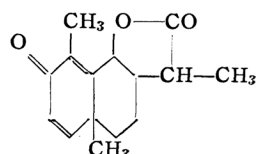


Studies on Santonin. II. Experiments on the Synthesis of Santonin. Part II. Preparation of a Stereoisomeride of Santonin

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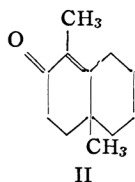
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Since the structure (I) had been established for santonin by Clemo, Ruzicka and others¹⁻⁵⁾ the synthesis of this compound was unsuccessful, despite of the efforts of several investigators^{6,7,8)}. Recently Abe, Harukawa, Ishikawa, Miki, Sumi and Toga in Japan^{9,10)} reported the success of the synthesis of one active and three racemic stereoisomerides of santonin, though the details of the investigations are not published. The present writers have also succeeded independently synthesizing by another route a stereoisomeride of santonin which differs probably from the isomerides obtained by Abe et al.

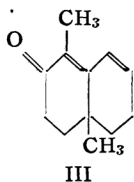


I

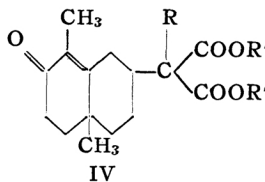
Gunstone and Heggie¹¹⁾ showed the easy way to obtain 2,3,4,5,6,10-hexahydro-2-oxo-1,10-dimethyl-naphthalene (III) through 2,3,4,5,6,7,8,10-octahydro-2-keto-1,10-dimethyl-naphthalene (II) in a moderate yield. The writers found that alkyl malonates condensed with the dienone (III) on the 7-position in the presence of sodium methylate and produced



II



III



IV

2,3,4,5,6,7,8,10-octahydro-2-oxo-7-naphthyl-malonates (IV) in a moderate yield. Malonates generally condense with α,β -unsaturated carbonyl system $C=C-C=O$ at the β -position; the condensation is widely known as

Michael-condensation. But this condensation never occurs with the enone (II), because probably the β -position (9-position of naphthalene) is highly sterically hindered. On the contrary, malonates easily condense with dienone (III) at the δ -position (7-position of naphthalene). The position was confirmed by selenium-dehydrogenation of the compound obtained by hydrogenation of the condensation product of diethyl methylmalonate and (III) the compound obtained by selenium-dehydrogenation was identified with 1-methyl-7-ethyl-naphthalene by the mixed melting point determination of picrate, mp. 94°.

1) Clemo, Haworth, Walton, *J. Chem. Soc.*, **1929**, 2368; *ibid.* **1930**, 1110.

2) Clemo, Haworth, *ibid.* **1930**, 2579.

3) Ruzicka, Eichenberger, *Helv. Chim. Acta.*, **13**, 1117.

4) Tshitschibabin, Schtschukina, *Ber.* **63**, 2793.

5) Wedekind, Tettweiler, *Ber.* **64**, 387; *ibid.* **64**, 1117.

6) Paranjape, Phalnikar, Bhide, Nargund, *Rasayanam* **1**, 233 (1943); *C. A.* **38**, 4266 (1944). (Note: They reported the synthesis of santonin, but none has succeeded to check it.)

7) Gunstone, Heggie, *J. Chem. Soc.*, **1952**, 1354, 1437.

8) Clemo, McQuillin, *ibid.* **1952**, 3835, 3839.

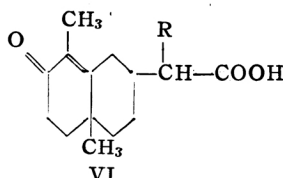
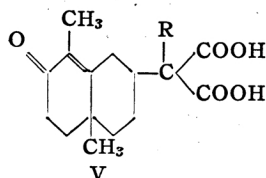
9) *Japan Acad.*, **28**, 425 (1952).

10) *ibid.* **29**, 113 (1953).

11) *J. Chem. Soc.*, **1952**, 1440.

Dicarboxylic acids (V) were obtained by alkaline hydrolysis of esters (IV), and divided into a crystalline substance and a semisolid

oil. Acids (V) were changed by decarboxylation to monocarboxylic acids (VI) which were divided into crystal and semisolid oil.

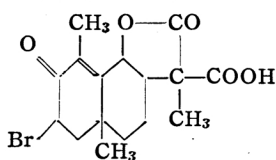


The melting point of (V), (VI) and 2,4-dinitrophenyl-hydrazone was as follows:—

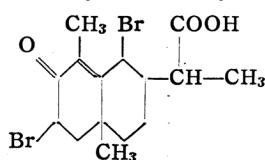
R	System	V	VI	2, 4-dinitro-phenyl-hydrazone
H	A	185°	145°	245°
	B	oil	135°	235°
CH ₃	A	183°	125°	235°
	B	oil?	oil?	?

By bromination, crystalline forms of (V) and (VI) (R=CH₃) yielded bromolactone-carboxylic acid (VII) (mp. 176°) and dibromo-carboxylic

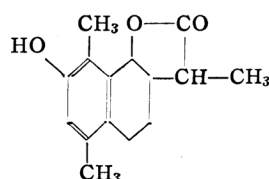
acid (VIII), (mp. 146°) respectively. The constitution of these compounds was proved by analysis and sequent reactions.



VII



VIII



IX

They were dehydrobrominated by heating in an oil bath of about 170° with lutidine (In the case of (VII), decarboxylation also occurred) and produced the same santonin C*, a new isomeride of santonin, melting at 189—190°; $\lambda_{\text{max}}^{\text{EtOH}}$ 245 μ (log ϵ = 4.10). The melting point depressed to 138° when santonin C was admixed with an equal amount of natural santonin. The lactone is stable, never colorizes in the sun light, is easily soluble in chloroform and is able to be recrystallized from alcohol, etc. the attitude for various solvents resembling that of natural santonin.

When santonin C was treated with conc. hydrochloric acid, it yielded (\pm) β -desmotroposantonin (IX), melting at 231°, by dienone-phenol rearrangement, more easily than natural santonin. The desmotropo-santonin was identified by comparing with an authentic sample derived from natural santonin.

Experimental**

1. 2,3,4,5,6,7,8,10-Octahydro-2-oxo-1,10-dimethyl-naphthalene (II).⁽¹⁾

2-Methylcyclohexanone (99 g.), sodamide (18.4 g.) and ether (150 cc.) were stirred for 2–4 hours at

* Since Abe et al. designated their three isomerides, santonin A, B, and D. The writers named our sample santonin C.

** The melting point reported in this paper is uncorrected.

room temperature in a three necked flask protected with calcium chloride tube. (A stream of dry nitrogen is not necessary.) 1-Diethylaminopentan-3-one methiodide (135 g.) dissolved in methanol (50 cc.) was added gradually and stirring was continued for 4 hours. The mixture was left to stand overnight. Next day, the mixture was stirred for 2 hours at boiling point. The solution acidified with dil. hydrochloric acid, was extracted with ether. The ether extract was washed with 10% alkali carbonate solution, then with water, was dried, and the ether was distilled out. Octahydro-oxo-naphthalene (II), 45 g. (57%), thus obtained was light yellow oil, bp. 91–92°/0.5 mm. n_D^{20} 1.5217. 2, 4-dinitrophenylhydrazones was recrystallized from ethylacetate-methanol, scarlet plate: mp. 198–199°. (Found: C, 60.3; H, 6.5; N, 15.4%; Calcd. for C₁₈H₂₂O₄N₄: C, 60.3; H, 6.2; N, 15.6%.)

2. 2,3,4,5,6,10-Hexahydro-2-oxo-1,10-dimethyl-naphthalene (III).⁽¹⁾

Dry powder of N-bromosuccinimide (79 g.) was added to a solution of (II) (79 g.) in carbon tetrachloride (200 cc.) and the mixture was refluxed for 30 minutes after the first vigorous reaction ceased. Remaining succinimide was removed from the cold solution. After the removal of the solvent, the residue was refluxed with pyridine (200 cc.) for 2 hours. Hexahydro-oxo-naphthalene (III) (58 g. 73%), bp. 92–96°/0.25 mm., n_D^{18} 1.5562, was obtained. Semicarbazone melted at 210–212° (from alcohol.)

3. 2,3,4,5,6,7,8,10-Octahydro-2-oxo-1,10-dimethyl-7-naphthyl-malonic acid (V), (R=H).

Diethyl malonate (19 g.) and 10 g. of (III) were added with stirring to a solution of metallic sodium (1.3 g.) in methanol (15 cc.) at room temperature (20°). Stirring was continued for several hours and left to stand for 12–38 hours. The mixture was warmed at 50° with stirring for 2 hours. Acetic acid (5 cc.) was added to the cooled reaction mixture, then water was added, and the mixture was extracted with ether. The ether extract was washed with water and ether was distilled out. The fraction boiling at 160–185°/0.5 mm. (7 g.), which became a semisolid mass, was hydrolysed by refluxing with the solution of potassium hydroxide (7 g.) in aqueous methanol (45 cc.) for 2 hours. The reaction mixture was diluted with water and extracted with ether to remove neutral substances. An oil, alkali soluble, was obtained. It deposited crystals (2.0 g.), which were collected and washed with ether. This crystal is an isomeride of (V) (R=H), mp. 185° (with evolution of CO₂). (Found: C, 64.0; H, 6.8%; Calcd. for C₁₅H₂₀O₅: C, 64.3; H, 7.1%.) The mother liquor contains another isomeride of (V), (R=H).

4. 2,3,4,5,6,7,8,10-Octahydro-2-oxo-1,10-dimethyl-7-naphthyl-acetic acid (R=H).

I) *Acid A*:—The Above mentioned crystalline octahydro-oxo-dimethyl-naphthyl-malonic acid (2.0 g.) was distilled under reduced pressure in an oil bath held at 220°. The whole material distilled at ca. 190°/0.5 mm. and soon crystallized, mp. 144–145° (from ether). (Found: C, 71.2; H, 8.7%; Calcd. for C₁₄H₂₀O₃: C, 71.2; H, 8.5%.) 2,4-dinitrophenylhydrazones were scarlet crystal, mp. 244–245° (from acetic acid and methanol). (Found: C, 57.8; H, 5.6; N, 13.5; Calcd. for C₂₀H₂₄O₆N₄: C, 57.8; H, 5.8; N, 13.5%.)

II) *Acid B*:—Mother liquor of crystalline octahydro-oxo-dimethyl-naphthyl-malonic acid (V) described in 3. was distilled in the same manner as the case of acid A and 2 g. of semisolid mass was obtained. It was dissolved in ether. When the ether solution was concentrated, crystals (1.5 g.) were obtained; mp. 135° (from methanol). (Found: C, 71.5; H, 8.1%; Calcd. for C₁₄H₂₀O₃: C, 71.2; H, 8.5%.) 2,4-dinitrophenyl-hydrazone was scarlet crystal, mp. 235° (from acetic acid and methanol) (Found: C, 56.8; H, 6.5; N, 13.2%; Calcd. for C₂₀H₂₄O₆N₄: C, 57.8; H, 5.8; N, 13.5%).

5. α -(2,3,4,5,6,7,8,10-Octahydro-2-oxo-1,10-dimethyl-7-naphthyl)- α -methyl-malonic acid (V), (R=CH₃).

Diethyl methylmalonate (20 g.), hexahydro-oxo-naphthalene (III) (10 g.), sodium (1.3 g.) and methanol (15 cc.) were used. The processes were the same as in the case of 3. The product, distilled at 170–190°/0.3 mm., 8.5 g. was hydrolysed by using potassium hydroxide (8 g.) and aqueous methanol (80 cc.) From alkali soluble material obtained, crystals (2.8 g.) melting at 181–183° (when quickly heated, under the evolution of CO₂), recrystallized from methanol, were obtained. The weight of mother liquor was 2.8 g. The crystal

is an isomeride of (V), (R=CH₃). (Found: C, 65.8; H, 7.7%; Calcd. for C₁₅H₂₂O₅: C, 65.4; H, 7.5%).

6. α -(2,3,4,5,6,7,8,10-Octahydro-2-oxo-1,10-dimethyl-7-naphthyl) propionic acid (VI) (R=CH₃).

(VI) (R=CH₃) was obtained as a crystal mass by decarboxylation which occurred at distillation of crystalline naphthyl-methyl-malonic acid (V) (R=CH₃) (2.8 g.), bp. 180–185°/0.3 mm. The crystal of naphthyl propionic acid (1.9 g.) melted at 125° after recrystallization from ether. (Found: C, 72.3; H, 9.0%; Calcd. for C₁₅H₂₂O₃: C, 72.0; H, 8.8%.) 2,4-Dinitrophenylhydrazones were scarlet crystal, mp. 234–235° (from ethyl acetate-methanol) (Found: C, 57.2; H, 6.0; N, 13.1%; Calcd. for C₂₁H₂₆O₆N₄: C, 58.7; H, 6.0; N, 13.0%).

Dehydrogenation. Naphthyl-propionic acid mentioned above (1 g.) was hydrogenated in 20 cc. of acetic acid with Adams' platinum oxide (2 mol. of hydrogen was absorbed). The hydrogenated product was treated with selenium (4 g.) at 320° for 18 hours. The neutral product obtained by this treatment was distilled with sodium and converted directly into the picrate, golden yellow needles, mp. 94° (recrystallized from alcohol). Its melting point was underpressed on admixture with 7-ethyl-1-methyl-naphthalene picrate prepared by analogous treatment from natural santonin.

The mother liquor of (V), (R=CH₃) in the case of 5. was also distilled, and semisolid monocarboxylic acid (mixture?) (2 g., after purification by dissolving in potassium carbonate solution) which did not crystallize, was obtained. 2,4-Dinitrophenylhydrazones were obtained in two forms, one scarlet crystal, melted at ca. 220° and one ca. 195°. The one having higher melting point seems to be that of crystalline acid, mp. 125°, above mentioned, but both of them seem not pure. The semisolid carboxylic acid was also dehydrogenated by selenium after hydrogenation and 7-ethyl-1-methyl-naphthalene picrate, mp. 94°, was also obtained.

7. Santonin C

i) Octahydro-oxo-naphthyl-methyl-malonic acid V (R=CH₃), mp. 183°, (5 g.) was dissolved in 50 cc. of acetic acid under slight heating, and bromine (5.5 g.) dissolved in acetic acid (5 cc.) was added gradually. Bromine was soon decolorized and evolution of HBr occurred. The mixture was poured into 100 cc. of ice water. A crystal (2 g.) separated, was collected and washed with ether. It was bromolactone carboxylic acid (VII) mp. 176°. (Found: C, 50.0; H, 5.3%; Calcd. for C₁₆H₂₁O₅Br: C, 51.5; H, 5.6%).

The bromolactone carboxylic acid (2 g.) and lutidine (10 cc.) were heated at 170° in an oil bath for 2 hours. The mixture was poured into ice water and dil. hydrochloric acid was added. The mixture was extracted with ether and the extract was washed with 10% alkali carbonate solution and then with water. The ether solution was concentrated by evaporation. Crystals separated were collected and recrystallized from ethanol with small amount of active carbon. Rhombic plate (0.4 g.) mp. 189–190°, easily soluble in chloroform, was obtained;

$\lambda_{\text{max}}^{\text{EtOH}}$ 245 μ ($\log \epsilon = 4.10$) (Found: C, 73.3; H, 7.2%, Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_3$: C, 73.2; H, 7.3%). It was stable in sun light and never colorized.

ii) Octahydro-oxo-naphthyl-propionic acid (VI), ($\text{R}=\text{CH}_3$), mp. 125° (1.5 g.) was dissolved in chloroform (12 cc.) and bromine (2.0 g.) was added under stirring in the sun light. After decolorization of bromine, dry air was passed through the solution and chloroform was removed together with hydrogen bromide. A small amount of ether was added and crystals (0.8 g) separated were collected and washed with ether. It was (VIII), mp. 145–146°. (Found: C, 44.9; H, 5.3%; Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_3\text{Br}_2$: C, 44.2; H, 4.9%).

The dibromo-compound (0.8 g.) and lutidine (5 cc.) were heated in an oil bath held at 170° for 1 hour and by the same treatment as i), rhombic plate crystal of santonin C, mp. 189–190° (0.1 g.) was obtained.

Santonin C was obtained by the same treatment from crude bromolactone carboxylic acid or dibromocarboxylic acid from which crystals had not been separated.

Mother liquor of naphthyl-methyl-malonic acid and monocarboxylic acid derived from it also yielded santonin C, though the yield was small.

8. Dienone-phenol Rearrangement of Santonin C.

Santonin C (100 mg.) was mixed with 1 cc. of conc. hydrochloric acid. The crystals gradually dissolved and soon different crystals, needles ($(\pm)\beta$ -desmotroposantonin) were deposited. The sample, recrystallized from methanol, mp. 231°, which was undepressed on admixture with authentic (\pm) β -desmotroposantonin obtained from natural santonin. (Found: C, 73.5; H, 7.2%; Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_3$: C, 73.2; H, 7.3%).

Summary

A new isomeride of santonin, santonin C, was synthesized. The route consists of condensation of 2,3,4,5,6,10-hexahydro-2-oxo-1,10-dimethyl-naphthalene and diethyl methylmalonate, hydrolysis, bromination and dehydrobromination by lutidine.

The writers wish to express their grateful acknowledgement to Dr. Ryo Yamamoto for his stimulating interest in this work. They are also indebted to Messrs. S. Takai, N. Nishimura and Miss J. Kigami for the microanalyses and to Messrs. N. Ohi and M. Isaoka for the determination of ultraviolet absorption.

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