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## Alkaline Hydrolytic Pathway of the Antitumor Drug, Cyclophosphamide

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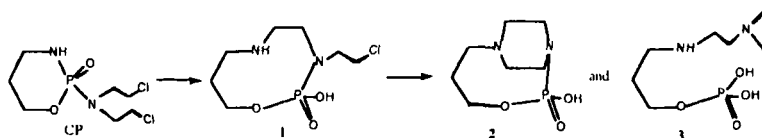
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## Alkaline Hydrolytic Pathway of the Antitumor Drug, Cyclophosphamide

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In an attempt to clarify the alkaline hydrolytic pathway of the antitumor agent, cyclophosphamide (CP), the time course of its degradation was monitored by <sup>31</sup>P NMR in 0.5 M KOH solution. After 16 hr at 25°C, 70% of CP is hydrolyzed ( $t_{1/2} \sim 9$  hr), leading to a mixture of 8 phosphorated compounds, among them only 4 represented more than 5% of the initial CP. The chemical shifts and the intensities of these compounds were as follows: 11.1 ppm, 30% of the initial CP (compound 1); 9.5 ppm, 12% (compound 2); 6.4 ppm, 9% (unknown) and 4.8 ppm, 9% (compound 3). The structures of compounds 1-3 were identified by NMR (<sup>13</sup>C and <sup>1</sup>H) and mass spectrometry after their isolation. The major degradation compound formed, the nine-membered ring compound 1, was also observed during CP hydrolysis at neutral or moderately acid pHs<sup>[1]</sup> and was detected in urine of patients treated with CP<sup>[2]</sup>. Compounds 2 and 3 were also formed during the hydrolysis of compound 1 in 0.5 M KOH solution. Based on the formation in time of the <sup>31</sup>P NMR signals in KOH solutions of CP and compound 1, the following scheme was established for the major degradation alkaline pathway of CP.



### References

- [1] V. Gilard, R. Martino, M. Malet-Martino, B. Kutscher, A. Muller, U. Niemeyer, J. Pohl, and E. Polymeropoulos, *J. Med. Chem.*, **37**, 3986 (1994).
- [2] C. Joqueviel, R. Martino, V. Gilard, M. Malet-Martino, P. Canal, and U. Niemeyer, *Drug Metab. Dispos.*, **26**, 418 (1998). (Supported by ARC, grant 6635).