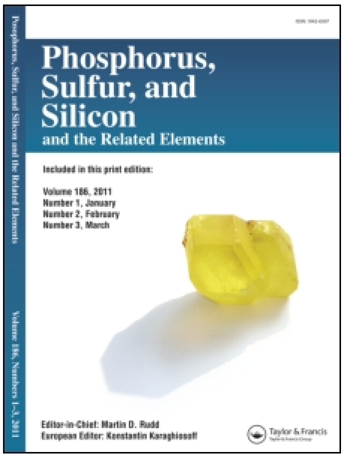

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Synthesis of 2-Phosphono Alkyl 1,2-Benzisoselenazol-3(2H)-ones

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SYNTHESIS OF 2-PHOSPHONO ALKYL 1,2-BENZISOSELENAZOL-3(2H)-ONES

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A series of 2-phosphonoalkyl 1,2-benzisoselenazol-3(2H)-ones were designed and synthesized via reaction 2-chloroselenobenzoyl chloride with 1-hydrazinobenzyl phosphonate. The structures of all new compounds were confirmed by spectroscopic methods and microanalyses.

Keywords: 1-Hydrazinobenzyl phosphonate; cyclization; ebselen

INTRODUCTION

In recent years, biologically active organoselenium compounds have been attracting considerable interest due to their unique and diverse potential of pharmacological importance, such as antitumor,[1] antiviral,[2] and antiinflammatory.[3] The discovery of the essential role played by seleno-organic compound ebselen (2-phenyl-1,2-benzisoselenazol-3(2H)-one) in the activity of the enzyme glutathione peroxidase (GSH-Px) against biological damage caused in vivo by reactive hydroperoxides, increased a striking interest in developing organoselenium compounds for therapy.[4] In our previous articles, a number of amino acid ester derivatives of benzisoselenazolone were synthesized and these compounds exhibited excellent pharmacological effects.[5] Here we report the synthesis of some 2-phosphonoalkyl 1,2-benzisoselenazol-3(2H)-ones **5**. The easily accessible 1-hydroxyalkylphosphonates reacted with mesyl chloride to give 1-mesyloxyalkylphosphonates **1**, which were allowed to react with hydrazine hydrate to produce 1-hydrazinoalkylphosphonates **2** in satisfactory yields. Compounds **5** were obtained by compounds **2** reacting with 2-chloroselenobenzoyl

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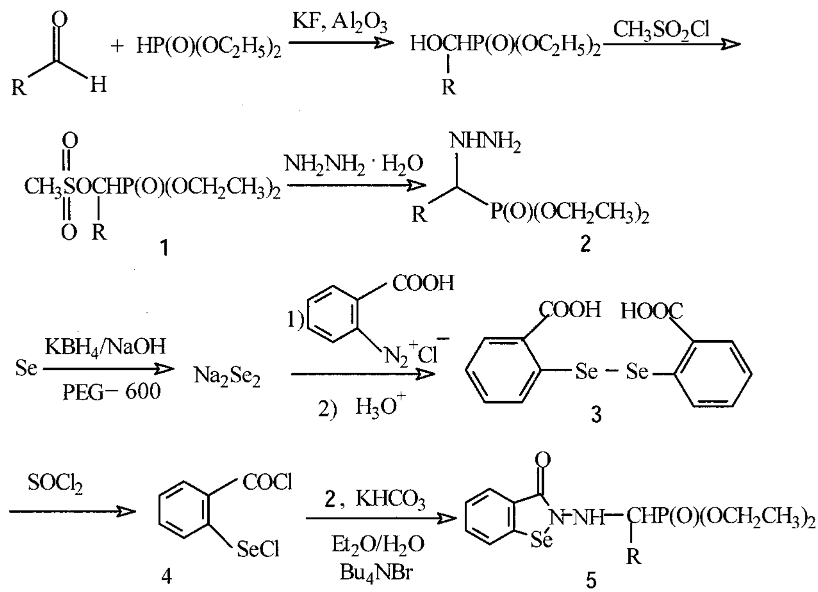
chloride **4**. The preliminary anticancer tests in vitro were carried out by the conventional method.

RESULTS AND DISCUSSION

Synthesis of 2-Phosphonoalkyl-1,2-benzisoselenazol-3(2H)-ones

The title compounds **5** were synthesized by a multistep route outlined in Scheme 1.



SCHEME 1

Preparation of the 1-hydrazinoalkylphosphonates **2** was readily accomplished in three-step sequence (40–50% overall yield) starting from aldehyde and diethyl phosphite.[6] First, 1-hydroxyalkylphosphonates can be synthesized by the solid-catalyzed condensation of diethyl phosphite and aldehyde. Then, 1-hydroxyalkylphosphonates reacted with mesyl chloride to give 1-mesyloxyalkylphosphonates **1**. With the mesyloxy substituent as a good leaving group, compounds **1** could be converted to other types of phosphonates. With hydrazine hydrate as the nucleophile, 1-hydrazinoalkylphosphonates **2** can be synthesized in good yield. Santaniello et al.[7] have reported that the reducing power of sodium borohydride in polyethylene glycols is enhanced and able to reduce carbonyl compounds. Similarly, under the PEG-KBH_4 reaction system, 1 mmol of selenium was efficiently reduced to $Se–Se^{2-}$ anion by only 0.018 mmol of KBH_4, catalyzed by PEG-600 in aqueous NaOH. Thus, $Se–Se^{2-}$ anion was allowed to react with 2-carboxybenzenediazonium chloride, and the reaction mixture was then acidified to give 2,2′-diselenobis(benzoic acid) **3** in a yield of 90%. **3** was treated with excess thionyl chloride to provide the intermediate 2-(chloroseleno)benzoyl chloride **4** in a yield of 80%. The reaction of **4** with each 1-hydrazinoalkylphosphonate was carried out under the ether-water-$NaHCO_3$ reaction system in the presence of phase transfer catalyst Bu_4NBr to give products **5** in a yield of 45–78%.

The Structures of the Products

The structure of all compounds prepared were confirmed by ^1H NMR, ^{31}P NMR, IR, MS spectroscopy, and elemental analysis. In the ^1H NMR spectra of **5**, the chemical shift of H atom in CH(R = aryl) is in the range of δ6.13–6.31. Owing to the deshielding effect of the α-benzene ring, these chemical shifts are much bigger than those of CH(R=alkyl), which are in the range of δ3.35–4.06. Moreover, the H atom in CH(R=aryl) appears as double doublet due the coupling effects of the P atom and H in NH ($^2J_{PCH} = 21.0–23.0$ Hz, $^3J_{HNCH} = 11.0–12.6$ Hz) while that when R=alkyl exhibits complicated peaks due to the phosphorus atom coupling, C—H coupling and N—H coupling. The IR spectra of compounds **5** show normal stretching absorption bands, indicating the existence of groups C=O(1644–1658 cm^{-1}), P=O(1248–1257 cm^{-1}), and N—H(3337–3354 cm^{-1}). The EI-MS spectra of **5** record the existence of molecular ion peaks, indicating that the heterocycle skeletons are of some stability, the major MS peaks, particularly m/e 199, 156, 137 are common to all compounds, other ion peaks were consistent with their structures and can be clearly assigned. Because there are two major isotope of selenium (approximatively 2:1), the ion which contain two isotopes of selenium abundance ratio is about 2:1.

EXPERIMENTAL

Elemental analyses were performed with CHN PE983 elementary analyzer. NMR spectra were taken on Varian XL200 spectrometer, TMS was used as an internal standard for ^1H NMR, and 85% H_3PO_4 was used as an external standard for ^{31}P NMR. Mass spectra were recorded on a Hewlett-Packard 5988A instrument. IR spectra were recorded on a NICOLET AVATAR360. Melting points were determined with a model X4 apparatus and are uncorrected.

TABLE I Experimental Data of Compound **5**

No.	R	State Mp (°C)	Yield[a] (%)	Molecular formula	Found/Calcd. (%) C	H	N
5a	H	Yellowish syrup	45.4	$C_{12}H_{17}N_2O_4PSe$ 363.2	39.69 (39.75)	4.72 (4.81)	7.71 (7.65)
5b	Me	Yellowish syrup	50.7	$C_{13}H_{19}N_2O_4PSe$ 377.2	41.40 (41.68)	5.08 (5.13)	7.43 (7.52)
5c	Ph	134–135	73.6	$C_{18}H_{21}N_2O_4PSe$ 439.2	49.22 (49.11)	4.82 (4.87)	6.38 (6.23)
5d	4-MePh	122–123	75.5	$C_{19}H_{23}N_2O_4PSe$ 453.3	50.35 (50.17)	5.11 (5.19)	6.18 (6.09)
5e	4-MeOPh	114–115	68.2	$C_{19}H_{23}N_2O_5PSe$ 469.3	48.63 (48.57)	4.94 (4.92)	5.97 (5.88)
5f	4-ClPh	128–129	74.6	$C_{18}H_{20}ClN_2O_4PSe$ 473.7	45.64 (45.82)	4.26 (4.33)	5.91 (5.97)
5g	3-ClPh	106–107	72.3	$C_{18}H_{20}ClN_2O_4PSe$ 473.7	45.64 (45.49)	4.26 (4.31)	5.91 (5.96)
5h	3,4-OCH_2OPh	148–149	78.0	$C_{19}H_{21}N_2O_6PSe$ 483.3	47.22 (47.38)	4.38 (4.29)	5.80 (5.74)
5i	2-Furyl	93–94	64.8	$C_{16}H_{19}N_2O_5PSe$ 429.2	44.77 (45.62)	4.46 (4.43)	6.53 (6.47)

[a]Yield determined by isolation based on **4**.

TABLE II NMR, IR, and MS Spectral Data of Compound **5**

No.	^{1}H NMR (200 MHz, $CDCl_3$, TMS) or ^{31}PNMR (200 MHz, $CDCl_3$, 85% H_3PO_4) δ (ppm), J (Hz)	IR (ν, cm^{-1}, KBr)	MS (M/e, %)
5a	11.67 (d, 1H, NH), 7.27–7.43 (m, 4H, C_6H_4), 3.35 (dd, 2H, CH $^2J_{PCH} = 21.4$, $^3J_{HNCH} = 12.4$), 3.87–4.03 (m, 4H, $2CH_2$), 1.26 (t, 6H, $2CH_3$, $^3J_{HCCH} = 7.2$ Hz). ^{31}P: 21.36 (s)	3342 (NH) 1656 (s, C=O) 1252 (s, P=O)	440 (M^+, 9.3), 199 (100), 166 (25.4), 156 (27.8), 137 (34.6)
5b	11.53 (d, 1H, NH), 7.19–7.36 (m, 4H, C_6H_4), 3.83–4.06 (m, 4H, $2CH_2$), 3.30 (m, 1H, CH), 1.76 (dd, 3H, CH_3, $^3J_{HCCH} = 7.2$, $^3J_{PCCH} = 16.8$), 1.18 (t, 6H, $2CH_3$, $^3J_{HCCH} = 7.0$)	3337 (NH) 1658 (s, C=O) 1255 (s, P=O)	478 (M^+, 6.5), 199 (100), 180 (23.0), 156 (24.6), 137 (46.3)
5c	11.67 (d, 1H, NH), 7.23–7.67 (m, 9H, $C_6H_4 + C_6H_5$) 6.13 (dd, 1H, CH, $^2J_{PCH} = 21.0$, $^3J_{HNCH} = 6.8$), 3.94–4.08 (m, 4H, $2CH_2$), 1.20 (t, 6H, $2CH_3$, $^3J_{HCCH} = 7.2$). ^{31}P: 22.45(s)	3345 (NH) 1648 (s, C=O) 1255 (s, P=O)	440 (M^+, 5.8), 242 (27.1), 199 (100), 156 (13.5), 137 (28.3)
5d	11.72 (d, 1H, NH), 7.24–7.78 (m, 8H, $2C_6H_4$) 6.26 (dd, 1H, CH, $^2J_{PCH} = 23.0$, $^3J_{HNCH} = 11.0$), 3.86–4.10 (m, 4H, $2CH_2$), 2.23 (s, 3H, $ArCH_3$, 1.12 (t, 6H, $2CH_3$, $^3J_{HCCH} = 7.2$)	3347 (NH) 1653 (s, C=O) 1257 (s, P=O)	454 (M^+, 6.7), 256 (21.3), 199 (100), 156 (32.4), 137 (16.5)
5e	11.46 (d, 1H, NH), 7.28–7.63 (m, 8H, $2C_6H_4$) 6.16 (dd, 1H, CH, $^2J_{PCH} = 23.0$, $^3J_{HNCH} = 12.0$), 3.96–4.13 (m, 4H, $2CH_2$), 3.77 (s, 3H, $ArOCH_3$, 1.23 (t, 6H, $2CH_3$, $^3J_{HCCH} = 7.0$)	3343 (NH) 1644 (s, C=O) 1250 (s, P=O)	470 (M^+, 8.3), 272 (3.24), 199 (100), 156 (16.4), 137 (20.6)
5f	11.60 (d, 1H, NH), 7.21–7.43 (m, 8H, $2C_6H_4$) 6.23 (dd, 1H, CH, $^2J_{PCH} = 21.0$, $^3J_{HNCH} = 11.4$), 3.88–4.03 (m, 4H, $2CH_2$), 1.25 (t, 6H, $2CH_3$, $^3J_{HCCH} = 7.2$)	3337 (NH) 1652 (s, C=O) 1249 (s, P=O)	474 (M^+, 4.7), 276 (16.5), 199 (100), 156 (24.5), 137 (28.6)
5g	11.54 (d, 1H, NH), 7.34–7.56 (m, 8H, $2C_6H_4$) 6.31 (dd, 1H, CH, $^2J_{PCH} = 21.0$, $^3J_{HNCH} = 12.6$), 3.84–4.07 (m, 4H, $2CH_2$), 1.23 (t, 6H, $2CH_3$, $^3J_{HCCH} = 7.0$)	3338 (NH) 1648 (s, C=O) 1252 (s, P=O)	474 (M^+, 5.4), 276 (14.3), 199 (100), 156 (23.4), 137 (26.7)
5h	11.48 (d, 1H, NH), 7.28–7.58 (m, 7H, $C_6H_4 + C_6H_3$), 6.25 (dd, 1H, CH, $^2J_{PCH} = 21.6$, $^3J_{HNCH} = 11.6$), 4.56 (s, 2H, OCH_2O), 3.89–4.07 (m, 4H, $2CH_2$), 1.19 (t, 6H, $2CH_3$, $^3J_{HCCH} = 7.0$)	3346 (NH) 1656 (s, C=O) 1256 (s, P=O)	484 (M^+, 8.5), 286 (25.6), 199 (100), 156 (27.5), 137 (32.4)
5i	11.62 (d, 1H, NH), 6.15–8.09 (m, 7H, $C_6H_4 + C_6H_3$), 6.25 (dd, 1H, CH, $^2J_{PCH} = 21.4$, $^3J_{HNCH} = 11.0$), 4.56 (s, 2H, OCH_2O), 3.86–4.23 (m, 4H, $2CH_2$), 1.15 (t, 6H, $2CH_3$, $^3J_{HCCH} = 7.0$). ^{31}P: 21.3	3354 (NH) 1652 (s, C=O) 1248 (s, P–O)	430 (M^+, 14.6), 232 (34.7) 199 (100), 156 (36.4), 137 (28.3)

2-Chloroseleno benzoyl chloride **4**[8] and 1-hydrazinobenzyl phosphonate **2**[6] have been prepared following literature methods.

2-Phosphonoalkyl 1,2-Benzisoselenazol-3(2H)-ones 5

To a stirred mixture of α-hydrazinobenzyl phosphonate (5 mmol), potassium bicarbonate (16 mmol) and tetrabutylammonium bromide (catalytic amount) in H_2O(10 mL)-ether(25 mL) system cooled with an ice bath was added a solution of 2-chloroseleno benzoyl chloride **2** (5 mmol) in 20 mL of ether over 30 min. Then the mixture was stirred for an additional 7 h at room temperature. The organic product was extracted with ether, and the layers were separated. Combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/petroleum ether.

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