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## The Use of Silver Phenyl Benzyl Phosphate for the Synthesis of Monophenyl Esters of Phosphatidic Acids

(Preliminary Communication)

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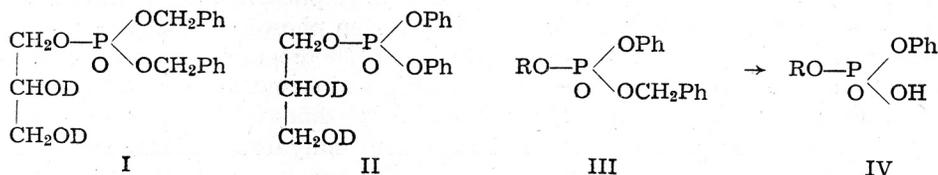
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Hessel, Morton, Todd, and Verkade<sup>1</sup> have shown that dibenzyl esters of  $\alpha$ -glycerophosphatidic acids I (D = acyl group), when shaken at room temperature in an ethanolic medium with hydrogen under slightly more than atmospheric pressure in the presence of a palladium/active carbon catalyst according to Verkade, Cohen, and Vroege<sup>2</sup> are smoothly hydrogenolyzed; 2 moles of hydrogen per mole of ester are rapidly absorbed, resulting in the formation of the corresponding phosphatidic acids and toluene. As was subsequently found in our laboratory, the same applies to the dibenzyl esters of glycolphosphatidic acids.

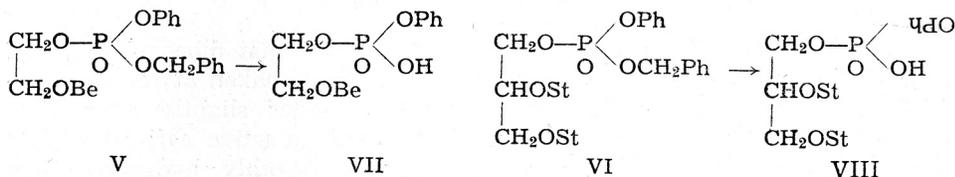
In contrast with this, Uhlenbroek and Verkade<sup>3</sup> found that diphenyl esters of  $\alpha$ -glycerophosphatidic acids II (D = acyl group) remain unchanged under identical experimental conditions. In this case, however, it was found possible to effect the hydrogenolysis by the use of a platinum/active carbon catalyst; in the course of a few hours 8 moles of hydrogen per mole of ester are then absorbed, resulting in the formation of the corresponding phosphatidic acids and cyclohexane. Previously it had already been established by van der Neut, Uhlenbroek, and Verkade<sup>4</sup> that the hydrogenolysis of the diphenyl esters of glycolphosphatidic acids can be carried out with platinum/active carbon, but not with palladium/active carbon, and also with platinum dioxide according to Adams *c. s.*, but not with palladous oxide.

The cause of this difference in behaviour between palladium and platinum catalysts is in all probability that the hydrogenolysis cannot take place until after hydrogenation of the phenyl group and the latter process only proceeds with platinum catalysts like those mentioned.



The question of course occurred to us how phenyl benzyl esters of phosphatidic acids III, naturally with a R-O linkage that is not hydrogenolyzed under the appropriate experimental conditions, will behave when treated with

hydrogen in the presence of a palladium catalyst. It was to be expected that the benzyloxy group alone will be attacked and that consequently monophenyl esters of phosphatidic acids IV will be formed. This was actually found to be the case. Thus, for example, starting from the compounds V and VI (St = stearyl; Be = behenoyl), by shaking at room temperature in an ethanolic medium with hydrogen under slightly more than atmospheric pressure in the presence of a palladium/active carbon catalyst according to Verkade, Cohen, and Vroege<sup>2</sup> or a similar catalyst, the corresponding monophenyl esters VII and VIII were obtained in yields of about 90%. Per mole of ester 1 mole of hydrogen is absorbed in the course of a few minutes, after which, even upon several hours' continued shaking, no further absorption of hydrogen is to be observed.

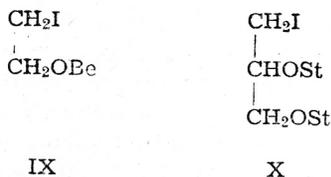


It should be noted that as a rule this method of preparation of the monophenyl esters in question is obviously and unfortunately confined to such compounds as contain no component acids which can be reduced under the conditions of the hydrogenolysis, for example an unsaturated fatty acid (oleic acid, etc.). Since unsaturated fatty acids play an important part as component acids of naturally occurring phosphatidic acids, phosphatides, etc., we have investigated whether the catalyst according to Lindlar<sup>5</sup>, which is accepted not to cause hydrogenation of double bonds, can be used for the preparation of monophenyl esters of phosphatidic acids with unsaturated component acids. This appeared not to be the case; in the presence of this catalyst (palladium-lead) no hydrogenolysis of the benzyloxy group takes place.

As a consequence of the above suggestion with regard to the presumable cause of the difference in behaviour between palladium and platinum catalysts it would seem probable to us that phenyl cyclohexyl esters of phosphatidic acids will also be found suitable for the preparation of monophenyl esters by the method described. This possibility we hope shortly to investigate.

As one of the two starting products for the synthesis of phenyl benzyl esters of phosphatidic acids, silver phenyl benzyl phosphate is required. In order to prepare this compound, dibenzyl hydrogen phosphite is oxidized with sulphuryl chloride to dibenzyl chlorophosphate (= dibenzyl phosphorochloridate), and the latter in the crude state is brought into reaction with anhydrous potassium phenolate, as a result of which phenyl dibenzyl phosphate is produced; when the latter compound is boiled with anhydrous sodium iodide in acetone solution<sup>6</sup>, sodium phenyl benzyl phosphate is obtained, which is converted in the usual manner into the silver salt. In dry condition the colourless silver salt is very stable. It had previously been prepared already in a slightly different way by Baddiley, Clark, Michalski, and Todd<sup>7</sup>.

The other starting product is a halogeno compound of appropriate structure. Thus, for the synthesis of the phenyl benzyl esters of phosphatidic acids V and VI given as examples the compounds IX and X were used as such.



The desired phenyl benzyl esters of phosphatidic acids are obtained in yields of 80—85% by the reaction between perfectly dry silver phenyl benzyl phosphate and a boiling solution of the appropriate halogeno compound in a neutral medium, usually dry benzene.

If phenyl benzyl chlorophosphate (= phenyl benzyl phosphorochloridate) were available, the phenyl benzyl esters of phosphatidic acids might also be prepared by the reaction between the first-mentioned compound and the appropriate hydroxy compound in the presence of dry pyridine. For the preparation of the compounds of types V and VI a monoacylglycol and an  $\alpha\beta$ -diacylglycerol respectively would then have to serve as starting products. Unfortunately, we have not, however, succeeded so far in preparing phenyl benzyl chlorophosphate in a pure state.

The monophenyl esters of phosphatidic acids hitherto prepared by us are colourless, readily crystallizing substances, which are not stable, not even with careful exclusion of moisture; the melting point is gradually lowered and the smell of phenol develops.

Upon titration in alcoholic solution with dilute aqueous alkali hydroxide, using phenolphthalein as indicator, the substances behave as monobasic acids; the equivalent weights found were in very good accordance with those calculated.

When the monophenyl esters, dissolved in dioxan, are shaken with hydrogen under slightly more than atmospheric pressure in the presence of a platinum/active carbon catalyst according to Uhlenbroek and Verkade<sup>3</sup>, 4 moles of hydrogen per mole of ester are slowly absorbed and the corresponding phosphatidic acids are obtained in a very good yield. The reaction products were found to be identical with those which are formed upon complete hydrogenolysis of the corresponding diphenyl esters, dibenzyl esters or phenyl benzyl esters, as was hardly to be otherwise expected.

The phenyl benzyl esters and the monophenyl esters of phosphatidic acids hitherto prepared by us all have sharp melting points. This applies also to the esters of types VI and VIII respectively; thus, for example, the phenyl benzyl ester of  $\beta\gamma$ -dipalmitoylglycerol- $\alpha$ -phosphoric acid melts at 42—43° and the monophenyl ester of  $\beta\gamma$ -dipalmitoylglycerol- $\alpha$ -phosphoric acid at 54.5—55.5°. This fact calls for a slightly more detailed discussion.

The molecule of a phenyl benzyl ester of type VI contains two asymmetrical atoms, namely the central carbon atom of the glycerol moiety and the phosphorus atom. Upon reaction of silver phenyl benzyl phosphate with a synthetic, *i. e.* racemic,  $\alpha\beta$ -diacylglycerol- $\alpha$ -iodohydrin the formation of two diastereoisomeric phenyl benzyl esters of type VI, each a racemic mixture or a racemic compound of two optical antipodes, is therefore to be expected. In this connection reference is made in passing to recent work<sup>8</sup> on the resolution of compounds containing tetravalent phosphorus, which are more closely related to those with which we are at present concerned than the phosphorus compounds formerly resolved; it is beyond doubt that these phosphorus compounds behave »normally« in stereochemical respect. The fact that we invariably isolated a substance with a sharp melting point in a yield of 80—85% may therefore undoubtedly be interpreted in the sense that one of the diastereoisomeric phenyl benzyl esters at least is formed in a highly preponderating degree.

With the corresponding monophenyl esters of type VIII the situation is doubtful. In our opinion it may be regarded as certain that in the anion of these monobasic acids the phosphorus atom has two equal valencies, *i. e.* is not asymmetrical. However, this implies by no means that this must also be the case with the acids, particularly in the crystalline state, *i. e.* that here the possibility of the existence of two diastereoisomers, each a racemic mixture or a racemic compound of two optical antipodes, is to be ruled out. Indeed, questions about crystal structure, bonding around the phosphorus atom, possible occurrence of tautomerism, etc. here suggest themselves, to which no answers can as yet be given. It may suffice for us to have made the above short remarks. They apply, among others, also to  $\alpha$ -phosphatides and to  $\beta$ -phosphatides with two different fatty acids as component acids; it is curious that — at least as far as we are aware — the stereochemistry of these compounds has never yet been regarded in this light.

The fact that in the hydrogenolysis of the phenyl benzyl esters of type VI we invariably isolated in a yield of about 90% a substance with a sharp melting point may undoubtedly be interpreted to imply that the monophenyl esters of type VIII obtained by us are homogeneous.

Starting from the monophenyl esters of types VII and VIII, colourless silver salts which are very stable, even when exposed to light, can be obtained in very good yields, either by treatment of an acetone solution of the ester, *i. e.* the monobasic acid, with an aqueous solution of silver nitrate or in the more usual way *via* the sodium salt. The silver salts can be very readily recrystallized from certain organic solvents, for example from absolute ethanol.

The monophenyl esters of phosphatidic acids and the silver salts derived therefrom are very suitable starting materials for further syntheses, *e. g.* of pyrophosphatidic acids, (mixed) biphosphatidic acids, certain types of phosphatides and lysophosphatides, etc. It is beyond the scope of this preliminary communication to go into this more in detail.

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## IZVOD

**Upotreba srebrnog fenil benzil fosfata u sintezi monofenil estera fosfatidnih kiselina**

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U obliku prethodnog priopćenja opisana je upotreba fenil benzil fosfata u sintezi monofenil estera fosfatidnih kiselina. Srebrni fenil benzil fosfat može se prirediti iz natrijske soli, koja se dobije tako, da se dibenzil kiseli fosfit oksidira sa sulfuril kloridom u dibenzilklorofosfat, koji ako se obradi s bezvodnim kalijevim fenolatom daje fenil dibenzil fosfat. Pomoću bezvodnog natrijskog jodida prevodi se fenil dibenzil fosfat u natrijsku sol fenil benzil fosfata. Reakcijom između srebrnog fenil benzil fosfata i odgovarajućih halogeno spojeva, dobiju se pripadni fenil benzil esteri fosfatidnih kiselina s iskorištenjem od 80–85%. Fenil benzil esteri fosfatidnih kiselina mogu se debenzilirati pomoću vodika u prisutnosti paladijskog katalizatora, pri čemu se dobiju monofenil esteri fosfatidnih kiselina. Fenil benzil esteri i monofenil esteri fosfatidnih kiselina priređeni u okviru ovoga rada imaju oštra tališta a dobiveni su u iskorištenju od 80–85%, što dokazuje da su navedeni spojevi homogeni.

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