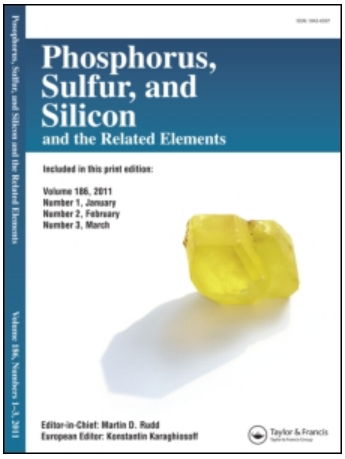

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A Convenient Method for the Synthesis of Cyclophosphamide Analogues

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A Convenient Method for the Synthesis of Cyclophosphamide Analogues

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Several new 2-[bis(2-chloroethyl)amino)]-7-methoxyl-3-alkyl-4-methyl-1,3,2-benzoxazaphosphorin-2-oxides(3a-e) have been synthesized by cyclic condensation of bis(2-chloroethyl)amino phosphoryl dichloride and 2-(1-alkylamino) ethyl-4-methoxylphenol. The title compounds are characterized by NMR, ESI-Q-TOF, and ESI-MS.

Keywords Cyclophosphamide analogues; N,N-di-(2-chloro)ethylaminophosphorodichloridate; paeonia

INTRODUCTION

The paeonia species (paeoniaceae), a traditional Chinese herb, has been used as an analgesic and anti-inflammatory drug. It also has a beneficial effect in prevention and treatment of thomboembolic diseases. Paeonol (2′-hydrooxy-4′-methoxyacetophenone), the effective component of Cortex Moutan, is proved to have a variety of effects, including antibacteria,[1] antiinflammation,[2] relieving pain,[3] anti-hypersensitive,[4] strengthening the immune system,[5]and anticancer.[6]

Cyclophosphamide (the generic name for Cytoxan, Neosar), a nitrogen mustard alkylating agent, is used to treat various types of autoimmune disorders as a "prodrug." It is converted in the liver to active forms that have chemotherapeutic activity.[7–9] The main use of cyclophosphamide is together with other chemotherapy agents in the treatment of lymphomas, some forms of leukemia, and some solid tumors. It also works by decreasing the immune system's response to

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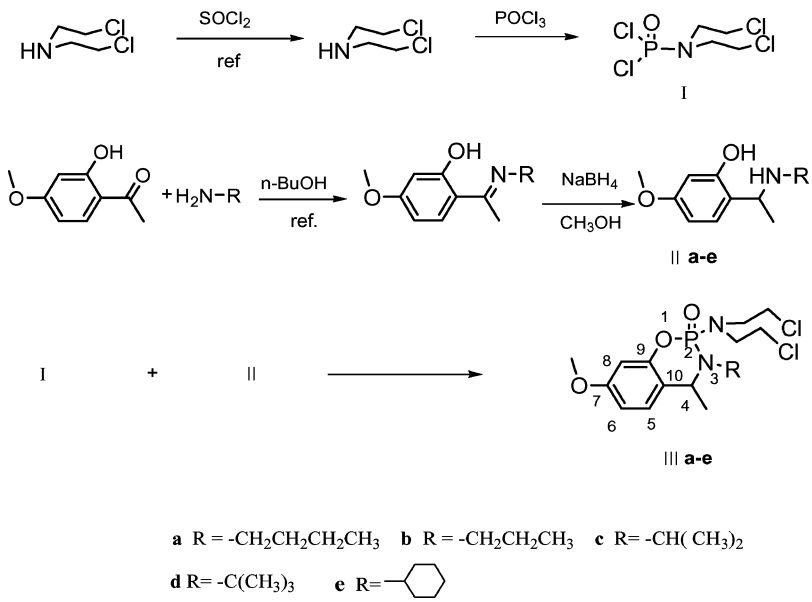

a R = -$CH_2CH_2CH_2CH_3$ **b** R = -$CH_2CH_2CH_3$ **c** R= -$CH(CH_3)_2$

d R= -$C(CH_3)_3$ **e** R=

SCHEME 1

various diseases. Cyclophosphamide is converted by mixed function oxidase enzymes in the liver to active metabolites. The main active metabolite, 4-hydroxycyclophosphamide, exists in equilibrium with its tautomer, aldophosphamide. Aldophosphamide could be converted into phosphoramide mustard and acrolein in tumor cells, whereas, most aldophosphamide can only be transformed into carboxyphosphamide by the enzyme aldehyde dehydrogenase (ALDH), which mainly exists in normal cell.[10] In efforts to obtain potential anticancer prodrugs, modifications of cyclophosphamide led to the design and synthesis of many cyclic and acyclic phosphoramidate agents in the past decades. In order to search new compounds with higher antitumor activities and lower toxicity, we report a convenient method for synthesis of some new cyclophosphamide analogues (Scheme 1), cyclophosphamide paeonol analogues. They were designed and synthesized on the basis of associate principle by combinations of paeonol and N,N–di-(2-chloro)ethylamino-phosphorodichloridate, and their structures were determined by electrospray quadrupole time-of-flight (ESI-Q-TOF), electrospray-mass spectrometry (ESI-MS), and NMR.

EXPERIMENTAL

^{1}H-NMR, ^{13}C-NMR and, ^{31}P-NMR spectra were on a Bruker-DTX-400, chemical shifts were expressed in parts per million positive values

downfield from internal TMS (^{1}H) and external 85% H_3PO_4 (^{31}P), coupling constants were expressed in Hertz. MS was recorded on Bruke Esquire-3000 and Micromass Q-TOF. Melting point was recorded on a microscopical determinator XT4 A (the thermometer was not adjusted).

Synthesis of N,N–di-(2-chloro)ethylamino-phosphorodichloridate(compound I)

To a magnetically stirred solution of phosphorus oxychloride (0.02 mol, 1.8 ml) in 50 ml methylene chloride at −5°C was added dropwise to a solution of bis(2-chloromethyl) amine hydrochloride (0.02 mol, 3.55 g) and triethylamine (0.02 mol, 2.78 ml) in 50 ml methylene dichloride over 1 h. The reaction mixture was stirred overnight at room temperature, concentrated in vacuo and mixed with benzene. The precipitated amine salt was filtered off and the filtrate was crystallized in acetone/petroleum ether to give colorless crystals, m.p.47°C(lit[8]).

Synthesis of 2-(1-cyclohexylamino) ethyl-4-methoxylphenol(Compound IIe)

A solution of paeonol (0.03 mol, 4.98 g) in 10 ml dry n-BuOH was added to a stirred solution of cyclohexylamine(0.03 mol, 3.45 ml) and catalytic amount of TsOH in 30 ml dry n-BuOH. The reaction mixture was refluxed for 12 h. The reaction solution was concentrated in a rota evaporator and recrystallization from ethanol afforded the light yellow crystal (shiff base); $NaBH_4$ was added to a solution of the shiff base on ice bath, and the mixture was allowed to react for 2 h on ice bath. After reaction, AcOEt (50 ml) was added, the mixture was washed with brine and dried over $MgSO_4$. Then the solvent was evaporated off and the product was obtained as light yellow liquid. The synthesis of (**IIa–d**) was followed with the same procedure.

2-[bis(2-chloroethyl)amino]-7-methoxyl-3-cyclohexyl-4-methyl-1,3,2-benzoxazaphosphorin-2-oxides(IIIe) was prepared by the following procedure

N,N–di-(2-chloroethyl)amino-phosphorodichloridate (I) (2.59 g, 0.01 mol) in dry THF (20 ml) was added dropwise to a stirred solution of 2-(1-cyclohexylamino) ethyl-4-methoxylphenol (IIe)(2.49 g, 0.01 mol) and triethylamine (2.78 ml, 0.02 mol) in dry THF on ice bath 0°C. The reaction mixture was stirred at room temperature for 2 h and for another 6 h at 61°C. Solid triethylamine hydrochloride was filtered

off and the filtrate was concentrated in a rota evaporator. The residue was purified by silica gel column chromatography to give light yellow liquid. The synthesis of Substituted benzoxazaphosphorin-2-oxides (**IIIa–d**) was followed with the same procedure.

Compound **IIIa** ($C_{17}H_{27}Cl_2N_2O_3P$) ^{1}H-NMR ($CDCl_3$ 400MHz) δ: 6.95 (d, J = 8.30 Hz, 1H, 5-H), 6.65 (d, J = 2.46 Hz, 1H, 8-H), 6.62 (m, 1H, 6-H), 4.25 (m, 1H, 4-H), 3.77 (s, 3H, -OC$\underline{H}_3$), 3.77–3.43 (m, 8H, –N(C$\underline{H}_2$C$\underline{H}_2$Cl)$_2$), 3.12–2.93 (m, 2H, –C$\underline{H}_2$CH$_2$CH$_2$CH$_3$), 1.68–1.64 (m, 2H, –CH$_2$C$\underline{H}_2$CH$_2$CH$_3$), 1.41 (d, 3H, J = 6.66 Hz, –CHC$\underline{H}_3$), 1.36–1.26 (m, 2H, –CH$_2$CH$_2$C$\underline{H}_2$CH$_3$), 0.94 (m, 3H, –CH$_2$CH$_2$CH$_2$C$\underline{H}_3$); ^{13}C-NMR ($CDCl_3$ 400 MHz) δ: 159.98 (7-C), 149.54 (9-C), 126.76 (6-C), 122.74 (8-C), 111.11 (5-C), 104.79 (10-C), 55.52 (–N(CH$_2$CH$_2$Cl)$_2$), 49.69 (–N$\underline{C}$H$_2$CH$_2$CH$_2$CH$_3$), 46.38 (4-C), 42.39 (–N ($\underline{C}$H$_2\underline{C}$H$_2$Cl)$_2$), 30.72 (–NCH$_2\underline{C}$H$_2$CH$_2$CH$_3$), 24.03 (4-$\underline{C}$H$_3$), 20.23 (–NCH$_2$CH$_2\underline{C}$H$_2$CH$_3$), 13.85 (–NCH$_2$CH$_2$CH$_2\underline{C}$H$_3$); ^{31}P-NMR ($CDCl_3$ 400 MHz) δ: 11.11; ESI-MS, m/z: 409[M+H]$^+$. A molecular formula of $C_{17}H_{27}Cl_2N_2O_3P$ was determined from the molecular ion peak at 409.1130 m/z [M+H]$^+$ (calc.408.1136 for $C_{17}H_{27}Cl_2N_2O_3P$) obtained by ESI-Q-TOF.

Compound **IIIb** ($C_{16}H_{25}Cl_2N_2O_3P$) ^{1}H-NMR ($CDCl_3$ 400 MHz) δ: 6.95 (d, J = 8.24 Hz, 1H, 5-H), 6.65 (d, J = 2.46 Hz, 1H, 8-H), 6.63 (m, 1H, 6-H), 4.25 (m, 1H, 4-H), 3.77 (s, 3H, 7-OC$\underline{H}_3$), 4.24–3.43 (m, 8H, –N(C$\underline{H}_2$C$\underline{H}_2$Cl)$_2$), 2.90–3.08 (m, 2H, –NC$\underline{H}_2$CH$_2$CH$_3$), 1.71–1.68 (m, 2H., –NCH$_2$C$\underline{H}_2$CH$_3$), 1.41 (d, J = 6.56, 3H, 4-C$\underline{H}_3$), 0.91 (m, 3H, –NCH$_2$CH$_2$C$\underline{H}_3$); ^{13}C-NMR ($CDCl_3$ 400 MHz) δ: 159.92 (7-C), 149.48 (9-C), 126.68 (6-C), 122.67 (8-C), 111.06 (5-C), 104.73 (10-C), 55.52 (–N($\underline{C}$H$_2$CH$_2$Cl)$_2$), 49.61 (–N$\underline{C}$H$_2$CH$_2$CH$_3$), 48.30 (4-C), 42.30 (–N(CH$_2\underline{C}$H$_2$Cl)$_2$), 23.99 (–NCH$_2\underline{C}$H$_2$CH$_3$), 21.79 (4-CH$_3$), 11.27 (–NCH$_2$CH$_2\underline{C}$H$_3$); ^{31}P-NMR ($CDCl_3$ 400 MHz) δ: 11.15; ESI-MS, m/z: 395[M+H]$^+$. A molecular formula of $C_{16}H_{25}Cl_2N_2O_3P$ was determined from the molecular ion peak at 395.0901 m/z [M+H]$^+$ (calc. 394.0890 for $C_{16}H_{25}Cl_2N_2O_3P$) obtained by ESI-Q-TOF.

Compound **IIIc** ($C_{16}H_{25}Cl_2N_2O_3P$) ^{1}H-NMR ($CDCl_3$ 400 MHz)δ: 7.01 (d, J = 8.20 Hz, 1H, 5-H), 6.50 (d, J = 2.45 Hz, 1H, 8-H), 6.46 (m, 1H, 6-H), 5.20 (m, 1H, 4-H), 3.81 (s, 3H, –OC$\underline{H}_3$), 3.77–3.68 (m, 8H, –N(C$\underline{H}_2$C$\underline{H}_2$Cl)$_2$), 3.10 (m, 1H, –C$\underline{H}$ (CH$_3$)), 1.36 (d, J = 6.65 Hz, 3H, 4-C$\underline{H}_3$), 1.18 (m, 6H, –CH (C$\underline{H}_3$)); ^{13}C-NMR ($CDCl_3$ 400 MHz) δ: 159.03 (7-C), 149.84 (9-C), 125.86 (6-C), 119.71 (8-C), 111.06 (5-C), 105.15 (10-C), 55.50 (–N($\underline{C}$H$_2$CH$_2$Cl)$_2$), 49.56 (–N$\underline{C}$H (CH$_{3)2}$), 47.91 (4-C), 42.33 (–N (CH$_2\underline{C}$H$_2$Cl)$_2$), 29.36 (–NCH$_2$ ($\underline{C}$H$_3$)$_2$), 26.49 (4-$\underline{C}$H$_3$);^{31}P-NMR ($CDCl_3$ 400 MHz) δ: 11.87; ESI-MS, m/z: 395[M+H]$^+$. A molecular formula of $C_{16}H_{25}Cl_2N_2O_3P$ was determined from the molecular ion peak at 395.0901 m/z [M+H]$^+$ (calc. 394.0890 for $C_{16}H_{25}Cl_2N_2O_3P$) obtained by ESI-Q-TOF.

Compound **IIId** ($C_{17}H_{27}Cl_2N_2O_3P$) ^{1}H-NMR ($CDCl_3$ 400 MHz) δ: 7.03 (d, J = 8.36 Hz, 1H, 5-H), 6.58 (d, J = 2.32Hz, 1H, 8-H), 6.47 (m, 1H, 6-H), 5.18 (m, 1H, 4-H), 3.94 (s, 3H, –OC$\underline{H}_3$), 3.97–3.63 (m, 8H, –N($C\underline{H}_2C\underline{H}_2Cl)_2$), 1.35 (d, J = 6.59Hz, 3H, 4-C$\underline{H}_3$),1.30 (s, 9H, –C($C\underline{H}_3)_3$); ^{13}C-NMR ($CDCl_3$ 400-MHz) δ: 159.01 (7-C), 149.50 (9-C), 125.46 (6-C), 119.72 (8-C), 111.07 (5-C), 106.17 (10-C), 55.47 (–N($\underline{C}H_2CH_2Cl)_2$), 50.16 (4-C), 42.07(–N($CH_2\underline{C}H_2Cl)_2$), 29.36(–C($\underline{C}H_3)_3$), 21.79 (4-$CH_3$), 11.27 (–$NCH_2CH_2\underline{C}H_3$);^{31}P-NMR ($CDCl_3$ 400 MHz) δ: 11.73; ESI-MS, m/z: 409[M+H]$^+$. A molecular formula of $C_{17}H_{27}Cl_2N_2O_3P$ was determined from the molecular ion peak at 409.1130 m/z [M+H]$^+$ (calc. 408.1136 for $C_{17}H_{27}Cl_2N_2O_3P$) obtained by ESI-Q-TOF.

Compound **IIIe** ($C_{19}H_{29}Cl_2N_2O_3P$) ^{1}H-NMR ($CDCl_3$ 400 MHz) δ: 7.04 (d, J = 8.30 Hz, 1H, 5-H), 6.50 (d, J = 2.56 Hz, 1H, 8-H), 6.45 (m, 1H, 6-H), 4.31 (m, 1H, 4-H), 4.08 (m, 1H, –NC$\underline{H}(CH_2)_5$), 3.89 (s, 3H, –OCH_3), 3.80–3.73 (m, 8H, –N($C\underline{H}_2C\underline{H}_2Cl)_2$), 1.34 (d, J = 6.59 Hz, 3H, 4-C$\underline{H}_3$), 1.89–1.38 (m, 10H, –NCH($C\underline{H}_2)_5$); ^{31}P-NMR ($CDCl_3$ 400 MHz) δ: 11.03; ESI-MS, m/z: 436[M+H]$^+$. A molecular formula of $C_{19}H_{29}Cl_2N_2O_3P$ was determined from the molecular ion peak at436.3261 m/z [M+H]$^+$ (calc. 435.3249 for $C_{19}H_{29}Cl_2N_2O_3P$) obtained by ESI-Q-TOF.

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