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Synthesis of 2-methoxy-6-oxo-1, 4, 2-diazaphosphorinane-2-oxide, A New Potential Antitumor Phosphorus Heterocycle Compound

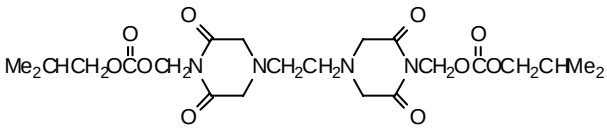
Liang XU, Guang Rong ZHENG, Min XIA, Jun Chao CAI*

Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 200031

Abstract: 2-methoxy-6-oxo-1, 4, 2-diazaphosphorinane-2-oxide **8**, phosphorus counterpart of 2, 6-dioxopiperazine, was synthesized as antitumor agent. The new phosphorus heterocycle compound **8** is the key intermediate in the synthesis of phosphorus counterpart of bisdioxopiperazine.

Keywords: Antitumor activity, phosphorus heterocycle compound, 2,6-dioxopiperazine.

The discoveries that the bisdioxopiperazines ICRF-154[1], ICRF-159(razoxane)[1] and MST-16(sobuzoxan)[2] are inhibitors of mammalian DNA topoisomerase II[3-5], have led to a renewed interest in these compounds as antitumor agents[6]. Among the drugs, MST-16 (sobuzoxan) was approved in Japan (in 1994) as a potent antitumor agent for treatment of adult T-cell leukemia and malignant lymphoma[2]. However, the bisdioxopiperazines exhibited extremely small water-solubility, which reduced its absorption in clinical application. This discrepancy prompt us to synthesize some water-soluble derivatives and analogues. In this study, we synthesized the phosphorus counterpart of dioxopiperazine 2-methoxy-6-oxo-1, 4, 2-diazaphosphorinane-2-oxide **8**, and we believe that it will be a versatile precursor to synthesize the phosphorus counterpart of bisdioxopiperazine.

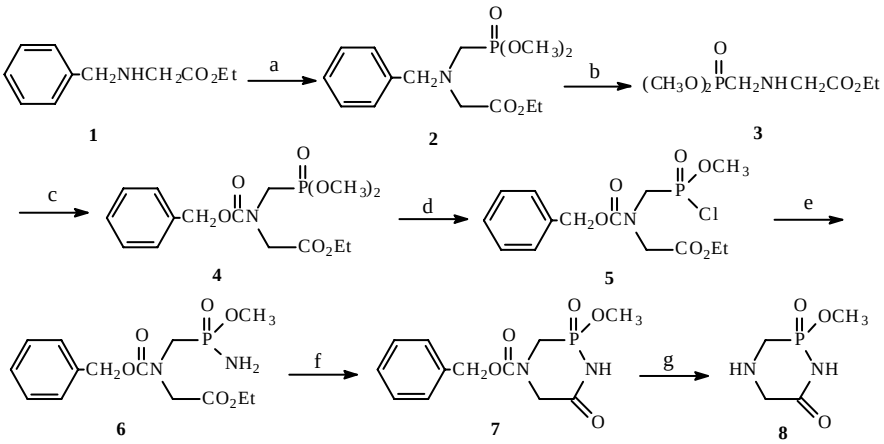


MST-16 (Sobuzoxan)

Mannich condensation of **1** with formaldehyde and dimethyl phosphite gave N-benzyl- N-dimethylphosphonomethyl ethyl glycinate **2**, which upon catalytic hydrogenation with 5%Pd-C afforded glyphosate triester in excellent yield (**scheme 1**). Protection of the secondary amino group with benzyloxycarbonyl chloride (CbzCl) generated amide **4**. Treatment of the carbamate **4** with PCl_5 in CCl_4 at 40℃ for 18hrs gave monoalkylphosphono- chloride **5** which was then used directly to amination with NH_3 in dry chloroform at -15℃ to produce the corresponding phosphonamide **6**. Subsequent cyclization of **6** with t-BuOK in t-BuOH at room temperature furnished the key intermediate 4-benzyloxycarbonyl-2-methoxy-6-oxo-1,4,2-diazaphosphorinane-2-oxide **7**. Catalytic hydrogenation of **7** with 10%Pd-C in THF afforded the desired product **8** in high yield. The antitumor activity of **7** and **8** are under evaluation. Chemical

synthesis and biological investigation of phosphorus counterpart of bisdioxopiperazine are in progress.

Scheme 1



a) CH_2O, $(CH_3O)_2POH$, 0℃15min then 100℃ 2h, 73%. b) H_2/Pd-C, 100%. c) CbzCl, Et_3N, $CHCl_3$, 0℃, 78%. d) PCl_5, CCl_4, 40℃ 20h. e) NH_3, $CHCl_3$, -15℃, 56% in two steps. f) t-BuOK/t-BuOH, r.t.3h, 62%. g) H_2/Pd-C, THF, 95%.

Acknowledgment

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References and notes

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7. Data of **8**: IR (KBr) 3313, 3049, 2830, 1693, 1467, 1201, 1035, 962 cm^{-1}. ^{1}HNMR (d^6-DMSO, 400MHz) δ_H 3.0 (2H, dd, J=3.8, 11.8Hz), 3.4 (2H, m), 3.7 (3H, d, J=11Hz), 9.6 (1H, s, br). ^{31}PNMR (H_3PO_4, 300MHz) δ_P 19 ppm. EIMS (*m/z*): 164(M^+), 124, 109, 79. Anal Calcd for $C_4H_9N_2O_3P$: C, 29.26; H, 5.48; N, 17.07. found: C, 29.02; H, 5.56; N, 17.23.

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