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Synthesis of Bicyclic “Preactivated” Analogues of Cyclophosphamide

B. Lilo^a; D. Bouchu^a

^a Université Lyon I, Laboratoire de Synthèse Organique Appliquée, Villeurbanne, Cedex, France

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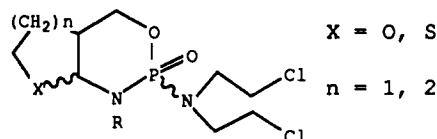
SYNTHESIS OF BICYCLIC "PREACTIVATED" ANALOGUES OF CYCLOPHOSPHAMIDE

B.LILO and D.BOUCHU

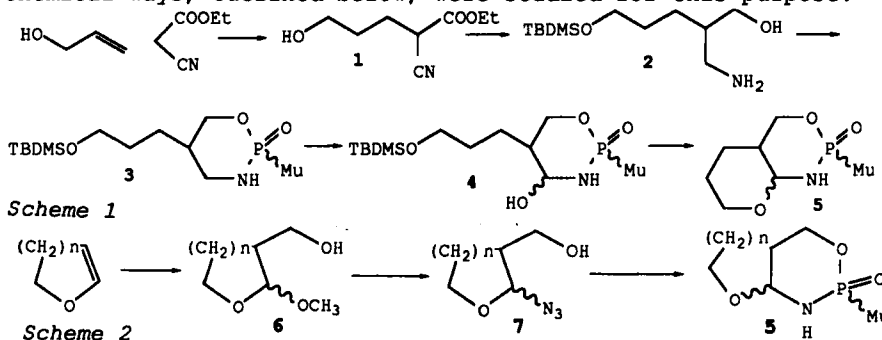
Université Lyon I, Laboratoire de Synthèse Organique
 Appliquée 43, bd du 11 Novembre 1918, 69622
 Villeurbanne Cedex, France

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 "phosphoramidate mustard" in tumor cells (1). Unfortunately, hydroxycyclophosphamide itself is very unstable and many attempts 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.



In the first approach (scheme 1) the C-4 hydroxylation of 4 is the key reaction. In scheme 2 the key intermediate is the azidoalcohol 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 azidoalcohol 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).