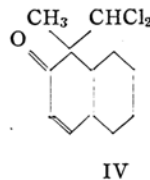
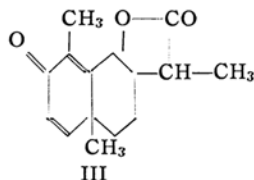
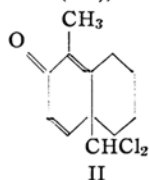
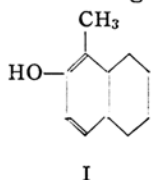


# Studies on Santonin. I. Experiments on the Synthesis of Santonin. Part I. Preparation of 2-Keto-1, 10-dimethyl-decalin

By Masanao MATSUI, Seiichi KITAMURA, Yoshio SUZUKI and  
Michiko HAMURO

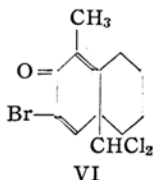
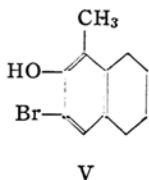
(Received July 22, 1953)

*ac*-Tetrahydro-1-methyl-2-naphthol (I) is easily obtained from  $\beta$ -naphthol through methylene-dinaphthol and 1-methyl-2-naphthol<sup>1,2)</sup>. T. Harukawa and H. Ishikawa<sup>3)</sup> prepared 2, 5, 6, 7, 8, 10-hexahydro-2-oxo-1-methyl-10-dichloro-methyl-naphthalene (II) from *ac*-tetrahydro-1-methyl-2-naphthol by the method analogous to that of Woodward<sup>4)</sup>. We who aimed from this material to prepare the substance resembling santonin (III), checked



We knew therefore that it is difficult to introduce any radical into the hydrobenzene ring of (II).

Then we turned our attention to the starting material, *ac*-tetrahydro-1-methyl-2-naphthol (II) and tried to introduce a double linkage into its hydrobenzene ring. We treated this naphthol with bromosuccinimide to introduce bromine to the 8-position, but this trial also failed. Considering the fact that the substance obtained by this trial was not dehydrobrominated by alkali in the warm, and showing that bromine exists in the benzene ring and from the results of the bromination of other phenols, replacement of the 3-position of (II) was the most probable. The product obtained was considered to be 1-methyl-3-bromo-tetrahydro-2-naphthol (V), which reacted with chloroform in the presence of sodium hydroxide and yielded dichloromethyl-dienone (VI), mp. 153°.

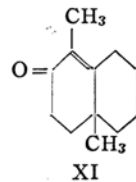
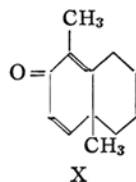
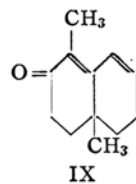
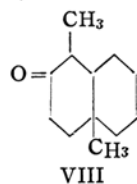
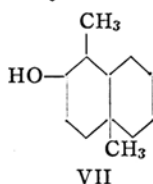


We gave up the first plan and tried to

Harukawa's experiment and obtained the reported substance (II) in a lower yield. However, besides this substance we obtained another dienone melting at 63°, probably expressed by the structure (IV).

The substance (II) was so stable that it did not react with bromine and was hardly oxidized by potassium permanganate or phthalmonoper acid.

prepare 2, 3, 4, 5, 6, 10-hexahydro-2-oxo-1, 10-dimethyl-naphthalene (IX) from dichloromethyl dienone (II) above mentioned.



(II) was hydrogenated in an autoclave with Raney Nickel at room temperature. The temperature gradually rose with the consumption of hydrogen and at the end of hydrogenation reached 80°. One mol. of the sample (II) absorbed about 5 mol. of hydrogen and dimethyl-decahydro-naphthol (VII) was obtained. It is a light yellow oil, boiling at 85-100°/0.5 mm.  $n_D^{18}$  1.5075. 3,5-Dinitrobenzoate was oil which was probably the mixture of stereoisomerides. (VII) was oxidized by chromium trioxide in acetic acid and a ketone, bp. 75-85°/0.5 mm.  $n_D^{18}$  1.4955 was obtained. This ketone is 2-oxo-1, 10-dimethyl-decaline (VIII), because its 2,4-dinitrophenylhydrazone (mp. 186°) was the same as the

1) K. Fries and E. Hubner, *Ber.* 39, 439, 441 (1906).

2) Cornforth, Cornforth and Robinson. *J. Chem. Soc.* 1942, 682.

3) *J. Pharm. Japan*, 70, 338 (1950).

4) Woodward, *J. Am. Chem. Soc.*, 62, 1208 (1940).

one derived from hydrogenation product of 2,3,4,5,6,7,8,10-octahydro-2-oxo-1,10-dimethylnaphthalene (XI) which was prepared from 2-methyl-cyclohexanone and dimethylaminopentanone methiodide by the method of Gunstone and Heggie<sup>5</sup>.

Bromination and dehydrobromination by pyridine yielded liquid unsaturated ketone boiling at 65–85°/0.3 mm.  $n_D^{20}$  1.5145–1.5300, 2,4-dinitrophenylhydrazone melting at 189°. This product was probably the mixture of IX, X and XI. ( $n_D^{20}$  of IX, X and XI are 1.5590–1.5320 and 1.5260 and 2,4-dinitrophenylhydrazones of IX, X and XI melt at 216°, 238–239° and 198–199° respectively<sup>5</sup>).

### Experimental

#### 1. *ac*-Tetrahydro-1-methyl-2-naphthol (I)

$\beta$ -Naphthol condensed with formaldehyde in the presence of sodium acetate in alcohol to give methylene-dinaphthol, mp. 192°, in a theoretical amount. The methylene-dinaphthol was reduced by zinc and sodium hydroxide aqueous solution to 1-methyl-2-naphthol<sup>11</sup>, bp. 160–162°/25 mm., mp. 110° (60%). The naphthol was reduced at 110°/100 atm. p. with hydrogen and Raney nickel in alcohol to give *ac*-tetrahydro-1-methyl-2-naphthol, mp. 113° (82%)<sup>6</sup>.

#### 2. 2, 5, 6, 7, 8, 10-Hexahydro-2-oxo-10-dichloromethyl-naphthalene (II)<sup>2</sup>

(I) (70 g.) was dissolved in 700 g. of 10% sodium hydroxide aqueous solution in a 31 four necked flask. Chloroform (250 g.) and 190 g. of 40% sodium hydroxide aqueous solution were dropped separately but simultaneously from two dropping funnels at 75° during 3 hrs. with stirring which was continued for 45 min. after the addition was over. The cooled mixture was extracted with chloroform (500 cc.) and the extract was washed with 5% sodium hydroxide aqueous solution and then with water. After the evaporation of the solvent, the residue was dissolved in 70 cc. of methanol and the solution was left to stand overnight in a refrigerator. Separated crystals (15 g.) were collected and recrystallized from methanol. 11 g. of (II), mp. 155°, was obtained. (Found: C, 58.70; H, 5.1%; Calcd. for  $C_{12}H_{14}OCl_2$  C, 58.8; H, 5.7%.)

The mother liquor of the crystals was distilled, and the fraction boiling at 150–175°/0.25 mm. was collected (35 g.). It was dissolved in methanol (100 cc.) and cooled by dry ice, to give crystals (11 g.), mp. 57–59°. The sample was treated with ether and 3 g. of insoluble crystals (mp. 155°) were obtained. The ether solution, separated from the crystal was washed with 5% sodium hydroxide aqueous solution several times and with water 3 times. Then the ether was removed and the residue was recrystallized from methanol. The substance melting at 63°, a yellowish large prism, was obtained. This is considered to be 1,2,

5,6,7,8-hexahydro-2-oxo-1-methyl-1-dichloromethylnaphthalene (IV). (Found: C, 59.5; H, 5.0; Cl, 28.3% Calcd for  $C_{12}H_{14}OCl_2$ : C, 58.8; H, 5.7; Cl, 28.7%)

#### 3. *ac*-Tetrahydro-1-methyl-3-bromo-2-naphthol (V)

A mixture of *ac*-tetrahydro-1-methyl-2-naphthol (158 g.), bromosuccinimide (178 g.) and carbon tetrachloride (1 l.) was refluxed for 1 hour. After 100 g. of succinimide were recovered by filtration, carbon tetrachloride was removed. The crystals obtained were recrystallized from petroleum ether (bp. 40–60°), giving 78 g. of (V) mp. 71°, (Found: C, 55.06; H, 5.20; Br, 33.5%, Calcd. for  $C_{11}H_{11}OBr$ : C, 55.2; H, 5.0; Br, 29.2%)

#### 4. 2, 5, 6, 7, 8, 10-Hexahydro-2-oxo-1-methyl-10-dichloromethyl-3-bromo-naphthalene (VI)

The substance (V) (120 g.), 10% sodium hydroxide aqueous solution (1500 g.) and chloroform (280 g.) were treated in the same manner as case 2. and 12 g. of the desired product (VI) mp. 153°, was obtained. (Found: C, 44.2; H, 4.4%; Calcd. for  $C_{12}H_{13}OCl_2Br$ : C, 44.4; H, 4.3%)

#### 5. 2-Hydroxy-1,10-dimethyl-decalin (VII)

A solution of 20 g. of (II) in 200 cc. of 5% potassium hydroxide-methanol solution was hydrogenated with 5 g. of Raney nickel catalyst under an initial pressure of 50 atm. p. in 0.5 l. autoclave at first at 20° and at 80° when hydrogenation was over. Twenty hrs. were required and ca. 10 l. of hydrogen was consumed. The hydrogenated solution, after removing the catalyst, was distilled. The fraction boiling at 85–100°/0.3 mm.,  $n_D^{18}$  1.5075, which was (VII), was collected. The yield was 16.8 g. (Found: C, 78.2; H, 10.4%; Calcd. for  $C_{12}H_{22}O$ : C, 79.1; H, 12.1%.) 3,5-Dinitrobenzoate was an oil. Hence the existence of stereoisomerides is probable.

#### 6. 2-Oxo-1,10-dimethyl-decalin (VIII)

In a solution of (VIII) (32 g.) and 500 cc. of acetic acid, 15 g. of chromium trioxide in 120 cc. of water dissolved in 300 cc. of acetic acid was dropped under stirring at 15°. After the addition, when the required 2 hrs., was over, stirring was continued for 3 hrs. and the reaction mixture was left to stand overnight. Water (1.9 l.) was added and the mixture was extracted with petroleum ether (bp. 40–60°) five times, using each time 200 cc. of the solvent. The extract was combined and washed with water. 2-Oxo-1,10-dimethyl-decalin (VIII) yellowish oil boiling at 75–85°/0.5 mm.,  $n_D^{18}$  1.4955 was obtained, (Gunstone and Heggie reported bp. 76–78°/0.5 mm.,  $n_D^{19}$  1.4945)<sup>5</sup>. 2,4-Dinitrophenylhydrazone melting at 186°, recrystallized from methanol, gave no melting point depression on admixture with the sample (186°) prepared by another method<sup>5</sup>. (Found: C, 60.4; H, 7.0%; Calcd. for  $C_{18}H_{24}O_4N_4$ : C, 60.0; H, 6.7%.)

#### 7. Bromination and Dehydrobromination of (VIII)<sup>5</sup>.

Three g. of 2-oxo-1,10-dimethyl-decalin was dissolved in 100 cc. anhydrous ether and 2.8 g of bromine was dropped under stirring and cooled with ice-water. After decolorization, ether was removed and 10 cc. of pyridine was added. The

5) *J. Chem. Soc.*, 1952, 1441.

6) R.H. Martin and Robert Robinson, *J. Chem. Soc.*, 1943, 491-7.

mixture was refluxed for 2 hrs. An unsaturated ketone (1.1 g.), bp. 65–85°/0.3 mm.,  $n_D^{20}$  1.5145–1.5300, was obtained. 2,4-Dinitrophenylhydrazone, recrystallized from ethanol, was dark red and melted at 189°.

### Summary

2-oxo-1,10-dimethyl-decalin (VIII) was synthesized from (I), according to the following course, (I)→(II)→(VII)→(VIII). The sample obtained was the same as the one derived

from the condensation product of 2-methyl-cyclohexanone and diethylamino-pentanone methiodide.

The writers wish to express their hearty thanks to Dr. Ryo Yamamoto for his stimulating interest in this work, and they are also indebted to Messrs. S. Takai, N. Nishimura, T. Sano and Miss. J. Kigami for the microanalyses.

*Sumitomo Chem. Co. Ltd, Osaka*

---