

The Chemistry of the Natural Order *Cupressales*

IX*. The Synthesis of Hexahydrothujic Acid

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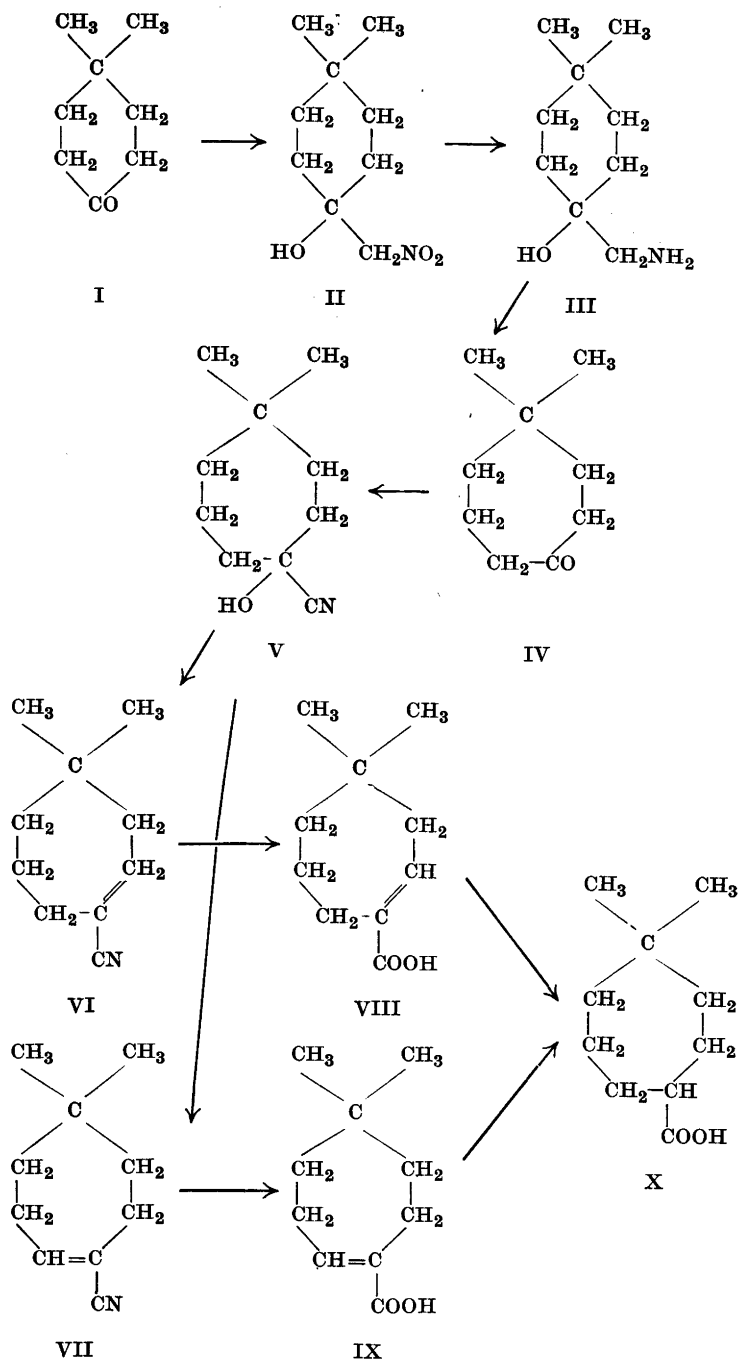
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In a previous communication¹ the partial synthesis of thujic acid from hexahydrothujic acid was reported. In order to complete the total synthesis of thujic acid the synthesis of hexahydrothujic acid remained to be carried out. This has now been done and forms the subject of the present paper.

A convenient way of obtaining the starting material for this synthesis *viz.* 4,4-dimethylcyclohexanone, has been described by Miller and Adams² who obtained it by catalytic hydrogenation of 4-methyl-4-dichloromethylcyclohexa-2,5-dienone and oxidation of the 4,4-dimethylcyclohexanol obtained. The drawback of this method is the low yield obtained in the preparation of 4-methyl-4-dichloromethylcyclohexa-2,5-dienone as described by Auwers and Keil.³ We therefore investigated the hydrogenation of the more readily obtainable 4-methyl-4-trichloromethylcyclohexa-2,5-dienone⁴. However, in spite of several experiments with different catalysts under different conditions the desired material could not be obtained, and the reduction products always contained chlorine. These were not studied further, and this approach was abandoned, in favour of the original method of Miller and Adams².

The 4,4-dimethylcyclohexanone (I) was next converted into 4,4-dimethylcycloheptanone (IV). This was first carried out by diazomethane ring enlargement⁵, but this method gave only a poor yield of the desired ketone and the method described by Dauben Jr., Ringold, Wade and Anderson Jr.⁶ proved much more satisfactory. (The author wishes to express his thanks to Dr. Anderson for placing the information contained in this paper to his disposal prior to publication). This method, with slight modifications, gave a reasonable yield of 4,4-dimethylcycloheptanone (IV). This compound has been

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obtained as a degradation product of thujic acid ⁷ and comparison of the semicarbazones and bis-*p*-nitrobenzylidene derivatives established the identity of the two ketones.

The 4,4-dimethylcycloheptanone (IV) was converted via the cyanohydrin (V) and the unsaturated nitrile (presumably a mixture of VI and VII) into the unsaturated acid, which evidently was a mixture of (IX) and (X). These acids are the same as those obtained from hexahydrothujic acid and in view of the difficulty of separating them ¹, the mixture was hydrogenated directly to 4,4-dimethylcycloheptanecarboxylic acid (X), a liquid which was characterised as its *p*-bromophenacyl ester and amide. These derivatives were identical (mixed m.p.) with the corresponding derivatives of hexahydrothujic acid obtained by the hydrogenation of thujic acid. The reactions used in this synthesis are outlined in the chart on p. 855.

These reactions thus complete the total synthesis of thujic acid.

EXPERIMENTAL

4,4-Dimethyl-1-nitromethylcyclohexanol (II). A mixture of dimethylcyclohexanone (8.4 g) and nitromethane (6.5 g) was added dropwise to a stirred solution of sodium (1.55 g) in absolute alcohol (35 ml). The temperature rose gradually to 40° and a thick white precipitate formed. Stirring was continued for an additional 4 hours. The mixture was cooled and the precipitate, collected by filtration, was dried on a porous plate and treated, with cooling, with acetic acid (5 g) in water (35 ml). The oil which separated was taken up in ether, and the ether solution was washed with a saturated salt solution, dried, and evaporated. The residue distilled as a thick colourless oil. (Found: C, 57.7; H, 8.9; C₉H₁₇O₃N requires C, 57.7; H, 9.2 %.)

4,4-Dimethylcycloheptanone (IV). *4,4-Dimethyl-1-nitromethylcyclohexanol* (9 g) was dissolved in acetic acid (50 ml) and hydrogenated at 2 atm. pressure in the presence of Raney-nickel catalyst. The mixture was warmed to about 30°, to start the reaction and this temperature was maintained until 3.2 l of hydrogen had been absorbed (theoretical 3.3 l). Most of the acetic acid was evaporated under reduced pressure and water (60 ml) was added. The clear stirred solution of the acetate of *4,4-dimethyl-1-aminomethylcyclohexanol* (III) was treated at -5° with sodium nitrite (6.5 g) dissolved in water (20 ml). Stirring was continued until evolution of nitrogen had ceased, and the mixture was set aside over night and then steam distilled. The product which distilled was taken up in ether and treated with a saturated solution of sodium bisulphite. The bisulphite compound was decomposed with sodium hydrogen carbonate and the oil thus obtained distilled, giving *4,4-dimethylcycloheptanone* as a colourless oil (2.3 g; 35 %). b.p. 69–72°/7 mm (Found: C, 76.9; H, 11.7; C₉H₁₆O requires C, 77.1; H, 11.5 %).

4,4-Dimethylcycloheptanone was characterised as its semicarbazone, m.p. 173–174° and bis-*p*-nitrobenzylidene derivative, m.p. 158–160°, both of which were identical (mixed m.p.) with the corresponding derivatives obtained by degradation of thujic acid ⁷.

4,4- and 5,5-Dimethylcycloheptenyl cyanides (VI and VII). A mixture of *4,4-dimethylcycloheptanone* (2.0 g), sodium bisulphite (3.0 g) and water (5 ml) was stirred until it formed a thick mass. Thereafter a solution of potassium cyanide (1.5 g) in water (3 ml) was

added dropwise and the stirring was continued for a further 4 hours. The 4,4-dimethylcycloheptanone cyanohydrin thus formed was extracted with ether, and the ether solution was washed with dilute hydrochloric acid and evaporated. The residual oil, without further purification, was dissolved in pyridine (2 ml) and thionyl chloride (1.5 ml) was added. The mixture turned brown and heat was evolved. The following morning the excess of thionyl chloride was evaporated under reduced pressure and the residue was poured into water. The aqueous solution was extracted with ether and the ether solution was washed with hydrochloric acid and sodium bicarbonate and evaporated, yielding an oil which distilled at 92–104°/8 mm (yield 1.1 g). In view of the large boiling interval and the analysis (Found: C, 78.4; H, 9.9; $C_{10}H_{15}N$ requires C, 80.5; H, 10.2 %), this material was apparently not quite pure and apparently contained some unreacted 4,4-dimethylcycloheptanone cyanohydrin.

4,4- and 5,5-Dimethylcycloheptene carboxylic acids (VIII and IX). The crude unsaturated cyanide obtained above (1.0 g) was boiled with sodium hydroxide (2.0 g) in water (4 ml) and alcohol (10 ml) until no more ammonia was evolved (48 hours). The alcohol was distilled off and water was added to the residue. The oily acid which precipitated on acidification was taken up in ether, and the ether solution was extracted with sodium carbonate solution. The acid recovered from the sodium carbonate solution was still an oil and was distilled in vacuum giving 0.4 g of an oil that rapidly solidified, m.p. 45–55°. No attempt was made to separate the isomerides. (Found: C, 71.0; H, 9.6; $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.6 %.)

4,4-Dimethylcycloheptanecarboxylic acid (X). The mixture of 4,4- and 5,5-dimethylcycloheptanecarboxylic acids (0.4 g) dissolved in alcohol was hydrogenated in the presence of a PtO_2 -catalyst (30 mg). The uptake of hydrogen amounted to 51 ml (calc. 53 ml). The catalyst was removed and the alcohol was evaporated, giving 4,4-dimethylcycloheptanecarboxylic acid as a colourless oil. The substance was characterised as its p-bromophenacyl ester and amide. The former was first obtained as long needles, m.p. 69–70°, but after recrystallisation from dilute methanol formed leaflets, m.p. 66–67°. (Found: C, 58.8; H, 6.3; $C_{18}H_{23}O_3Br$ requires C, 58.5; H, 6.3 %.) The same dimorphism is observed with the p-bromophenacyl ester of hexahydrothujic acid⁷ and the mixed m.p. was not depressed. The amide was obtained as leaflets, m.p. 146–147°. (Found: C, 71.2; H, 11.2; $C_{10}H_{19}ON$ requires C, 70.9; H, 11.3 %) undepressed in admixture with the amide of hexahydrothujic acid, m.p. 146.5–147.5⁷.

SUMMARY

The synthesis of 4,4-dimethylcycloheptanecarboxylic acid (hexahydrothujic acid) is described. This synthesis completes the total synthesis of thujic acid.

The analyses were carried out by Mr. J. Hukki of this Department.

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