DIOL LIPIDS

XIII. Synthesis of Coixenolide, a Diol Lipid from the Seeds of Coix Lachryma

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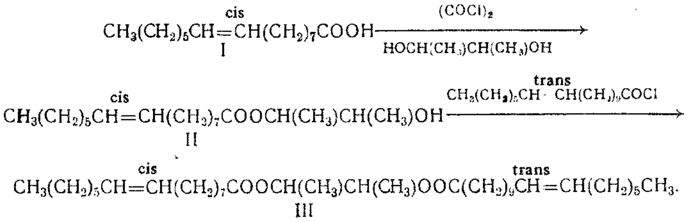
Khimiya Prirodnykh Soedinenii, Vol. 6, No. 2, pp. 170–173, 1970

UDC 547.915+665.3

Neutral diol lipids are widely distributed in nature and are minor components of a number of fats and oils [1]. At present, only two compounds of this type have been isolated from natural sources: ethylene glycol dipalmitate from the lipids of regenerating rat liver [2] and coixenolide, the mixed ester of meso-butane-2, 3-diol with palmitoleic and trans vaccenic acids from the seeds of the far-eastern plant Coix lachryma Jobi L. var. Ma-yuen [3, 4].

Coixenolide attracts attention not only as a representative of a new class of lipids, but also because, according to Japanese workers, it possesses antitumoral activity [4]. In this communication we describe a total synthesis of this compound by the following route:



$$\underset{\mathrm{I}}{CH_3(CH_2)_5CH\overset{\mathrm{cis}}{=}CH(CH_2)_7COOH} \xrightarrow[HOCH(CH_3)CH(CH_3)OH]{(COCl)_2}$$

$$\underset{\mathrm{II}}{CH_3(CH_2)_5CH\overset{\mathrm{cis}}{=}CH(CH_2)_7COOCH(CH_3)CH(CH_3)OH} \xrightarrow{CH_3(CH_2)_5CH\overset{\mathrm{trans}}{=}CH(CH_2)_9COCl}$$

$$\underset{\mathrm{III}}{CH_3(CH_2)_5CH\overset{\mathrm{cis}}{=}CH(CH_2)_7COOCH(CH_3)CH(CH_3)OOC(CH_2)_9CH\overset{\mathrm{trans}}{=}CH(CH_2)_5CH_3}.$$

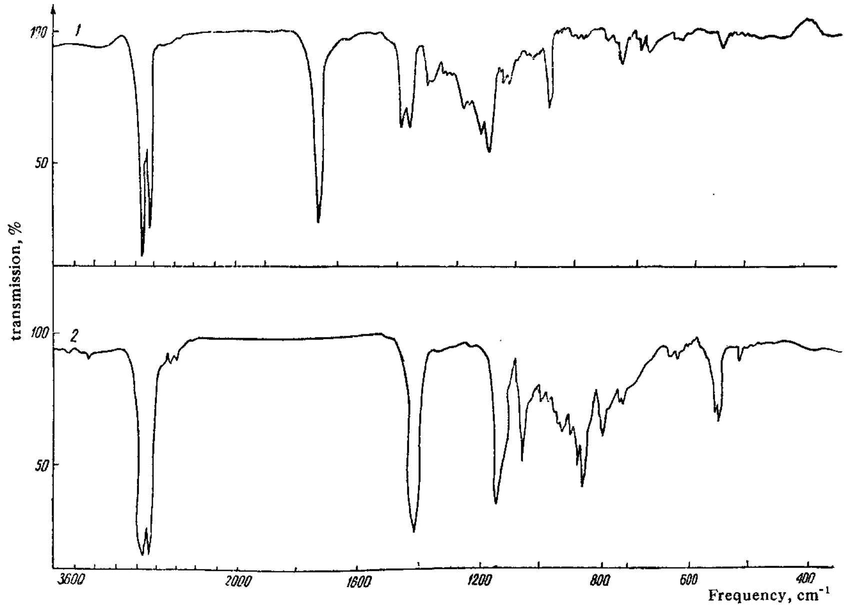
Palmitoleic acid I was obtained by the stereospecific method of synthesizing cis unsaturated fatty acids [5] based on the Wittig reaction; trans vaccenic acid was synthesized by the isomerization of cis-octadec-11-enoic acid, which was likewise synthesized by the method mentioned above [5]. The treatment of an excess of meso-butane-2, 3-diol with palmitoleoyl chloride gave 2-(cis-hexadec-9-enoyloxy)-butan-3-ol (II). The reaction of the latter with trans vaccenoyl chloride formed erythro-2-(cis-hexadec-9-enoyloxy)-3-(trans-octadec-11-enoyloxy) butane (III) (coixenolide). The catalytic hydrogenation of the unsaturated diester III gave tetrahydrocoixenolide (for IR spectrum, see figure).

EXPERIMENTAL

trans Vaccenic acid. A mixture of 1.58 g of methyl cis vaccenate [5] and 0.1 g of selenium was heated at 200° C in an atmosphere of nitrogen for 2 hr. The reaction product was chromatographed on 250 g of type KSK silica gel (75–100 mesh) impregnated with 90 g of silver nitrate [6] in the hexane–ether (2 : 5) system. The first fraction of the eluate (105 ml) gave 0.45 g of methyl trans vaccenate. The second fraction (160 ml) contained a mixture of the cis and trans vaccenates (0.12 g). The third fraction (100 ml) yielded 0.36 g of methyl cis vaccenate. The methyl trans vaccenate was hydrolyzed by being heated with 5 ml of a 5% solution of caustic soda in 80% methanol. Acidification and ethereal extraction yielded 0.40 g of trans vaccenic acid with mp 40–42° C [7].

2-(cis-Hexadec-9-enoyloxy)butan-3-ol (II). A solution of 1.2 g of cis-hexadec-9-enoyl chloride in 5 ml of ether was added over 1 hr at 0° C to a solution of 1.2 g of meso-butane-2, 3-diol and 0.35 g of pyridine in 10 ml of ether. The acid chloride had been prepared by boiling (1.5 hr) palmitoleic acid [5] with oxalyl chloride and subsequent elimination of the excess of oxalyl chloride in vacuum. The reaction mixture was stirred at 0° C for 30 min, warmed to room temperature, treated with HCl, and extracted with ether. The ethereal extract was washed with 5% sodium bicarbonate solution and with water and was dried with magnesium sulfate, filtered through a column (100 × 20 mm) containing activated carbon, and evaporated. The residue was chromatographed on 100 g of neutral alumina (activity grade V), the reaction product being eluted with hexane–ether (10 : 1). The first fraction of the eluate was discarded. Evaporation of the second fraction yielded 0.58 g (40.5%) of 2-(cis-hexadec-9-enoyl-oxy)butan-3-ol, $C_{20}H_{33}O_3$, n_D^{20} 1.4650, α_4^{20} 0.9049; MR_D, found 97.71; MR_D, calculated 97.26.

Coixenolide (III). At 0° C, a solution of 0.41 g of trans-octadec-11-enoyl chloride, obtained by heating trans vaccenoic acid with oxalyl chloride (see above) in 10 ml of ether was added to a solution of 0.46 g of the hydroxyester II and 0.12 g of pyridine in 15 ml of ether. The reaction mixture was left at room temperature for 12 hr and was then treated with 10 ml of 5% HCl and extracted with ether. The extract was washed with water, dried with magnesium sulfate, and evaporated. Coixenolide was isolated from the residue by preparative thin-layer chromatography on neutral alumina (activity grade IV) in the heptane–ether (10 : 1) system, using four plates (18 × 24 cm) with 100 g of alumina on each for the separation of 0.9 g of the mixture of reaction products. Each plate was sprayed with a 1% solution of potassium permanganate in 2 N H_2SO_4, and the zone with R_f 0.56 was cut out and extracted with moist ether. The ethereal solution was dried and evaporated. The yield of coixenolide was 0.40 g (48.4%), n_D^{20} 1.4594, d_4^{20} 0.8945, MR_D found 180.45; MR_D calculated 180.06. The IR spectrum is given in the figure.



IR spectra of coixenolide (1) and of tetrahydrocoixenolide (in KBr) (2).

Found, %: C 77.37; H 11.85. Calculated for $C_{38}H_{70}O_4$, %: C 77.28; H 11.86.

Tetrahydrocoixenolide. In the presence of 0.01 g of Adams platinum catalyst, 0.1 g of coixenolide was hydrogenated in 5 ml of n-hexane until the absorption of hydrogen ceased (30 min). The solution was filtered and evaporated. Thin-layer chromatography of the colorless crystalline product on neutral alumina (activity grade IV) in the heptane–ether (10 : 1) system yielded 80 mg of tetrahydrocoixenolide, $C_{38}H_{74}O_4$, mp 54–55.5° C. Literature data: mp 60° C [3]. The IR spectrum is given in the figure.

CONCLUSIONS

A total synthesis of coixenolide, a diol lipid isolated from the seeds of **Coix lachryma Jobi** L., has been described.

REFERENCES

1. L. D. Bergel'son, Progr. Chem. Fats Lipids, 10, 239, 1969.
2. V. A. Vaver, G. A. Popkova, A. N. Ushakov, and L. D. Bergel'son, Chem. Phys. Lipids, 3, 78, 1969.
3. A. Tanimura, Chem. Pharm. Bull. (Tokyo), 9, 47, 1961.
4. Tukita, and A. Tanimura, Chem. Pharm. Bull. (Tokyo), 9, 43, 1961.
5. L. D. Bergel'son, V. A. Vaver, V. Yu. Kovtun, L. B. Senyavina, and M. M. Shemyakin, ZhOKh, 32, 1808, 1962.
6. L. J. Morris, Chem. and Ind., 1238, 1962.

7. W. J. Gensler, E. M. Behrmann, and L. R. Thomas, J. Amer. Chem. Soc., 73, 1071, 1951.

1 August 1969

Institute of the Chemistry of Natural Compounds AS USSR