STUDIES IN THE FIELD OF THE SYNTHESIS OF LIPOID COMPOUNDS

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1965

SovietRxiv

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Abstract

Full Text

UDC 547.915.5

CHEMISTRY

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(Presented by Academician M. I. Kabachnik, 8 IV 1965)

The synthesis of diester glycerophosphatides of the lecithin type (ˆ1), cephalin (ˆ2), and phosphatidylserine (ˆ3) made it possible to proceed to the preparation of inositol phosphatides, which in structure are diphosphoinositides (Scheme 1), as well as compounds of more complex structures that include amino-acid residues (Schemes 2 and 3).

Scheme 1

In the reaction of a molar amount of the 1,2,4,5-di-*O*-cyclohexylidene derivative of myoinositol (I, m.p. 173-174°) with phosphorus oxychloride (2 mol) and subsequent condensation with a half-molar amount of α,β-distearoylglycerol (II, m.p. 70-71°), (ˆ4) 1-[α-(α',β-distearoyl)glycerophosphoryl]-4-phosphatmyoinositol (III, $R = C_{17}H_{35}$) was obtained. Yield 16.6%. M.p. 161-163°. R_f 0.15 (thin-layer chromatography on silicic acid in the chloroform—methyl alcohol—water system, in ratios 80 : 25 : 5).

Found, %: C 58.32; H 9.49; P 6.67
$C_{45}H_{88}O_{16}P_2$. Calculated, %: C 58.00; H 9.52; P 6.61

IR spectrum: 3400-3200 (OH); 2960, 2931, 2865, 1475, 1385, 780 (CH, CH_2, CH_3); 1750, 1185 (COOR); 1250 (P = O); 1120, 1050 (POC); 960 (P—OH) cm^{-1}.

By the action of phosphorus oxychloride (2 moles) and the same amount of α,β-distearoylglycerol (II) on a molar amount of 1,2,4,5-di-*O*-cyclohexylidenemyoinositol

Scheme 2: reaction scheme showing conversion of α,β-distearoylglycerol (II) with β-phthalimidoethyl phosphorodichloridate (V), tetraacetylmyoinositol (VII), intermediate (VIII), and hydrazine to the final ethanolamine myoinositol phospholipid (IX); where $R = C_{17}H_{35}$, $Ac = COCH_3$.

Figure 2: Scheme 2: reaction scheme showing conversion of α,β-distearoylglycerol (II) with β-phthalimidoethyl phosphorodichloridate (V), tetraacetylmyoinositol (VII), intermediate (VIII), and hydrazine to the final ethanolamine myoinositol phospholipid (IX); where $R = C_{17}H_{35}$, $Ac = COCH_3$.

(I), 1,4-bis-[α-(α',β-distearoyl)-glycerylphosphoryl]-myoinositol (IV) was synthesized (4). Yield 14.8%. M.p. 131-131.5°. R_f 0.69 (thin-layer chromatography on silicic acid in the system chloroform—methyl alcohol—water in ratios of 80 : 25 : 2).

Found %: C 64.98; H 10.36; P 4.02

$C_{84}H_{164}O_{20}P_2$. Calculated %: C 64.91; H 10.49; P 3.98

IR spectrum: 3400-3200 (OH); 2959, 2933, 2861, 1480, 1382, 718 (CH, CH_2, CH_3); 1745, 1180 (COOR), 1240 ($P = O$); 1120, 1065 (POC); 960 (P—OH) cm^{-1}.

Substances of the type of the diester compounds synthesized by us are, as Collins believes (5), products of the half-decay in the process of isolation from natural sources of triester phosphatides. The latter compounds are one of the principal forms of existence of complex lipids in the organism (5).

We synthesized a triester (IX) having the structure of cephalin, the free hydroxyl group of which is linked by an ether bond with the first hydroxyl group of myoinositol (Scheme 2).

Scheme 2

By phosphorylation of α,β-distearoylglycerol (II) with β-phthalimidoethylphosphoric acid dichloroanhydride (V, m.p. 74.5-75°) and subsequent condensation with 3,4,5,6-tetraacetylmyoinositol (VII, m.p. 134-136°), we obtained α-(α',β-distearoyl)-glycerylphosphoryl-[1-(3,4,5,6-tetraacetylmyoinositol)]-*N*-phthaloylethanolamine (VIII). Yield 18.3%. M.p. 48.5-49°. R_f 0.65 (thin-layer chromatography on silicic acid in ether).

Found %: C 62.50; H 8.45; N 1.30; P 2.78

$C_{63}H_{102}O_{19}NP$. Calculated %: C 62.63; H 8.43; N 1.16; P 2.56

After removal of the phthaloyl and acetyl protections by the action of hydrazine hydrate on compound (VIII), we isolated α-(α',β-distearoyl)-glycerylphosphoryl-(1-myoinositol)-ethanolamine (IX). Yield 64.6%. M.p.

67.5-68°. R_f 0.49 and 0.68 (thin-layer chromatography on silicic acid in the systems diisobutyl ketone—acetic acid—water (45 : 25 : 5) and chloroform—methanol (4 : 1), respectively).

Found %: C 62.1; H 10.07; N 1.80; P 3.29

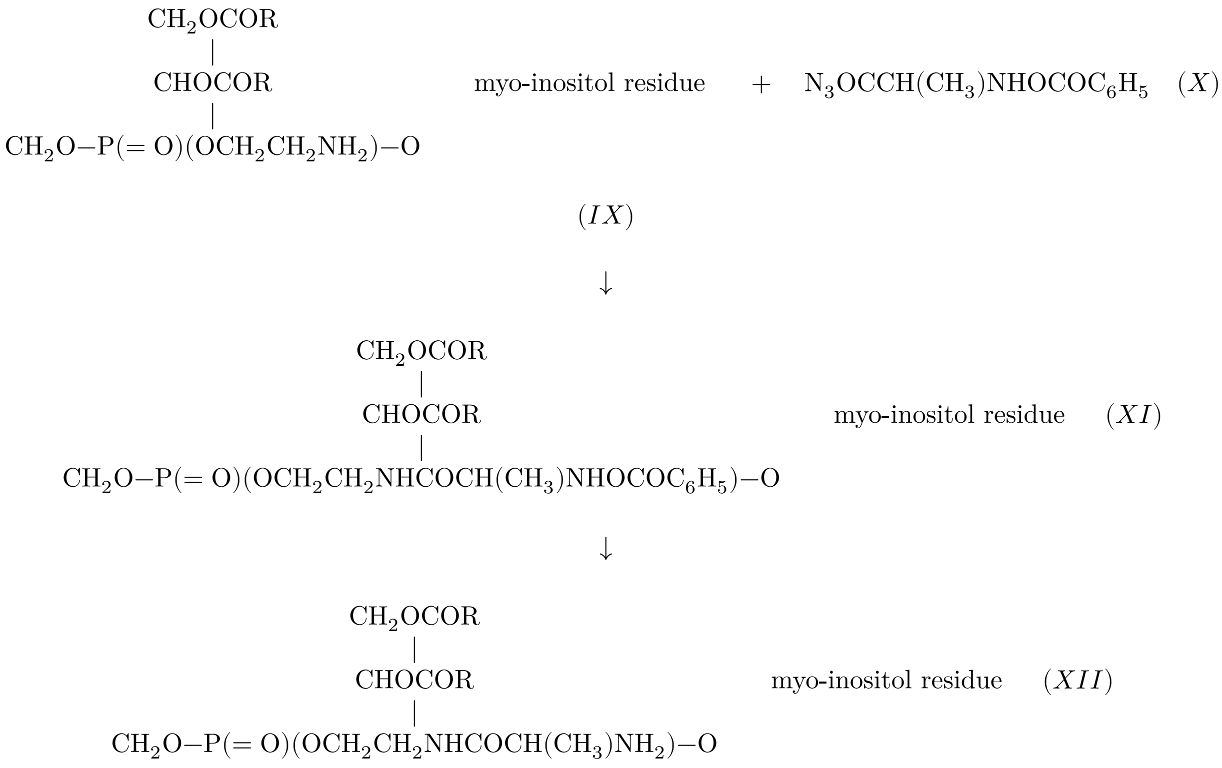
$C_{47}H_{92}O_{13}NP$. Calculated %: C 62.01; H 10.18; N 1.53; P 3.40

In the IR spectrum of triester (IX), in comparison with the spectrum of the diester compounds (III) and (IV), the band at 960 cm^{-1}, characterizing vibrations of the P—OH group, disappears, which confirms the triester structure (IX). The spectrum of compound (IX) differs from the spectrum of substance (VIII) by the presence in the latter of additional bands at 1715, 1395 (N—CO), and 1439 cm^{-1} (C = C of the benzene ring), which is due to the presence in compound (VIII) of a protective phthaloyl grouping.

At present there are data on the presence in phosphatide fractions from tissues and organs of amino acids and peptides attached to phosphatides (6). Lipid-protein complexes of this type play a major role both in the structural organization of cells of living organisms and in their biological activity (7).

The synthesis of a similar compound was carried out by us on the basis of α-(α',β-distearoyl)-glycerylphosphoryl-(1-myo-inositol)-ethanolamine (IX) and N-carbobenzoxyalanine azide (X), obtained from the corresponding hydrazide (m.p. 137-138°) (Scheme 3).

Scheme 3



$$\begin{array}{c} CH_2OCOR \\ | \\ CHOCOR \\ | \\ CH_2O{-}P(=O)(OCH_2CH_2NH_2){-}O \end{array} \text{ myo-inositol residue } + \; N_3OCCH(CH_3)NHOCOC_6H_5 \quad (X)$$

$$(IX)$$

$$\downarrow$$

$$\begin{array}{c} CH_2OCOR \\ | \\ CHOCOR \\ | \\ CH_2O{-}P(=O)(OCH_2CH_2NHCOCH(CH_3)NHOCOC_6H_5){-}O \end{array} \text{ myo-inositol residue } \quad (XI)$$

$$\downarrow$$

$$\begin{array}{c} CH_2OCOR \\ | \\ CHOCOR \\ | \\ CH_2O{-}P(=O)(OCH_2CH_2NHCOCH(CH_3)NH_2){-}O \end{array} \text{ myo-inositol residue } \quad (XII)$$

where $R = C_{17}H_{35}$

By condensation of triester (IX) with N-carbobenzoxyalanine azide (X), we synthesized α-(α',β-distearoyl)-glycerylphosphoryl-(1-myo-inositol)-ethanolamino-N-(N′-carbobenzoxyalanine) (XI). Yield 70.5%. M.p. 88.5-89°. R_f 0.80 and 0.77 (thin-layer chromatography in the systems diisobutyl ketone—acetic acid—water (45 : 25 : 5) and chloroform—methyl alcohol (4 : 1), respectively).

Found, %: C 62.90; H 9.56; N 2.31
$C_{58}H_{103}O_{16}N_2P$. Calculated, %: C 62.45; H 9.30; N 2.51

The final compound, α-(α',β-distearoyl)-glycerylphosphoryl-(1-myo-inositol)-ethanolamino-*N*-alanine (XII), was obtained after removal of the carbobenzoxy group by hydrogenolysis of substance (XI) in the presence of palladium on charcoal, in 78.7% yield. Mp 128-128.5°. R_f 0.50 and 0.75 (thin-layer chromatography on silicic acid in the systems diisobutyl ketone—acetic acid—water (45 : 25 : 5) and chloroform—methanol (4 : 1), respectively).

Found, %: C 64.99; H 9.70; N 2.74
$C_{50}H_{97}O_{14}N_2P$. Calculated, %: C 65.27; H 9.96; N 2.85

The structure of the phosphatidyl peptide (XII) was confirmed by comparison of its IR spectrum with the spectrum of the triester (IX). In both spectra analogous absorption bands of the same intensity were found, except for the appearance in the spectrum of substance (XII) of a broad band at 1640–1620 cm^{-1}, which is due to the formation of an amide group in the synthesis of compound (XII) from the triester (IX).

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Received
6 IV 1965

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