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VINYL PHOSPHONATES: A CONVENIENT ROUTE TO PHOSPHONIC ACID ANALOGUES OF PHOSPHATE MONOESTERS

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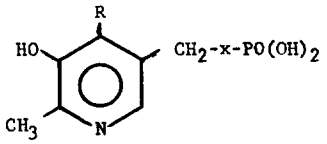
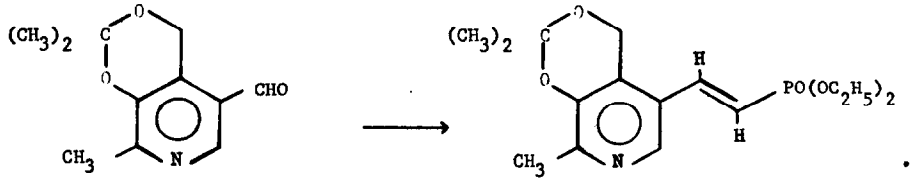
Phosphonic acids which are analogous to biologically important phosphate monoesters, such as pyridoxal phosphate (Ia), contain a methylene group in place of the ester oxygen (e.g. Ib).[1] Because such phosphonic acids[2] are of potential value for biochemical studies,[3] we have developed a convenient method for their synthesis. The synthesis of the phosphonic acid analogue (IIb) of pyridoxol phosphate (IIa) is illustrative.

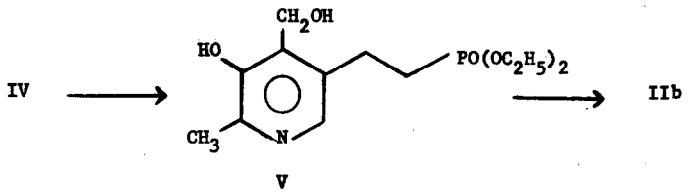


I a, R = -CHO, x = O
b, R = -CHO, x = CH_2
II a, R = $-CH_2OH$, x = O
b, R = $-CH_2OH$, x = CH_2

In the key first step the potential methylene and phosphorus groups were introduced simultaneously by condensation of α^4,3-O-isopropylideneisopyridoxal[4] (III) with tetraethyl methylenediphosphonate[5,6] in benzene in the presence of sodium hydride to give the desired trans-vinyl phosphonate[7] (IV), m.p. 67-68°, isolated as the hydrochloride salt, m.p. 147-149°, in 90-95% yield. The latter upon hydrolysis in aqueous formic acid followed by catalytic hydrogenation (Pd-C) and neutralization gave the saturated diester (V), m.p. 108-109°, in 75-80% yield. Hydrolysis of V in concentrated hydrochloric acid for 12 hr. furnished the syrupy hydrochloride salt which, upon treatment with silver carbonate followed by deionization, afforded the desired free acid (IIb) [m.p. > 270°, $\lambda_{max}^{0.1\ \underline{N}\ HCl}$ 292 mμ (ε = 9300)] in 60-70% yield.[8,9]



III IV



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As a first step in assessing the biological properties of the phosphonic acid (IIb) the inhibitory effect of IIb on the pyridoxal phosphate (PPal)-dependent enzyme, tyrosine decarboxylase, was determined. The assay consisted of the simultaneous preincubation of PPal and IIb with borohydride-reduced tyrosine decarboxylase apoenzyme for 30 min. at 37° in acetate buffer (pH 5.5). Decarboxylation of L-tyrosine was measured by the standard manometric assay.[10] Using varying amounts of IIb it was determined that the $[I/S]_{0.50}$[11] for IIb was approx. 15,000. Similar assay of pyridoxol phosphate (IIa, PPol) gave an $[I/S]_{0.50}$ of approx. 70. The marked difference in inhibitory power of IIb and PPol in this test system is of considerable interest and is being studied further.

Use of vinyl phosphonates as key intermediates in the synthesis of phosphonic acid analogues of other biologically important phosphate monoesters is now in progress and will be reported in due course.

References

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2. The synthesis of nucleoside di- and triphosphate analogues wherein one of the pyrophosphate anhydride oxygens has been replaced by a methylene unit has been described [T.C. Myers, K. Nakamura, and A.B. Danielzadeh, J. Org. Chem., 30, 1517 (1965); T.C. Myers, K. Nakamura, and J.W. Flesher, J. Am. Chem. Soc., 85, 3292 (1963)].

3. Cf., L. Simon, T. Myers, and M. Mednieks, Biochim. Biophys. Acta, 103, 189 (1965).

4. W. Korytnyk, E.J. Kris, and R.P. Singh, J. Org. Chem., 29, 574 (1964).

5. G.M. Kosolapoff, J. Am. Chem. Soc., 75, 1500 (1953).

6. An analogous, Wittig-type reaction had been conducted earlier using benzaldehyde [W.S. Wadsworth, Jr., and W.D. Emmons, J. Am. Chem. Soc., 83, 1733 (1961)].

7. The phosphonate modification of the Wittig reaction normally gives a high proportion of trans-isomer [D.H. Wadsworth, O.E. Schupp, III, E.J. Seus, and J.A. Ford, Jr., J. Org. Chem., 30, 680 (1965)]. For IV, the H-H coupling constants of the α-(to the phosphorus) and β-hydrogens (J, 17 cps) and the P-H coupling constants (J, 17 and 20 cps, respectively) are in accord with a trans-configuration.

8. No evidence for cyclic ester formation was adduced.

9. All new compounds had analytical data in excellent accord with expected values.

10. I.C. Gunsalus and R.A. Smith, in "Methods in Enzymology," Vol. 3, S.P. Colowick and N. O. Kaplan, Ed., Academic Press, London, 1957, p. 963.

11. $[I/S]_{0.50}$ = ratio of inhibitor to cofactor (at final concentration of 3×10^{-8} M PPal) to give 50% inhibition of enzymic activity at 60-70% saturation of the enzyme by PPal.