Synthesis of *dl*-aleprylic acid

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ABSTRACT *dl*-Aleprylic acid [7-(cyclopent-2′-en-1′-yl)-heptanoic acid], a natural constituent of chaulmoogra oil with reputed antileprosy properties, has been synthesized. Electrolysis of a mixture of (cyclopent-2′-en-1′-yl)-acetic acid and methyl monoester of heptanedioic acid in methanol yielded, after saponification of the reaction products, the racemic mixture.

SUPPLEMENTARY KEY WORDS Kolbe reaction · cross coupling · cyclopent-2-enyl fatty acid

ALEPRYLIC ACID, 7-(cyclopent-2′-en-1′-yl)-heptanoic acid, is a minor component of the seed oil of the tropical plant *Hydnocarpus wightiana* Blume, which belongs to the family Flacourtiaceae (1, 2). Its homologues, *d*-chaulmoogric and *d*-aleprestic acids, were previously synthesized by the Kolbe electrolytic reaction, and their stereochemistry has been discussed (3, 4).

This paper deals with the first synthesis of racemic aleprylic acid by a similar procedure. Electrolysis in methanol of a mixture of 2-(cyclopent-2′-en-1′-yl)-acetic acid and the monomethyl ester of heptanedioic acid gave the desired acid as an unsymmetrical coupling product. The anode was often covered with polymerized products, and a reversal of electrodes was sometimes necessary.

After the reaction the acidic fraction was purified by fractional distillation and recrystallization to give pure *dl*-aleprylic acid (mp 32.0°C).

The melting point of the synthesized *dl*-acid was identical with that of the naturally occurring *d*-isomer, and the IR spectrum and elemental analysis of the *dl*-acid also supported the structure of aleprylic acid. This acid oxidizes gradually on standing in air.

1,2-di-(cyclopent-2′-en-1′-yl)-ethane, one of the symmetrical coupling products, could not be isolated from this reaction; this agrees with Wladislaw's observation (4).

METHODS

Apparatus for Electrolysis

The cell was a flat-bottomed cylindrical glass vessel (3.5 cm in diameter and 18.8 cm high) which had a ground glass cover with holes for venting and accommodating the electrodes. Two platinum plates (2 cm square) were placed parallel to each other about 2 mm apart. The current was taken from a DC power supply through a rheostat and an ammeter. The vessel was maintained at 40–50°C by immersion in an ice bath. The current was applied until the cell contents became slightly alkaline.

Synthesis

A mixture of 6.4 g (0.05 mole) of 2-(cyclopent-2′-en-1′-yl)-acetic acid (K & K Laboratories Inc., Plainview, New York; shown to be 98% pure by gas–liquid chromatography) and 8.7 g (0.05 mole) of methyl hydrogen heptanedioate was electrolyzed for 9.5 hr in 50 ml of methanol containing 70 mg of sodium metal, with an average current of 0.4–0.6 amp. The cell contents were diluted with 50 ml of water and extracted twice with 60 ml of ether. The ether extract was washed twice with 20 ml of water and dried over anhydrous calcium chloride. After evaporation of the solvent, the residual oil (11.7 g) was hydrolyzed by refluxing with 100 ml of 10% ethanolic KOH for 3 hr under a stream of nitrogen. After removal of a large part of the ethanol on a water-bath, the hydrolysate was extracted with 20 ml of pentane to remove the neutral fraction. The aqueous phase was acidified by the addition of an excess of 36% hydrochloric acid and extracted twice with 60 ml of ether to obtain the acidic fraction. The neutral fraction consisted of 0.1 g of a mixture of oils whose composition was not deter-

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mined. The acidic fraction was treated with 40 ml of cold petroleum ether (bp 36.5–53.5°C). The petroleum ether-insoluble fraction consisted of 3.2 g of a white powder, probably crude 1,10-decanedioic acid.

The petroleum ether-soluble fraction weighed 4.4 g. Distillation of this fraction gave 1.6 g of a yellow liquid (yield, 16.1% based on the monobasic acid), bp 158–164°C/2 mm Hg.

The liquid solidified at room temperature, and it was recrystallized from acetone to give white crystals melting at 31.5°C. However, the elemental analysis (found: C, 72.27; H, 10.10) indicated that the product was not entirely pure. This product was then converted into the S-benzylthiouronium salt. The salt was recrystallized from 25 ml of 95% C_2H_5OH to give 0.2 g of white needles, mp 148–149.0°C.

Analysis: $C_{20}H_{30}O_2N_2S$(362.46);
calculated: C, 66.27; H, 8.34; N, 7.73
found: C, 66.28; H, 8.11; N, 7.93

After decomposition of the salt with three times the theoretical amount of 10% hydrochloric acid, the desired acid was purified by recrystallization from acetone at low temperature. The acid melted at 32.0°C.

Analysis: $C_{12}H_{20}O_2$(196.28);
calculated: C, 73.43; H,10.27
found: C, 73.18; H, 10.29

The IR spectrum of the acid showed bands at 3100 (=C-H), 2600 (OH), 1715 (C=O), 1610 (CH=CH), and 720 (—$(CH_2)_6$—) cm^{-1}.

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