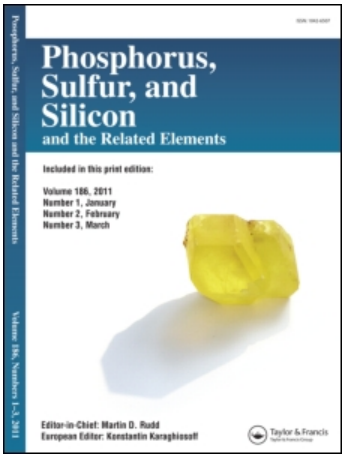

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A New Method of Preparation of Ifosfamide and Cyclophosphamide; Synthesis of Side Products

ULF NIEMEYER[a], BERNHARD KUTSCHER[a], JÜRGEN ENGEL[a], AXEL KLEEMANN[a], ION NEDA[b], RALF SONNENBURG[b] and REINHARD SCHMUTZLER[b]

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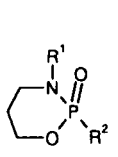
This study focusses on the preparation of ifosfamide (**1**; R^1=CH_2CH_2Cl, R^2=$NHCH_2CH_2Cl$) and cyclophosphamide (**2**; R^1=H, R^2=$N(CH_2CH_2Cl)_2$), standard drugs in tumor therapy, in order to avoid the alkylating educts like 2-chloroethylamine by introducing chlorine in the final reaction step. The reaction of the trimethylsilyl compounds (**3**; R^1=CH_2CH_2Cl, R^2=$NHCH_2CH_2OSiMe_3$) and (**4**; R^1=H, R^2=$N(CH_2CH_2OSiMe_3)_2$), respectively, with 2-chloro-1,3,5-trimethyl-1,3,5-triaza-$\sigma^3\lambda^3$-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**; R^1=CH_2CH_2Cl, R^2=Cl) and 2-chloroethylamine, the side products (**6**) and (**7**) were isolated and identified by ^{1}H- ^{13}C- and ^{31}P-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.



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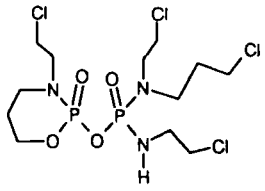

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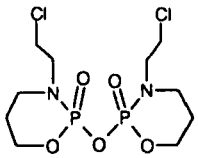

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