Tetrahedron Letters No.30, pp. 2575-2578, 1970. Pergamon Press. Printed in Great Britain.

STUDIES TOWARDS A SYNTHESIS OF PHOSPHATIDYLINOSITOL

Patricia A. Gent, Roy Gigg and C.D. Warren

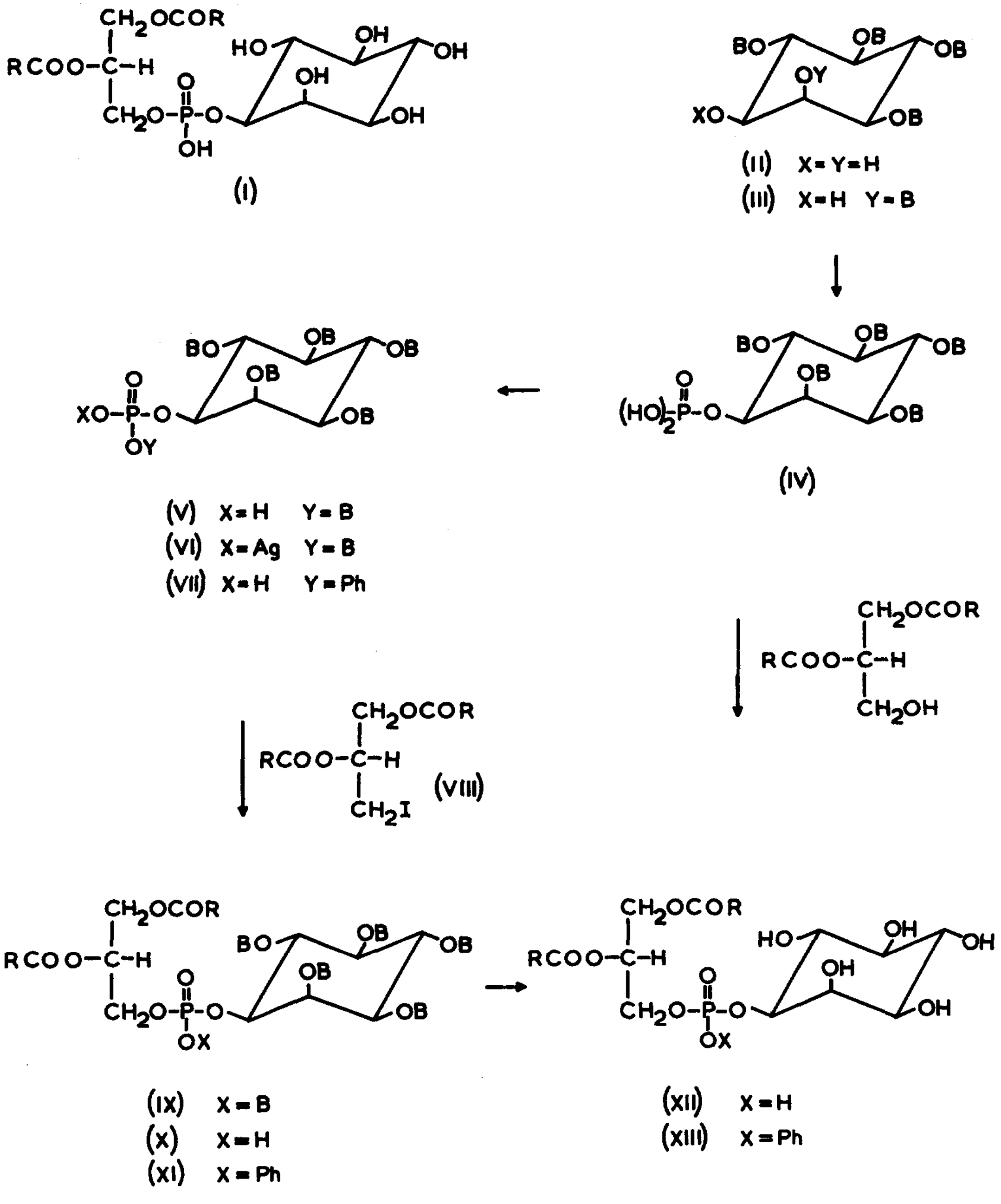
National Institute for Medical Research, Mill Hill, London, N.W.7.

(Received in UK 18 May 1970; accepted for publication 27 May 1970)

Phosphatidylinositol (I)[1] is a component of the phospholipids of plant, animal and bacterial cell membranes and its complete structure was established by the degradative studies of Ballou and Pizer[2]. Several complex derivatives of phosphatidylinositol also occur in animal and bacterial cell membranes[1].

An isomer of phosphatidylinositol in which the inositol was phosphorylated on the 2-position (axial hydroxyl group) has been prepared[3] previously and a recent preliminary communication[4] has described a synthesis of phosphatidylinositol. We have described[5,6] the synthesis of the racemic 2, 3, 4, 5, 6-penta-O-benzylmyoinositol (III) from the 3, 4, 5, 6-tetra-O-benzylmyoinositol (II) by using the allyl ether for protection and subsequently[6] we have described the conversion of compound (III) into the racemic phosphate esters (IV) and (V) which are suitable intermediates for investigating routes for a synthesis of phosphatidylinositol.

In the first method, the silver salt (VI) was condensed with the optically active dipalmitoyl ester (VIII)[7] to give the phosphate triester (IX) as a syrup which was purified by chromatography on neutral alumina (Found: C, 74.0; H, 8.0; P, 2.2. $C_{83}H_{115}O_{13}P$ requires C, 73.8, H, 8.6; P, 2.3%). Compound (IX) was treated with sodium iodide in dry acetone[8] to give the sodium salt of the phosphate diester (X) which was purified by chromatography on neutral alumina and acidified to give the free acid (X) as a syrup (Found: C, 72.6; H, 8.1; P, 2.5. $C_{76}H_{109}O_{13}P$ requires C, 72.35; H, 8.7; P, 2.5%). Hydrogenation of compound (X) over palladium on charcoal gave the diastereoisomeric mixture of phosphatidylinositols (XII) which were recrystallized from methanol (Found: C, 60.6; H, 9.95; P, 3.3 $C_{41}H_{79}O_{13}P$ requires C, 60.7; H, 9.8; P, 3.8%) $[\alpha]_D + 2.5°$ (c 0.8 in chloroform-methanol 2:1).



$R = -(CH_2)_{14}CH_3$ $B = -CH_2Ph$

In the second method compound (X) was prepared directly from the phosphate (IV) by condensation with 1,2-di-O-palmitoyl-L-glycerol in the presence of triisopropylbenzenesulphonyl chloride[9] in dry pyridine and was purified by chromatography on neutral alumina.

Condensation of the silver salt of the phenyl phosphate (VII)[6] with the racemic iodo compound (VIII) gave the phosphate triester (XI). Successive hydrogenations of this compound with (a) palladium on charcoal - to remove the benzyl groups and give compound (XIII) and (b) platinum - to remove the phenyl group from compound (XIII) - led to a mixture of products including diglycerides. It is known[10] that phosphate triesters with adjacent hydroxyl groups [such as compound XIII)] are very labile and the mixture of products presumably arises from decomposition of compound (XIII) before the phenyl group can be removed. By contrast, the hydrogenolysis of the phosphate diester (X) gave quantitative yields of the product (XII). Preobrazhenskii and his coworkers have described resolutions of the 3,4,5,6-tetra-O-benzylmyoinositol (II)[11] and of 2,3,4,5,6-penta-O-benzylmyoinositol (III)[12] and in their preliminary communication[4] describe a synthesis of phosphatidylinositol, with the complete stereochemistry of the natural product, by hydrogenolysis of compound (XI) with palladium and platinum catalysts. No experimental details are reported but a yield of 49% is recorded for the hydrogenolysis stage. In view of the known lability of compounds related to compound (XIII) and of our own experience with this compound we consider that the two routes outlined above for the synthesis of the diastereoisomeric mixture of phosphatidylinositols, via compound (X), will be more satisfactory for the synthesis of the fully optically active compound than the route via compound (XI).

References

1. B.A. Klyashchitskii, S.D. Sokolov & V.I. Shvets, Russ.Chem.Rev., 1969, 38, 345.
2. C.E. Ballou & L.I. Pizer, J. Amer.Chem.Soc., 1959, 81, 4745; 1960, 82, 3333.
3. J.H. Davies & T. Malkin, Chem. and Ind., 1959, 1155.
4. E.G. Zhelvakova, B.A. Klyashchitskii, V.I. Shvets, R.P. Evstigneeva & N.A. Preobrazhenskii, Zhur. obshchei Khim., 1970, 40, 248.
5. R. Gigg & C.D. Warren, Tetrahedron Letters, 1966, 2415.
6. R. Gigg & C.D. Warren, J. Chem. Soc. (C), 1969, 2367.

7. N.Z. Stanacev & M. Kates, Canad. J. Biochem. Physiol., 1960, 38, 297.

8. L. Zervas & I. Dilaris, J. Amer. Chem. Soc., 1955, 77, 5354.

9. R. Lohrmann & H.G. Khorana, J. Amer. Chem. Soc., 1966, 88, 829; R. Aneja, J.S. Chadha & A.P. Davies, Tetrahedron Letters, 1969, 4183.

10. D.N. Brown, Ann. New York Acad. Sci., 1969, 165, 687.

11. B.A. Klyashchitskii, G.D. Stradhova, V.I. Shvets, S.D. Sokolov & N.A. Preobrazhenskii, Doklady Akad. Nauk. S.S.S.R., 1969, 185, 594; Zhur. obshchei Khim., 1970, 40, 236.

12. B.A. Klyashchitskii, V.V. Pimenova, V.I. Shvets, S.D. Sokolov & N.A. Preobrazhenskii, Zhur. obshchei Khim., 1969, 39, 2373.