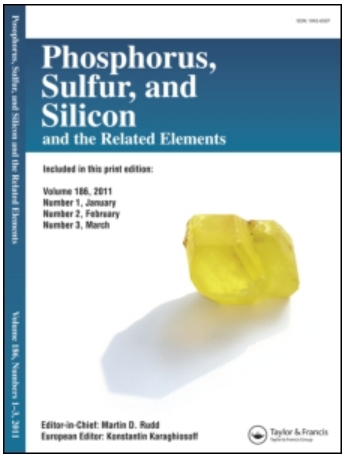

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Synthesis of Bicyclic "Preactivated" Analogues of Cyclophospamide

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SYNTHESIS OF BICYCLIC "PREACTIVATED" ANALOGUES OF CYCLOPHOSPAMIDE

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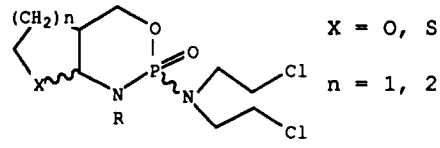
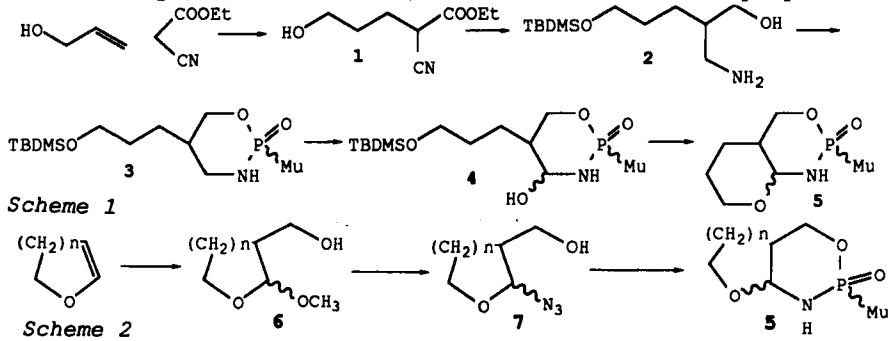
Studies on the metabolism of Cyclophosphamide (CPA), one of the most widely used anticancer agents, have shown that hydroxycyclophosphamide (4-hydroxy-CPA) is a major metabolite in the process which lead to the liberation of the ultimate cytostatic agent "phosphoramide mustard" in tumor cells (1). Unfortunately, hydroxycyclophosphamide itself is very unstable and many attemps have been made to synthesize more stable derivatives. One of the most successful was accomplished by ASTA GRUPPE who introduced Mafosfamide (4-sulfoethylthio-cyclophosphamide) as a stable derivative of 4-hydroxy-CPA (2).

We have ourselves undertaken the synthesis of bicyclic "preactivated" analogues of cyclophosphamide of the type :



Two chemical ways, outlined below, were studied for this purpose.



Scheme 1

Scheme 2

In the first approach (scheme 1) the C-4 hydroxylation of **4** is the key reaction. In scheme 2 the key intermediate is the azidoalcool **7** obtained by reaction of compound **6** with TMSA and $TiCl_4$. We are currently studying the direct cyclisation to **5** by the Staudinger reaction of a suitable tricoordinated phosphorus derivative with the azidoalcool **7**.

(1) For a review : G.Zon, Prog. Med. Chem., 19, 205 (1982).
(2) U. Niemeyer, J. Engel, G. Scheffler, K. Molke, D. Sauerbier, W. Weigert, Invest. New Drugs, 2, 133 (1984).