INVESTIGATIONS IN THE FIELD OF LIPIDS

XLIII. Synthesis of Neutral Plasmalogens

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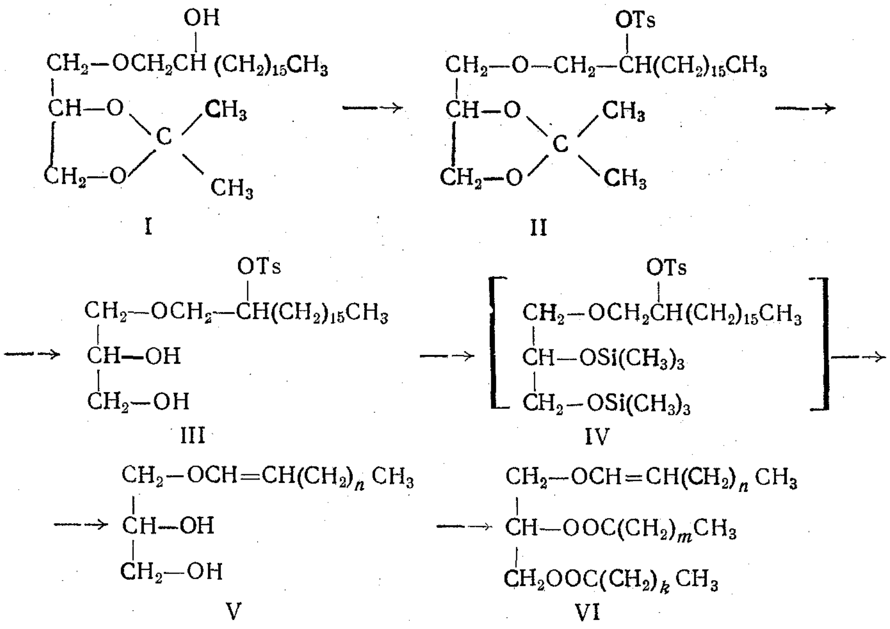
Plasmalogens with C_{16} and C_{18} aldehydogenic components make up the bulk of natural lipids of the vinyl ether type found in various organs and animal tissues (regular elements of the blood, cardiac muscle, nerve tissues, etc.) [1].

The present paper describes a method for the preparation of α-O-(octadec-1-enyl)-β, α'-diacylglycerols with stearic acid residues (VI, n = 15, m = k = 16) and palmitic acid residues (VI, n = 15, m = k = 14) by the route that we have used for the synthesis of neutral plasmalogens with shorter aldehydogenic residues [2–4]. In addition, we also describe the synthesis, from the α-hexadec-1-enyl (V, n = 13) and α-pentadec-1-enyl (V, n = 12) ethers of glycerol obtained previously [4], of the new neutral plasmalogens α-O-(hexadec-1-enyl)-β, α'-distearoylglycerol (VI, n = 13, m = = k = 16) and α-O-(pentadec-1-enyl)-β, α'-dipalmitoylglycerol (VI, n = 12, m = k = 14).



α-(2-Hydroxyoctadecyl) β, α'-isopropylideneglyceryl ether (I), prepared by the condensation of 1, 2-epoxyoctadecane with α, β-isopropylideneglycerol was converted into the tosylate (II), which was hydrolyzed in an acid medium to α-O-(2-tosyloxyoctadecyl) glycerol (III). The latter was converted into the α-octadec-1-enyl ether of glycerol (V, n = = 15) via the dehydrotosylation of the tosylate of α-(2-hydroxydecyl) β, α'-bis-(O-trimethylsilyl) glyceryl ether (IV). The acylation of the α-octadec-1-enyl ether of glycerol (V, n = 15) with stearoyl and palmitoyl chlorides under the usual conditions of the introduction of acyl residues into molecules of glycerol and its derivatives led to the formation of the plasmalogens (VI, n = 15, m = k = 16; VI, n = 15, m = k = 14).

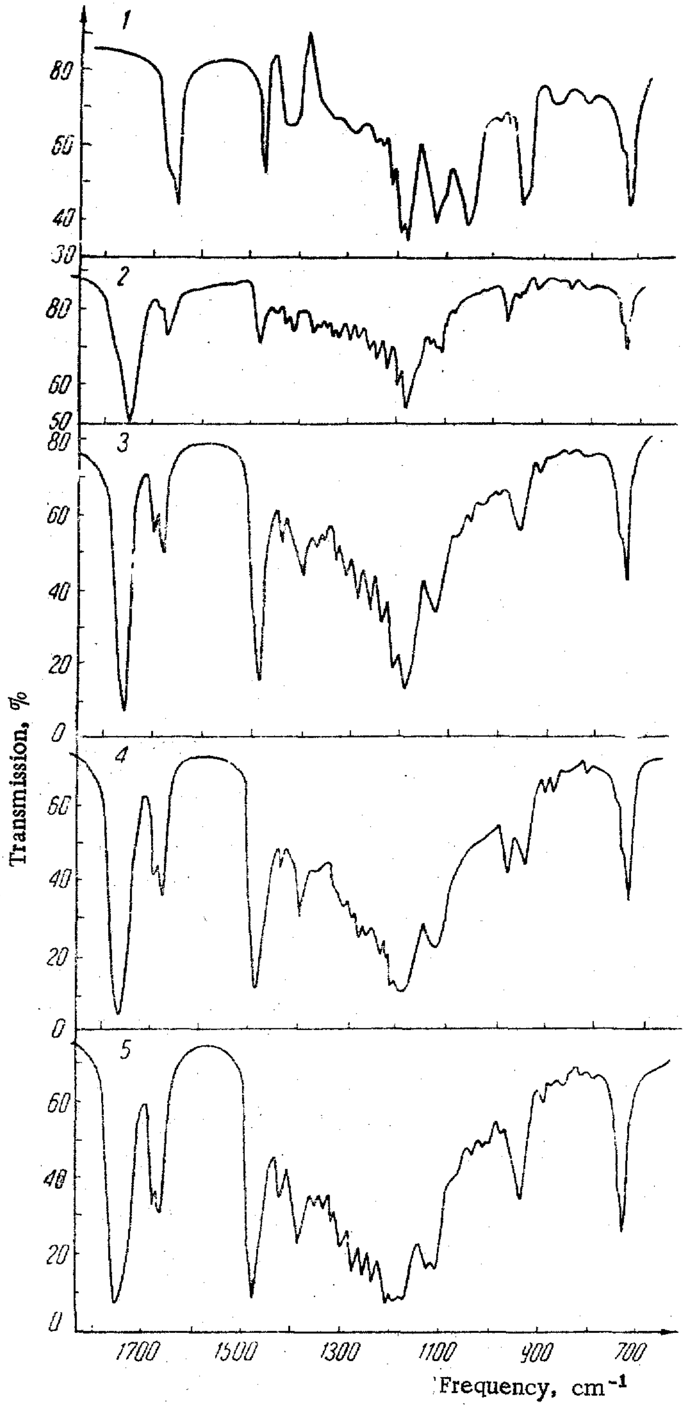
Similarly, the esterification of the α-hexadec-1-enyl (V, n = 13) and the α-pentadec-1-enyl (V, n = 12) ethers of glycerol with the same acyl chlorides gave α-O-(hexadec-1-enyl)-β, α'-distearoylglycerol (VI, n = 13, m = k = 16) and α-O-(pentadec-1-enyl)-β, α'-dipalmitoylglycerol (VI, n = 12, m = k = 14).

The IR spectra of the α-(octadec-1-enyl) ether of glycerol (V, n = 15) and of the plasmalogens (VI) (figure) showed that the substances synthesized are mixtures of the respective cis (735 cm^{-1}, shoulder in the band of the rocking vibrations of the methlene group at 720, 1670 cm^{-1}) and trans (930, 1660 cm^{-1}) forms [2–4].

The physicochemical properties of the neutral plasmalogens (VI) obtained are shown by the figures given in the table.

Experimental

α-(2-Hydroxyoctadecyl) β, α'-isopropylideneglyceryl ether (I). A solution of 0.72 g of potassium isopropylideneglyceroxide in 51.3 g of α, β-isopropylideneglycerol was treated with 10.0 g of 1, 2-epoxyoctadecane [bp 132–134°C at 0.6 mm, mp 26.2–26.8°C, R_f 0.70, alumina of activity grade III, hexane-ether (10:1)] and, with stirring, the mixture was heated at 110–112°C in a current of dry nitrogen for 12 hr. Then the unreacted α, β-isopropylideneglycerol was distilled off in vacuum (15 mm). The residue was diluted with 60 ml of ether and poured into 75 ml of water; the



IR spectra (UR-10, thin layer) 1) α-Octadec-1-enyl ether of glycerol (V, n = 15); 2) α-O-(octadec-1-enyl)-β, α'-distearoylglycerol (VI, n = 15, m = k = 16); 3) α-O-(octadec-1-enyl)-β, α'-dipalmitoylglycerol (VI, n = 15, m = k = 14); 4) α-O-(hexadec-1-enyl)-β, α'-distearoylglycerol (VI, n = 13, m = k = 16); 5) α-O-(pentadec-1-enyl)-β, α'-dipalmitoylglycerol (VI, n = 12, m = k = 14).

ethereal layer was separated off and the substance was extracted from the aqueous layer with ether (4 × 30 ml). The combined ethereal extract was dried with sodium sulfate, the solvent was driven off, and the substance was distilled. Yield 11. 3 g (75. 7%), bp 174–175°C (0. 1 mm).

0. 5 g of the substance was chromatographed on 7 g of silica and eluted with a mixture of benzene and ether (9:1), mp 45–46. 5°C, R_f 0. 17 [alumina, activity grade II, hexane-ether (3:2)].

Found, %: C 72. 13; H 12. 04. Calculated for $C_{24}H_{48}O_4$, %: C 71. 95; H 12. 08.

Physicochemical Properties of the Neutral Plasmalogens

Compound	Mp, °C	R_f*	Found, %		Formula	Calculated, %	
			C	H		C	H
(VI) $n=15, m=k=16$	57.5–58.1**	0.61	78.44	12.30	$C_{57}H_{110}O_5$	78.20	12,66
(VI) $n=15, m=k=14$	52.2–53.7***	0.60	78.01	12.88	$C_{53}H_{102}O_5$	77.69	12.55
(VI) $n=13, m=k=16$	40.8–41.9****, 48.7–50.6**	0.60	77.97	12.54	$C_{55}H_{106}O_5$	77.95	12.61
(VI) $n=12, m=k=14$	52.0–52.3***	0.60	77.28	12.64	$C_{50}H_{96}O_5$	77.26	12.45

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*Alumina, activity grade III, petroleum ether-ether (4:1).

**Methyl alcohol-chloroform (2:1).

***Acetone-methyl alcohol (2:1).

****From acetone; on storage (1. 5 months) the melting point of the sample rose to 43. 9°–46. 1° C (deformation at 42° C), which is due to polymorphic transformations.

Tosylate of the α-(2-hydroxoctadecyl) ether of β, α'-isopropylideneglycerol (II). A solution of 3. 7 g of α-(2-hydroxyoctadecyl) β, α'-isopropylideneglyceryl ether (I) in 1. 4 ml of pyridine was mixed at 0°C with a solution of 1. 5 g of p-toluenesulfonyl chloride in 1. 5 ml of pyridine and the mixture was stirred at 18–20°C for 24 hr. It was then poured into 25 ml of ice water and the substance was extracted with ether (4 × 15 ml). The combined ethereal extract was washed with water (20 ml) and dried with sodium sulfate. The solvent was evaporated off and the residual pyridine was eliminated under vacuum (1 mm). Yield 4. 0 g (78. 1%). The substance was purified finally by chromatography on alumina (activity grade III) with elution by a mixture of petroleum ether and ether (3:1). Yield 3. 5 g (68. 34%). On standing, the substance slowly crystallized, mp 39. 2–41. 4°C, R_f 0. 50 [alumina, activity grade II, petroleum ether-ether (3:1)].

Found, %: C 66. 87; H 10. 05. Calculated for $C_{31}H_{54}O_6S$, %: C 67. 11; H 9. 81.

α-O-(2-Tosyloxyoctadecyl) glycerol (III). 40 ml of 0. 5 N hydrochloric acid was added to 3. 0 g of the tosylate of α-(2-hydroxyoctadecyl) β, α'-isopropylideneglyceryl ether (II), and the resulting emulsion was vigorously stirred at 60–62°C for 3 hr. Then the reaction mixture was cooled to 18–20°C and extracted with ether (3 × 25 ml). The combined extract was washed with a saturated solution of sodium carbonate to neutrality and was dried with sodium sulfate. After the elimination of the ether, 2. 70 g of a substance in the form of a viscous, partially crystallizing liquid was obtained. This was chromatographed on 35 g of silica. A mixture of benzene and ether (3:2) eluted the initial tosylate of α-(2-hydroxyoctadecyl) β, α'-isopropylideneglyceryl ether (II), and ether eluted the α-O-(2-tosyloxyoctadecyl) glycerol (III). Yield 2. 15 g (77. 34%), mp 37–39°C, deformation at 31°C, R_f 0. 64 [alumina, activity grade III, ether-methyl alcohol-acetic acid (23. 5:1. 5:0. 5)].

Found, %: C 65. 04; H 10. 10. Calculated for $C_{28}H_{50}O_6S$, %: C 65. 33; H 9. 79.

Tosylate of α-(2-hydroxyoctadecyl) β, α'-bis-(O-trimethylsilyl) glyceryl ether (IV). At 0°C, a solution of 1. 16 g of trimethylchlorosilane (bp 56. 5–57. 5°C) in 2 ml of cyclohexane was added in drops to a solution of 1. 2 g of α-O-(2-tosyloxyoctadecyl) glycerol (III) in a mixture of 10 ml of cyclohexane and 0. 55 g of pyridine, and stirring was continued at 18–20°C for 15–20 hr and then at 40°C for 2 hr. The reaction mixture was cooled to 18°C, the precipitate of pyridine hydrochloride was separated off and washed with 5 ml of cyclohexane, and the combined filtrate was evaporated in vacuum. This gave 1. 5 g of a substance which was used for dehydrotosylation without purification.

α-Octadec-1-enyl ether of glycerol (V, n = 15). A solution of 1. 5 g of the tosylate of α-(2-hydroxyoctadecyl) β, α'-bis-(O-trimethlsilyl) glyceryl ether (IV) in 4 ml of tert-butyl alcohol was heated to 80°C in a current of dry nitrogen and, with stirring, a solution of 0. 26 g of potassium in 6 ml of tert-butyl alcohol was added over 20 min. The reaction mixture, cooled to 18–20°C, was diluted with 15 ml of ether, and the precipitate of potassium p-toluenesulfonate was separated off and washed with 5 ml of ether. The combined filtrate was extracted with water (15 ml) and dried with sodium sulfate. After elimination of the solvent, 0. 8 g of an oily, partially crystallizing substance was obtained. 300 mg of the latter was purified by chromatography on 8 g of silica. By-products of nonacetal type were eluted with petroleum ether-ether (4:1) [2], and the α-octadec-1-enyl ether of glycerol (V, n = 15) was eluted with petroleum ether-ether (7:3). Yield 115 mg (38.3% on the α-O-(2-tosyloxyoctadecyl) glycerol (III), mp 57–58.5°C, deformation at 41°C, R_f 0.53 [alumina, activity grade III, ether-methyl alcohol (19:1)].

Found, %: C 73.77; H 12.42. Calculated for $C_{21}H_{42}O_3$, %: C 73.65; H 12.36.

α-O-(Octadec-1-enyl)-β, α'-distearoylglycerol (VI, n = 15, m = k = 16). A solution of 1.12 g of stearoyl chloride in 5.6 ml of chloroform was added over 1 hr at 0° C to a solution of 500 mg of the crude α-octadec-1-enyl ether of glycerol (V, n = 15) in 7 ml of chloroform and 300 mg of pyridine. The reaction mixture was left at 18–20°C for 48 hr and was then diluted with 70 ml of ether, washed with water, and dried with sodium sulfate. Elimination of the ether gave 1.27 g of crude plasmalogen. Purification of 0.85 g of the latter was carried out by chromatography in a thin layer of alumina [activity grade III, in the petroleum ether-ether (9:1) system]. Yield 90 mg [10.6% calculated on the α-O-(2-tosyloxyoctadecyl) glycerol (IV)].

α-O-(1-Octadecenyl)-β, α'-dipalmitoylglycerol (VI, n = 15, m = k = 14) was synthesized by the acylation of the α-octadec-1-enyl ether of glycerol (V, n = 15) with palmitoyl chloride under the same conditions.

α-O-(Hexadec-1-enyl)-β, α'-distearoylglycerol (VI, n = 13, m = k = 16) and α-O-(pentadec-1-enyl)-β, α'-dipalmitoylglycerol (VI, n = 12, m = k = 14) were synthesized similarly by the esterification of the corresponding α-alk-1-enyl ethers (V, n = 13, and V, n = 12).

Summary

1. The synthesis of the following neutral plasmalogens has been effected: α-O-(octadec-1-enyl)-β, α'-distearoylglycerol, α-O-(octadec-1-enyl)-β, α'-dipalmitoylglycerol, α-O-(hexadec-1-enyl)-β, α'-distearoylglycerol, and α-O-(pentadec-1-enyl)-β, α'-dipalmitoylglycerol.

2. During the synthesis, the following compounds were isolated and characterized by their physicochemical constants: the α-octadec-1-enyl ether of glycerol, α-(2-hydroxyoctadecyl) β, α'-isopropylideneglyceryl ether, the tosylate of α-(2-hydroxyoctadecyl) β, α'-isopropylideneglyceryl ether, and α-O-(2-tosyloxyoctadecyl) glycerol.

3. The IR spectra of the α-octadec-1-enyl ether of glycerol and the neutral plasmalogens have been studied.

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