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Synthesis and Bioactivities of Novel Organogermanium Sesquioxides Containing α-Aminophosphonate Groups

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ABSTRACT: *In order to search for novel antitumor drugs with high activity and low toxicity, a series of novel organogermanium sesquioxides containing α-aminophosphonate groups were synthesized by the hydrolysis of O,O-diphenyl N-trichlorogermylpropiono-α-aminophosphonates. Their structures were confirmed by ^{1}H NMR, ^{31}P NMR, and IR spectroscopy and by elemental analysis. Data of ^{1}H NMR and IR spectroscopy indicated that the title compounds are polymeric organogermanium sesquioxides. The results of bioassay showed that the products possess potential anticancer activities.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 209–212, 1999

INTRODUCTION

During the past two decades, carboxyethylgermanium sesquioxide, Ge-132, $[O_3(GeCH_2CH_2COOH)_2]$ and its derivatives have attracted considerable attention because these organogermanium sesquioxides exhibited anticancer activities [1,2]. In 1993, Kurono et al. synthesized phosphonoethylgermanium sesquioxide $[O_{3/2}GeCH_2CH_2PO(OH)_2]$, which possesses higher antitumor activity than Ge-132 [3]. Encouraged by these promising results, we developed the idea that the incorporation of a germanium residue into α-aminophosphonic acids and their derivatives, which have antibacterial and antitumor activities [4,5], would enhance their antitumor activities to a significant degree, while their toxicity would be reduced at the same time. Therefore, we designed and synthesized a series of the title products. The results of bioassay showed that the products possess potential anticancer activities.

RESULTS AND DISCUSSION

Synthesis of the Products

The title compounds were synthesized as shown in Scheme 1.

The hydrolysis of O,O-diphenyl N-trichlorogermylpropiono-α-aminophosphonates must be carried out at pH = 7–8 with saturated sodium hydrocarbonate. When the acidity is too strong (pH < 7), the hydrolysis of organogermanium trichlorides is incomplete; when the basity is too strong (pH > 8), the phosphonate ester can hydrolyze, and a by-product is formed. Besides this, the pH value of the solution may affect the degree of polymerization (D.P.) and solubility of the product. When the pH value of the solution is large, the D.P. is small and the solubility of the product is acceptable. Moreover, the amount of solvent affects isolation of the products. We have found that, when the volume of solvent is half that of water, it is easy to isolate products. The product is purified by washing the crude product with distilled water and organic solvent.

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The Structures of the Products

All the products were white powders, and their structures were confirmed by ^{1}H NMR, ^{31}P NMR, and IR spectroscopy and by elemental analysis. The data are listed in Table 1.

All the products give no indication of decomposition or melting below 300°C. The IR spectra (KBr) of all of the products have a strong absorption at 800–900 cm^{-1}; characteristic of a germanium–oxygen network of the type -Ge(-O-)$_3$ [6]. No absorptions attributable to Ge–OH species, which should have a strong and broad absorption at 3100–3500 cm^{-1} [7,8], were noted. In the ^{1}H NMR spectra of all of the products, the proton of the group GeOH, which should be at the range of δ 1.5–4.0 [7,8], was not apparent. Hence, we concluded that the title compounds are polymeric organogermanium sesquioxides, like Ge-132, which has an infinite sheet structure in which the basic unit of the network is a 12-membered ring made up of six Ge tetrahedra bridged by O atoms [9].

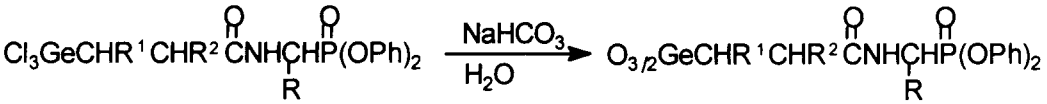
The ^{1}HNMR data of all of the products are listed in Table 2. We can see from Table 2 that all of the protons of the groups GeCHR^1 and CHR^{2}CO show broad peaks, and the protons of GeCHR^1 appear at higher fields. The H atom at the α-C (R = aryl) sometimes exhibits a dd peak due to the coupling of the P atom and the (N-)H atom but sometimes exhibits as a broad peak.

The ^{31}PNMR data of products **d, f, p,** and the corresponding intermediate diphenyl α-aminophosphonate are listed in Table 3. We can see from Table 3 that the more bulky the substituent *R* is, the greater is δ_p of the product, and the δ_p of the product is less than the δ_p of the corresponding intermediate α-aminophosphonate. This is due to the effect of steric hindrance.

The IR data of products **a, b, c, e, f, o,** and **p** are listed in Table 4. We can see from Table 4 that all absorption bands appear as expected. For b, 3253.0 cm^{-1} (s) corresponds to the N–H stretching absorption band, 1644.8 cm^{-1} (s) to the C=O stretching absorption band, 1240.2 cm^{-1} (s) and 1204.9 cm^{-1} (s) to the P=O stretching absorption bands, 1181.1 cm^{-1} (s) and 1156.0 cm^{-1} (s) to the C–O stretching absorption bands in the Ph-O-P group, 926.9 cm^{-1} (s) to the P–O stretching absorption band in the P-O-Ph group, 888.3 cm^{-1} (s) to the Ge–O characteristic absorption band, 754.9 cm^{-1} and 682.8 cm^{-1} to the phenyl ring absorption bands, and 571.6 cm^{-1} to the Ge–CH_2 stretching absorption band.

BIOLOGICAL ACTIVITY

The results of bioassay showed that the products exhibit activity against KB in vitro. For example, at 10 μg/mL, the inhibition rate of compounds **b, c, d, f,** and **i** to KB attain 20.7%, 18.0%, 17.3%, 19.3%, and 16.0%, respectively. These results are promising.



SCHEME 1

TABLE 1 Physical Constants of Products

Compds.	*R*^{1}	R^2	R	Yield (%)	*Elemental C*	*Analysis* (%) *H*	*Found* (*Calcd.*) *N*
a	H	H	H	83.3	46.06 (46.32)	4.26 (4.13)	3.32 (3.38)
b	H	H	Me	92.9	47.25 (47.61)	4.46 (4.46)	2.90 (3.27)
c	H	Me	Me	92.9	48.56 (48.81)	4.78 (4.78)	2.70 (3.16)
d	Me	H	Me	90.5	48.81 (48.81)	5.09 (4.78)	2.94 (3.16)
e	H	H	Pr^n	90.5	49.64 (49.94)	5.15 (5.07)	2.83 (3.07)
f	H	H	Pr^i	92.9	49.80 (49.94)	4.77 (5.07)	3.45 (3.07)
g	H	H	Bu^n	88.1	50.81 (51.00)	5.26 (5.35)	2.65 (2.97)
h	H	H	CH_2Ph	90.7	54.38 (54.70)	4.36 (4.59)	2.53 (2.77)
i	H	H	Ph	90.7	53.76 (53.82)	4.73 (4.31)	2.56 (2.85)
j	H	H	4-MeO-C_6H_4	88.4	53.29 (53.02)	4.52 (4.45)	2.66 (2.69)
k	H	H	4-Me-C_6H_4	93.0	54.30 (54.70)	4.58 (4.59)	2.70 (2.77)
l	H	H	3-Cl-C_6H_4	95.4	49.84 (50.29)	4.00 (3.84)	2.56 (2.67)
m	H	H	4-Cl-C_6H_4	97.7	50.06 (50.29)	4.02 (3.84)	2.46 (2.67)
n	H	H	3-NO_2-C_6H_4	93.0	48.96 (49.30)	3.58 (3.76)	5.60 (5.23)
o	H	H	4-NO_2-C_6H_4	97.7	49.00 (49.30)	3.76 (3.76)	4.98 (5.23)
p	H	H	2,4-Cl_2-C_6H_3	79.6	47.27 (47.20)	3.53 (3.42)	2.52 (2.50)

TABLE 2 ^{1}HNMR Data of Products

Compds.	δ(*CF_3COOD*)
a	2.53(br., 2H, $GeCH_2$); 3.35(br., 2H, CH_2CO); 4.54(dd, 2H, CH_2PO, $^2J_{PH}$ = 12.9 Hz, $^2J_{HH}$ = 5.3 Hz); 8.72(br., 1H, CONH); 7.23–7.52(m, 10H, Ph).
b	1.76(dd, 3H, CH_3, $^3J_{PH}$ = 18.3 Hz, $^3J_{HH}$ = 7.0 Hz; 2.40(br., 2H, $GeCH_2$); 3.19(br., 2H, CH_2CO); 5.01(br., 1H, CHPo); 8.65(d, 1H, CONH, $^3J_{HH}$ = 9.5 Hz); 7.10–7.41(m, 10H, Ph).
c	1.51 [dd, 3H, CH_3(CHPO), $^3J_{PH}$ = 24.6 Hz, $^3J_{HH}$ = 6.6 Hz]; 1.74 [d, 3H, CH_3(CHCO), ^3J = 7.5 Hz]; 2.60(br., 2H, $GeCH_2$); 3.40(br., 1H, CHCO); 4.90–5.12(m, 1H, CHPO); 8.51(br., 1H, CONH); 7.06–7.34(m, 10H, Ph).
d	1.72 [d, 3H, CH_3(CHGe), $^3J_{HH}$ = 6.5 Hz]; 1.94 [dd, 3H, CH_3(CHPO), $^3J_{PH}$ = 18.4 Hz, $^3J_{HH}$ = 8.0 Hz]; 3.10(br., 1H, GeCH); 3.60(br., 2H, CH_2CO); 5.25(br., 1H, CHPO); 8.80(br., 1H, CONH); 7.26–7.62(m, 10H, Ph).
e	0.72(t, 3H, CH_3, $^3J_{HH}$ = 7.5 Hz); 0.96–1.52(m, 4H, CH_2CH_2); 2.04(br., 2H, $GeCH_2$); 2.92(br., 2H, CH_2CO); 4.76(br., 1H, CHPO); 8.36(br., 1H, CONH); 7.00–7.36(m, 10H, Ph).
f	0.88(d, 6H, CH_3, $^3J_{HH}$ = 7.3 Hz); 2.04(br., 2H, $GeCH_2$); 2.18–2.50(m, 1H, $CHMe_2$); 2.90(br., 2H, CH_2CO); 4.72(br., 1H, CHPO); 8.50(br., 1H, CONH); 6.96–7.36(m, 10H, Ph).
g	0.68(t, 3H, CH_3, $^3J_{HH}$ = 7.5 Hz; 0.88–1.44(m, 6H, $CH_2CH_2CH_2$); 2.08(br., 2H, $GeCH_2$); 2.92(br., 2H, CH_2CO); 4.76(br., 1H, CHPO); 8.40(br., 1H, CONH); 7.00–7.44(m, 10H, Ph).
h	2.36(br., 2H, $GeCH_2$); 3.15(br., 2H, CH_2CO); 3.45(br., 2H, CH_2Ph); 5.33(br., 1H, CHPO); 8.70(br., 1H, CONH); 7.16–7.49(m, 15H, Ph).
i	2.04(br., 2H, $GeCH_2$); 2.96(br., 2H, CH_2CO); 5.77(dd, 1H, CHPO, $^2J_{PH}$ = 21.6 Hz, $^3J_{HH}$ = 9.0 Hz; 9.20(br., 1H, CONH); 6.90–7.44(m, 15H, Ph).
j	2.48(br., 2H; $GeCH_2$); 3.35(br., 2H, CH_2CO); 4.12(s, 3H, OMe); 6.00(br., 1H, CHPO); 9.47(br., 1H, CONH); 6.81–7.58(m, 14H, Ph).
k	2.50(br., 5H, $GeCH_2$, Me); 3.38(br., 2H, CH_2CO); 6.00(dd, 1H, CHPO, $^2J_{PH}$ = 20.8 Hz, $^3J_{HH}$ = 9.1 Hz; 9.46(br., 1H, CONH); 6.74–7.52(m, 14H, Ph).
l	2.50(br., 2H, $GeCH_2$); 3.38(br., 2H, CH_2CO); 6.03(dd, 1H, CHPO, $^2J_{PH}$ = 20.8 Hz, $^3J_{HH}$ = 8.3 Hz); 9.53(br., 1H, CONH); 6.85–7.63(m, 14H, Ph).
m	2.49(br., 2H, $GeCH_2$); 3.34(br., 2H, CH_2CO); 6.04(dd, 1H, CHPO, $^2J_{PH}$ = 20.3 Hz, $^3J_{HH}$ = 8.7 Hz; 9.53(br., 1H, CONH); 6.78–7.52(m, 14H, Ph).
n	2.45(br., 2H, $GeCH_2$); 3.35(br., 2H, CH_2CO); 6.19(dd, 1H, CHPO, $^2J_{PH}$ = 21.6 Hz, $^3J_{HH}$ = 6.6 Hz); 9.65(br., 1H, CONH); 6.90–8.57(m, 14H, Ph).
o	2.51(br., 2H, $GeCH_2$); 3.38(br., 2H, CH_2CO); 6.18(dd, 1H, CHPO, $^2J_{PH}$ = 21.6 Hz, $^3J_{HH}$ = 8.3 Hz); 6.94–8.48(m, 14H, Ph).
p	2.49(br., 2H, $GeCH_2$); 3.35(br., 2H, CH_2CO); 6.66(dd, 1H, CHPO), $^2J_{PH}$ = 21.6 Hz, $^3J_{HH}$ = 8.3 Hz); 9.54(br., 1H, CONH); 6.85–7.58(m, 13H, Ph).

TABLE 3 ^{31}PNMR Data of **d, f, p,** and the Corresponding Diphenyl α-Aminophosphonates

Compds.	δ_p *of product*	δ_p *of Corresponding Diphenyl α-Aminophosphonate*
d	17.55	22.52
f	17.08	21.77
p	13.16	16.15

Further studies on anticancer activities of the products are underway.

EXPERIMENTAL

All the melting points were determined with a Thomas–Hoover melting-point apparatus and are uncorrected. IR spectra were recorded with a Shimadu-435 spectrometer. ^{1}H NMR spectra were recorded with a Bruker AC-P200 instrument, tetramethylsilane being used as an internal standard. Elemental analyses were carried out with a Yanaco CHN Corder MT-3 elemental analyzer.

Synthesis of Intermediates

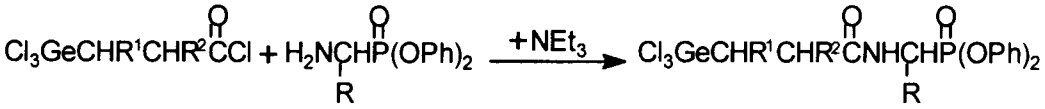
O,O-diphenyl N-trichlorogermylpropiono-α-aminophosphonates were prepared as follows [10]:

Synthesis of the Products

A 0.5 g amount of O,O-diphenyl N-trichlorogermylpropiono-α-aminophosphonate was dissolved in 10 mL of dichloromethane. To the stirred solution was added dropwise a saturated sodium hydrocarbonate solution (approximately 20 mL). The reaction mixture was stirred for 10 hours at pH = 7–8. The water phase was extracted three times with 20 mL of dichloromethane. The extraction solvent was combined with the organic phase. The solvent was removed by distillation to give a white solid. The solid was then washed successively with distilled water and ether (or acetone). Finally, a white powder was obtained.

TABLE 4 IR Data of Some Products

Compds.	*IR*(cm^{-1}) (*KBr*)
a	3269.5, 3058.5, 2912.5, 1647.7, 1590.6, 1487.7, 1259.8, 1207.3, 1183.5, 1157.2, 932.9, 889.1, 796.3, 757.6, 685.2, 558.8.
b	3253.0, 3044.5, 2920.5, 1644.8, 1589.2, 1485.5, 1240.2, 1204.9, 1181.1, 1156.0, 926.9, 888.3, 793.5, 754.9, 682.8, 571.6.
c	3258.0, 3091.5, 2961.5, 1645.8, 1589.9, 1530.7, 1487.5, 1235.9, 1206.9, 1183.9, 1157.7, 928.7, 890.0, 800.2, 753.1, 700.2, 573.9.
e	3261.5, 3055.5, 2950.5, 1648.0, 1590.6, 1488.0, 1262.1, 1209.0, 1185.9, 1158.1, 930.0, 895.5, 796.5, 759.1, 685.6, 582.6.
f	3271.5, 3058.5, 2922.5, 1649.3, 1591.8, 1488.3, 1262.3, 1208.1, 1185.4, 1157.0, 926.5, 892.7, 791.6, 755.7, 684.9, 583.1.
o	3273.5, 3109.5, 2920.0, 1655.2, 1590.2, 1520.9, 1487.0, 1347.3, 1264.3, 1204.8, 1179.7, 1156.6, 933.3, 898.5, 792.7, 759.7, 685.9, 584.2.
p	3257.5, 3061.0, 2944.5, 1680.4, 1588.9, 1486.9, 1256.2, 1204.2, 1180.0, 1157.4, 937.4, 877.7, 762.3, 685.6, 587.3.



SCHEME 2

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