Synthesis and Bioactivity of Some New 3-Alkyl-2,4-diisopropyl-1,2,4,5-tetrahydro-benzo[e][1,3,2]-diazaphosphepine 3-sulfides / selenides

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Received 31 July 2007; Accepted 20 September 2007

Abstract: Preparation of a series of novel seven membered heterocyclic compounds, 3-alkyl-2,4-diisopropyl-1,2,4,5-tetrahydro-benzo[e][1,3,2] diazaphosphepine 3-sulfides / selenides (**8a-l**) was accomplished in four steps. The synthetic route involves α,α' -dibromo-*o*-xylene (**1**) with two moles of isopropylamine (**2**) in the presence of triethylamine (TEA) in dry tetrahydrofuran (THF) at low temperature to form the compound **3**. This on treatment with phosphorus tribromide (**4**) in the presence of TEA in dry THF to form the corresponding phosphorobromodite (**5**). This on subsequent reaction with different Grignard reagents (**6**) in dry THF under N_2 atmosphere formed the compounds **7**. They are converted to the corresponding sulfides and selenides (**8a-l**) by reacting them with sulfur and selenium respectively. Their structures were established by elemental analysis, IR, 1H , ^{13}C , ^{31}P NMR and mass spectral data. All the title compounds were screened for their antibacterial activity. Most of the compounds exhibited significant antimicrobial activity.

Keywords: α,α' -Dibromo-*o*-xylene, Isopropylamine, Phosphorus tribromide, Grignard reagents, Sulfur, Selenium, Antibacterial activity.

Introduction

Cyclic and acyclic organophosphorus compounds having a nitrogen atom are known to exhibit antitumour activity¹⁻³. Phosphorus compounds containing carbamate moieties are an important class of antitumour agents⁴, pesticides⁵ and bactericides⁶⁻⁷. Phosphorylated nitrogen mustard compounds are proven drugs in cancer chemotherapy⁸⁻¹¹. Organophosphate moiety is an important pharmacophore in agricultural and pharmaceutical

chemistry¹². Phosphocin / phosphepin and their related derivatives containing this group represent an important class of pesticides, antibiotics, herbicides and antiviral agents¹³. Some of them are well known for their insecticidal activities¹⁴ and as known to degrade hydrolytically and enzymatically to non-toxic residues. Discovery of their fungicidal properties constitutes a recent development¹⁵.

Experimental

General Procedures

Solvents were used after purifying them by the established procedures. Progress of the reaction and purity of the compounds were monitored by thin layer chromatography (TLC) using n-hexane and ethylacetate (1:2 by volume) as eluting system on silica gel (60-120 mesh) and iodine as visualizing agent, melting points were determined in open capillary tubes on Mel-temp apparatus and were uncorrected. Micro analysis was performed at CDRI, Lucknow, India. IR spectra were recorded as KBr pellets on Nicolet 380 double beam spectrophotometer ($\bar{\nu}$ in cm^{-1}) in Environmental Engineering Lab, S.V.University, Tirupati. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C , 161.9 MHz for ^{31}P NMR as solutions in DMSO-d_6 and CDCl_3 . The ^1H and ^{13}C NMR chemical shifts are referenced to TMS, and ^{31}P NMR spectra to 85% H_3PO_4 (*ortho* phosphoric acid). ^1H , ^{13}C and ^{31}P NMR spectral data was performed at Indian Institute of Science, Bangalore, India. Mass spectra were recorded on a Jeol SX 102 DA / 600 mass spectrometer using Argon/Xenon (6 kv, 10 mA) as the FAB (fast atom bombardment) gas and also a Shimadzu QP-2000 GC-MS (gas chromatography-mass spectroscopy) instrument.

Preparation of Alkyl magnesium bromide (6a-l)

In a dry 100 mL three necked round bottomed flask fitted with dropping funnel, a reflux condenser with a calcium chloride tube, a nitrogen inlet and a thermometer, magnesium turnings (0.12 g, 0.005 mole) and 5 mL of dry THF were placed. The reaction mixture was stirred and alkyl bromide (0.005 mole) in 10 mL of dry THF was added at 10-15°C for 10 min. When reaction started, the temperature increased to 40-45°C. The mixture was cooled to room temperature and stirring was continued until the magnesium metal was dissolved.

General experimental procedure for 8a-l

α,α' -Dibromo-*o*-xylene (**1**) (1.31 g, 0.005 mole) with two moles of isopropylamine (**2**) (0.85 g, 0.01 mole) in the presence of triethylamine (TEA) in dry tetrahydrofuran (THF) stirred at low temperature for 2-3 h. The progress of this reaction was judged by the TLC analysis. The reaction mixture was filtered to remove triethylamine hydrobromide. To the filtrate a solution of phosphorus tribromide (**4**) (0.909 g, 0.005 mole) in dry THF (20 mL) was added in the presence of TEA (0.01 mole) and stirred for 20 minutes under N_2 atmosphere. After completion of the addition, the temperature of the reaction mixture was raised to room temperature and stirred for one hour to form the intermediate phosphorobromidite (**5**). The progress of the reaction was judged by TLC analysis. The reaction mixture was filtered under nitrogen atmosphere to remove triethylamine hydrobromide. The Grignard reagent (**6a-l**) was cooled to 15°C and compound **5** was added slowly in fifteen minutes under nitrogen. The progress of the reaction was monitored by TLC analysis (hexane : ethyl acetate, in 1:2). After completion of the reaction, the mixture was cooled to 5°C and added sulfur powder / selenium metal and heated slowly up to gentle reflux with stirring for two hours for the completion of the reaction as indicated by TLC analysis the reaction mixture was washed with saturated NaCl

solution and dried over anhydrous MgSO_4 and the solvent was removed in a rota-evaporator. The residue was purified by column chromatography using silica gel (60-120 mesh) as adsorbent and hexane and ethylacetate (1:2) as an eluent to afford pure compounds **8a-l**. The spectral and analytical data for **8a-l** are presented below.

3-Ethyl-2, 4-diisopropyl-1, 2, 4, 5-tetrahydro-benzo[e][1,3,2] diazaphosphepine-3-sulfide (8a)

Yield (%) : 79. m.p : 111-113°C. IR (KBr): 774 (P=S), 737 (P-N), 1056 (N-C) cm^{-1} . ^1H NMR (CDCl_3): δ 7.33 (d, J = 8.2 Hz, 2H, 6 & 9-H), 7.45 (d, J = 8.1 Hz, 2H, 8 & 7-H), 4.42-4.40 (m, 4H, $-\text{CH}_2$), 5.11-5.08 (m, 2H, $-\text{CH}$), 1.51 (d, J = 7.6 Hz, 12H, $-\text{CH}_3$), 1.81 (m, 2H, $-\text{CH}_2$), 1.20 (t, J = 11.2 Hz, 3H, $-\text{CH}_3$). ^{31}P NMR: (85%, H_3PO_4): δ 60.21. Anal. Calcd for $\text{C}_{16}\text{H}_{27}\text{PN}_2\text{S}$: C, 61.90; H, 8.76; N, 9.02; Found: C, 61.83; H, 8.70; N, 8.96.

3-Ethyl- 2, 4-diisopropyl- 1, 2, 4, 5-tetrahydro-benzo[e][1,3,2] diazaphosphepine-3-selenide (8b).

Yield (%) : 81. m.p : 260-262°C. IR (KBr): 622 (P=Se), 752 (P-N), 1060 (N-C) cm^{-1} ; mass (m/z) (%) : 357 (87.7), 329 (35.1), 285 (100), 207 (78.9), 120 (17.5). ^1H NMR (DMSO): δ 7.31 (d, J = 8.3 Hz, 2H, 6 & 9-H), 7.44 (d, J = 8.0 Hz, 2H, 8 & 7-H), 4.40-4.37 (m, 4H- CH_2), 5.09-5.05 (m, 2H, $-\text{CH}$), 1.48 (d, J = 7.7 Hz, 12H, $-\text{CH}_3$), 1.79 (m, 2H, $-\text{CH}_2$), 1.19 (t, J = 11.4 Hz, 3H, $-\text{CH}_3$). ^{13}C NMR (DMSO): δ 134.7 (C-10 & C-11), 129.1 (C-6 & C-9), 123.9 (C-8 & C-7), 44.9 (J = 5.2 Hz, $-\text{CH}_2$), 55.7 (J = 9.5 Hz, $-\text{CH}-(\text{CH}_3)_2$), 29.7 (J = 4.7 Hz, $-\text{CH}-(\text{CH}_3)_2$), 19.4 (J_{PC} = 139.4 Hz, $-\text{CH}_2-\text{CH}_3$), 9.9 ($-\text{CH}_2-\text{CH}_3$). ^{31}P NMR: (85%, H_3PO_4): δ 90.31. Anal. Calcd for $\text{C}_{16}\text{H}_{27}\text{PN}_2\text{Se}$: C, 53.78; H, 7.61; N, 7.83; Found: C, 53.71; H, 7.58; N, 7.78.

3-Allyl- 2, 4-diisopropyl-1, 2, 4, 5-tetrahydro-benzo[e][1,3,2] diazaphosphepine-3-sulfide (8c).

Yield (%) : 80. mp : 114-116°C. IR (KBr): 776 (P=S), 738 (P-N), 1058 (N-C) cm^{-1} ; ^1H NMR (CDCl_3): δ 7.32 (d, J = 8.5 Hz, 2H, 6 & 9-H), 7.46 (d, J = 8.3 Hz, 2H, 8 & 7-H), 4.41-4.38 (m, 4H, $-\text{CH}_2$), 5.13-5.09 (m, 2H, $-\text{CH}$), 1.50 (d, J = 7.8 Hz, 12H, $-\text{CH}_3$), 3.11-3.06 (m, 2H, $-\text{CH}_2$), 6.02-5.90 (m, H, $-\text{CH}$), 5.40 (d, J = 5.7 Hz, 2H, $-\text{CH}_2$). ^{31}P NMR: (85%, H_3PO_4): δ 63.17. Anal. Calcd for $\text{C}_{17}\text{H}_{27}\text{PN}_2\text{S}$: C, 63.32; H, 8.43; N, 8.68; Found: C, 63.28; H, 8.38; N, 8.60.

3-Allyl- 2, 4-diisopropyl- 1, 2, 4, 5-tetrahydro-benzo[e][1,3,2] diazaphosphepine-3-selenide (8d).

Yield (%) : 82. mp : 240-242°C. IR (KBr): 619 (P=Se), 730 (P-N), 1061 (N-C) cm^{-1} ; mass (m/z) (%) : 371 (M+3, 84.8), 311 (81.8), 253 (100), 167 (57.5), 113 (90.1). ^1H NMR (DMSO): δ 7.30 (d, J = 8.6 Hz, 2H, 6 & 9-H), 7.44 (d, J = 8.1 Hz, 2H, 8 & 7-H), 4.38-4.34 (m, 4H, $-\text{CH}_2$), 5.10-5.06 (m, 2H, $-\text{CH}$), 1.49 (d, J = 7.9 Hz, 12H, $-\text{CH}_3$), 3.09-3.03 (m, 2H, $-\text{CH}_2$), 5.98-5.90 (m, H, $-\text{CH}$), 5.38 (d, J = 5.8 Hz, 2H, $=\text{CH}_2$). ^{31}P NMR: (85%, H_3PO_4): δ 92.12. Anal. Calcd for $\text{C}_{17}\text{H}_{27}\text{PN}_2\text{Se}$: C, 55.28; H, 7.36; N, 7.58; Found: C, 55.21; H, 7.31; N, 7.52.

2,3,4-Triisopropyl-1,2,4,5-tetrahydro-benzo[e][1,3,2]diazaphosphepine-3-sulfide(8e)

Yield (%) : 77. mp : 155-157°C. IR (KBr): 769 (P=S), 730 (P-N), 1053 (N-C) cm^{-1} . ^1H NMR (CDCl_3): δ 7.34 (d, J = 8.8 Hz, 2H, 6 & 9-H), 7.43 (d, J = 8.3 Hz, 2H, 8 & 7H), 4.45-4.41 (m, 4H, $-\text{CH}_2$), 5.21-5.16 (m, 2H, $-\text{CH}$), 1.52 (d, J = 7.5 Hz, 12H, $-\text{CH}_3$), 2.23-2.10 (m, H, $-\text{CH}$), 1.50-1.20 (m, 6H, $-\text{CH}_3$). ^{13}C NMR (DMSO): δ 133.8 (C-10 & C-11), 129.3 (C-6 & C-9), 122.5 (C-8 & C-7), 46.3 (J = 5.3 Hz, $-\text{CH}_2$), 53.5 (J = 9.6 Hz, $-\text{CH}-(\text{CH}_3)_2$),

30.8 ($J = 4.7$ Hz, $-\text{CH}-(\text{CH}_3)_2$), 31.5 ($J_{\text{PC}} = 139.4$ Hz, $-\text{CH}-(\text{CH}_3)_2$), 11.8 ($J = 4.7$ Hz, $-\text{CH}-(\text{CH}_3)_2$). ^{31}P NMR: (85%, H_3PO_4): δ 64.31. Anal. Calcd for $\text{C}_{17}\text{H}_{29}\text{PN}_2\text{S}$: C, 62.92; H, 9.02; N, 8.63; Found: C, 62.86; H, 8.87; N, 8.58.

2,3,4-Triisopropyl-1,2,4,5-tetrahydro-benzo[e][1,3,2]diazaphosphepine-3-selenide (8f)

Yield (%): 79. mp: 255-257°C. IR (KBr): 627 (P=Se), 759 (P-N), 1038 (N-C) cm^{-1} . ^1H NMR (CDCl_3): δ 7.31 (d, $J = 8.6$ Hz, 2H, 6 & 9-H), 7.41 (d, $J = 8.2$ Hz, 2H, 8 & 7-H), 4.34-4.39 (m, 4H, $-\text{CH}_2$), 5.19-5.14 (m, 2H, $-\text{CH}$), 1.50 (d, $J = 7.5$ Hz, 12H, $-\text{CH}_3$), 2.20-2.08 (m, H, $-\text{CH}$), 1.48-1.19 (m, 6H, $-\text{CH}_3$). ^{31}P NMR: (85%, H_3PO_4): δ 91.17. Anal. Calcd for $\text{C}_{17}\text{H}_{29}\text{PN}_2\text{Se}$: C, 54.98; H, 7.87; N, 7.54; Found: C, 54.93; H, 7.81; N, 7.50.

3-Isobutyl-2,4-diisopropyl-1,2,4,5-tetrahydro-benzo[e][1,3,2]diazaphosphepine-3-sulfide (8g)

Yield (%): 77. mp: 160-162°C. IR (KBr): 778 (P=S), 752 (P-N), 1051 (N-C) cm^{-1} . ^1H NMR (CDCl_3): δ 7.36 (d, $J = 8.8$ Hz, 2H, 6 & 9-H), 7.43 (d, $J = 8.3$ Hz, 2H, 8 & 7-H), 4.45-4.37 (m, 4H, $-\text{CH}_2$), 5.10-5.00 (m, 2H, $-\text{CH}$), 1.55 (d, $J = 7.6$ Hz, 12H, $-\text{CH}_3$), 1.49-1.44 (m, 2H, $-\text{CH}_2$), 1.81-1.75 (m, H, $-\text{CH}$), 1.12-1.08 (m, 6H, $-\text{CH}_3$). ^{31}P NMR: (85%, H_3PO_4): δ 63.57. Anal. Calcd for $\text{C}_{18}\text{H}_{31}\text{PN}_2\text{S}$: C, 63.87; H, 9.23; N, 8.27; Found: C, 63.81; H, 9.18; N, 8.21.

3-Isobutyl-2,4-diisopropyl-1,2,4,5-tetrahydro-benzo[e][1,3,4]diazaphosphepine-3-selenide (8h)

Yield (%): 78. mp: 228-230°C. IR (KBr): 624 (P=Se), 734 (P-N), 1052 (N-C) cm^{-1} . mass (m/z) (%): 385 (9.3), 339 (54.5), 240 (12.1), 188 (100), 157 (81.8), 120 (75.7), 83 (60.6). ^1H NMR (DMSO): δ 7.35 (d, $J = 8.9$ Hz, 2H, 6 & 9-H), 7.42 (d, $J = 8.4$ Hz, 2H, 8 & 7-H), 4.43-4.35 (m, 4H, $-\text{CH}_2$), 5.08-4.98 (m, 2H, $-\text{CH}$), 1.54 (d, $J = 7.7$ Hz, 12H, $-\text{CH}_3$), 1.46-1.40 (m, 2H, $-\text{CH}_2$), 1.79-1.73 (m, H, $-\text{CH}$), 1.11-1.06 (m, 6H, $-\text{CH}_3$). ^{13}C NMR (DMSO): δ 134.7 (C-10 & C-11), 129.3 (C-6 & C-9), 122.7 (C-8 & C-7), 46.3 ($J = 5.3$ Hz, $-\text{CH}_2$), 55.7 ($J = 9.4$ Hz, $-\text{CH}-(\text{CH}_3)_2$), 30.8 ($J = 4.6$ Hz, $-\text{CH}-(\text{CH}_3)_2$), 44.9 ($J_{\text{PC}} = 138.2$ Hz, $-\text{CH}_2-\text{CH}-(\text{CH}_3)_2$), 21.4 ($J = 5.2$ Hz, $-\text{CH}_2-\text{CH}-(\text{CH}_3)_2$), 19.4 ($-\text{CH}_2-\text{CH}-(\text{CH}_3)_2$). ^{31}P NMR: (85%, H_3PO_4): δ 90.15. Anal. Calcd for $\text{C}_{18}\text{H}_{31}\text{PN}_2\text{Se}$: C, 56.09; H, 8.10; N, 7.26; Found: C, 56.03; H, 8.05; N, 7.20.

3-Propyl-2,4-diisopropyl-1,2,4,5-tetrahydro-benzo[e][1,3,4]diazaphosphepine-3-sulfide (8i)

Yield (%): 76. mp: 130-132°C. IR (KBr): 770 (P=S), 735 (P-N), 1043 (N-C) cm^{-1} . mass (m/z) (%): 324 (M+2, 42.5), 275 (25), 231 (50.0), 190 (50.0), 146 (100), 132 (45), 59 (25). ^1H NMR (CDCl_3): δ 7.40 (d, $J = 9.0$ Hz, 2H, 6 & 9-H), 7.47 (d, $J = 8.3$ Hz, 2H, 8 & 7-H), 4.48-4.40 (m, 4H, $-\text{CH}_2$), 5.10-5.01 (m, 2H, $-\text{CH}$), 1.60 (d, $J = 7.8$ Hz, 12H, $-\text{CH}_3$), 2.40-2.25 (m, 2H, $-\text{CH}_2$), 1.31-1.25 (m, 2H, $-\text{CH}_2$), 0.96 (d, $J = 5.9$ Hz, 3H, $-\text{CH}_3$). ^{13}C NMR (CDCl_3): δ 134.2 (C-10 & C-11), 129.4 (C-6 & C-9), 122.7 (C-8 & C-7), 46.4 ($J = 5.4$ Hz, $-\text{CH}_2$), 55.7 ($J = 9.5$ Hz, $-\text{CH}-(\text{CH}_3)_2$), 29.6 ($J = 4.7$ Hz, $-\text{CH}-(\text{CH}_3)_2$), 29.1 ($J_{\text{PC}} = 139.8$ Hz, $-\text{CH}_2-\text{CH}_2-\text{CH}_3$), 17.6 ($J = 4.7$ Hz, $-\text{CH}_2-\text{CH}_2-\text{CH}_3$), 8.7 ($J = 15.6$ Hz, $-\text{CH}_2-\text{CH}_2-\text{CH}_3$). ^{31}P NMR: (85%, H_3PO_4): δ 65.13. Anal. Calcd for $\text{C}_{17}\text{H}_{29}\text{PN}_2\text{S}$: C, 62.92; H, 9.02; N, 8.63; Found: C, 62.85; H, 8.95; N, 8.57.

3-Propyl-2,4-diisopropyl-1,2,4,5-tetrahydro-benzo[e][1,3,4]diazaphosphepine-3-selenide (8j)

Yield (%): 78. mp: 222-224°C. IR (KBr): 623 (P=Se), 753 (P-N), 1047 (N-C) cm^{-1} . ^1H NMR (DMSO): δ 7.38 (d, $J = 8.8$ Hz, 2H, 6 & 9-H), 7.45 (d, $J = 8.5$ Hz, 2H, 8 & 7-H),

4.45-4.38 (m, 4H, -CH₂), 5.08-5.00 (m, 2H, -CH), 1.58 (d, $J = 8.0$ Hz, 12H, -CH₃), 2.38-2.21 (m, 2H, -CH₂), 1.30-1.24 (m, 2H, -CH₂), 0.94 (d, $J = 8.0$ Hz, 3H, -CH₃). ³¹P NMR: (85%, H₃PO₄): δ 92.16. Anal. Calcd for C₁₇H₂₉PN₂Se: C, 54.98; H, 7.87; N, 7.54; Found: C, 54.91; H, 7.83; N, 7.50.

3-Butyl-2,4-diisopropyl-1,2,4,5-tetrahydro-benzo[e][1,3,4]diazaphosphepine-3-sulfide (8k)

Yield (%): 80. mp: 125-127°C. IR (KBr): 768 (P=S), 750 (P-N), 1059 (N-C) cm⁻¹. ¹H NMR (CDCl₃): δ 7.35 (d, $J = 8.9$ Hz, 2H, 6 & 9-H), 7.43 (d, $J = 8.4$ Hz, 2H, 8 & 7-H), 4.46-4.41 (m, 4H, -CH₂), 5.11-5.03 (m, 2H, -CH), 1.53 (d, $J = 8.2$ Hz, 12H, -CH₃), 2.18-2.12 (m, 2H, -CH₂), 1.53-1.46 (m, 2H, -CH₂), 1.21-1.18 (m, 2H, -CH₂), 0.94 (d, $J = 6.0$ Hz, 3H, -CH₃). ³¹P NMR: (85%, H₃PO₄): δ 66.11. Anal. Calcd for C₁₈H₃₁PN₂S: C, 63.87; H, 9.23; N, 8.27; Found: C, 63.78; H, 9.16; N, 8.23.

3-Butyl-2,4-diisopropyl-1,2,4,5-tetrahydro-benzo[e][1,3,4]diazaphosphepine-3-selenide (8l)

Yield (%): 83. mp: 230-232°C. IR (KBr): 625 (P=Se), 751 (P-N), 1057 (N-C) cm⁻¹. ¹H NMR (DMSO): δ 7.32 (d, $J = 8.7$ Hz, 2H, 6 & 9-H), 7.41 (d, $J = 8.3$ Hz, 2H, 8 & 7-H), 4.44-4.40 (m, 4H, -CH₂), 5.10-5.02 (m, 2H, -CH), 1.51 (d, $J = 8.3$ Hz, 12H, CH₃), 2.20-2.16 (m, 2H, -CH₂), 1.51-1.44 (m, 2H, -CH₂), 1.20-1.16 (m, 2H, -CH₂), 0.92 (d, $J = 6.2$ Hz, 3H, -CH₃). ³¹P NMR: (85%, H₃PO₄): δ 91.38. Anal. Calcd for C₁₈H₃₁PN₂Se: C, 56.09; H, 8.10; N, 7.26; Found: C, 56.05; H, 8.07; N, 7.21.

Results and Discussion

The synthetic routes for the title compounds (**8a-l**) involves reaction of α,α' -dibromo-*o*-xylene¹⁶ (**1**) with two moles of isopropylamine (**2**) in the presence of TEA in dry THF. This on further reaction with PBr₃ (**4**) and different Grignard reagents (**6**) in THF under N₂ atmosphere yielded trivalent phosphorus compounds (**7a-l**). These are further treated with sulfur and selenium to get the corresponding sulfides and selenides (**8a-l**) at reflux temperature (Scheme-1) in 76-83% overall yield. Thin layer chromatography was employed to monitor the reaction progress and to determine the purity of the products. All the title compounds (**8a-l**) were readily soluble in polar solvents and melted in the range of 111-262°C. The chemical structures of all the new compounds (**8a-l**) are confirmed by elemental analysis, IR, ¹H, ¹³C and ³¹P NMR and mass spectral data. Compounds exhibited characteristic IR stretching frequencies in the regions¹⁷⁻¹⁹ 768-778, 619-627, 730-759 and 1038-1061 cm⁻¹ for P=S, P=Se, P-N and N-C respectively.

The aromatic protons of the benzene ring of **8a-l** showed as two distinct doublets¹⁶ one at δ 7.30-7.40 ($J = 8.2$ -9.0 Hz) and the other at δ 7.41-7.47 ($J = 8.0$ -8.5 Hz) due to different chemical nature of the 6 & 9-H and 7 & 8-H protons. The bridged -CH₂ and N-CH of isopropyl moiety protons appeared as multiplets due to coupling adjacent protons at δ 4.35-4.48 and δ 5.00-5.21 respectively. The -CH₃ protons of isopropyl group appeared as a doublet at δ 1.48-1.60 ($J = 7.5$ -8.3 Hz). The protons of the P-C_{aliphatic} moiety of the side chain present in **8a-l** exhibited signals in the expected range.

¹³C NMR spectral data of compounds **8b**, **8e**, **8h** and **8i** are in agreement with the literature data²⁰. The bridged methylene carbons are magnetically equivalent and methyne carbons of isopropyl group also same in nature. Carbon resonances of the side chain alkyl groups, only three carbons in the side chain experienced coupling with phosphorus.

The 4-carbon did not show any coupling with phosphorus. The significance of this high-low-high coupling profile is yet to be defined perhaps this may arise atleast in part, from γ -type interactions as illustrated²¹.

Compd.	R	X
8a	-CH ₂ -CH ₃	S
8b	-CH ₂ -CH ₃	Se
8c	-CH ₂ -CH=CH ₂	S
8d	-CH ₂ -CH=CH ₂	Se
8e		S
8f		Se
8g		S
8h		Se
8i	-CH ₂ -CH ₂ -CH ₃	S
8j	-CH ₂ -CH ₂ -CH ₃	Se
8k	-CH ₂ -CH ₂ -CH ₂ -CH ₃	S
8l	-CH ₂ -CH ₂ -CH ₂ -CH ₃	Se

Scheme - 1

³¹P NMR chemical shifts^{17,20,22,23} of **8a-l** appeared in the region 60.21-92.16 ppm. It is observed that ³¹P NMR chemical shifts of P(III) derivatives appeared at downfield when compared to P(V) derivatives depending on the atoms attached to phosphorus.

In their FAB mass spectra, molecular ions were observed at *m/z* 357 (87.7), 371 (84.8), 385 (9.3) and 324 (42.5) corresponding to the compounds **8b**, **8d**, **8h** and **8i** respectively²⁴.

Antibacterial Activity

Compounds **8a-l** were screened for their antibacterial activity²⁰ (Table-1) against gram positive bacteria, *Staphylococcus aureus*, *Bacillus faecalis* and gram negative bacteria, *Escherichia coli*, *Klebsiella pneumoniae* by the disc diffusion method^{25,26}, in luria baertani nutrient agar medium at various concentrations (100, 200 µg/mL). These solutions containing 10⁶ cells / mL were added to each Whatmann No.1 (made in UK) filter paper disc (6 mm diameter) and DMSO was used as the control. The freshly prepared agar medium containing bacterial species was loaded to the discs by using micropipette. These plates were incubated at 35°C and examined for zone of inhibition around each disc after 24 hrs. The results were compared with the activity of the standard antibiotic Penicillin (100 µg/mL), made in our lab and was used.

The compound **8k** showed almost equal activity against gram positive bacteria, *Bacillus faecalis* when compared to that of the standard. The compound **8e** exhibited more activity against gram negative bacteria *Escherichia coli* when compared to that of *Penicillin*.

Table 1. Antibacterial activity^a of some new 3-alkyl-2,4-diisopropyl-1,2,4,5-tetrahydro-benzo[e][1,3,2] diazaphosphepine 3-sulfides / selenides (**8a-l**).

Compd.	<i>Staphylococcus aureus</i>		<i>Bacillus faecalis</i>		<i>Escherichia coli</i>		<i>Klebsiella pneumoniae</i>	
	100	200	100	200	100	200	100	200
	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL
8a	7	10	6	11	6	10	7	10
8b	6	11	6	10	7	11	7	10
8c	6	10	6	11	6	10	7	11
8d	6	9	8	14	6	8	7	12
8e	6	10	7	10	10	14	8	12
8f	7	11	7	10	6	9	9	13
8g	6	8	7	12	6	9	8	13
8h	7	11	8	12	7	11	9	12
8i	7	12	8	13	6	13	6	10
8j	6	9	8	14	6	10	8	13
8k	7	13	10	13	7	12	8	12
8l	6	9	8	11	7	11	9	12
Penicillin ^b	13		11		9		12	

^aConcentration in ppm, ^bStandard antibacterial compound

Conclusion

We successfully synthesized a series of novel 3-alkyl-2,4-diisopropyl-1,2,4,5-tetrahydro-benzo[e][1,3,2]diazaphosphepine 3-sulfides / selenides in high yields by adopting a simple and strait forward procedure. The advantages are less reaction times, low cost of the starting chemicals, simple experimental procedure and also these compounds exhibited significant antibacterial activity.

Acknowledgements

The authors express thanks to Prof. C. Devendranath Reddy and Dr. C. Suresh Reddy, Sri Venkateswara University, Tirupati, for their encouragement and the Directors of CDRI, Lucknow and SIF, IISC, Bangalore, for the elemental analyses and spectral data.

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