INVESTIGATIONS IN THE FIELD OF LIPIDS

XXXVIII. Synthesis of α-O-(1-pentadecenyl)-β, α'-distearoylglycerol

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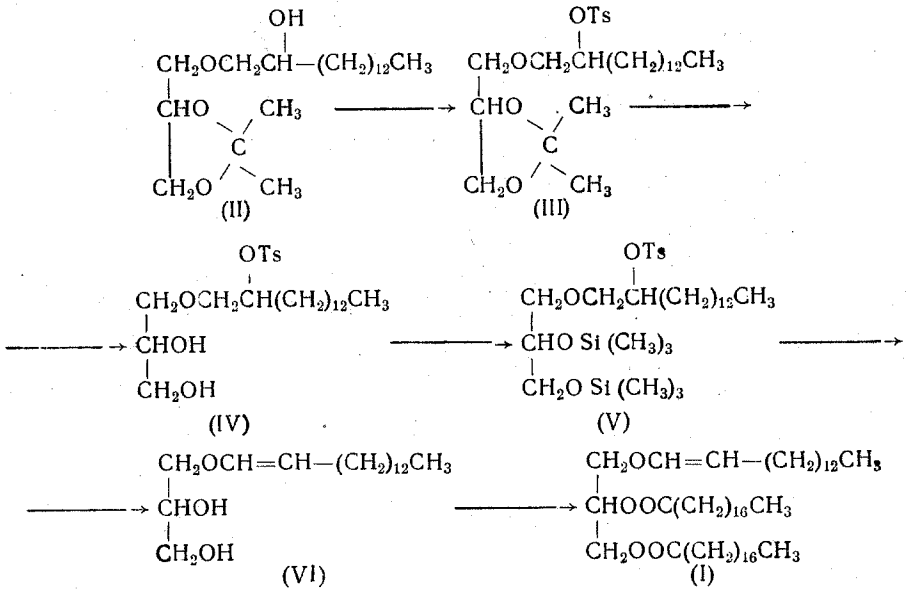
Neutral plasmalogens containing a C_{15} aldehydogenic residue with a normal or a branched chain are concentrated in considerable amounts in some natural sources such as in milk fat, in ox cardiac muscle, etc. [1].

The present paper, which is a continuation of our investigations on the neutral lipids of the vinyl ether type [2-5], describes the preparation of α-O-(1-pentadecenyl)-β, α'-distearoylglycerol (I) by a method based on the condensation of the oxides of the higher olefins with glycerol derivatives.



α-(2-Hydroxypentadecyl)-β, α'-isopropylideneglycerol (II), obtained by the reaction of 1,2-epoxypentadecane with α, β-isopropylideneglycerol in the presence of potassium isopropylideneglyceroxide, was converted into the tosylate of α-(2-hydroxypentadecyl)-β, α'-isopropylideneglycerol (III). The latter was hydrolyzed in an acid medium to α-O-(2-tosyloxypentadecyl)glycerol (IV). The transition from the tosylate (IV) to the α-pentadec-1-enyl ether of glycerol (VI) was effected by means of the dehydrotosylation of the tosylate of α-(2-hydroxypentadecyl)-β, α'-bis-O-(trimethylsilyl)glycerol (V). The trimethylsilyl residues introduced into the molecule of the tosylate (IV) ensured the necessary specificity of the dehydrotosylation reaction and were readily removed during this reaction and the isolation of the α-pentadec-1-enyl ether of glycerol (VI).

A study of the IR spectrum of substance (VI) shows the presence in it of a vinyl ether structure in the cis (735 cm^{-1}) and trans (930, doublet (1660-1675 cm^{-1}) forms. Esterification of the α-pentadec-1-enyl ether of glycerol (VI) with stearoyl chloride in the presence of pyridine and chloroform led to α-O-(pentadec-1-enyl)-β, α'-distearoylglycerol (I), whose structure was shown by its IR spectrum. The most characteristic features of the spectrum of the neutral plasmalogen (I) are the bands at 735, 930, 1660-1675 cm^{-1} (-OCH=CH group) and 1745 cm^{-1} (>C=O) (see figure).

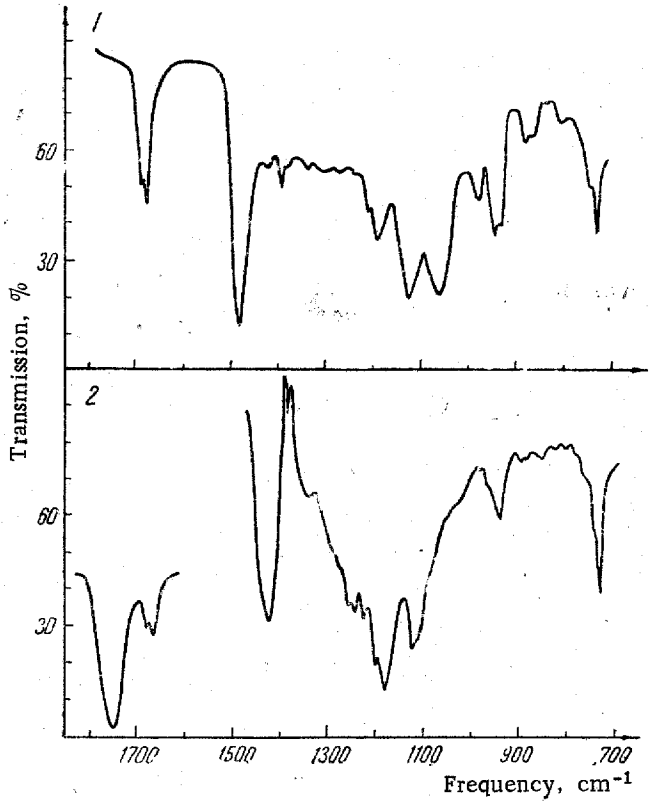
The compounds synthesized were purified by absorption chromatography, and the purity of the substances and the course of the reaction were followed by thin-layer chromatography.

Experimental

α-(2-Hydroxypentadecyl)-β, α'-isopropylideneglycerol (II). A solution of 1.37 g of potassium isopropylideneglyceroxide in 97.8 g of α, β-isopropylideneglycerol (bp 80°-82.6° C at 12 mm) was treated with 16.7 g of 1,2-epoxypentadecane [(bp 96.5°-100° C at 0.3 mm), d_4^{20} 0.8453, n_D^{20} 1.4426, R_f 0.75 (alumina, activity grade II, benzene), MR_D 70.95, calc. for $C_{15}H_{30}O$, 70.91] and the mixture was stirred for 13 hr in a current of dry nitrogen at 110°-115° C. Then the bulk of the initial α,β-isopropylideneglycerol was distilled off in vacuum (12-15 mm) and the residue was diluted with 50 ml of ether and poured into 100 ml of water; the ethereal layer was separated off, and the substance was extracted from the aqueous layer with ether (4 × 40 ml). The combined ethereal extract was dried with potassium

carbonate. The residue after the elimination of the solvent was distilled. Yield 19.97 g (75.6%), bp 159°–160° C (0.3 mm), mp 26°–28° C. For final purification, 1.0 g of the substance was chromatographed on 16 g of silica. The initial 1,2-epoxypentadecane was eluted with benzene and the α-(2-hydroxypentadecyl)-β, a'-isopropylideneglycerol (II) was eluted with a mixture of benzene and ether (9:1). Yield 0.92 g (69.5%), mp 28.5°–30° C, R_f 0.23 [alumina, activity grade II, benzene-ether (9:1)].

Found, %: C 70.38; H 11.80. Calculated for $C_{21}H_{42}O_4$, %: C 70.34; H 11.81.



IR spectra (UR-10, thin layer) of the α-pentadec-1-enyl ether of 1) glycerol and 2) α-O-(pentadec-1-enyl)-β, α'-distearoylglycerol.

Tosylate of α-(2-hydroxypentadecyl)-β, α'-isopropylideneglycerol (III). With cooling to 0° C, a solution of 7.44 g of p-toluenesulfonyl chloride in 7.5 ml of pyridine was added to a solution of 13.5 g of α-(2-hydroxypentadecyl)-β, α'-isopropylideneglycerol (II) in 5.7 ml of pyridine. The reaction mixture was kept for 22 hr at 18°–20° C and was poured into 120 ml of ice water. The substance was extracted with ether (4 × 50 ml) and the combined ethereal extract was washed with water (50 ml) and dried with magnesium sulfate. The solvent and the residual pyridine were eliminated in vacuum. This gave the tosylate of α-(2-hydroxypentadecyl)-β, α'-isopropylideneglycerol (III). Yield 17.75 g (91.90%). A 1.0-g sample of the substance was chromatographed on 12 g of silica and eluted with a mixture of petroleum ether and ethyl ether (85:15). Yield 0.78 g (71.68%), d_4^{20} 1.038, n_D^{20} 1.4858, R_f 0.49 [alumina, activity grade II, benzene-ether (9:1)], MR_D 141.80, calc. 140.98.

Found, %: C 65.95; H 9.29. Calculated for $C_{28}H_{48}O_6S$, %: C 65.59; H 9.44.

α-O-(2-Tosyloxypentadecenyl)glycerol (IV). A mixture of 16.7 g of the tosylate of α-(2-hydroxypentadecyl)-β, α'-isopropylideneglycerol (III) and 230 ml of 0.5 N hydrochloric acid was stirred for 2 hr at 58°–60° C. The reaction mixture, cooled to 18°–20°C, was extracted with ether (4 × 50 ml). The ethereal extract was washed with a saturated solution of potassium carbonate to neutrality and was dried with sodium sulfate. After the elimination of the solvent, 14.5 g of a viscous liquid was obtained. For purification, the substance was chromatographed on 120 g of silica. A mixture of benzene and ether (1:1) eluted the initial tosylate of α-(2-hydroxypentadecyl)-β, α'-isopropylideneglycerol (III) and ether eluted the α-O-(2-tosyloxypentadecyl)glycerol (IV). Yield: 10.8 g (70.1%), d_4^{20} 1.072, n_D^{20} 1.4951, R_f 0.59 [alumina, activity grade II, ether-methyl alcohol-acetic acid (23.5:1.5:0.5)], MR_D 128.60, calc. 129.09.

Found, %: C 63.40; H 9.13. Calculated for $C_{25}H_{44}O_6S$, %: C 63.52; H 9.39.

Tosylate of α-(2-hydroxypentadecyl)-β, α'-bis-(O-trimethylsilyl)glycerol (V). In drops, at 0°–4° C, a solution of 5.07 g of trimethylchlorosilane (bp 56°–57° C) in 8.8 ml of cyclohexane was added to a solution of 4.2 g of α-O-(2-tosyloxypentadecyl)glycerol (IV) in a mixture of 22 ml of cyclohexane and 2.43 g of pyridine, and the mixture was stirred for 22 hr at 18°–20° C and then for 2 hr at 40°–50° C. After the end of the reaction, the pyridine hydrochloride was separated off and washed with 25 ml of cyclohexane. The combined filtrate was evaporated in vacuum to give 5.2 g of a substance with R_f 0.55 [alumina, activity grade II, heptane-ether (7:3)]. In view of its high lability the crude product was subjected to dehydrotosylation without purification.

α-Pentadec-1-enyl ether of glycerol (VI). Over 30 min with vigorous stirring in a current of dry nitrogen, a solution of potassium tert-butoxide (0.85 g of potassium and 18 ml of tert-butyl alcohol) was added to a solution of 5.2 g of the tosylate of α-(2-hydroxypentadecyl)-β, α'-bis-(O-trimethylsilyl)glycerol (V), a voluminous precipitate being deposited. After cooling to 18°–20° C, the reaction mixture was diluted with 50 ml of ether and the precipitate of potassium p-toluenesulfonate was filtered off and washed with 20 ml of ether. The combined ethereal solution was washed with 50 ml of water and dried with sodium sulfate. Elimination of the solvent gave 2.7 g of substance. A 1.0-g sample of this substance was chromatographed on 20 g of silica; a mixture of benzene and ether (4:1) eluted by-products of nonacetal nature [4], and ether eluted the α-1-pentadecenyl ether of glycerol (VI). Yield 0.40 g [38.0% calculated on the α-O-(2-tosyloxypentadecenyl)glycerol (IV)], mp 25°–30° C, R_f 0.52 [alumina, activity grade II, ether-methyl alcohol (19:1)].

Found, %: C 72.11; H 11.82. Calculated for $C_{18}H_{36}O_3$, %: C 71.95; H 12.08.

α-O-(Pentadec-1-enyl)-β, α'-distearoylglycerol (I). In drops at 0° C, a solution of 1.05 g of stearoyl chloride (bp 157°–159° C at 0.6 mm) in 2 ml of chloroform was added over 40 min to a solution of 0.5 g of the crude α-pentadec-1-enyl ether of glycerol (VI) in 1 ml of pyridine and 3 ml of chloroform. The reaction mixture was stirred for 12 hr at 18°–20° C, diluted with 50 ml of ether, washed with water, and dried with sodium sulfate. Elimination of the ether gave 1.35 g of a substance which was purified by means of chromatography in a thin layer of alumina [activity grade III in the petroleum ether-ethyl ether (22:3) system]. Yield 123 mg [9.1% calculated on the α-O-(2-tosyloxypentadecyl)-glycerol (IV)], mp 38.6°–39.9° C, R_f 0.73 [alumina, activity grade IV, petroleum ether-diethyl ether (4:1)].

Found, %: C 77.86; H 12.35. Calculated for $C_{54}H_{104}O_5$, %: C 77.82; H 12.58.

After recrystallization from a mixture of methyl alcohol and chloroform (2:1), mp 50.3°–51.2° C.

Summary

1. α-O-(Pentadec-1-enyl)-β, α'-distearoylglycerol, a neutral plasmalogen found in milk fat, cardiac muscle, etc., has been prepared.

2. In performing the synthesis by the method selected, we have isolated and characterized by their physicochemical constants α-(2-hydroxypentadecyl)-β, α'-isopropylideneglycerol, the tosylate of α-(2-hydroxypentadecyl)-β, α'-isopropylideneglycerol, α-O-(2-tosyloxypentadecyl)glycerol, and the α-pentadec-1-enyl ether of glycerol.

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