

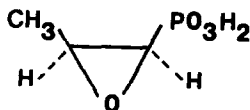
THE PREPARATION AND ACID-CATALYSED REARRANGEMENTS OF EPOXY-PHOSPHOLANES

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Interest in the preparation and reactions of phosphorus compounds containing an epoxy-grouping has been generated by the discovery of phosphomycin (1), a simple wide-spectrum antibiotic.¹



We wish to report the synthesis of epoxy-phospholanes and their rearrangement, catalysed by boron trifluoride, to stable enols and phospholan-3-ones.

Direct oxidation of the double bond of phosphol-2-enes is known to be difficult.² Small yields of epoxides have been formed directly from the phospholene by prolonged treatment with trifluoroperacetic acid³ but treatment with *m*-chloroperbenzoic acid in refluxing dichloroethane for 24h in the presence of 2,4,6-tri-*t*-butylphenol⁴ gave us only starting material.

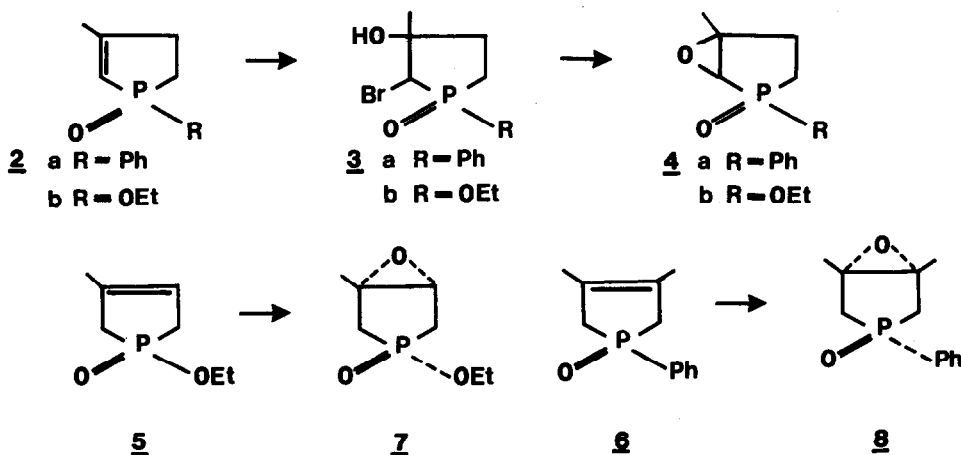
We have found that high yields of epoxy-phospholanes can be obtained from phospholenes by formation of the bromohydrin followed by treatment with base.

Reaction of 2a with *N*-bromoacetamide in aqueous media gave the bromohydrin (3a, 93%) as a mixture of isomers, m.p. 150-157°(CCl₄),⁵ τ (CDCl₃) 1.88-2.52 (5H,m), 4.13 (1H,broad s), 5.63-5.78 (1H,m), 7.27-8.07 (4H,m), 8.32 (3H,s). No splitting of the n.m.r. signal of the hydroxyl proton was observed using DMSO as solvent, indicating the presence of a tertiary alcohol.⁶ Similarly, 2b gave 3b (70%) b.p. 190-197°/0.6mm, as a mixture of isomers, τ (CDCl₃) 5.55 (1H,s), 5.55-6.17 (2H,m), 7.43-8.25 (4H,m), 8.48 (3H,s), 8.62 (3H,t, J_{HH} 7Hz).

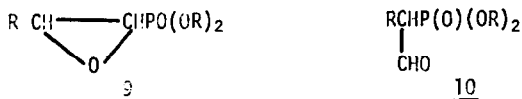
Treatment of 3a with potassium acetate in acetone gave the epoxide (4a, 80%). One isomer was obtained pure by fractional crystallisation from carbon tetrachloride, m.p. 102-103°, τ (CDCl₃) 2.20-2.53 (5H,m), 6.68 (1H,d, J_{PH} 27 Hz), 7.57-8.17 (4H,m), 8.40 (3H,d, J_{PH} 2 Hz).

Similarly, 3b gave 4b (70%) b.p. 152-154°/0.2mm., τ (CDCl_3 , one isomer)⁷ 5.40-6.13 (2H,m), 6.82 (1H,d, J_{PH} 28 Hz), 7.73-8.10 (4H,m), 8.43 (3H, d, J_{PH} 1Hz), 8.57 (3H,t, J_{HH} 7 Hz), τ (CDCl_3 , other isomer)⁷ 5.40-6.13 (2H,m), 6.87 (1H,d, J_{PH} 28 Hz), 7.73-8.10 (4H,m), 8.45 (3H,d, J_{PH} 1 Hz) 8.60 (3H, t, J_{HH} 7 Hz).

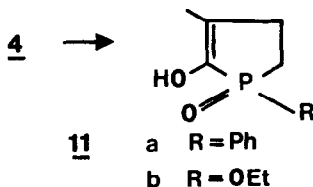
Epoxides of phosphol-3-enes can be prepared by direct oxidation² or via the bromohydrin. Arbuzov and his co-workers have reported that oxidation of the phosphol-3-ene oxides (5) and (6) with peracetic acid gave only one isomer of the corresponding epoxides. These were shown to be the trans isomers by dipole moment measurements.⁸ We hoped to be able to obtain both isomers using the bromohydrin route but surprisingly reaction of (5) with NBA followed by treatment with potassium acetate gave only one isomer (7, 82% overall), identical with the compound formed by direct oxidation. These observations suggest that there is electronic repulsion between the P=O bond and the oxidant which hinders attack on the same side as P=O on the one hand, but enhances the approach of the electrophile on that side in the formation of the bromohydrins on the other. Steric factors appear not to be significantly different for approach from either side. Inspection of models shows that interaction between the reagent and the P=O bond would be greater for phosphol-3-enes than for phosphol-2-enes. In agreement with this hypothesis we found that epoxide 4a was formed as an 85:15 mixture of isomers whereas 4b was formed as a 50:50 mixture, indicated by the n.m.r. resonance of the oxirane proton, showing the obvious greater difference between oxygen and phenyl in 2a compared to oxygen and ethoxy in 2b. We presume that the major isomer has the epoxide trans to the P=O bond. We are continuing our investigations into the directing influence of the P=O bond in these and other reactions.



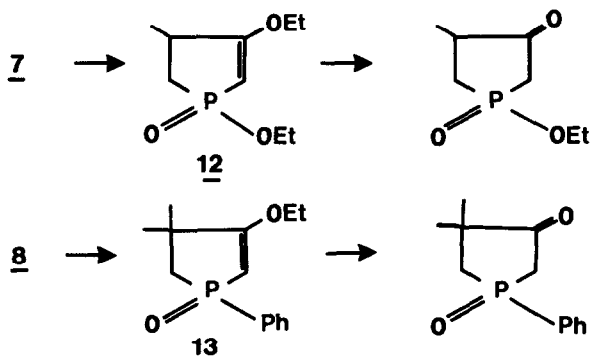
Griffin and Kundu⁹ have observed specific phosphono-group migrations in the rearrangements of epoxyethylphosphonates (9) to α -formylmethylphosphonates (10). It was of interest to see if one could obtain similar rearrangements when the epoxides 4 were treated in the same manner, a process which would lead to ring contraction.



Reaction of 4a with BF_3 was carried out in refluxing benzene to yield a white crystalline material (11a, 40%) m.p. $151\text{--}153^\circ$ $\tau(\text{CDCl}_3)$ 1.35 (1H,s), 2.30-2.70 (5H,m), 7.28-8.25 (4H,m), 8.17 (3H,s). The infrared spectrum indicated hydrogen bonded hydroxyl as a broad band around 2750cm^{-1} and strong C=C absorption at 1665cm^{-1} . There was no indication of carbonyl absorption in nujol or CHCl_3 solution, in contrast to phospholan-3-ones, which show a variable infrared spectrum.^{10,11} Similarly, 4b as a mixture of isomers, gave (11b, 50%), m.p. $87.5\text{--}92^\circ$, $\tau(\text{CDCl}_3)$ 1.42 (1H,s), 5.80 (2H,dq, J_{PH} 7 Hz, J_{HH} 7 Hz), 7.33-8.32 (4H,m), 8.22 (3H,s), 8.65 (3H,t, J 7 Hz), $\nu_{\text{max.}}$ (nujol) $2700, 1660\text{cm}^{-1}$.



The stability of the enol form is probably due to strong intramolecular hydrogen bonding with the phosphoryl group but may also be due in part to $d_{\pi}\text{--}p_{\pi}$ resonance with the double bond.¹²



Treatment of the epoxides (7) and (8) with boron trifluoride-etherate in dry benzene gave the vinyl ethers (12) and (13) respectively, in about 40% yield, which are formed by hydrogen

or methyl migration followed by O-alkylation of the enolate anions by the etherate. The vinyl ethers could be converted to the corresponding ketones by hydrolysis with dilute acid. The ketones showed variable infrared spectra and exist mainly as the enols in the solid state and as the ketones in dichloromethane solution.

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References and Footnotes

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