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Abstract

Full Text

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SYNTHESIS OF DIHYDROAMBRETTOLIDE

Macrocyclic lactones of composition C_{14}—C_{17} possess an odor valuable for perfumery, having a musky character. The synthesis of lactones of this kind is associated with considerable difficulties, both in obtaining the starting ω-hydroxy acids and in their lactonization. At present, the best-developed method for the synthesis of ω-hydroxy acids is the electrolysis of salts of monoethyl esters of dicarboxylic acids, followed by conversion of one of the carbethoxy groups of the resulting ester into a hydroxymethyl or hydroxy group. In this way, 16-hydroxyhexadecanoic acid was obtained from azelaic acid (^{1}), and 17-hydroxyheptadecanoic acid from sebacic acid (^{2}). In the manufacture of thibetolide, 15-hydroxypentadecanoic acid is obtained by condensation of 11-acetoxyundecanoic acid with the monoester of adipic acid (^{3}). In recent years, a method has been developed for obtaining ω-hydroxy acids on the basis of $\alpha, \alpha, \alpha, \omega$-tetrachloroalkanes (^{4}). In the present work a new route is proposed for the synthesis of macrocyclic lactones, which in a number of cases may prove more convenient than existing ones. In obtaining macrocyclic lactones by this route, cyclic ketones and unsaturated alcohols are used as starting substances. An example is the synthesis of dihydroambrettolide (hexadecanolide) from cyclopentanone and undecenol acetate, carried out according to the following scheme.

$$\text{(I)} \quad \text{cyclopentanone} + \mathrm{CH_2{=}CH(CH_2)_8{-}CH_2OCOCH_3} \ \text{(II)} \longrightarrow$$

$$\text{(III)} \quad \text{2-}[\mathrm{(CH_2)_{10}{-}CH_2OCOCH_3}]\text{cyclopentanone} \xrightarrow{\mathrm{CrO_3}} \mathrm{HOOC{-}(CH_2)_3{-}C({=}O){-}(CH_2)_{10}{-}CH_2OH} \quad \text{(IV)}$$

$$\xrightarrow{\mathrm{Zn+HCl}} \mathrm{HOOC{-}(CH_2)_{14}{-}CH_2OH} \quad \text{(V)} \longrightarrow \mathrm{CH_2{-}(CH_2)_{14}{-}C({=}O){-}O} \quad \text{(VI)}$$

The addition reaction of cyclopentanone to undecenol acetate (II) is initiated by tert-butyl peroxide and proceeds by a radical mechanism. Oxidation of the 1:1 adduct (III) with chromic anhydride in acetic acid and subsequent hydrolysis of the reaction products leads to the formation of 5-keto-16-hydroxyhexadecanoic acid (IV) in a yield of $\sim$ 55%. Reduction of this acid gave 16-hydroxyhexadecanoic acid (V), and from the latter, dihydroambrettolide (VI). Lactonization of the hydroxy acid was carried out by thermal depolymerization of its polyester in a glycerol medium according to the known procedure (^{3}). By the same procedure, 5-ketohexadecanolide was obtained from 5-keto-16-hydroxyhexadecanoic acid.

Experimental Part

Undecen-1-ol-11 was obtained in a yield of ~ 95% by reduction of the methyl ester of undecylenic acid with metallic sodium in boiling butyl alcohol. Undecen-1-ol-11 acetate (b.p. 95—100°/2 mm, d_4^{20} 0.8786, n_D^{20} 1.4392) was prepared in the usual manner from the alcohol and acetic anhydride.

11-(2′-Ketocyclopentyl)undecyl acetate. The reaction was carried out according to the previously described procedure (^{5}). To 336 g (4 moles) of cyclopen-

at 128-130° over 6 h, a solution of 106.2 g (0.5 mole) of undec-1-en-11-ol acetate and 14.6 g (0.1 mole) of tert-butyl peroxide in 84 g (1 mole) of cyclopentanone was added. The reaction mixture was heated for another two hours, after which distillation gave the peroxide-decomposition products, 377 g of cyclopentanone, 18.5 g of unreacted acetate, and 100 g of 11-(2′-ketocyclopentyl)undecyl acetate, b.p. 168°/1 mm, n_D^{20} 1.4622, d_4^{20} 0.9576, MR 85.14; calculated 85.20. Yield of the 1 : 1 adduct: 67.3% based on the amount taken and 81.5% based on the acetate that entered into reaction. High-boiling residue, 25 g.

5-Keto-16-oxyhexadecanoic acid. To a solution of 98.5 g (0.33 mole) of 11-(2′-ketocyclopentyl)undecyl acetate in 100 ml of acetic acid, with stirring for 15 min at 50°, was added a solution of 55 g (0.55 mole) of chromic anhydride in 400 ml of acetic acid and 10 ml of water. The reaction mass was stirred for another 2 h at 45-50°, after which, to reduce the unreacted chromic anhydride, 50 ml of ethanol was added. After evaporation on a rotary evaporator to a weight of 300 g, the reaction mixture was heated for 3 h at 100° with 625 g of 36% KOH solution, diluted with water, neutralized with conc. hydrochloric acid, and repeatedly extracted with hot benzene. After cooling, 48.7 g of 5-keto-16-oxyhexadecanoic acid was isolated from the benzene solution. The mother liquor was evaporated, the residue dissolved in alcoholic alkali, diluted 1 : 1 with water, and extracted with benzene. From the benzene solution, 17.7 g (0.07 mole) of 11-(2′-ketocyclopentyl)undecanol (m.p. 37.5°) was isolated by distillation, and from the aqueous-alcoholic solution 4 g of 5-keto-16-oxyhexadecanoic acid; the total yield of the latter was 52 g (54.8% based on the amount taken, 68.2% based on the acetate that entered into reaction), m.p. 101°, acid number 195.7; calculated 195.9.

Found, %: C 66.78, 66.77; H 10.44, 10.90
$C_{17}H_{30}O_4$. Calculated, %: C 67.10; H 10.56

16-Oxyhexadecanoic acid. A mixture consisting of 44.1 g (0.154 mole) of 5-keto-16-oxyhexadecanoic acid, 100 ml of water, and 125 ml of conc. hydrochloric acid was boiled for 20 h with 150 g of granulated amalgamated zinc. During boiling, an additional 250 ml of conc. hydrochloric acid was added to the reaction mixture (in 50-ml portions). 40.4 g of crude oxy acid was obtained, which, after boiling with alcoholic alkali and subsequent acidification, had m.p. 94.5-95° (from benzene), acid number 210.7; calculated 206.

Literature data (3): m.p. 94°.

Hexadecanolide. 17.4 g (0.064 mole) of 16-oxyhexadecanoic acid was slowly heated in vacuo to 215° and then kept at this temperature for 1.5 h. As a result, a polyester with m.p. 84° was obtained. To the polyester were added 1.7 g of the dipotassium salt of sebacic acid and 40 ml of glycerol. The resulting mass was heated at 180–200° in a three-necked flask with a Claisen head at 1–3 mm residual pressure. The lactone formed was slowly distilled off with glycerol, while new portions of glycerol were continuously introduced into the flask. In all, 11.9 g of crude hexadecanolide was obtained (yield 73%), m.p. 33.5–33.8° after recrystallization from 80% ethyl alcohol. Literature data (3): m.p. 33°.

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Note: Figure translations are in progress. See original paper for figures.