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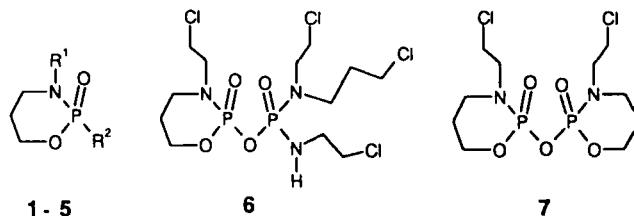
A New Method of Preparation of Ifosfamide and Cyclophosphamide; Synthesis of Side Products

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This study focusses on the preparation of ifosfamide (1; R¹=CH₂CH₂Cl, R²=NHCH₂CH₂Cl) and cyclophosphamide (2; R¹=H, R²=N(CH₂CH₂Cl)₂), standard drugs in tumor therapy, in order to avoid the alkylating educts like 2-chloroethylamine by introducing chlorine in the final reaction step. The reaction of the trimethylsilyl compounds (3; R¹=CH₂CH₂Cl, R²=NHCH₂CH₂OSiMe₃) and (4; R¹=H, R²=N(CH₂CH₂OSiMe₃)₂), respectively, with 2-chloro-1,3,5-trimethyl-1,3,5-triaza-σ³λ³-2-phosphorin-4,6-dione, followed by chlorination of the resulting product with sulphuryl chloride, furnished the cytotoxic drugs (1) and (2) [1].

In the case of ifosfamide, produced by condensation of compound (5; R¹=CH₂CH₂Cl, R²=Cl) and 2-chloroethylamine, the side products (6) and (7) were isolated and identified by ¹H-, ¹³C- and ³¹P-n.m.r. and by MS investigations. Compound (6) was gained by reaction of compound (5) with 2-chloroethylamine and the half equivalent amount of triethylamine. Compound (7) was synthesized from diphosphoryl tetrachloride and N-2-chloroethyl-3-hydroxypropyl-amine hydrochloride in the presence of triethylamine or by treatment of compound (5) with sodium hydroxide.



References

- [1] I. Neda, R. Sonnenburg, R. Schmutzler, U. Niemeyer, B. Kutscher, J. Engel, A. Kleemann, *Z. Naturforsch.*, **52 b**, 943-946 (1997).