Synthesis and Biological Studies of Some Sulfur, Selenium and Tellurium Organic Compounds Based on Diethanolamine


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Abstract—Several new and known bis(2-(arylchalcogeno)ethyl)amines (i.e. HN(CH2CH2EAr)2; where E= S, Se and Te, Ar = C6H5, 4-CH3C6H4, 4-CH3OC6H4, 4-CH3CH2OC6H4, 4-BrC6H4, 4-ClC6H4 and 4-PhC6H4) were prepared by the reaction of bis(chloroethyl)amine with lithium arylthiolate or with the corresponding sodium arylchalcogenate (generated in situ by borohydride reduction of R2Ee2; i.e. ArE- Na⁺; E= Se and Te). All compounds were obtained in good yield and characterized by elemental analysis, IR, 1H and 13C NMR and mass spectroscopic data. Antibacterial activity study of these compounds showed some promising activity against S. aureus, P. aeruginosa and E. coli.

Key words—Diethanolamine, organotellurium, selenium, sodium arylchalcogenate, diaryl dichalcogenides, biological activity.

1 INTRODUCTION

DIETHANOLAMINE has been used as surfactants for detergents and cleaning agent formulations and as a gas purification agent to remove carbon dioxide or hydrogen sulfide gas. Furthermore, diethanolamine was also used as an anticorrosion agent in metalworking fluids, and in preparations of agricultural chemicals. In addition, diethanolamine is raw materials to synthesize drugs and it is also a cross linking agent for production of high elasticity polyurethane foam [1-3].

Selenium and tellurium compounds were considered a poison for many years, until non-toxic selenium and tellurium compounds with high biological activity were found [4–10]. A variety of organoselenium compounds with potential antioxidant activity, including ebselen analogues, benzoselenazolines, diaryl diselenides, selenamide and related derivatives have been reported in a variety of pathological situations [8-12]. Like organoselenium compounds, a number of organotellurium compounds exhibited high glutathione peroxidase-like activity [2–5]. The literature [4–12] indicates that among organotellurium compounds, mainly telluranes (four-valent tellurium compounds), showed high biological activity. Thus, the present work describes the synthesis of some new and known organosulfur, organoselenium and organotellurium compounds based on diethanolamine in order to study their biological activity.

2 EXPERIMENTAL

2.1 Physical measurements

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. FT-IR spectra were recorded on FT-IR spectrophotometer -8400s Shimadza as KBr disc. The 1H and 13C NMR spectra were measured on a Bruker spectrometer at 400 (1H NMR) MHz and 100 (13C NMR) MHz using CDCl3 solution with TMS as internal standard. Elemental analyses were determined on an MT-3 elemental analyzer within ±5 % of the theoretical values. Mass spectra were recorded on a HP-5988A MS instrument at 70 eV.

2.2 Synthesis

All reactions were carried out under nitrogen or argon atmosphere and monitored by conventional TLC method. All organic solvents were dried prior to use according to standard methods. Diphenyl diselenide[13], bis(4-methylphenyl) diselenide [14], bis(4-methoxyphenyl) diselenide [14], bis(4-ethoxyphenyl) diselenide [14], bis(4-hexylphenyl) diselenide [14] and bis(4-phenylphenyl) diselenide[14] were prepared according to literature methods. Diphenyl ditelluride[15], bis(4-methoxyphenyl) ditelluride[15], bis(4-ethoxyphenyl) ditelluride[15], bis(4-ethylphenyl) ditelluride[16], bis(4-bromophenyl) ditelluride[16], bis(4-chlorophenyl) ditelluride[16] and bis(4-phenylphenyl) ditelluride[16] were prepared according to literature methods. Diphenyl ditelluride[15], bis(4-methoxyphenyl) ditelluride[15], bis(4-ethoxyphenyl) ditelluride[15], bis(4-ethylphenyl) ditelluride[16], bis(4-bromophenyl) ditelluride[16], bis(4-chlorophenyl) ditelluride[16] and bis(4-phenylphenyl) ditelluride[16] were prepared by chlorination of diethanolamine with thionyl chloride in CHCl3 as described in a literature method[17]. All the above compounds were characterized according to their mp’s and IR spectra. Diphenyl disulfide and bis(4-methoxyphenyl) disulfide were obtained from Aldrich-Sigma company and used without further purification.

2.2.1 Bis(2-(phenylthio)ethyl)amine (1)

To 0.18 mole of phenyllithium in 100 cm³ THF was added cautiously sulfur(5.77 g; 0.18 g. atom). The reaction was exothermic; the stirring was continued until all the sulfur had been disappeared. The resulting solution was stirred for additional 1 h at room temperature. The solution was cooled in ice-
bath and a solution of bis(2-chloroethyl)amine (12.07 g; 0.085 mol) in dry THF (100 cm³) was added drop wise to the rapidly stirred solution of PhSILi. After the addition was complete, the reaction mixture was stirred for 12 h at room temperature. The resulting solution was hydrolyzed with distilled water and the extract with dichloromethane (5 x 50 cm³). The organic layer was dried over anhydrous calcium chloride. Solvent was removed by rotary evaporator, to give a yellow solid product. Recrystallization of the product from a mixture of ethyl acetate-CH₂Cl₂ gave compound 1 as a pale-yellow solid in 56% yield. M.p. 54-55°C.

Synthesis of bis(2-(aryl diselenide) (2)

Synthesis of bis(2-(aryl diselenide) was similar to the method used for compounds 1, except that 4-MeOPhSILi was used instead of PhSILi. A pale yellow solid was obtained in 45% yield. M.p. 63-64°C.

Synthesis of bis(2-(aryl diseleno)ethyl)amine (3-9)

Compounds 3-9 were prepared according to the previously reported method [19] and as follows: To a solution of diaryl diselenide (20 mmol), sodium hydroxide (8.602 g, 0.22 mol) and ethanol (150 mL) was added NaBH₄ (1.015 g, 27 mmol) in a small portion. The resulting solution was stirred for 4 hours at room temperature until the yellow colour disappeared. Bis(2-chloroethyl)amine (3.57 g, 20 mmol) was added in small portions during 1 h. The resulted solution was stirred for 3 h at room temperature. The solvent was removed by a rotary evaporator. The residue was dissolved in CH₂Cl₂ (50 mL) and then water (100 mL) was added to it. The organic phase was separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 25 mL). The combined extracts were dried over anhydrous Na₂SO₄. The solvent was removed and the residue was purified by column chromatography (SiO₂, hexane/ethyl acetate). A white precipitate of the corresponding compound was obtained.

2.2.3 Bis-(2-phenylseleno)ethyl)amine(3)

Yield: 91%, m.p 54-55°C.

Anal. Calcd. for C₁₆H₁₈NS: C, 70.14; H, 5.00; N, 3.65%; Found: C, 70.09; H, 4.94; N 3.53%. ¹H NMR(CDCCl₃): 1.71 (s, 1H), 2.89 (d, 4H, J = 6.4 Hz), 3.04 (d, 4H, J = 6.5 Hz), 7.28 (d, 6H, J = 6.6 Hz), 7.53 (d, 4H, J = 6.4 Hz); ¹³C NMR(CDCCl₃): 133.07, 129.71, 129.17, 127.12, 48.57, 28.75. El MS: m/z [M⁺] = 385.

2.2.4 Bis-(2-(methylphenylseleno)ethyl)amine (4)

White solid. Yield: 78%, m.p 105-106°C.

Anal. Calcd. for C₁₆H₁₈NS: C, 72.56; H, 5.64; N, 3.41%; Found: C, 72.39; H, 5.24; N 3.33%. ¹H NMR(CDCCl₃): 1.70 (sb, 1H, NH), 2.01 (t, 4H, J = 6.4 Hz), 3.32 (t, 4H, J = 6.6 Hz), 7.08 (d, 6H, J = 6.5 Hz), 7.22 (d, 4H, J = 6.4 Hz); ¹³C NMR(CDCCl₃): 21.3, 28.4, 38.8, 127.5, 131.2, 134.7, 138.2. El MS: m/z [M⁺] = 413.

2.2.5 Bis-(2-(4-methoxyphenylseleno)ethyl)amine (5)

White solid. Yield: 88%, m.p 65-67°C.

Anal. Calcd. for C₁₈H₁₈NOSe: C, 48.77; H, 5.23; N, 3.16%; Found: C, 48.49; H, 5.24; N 3.13%. ¹H NMR(CDCCl₃): 1.72 (sb, 1H, NH), 1.92 (t, 4H, CH₂Se), 2.03 (t, 4H, CH₂N), 4.30 (s, 6H, OCH₃), 6.62 (d, 4H, J = 6.4 Hz), Ar-H). 7.21 (d, 4H, J = 6.4 Hz, Ar-H): ¹³C NMR(CDCCl₃): 28.3, 27.5, 55.4, 112.4, 121.7, 131.6, 159.7. El MS: m/z [M⁺] = 445.

2.2.6 Bis-(2-(4-ethoxyphenylseleno)ethyl)amine (6)

White solid. Yield: 84%, m.p. 95-96°C.

Anal. Calcd. for C₁₈H₁₈NOSe: C, 50.96; H, 5.77; N, 2.97%; Found: C, 50.78; H, 5.64; N 2.73%. ¹H NMR(CDCCl₃): 1.68 (sb, 1H, NH), 1.81-1.95 (m, 10H, CH₃ + CH₂Se), 2.11 (t, 4H, CH₂N), 4.82 (q, 4H, OCH₂), 6.82 (d, 4H, J = 6.8 Hz, Ar-H), 7.21 (d, 4H, J = 6.6 Hz, Ar-H): ¹³C NMR(CDCCl₃): 13.7, 26.2, 38.3, 63.8, 113.5, 120.9, 132.1, 160.2. El MS: m/z [M⁺] = 473.

2.2.7 Bis-(2-(4-bromophenylseleno)ethyl)amine (7)

White solid. Yield: 89%, m.p 70-72°C.

Anal. Calcd. for C₁₈H₁₈BrSe: C, 35.52; H, 3.17; N, 2.59%; Found: C, 34.98; H, 2.96; N 2.33%. ¹H NMR(CDCCl₃): 1.61 (sb, 1H, NH), 1.82 (t, 4H, CH₂Se), 2.11 (t, 4H, CH₂N), 7.18 (d, 4H, J = 6.6 Hz, Ar-H), 7.51 (d, 4H, J = 6.6 Hz, Ar-H): ¹³C NMR(CDCCl₃): 32.6, 49.7, 119.2, 128.6, 131.6, 134.8. El MS: m/z [M⁺] = 545.

2.2.8 Bis-(2-(4-chlorophenylseleno)ethyl)amine (8)

White solid. Yield: 75%, m.p 100-102°C.

Anal. Calcd. for C₁₈H₁₈ClSe: C, 42.50; H, 3.79; N, 3.10%; Found: C, 42.47; H, 2.97; N 2.86%. ¹H NMR(CDCCl₃): 1.69 (sb, 1H, NH), 2.33 (t, 4H, CH₂Se), 3.18 (t, 4H, CH₂N), 7.21 (s, 8H, Ar-H): ¹³C NMR(CDCCl₃): 32.7, 50.1, 128.8, 130.7, 131.0, 133.9.

2.2.9 Bis-(2-(4-phenylphenylseleno)ethyl)amine (9)

White solid. Yield: 81%, m.p 121-123°C.

Anal. Calcd. for C₂₆H₂₄Se: C, 62.81; H, 5.08; N, 2.62%; Found: C, 62.74; H, 4.95; N 2.38%. ¹H NMR(CDCCl₃): 2.01 (sb, 1H, NH), 2.23 (t, 4H, CH₂Se), 3.15 (t, 4H, CH₂N), 7.35-7.49 (m, 10H, Ar-H), 7.54 (d, 4H, J = 7.3 Hz, Ar-H), 7.64 (d, 4H, J = 7.5Hz, Ar-H).

Synthesis of bis(2-(aryltelluro)ethyl)amine (10-16)

Compounds 10-16 were prepared by the following general method:

Diary ditelluride (2.0 mmol) was dissolved in 30 cm³ of ethanol and the solution set to reflux under nitrogen atmosphere. A solution of sodium borohydride in NaOH (10%) was added dropwise to the refluxing solution of the ditelluride under nitrogen atmosphere until it became colourless. Bis-(2-chloroethyl)amine hydrochloride (0.357 g, 2.0 mmol) dissolved in 10 cm³ of ethanol was added to this solution with constant stirring. The reaction mixture was refluxed for 3 h, cooled to room temperature and poured into ice cold water (100 cm³) in which 0.2 g of NaHCO₃ was dissolved. The compound was extracted into chloroform (200 cm³) from this aqueous mixture. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure by a rotary evaporator, resulting in a white solid, which was extracted into hexane. Recrystallization from
chloroform gave a white solid.

The melting points and spectroscopic data of all prepared compounds follow

2.2.10 Bis(2-phenyltelluro)ethylamine (10)
Yield: 91%, m.p. 70-72°C.
Anal. Calcd. for C₇₆H₇₁N₂O₂Te: C, 39.99; H, 3.99; N, 2.91%; Found: C, 40.11; H, 3.84; N 3.23%. ¹H NMR(CDCl₃): 1.30 (s, 1H), 2.82 (t, 4H, CH₂Te, J = 6.5 Hz), 3.39 (t, 4H, CH₂N, J = 6.6 Hz), 7.07-7.33 (m, 6H, Ar-H), 7.42-7.46 (m, 4H, Ar-H); ¹³C NMR (CDCl₃): 43.7, 48.2, 117.0, 127.1, 129.3, 131.3.

2.2.11 Bis(4-methylphenyltelluro)ethylamine (11)
White solid. Yield: 72%; m.p. 56-58°C.
Anal. Calcd. for C₇₆H₇₁N₂O₂Te: C, 42.51; H, 4.56; N, 2.75%. Found: C, 42.39; H, 4.24; N 2.52%. ¹H NMR(CDCl₃): 1.70 (sb, 1H, NH), 2.01 (t, 4H, CH₂Te, J = 6.4 Hz), 3.32 (t, 4H, CH₂N, J = 6.6 Hz), 7.08 (d, 6H, J = 5.6 Hz, Ar-H), 7.22 (d, 4H, J = 6.6 Hz, Ar-H); ¹³C NMR (CDCl₃): 21.6, 28.4, 38.8, 127.3, 131.2, 134.7, 138.2. El MS: m/z [M]+ = 513.

2.2.12 Bis(4-methoxyphenyltelluro)ethylamine (12)
White solid. Yield: 79%; m.p. 62-64°C.
Anal. Calcd. for C₇₆H₇₁N₂O₂Te: C, 43.99; H, 4.29; N, 2.59%. Found: C, 40.12; H, 4.24; N 2.55%. ¹H NMR(CDCl₃): 1.08 (sb, 1H, NH), 2.57 (t, 4H, CH₂Te), 3.38-3.45 (m, 4H, CH₂N), 3.77 (s, 6H, OCH₃), 7.11 (d, 4H, J = 6.4 Hz, Ar-H), 7.23 (d, 4H, J = 6.4 Hz, Ar-H); ¹³C NMR (CDCl₃): 38.8, 48.5, 56.0, 115.3, 127.5, 134.4, 158.4. El MS: m/z [M]+ = 545.

2.2.13 Bis(4-ethoxyphenyltelluro)ethylamine (13)
White solid. Yield: 81%; m.p. 73-75°C.
Anal. Calcd. for C₇₆H₇₁N₂O₂Te: C, 42.24; H, 4.79; N, 2.46%. Found: C, 42.17; H, 4.66; N 2.32%. ¹H NMR(CDCl₃): 1.41 (t, 6H, CH₂), 1.81 (sb, 1H, NH), 2.93 (t, 4H, CH₂Te), 3.01 (t, 4H, CH₂N), 4.04 (q, 4H, OCH₂), 6.87 (d, 4H, J = 6.6 Hz, Ar-H), 7.25 (d, 4H, J = 6.6 Hz, Ar-H); ¹³C NMR (CDCl₃): 48.6, 43.9, 63.9, 116.9, 127.5, 135.2, 157.9.

2.2.14 Bis(4-bromophenyltelluro)ethylamine (14)
White solid. Yield: 79%; m.p. 77-78°C.
Anal. Calcd. for C₇₆H₇₁Br₂N₂O₂Te: C, 30.11; H, 2.68; N, 2.19%. Found: C, 29.92; H, 2.47; N 2.03%. ¹H NMR(CDCl₃): 1.44 (sb, 1H, NH), 2.72 (t, 4H, CH₂Te), 3.31 (t, 4H, CH₂N), 7.26 (d, 4H, J = 7.3 Hz, Ar-H), 7.65 (d, 4H, J = 6.6 Hz, Ar-H); ¹³C NMR (CDCl₃): 32.6, 48.6, 109.2, 128.5, 131.6, 137.2. El MS: m/z [M]+ = 645.

2.2.15 Bis(4-chlorophenyltelluro)ethylamine (15)
White solid. Yield: 69%; m.p. 88-89°C.
Anal. Calcd. for C₇₆H₇₁Cl₂N₂O₂Te: C, 34.98; H, 3.12; N, 2.55%. Found: C, 35.03; H, 2.96; N 2.36%. ¹H NMR(CDCl₃): 1.67 (sb, 1H, NH), 2.99 (t, 4H, CH₂Te), 3.42 (t, 4H, CH₂N), 7.39 (d, 4H, Ar-H), 7.64 (d, 4H, Ar-H); ¹³C NMR (CDCl₃): 44.9, 48.6, 127.5, 130.1, 133.4, 1339.

2.2.16 Bis(4-phenyltelluro)ethylamine (16)
White solid. Yield: 75%; m.p. 112-113°C.
Anal. Calcd. for C₇₆H₇₁N₂O₂Te: C, 53.15; H, 4.30; N, 2.21%. Found: C, 53.1174; H, 4.05; N 2.31%. ¹H NMR(CDCl₃): 1.95 (sb, 1H, NH), 2.78 (t, 4H, CH₂Te), 3.21 (t, 4H, CH₂N), 7.37-7.46 (m, 6H, Ar-H), 7.61-7.64 (m, 4H, Ar-H), 7.80 (d, 4H, Ar-H), 7.88 (d, 4H, J = 7.5Hz, Ar-H); ¹³C NMR (CDCl₃): 44.8, 48.5, 127.3, 127.5, 128.3, 128.8, 129.9, 133.0, 140.9.

3 ANTIBACTERIAL ACTIVITY

Compounds 1-16 were tested for their antibacterial activity by using cup plate agar diffusion method [18] and the inhibition zones were measured in millimeter (mm). The nutrient agar broth prepared by the usual method, was inoculated aseptically with 0.5 mL of 24 h old subculture of S. aureus, P. aeruginosa and E. coli in separate conical flasks at 40-50°C and mixed well by gentle shaking. About 25 mL of the contents of the flask were poured and evenly spread in petridish (90 mm in diameter) and allowed to set for 2h. The cups (10 mm in diameter) were formed by the help of borer in agar medium and filled with 0.04 mL (40 μg/mL) solution of sample in DMF. The plates were incubated at 37°C for 24 h and the control was also maintained with 0.04 mL of DMF in similar manner and the zones of inhibition of the bacterial growth were measured in millimeter and recorded in Table 1.

4 RESULTS AND DISCUSSION

Chlorination of diethanolamine with thionyl chloride in CHCl₃ gave 2-(chloroethyl)amine hydrochloride as a white solid in 77% yield. The latter compound reacted with lithium arylithiolate and with sodium arylclogenenates (i.e. NaEAr (E=Se/Te)), generated in situ by NaBH₃ reduction of the corresponding diaryldichalogenides (Ar₂E₂) in alkaline ethanol to give compounds 1-2 and 3 - 16, respectively in good yields, Scheme 1. Compounds 3, 11, and 13 were previously reported [19, 20]. All compounds are fairly soluble in organic solvents such as chloroform and dichloromethane.
From Table 1 it can be concluded that all the compounds have significant for activity against bacterial. Compounds 9 and 16 showed minimum activity against all strains. This may be due to the presence of a phenyl substituent, which makes slow diffusion through the cell membrane. In general, all compound showed good antibacterial activity.

5 ACKNOWLEDGMENTS

The financial support of this work by Ministry of Higher Education and Scientific Research/Research and Development (Grant No. 593) is hereby gratefully acknowledged.

REFERENCES


### TABLE 1. Microbiological evaluation of compounds 1 – 16.

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From Table 1 it can be concluded that all the compounds have significant for activity against bacterial. In general compounds containing sulfur and selenium (i.e. compounds 1 – 9) are more active against the bacteria than analogous tellurium derivatives (i.e. compounds 10 – 16), Table 1. Remarkable inhibition was observed in compounds containing methoxy, ethoxy and methyl substituents, Table 1. It seems that the methyl, methoxy and ethoxy group at para position are very significant for activity against bacterial. Compounds 9 and 16 showed minimum activity against all strains. This may be due to the presence of a phenyl substituent, which makes slow diffusion through the cell membrane. In general, all compound showed good antibacterial activity.


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