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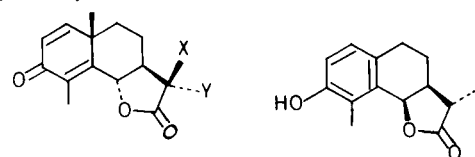
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(±)-1-Nordesmotroposantonin (**2**), a thermolysis product of santonin, and its isomer, α -(1,2,3,4-tetrahydro-1,7-dihydroxy- α ,6-dimethyl-2-naphthalene)acetic acid γ -lactone (**3**) were synthesized from 4-(4-methoxy-3-ethylphenyl)butanoic acid.

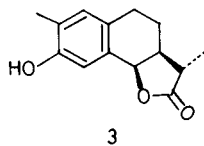
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Santonin is a naturally occurring compound and has been utilized as an important vermicide [1]. Its total synthesis has been established by Abe, *et al.* [2]. (±)-1-Nordesmotroposantonin (**2**) is a thermolysis product of β -santonin (**1b**) [3]. The synthesis of **2** has never been reported. As our



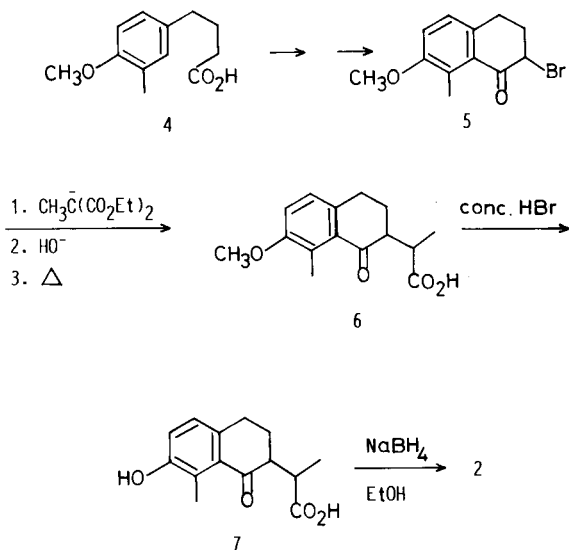
1a: α -Santonin (X = H, Y = CH₃)

1b: β -Santonin (X = CH₃, Y = H)



continuous interest in both the chemistry of γ -butyrolactones [4] and biological activities, we carried out the synthesis of **2** and its isomer **3**. The reaction sequence in the total synthesis of **2** is shown in Scheme 1.

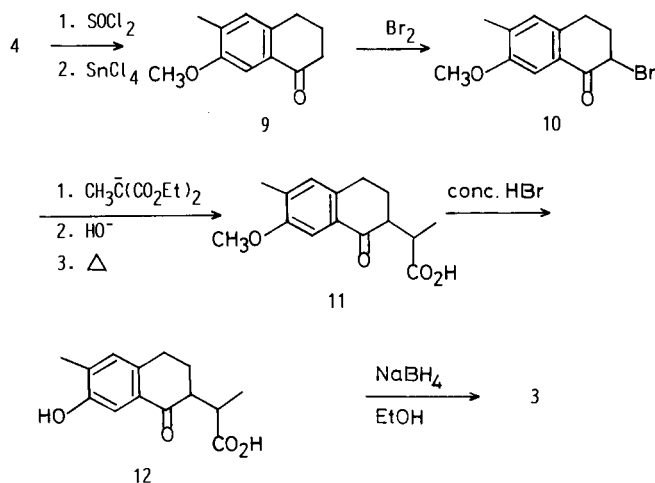
Scheme 1



The starting material, 2-bromo-7-methoxy-8-methyl-1-tetralone (**5**) can be prepared *via* 4 steps from 4-(4-methoxy-3-methylphenyl)butanoic acid (**4**) by the known method [5]. Reaction of **5** with diethyl methylmalonate in the presence of sodium ethoxide gave the substitution product which was hydrolyzed and decarboxylated to give a propionic acid derivative **6** in 36% yield. Hydrolysis of the methoxy group of **6** with concentrated hydrobromic acid afforded a 7-hydroxy derivative **7** in 74% yield. Reduction of **7** with sodium borohydride in ethanol gave (±)-1-nordesmotroposantonin (**2**) in 59% yield. ¹H nmr data were identical with those of the authentic sample [3].

Furthermore, an analog of **2**, α -(1,2,3,4-tetrahydro-1,7-dihydroxy- α ,6-dimethyl-2-naphthalene)acetic acid γ -lactone (**3**) was prepared from **4** *via* 5 steps. The reaction sequence was shown in Scheme 2. Compound **4** was converted to 7-methoxy-6-methyl-1-tetralone (**9**) in 81% yield by Friedel-Crafts reaction of the corresponding acid chloride. Bromination of **9** gave 2-bromo-7-methoxy-6-methyl-1-tetralone (**10**) quantitatively. Introduction of propionic acid moiety at the α -position of the carbonyl group of **10**

Scheme 2



was conducted by the same procedure as shown for **6**. Treatment of **11** with concentrated hydrobromic acid afforded α -(1,2,3,4-tetrahydro-7-hydroxy-6-methyl-1-oxo-2-naphthyl)propionic acid (**12**) in 90% yield. Reduction of

12 with sodium borohydride and the subsequent treatment with acid gave the lactone **3** in 45% yield. The stereochemistry of the lactone ring was deduced to be *cis*-configuration from that of **2**. The present system offers a convenient route to the synthesis of santonin related compounds.

EXPERIMENTAL

The melting and boiling points are uncorrected. Elemental analyses were carried out by Mr. Eiichiro Amano of our laboratory. Infrared (ir) spectra were obtained with a JASCO Model A-102 infrared spectrophotometer. The ¹H nmr spectra (60 MHz) were recorded with a JEOL JNM-FX100 apparatus, with deuteriochloroform as a solvent. All chemical shifts are reported in δ units downfield from internal TMS, and J values are given in Hertz. Column chromatography was accomplished with 100-200 mesh Wakogel C-200.

2-Bromo-7-methoxy-8-methyl-1-tetralone (**5**).

This compound was prepared according to the known method [5].

α -(1,2,3,4-Tetrahydro-7-methoxy-8-methyl-1-oxo-2-naphthyl)propionic Acid (**6**).

Sodium (0.25 g, 0.011 g-atom) was dissolved in a solution of dry benzene (15 ml) and absolute ethanol (1 ml). Diethyl methylmalonate (2.87 g, 16.5 mmoles) was added and the mixture was stirred until the sodium dissolved completely. A solution of **5** (1.82 g, 6.76 mmoles) in dry benzene (15 ml) was added dropwise and the mixture was stirred for 12 hours at room temperature and then heated under reflux for 3 hours. After removal of the solvent, 8 ml of 45% potassium hydroxide and 10 ml of methanol were added and the mixture was heated at 60-70° for 4 hours. The solvent was evaporated and the residue was dissolved in water. After the mixture was washed with ether, the aqueous layer was acidified with dilute hydrochloric acid. The organic materials were extracted with ethyl acetate and the solvent was evaporated. After the residue was heated at 180° for 3 minutes, the crude product was chromatographed on silica gel (hexane/ethyl acetate, 10/1-1/1) to give 640 mg (36%) of **6**; ir (neat): 3600-2500 (OH, COOH), 1700 (C=O), 1675 (C=O), 1258, 920, 817 cm^{-1} ; ¹H nmr (deuteriochloroform): δ 1.20 (3H, d, J = 7 Hz, CHCH₃), 2.46 (3H, s, CH₃), 1.5-3.4 (6H, m), 3.80 (3H, s, OCH₃), 6.99 (2H, s, =C-H), 8.70 (1H, br s, CO₂H).

Anal. Calcd. for C₁₅H₁₈O₄: C, 68.69; H, 6.92. Found: C, 68.55; H, 6.75.

α -(1,2,3,4-Tetrahydro-7-hydroxy-8-methyl-1-oxo-2-naphthyl)propionic Acid (**7**).

A mixture of **6** (545 mg, 2.08 mmoles) and 2.3 ml of concentrated hydrobromic acid was heated under reflux for 4 hours and then cooled. The organic materials were extracted with ethyl acetate and the combined extracts were washed with water and dried over magnesium sulfate. Evaporation of the solvent gave 382 mg (74%) of **7**; ir (potassium bromide): 3400 (OH), 1720 (C=O), 1680 cm^{-1} . This was used for the next step without further purification.

(\pm)-1-Nordesmotroposantonin (**2**).

To a solution of **7** (382 mg, 1.53 mmoles) in 17 ml of absolute ethanol was added sodium borohydride (1.0 g, 40 mmoles) at 0°. The mixture was stirred for 30 minutes and subsequently 5 ml of acetone was added to decompose unreacted sodium borohydride. The mixture was neutralized with dilute hydrochloric acid and the organic materials were extracted with ethyl acetate. The combined extracts were washed with water and dried over magnesium sulfate. The solvent was evaporated to give 210 mg (59%) of **2**, mp 232-234° (from acetone) (lit [3] mp 230°). Spectral data were consistent with those of the literature [3].

7-Methoxy-6-methyl-1-tetralone (**9**).

The method of Bachmann [6] was applied. To 22.4 g (0.108 mole) of **4** was added dry ether (200 ml), ten drops of pyridine, and thionyl chloride (60 ml, 98 g, 0.83 mole) successively. The mixture was stirred for 2 hours at room temperature. Concentration of the mixture *in vacuo* gave the acid chloride of **4**, which was dissolved in dry benzene (300 ml) and then cooled. Stannic chloride (44 ml, 99.5 g, 0.26 mole) was added, and the mixture was stirred for 1 hour at -10.5° and then poured into cooled diluted hydrochloric acid (50 ml of concentrated hydrochloric acid and 100 ml of water). The organic materials were extracted with ether, and the combined extracts were washed with water, aqueous ammonium hydroxide, and water, and dried over magnesium sulfate. After removal of the solvent, the residual oil was distilled to give 16.6 g (81%) of **9**, bp 115-117° (0.2 mm) (lit [7] 125° (0.4 mm)); mp 45-46° (from ethyl acetate); ir (neat): 1675, 1610, 1499, 1337, 1270, 1043 cm^{-1} ; ¹H nmr (deuteriochloroform): δ 2.23 (3H, s, CH₃), 1.8-3.0 (6H, m, CH₂), 3.83 (3H, s, OCH₃), 6.98 (1H, s, C=C-H), 7.43 (1H, s, C=C-H).

2-Bromo-7-methoxy-6-methyltetralone (**10**).

To a solution of **9** (3.21 g, 16.9 mmoles) in dry ether (650 ml) was added dropwise bromine (3.01 g, 23.2 mmoles). The mixture was stirred for 30 minutes and then poured into water. The ethereal layer was washed with saturated sodium bicarbonate and water, and dried over magnesium sulfate. Removal of the solvent gave 4.53 g (100%) of **10**, mp 98-100° (lit [5] 116-117°). Spectral data were consistent with those reported [5].

α -(1,2,3,4-Tetrahydro-7-methoxy-6-methyl-1-oxo-2-naphthyl)propionic Acid (**11**).

To a stirred mixture of dry benzene (37 ml), dry ethanol (2.4 g), and sodium (0.63 g, 28 mmoles) was added dropwise diethyl methylmalonate (7.0 g, 40.3 mmoles). After the sodium was dissolved, a solution of **10** (4.53 g, 16.9 mmoles) in dry benzene (37 ml) was added dropwise during a period of 30 minutes. The mixture was stirred for 12 hours at room temperature and then heated under reflux. After the solvent was evaporated, the residue was heated at 60-70° for 4 hours with a mixture of 45% potassium hydroxide (20 ml) and methanol (24 ml). The neutral portion was removed by the extraction with ether and the aqueous layer was acidified with diluted hydrochloric acid. The organic materials were extracted with ether and the combined extracts were concentrated. The residue was heated at 180° for decarboxylation. The crude product was recrystallized to give 1.72 g (39%) of **11**, mp 150-152°; ir (potassium bromide): 3600-2500, 1700, 1665, 1608, 1497, 1257, 1200, 1038 cm^{-1} ; ¹H nmr (deuteriochloroform): δ 1.15 (3H, d, J = 8 Hz, CH₃), 2.22 (3H, s, CH₃), 1.7-3.3 (6H, m, >CHCH₂CH₂, CHCH₃), 3.82 (3H, s, OCH₃), 7.00 (1H, s, C=C-H), 7.44 (1H, s, C=C-H), 7.81 (1H, br s, CO₂H).

Anal. Calcd. for C₁₅H₁₈O₄: C, 68.69; H, 6.92. Found: C, 68.60; H, 6.81.

α -(1,2,3,4-Tetrahydro-7-hydroxy-6-methyl-1-oxo-2-naphthyl)propionic Acid (**12**).

A mixture of **11** (1.46 g, 5.57 mmoles) and concentrated hydrobromic acid (7 ml) was heated under reflux. The organic materials were extracted with ethyl acetate, and the combined extracts were washed with water and dried over magnesium sulfate. Concentration of the solvent gave 1.24 g (90%) of **12**, mp 217-218° (from benzene); ir (potassium bromide): 3420, 1700, 1653, 1607, 1503, 1251, 1183, 930 cm^{-1} ; ¹H nmr (DMSO-d₆): δ 1.10 (3H, d, J = 7 Hz, CH₃), 2.15 (3H, s, CH₃), 1.8-3.1 (6H, m), 7.00 (1H, s, C=C-H), 7.1 (1H, br s, OH), 7.27 (1H, s, =C-H), 9.4 (1H, br s, CO₂H).

Anal. Calcd. for C₁₄H₁₆O₄: C, 67.73; H, 6.50. Found: C, 67.92; H, 6.65.

α -(1,2,3,4-Tetrahydro-1,7-dihydroxy- α ,6-dimethyl-2-naphthalene)acetic Acid γ -Lactone (**3**).

To a solution of **12** (1.20 g, 4.85 mmoles) in 70 ml of absolute ethanol was added sodium borohydride (1.0 g, 37 mmoles) at 0°. The mixture was stirred for 1 hour at room temperature. Acetone (5 ml) was added and the mixture was acidified with diluted hydrochloric acid. The organic materials were extracted with ethyl acetate and the combined extracts were washed with water, and dried over magnesium sulfate. Concentration of the solvent gave 500 mg (45%) of **3**, mp 200-203°; ir (potassium

bromide): 3460, 1743, 1193, 1107 cm^{-1} ; ^1H nmr (deuteriochloroform/DMSO- d_6 , 1/1): δ 1.16 (3H, d, $J = 7$ Hz, CH_3), 2.18 (3H, s, CH_3), 2.3-3.8 (6H, m), 5.16 (1H, d, $J = 6$ Hz, CHOCO), 6.81 (2H, s, C=C-H), 8.85 (1H, s, OH); ms: 232 (8, M^+), 173 (23), 159 (38), 44 (81), 43 (100).

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_3$: C, 72.39; H, 6.94. Found: C, 72.31; H, 6.82.

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