 1 hr. After the solvent and excess thionyl chloride were removed at reduced pressure, the residue was distilled to afford 11.6 g. (93% yield) of an oil, b. p. 133∼137°C/0.5 mmHg, n_D^{18} 1.5480. After standing at room temperature it solidified to give srystals, m. p. 45∼46°C. IR spectrum: 1765 cm^{-1} (in chloroform).

Anilide: recrystallized from aqueous ethanol, m. p. 138∼141°C.

Found: C, 82.09; H, 8.25; N, 4.77. Calcd. for $C_{21}H_{25}ON$: C, 82.04; H, 8.25; N, 4.56%.

3-(5, 8-Dimethyl-1, 2, 3, 4-tetrahydro-2-naphthyl)-butanone-2 (V).—To a suspension of 1 g. of magnesium in 60 cc. of absolute ether, a stream of methyl bromide was passsed with stirring for 1 hr. until the magnesium disappeared. Then, at room temperature and in an atmosphere of nitrogen, 2.3 g. of cadmium chloride (dried at 130°C) was added during 5 min., and the reaction mixture was refluxed for 45 min. After 28 cc. of ether was removed by distillation, 30 cc. of benzene was added and then 28 cc. of benzene-ether mixture was evaporated under vigorous stirring to disperse the solid mass which formed. After 25 cc. of benzene was added, the viscous material adhering to the wall of the reaction flask was dislodeged by scratching with a spatula. A solution of 6 g. of the acid chloride IV in 10 cc. of benzene was slowly added, and stirring under refluxing was continued for 1.5 hr. The reaction mixture was decomposed by adding a mixture of 20 cc. of water and 20 cc. of 4 N sulfuric acid, and extracted twice with benzene. After washing with water, 5% sodium carbonate solution and saturated aqueous sodium chloride, the benzene solution was dried over anhydrous magnesium sulfate. Evaporation of the solvent gave an oil, which distilled at 154∼155°C/0.5 mmHg (bath temp. 180∼200°C) and weighed 3.8 g. (yield, 69%), n_D^{18} 1.5342, $[\alpha]_D^{22}$ +69.5° (*c* 2.74, in 95% ethanol). IR spectrum: 1700 cm^{-1} (in chloroform).

Found: C, 82.31; H, 9.61. Calcd. for $C_{12}H_{22}O$: C, 83.43; H, 9.63%.

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[7] T. Nakatsuka and Y. Hirose, *Bull. Agr. Chem. Soc. Japan*, **20**, 215 (1956); ibid., **23**, 140 (1959).

* All melting points are uncorrected. The analyses were performed in the Microanalytical Laboratory of the Institute of Polytechnics, Osaka City University.

[8] Elsevier's "Encyclopedia of Organic Chemistry", Series III, Vol. 12B, Elsevier Pub. Co. Inc., New York-Amsterdam (1948), pp. 3326, 3456.

[9] D. Gucci, *Gazz. chim. ital.*, **19**, 367 (1889) (*Chem. Zentr.*, **1889**, II, 595); G. Grassi-Gristaldi, ibid., **19**, 382 (1889) (*Chem. Zentr.*, **1889**, II, 597).

[10] G. Grassi-Cristaldi, ibid., **26**, 459 (1896) (*Chem. Zentr.*, **1897**, I, 170).

Semicarbazone: recrystallized from ethanol, decomp. p. 216~225°C.

Found: C, 71.07; H, 9.05; N, 14.80. Calcd. for $C_{17}H_{25}ON_3$: C, 71.04; H, 8.77; N, 14.62%.

1-(5, 8-Dimethyl-1,2,3,4-tetrahydro-2-naphthyl)-ethanol (VII).—A mixture of 3.12 g. of the ketone V and 32 cc. of chloroform which contained 2.53 g. of perbenzoic acid was kept in a dark place at room temperature for one week. After 50 cc. of ether was added, the solution was washed with 1N sodium hydrogen carbonate and saturated sodium chloride solution. After drying with anhydrous magnesium sulfate, the solvent was removed to give a viscous oil, which was dissolved in a solution of 1.7 g. of the Girard P reagent in 40 cc. of 99% ethanol. Then 2.31 g. of acetic acid was added, and the solution was refluxed on a water bath for 1 hr. The pale yellow solution was cooled in an ice bath, and brought to pH 7 by adding a solution of 1.85 g. of sodium carbonate in 200 cc. of water. The turbid aqueous solution was extracted with six portions of 50 cc. of benzene.

The Acetate Fraction.—The benzene extract was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Removal of the solvent gave a viscous oil, which was directly hydrolyzed by boiling with a mixture of 0.8 g. of potassium hydroxide in 15 cc. of methanol for 2 hr. After the solvent was removed on a water bath, the residue was diluted with 20 cc. of water and extracted with ether. The ether extract was washed with water and saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed and the residue was distilled to give 0.8 g. of an oil, b. p. 140~180°C (bath temp.)/0.1 mmHg. Since the infrared spectrum showed the contamination with a small amount of the unchanged ketone V, the alcohol VII was purified by chromatography on Florisil (10 g.). Elution with petroleum ether (b. p. 60~80°C) gave unchanged ketone, followed by alcohol VII which was eluted with benzene-petroleum ether. IR spectrum: 3340 cm^{-1} (in chloroform). $[\alpha]_D^{20}$ +63.2° (c 2.12, in pyridine).

The Ketone Fraction.—From the aqueous solution separated from the ester, 0.84 g. of ketone V was recovered.

(5, 8-Dimethyl-1,2,3,4-tetrahydro-2-naphthyl)-methylketone (VIII).—Pyridine-chromic anhydride complex was prepared by careful addition of 0.9 g. of chromic anhydride in 16 cc. of pyridine cooled at 15~20°C. A solution of 0.618 g. of alcohol VII in 16 cc. of pyridine was added to the suspension of the complex, and the solution was allowed to stand at room temperature overnight. After being diluted with 400 cc. of water, the reaction mixture was extracted six times with total amount, of 500 cc. of ether. The ether extract was washed with saturated sodium sulfate solution four times, and dried over anhydrous magnesium sulfate.

After evaporation of the solvent, the residue distilled at 120~140°C (bath temp.)/0.1 mmHg and weighed 0.589 g. IR spectrum: 1700 cm^{-1} (in chloroform). $[\alpha]_D^{21}$ +51.6° (*c* 1.95, in ethanol), 2,4-Dinitrophenylhydrazone: bright yellow needles from ethanol-ethyl acetate, m. p. 206~207°C. Found: C, 62.93; H, 6.08; N, 14.48. Calcd. for $C_{20}H_{22}O_4N_4$: C, 62.81: H, 5.80 N, 14.65%.

(+)-Occidol (I).—To the Grignard solution prepared from 0.3 g. of magnesium and 0.54 g. of methyl iodide in 20 cc. of anhydrous ether, a solution of 0.5 g. of ketone VIII in 10 cc. of ether was added, and the reaction mixture was refluxed for 1 hr. The Grignard complex was decomposed by adding 1.5 cc. of saturated ammonium chloride solution, and the clear ether supernatant was decanted. The residue was washed three times with ether, and the combined extracts and washings were dried over anhydrous magnesium sulfate. Removal of the solvent gave a viscous oil (0.574 g.) which was purified by chromatography on 13 g. of Florisil. The fractions which were eluted with petroleum ether-benzene (17 : 3), after evaporation of the solvent, crystallized upon rubbing and weighed 0.388 g. Recrystallization from petroleum ether (b. p. 50~60°C) gave crystals which melted at 69~70°C.

The mixed melting point determination and the comparison of infrared spectra (in chloroform) with an authentic sample established their identity. $[\alpha]_D^{17}$ +76.7° (*c* 0.90, in chloroform). Found: C, 82.35; H, 10.22. Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16%.

The author is very grateful to Dr. H. Watanabe, Fujisawa Pharm. Co., for his generous supply of (−)-santonin. This work was partially supported by the grant-in-aid for Fundamental Scientific Research from the Ministry of Education to which the author's thanks are due.

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