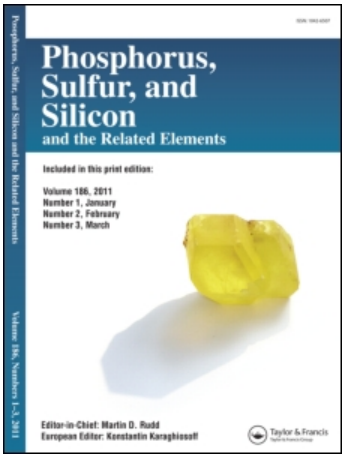

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Hydrolytic Pathway of Isophosphoramide Mustard (IPM), the Cytotoxic Metabolite of the Anticancer Drug Ifosfamide

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Online publication date: 27 October 2010

To cite this Article Breil, Stephane , Gilard, Veronique , Legay, Remi , Martino, Robert , Malet-Martino, Myriam and Niemeyer, Ulf(2002) 'Hydrolytic Pathway of Isophosphoramide Mustard (IPM), the Cytotoxic Metabolite of the Anticancer Drug Ifosfamide', Phosphorus, Sulfur, and Silicon and the Related Elements, 177: 8, 1939 — 1940
To link to this Article: DOI: 10.1080/10426500213397
URL: http://dx.doi.org/10.1080/10426500213397

Phosphorus, Sulfur and Silicon, 2002, Vol. 177:1939–1940

1042-6507/02 $12.00 + .00
DOI: 10.1080/10426500290093991

HYDROLYTIC PATHWAY OF ISOPHOSPHORAMIDE MUSTARD (IPM), THE CYTOTOXIC METABOLITE OF THE ANTICANCER DRUG IFOSFAMIDE

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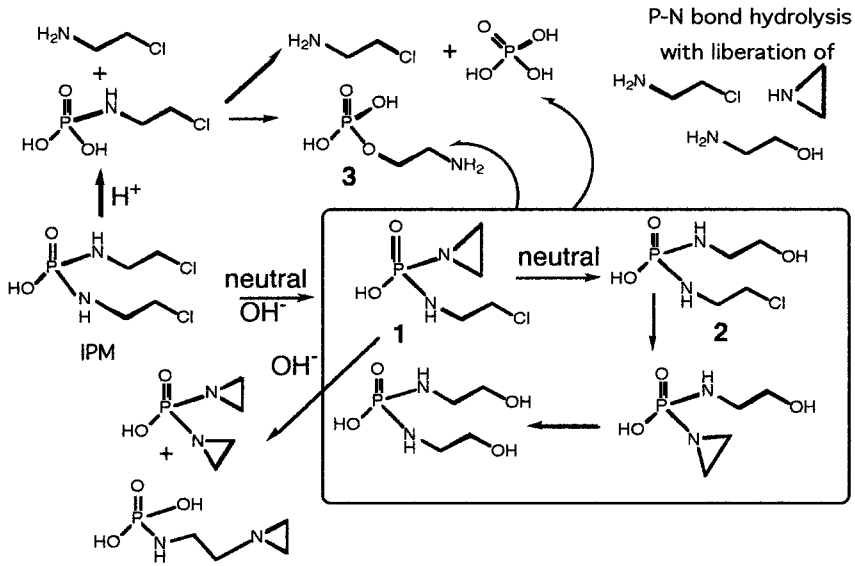
(Received July 29, 2001; accepted December 25, 2001)

IPM is the alkylating metabolite of the anticancer oxazaphosphorine drug ifosfamide (Holoxan). The alkylation chemistry of IPM by nucleophiles was extensively studied, but the concurrent P—N bond hydrolysis pathway is not well documented. We used NMR spectroscopy



SCHEME 1

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(^{31}P, ^{1}H, ^{13}C) to determine the products of IPM degradation in buffered solutions at pH ranging from 1 to 13. The complex hydrolytic scheme (Scheme 1) was established.

^{31}P NMR analysis of the urinary excretion in rats treated with ifosfamide showed that the three IPM degradation products **1**, **2**, and **3** represented 60–80% of excreted IPM.