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Abstract

Full Text

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SYNTHESIS OF NEUTRAL PLASMALOGENS

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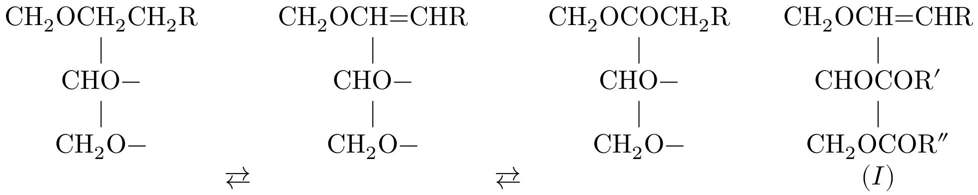
In lipid mixtures of natural origin, alcohols, aldehydes, and acids of the aliphatic series occur in the form of glycerol derivatives. The pathways of biosynthesis of these compounds have not yet been sufficiently investigated. It is, however, quite probable that in metabolic processes they are connected by oxidation-reduction transformations.



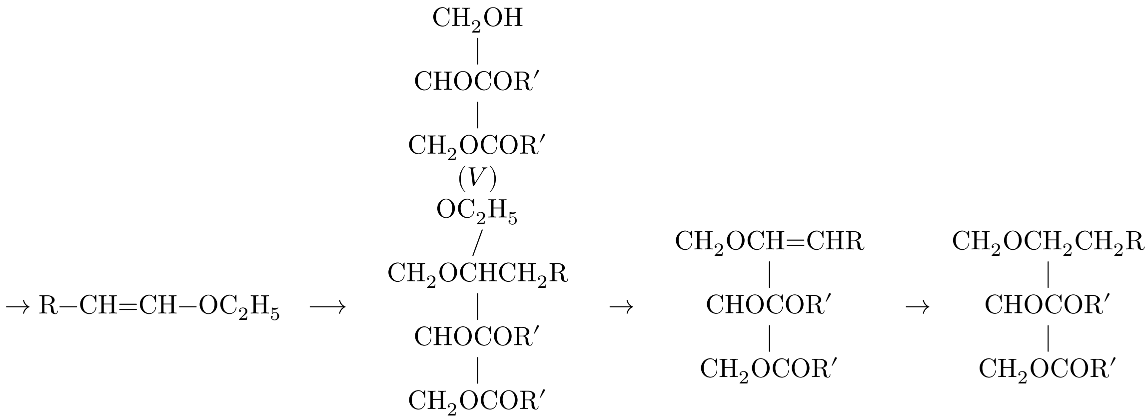
$$\begin{array}{ccccccc}
\mathrm{CH_2OCH_2CH_2R} & & \mathrm{CH_2OCH{=}CHR} & & \mathrm{CH_2OCOCH_2R} & & \mathrm{CH_2OCH{=}CHR} \\
| & & | & & | & & | \\
\mathrm{CHO-} & & \mathrm{CHO-} & & \mathrm{CHO-} & & \mathrm{CHOCOR'} \\
| & & | & & | & & | \\
\mathrm{CH_2O-} & & \mathrm{CH_2O-} & & \mathrm{CH_2O-} & & \mathrm{CH_2OCOR''} \\
 & \rightleftarrows & & \rightleftarrows & & & (I)
\end{array}$$

The least studied from the standpoint of biological role is the group of aldehydogenic lipids, the so-called plasmalogens, which includes both phosphatide and neutral compounds. Neutral plasmalogens were first isolated in 1961 (^{1}) and are α-O-(cis-1-alkenyl)-β,α'-diacylglycerols (I). The synthetic preparation of 1-alkenyl ethers of glycerol is associated with considerable difficulties (^{2}).

We have proposed and carried out, using derivatives of palmitic and stearic acids as examples, a method for the synthesis of neutral plasmalogens based on mutual transformations of 1-alkenylethyl ethers and acetals of the aldehydes C_{16} and C_{18} (Scheme 1).

Scheme 1

$$\underset{(II)}{\mathrm{RCH_2CHO}} \rightarrow \underset{(III)}{\mathrm{RCH_2CH(OC_2H_5)_2}} \rightarrow$$



$$\begin{array}{c} CH_2OH \\ | \\ CHOCOR' \\ | \\ CH_2OCOR' \\ (V) \end{array}$$

$$\rightarrow R{-}CH{=}CH{-}OC_2H_5 \longrightarrow \begin{array}{c} OC_2H_5 \\ / \\ CH_2OCHCH_2R \\ | \\ CHOCOR' \\ | \\ CH_2OCOR' \end{array} \rightarrow \begin{array}{c} CH_2OCH{=}CHR \\ | \\ CHOCOR' \\ | \\ CH_2OCOR' \end{array} \rightarrow \begin{array}{c} CH_2OCH_2CH_2R \\ | \\ CHOCOR' \\ | \\ CH_2OCOR' \end{array}$$

(*IV*) (*VI*) (*VII*) (*VIII*)

From literature data for low-molecular-weight compounds it is known that 1-alkenyl ethers and acetals of the aliphatic series, as a rule, readily undergo mutual transformations. Thus, under acid catalysis it is possible to obtain an acetal from an aldehyde, to split off one molecule of alcohol with formation of a 1-alkenyl ether, to add a molecule of another alcohol across the double bond of the alkenyl ether, and to synthesize an unsymmetrical acetal, from which conversion to a 1-alkenyl ether of a new structure is possible (^{3}). The principal condition for carrying out such transformations on a preparative scale is the correct choice of the process conditions (temperature, pressure, reaction time, etc.), catalysts, and the structure of substituents.

The starting aldehydes (*II*) are obtained by reduction of acids or their amides (^{4}) and are converted into acetals (*III*) by heating with alcohol and ethyl orthoformate in the presence of *p*-toluenesulfonic acid (^{5}). 1-Alkenylethyl ethers (*IV*) are synthesized by splitting off alcohol during distillation of the diethyl acetals, using sulfanilic acid as catalyst (see Table 1).

Table 1

Physicomechanical constants of the synthesized diethyl acetals (III) and 1-alkenylethyl ethers (IV)

Substance	Serial number	B.p., °C (mm Hg)	d_4^{20}	n_D^{20}	MR_D found	MR_D calculated	Found, % C	Found, % H	Calculated, % C	Calculated, % H	Yield, %
Diethyl acetal of palmitic aldehyde	III, R = $C_{14}H_{29}$	155–158 (0.2)	0.8474	1.4394	97.62	97.85	76.42	13.38	76.38	13.46	86.5
Diethyl acetal of stearic aldehyde	III, R = $C_{16}H_{33}$	144–145 (0.05)	0.8436	1.4418	107.3	107.2	77.12	13.50	77.19	13.45	87.3
Diethyl acetal of oleic aldehyde	III, R = $C_{16}H_{31}$	–	0.8539	1.4461	106.4	106.6	77.33	12.86	77.55	13.02	71.8
1-Hexadecenyl ethyl ether	IV, R = $C_{14}H_{29}$	135–138 (0.5)	0.8352	1.4485	86.12	86.38	80.30	13.54	80.52	13.51	57.2
1-Octadecenyl ethyl ether	IV, R = $C_{16}H_{33}$	148–151 (0.5)	0.8219	1.4514	97.02	96.83	81.20	13.60	81.08	13.65	55.2
1,9-Octadecadienyl ethyl ether	IV, R = $C_{16}H_{31}$	150–153 (1)	0.8339	1.4570	96.23	95.69	81.30	12.81	81.58	13.06	32.3

Table 2

Physicochemical constants of the synthesized unsymmetrical acetals (VI), neutral plasmalogens (VII), and products of their hydrogenation (VIII)

Substance	Serial number	M.p., °C	Iodine number, found	Iodine number, calculated	Found, % C	Found, % H	Calculated, % C	Calculated, % H	Yield, %
α-O-(1-ethoxyhexadecyl)-β,α′-dipalmitate	R′ = $C_{15}H_{31}$ VI, R = $C_{14}H_{29}$	58—59	–	–	76.03	12.29	76.04	12.52	73.1
α-O-(1-ethoxyoctadecyl)-β,α′-distearate	R′ = $C_{17}H_{35}$ VI, R = $C_{16}H_{33}$	61—62	–	–	76.79	12.58	76.89	12.66	64.2
α-O-(1-hexadecenyl)-β,α′-dipalmitate	R′ = $C_{15}H_{31}$ VII, R = $C_{14}H_{29}$	30—31.5	30.8	32.0	77.14	12.30	77.40	12.49	27.2
α-O-(1-octadecenyl)-β,α′-distearate	R′ = $C_{17}H_{35}$ VII, R = $C_{16}H_{33}$	44—45.5	27.2	28.8	78.63	12.40	78.35	12.68	20.6
α-Chimyl-β,α′-dipalmitate	R′ = $C_{15}H_{31}$ VIII, R = $C_{14}H_{29}$	52.5—53	–	–	77.33	12.51	77.21	12.70	91.1
α-Batyl-β,α′-distearate	R′ = $C_{17}H_{35}$ VIII, R = $C_{16}H_{33}$	60—61	–	–	78.15	13.01	78.01	12.86	90.4

1-Alkenylethyl ethers containing 16 and 18 carbon atoms in the chain had not previously been obtained. Study of the behavior of compounds (IV) on thin-layer chromatography on alumina, as well as the character of their IR spectra, indicates that they are mixtures of *cis* and *trans* isomers.

Fig. 1. IR spectra of neutral plasmalogens (VII) and products of their hydrogenation (VIII)

Figure 1: Fig. 1. IR spectra of neutral plasmalogens (VII) and products of their hydrogenation (VIII)

It has been established by the work of M. F. Shostakovsky and other investigators ([6,7]) that compounds containing hydroxyl groups readily undergo nucleophilic addition reactions at the double bond of simple vinyl ethers. In our case, 1-alkenylethyl ethers (IV, $R = \mathrm{C_{14}H_{29}};\ \mathrm{C_{16}H_{33}}$) in the presence of p-toluenesulfonic acid are made to react with α,β-diglycerides ($V,\ R' = \mathrm{C_{15}H_{31}};\ \mathrm{C_{17}H_{35}}$). The choice of saturated monocarboxylic diglycerides is determined by the fact that the presence of multiple bonds in the acyl radicals may interfere with the analytical determination of the double bond of the 1-alkenyl ethers of diglycerides—the final products of the synthesis. In addition, precisely such derivatives are most readily available as starting materials and can be thoroughly purified of impurities ([8]).

Fig. 1. IR spectra of neutral plasmalogens (VII) and products of their hydrogenation (VIII)

As the condensation product, crystalline compounds are isolated which, according to thin-layer chromatography, elemental analysis, and IR spectra, are unsymmetrical acetals of palmitic and stearic aldehydes, ethyl alcohol, and the corresponding diglyceride (VI) (Table 2).

The unsymmetrical acetals (VI) are then heated in the presence of sulfanilic acid. In this process a molecule of ethyl alcohol is eliminated and α-O-(1-alkenyl)-β,α'-diacylglycerides (VII) are formed (Table 2). Among the reaction products, compounds (VII) are readily detected by means of thin-layer chromatography when developed with iodine vapors. Purification is carried out by adsorption chromatography on silicic acid. The structure and purity of the isolated substances (VII) are established by elemental analysis, iodine numbers, and IR spectra.

The IR spectra of (VII) do not contain absorption maxima in the region 3200-3600 cm^{-1}, which indicates the absence of free hydroxyl groups in the molecule; they have an absorption band at 1660 cm^{-1}, indicating the presence of a double bond, and an absorption band at 1120 cm^{-1}, characteristic of a simple ether grouping. In the region 1200-1350 cm^{-1} there is a progression of bands characteristic of glyceride derivatives of stearic and palmitic acids ([9]). The absorption of the carbonyl and —O—C—groups (1740 and 1180 cm^{-1}) corresponds to the presence of ester groupings in the molecule. Thus, the structure of the IR spectra confirms the structure of the synthesized compounds (Fig. 1). The presence in the IR spectra of (VII) of weak absorption maxima at 945 cm^{-1} agrees with our assumptions regarding the formation, alongside cis and trans isomers, analogously to the case of 1-alkenylethyl ethers (IV).

The neutral plasmalogens (VII) obtained are subjected to hydrogenation, the hydrogenation products being identical in melting points, chromatographic behavior, and IR spectra with α-chimyl dipalmitate (VIII, R = $C_{14}H_{29}$, R′ = $C_{15}H_{31}$) (^{10}) and α-batyl distearate (VIII, R = $C_{16}H_{33}$; R′ = $C_{17}H_{35}$) (^{11}), respectively.

Upon hydrolysis of compounds (VII) with methanolic alkali and aqueous hydrogen chloride, the starting aldehyde (II) is obtained, identified as the 2,4-dinitrophenylhydrazone.

The method we have developed for the synthesis of 1-alkenyl ethers of the type of neutral plasmalogens (VII) has been applied to the synthetic preparation of unsaturated representatives of this group of natural lipids; moreover, in carrying it out there are no limitations either on the aldehydes or on the acids. The same principle underlies the preparation of phosphatide plasmalogens of the lecithin, cephalin, and other types.

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