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PHOSPHONATE AND PHOSPHATE MONOESTER HYDROLYSIS

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ABSTRACT: The reaction of phosphonate and phosphate monoesters with an epoxide yields β-hydroxyalkyl derivatives which upon treatment with base quantitatively release the original alcohol moiety of the ester in a relatively rapid simple procedure.

The resistance of phosphate monoesters to hydrolysis under both basic and acidic conditions is well known.[1] A rate maximum has been observed at about pH 4-4.5, which is attributed to reaction via metaphosphate release.[1a,c] However, even under these conditions the reaction of unactivated monoalkyl phosphates is slow and requires elevated temperatures. In practical terms, the requirements for the complete hydrolysis of dialkyl phosphates or monoalkyl phosphonates are no less stringent, especially in the case of large alkyl groups. This situation has prompted a search for sophisticated catalysts for these hydrolyses,[2] and the elegant work of J. Chin has lately produced cobalt complexes having the desired activity.[3] While these catalysts are very effective in the reaction of simple phosphates in aqueous medium, their applicability to phosphate or phosphonate esters bearing large hydrophobic residues remains to be demonstrated.

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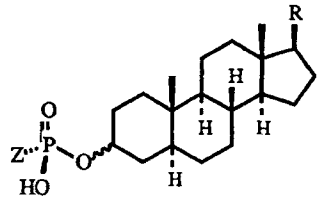
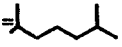
We were faced with the problem of releasing steroidal alcohols from their phenylphosphonate and their phosphate monoesters. Examples of the esters in question are 3β-cholestanyl hydrogen phenylphosphonate (**1**) and its $\Delta^{9,11}$ derivative (**2**), 5α-androstan-3α-yl hydrogen phenylphosphonate (**3**) and its $\Delta^{14,15}$ derivative (**4**), 5α-androstan-3α-yl dihydrogen phosphate (**5**) and its 3β isomer (**6**) (FIG. 1). Refluxing 5% KOH in methanol-dioxane (1/1) for 2.5 h or 1N HCl in dioxane-H_2O (2/1) at 100° for 50 h were ineffective. A biphasic system (toluene/1M phosphate buffer pH = 4.2) at reflux for 7 days caused only ~50% hydrolysis.



1 3β–O; Z = C_6H_5; R =  **5** 3α–O; Z = OH; R = H

3 3α–O; Z = C_6H_5; R = H **6** 3β–O; Z = OH; R = H

FIG. 1

Using the known instability of RNA in the presence of alkali as a guide,[4] the following simple and convenient two step hydrolytic procedure was therefore developed. (1) The phosphonic (or phosphoric) acid is reacted with an epoxide, thus appending a β-hyroxyethyl ester residue to the phosphorus. (2) Base treatment of this product results in the expulsion of the original alcoholic residue by an internal displacement executed by the β-alkoxide[4,5] (FIG. 2). It is noteworthy that in the case of phosphonate monoesters, the energetic preferences governing location of groups in the intermediate trigonal bipyramid transited during step 2, require the original alkoxy ligand (in our case the sterol moiety) to adopt an apical position. Its expulsion is therefore imminent and does not require prior pseudorotation.[6]

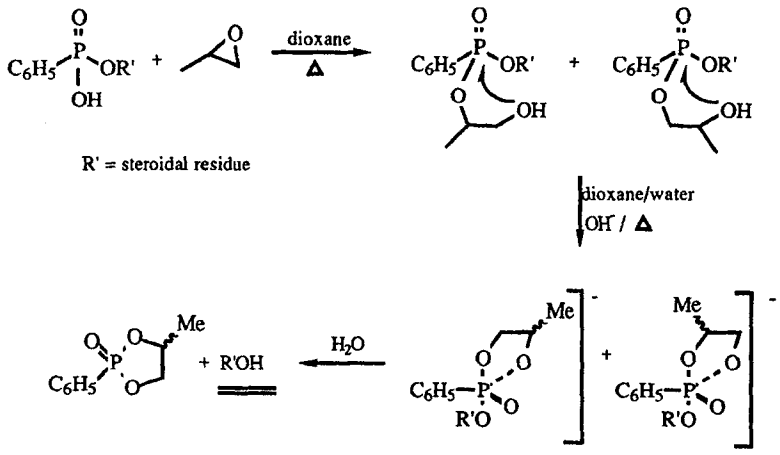


FIG. 2

The reaction of a phosphate monoester with an epoxide leads to a triester bearing two β-hydroxylethyl functions. Base catalyzed intramolecular ring closure can result in the expulsion of one of these or of the desired alcohol (FIG. 3). In the

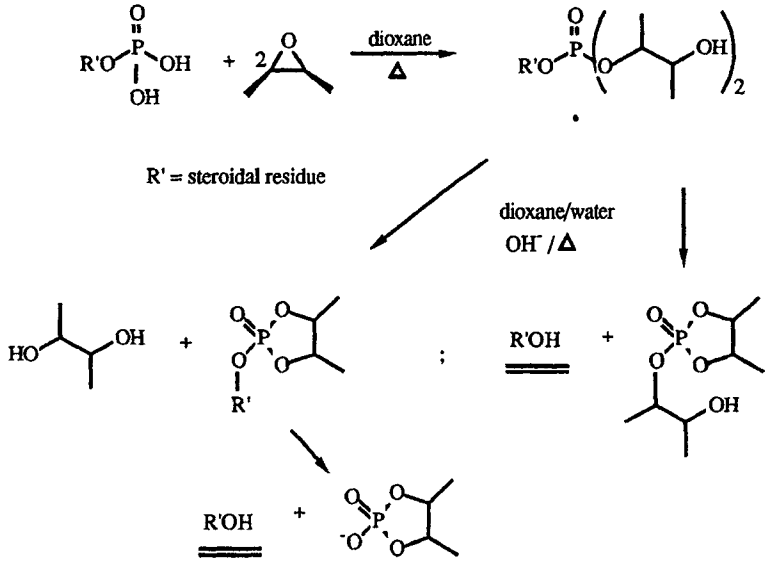


FIG.3

former case further hydrolysis of the intermediate 5-membered ring triester leading to the desired alcohol release would require a pseudorotation. Either way, steric considerations should favor apical placement of a bulky steroidal substituent, thus facilitating its leaving.

In the event, the proposed procedure as detailed in the Experimental Section, using either epoxypropane or *cis*-2,3-epoxybutane, leads to essentially quantitative recovery of the steroidal alcohols from the hydrolysis of both phenylphosphonate and phosphate monoesters.

Experimental Section.

Steryl phenylphosphate mono-ester hydrolysis. In a typical experiment a solution of 30 mg (72 μmole) of 3 and 0.75 ml of epoxypropane (racemate) in 1.5 ml 1,4-dioxane was heated in a closed ampule at 80° for 20 h. Completion of reaction was confirmed by tlc (silica; ethyl acetate:hexane 3:1). Volatiles were removed under vacuum, and the residue was identified as a mixture of 2'-hydroxypropyl 5α-androstan-3α-yl phenylphosphonate (7) and 1'-hydroxy-2'-propyl 5α-androstan-3α-yl phenylphosphonate (8) in approximately equal amounts. However, each of these is an unresolved mixture of stereoisomers due to the existence of chiral centers at the phosphorous and the 2'-carbon of the propyl moiety.

^{1}H NMR (300 MHz; $CDCl_3$), assignments with aid of COSY expts: δ 0.678 (brs, 18-CH_3), 0.752, 0.759, 0.763 (three brs, 19-CH_3). 1.16, 1.18 (two d, J = 6 Hz, $POCH_2CH(OH)C\underline{H}_3$), 1.20, 1.32 (two d, J = 6 Hz, $POCH(CH_2OH)C\underline{H}_3$), 3.575-3.679, 3.589-3.750 (m, $C\underline{H}_2OH$), 3.780-4.090 (m, CH_2OP), 3.920-4.091 (m, C<u>H</u>OH), 4.350-4.471, 4.610-4.810 (m, CHOP), 4.706-4.840 (m, 3β-CH), 7.42-7.61 (m, arom. m+p), 7.78-7.88 (m, arom. o).

The above mixture was redissolved in 1.5 ml of 1,4-dioxane and 1 ml of 50% aqueous KOH was added. The reaction mixture was heated at 80° with

stirring for 2.25 h. Completion of reaction was confirmed by tlc (as above). The cooled reaction mixture was taken up in methylene chloride, and the organic phase washed with water, dried over $MgSO_4$ and evaporated to give a quantitative yield of 5α-androstan-3α-ol, identified by comparison with an authentic sample.

The other sterol phenylphosphonate monoesters were quantitatively hydrolyzed to the sterols in the same manner. In all cases approximately equimolar amounts of the 1-propyl and 2-propyl esters were obtained in the first step. The PMR of the propyl residues appeared as partially overlapping multiplets in the same regions as listed above for the esters derived from 5α-androstan-3α-ol. The chemical shifts of other characteristic protons on the steroid skeletons were unexceptional.

Steryl phosphate mono-ester hydrolysis. For reasons of economy, in these cases (**5** and **6**) only a fourfold molar ratio of epoxide to steroid was used. In other respects the two step procedure was as described above. Either epoxypropane or *cis*-2,3-epoxy-butane proved equally effective.

The PMR spectra of the β-hydroxy phosphate ester intermediate showed that both of the free POH groups of the phosphate monoester had each reacted with an epoxide, yielding a bis-(β-hydroxy) phosphate triester. The presence of chiral carbons in both β-hydroxyalkyl residues results in a mixture of stereoisomers. However, their limited number, as evidenced by the number of different $POCHCH_3$ groups discernible in the PMR spectra (≤4, see below) indicates that the epoxide opening is stereospecific, presumably *trans*.

Di-(3'-hydroxy-2'-butyl)-5α-androstan-3β-yl phosphate. ^1H NMR (200 MHz; $CDCl_3$), assignment checked by decoupling, δ 0.685 (s, 3H, 18-CH_3), 0.822 (s, 3H, 19-CH_3), 1.162, 1.173 (two d, J = 6.4 Hz, 6H, CH(OH)C$\underline{H}_3$), 1.297, 1.311, 1.325 (three d, J = 6.2 Hz, 6H, CH(OP)C$\underline{H}_3$), 3.62-3.82 (m, 2H, 3'-C$\underline{H}$OH), 4.15-4.45 (m, 3H, 3α-CH, 2'-CHOP).

Di-(3'-hydroxy-2'-butyl)-5α-androstan-3α-yl phosphate. ^{1}H NMR (200 MHz; $CDCl_3$), δ 0.690 (s, 3H, 18-CH_3), 0.786 (s, 3H, 19-CH_3), 1.168, 1.181 (two d, J =6.4 Hz, 6H, CH(OH)CH_3), 1.305, 1.315, 1.326, 1.335 (four d, J = 6 Hz, 6H, CH(OP)CH_3), 3.6 -3.82 (m, 2H, 3'-CHOH), 4.1-4.42 (m, 2H, 2'-CHOP), 4.6-4.8 (m, 1H, 3β-CH).

The resolution of four different CH(OP)CH_3 absorptions in the case of the 3α isomer, as compared to only three for the 3β isomer is attributed to the more pronounced effect of the sterically closer chiral steroid skeleton in the former, axial, isomer.

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