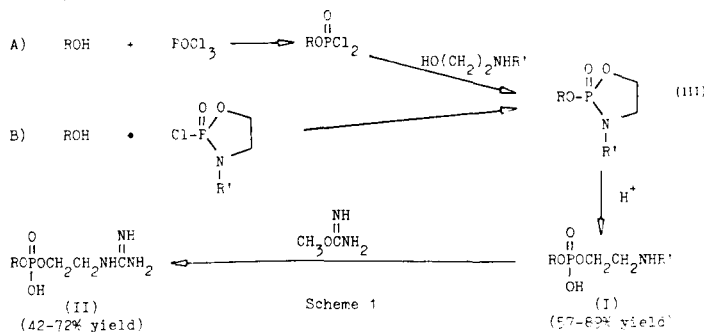


THE USE OF 1,3,2-OXAZOPHOSPHOLIDIN-2-ONES IN THE SYNTHESIS OF NATURALLY OCCURRING HELMINTHIC PHOSPHODIESTERS

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Our preliminary findings on the use of 1,3,2-oxazaphospholidin-2-ones as useful synthons in the synthesis of naturally occurring helminthic phosphodiester (I) are reported. Since the initial isolation of lombricine (II, $R = \text{NH}_2(\text{CO}_2\text{H})\text{CHCH}_2$) and its precursor, serine ethanolamine phosphodiester (I, $R = \text{NH}_2(\text{CO}_2\text{H})\text{CHCH}_2$, $R' = \text{H}$) (Beatty et al 1959), in the earthworm (*Lumbricus terrestris*), several other related phosphodiester have been isolated from differing worm species (Thoai & Robin 1969). Research to date has shown these phosphodiester (II) to be unique to worm species. The guanidated phosphodiester are thought to play a role similar to creatine and arginine in high energy phosphate regulation (Thoai & Robin 1969). If it can be shown that these phosphodiester are also present in parasitic worms then it should be possible to chemotherapeutically exploit the difference between the energy metabolism of worms and their hosts. Authentic phosphodiester were required to facilitate the screening of parasitic worms for such compounds. The literature synthesis of worm phosphodiester involves lengthy reaction schemes and extensive purification giving very low overall yields. We therefore have focused our attention on developing a convenient and versatile synthetic route to these phosphodiester by using the synthon 1,3,2-oxazaphospholidin-2-ones (III) as potential phosphoethanolamine moieties. We have found that 2-alkoxy or aryloxy-1,3,2-oxazaphospholidin-2-ones can be successfully made in situ in a one-pot reaction in high yields by either reacting the appropriate alcohol with phosphorous oxychloride to form the phosphoric acid dichloride and then coupling it to the corresponding aminoalcohol (route A); or reacting phosphorous oxychloride with the aminoalcohol to form the 2-chloro-1,3,2-oxazaphospholidin-2-ones which can be coupled to the desired alcohol (route B).



The 2-alkoxy or aryloxy-1,3,2-oxazaphospholidin-2-ones, once formed, can be ring opened by acid treatment which causes exclusive N-P bond fission yielding the phosphodiester in moderate to good yields. To date six phosphodiester (I) have been synthesised and fully characterised by the above routes. Four guanidated phosphodiester (II) have been made in moderate yields by reacting the corresponding phosphodiester with O-methylisourea.

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Beatty, I.M., et al (1959) Nature 183:591-2

Thoai, N.V. & Robin, Y. (1969) Chemical Zoology 4:163-203