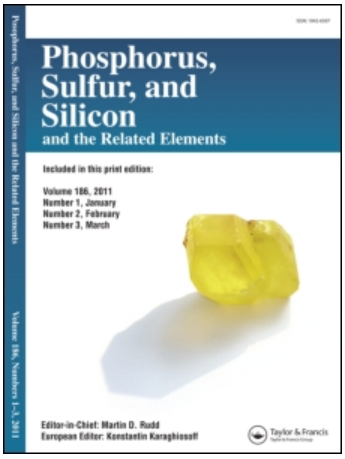

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SYNTHESIS OF 1,2-CYCLIC MONOACYL-RAC-GLYCEROTHIO-PHOSPHATES OF CANTHARIDIN ANALOGUES

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SYNTHESIS OF 1,2-CYCLIC MONOACYL-RAC-GLYCEROTHIO-PHOSPHATES OF CANTHARIDIN ANALOGUES

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A series of 1,2-cyclic monoacyl-rac-glycerothiophosphates of cantharidin and its analogues were synthesized in a one-pot procedure in overall yields of 44~55.5% by means of hexaethylphosphorus triamide, activated by a catalytic amount of iodine, as phosphorylating reagent. Their structures were confirmed by ^{1}H NMR, ^{31}P NMR, IR and elemental analysis.

Keywords: Synthesis; cantharidin and its analogues; cyclic glycerothiophosphate

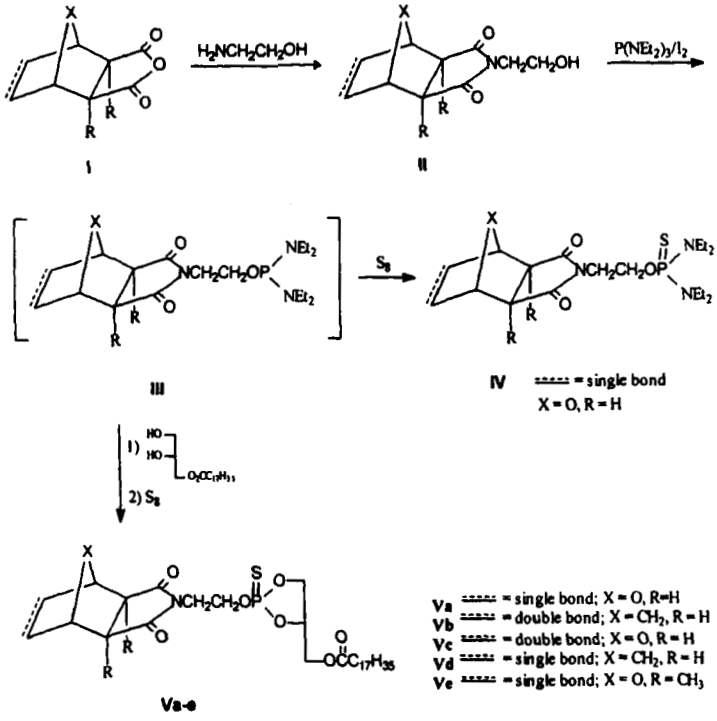
INTRODUCTION

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 1,2-cyclic monoacyl-rac-glycerothiophosphates of cantharidin analogs as new models of phospholipids.

* Correspondence Author.

RESULTS AND DISCUSSION

Compound **Va~e** were obtained by a one-pot (two-step) reaction from N-hydroxyethyl compound **II** by means of phosphorus triamide, activated by iodine, as a phosphorylating reagent under mild conditions (**Scheme 1**). Thus the activated phosphorus triamide was reacted with compound **II** in dry benzene on moderate heating (60~70°C) to form the intermediate bis(N,N-diethylamido)phosphite (**III**). This was proved by transformation of **III** to the corresponding thiophosphate derivative (**IV**) by directly adding sulfur to the reaction mixture. The consecutive treatment of the intermediate **III** with an equivalent amount of monostearin and sulfur at the same condition for 5h and 30min respectively afforded the title compounds **Va~e**, which were isolated by column chromatography. The spectroscopic data of the products were listed in Tables I and II.

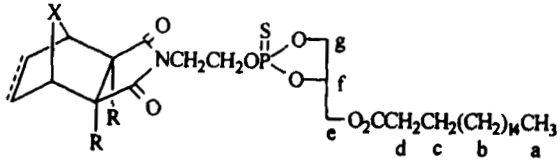


I II III IV ----- = single bond X = O, R = H

Va-e

SCHEME 1

TABLE I ^{1}H NMR and ^{31}P NMR Data of Compounds **Va–e**



Compd.	*^{1}H NMR, & ^{31}P NMR Data (δ, $CDCl_3$)*
Va	0.85(t, 3H, Ha), 1.22(s, 28H, Hb), 1.60(m, 4H, CH_2CH_2), 1.83(m, 2H, Hc), 2.33(t, 2H, Hd), 2.91(s, 2H, COCH), 3.77(t, 2H, NCH_2), 4.10(m, 2H, He), 4.22(t, 2H, OCH_2), 4.33(m, 1H, Hg), 4.43(m, 1H, Hg), *4.76(m, 1H, Hf)*, 4.85(s, 2H, OCH) ^{31}P NMR: 84.13
Va′	0.84(t, 3H, Ha), 1.21(s, 28H, Hb), 1.56–1.59(m, 4H, CH_2CH_2), 1.83(m, 2H, Hc), 2.32(t, 2H, Hd), 2.90(s, 2H, COCH), 3.71(t, 2H, NCH_2), 4.13(m, 2H, He), 4.29(t, 2H, OCH_2), 4.36(m, 2H, Hg), *4. 72(m, 1H, Hf)*, 4.83(s, 2H, OCH) ^{31}P NMR: 83.89
Vb	0.85(t, 3H, Ha), 1.22(s, 28H, Hb), 1.51(m, 2H, CH_2bridge), 1.61(m, 2H, Hc), 2.33(t, 2H, Hd), 2.71(s, 2H, COCH), 3.26(s, 2H, =CCH), 3.75(t, 2H, NCH_2), 4.11(m, 2H, He), 4.23(t, 2H, OCH_2), 4.33(m, 1H, Hg), 4.46(m, 1H, Hg), *4.76(m, 1H, Hf)*, 6.26(s, 2H, =CH) ^{31}P NMR: 83.93
Vb′	0.85(t, 3H, Ha), 1.23(s, 28H, Hb), 1.51(m, 2H, CH_2bridge), 1.66(m, 2H, Hc), 2.34(t, 2H, Hd), 2.71(s, 2H, COCH), 3.25(s, 2H, =CCH), 3.74(t, 2H, NCH_2), 4.14(m,2H,He), 4.28(t, 2H, OCH_2), 4.31(m, 1H, Hg), 4.36(m, 1H, Hg), *4.73(m, 1H, Hf)*, 6.26(s, 2H, =CH) ^{31}P NMR: 83.70
Vc	0.85(t, 3H, Ha), 1.22(s, 28H, Hb), 1.59(m, 2H, Hc), 2.32(t, 2H, Hd), 2.87(s, 2H, COCH), 3.73(t, 2H, NCH_2), 4.08(m, 2H, He), 4.20(t, 2H, OCH_2), 4.31(m, 1H, Hg), 4.40(m, 1H, Hg), *4.78(m, 1H, Hf)*, 5.24(s, 2H, OCH), 6.48(s, 2H, =CH) ^{31}P NMR: 84.06
Vc′	0.85(t, 3H, Ha), 1.23(s, 28H, Hb), 1.61(m, 2H, Hc), 2.33(t, 2H, Hd), 2.89(s, 2H, COCH), 3.75(t, 2H, NCH_2), 4.19(m, 2H, He), 4.29(m, 1H, Hg), 4.36(t, 2H, OCH_2), 4.43(m, 1H, Hg), *4.73(m, 1H, Hf)*, 5.24(s, 2H, OCH), 6.48(s, 2H, =CH) ^{31}P NMR: 83.80
Vd	0.83(t, 3H, Ha), 1.21(s, 28H, Hb), 1.32(m, 4H, CH_2CH_2), 1.60(m, 4H, CH_2 bridge and Hc), 2.32(t, 2H, Hd), 2.61(s, 2H, COCH), 2.65(s, 2H, CH), 3.72(t, 2H, NCH_2), 4.08(m, 2H, He), 4.22(t, 2H, OCH_2), 4.28(m, 1H, Hg), 4.42(m, 1H, Hg), *4.77(m, 1H, Hf)* ^{31}P NMR: 83.95
Vd′	0.85(t, 3H, Ha), 1.22(s, 28H, Hb), 1.29(m, 4H, CH_2CH_2), 1.76(m, 4H, CH_2 bridge and Hc), 2.34(t, 2H, Hd), 2.63(s, 2H, COCH), 2.67(s, 2H, CH), 3.73(t, 2H, NCH_2), 4.17(m, 2H, He), 4.28(t, 2H, OCH_2), 4.33(m, 1H, Hg), 4.42(m, 1H, Hg), *4.74(m, 1H, Hf)* ^{31}P NMR: 83.70
Ve	0.84(t, 3H, Ha), 1.15(s, 6H, CH_3), 1.63(m, 2H, Hb), 1.76(m, 4H, CH_2CH_2), 2.33(t, 2H, Hc), 3.78(t, 2H, NCH_2), 4.13(m, 2H, He), 4.21(t, 2H, OCH_2), 4.33(m, 1H, Hg), 4.42(m, 1H, Hg), 4.54(s, OCH), *4.76(m, 1H, Hf)* ^{31}P NMR: 83.95
Ve′	0.85(t, 3H, Ha), 1.15(s, 6H, CH_3), 1.63(m, 2H, Hb), 1.76(m, 4H, CH_2CH_2), 2.33(t, 2H, Hc), 3.75(t, 2H, NCH_2), 4.17(m, 2H, He), 4.27(m, 1H, Hg), 4.34(t, 2H, OCH_2), 4.40(m, 1H, Hg), 4.53(s, OCH), *4.74(m, 1H, Hf)* ^{31}P NMR: 83.63

TABLE II IR Data of Compounds **Va~e**

Compd.	*IR (KBr film, cm^{-1})*
Va	3403, 2918, 2904, 1770, 1742, 1701, 1466, 1451, 1394, 1328, 1209, 1162, 1124, 1046, 1003, 977, 942, 843, 795, 742, 680, 572
Vb	3402, 2917, 2904, 1767, 1737, 1699, 1464, 1439, 1388, 1323, 1209, 1183, 1114, 1045, 993, 938, 895, 807, 771, 715, 637
Vc	3405, 2926, 2904, 1769, 1732, 1695, 1466, 1438, 1399, 1359, 1257, 1186, 1143, 1075, 1019, 956, 924, 876, 805, 777, 721
Vd[a]	2918, 2909, 1766, 1739, 1699, 1465, 1390, 1324, 1185, 1053, 990, 943, 800
Ve[a]	2910(89.3)[b] , 1771(37.6), 1738(69.0), 1701(92.3), 1464(48.1), 1423(44.5), 1400(57.1), 1380(42.2), 1333(44.0), 1253(43.9), 1164(49.1), 1044(58.1), 995(71.3), 943()48.9), 896(50.6), 828(44.4), 805(43.8), 776(37.6), 683(37.2)
Ve'[a]	2909(89.6), 1771(42.0), 1739(71.9), 1700(93.6), 1464(52.1), 1423(49.2), 1400(62.7), 1380(47.0), 1333(49.4), 1255(33.9), 1164(55.0), 1079(57.6), 1048(59.9), 1007(73.4), 972(56.9), 945(58.3), 895(55.6), 829(49.9), 802(51.9), 776(45.0), 682(31.3)

a. IR spectra were recorded as thin film
b. Data in parentheses are the intensity of absorption peak

The title compound **Va~e** may be discussed as 4-substituted 1,3,2-dioxaphospholane which possesses two chiral centers, e.g. CH and P, and consequently exists as two pair of enantiomers which form a pair of diastereoisomers 2RS,4RS and 2RS,4SR (**Fig. 1**). The 2RS,4RS and 2RS,4SR diastereoisomers represent the cis- and trans-isomers of the 1,3,2-dioxaphospholane respectively and they are readily-separable because of their difference of physicochemical properties.

In the ^1H NMR of 1,3,2-dioxaphospholanes **Va~e** the chemical shift of proton on C-4 (*Hf*) of cis isomer is higher than that of the trans-isomer (see Table I). This phenomena could be explained as bellow. In the cis isomer the proton on C-4 and the P=S double bond locate on the same side of the five-membered ring, the chemical shift moves to low field because of the deshielding effect of the P=S double bond; in the trans-isomer the proton on C-4 and the P=S double bond place the opposite side of the five-membered ring, it is not affected by the anisotropic effect of P=S double bond, so the chemical shift locates in high field.

There are also some differences between the two isomers (Ve and Ve') in the IR spectrum (listed in table II).

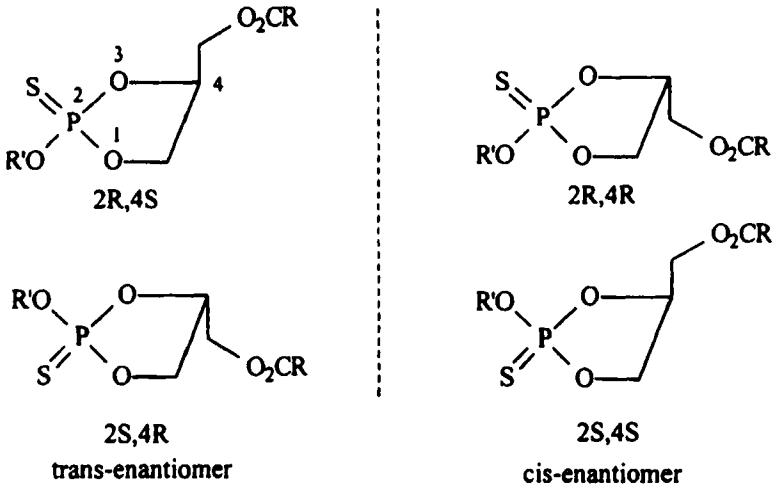


FIGURE 1

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 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 **I**, except cantharidin, were prepared according to the procedures reported in the literature[4–7].

General procedure for the preparation of compound II

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 **II** 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 IV

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 (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. ^1H NMR(δ,$CDCl_3$): 1.04(t,12H,CH_2CH_3), 1.58(m,2H,CH_2CH_2), 1.83(m,2H,CH_2CH_2), 2.88(s,2H,COCH), 3.02(q,8H, CH_2CH_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 Va~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 **II** (2 mmol) was added and the reaction mixture was continuously stirred at 60~70°C for about 1 hr. Then monostearin (2 mmol) was added, and the mixture was heated at 60~70°C for 5 hr. The resultant cyclic phosphite was transformed to thiophosphate (**V**) 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 (3:2) to afford oily products as a pair of diastereoisomers in pure form.

IVa oil, 29.3% yield, Rf value 0.585($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=3:2). Anal. Calcd. for: C, 59.12; H, 8.32; N, 2.22. Found: C, 58.68; H, 8.14; N, 2.31.

IVa′ oil, 23.0% yield, Rf value 0.425($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=3:2). Anal. Calcd. for $C_{31}H_{52}NO_8PS$: C, 59.12; H, 8.32; N, 2.22. Found: C, 59.03; H, 8.30; N, 2.33.

IVb oil, 24.8% yield, Rf value 0.615($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=3:2). Anal. Calcd. for $C_{32}H_{52}NO_7PS$: C, 61.41; H, 8.38; N, 2.24. Found: C, 61.24; H, 8.67; N, 2.09.

IVb′ oil, 19.2% yield, Rf value 0.315($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=3:2). Anal. Calcd. for $C_{32}H_{52}NO_7PS$: C, 61.41; H, 8.38; N, 2.24. Found: C, 61.96; H, 8.81; N, 2.45.

IVc oil, 25.5% yield, Rf value 0.738($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=3:2). Anal. Calcd. for $C_{31}H_{50}NO_8PS$: C, 59.31; H, 8.03; N, 2.23. Found: C, 59.18; H, 8.10; N, 2.30.

IVc′ oil, 19.9% yield, Rf value 0.538($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=3:2). Anal. Calcd. for $C_{31}H_{50}NO_8PS$: C, 59:31; H, 8.08; N, 2.23. Found: C, 58.89; H, 8.81; N, 2.33.

IVd oil, 28.7% yield, Rf value 0.662($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=3:2). Anal. Calcd. for $C_{32}H_{54}NO_7PS$: C, 61.22; H, 8.67; N, 2.23. Found: C, 61.50; H, 8.87; N, 2.14.

IVd' oil, 23.1% yield, Rf value 0.508($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=3:2). Anal. Calcd. for $C_{32}H_{54}NO_7PS$: C, 61.22; H, 8.67; N, 2.23. Found: C, 61.38; H, 8.96; N, 2.14.

IVe oil, 31.2% yield, Rf value 0.493($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=3:2). Anal. Calcd. for $C_{33}H_{56}NO_8PS$: C, 60.25; H, 8.58; N, 2.13. Found: C, 60.42; H, 8.64; N, 2.14.

IVe' oil, 24.3% yield, Rf value 0.338($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$=3:2). Anal. Calcd. for $C_{33}H_{56}NO_8PS$: C, 60.25; H, 8.58; N, 2.13. Found: C, 60.05; H, 8.74; N, 2.42.

Acknowledgements

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