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SYNTHESIS OF PLASMALOGEN WITH NATURAL CONFIGURATION

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A synthetic approach to plasmalogens with natural stereochemical configuration is reported and exemplified by the preparation of O-(1-hexadec-cis-1-enyl-2-stearoyl-sn-glycero-3-phosphoryl)-N,N-dimethylethanolamine (XI).

We have found new synthetic approaches to plasmalogens when carrying out investigations with a mixture of stereoisomers [1,2]. The reproduction of the fine molecular structure of plasmalogens necessitated the availability of an optically active starting compound to build up compounds of the 1-alk-1′-enyl-sn-glycerol series and obtain the cis-1-alkenyl-ether group.

These stereochemical problems were solved at the stage of the preparation of 1-alk-cis-1′-enyl-sn-glycidols (V) [3]. The synthesis of enantiomeric alkenyl glycidol ethers (IV,V) was effected by tosylating 3-(2′-tosyloxyalkyl)-sn-glycerol (I) in different positions [4], which gave compounds II or III (with the trityl group used for protection in the latter case). Treatment of II and III with tert.- C_4H_9OK led to the elimination of 2 moles of p-toluenesulfonic acid and to the concurrent formation of the 1-alkenyl-ether group and the closure of the oxyrane ring with respective retention or inversion of configuration at C_2. The elimination resulted in a mixture of cis- and trans-isomers that were chromatographically separated on argentated silica gel and the trans-isomer obtained was then made to undergo equilibrium catalytic isomerisation in the presence of selenium [3]. It was then shown [5] that the

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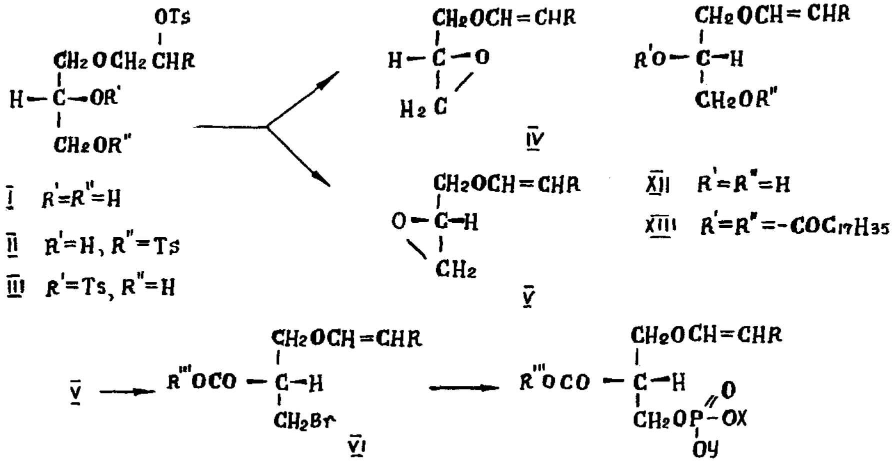
opening of the oxyrane ring in (V) by the bromoanhydride of stearic acid was directed to the formation of 1-alk-cis-1'-enyl-2-acyl-3-bromo-3-desoxy-sn-glycerol (VI), that could be used to synthesise various classes of plasmalogens. To obtain phosphatidal-N,N-dimethylethanolamine (XI) 1-hexadec-cis-1'-enyl-2-stearoyl-3-bromo-3-desoxy-sn-glycerol (VI) was condensed by boiling with silver salt of dibenzylphosphate in xylene (15 min.) in the presence of pyridine [6]. Chromatography on silicic acid gave analytically pure phosphate ester (VII). Yield 80.2%, m.p. 20-20.5°; $[\alpha]_D^{20}$ -2.6° (c=1, $CHCl_3$); Rf 0.5 (argentated silica gel G, hexane-ether ratio 1:3); IR spectrum (layer): 3040-3080, 1735, 1665, 1500, 1270, 1170, 1020, 700 cm^{-1}.



Ts = $-SO_2C_6H_4CH_3$-n

Bz = $-CH_2C_6H_5$

R = n-$C_{14}H_{29}$, R''' = n-$C_{17}H_{35}$

VII X=Y=Bz

VIII X=Bz, Y=Na

IX X=Bz, Y=Ag

X X=Bz, Y=$-(CH_2)_2N(CH_3)_2$

XI X=Na, Y=$-(CH_2)_2N(CH_3)_2$

Compound VII was boiled with sodium iodide in acetone to give sodium salt (VIII). Yield 97.4%, m.p. 53.5-54°; IR spectrum (layer): 3040-3080, 1735, 1665, 1500, 1235, 1170, 1100, 700 cm^{-1}.

Treatment of $AgNO_3$ in aqueous acetone mixture (1:2) resulted in silver salt (IX). Yield 79.6%, m.p. 60-61°; Rf 0.4 (unfixed layer of silicic acid, Chloroform-methanol-acetone ratio 10:1:1); IR spectrum (layer): 3040-3080, 1735, 1655, 1500, 1210, 1170, 1060, 700 cm^{-1}.

Reaction of salt (IX) with 2-chloroethyl-N,N-dimethylamine (boiling for 2 hours in C_6H_6) gave phosphate ester (X). Chromatography on silicic acid gave an analytically pure compound (X). Yield 92.4%, m.p. 17-18°; $[\alpha]_D^{24}$-2.6° (c=1.25, $CHCl_3$); Rf 0,5 (aluminium oxide of the fourth degree of activity, petroleum ether - ether ratio 1:3); IR spectrum ($CHCl_3$): 3040-3080, 1735, 1665, 1260, 1170, doublet 1050-1090, 1020 cm^{-1}.

Anionic debenzylation of compound (X) with sodium iodide in acetone led to O-(1-hexadec-cis-1'-enyl-2-stearoyl-sn-glycerol-3-phosphoryl)-N,N-dimethylethanolamine (XI) in the form of sodium salt that was purified by repeated precipitation from $CHCl_3$ by excess acetone at -30°. Yield 76.4%, m.p. 124-125°; $[\alpha]_{467}^{20}$ -8.3° (c=0.45, $CHCl_3$); Rf 0.67 (unfixed layer of silicic acid, $CHCl_3$, acetone - methanol ratio 10:3:3).

The optical purity of plasmalogen (XI) was ascertained by chemical correlation. To this end (XI) was treated with $LiAlH_4$ to obtain 1-hexadec-cis-1'-enyl-sn-glycerol (XII). Yield 96.0%, m.p. 37-39°; $[\alpha]_D^{20}$-2.1° (c=1, $CHCl_3$) lit [7]. $[\alpha]_D^{20}$-2.0° (c=2, $CHCl_3$). The resulting compound gave, on acylation, I-hexadec-cis-1'-enyl-2,3-distearoyl-sn-glycerol (XIII). Yield 82.2%, m.p.47.5-48.5°; Rf 0.25 (argentated silica gel G, petroleum ether- ether ratio 5:1); $[\alpha]_D^{20}$-3.3° (c=1.1, $CHCl_3$), lit. $[\alpha]_D^{20}$-3.6° [8] and 3.4° [9] (c=1.1, $CHCl_3$).

The cis-configuration of the double bond in VI-XIII was confirmed by the presence of a singlet in the IR spectra at 1665 cm^{-1} and the absence of the band at 930 cm^{-1}, as well as by the PMR spectrum of the neutral plasmalogen (XIII) (doublet at δ = 5.90 ppm, J = 6.53 cps [7]).

The reported method can be useful as a general synthetic approach to plasmalogens with a natural structure and various fat acids, aldehydes and nitrous bases.

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