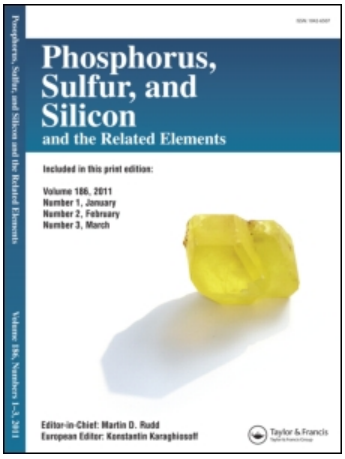

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF PHOSPHONODIPEPTIDE DERIVATIVES OF EXO-7-OXABICYCLO [2.2.1] HEPTANE-2,3-DICARBOXYLIC ANHYDRIDE

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To cite this Article Zhou, Zheng Hong , Zhang, Zhong Biao and Chen, Ru Yu(1999) 'SYNTHESIS OF PHOSPHONODIPEPTIDE DERIVATIVES OF EXO-7-OXABICYCLO [2.2.1] HEPTANE-2,3-DICARBOXYLIC ANHYDRIDE', Phosphorus, Sulfur, and Silicon and the Related Elements, 152: 1, 45 — 52
To link to this Article: DOI: 10.1080/10426509908031616
URL: http://dx.doi.org/10.1080/10426509908031616

Phosphorus, Sulfur and Silicon, 1999, Vol. 152, pp. 45-52
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SYNTHESIS OF PHOSPHONODIPEPTIDE DERIVATIVES OF EXO-7-OXABICYCLO [2.2.1] HEPTANE-2, 3-DICARBOXYLIC ANHYDRIDE

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(In final form January 06, 1999)

A series of phosphonodipeptide derivatives of norcantharidin (exo-7-oxabicyclo[2.2.1] heptane-2,3-dicarboxylic anhydride) were synthesized and their structures were confirmed by ^{1}H NMR, ^{31}P NMR, IR, MS and elemental analysis.

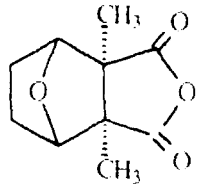
Keywords: Synthesis; phosphonodipeptide; norcantharidin; condensation reaction; coupling agent

INTRODUCTION

Cantharidin, exo-4a, 7a-dimethyl-4,7-epoxyhexahydroisobenzofuran-1, 3-dione (**1**), has displayed significant antitumor properties in vitro and in vivo. The adverse effects on urinary and gastrointestinal tracts prevent it to be accepted by the clinic[1]. The structural modification of cantharidin was pursued by us with the aim to decrease its toxicity and maintain or increase its efficacy. Organophosphorous-containing molecules of actual or potential pharmaceutical use, such as the α-aminophosphonic acid dipeptide, alaphosphin (**2**), which inhibits alanine racemase[2], are becoming increasingly important. We therefore designed and synthesized a series of phosphonodipeptide derivatives of norcantharidin with α-aminoalkylphos-

* Correspondence Author.

phonate in the C-terminal of amino acid structure, which may be interest in chemistry, biochemistry and pharmacology.



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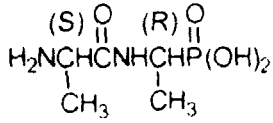

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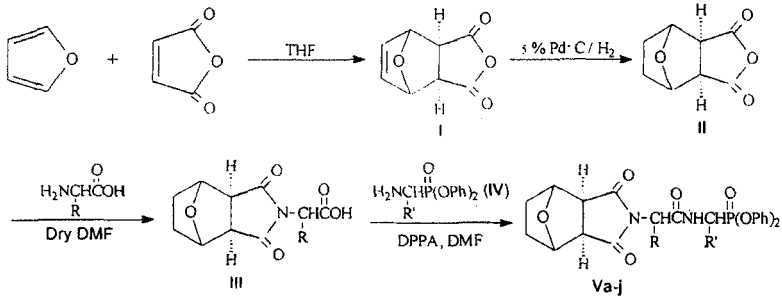
RESULTS AND DISCUSSION

Several hitherto unknown phosphonodipeptide derivatives of exo-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride, ten in all, were synthesized in good yields and high purity by the condensation reaction of compounds **III** and **IV** with DPPA (diphenyl phosphorazidate) as coupling agent in DMF (shown in Scheme 1). The spectroscopic data of the products were listed in Tables I, II, and III.



a R^1=sec-Butyl, R^2=2-ClC_6H_4.
b R^1=sec-Butyl, R^2=3-$O_2NC_6H_4$.
c R^1= $PhCH_2$, R^2=3-$O_2NC_6H_4$;
d R^1=$PhCH_2$, R^2=4-$CH_3C_6H_4$;
e R^1=sec-Butyl, R^2=4-$CH_3C_6H_4$.
f R^1=$PhCH_2$, R^2=C_6H_5;
g R^1=CH_3, R^2=4-ClC_6H_4;
h R^1=H, R^2=2,4-$Cl_2C_6H_3$,
i R^1=CH_3, R^2=3-$O_2NC_6H_4$;
j R^1= CH_3, R^2= C_6H_5.

SCHEME 1

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

Compd.	*Data of ^{1}H and ^{31}P NMR (δ, $CDCl_3$)*
Va	0.78(t, 3H, $CH_2\underline{CH_3}$), 0.96(d, 3H, $CH\underline{CH_3}$), 1.31(m, 2H, $\underline{CH_2}CH_3$), 1.55(m, 2H, CH_2CH_2), 1.79(m, 2H, CH_2CH_2), 2.56(m, 1H, $\underline{CH}CH_3$), 2.70(q, 1H, COCH), 2.84(q, 1H, COCH), 4.37(t, 1H, NCH), 4.85(d, 2H, OCH), 6.29–6.50(m, 1H, PCH, $J^2_{P\text{-}H}$=20.8Hz, $J^3_{H\text{-}H}$=9.2Hz), 6.86–6.90(d, $2H_{arom}$), 7.13–7.31(m, $12H_{arom}$), 8.29(m, 1H, CONH) ^{31}P NMR: 12.96
Vb	0.84(t, 3H, $CH_2\underline{CH_3}$), 0.99(d, 3H, $CH\underline{CH_3}$), 1.35(m, 2H, $\underline{CH_2}CH_3$), 1.57–1.86(m, 4H, CH_2CH_2), 2.64(m, 1H, $\underline{CH}CH_3$), 2.80(q, 1H, COCH), 3.02(q, 1H, COCH), 4.45(t, 1H, NCH), 4.83(t, 2H, OCH), 5.81–6.01(m, 1H, PCH, $J^2_{P\text{-}H}$=21.7Hz, $J^3_{H\text{-}H}$=8.3Hz), 6.99–7.28(m, $10H_{arom}$), 7.52(t, $1H_{arom}$), 7.81(d, $1H_{arom}$), 8.13(d, $1H_{arom}$), 8.29(d, $1H_{arom}$), 8.68(m, 1H, CONH) ^{31}P NMR: 12.10
Vc	1.58–1.86(m, 4H, CH_2CH_2), 2.79(q, 2H, COCH), 3.56(m, 2H, CH_2Ph), 4.77–4.93(dd, 2H, OCH), 5.02(q, 1H, NCH), 5.89–6.08(q, 1H, PCH, $J^2_{P\text{-}H}$=21.7Hz, $J^3_{H\text{-}H}$=9.2Hz), 7.01–7.30(m, $10H_{arom}$), 7.50(t, $2H_{arom}$), 7.79(dd, 1H, CONH), 7.80(d, $1H_{arom}$), 8.14(d, $1H_{arom}$), 8.38(m, $1H_{arom}$) ^{31}P NMR: 11.88, 12.17
Vd	1.48(d, 2H, CH_2CH_2), 1.76(d, 2H, CH_2CH_2), 2.31(s, 3H, CH_3), 2.67(q, 2H, COCH), 3.52(m, 2H, CH_2Ph), 4.60(s, 1H, OCH), 4.77(s, 1H, OCH), 4.92(q, 1H, NHC), 5.80–5.95(q, 1H, PCH, $J^2_{P\text{-}H}$=20.0Hz, $J^3_{H\text{-}H}$=8.8Hz), 6.89–7.35(m, $14H_{arom}$), 6.92(d, 1H, CONH) ^{31}P NMR: 13.70, 14.03
Ve	0.80(t, 3H, $CH_2\underline{CH_3}$), 0.97(d, 3H, $CH\underline{CH_3}$), 1.31(m, 2H, $\underline{CH_2}CH_3$), 1.54–1.85(m, 4H, CH_2CH_2), 2.31(s, 3H, CH_3), 2.55(m, 1H, $\underline{CH}CH_3$), 2.68(q, 1H, COCH), 2.85(q, 1H, COCH), 4.38(t, 1H, NCH), 4.77(dd, 2H, OCH), 5.71–5.91(m, 1H, PCH, $J^2_{P\text{-}H}$=20.0Hz, $J^3_{H\text{-}H}$=7.5Hz), 6.88–6.92(d, $2H_{arom}$), 7.08–7.33(m, $10H_{arom}$), 7.35-7.39(d, $2H_{arom}$), 8.28(m, 1H, CONH) ^{31}P NMR: 13.97, 14.18
Vf	1.51(d, 2H, CH_2CH_2), 1.77(d, 2H, CH_2CH_2), 2.68(q, 2H, COCH), 3.44(m, 2H, CH_2Ph), 4.61(s, 1H, OCH), 4.79(s, 1H, OCH), 4.94(q, 1H, NCH), 5.81–5.98(q, 1H, PCH, $J^2_{P\text{-}H}$=23.5Hz, $J^3_{H\text{-}H}$=9.2Hz), 6.88(d, 1H, CONH), 7.06–7.43(m, $15H_{arom}$) ^{31}P NMR: 13.52, 14.84
Vg	1.58(m, 5H, CH_3 and CH_2CH_2), 1.86(m, 2H, CH_2CH_2), 2.92(q, 2H, COCH), 4.74(m, 1H, NCH), 4.85-5.01(dd, 2H, OCH), 5.75–5.92(q, 1H, PCH, $J^2_{P\text{-}H}$=21.7Hz, $J^3_{H\text{-}H}$=9.2Hz), 6.88(d, 1H, CONH), 7.07–7.45(m, $14H_{arom}$) ^{31}P NMR: 13.02, 13.28
Vh	1.58–1.86(m, 4H, CH_2CH_2), 2.92(s, 2H, COCH), 3.76(q, 2H, NCH_2), 4.87(d, 2H, OCH), 6.35–6.58(q, 1H, PCH, $J^2_{P\text{-}H}$=24.2Hz, $J^3_{H\text{-}H}$=9.2Hz), 6.69(d, $2H_{arom}$), 7.06–7.37(m, $12H_{arom}$), 8.55(broad, 1H, CONH) ^{31}P NMR: 13.45
Vi	1.56–1.86(m, 7H, CH_3 and CH_2CH_2), 2.96(m, 2H, COCH), 4.76(m, 1H, NCH), 4.88(m, 2H, OCH), 5.89-6.08(q, 1H, PCH, $J^2_{P\text{-}H}$=23.3Hz, $J^3_{H\text{-}H}$=8.3Hz), 7.00–7.29(m, $10H_{arpm}$), 7.52(m, $2H_{arom}$), 7.81(d, $1H_{arom}$), 8.38(d, $1H_{arom}$), 8.15(broad, 1H, CONH) ^{31}P NMR: 11.98, 12.24
Vj	1.54–1.90(m, 4H, CH_2CH_2), 1.58(d, 3H, CH_3), 2.94(m, 2H, COCH), 4.71(m, 1H, NCH), 4.93(d, 1H, OCH), 5.04(d, 1H, OCH), 5.85–6.00(q, 1H, PCH, $J^2_{P\text{-}H}$=20.0Hz, $J^3_{H\text{-}H}$=9.2Hz), 6.82–7.50(m, $15H_{arom}$ and CONH) ^{31}P NMR: 13.63, 13.90

TABLE II The Data of IR Spectra of Compounds **Va-j**

Compd.	*IR (KBr film, cm^{-1})*
Va	3470, 1769, 1698, 1589, 1486, 1382, 1144, 935, 756, 684
Vb	3397, 1770, 1699, 1587, 1528, 1486, 1382, 1349, 1203, 1180, 938, 761, 683
Vc	3390, 1772, 1707, 1587, 1527, 1486, 1382, 1349, 1203, 1179, 937, 762, 684
Vd	3403, 1772, 1705, 1589, 1487, 1383, 1270, 1210, 1180, 1159, 942, 762, 687
Ve	3401, 1770, 1697, 1610, 1487, 1382, 1273, 1203, 1182, 1156, 932, 761, 685
Vf	3396, 1771, 1706, 1588, 1500, 1382, 1272, 1204, 1180, 932, 761, 686
Vg	3401, 1775, 1706, 1684, 1589, 1488, 1381, 1199, 1140, 944, 755, 684
Vh	3407, 1771, 1706, 1587, 1485, 1416, 1382, 1197, 1142, 947, 760, 685
Vi	3416, 1774, 1704, 1588, 1527, 1486, 1383, 1351, 1203, 179, 935, 762, 685
Vj	3410, 1772, 1702, 1590, 1488, 1357, 1262, 1199, 1177, 939, 761, 703

Besides the method shown in Scheme 1, two other routes were also carried out to prepare the title compounds. In route A, thionyl dichloride was applied to react with compound **III** to form corresponding acyl chloride, which was condensed with compound **IV** in the presence of triethylamine in chloroform to give compound **V**. In this synthetic method, the acyl chloride was moisture sensitive, sometimes the target compound could not be obtained successfully. In route B, DCC (dicyclohexylcarbonimide) was applied as the coupling agent in the reaction of compounds **III** and **IV**. The disadvantage of this procedure was that the product formed was often contaminated with DCU (dicyclohexylurea).

EXPERIMENTAL

All melting points were determ ined on a Yanaco apparatus and they are uncorrected. IR (KBr) were recorded on a shimadzu-IR435 spectrometer. ^{1}H NMR and ^{31}P NMR spectra were measured in $CDCl_3$ with TMS as an internal standard on a Brucket AC-P200N MR instrument and chemical shifts are expressed as δ units. Mass spectra were recorded by electron impact source (EI) on a HP-5988 spectrometer. Microanalysis were performed using Yanaco CHNCORDER MT-3 Analyzer. Compounds **I**[3], **II**[4], **IV**[5, 6] were prepared according to the procedures reported in the literature.

TABLE III The MS data of compounds **Va-j***

Compd.	$M^{+\cdot}$	$M_1=M^{+\cdot}-PhO$	$M_2=M^{+\cdot}-P(O)(OPh)_2$	$M_3=M^{+\cdot}-NH(R')P(O)(OPh)_2$	$M_4=M_3-CO$	$M_5=R'CH{:}\overset{+}{N}H_2$
Va	-	543(54)	403(7)	264(27)	236(100)	140(41)
Vb	-	554(86)	-	264(23)	236(100)	151(15)
Vc	-	588(100)	-	298(40)	270(80)	151(17)
Vd	650(4)	557(43)	417(45)	298(32)	270(100)	120(64)
Ve	616(2)	523(29)	383(49)	264(20)	236(100)	120(42)
Vf	-	543(73)	403(28)	298(45)	270(100)	106(42)
Vg	-	501(34)	361(13)	222(35)	194(100)	140(27)
Vh	-	521(34)	381(9)	208(28)	180(100)	174(40)
Vi	-	512(58)	372(4)	222(38)	194(100)	151(12)
Vj	-	467(34)	327(16)	222(23)	194(100)	106(41)

*Relative intensity in parentheses.

General procedure for the preparation of compound III

To a solution of exo-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride (8.4g, 50mmol) in dry DMF (20mL) was added amino-acid (50mmol). The reaction mixture was heated to reflux for 18h, cooled to room temperature, diluted with ethyl acetate (60mL), and ashed with saturated aqueous ammomium chloride solution (6×30mL). The organic phase was separated, dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was recrystallised from ethyl acetate-petroleum ether giving compound **III** as white crystalline solid.

N-(exo-7-oxa-5,6-dihydrohimoyl)glicine(R=H)

When washed with saturated aqueous ammomium chloride solution, precipitate appeared. The precipitate was recrystallised from ethanol-water(4:1) to afford product. Yield 42.1%; m.p. 198–199°C; ^1H NMR(DMSO-d_6): 1.63(m, 4H, CH_2CH_2), 3.14(s, 2H, COCH).

N-(exo-7-oxa-5,6-dihydrohimoyl)-(d, l)-alanine(R=Methyl)

Yield 50.0%; m.p. 187–189 °C; ^1H NMR($CDCl_3$): 1.52(d, 3H, CH_3), 1.58(m, 2H, CH_2CH_2), 1.86(m, 2H, CH_2CH_2), 2.90(s, 2H, COCH), 4.78 (q, 1H, NCH), 4.88(s. 2H, OCH), 7.92(broad, 1H, OH).

N-(exo-7-oxa-5, 6-dihydrohimoyl)-(d, l)-phenylalanine(R=Benzyl)

Yield 70.5%; m.p. 164–166 °C; ^1H NMR($CDCl_3$): 1.50(m, 2H, CH_2CH_2), 1.76(m, 2H, CH_2CH_2), 2.75(q, 2H, COCH), 3.40(m, 2H, $PhCH_2$), 4.67–4.80(d. 2H, OCH), 4.94(q, 1H, NCH), 7.10–7.23(m, $5H_{arom}$), 8.44(broad, 1H, OH).

N-(e-7-oxa-5, 6-dihydrohimoyl)-(d, l)-isoleucine(R=sec-Butyl)

Yield 80.6%; m.p. 120–122 °C ^1H NMR($CDCl_3$): 0.78(t, 3H, $CH_2\underline{CH_3}$), 1.01 (d, 3H, $CH\underline{CH_3}$), 1.40(m, 2H, $\underline{CH_2}CH_3$), 1.57(m, 2H, CH_2CH_2), 1.82(m. 2H, CH_2CH_2), 2.36(m, 1H, $\underline{CH}CH_3$), 2.90(q. 2H, COCH). 4.42(d, 1H, NCH), 4.85(s, 2H, OCH), 10.12(broad, 1H, OH).

General procedure for the preparation of compound V

To a solution of compound **III** (3mmol) in dry N,N-dimethyl formamide in an ice-salt bath, α-am inoalkylphosphonic diphenyl ester (**IV**, 3mmol), DPPA (3mmol) and triethylamine (6mmol) were added. The reaction mixture was then allowed to stir at room temperature. When the reaction was finished monitored by TLC, water was added, and the peptide was extracted with ethyl acetate (3×25 mL). After dried with magnesium sulfate, the organic phase was evaporated in vacuo. The residue was chromatographed on silica gel column eluted with petroleum ether-ethyl acetate (1:2) to afford amorphous or crystalline products.

Va White solid, 69.5% yield, m.p 65–66°C. Anal.Calcd. for $C_{33}H_{34}ClN_2O_7P$: C, 62.21; H, 5.38; N, 4.40. Found: C, 62.10; H, 5.19; N, 4.12.

Vb White solid, 82.6% yield, m.p 68–69°C. Anal.Calcd. for $C_{33}H_{34}N_3O_9P$: C, 61.20; H, 5.29: N, 6.49 Found: C, 60.99; H. 5.21; N, 6.52.

Vc White solid, 73.5% yield, m.p. 85–86°C. Anal.Calcd. for $C_{36}H_{32}N_3O_9P$: C, 63.43; H, 4.73; N. 6.16 Found: C. 63.13; H, 4.59; N, 6.16.

Vd White solid. 68.3% yield. m.p. 132–133°C. Anal.Calcd. for $C_{37}H_{35}N_2O_7P$: C. 68.30; H, 5.42: N, 4.31 Found: C, 68.25; H, 5.41; N, 4.30.

Ve White solid. 87.5% yield m.p. 58–59°C. Anal. Calcd. for $C_{33}H_{34}ClN_2O_7P$: C, 66.22; H, 6.05: N, 4 54 Found: C, 65.98; H, 5.91; N, 4.38.

Vf White solid, 84.9% yield. m.p. 63–64°C. Anal.Calcd. for $C_{36}H_{33}N_2O_7P$: C. 67.92; H, 5.23; N, 4.40. Found: C, 67.68: H. 5.35; N, 4.49.

Vg White solid, 86.6% yield, m.p. 161–162°C. Anal.Calcd. for $C_{30}H_{28}N_2O_7P$: C, 60.56; H, 4.74: N, 4.71 Found: C, 60.23; H, 4.74; N, 4.32.

Vh White solid. 60.7% yield m.p. 193–1 94°C. Anal.Calcd for $C_{29}H_{23}Cl_2N_2O_7P$: C. 56.60; H, 4.10: N, 4.55 Found: C. 56.36; H, 4.14; N. 4.38.

Vi White solid, 86.3% y ield, m.p 125–126°C. Anal.Calcd. for $C_{30}H_{28}N_3O_9P$: C. 59.50; H, 4.66; N, 6.94. Found: C. 59.32; H, 4.98; N, 6.80.

Vj White solid, 83.1% yield, m.p. 158–159°C. Anal.Calcd for $C_{30}H_{29}N_2O_7P$: C. 64.28; H, 5.22; N, 5.00. Found: C, 64.32; H, 5.32; N, 5.33.

Acknowledgements

This research work is supported by the National Natural Science Foundation of China and the State Key Laboratory of Elemento-Organic Chemistry.

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