Synthesis of β- and γ-Thujaplicins

By Shigeo KATSURA, Tatsuo MOROE and Norio IKEGAMI

(Received March 22, 1957)

Synthesis of α-, β- and γ-thujaplicins were reported by Nozoe[1] in 1950 and by Cook[2] in 1951. These methods were started with the preparation of the three isomers of Isopropylcycloheptanone by cyclization or ring enlargement, followed by oxidation to the dione compounds. Dehydrobromination after bromination afforded isomeric thujaplicins.

The present writers synthesized β-thujaplicins by the following two methods (A) and (B), which are herein described.

In the *A* method, perillaldehyde oxime (I) is used as the starting material and this is converted into tetrahydroperillamine (II) and via 4-isopropylcycloheptanone (IV) to the objective VI. The other *B* method starts with 4-isopropylcyclohexanone (VII) which is submitted to ring enlargement with nitromethane and via 4-isopropylcloheptanone to VI. The route of synthesis in this *A* method is shown in Fig. 1.

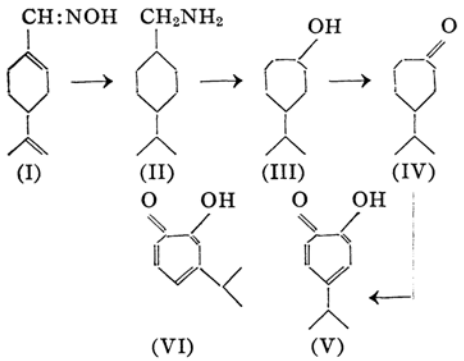

Fig. 1.

In this preparative method, perillartin, the oxime of perillaldehyde, was hydrogenated in ethanolic solution with nickel catalyst at 100°C and 100 atom., for about one hour and tetrahydroperillamine II was obtained in 63% yield. Ring enlargement of II was effected by the method of Ruzicka[3] and of Smith and Baer[4].

We prepared 4-isopropylcycloheptanol (III) in 31% yield by application of nitrous acid to the acetic acid solution of II at 40—50°C and its oxidation by the usual method gave 4-isopropylcycloheptanone (IV) in 50% yield.

Treatment of 4-isopropylcycloheptanone IV by the method of the afore-mentioned Nozoe and Cook, gave a mixture of β- and γ-thujaplicins(V), but the β-isomer was not isolated in pure state and was identified by paper chromatography[5].

The yield by this method of synthesis is 0.4% from the starting material, perillaldoxime, and it cannot be called an advantageous process since in the ring enlargement of perillamine, a fair amount of by-products form besides the objective 4-isopropylcycloheptanol (III), such as tetrahydroperillyl alcohol.

The route of synthesis in the *B* method is shown in Fig. 2.

In this method, the ring enlargement of isopropylcyclohexanone was effected by the nitromethane method of Dauben et al.[6]. The synthesis of thujaplicins from 4-isopropylcyclohexanone VII has not been made by this method as yet. The yield of

1) T. Nozoe, S. Seto and K. Kikuchi, *Proc. Japan Acad.*, **26**, 43 (1950); T. Nozoe, Y. Kitahara and S. Ito, ibid., **26**, 47, (1950); T. Nozoe, S. Seto, K. Kikuchi and H. Takeda, ibid., **27**, 146 (1951).

2) J. W. Cook, R. A. Raphael and A. I. Scott, *J. Chem. Soc.*, **1951** 695.

3) L. Ruzicka and W. Burgger, *Helv. Chim. Acta*, **9**, 399 (1926).

4) P. A. S. Smith and D. R. Baer, *J. Am. Chem. Soc.*, **74**, 6135 (1952).

5) E. Zavarin and A. B. Anderson, *J. Org. Chem.*, **21**, 332 (1956).

6) H. J. Dauben Jr., H. J. Ringold, R. H. Wade and A. G. Anderson, *J. Am. Chem. Soc.*, **73** 2359 (1951).

TABLE I
Rf VALUE OF THUJAPLICINS

Mobile Phase	Stationary Phase (% H_3PO_4)	β-Thujaplicin from Taiwan Hinoki)	γ-Thujaplicin (synthetic)	β- and γ-Thujaplicin mixture	
Ligroine-toluene (3 : 1)	17	0.45	0.32	0.44	0.32

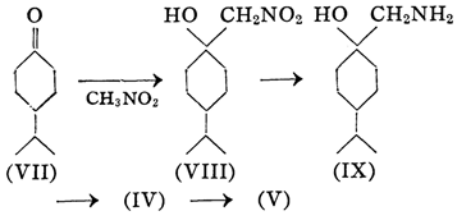

Fig. 2.

IV from VII is about 23.7% and further examination seems required as a synthetic method for thujaplicins. Derivation of IV to thujaplicins followed the same route as in A method. The starting material, 4-isopropylcyclohexanone VII was obtained according to the method described by Frank and Berry[7].

Experimental

Tetrahydroperillamine (II).—A mixture of 33 g. of perillartin (I) in 66 cc. of ethanol was submitted to hydrogenation with Raney nickel as a catalyst, at 100°C and 100 atm.. The catalyst was filtered off, ethanol was distilled off from the filtrate, and the residue was distilled under a reduced pressure, affording 21 g. of II, b. $p._{18}$ 100—115°C n_D^{21} 1.4772

4-Isopropylcycloheptanol (III).—A solution of 21 g. of II, 8.5 g. of glacial acetic acid, and 70 cc. of water was warmed to 40—50°C, and a solution of sodium nitrite in 20 cc. of water was added dropwise during thirty minutes. After stirring this mixture for thirty minutes at this temperature, the oily layer was separated and submitted to steam distillation. The oily distillate was distilled under a reduced pressure. B. $p._{12}$ 95—110°C, yield of III 6.5 g. (31%) n_D^{22} 1.4735.

4-Isopropylcycloheptanone (IV).—A mixture of 6.5 g. of III, 4.5 g. of potassium dichromate, 11 g. of 50% sulfuric acid and 10 g. of benzene was heated for thirty minutes at 50—60°C to effect oxidation and 3.3 g. (50%) of IV was obtained as an oil of b. $p._{15}$ 105—115°C. n_D^{22} 1.4689.

Semicarbazone: m. p. 153-4°C.

Anal. Found: C, 62.59; H, 9.62; N, 19.89%. Calcd. for $C_{11}H_{21}ON_3$: C, 62.6; H, 9.95; N, 19.9%.

Sodium Salt of Bromo-β- and -γ-thujaplicins.—To heated solution of 12 g. of IV dissolved in 25 cc. of dehydrated ethanol, a solution of 10.5 g. of selenium dioxide dissolved in 60 cc. of dehydrated ethanol was added dropwise during two hours and the mixture was stirred at the same temperature for five hours. After standing this over night, the precipitated selenium was filtered off, the filtrate was steam distilled, and the oily residue was extracted with benzene. The benzene extract was washed with water, dried, and benzene distilled off. The residue was distilled under a reduced pressure and 9.5 g. (79%) of a mixture of the diones, b. $p._{16}$ 130—140°C, was obtained. n_D^{25} 1.4730.

A solution of 15 g. of the foregoing dione mixture dissolved in 0.5 cc. of acetic anhydride and 4.5 cc. of glacial acetic acid was chilled to 0°C to 10°C and a solution of 29 g. of bromine in 3 cc. of gracial acetic acid was added dropwise during four hours. The mixture was stirred at this temperature for 1.5 hours, allowed to stand over night (during which a vigorous evolution of hydrogen bromide was observed), and further stirred for four hours while gradually raising the temperature of the reaction mixture to 60°C. The mixture was then submitted to steam distillation, the residual oil was extracted with ether, and a solid substance was filtered off. To this ether extract, 100 cc. of 10% sodium hydroxide solution was added, the crystals that separated out were collected by filtration, and dried, affording 13 g. (86%) of a mixture of sodium salts of bromo-β- and -γ-thujaplicins.

β- and γ-Thujaplicins.—Catalytic reduction of 13 g. of the sodium salt mixture of bromo-β- and γ-thujaplicins in ethanol, with $Pd(OH)_2$—$CaCO_3$ catalyst, was carried out. After filtration of the catalyst, ethanol was removed by low-pressure distillation and about 10 g. of a solid thus obtained was extracted with toluene. The toluene solution was extracted with phosphoric acid, the acid extract was decomposed with water, and further extracted with toluene. After washing with water and drying, toluene was distilled off and the residue was distilled under a reduced pressure. The oily distillate crystallized and was purified from petroleum ether to 50 mg. of γ-thujaplicin, m. p. 78°C. From this mother liquor, 800 mg. of a mixture of β- and γ-thujaplicin was obtained.

Results of paper chromatography of this mixture was as shown in Table I.

1-Nitromethyl-4-isopropyl-1-cyclohexanol (VIII).—A mixture of 150 g. of 4-isopropylcyclohexanone VII (b. $p._{14}$ 90—95°C, n_D^{21} 1.4570. Semicarbazone, m.p. 186—187°C) and 110 g. of nitromethane was added dropwise during 2.5 hours into sodium alkoxide (prepared from 27 g. of metallic sodium and 750 cc. of dehydrated ethanol) while being stirred at 40—43°C and a mixture was stirred for further nine hours at the same temperature. When cooled, the reaction mixture was cooled in

7) R. L. Frank, R. E. Berry and O. L. Shotwell, ibid., **71**, 3889 (1949).

ice, the reaction product was collected by filtration, and dried. About 400 g. of this sodium salt was placed in a three-necked flask, the flask was chilled in ice, and a thoroughly chilled solution of 142 g. of glacial acetic acid in 1200 cc. of water was added under stirring. After stirring this mixture for further thirty minutes (crystals precipitated out during chilling), this was neutralized and an oily layer was separated. The aqueous solution was extracted with ether, the ether extract was combined with the oily layer, dried, and ether distilled off. The residue was distilled off. The residue was distilled under a reduced pressure and 140 g. (93.9%) of VIII, b. $p._{15}$ 145—8°C was obtained. m. p. 56—58°C, n_D^{20} 1.4786.

Anal. Found: C, 60.58; H, 9.20; N, 7.04%. Calcd. for $C_{19}H_{19}O_3N$: C, 59.7; H, 9.45; N, 6.97%.

From the mother liquor of the sodium salt, 16 g. of the starting material VII was recovered.

1-Aminomethyl-4-isopropyl-1-cyclohexanol Acetate.—Using a stainless steel autoclave of 300-cc. capacity, 41 g. of VIII in 82 cc. of glacial acetic acid was hydrogenated with Raney nickel catalyst, cooling the autoclave at first, gradually warming to the room temperature, and hydrogenated at 30°±2°C for seven hours (absorption of hydrogen, 10.2 l.). After removal of the catalyst by filtration, the solvent was distilled off under a reduced pressure, and the residual oil was cooled with addition of a small amount of ether by which the oil solidified into crystals. The crystals were collected by filtration, the filtrate was diluted with water, and extracted with ether. The aqueous solution was concentrated to a small volume and the foregoing procedure was repeated, isolating a further crop of crystals, m. p. 119—125°C. Total yield of acetate, 38 g. (90%).

About 3 g. of 4-isopropylcyclohexanone VII was obtained from the ether extract, its semicarbazone, m. p. 185—7°C, did not show any melting point depression on admixture with semicarbazone of VII.

4-Isopropylcycloheptanone (IV).—A solution of 50 g. of 1-aminomethyl-4-isopropyl-1-cyclohexanol acetate dissolved in 32 g. of glacial acetic acid was diluted with 52 cc. of water, chilled to 0°C, and 60 g. of sodium nitrite solution was added dropwise during two hours (vigorous effervescence). After stirring for one hour at the same temperature, the reaction mixture was allowed to stand over night, neutralized with sodium bicarbonate, and an oily layer was separated. The oil was steam distilled and the oily distillate was distilled under a reduced pressure, affording 20 g. of a fraction of b. $p._{17}$ 90—112°C. This was purified through the semicarbazone and decomposed with oxalic acid, b. $p._{17}$ 108—110°C. Yield 14 g. (28%). n_D^{26} 1.4625. Semicarbazone, m. p. 144—5°C.

Anal. Found: C, 62.75; H, 9.95; N, 20.50%. Calcd. for $C_{11}H_{21}ON_3$: C, 62.6; H, 9.95; N, 19.9%).

The infrared spectrum of IV exhibited an absorption of C=0 at 1694 cm^{-1}.

Summary

β- and γ-Thujaplicins were synthesized through 4-isopropylcycloheptanone from perillaldehyde and 4-isopropylcyclohexanone.

Research Laboratory Takasago Perfumery Co., Ltd. Kamata, Tokyo