Chemistry

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Figure 1: Reaction scheme: routes A, B, and C for the synthesis of phospholipids, showing intermediates (I)-(XI) with substituents OH, OOCR, OOCR′, $OPOCH_2CH_2N(CO)_2C_6H_4$, and related groups.

Abstract

Full Text

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V. I. Shvets, N. A. Bogoslovskii, V. M. Polyachenko, L. V. Volkova, G. I. Samokhvalov, and N. A. Preobrazhenskii

Synthesis of Phospholipids Containing Residues of Higher Polyenoic Acids of the Aliphatic Series

(Presented by Academician A. N. Nesmeyanov, February 18, 1961)

The study and synthesis of triglycerides ([1]) make it possible to proceed to the synthetic preparation of more complex natural substances—phospholipids. The present work is devoted to the synthesis of cephalins containing residues of stearic, oleic, linoleic, and linolenic acids. These compounds are of interest, since it is known that structures of this type play an important role in biological processes ([2]) and are constituents of certain enzyme systems ([3]).

The synthesis is carried out by three routes: from α,β-diglycerides obtained from α-benzylglycerol (A) or α,α'-benzylideneglycerol (B), and from glycerol diacylhydrides (C).

A. In the first case ([4]), the acid chlorides of brominated unsaturated acids were used for the acylation of α-benzylglycerol. The purpose of this was to prevent saturation of the double bonds during reductive debenzylation.

α-Benzylglycerol (I) was acylated with the acid chlorides of 9,10,12,13-tetrabromostearic and 9,10,12,13,15,16-hexabromostearic acids in chloroform in the presence of quinoline to give α-benzylglycerides (II).

α,β-Di-9,10,12,13-tetrabromostearoyl-benzylglycerol (II, $R = R' = -(CH_2)_7(CHBrCHBrCH_2)_2(CH_2)_4H$). M.p. 67.5–68.0° (from ether).

$C_{46}H_{74}O_5Br_8$.	Found, %:	C 41.19; H 5.60; Br 47.52
	Calculated, %:	C 41.08; H 5.54; Br 47.68

α,β-Di-9,10,12,13,15,16-hexabromostearoylbenzylglycerol (II, R = R′ = –$(CH_2)_7(CHBrCHBrCH_2)_3CH_3$). M.p. 161–162° (from dioxane). Found, %: Br 57.80. $C_{46}H_{70}O_5Br_{12}$. Calculated, %: Br 57.74.

On reductive debenzylation of compound II (hydrogen and palladium black), the following were obtained:

α,β-Di-9,10,12,13-tetrabromostearoylglycerol (III, R = R′ = –$(CH_2)_7(CHBrCHBrCH_2)_2(CH_2)_4H$). M.p. 71–72° (from methanol). Found, %: Br 50.52. $C_{39}H_{68}O_5Br_8$. Calculated, %: Br 50.90.

α,β-Di-9,10,12,13,15,16-hexabromostearoylglycerol (III, R = R′ = –$(CH_2)_7(CHBrCHBrCH_2)_3CH_3$). M.p. 168–169° (from dioxane). Found, %: Br 61.08; 60.94. $C_{39}H_{64}O_5Br_{12}$. Calculated, %: Br 61.11.

The next stage in the synthesis of α,β-diglycerides was debromination with activated zinc in acetone, as a result of which the following were isolated:

α,β-Dilinoleoylglycerol (III, R = R′ = –$(CH_2)_7(CH{=}CHCH_2)_2{-}(CH_2)_4H$); d_4^{20} 0.9421; n_D^{20} 1.4832; MR_D found 182.9; calculated 182.74. Iodine number found 162.2; 162.6; calculated 164.0.

$C_{39}H_{68}O_5F_4$. Found, %: C 76.39; H 10.80
Calculated, %: C 76.12; H 11.00

α,β-Dilinolenoylglycerol (III, R = R′ = –$(CH_2)_7(CH{=}CHCH_2)_3CH_3$) d_4^{20} 0.9716; n_D^{20} 1.4960; MR_D found 184.1; calculated 184.33. Iodine number found 244.1; 246.0; calculated 248.1.

$C_{39}H_{64}O_5F_6$. Found, %: C 76.36; 76.29; H 9.61; 9.40
Calculated, %: C 76.47; H 10.46

After debromination, diglycerides with cis double bonds in the residues of unsaturated acids were isolated. To introduce the phosphorus-containing part, a method using phthaloid protection of the amino group of ethanolamine was applied ([5]).

α,β-Diglycerides (III) were condensed with β-phthalimidoethylphosphoryl dichloride in chloroform in the presence of triethylamine. The acid chlorides were hydrolyzed with water to N-phthalimido-α-cephalins (IV).

Distearoyl-N-phthalimido-α-cephalin (IV, R = R′ = –$(CH_2)_{17}H$). M.p. 48–48.5° (from methanol).

$C_{49}H_{84}O_{10}NP$. Found, %: C 67.37; H 9.21; N 1.72
Calculated, %: C 67.23; H 9.59; N 1.60

Dilinoleoyl-N-phthalimido-α-cephalin (IV, R = R′ = –$(CH_2)_7{-}(CH{=}CHCH_2)_2(CH_2)_4H$). Oily substance.

$C_{49}H_{76}O_{10}NP$. Found, %: C 67.66; H 8.76; N 1.76
Calculated, %: C 67.41; H 8.83; N 1.61

Dilinolenoyl-N-phthalimido-α-cephalin (IV, $R = R' = -(CH_2)_7-(CH{=}CHCH_2)_3(CH_3)$). Oily substance.

$C_{49}H_{72}O_{10}NP$. Found, %: C 68.65; H 8.44; N 1.73
Calculated, %: C 68.00; H 8.38; N 1.61

The final stage of the synthesis was the preparation of α-cephalins (V). Distearoyl-, dilinoleoyl-, and dilinolenoyl-α-cephalins were isolated. Distearoyl-α-cephalin (V, $R = R' = -(CH_2)_{17}H$) was obtained by treating distearoyl-N-phthalimido-α-cephalin with hydrazine hydrate in alcohol. M.p. 180.5–181° ([6]) (from a chloroform–methanol mixture, 1:2).

$C_{41}H_{82}O_8NP$. Found, %: C 66.07; H 10.97; N 1.95
Calculated, %: C 65.96; H 10.97; N 1.88

Treatment of the sodium salts of dilinoleoyl- and dilinolenoyl-N-phthalimido-α-cephalins in ethylene glycol monoethyl ether with hydrazine hydrate

led to the corresponding cephalins. Dilinoleoyl-α-cephalin (V, $R = R' = -(CH_2)_7(CH{=}CHCH_2)_2(CH_2)_4H$). Waxy substance. Iodine value found 135.92; 136.34; calculated 137.2.

Found, %: C 66.31; 66.62; H 9.90; 10.16; N 1.95; 1.96
$C_{41}H_{74}O_8NPF_4$. Calculated, %: C 66.60; H 10.01; N 1.90

Dilinolenoyl-α-cephalin (V, $R = R' = -(CH_2)_7(CH{=}CHCH_2)_3CH_3$). Waxy substance. Iodine value found 202.15; calculated 202.12.

Found, %: C 65.25; H 8.88; N 2.03
$C_{41}H_{72}O_9NPF_6$. Calculated, %: C 65.26; H 9.62; N 1.87

B. In the second case the starting α,β-diglycerides were obtained from α,α'-benzylideneglycerol. On acylation of α,α'-benzylideneglycerol with stearic acid chloride in pyridine, α,α'-benzylidenestearoylglycerol was obtained (VI, $R' = -(CH_2)_{17}H$). M.p. 58–59° (from alcohol and from an alcohol–petroleum ether mixture, 1:1).

Found, %: C 75.11; H 10.33
$C_{28}H_{46}O_4$. Calculated, %: C 75.30; H 10.38

Upon cleavage of the benzylidene group with boric acid in dioxane, compound VI was converted into β-stearoylglycerol (VII, $R' = -(CH_2)_{17}H$). M.p. 74–75° (from petroleum ether). On reduction of VI (hydrogen and palladium black on charcoal), VII, $R' = -(CH_2)_{17}H$, was likewise obtained, with m.p. 75–75.4°. β-Stearoylglycerol (VII, $R' = -(CH_2)_{17}H$) was acylated with oleic and linoleic acid chlorides in benzene in the presence of pyridine to give α,β-diglycerides: α-oleoyl-β-stearoylglycerol (III, $R = -(CH_2)_7CH{=}CH(CH_2)_8H$), $R' = -(CH_2)_{17}H$). M.p. 19–20° (from alcohol). Iodine value found 42.0; calculated 40.75.

Found, %: C 75.51; H 11.84
$C_{39}H_{74}O_5F$. Calculated, %: C 75.19; H 11.97

α-Linoleoyl-β-stearoylglycerol (III, R = $-(CH_2)_7(CH{=}CHCH_2)_2{-}(CH_2)_4H$; R′ = $-(CH_2)_{17}H$). M.p. 9-10° (from a mixture of methanol–alcohol–water, 24:8:1). d_4^{20} 0.9274; n_D^{20} 1.4708; MR_D found 187.1; calculated 186.2. Iodine value found 80.9; calculated 81.7.

Found, %: C 75.57; 75.41; H 11.65; 11.78
$C_{39}H_{72}O_5F_2$. Calculated, %: C 75.43; H 11.69

Introduction of the phosphorus-containing part into α-oleoyl-β-stearin was carried out as in the first method. α-Oleoyl-β-stearoyl-N-phthalimido-α'-cephalin and α-oleoyl-β-stearoyl-α'-cephalin were isolated. α-Oleoyl-β-stearoyl-N-phthalimido-α'-cephalin (IV, R = $-(CH_2)_7CH{=}CH(CH_2)_8H$, R′ = $-(CH_2)_{17}H$). d_4^{20} 1.037; n_D^{20} 1.4892; MR_D 243.8. $C_{49}H_{82}O_{10}NPF$. Calculated 242.36.

Found, %: C 67.04; 67.27; H 9.48; 9.18
$C_{49}H_{82}O_{10}NP$. Calculated, %: C 67.17; H 9.43

α-Oleoyl-β-stearoyl-α'-cephalin (V, R = $-(CH_2)_7CH{=}CH{-}(CH_2)_8H$, R′ = $-(CH_2)_{17}H$). M.p. 183-186°. Iodine value found 32.8; calculated 34.03.

Found, %: C 65.91; H 10.33; P 4.29
$C_{41}H_{80}O_8NPF$. Calculated, %: C 66.01; H 10.80; P 4.15

α-Linoleoyl-β-stearoyl-α'-cephalin was obtained by treating α-linoleoyl-β-stearin with phosphorus oxychloride in cyclohexane, and then with β-oxyethylphthalimide in the presence of quinoline and pyridine. The chloro derivative was hydrolyzed with water (IV). The phthaloyl protection was removed with hydrazine hydrate in alcohol (V).

α-Linoleoyl-β-stearoyl-N-phthalimido-α'-cephalin (IV, R = $-(CH_2)_7(CH{=}CHCH_2)_2(CH_2)_4H$, R′ = $-(CH_2)_{17}H$). Syrupy substance.

Found, %: C 65.70; H 9.48; P 3.54
$C_{49}H_{80}O_{10}NP$. Calculated, %: C 66.33; H 9.22; P 3.55

α-Linoleoyl-β-stearoyl-α'-cephalin (V, R = $-(CH_2)_7(CH{=}CHCH_2)_2 \cdot$

$(CH_2)_4H$, $R' = -(CH_2)_{17}H$). M.p. 181-183°. Iodine value found 68.1; calculated 68.0.

Found, %: C 65.98; H 10.64; P 4.15
$C_{41}H_{78}O_8NPF_2$. Calculated, %: C 66.18; H 10.57; P 4.17

B. In the third case ([8]), diacyliodohydrins of glycerol were introduced into reaction with the silver salt of benzyl-β-phthalimidoethylphosphoric acid. On acylation of α-iodohydrin of glycerol (VIII) in a mixture of pyridine with chloroform with one mole of oleic acid chloride, α-oleoyl-α'-iodohydrin glycerol was obtained (IX, $R = -(CH_2)_7CH = CH(CH_2)_8H$)–an amorphous substance ([9]). Iodine value found 54.36; calculated 54.41.

Found, %: C 54.33; 54.36; H 8.52; 8.49
$C_{21}H_{39}O_3JF$. Calculated, %: C 54.05; H 8.43

Acylation of IX with stearic acid chloride in benzene in the presence of triethylamine led to α-oleoyl-β-stearoyl-α'-iodohydrin glycerol (X, $R = -(CH_2)_7CH = CH - (CH_2)_8H$, $R' = -(CH_2)_{17}H$)—a viscous liquid. Iodine value found 33.76; calculated 34.63.

Found, %: C 64.26; 64.30; H 10.22; 10.26
$C_{39}H_{73}O_4JF$. Calculated, %: C 63.92; H 10.04

The phosphorus-containing portion was introduced by the interaction of X and the silver salt of benzyl-β-phthalimidoethylphosphoric acid. M.p. 186–188° (with decomposition).

Found, %: C 43.65; 43.67; H 3.33; 3.33; N 3.09; 3.20
$C_{17}H_{15}O_6NAgP$. Calculated, %: C 43.61; H 3.23; N 2.99

On interaction of X with the silver salt in benzene, benzyl-(3′-phthalimidoethyl)-(α-oleoyl-β-stearoyl-α'-glyceryl)-phosphate was obtained (XI, $R = -(CH_2)_7CH = CH(CH_2)_8H$, $R' = -(CH_2)_{17}H$), which was boiled with lithium bromide in acetone; as a result the lithium salt of β'-phthalimidoethyl-(α-oleoyl-β-stearoyl-α'-glyceryl)-phosphoric acid was isolated. M.p. 117.5–118.5° (from alcohol). Iodine value found 29.29; calculated 28.77.

Found, %: C 66.54; 66.49; H 9.36; 9.45; N 1.74; 1.62
$C_{49}H_{81}O_{10}NLiPF$. Calculated, %: C 66.73; H 9.26; N 1.59

On treatment of the lithium salt with hydrazine hydrate in alcohol, the corresponding α-cephalin was obtained.

α-Oleoyl-β-stearoyl-α'-cephalin (V, $R = -(CH_2)_7CH = CH - (CH_2)_8H$, $R' = -(CH_2)_{17}H$). M.p. 184–185° (from alcohol). Iodine value found 32.69; calculated 34.01.

Found, %: C 65.93; 66.03; H 10.62; 10.70; N 1.98; 2.10
$C_{41}H_{80}NO_8PF$. Calculated, %: C 66.01; H 10.81; N 1.88

In the isolation of the final and intermediate compounds of the synthesis, chromatography on silicic acid was used.

To prove the structure of the obtained α,β-diglycerides, as well as of the α-cephalins, the unsaturated compounds obtained were converted into saturated ones and identified with known ([6],[10]) substances.

Moscow Institute of Fine Chemical Technology
named after M. V. Lomonosov

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