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SYNTHESIS OF GLYCEROPHOSPHOLIPID CONJUGATES OF CANTHARIDIN AND ITS ANALOGUES

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Abstract: A series of glycerophospholipid conjugates of cantharidin and its analogues were synthesized in a one-pot reaction, using hexaehtyl phosphorus triamide, activated by a catalytic amount of iodine, as the phosphorylating reagent. The structures of the title compounds were confirmed by ^{1}H NMR, ^{31}P NMR, IR and elemental analysis.

Mylabris, the dried body of the Chinese blister beetle, has been used as Chinese medicine for over 2000 years. Its active constituent, cantharidin, has antitumor activities and causes leukocytosis[1]. The synthesis of cyclic glycerophospholipid containing cantharidin analogues has so far not been reported in literature. The conjugates of this type are not only new prodrugs of cantharidin antitumor agents but also may generate two cytotoxic groups against different target sites inside a neoplastic cell[2]. Such types of compounds may be of interest in chemistry, biochemistry and pharmacology. This paper deals with the synthesis of glycerophospholipid conjugate of cantharidin and its analogs as new models of phospholipids.

Compound **6a~e** were obtained by a one-pot (two-step) reaction from N-hydroxyethyl compound **2** by means of phosphorus triamide, activated by iodine, as a phosphorylating reagent under mild

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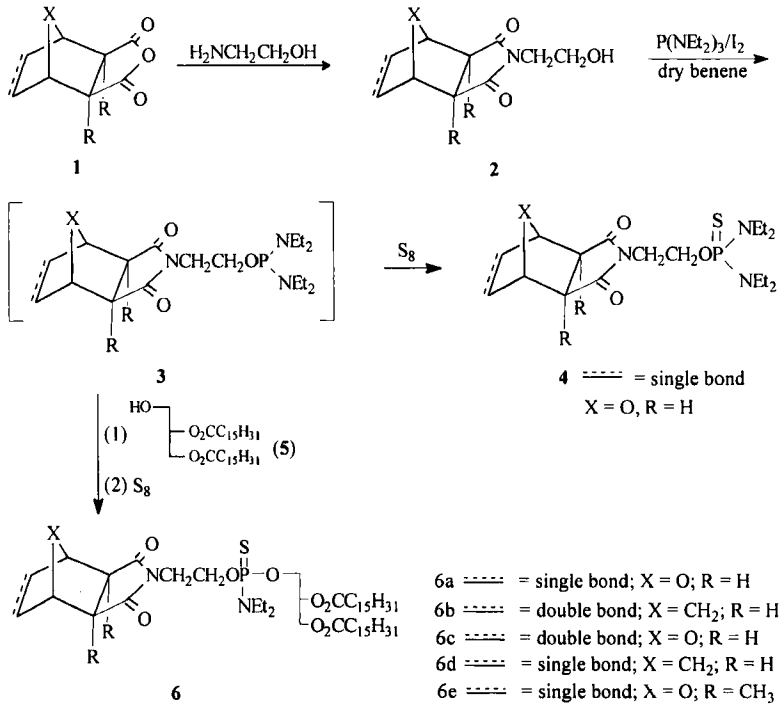
conditions (**Scheme 1**). Thus the activated phosphorus triamide was reacted with compound **2** in dry benzene on moderate heating (60~70°C) to form the intermediate bis(N,N-diethylamido)phosphite (**3**). This was proved by transformation of **3** to the corresponding thiophosphate derivative (**4**) by directly adding sulfur to the reaction mixture. The consecutive treatment of the intermediate **3** with an equivalent amount of dipalmitin (**5**) and sulfur at the same condition for 5h and 30min respectively afforded the title compounds **6a~e**, which were isolated by column chromatography. The spectroscopic data of the products were listed in Tables 1 and 2.

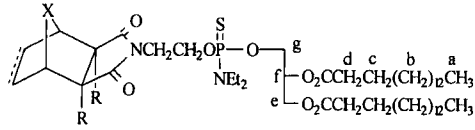


Scheme 1

EXPERIMENTAL

All melting points were determined on a Yanaco apparatus and they are uncorrected. IR were recorded on a shimadazu-IR435 spectrometer. NMR spectra were measured on a Brucker AC-P200 NMR instrument in $CDCl_3$ and chemical shifts are expressed as δ units, TMS being used as an

Table 1 ^{1}H NMR and ^{31}P NMR Data of Compounds **6a~e**



Compd.	^{1}H NMR、^{31}P NMR data (δ, J/Hz, $CDCl_3$)
6a	0.85(t, 6H, Ha, J^{3}_{H-H}=5.82), 1.00(t, 6H, $NCH_2\underline{CH_3}$, J^{3}_{H-H}=7.13), 1.22(s, 48H, Hb), 1.58(m, 4H, Hc), 1.83(m, 4H, CH_2CH_2), 2.31(t, 4H, Hd, J^{3}_{H-H}=4.27), 2.90(s, 2H, COCH), 3.13(q, 4H, $N\underline{CH_2}CH_3$, J^{3}_{H-H}=7.43), 3.70(t, 2H, NCH_2, J^{3}_{H-H}=5.81), 3.92(m, 2H, He), 4.09(m, 1H, Hg), 4.18(t, 2H, OCH_2, J^{3}_{H-H}=6.64), 4.30(m, 1H, Hg), 4.67(m, 1H, Hf), 4.83(s, 2H, OCH) ^{31}P NMR: 77.66
6b	0.85(t, 6H, Ha, J^{3}_{H-H}=5.84), 1.03(t, 6H, $NCH_2\underline{CH_3}$, J^{3}_{H-H}=7.06), 1.22(s, 48H, Hb), 1.48(m, 2H, CH_2 bridge), 1.58(m, 4H, Hc), 2.28(t, 4H, Hd, J^{3}_{H-H}=3.56), 2.69(s, 2H, COCH), 3.14(q, 4H, $N\underline{CH_2}CH_3$, J^{3}_{H-H}=7.05), 3.23(s, 2H, bridgehead CH), 3.73(t, 2H, NCH_2, J^{3}_{H-H}=5.79), 4.00(m, 2H, He), 4.09(m, 1H, Hg), 4.19(t, 2H, OCH_2, J^{3}_{H-H}=5.30), 4.32(m, 1H, Hg), 4.71 (m, 1H, Hf), 6.25(s, 2H, =CH) ^{31}P NMR: 77.31
6c	0.84(t, 6H, Ha,J^{3}_{H-H}=5.77), 1.03(t, 6H, $NCH_2\underline{CH_3}$, J^{3}_{H-H}=7.06), 1.22(s, 48H, Hb), 1.58(m, 4H, Hc), 2.28(t, 4H, Hd, J^{3}_{H-H}=6.00), 2.87(s, 2H, COCH), 3.13(q, 4H, $N\underline{CH_2}CH_3$, J^{3}_{H-H}=7.02), 3.70(t, 2H, NCH_2, J^{3}_{H-H}=5.81), 3.96(m, 2H, He), 4.02(m, 1H, Hg), 4.12(t, 2H, OCH_2, J^{3}_{H-H}=5.44), 4.37(m, 1H, Hg), 4.67(m, 1H, Hf), 5.22(s, 2H, OCH), 6.48(s, 2H, =CH) ^{31}P NMR: 77.61
6d	0.85(t, 6H, Ha, J^{3}_{H-H}=5.72), 1.04(t, 6H, $NCH_2\underline{CH_3}$, J^{3}_{H-H}=7.08), 1.22(s, 48H, Hb), 1.65(m, 10H, CH_2 bridge, CH_2CH_2 and Hc), 2.29(t, 4H, Hd, J^{3}_{H-H}=7.01), 2.61(s, 2H, COCH), 2.68(s, 2H,bridgehead CH), 3.13(q, 4H, $N\underline{CH_2}CH_3$, J^{3}_{H-H}=6.98), 3.70(t, 2H, NCH_2, 5.76), 3.98(m, 2H, He), 4.05(m, 1H, Hg), 4.14(t, 2H, OCH_2, J^{3}_{H-H}=5.32), 4.31(m, 1H, Hg), 5.21 (m, 1H, Hf), 6.25(s, 2H, =CH) ^{31}P NMR: 77.45
6e	0.85(t, 6H, Ha, J^{3}_{H-H}=5.87), 1.04(t, 6H, $NCH_2\underline{CH_3}$, J^{3}_{H-H}=7.07), 1.15(s, 6H, CH_3), 1.22(s, 48H, Hb), 1.60(m, 4H, Hc), 1.71(m, 4H, CH_2CH_2), 2.29(t, 4H, Hd, J^{3}_{H-H}=7.23), 3.15(q, 4H, $N\underline{CH_2}CH_3$, 7.03), 3.73(t, 2H, $N\underline{CH_2}CH_3$, 5.89), 4.00(m, 2H, He), 4.07(m, 1H, Hg), 4.12(t, 2H, OCH_2, J^{3}_{H-H}=5.45), 4.33(m, 1H, Hg), 4.52(s, 2H, OCH), 5.22(m, 1H, Hf) ^{31}P NMR: 77.28

Table 2 IR Data of Compound **6a~e**

Compd.	IR (thin film, cm^{-1})
6a	2910, 2901, 1772, 1738, 1702, 1463, 1422, 1395, 1330, 1238, 1204, 1160, 946, 884, 821, 790, 737
6b	2906, 2907, 1770, 1739, 1701, 1462,1 418, 1380, 1324, 1166, 1112, 1023, 995, 949, 787, 715
6c	2931, 2906, 1737, 1702, 1461, 1453, 1384, 1166, 1102, 1022, 999, 945
6d	3420, 2913, 1774, 1739, 1706, 1464, 1396, 1359, 1332, 1205, 1160, 1107, 1021, 948, 922, 875, 850, 821, 785, 718
6e	2925, 2904, 1737, 1702, 1463, 1419, 1377, 1335, 1227, 1198, 1163, 1080, 1050, 1022, 994, 956

internal standard for ^1H NMR and 85% H_3PO_4 as an external standard for ^{31}P NMR spectroscopy. Elemental analysis was carried out with a Yanaco CHNCORDER MT-3 Analyzer. Benzene was distilled from sodium before being used. Petroleum ether refers to a fraction of b.p. 60~90°C. Column chromatography was carried out with silica gel H(10~40 μm). Hexaethylphosphorus triamide was prepared according to the literature[3] and freshly distilled. Compounds **1**, except cantharidin, and compound **5** were prepared according to the procedures reported in the literature[4~8].

General procedure for the preparation of compound 2

To a solution of compound **I** in absolute ethanol was added aminoethanol with stirring. The reaction mixture was stirred at room temperature for 0.5 hour and then heated to reflux for 2 hours, cooled to room temperature and placed overnight, the crystal precipitated was gathered by filtering and washed by ethanol to afford compound **2** as white crystal.

N-hydroxyethyl exo-7-oxabycyclo[2.2.1]heptane-2,3-dicarboximide

Yield 78.1%; m.p. 158~159°C; ^{1}H NMR(δ, DMSO-d_6): 1.61(s, 4H, CH_2CH_2), 3.00(s, 2H, COCH), 3.30(s, 4H, NCH_2CH_2), 4.65(s, 2H, OCH);

N-hydroxyethyl exo-bicyclo[2.2.1]hept-5-ene-2,3-dicarboximide

Yield 74.8%; m.p. 145~146°C; ^{1}H NMR(δ, DMSO-d_6): 1.27(q, 2H, CH_2 bridge), 2.65(s, 2H, bridgehead CH), 3.07(s, 2H, COCH), 3.43(m, 4H, NCH_2CH_2), 6.29(s, 2H, =CH);

N-hydroxyethyl exo-7-oxabycyclo[2.2.1]hept-5-ene-2,3-dicarboximide

Yield 71.7%; m.p. 135~136°C(dec.); ^{1}H NMR(δ, DMSO-d_6):2.91(s, 2H, COCH), 3.40(s, 4H, NCH_2CH_2), 5.11(s, 2H, OCH), 6.54(s, 2H, =CH);

N-hydroxyethyl exo-bicyclo[2.2.1]heptane-2,3-dicarboximide

Yield 83.2%; m.p. 110~111°C; ^{1}H NMR(δ, DMSO-d_6):1.09(s, CH_2 bridge), 1.27-1.52(m, 4H, CH_2CH_2), 2.61(s, 2H, bridghead CH), 3.07(s, 2H, COCH), 3.33(s, 4H, NCHCH);

N-hydroxyethyl exo-2,3-dimethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboximide

Yield 80.1%; m.p. 62~63°C; ^{1}H NMR(δ, $CDCl_3$): 1.11(s, 6H, CH3), 1.74(m, 4H, CH_2CH_2), 2.50(s, 2H, OCH), 4.52(s, 4H, NCH_2CH_2).

Procedure for compound 4

A mixture of iodine (0.1 mmol) and hexaethylphosphorus triamide (2.1 mmol) in anhydrous benzene was stirred at 60~70°C for about 15 min until the reaction mixture became clear. Powdery N-hydroxyethyl exo-7-oxabicyclo[2.2.1]heptane-2,3-dicarboximide (2 mmol) was added and the reaction mixture was continuously stirred at 60~70°C for about 1 hr. Then sulfur (2.1 mmol) was added and the reaction mixture was kept under the same condition for 30 min. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel column eluted with petroleum ether-ethyl acetate (1:1) to afford oily product 0.62g (isolated yield: 74.3%). Rf value: 0.645($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=1:2). Anal. Calcd. for $C_{18}H_{32}N_3O_4PS$: C, 51.78; H, 7.73; N, 10.06. Found: C, 51.92; H, 7.67; N, 9.75. ^{1}H NMR(δ, $CDCl_3$): 1.04(t, 12H, $CH_2\underline{CH_3}$), 1.58(m, 2H,

CH_2CH_2), 1.83(m, 2H, CH_2CH_2), 2.88(s, 2H, COCH), 3.02(q, 8H, $\underline{CH_2}CH_3$), 3.71(t, 2H, NCH_2), 3.99(t, 2H, OCH_2), 4.83(s, 2H, OCH).

General procedure for the preparation of compound 6a~e

A mixture of iodine (0.1 mmol) and hexaethylphosphorus triamide (2.1 mmol) in anhydrous benzene was stirred at 60~70°C for about 15 min until the reaction mixture became clear. Powdery **2** (2 mmol) was added and the reaction mixture was continuously stirred at 60~70°C for about 1 hr. Then dipalmitin (2 mmol) was added , and the mixture was heated at 60~70°C for 5 hr. The resultant cyclic phosphite was transformed to thiophosphate (**6**) by adding sulfur (2.1 mmol) and keeping the reaction mixture at 60~70°C for 30 min. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel column eluted with petroleum ether-ethyl acetate to afford oily products in pure form.

6a oil, 53.2% isolated yield, Rf value 0.574($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=2:1). Anal. Calcd. for $C_{49}H_{89}N_2O_9PS$: C, 64.44; H, 9.82; N, 3.07. Found: C, 63.99; H, 9.96; N, 3.14.

6b oil, 55.6% isolated yield, Rf value 0.457($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=4:1). Anal. Calcd. for $C_{50}H_{89}N_2O_8PS$: C, 66.04; H, 9.87; N, 3.08. Found: C, 66.14; H, 10.08; N, 3.24.

6c oil, 49.8% isolated yield, Rf value 0.597($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=2:1). Anal. Calcd. for $C_{49}H_{87}N_2O_9PS$: C, 64.58; H, 9.62; N, 3.07. Found: C, 64.62; H, 9.65; N, 3.06.

6d oil, 57.1% isolated yield, Rf value 0.429($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=4:1). Anal. Calcd. For $C_{50}H_{91}N_2O_8PS$: C, 65.90; H, 10.07; N, 3.07. Found: C, 66.11; H, 9.81; N, 3.28.

6e oil, 52.5% isolated yield, Rf value 0.508($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=3:1). Anal. Calcd. for $C_{51}H_{93}N_2O_9PS$: C, 65.07; H, 9.96; N, 2.98. Found: C, 65.24; H, 10.10; N, 2.99.

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