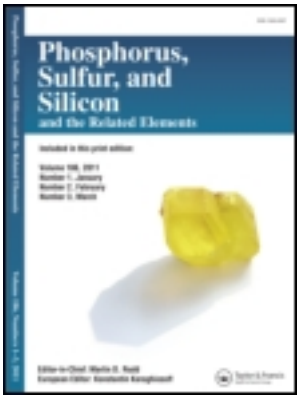

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Synthesis, Antimicrobial Activity, and ^{77}Se NMR of Some New Pyrrole Derivatives Containing a Diphenyl Selenide Moiety

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A simple and mild synthesis for pyrrolyl and pyrrolo[2,3-d]pyrimidinyl diphenyl selenides is described based on the reaction of active methylene compounds with 4′-nitro-4-acetylaminodiphenyl selenide. The sensitivity of ^{77}Se NMR spectra allowed differentiating the rather similar pyrrole compounds. The synthesized compounds were screened for their antifungal and antibacterial activities.

Keywords ^{77}Se NMR; antibacterial activity; antifungal activity; diphenyl selenide; keto enol tautomers; pyrrole

INTRODUCTION

The pyrrole nucleus plays a vital role in many compounds with biological activities[1–5] and, consequently, pyrrolo[2,3-d]pyrimidine derivatives[6,7] are insecticides, microbicides,[8] pro-oxidants,[9] and antimycobacterial agents.[10] Likewise, organo-selenium compounds are known to react as antioxidants[11] and as anticancerogens.[12–14] In view of these findings and in continuation of our work[15–17] on the synthesis of novel heterocyclic systems containing diaryl sulfide and diary selenide, we undertook the synthesis of some new pyrrole derivatives including the diphenyl selenide moiety.

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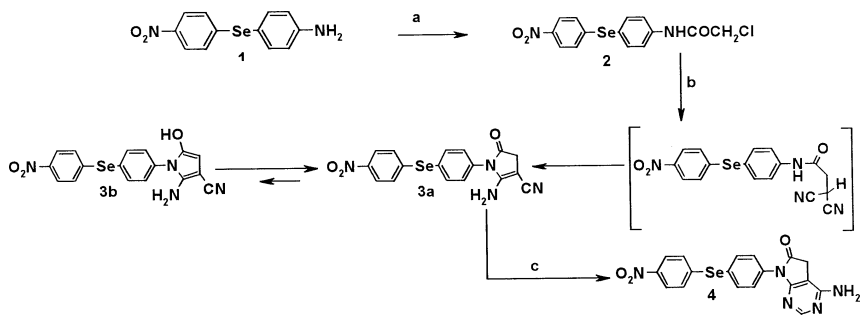
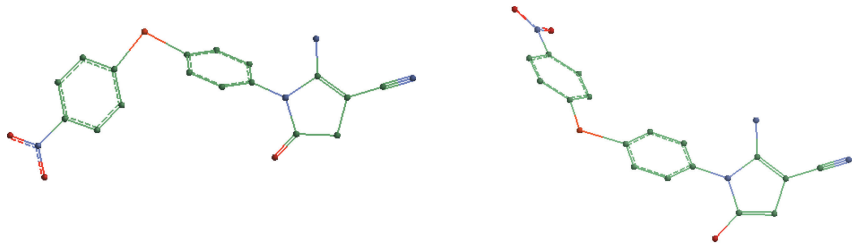
RESULTS AND DISCUSSION

The starting material 4′-nitro-4-chloroacetylaminodiphenyl selenide (**2**) was synthesized[16] from the reaction of **1** with chloroacetyl chloride in dioxane at 40°C. When **2** was refluxed with malononitrile in absolute ethanol in the presence of anhydrous potassium carbonate according to the Gewald method,[18] compound **3** was obtained. A ^{77}Se NMR peak at 463.8 ppm confirmed the presence of Se. The formation of **3** is assumed to proceed via alkylation of malononitrile followed by intramolecular cyclization.[19] The reaction of 3 with formamide yielded pyrrolo [2,3-d]pyrimidine derivative **4** (Scheme 1).



SCHEME 1 (a) $ClCOCH_2Cl$/dioxane; (b) $CH_2(CN)_2/K_2CO_3$; (c) $HCONH_2$.

The relative stability of the tautomers **3a** and **3b** were estimated from the calculated formation energies[20] (Figure 1). The keto form **3a** (ΔE = 48.2 kcal/mol) is more stable than enol form **3b** (ΔE = 57.2 kcal/mol), which is in agreement with ^{1}H NMR spectra, showing only a singlet of two protons from the CH_2 group of the pyrrole ring in **3a**.

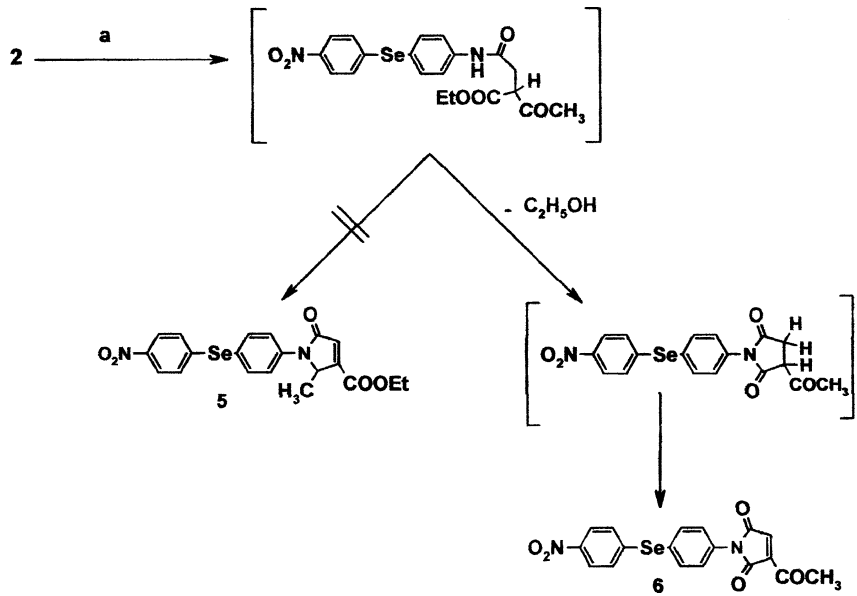


3a (keto) **3b** (enol)

ΔE = 48.2 kcal/mol ΔE = 57.2 kcal/mol

FIGURE 1 Tautomer energy calculation of Compound **3**.

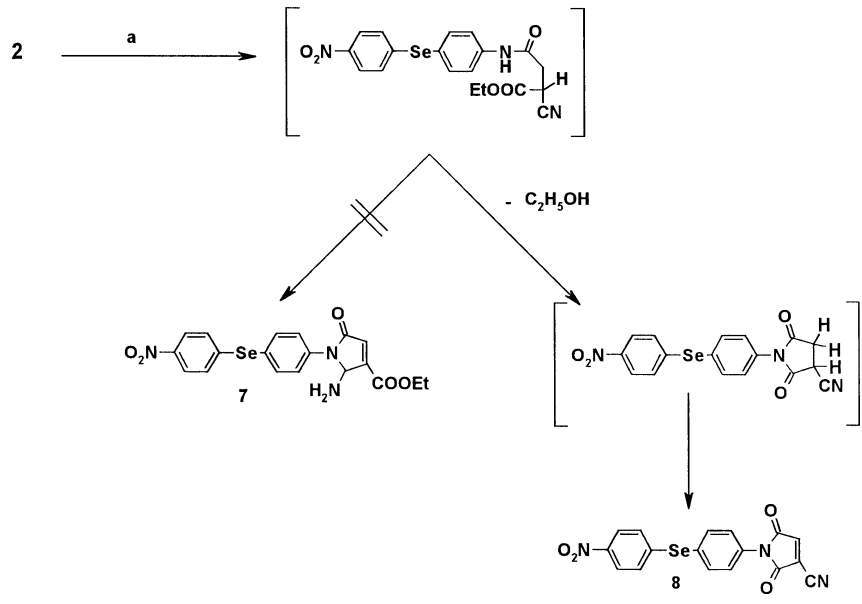
When compound **2** was reacted with ethyl acetoactate in refluxing DMF in the presence of anhydrous potassium carbonate, two possible structures, **5** and **6**, could be predicted. The structure of **5** was excluded on the basis of analytical and spectral data. In the ^{1}H NMR spectrum the OC_2H_5 fragment was not detected; only the singlet of the acetyl group was seen, which was also detected in the IR spectrum. The formation of compound **6** can be explained on the basis of an initial alkylation of ethyl acetoacetate followed by intramolecular cyclization to the intermediate dihydropyrrole, which is then oxidized[21] under the reaction condition to yield the novel pyrrole derivative **6** (Scheme 2).



SCHEME 2 (a) $H_2C(COOEt)(COCH_3)$.

In a similar manner, the reaction of ethyl cyanoacetate with compound **2** gave the pyrrole derivative **8**. The other possible compound **7** was discarded on the basis of analytical and spectral data (Scheme 3). The presence of selenium in **8** was detected at δ 453.9 ppm in the ^{77}Se NMR spectrum.

Despite the structural similarities of compound **2**, **3**, and **8**, the high sensitivity of ^{77}Se-NMR allowed an exact distinction of the compounds, (Table I).[22]



SCHEME 3 (a) $H_2C(COOEt)(CN)$.

BIOLOGICAL STUDIES

The newly synthesized compounds were screened for their antibacterial activity against *Bacillus cereus* and *Staphylococcus aureus* and for antifungal activity against *Candida albicans, Tricophyton rubrum*, and *Chrysosporium tropicum.* We used Chloramphenicol 5% for bacteria and Terbinafine 5% in the case of fungi as reference compounds. Compounds **2**, **3**, **6**, and **8** were tested using the disc-diffusion method[23,24]

TABLE I ^{77}Se NMR of Compounds 2, 3, and 8

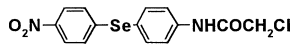
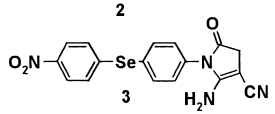
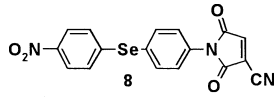
Compound structure	^{77}Se NMR (ppm)
 **2**	455.7
 **3**	463.8
 **8**	453.9

TABLE II Antimicrobial Sensitivity Test of Chemical Compounds (Expressed as Inhibition Zone in mm)

	Microbial species				
	G +ve bacteria		Fungal species		
Chemical compounds	*Bacillus cereus*	*Staphylococcus aureus*	*Candida albicans*	*Tricophyton rubrum*	*Chrysosporium tropicum*
2	8	9	—	—	—
3	8	10	—	—	—
6	—	—	—	—	—
8	10	10	—	—	—
*Reference compounds	**52**	**54**	**11**	**50**	**52**

*Reference compounds: *Chloramphenicol* 5% (bacteria), *Terbinafine* 5% (fungi).

All compounds were inactive against the three species of fungi tested and **6** was also inactive against bacteria. Compounds **2** and **3** showed weak activity against *Bacillus cereus.* Compound **3** showed moderate activity only against *Staphylococcus aureus*, whereas compound **8** showed moderate activity against two species of bacteria, *Bacillus cereus* and *Staphylococcus aureus*. The presence of the cyano group in compound **8** in addition to compound **3** is probably responsible for the moderate antibacterial activity.

by dissolving the individual compounds in DMSO to a solution of 5%. The results of the antibacterial and antifungal screening are presented in Table II.

CONCLUSION

The synthesized diphenyl selenide pyrrole derivatives **3**, **6**, and **8** and the diphenyl selenide derivative **2** have no antimycotic activity, whereas compounds **2**, **3**, and **8** act moderately against bacteria.

EXPERIMENTAL

The progress of reaction and the purity of the compounds were monitored by TLC. Melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus. Elemental analysis was performed on a Perkin Elmer 240C elemental analyzer; all of the results were in the range ±0.4%. IR spectra were recorded on a Pye-Unicam SP3-100 spectrophotometer using KBr wafer technique and MS spectra were recorded on a MS 902 instrument with EI ionization at 70 eV. ^{1}H NMR, ^{13}C NMR, and ^{77}Se NMR spectra (95 MHz) H decoupled, compound concentration 1% in $CDCl_3$ or DMSO with diphenyl diselenide 8% in $CDCl_3$ or DMSO as external standard ($\delta = 485$) corresponding to dimethylselenide ($\delta = 0$) were recorded on a Bruker Avance DRX 500

spectrometer at 25°C. The energy calculation of ground state equilibrium geometry was performed with AM1 in Spartan′02.[20]

4′-Nitro-4-chloroacetylaminodiphenyl Selenide (2)

4′-Nitro-4-chloroacetylaminodiphenyl selenide (**2**) was prepared as previously described[16] $C_{14}H_{11}ClN_2O_3Se$ (369.5) MS: m/z 370 [M^+, Se isotope pattern], IR: $\upsilon = 3290$ (NH); 1690 (C=O) cm^{-1} ; ^1H NMR ($CDCl_3$): $\delta = 4.2$ (s, 2H, CH_2); 7.3–8.0 (m, 8H, Ar-H); 8.5 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): 42.84, 120.98, 121.27, 121.57, 122.70, 123.98, 129.19, 129.37, 137.10, 137.21, 137.94, 144.07, 146.13, and 164.01. ^{77}Se NMR: $\delta = 455.7$ ppm.

4′-Nitro-4-(2-amino-3-cyano-4,5-dihydro-5-oxo-pyrrol-1-yl)-diphenyl Selenide (3)

4′-Nitro-4-(2-amino-3-cyano-4,5-dihydro-5-oxo-pyrrol-1-yl)-diphenyl selenide (**3**) was synthesized as described[16] $C_{17}H_{12}N_4O_3Se$ (399) MS: m/z 400 [M^+, Se isotope pattern]. IR: $\upsilon = 3490$–3380 (NH_2); 2200 (CN); 1710 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 3.5$ (s, 2H, CH_2); 6.8 (s, 2H, NH_2); 7.10–7.40 (m, 8H, Ar-H). ^{77}Se NMR: $\delta = 463.8$ ppm.

4′-Nitro-4-(4-amino-5,6-dihydro-6-oxo-pyrrolo[2,3-d]pyrimidin-7-yl)-diphenyl Selenide (4)

A solution of **3** (1 g, 0.0025 mol) in formamide (5 mL) was refluxed for 4 h. The solid obtained was recrystallized from dioxane, 0.55 g (52%); $C_{18}H_{13}N_5O_3Se$ (426), m.p. 250°C. IR: $\upsilon = 3420$–3350 (NH_2); 1690 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 3.45$ (s, 2H, CH_2); $\delta = 5.1$ (s, 2H,NH_2); $\delta = 7.10$–7.45 (m, 8H, Ar-H), 8.5 (s, 1H, pyrimidine-H).

4′-Nitro-4-(3-acetyl-2,5-dihydro-2,5-dioxo-pyrrol-1- yl)-diphenyl Selenide (6)

A mixture of **2** (1 g, 0.0027 mol) and ethyl acetoacetate (0.34 g, 0.0026 mol) in dimethylformamide (20 mL), containing anhydrous potassium carbonate (0.5 g), was heated under reflux for 2 h, left to cool, poured on to ice water, and neutralized by conc. HCl (pH = 7). Yellow crystals precipitated, recrystallized from ethanol, 0.7 g (56%); m.p. 140°C; $C_{18}H_{12}N_2O_5Se$ (415); MS: m/z 416 [M^+, Se isotope pattern]. IR: $\upsilon = 1710$ (C=O); 1720 ($COCH_3$) cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 3.42$ (s, 3H, CH_3); 6.8 (s, 1H, CH-pyrrole); 7.10–8.0 (m, 8H, Ar-H).

4′-Nitro-4-(3-cyano-2,5-dihydro-2,5-dioxo-pyrrol-1-yl)-diphenyl Selenide (8)

The compound was prepared in the same way as **6** using ethyl cyanoacetate instead of ethyl acetoacetate. Recrystallization from dioxane gave 0.53 g (50%); m.p. 120°C; $C_{17}H_9N_3O_4Se$ (398) MS: m/z 399 [M^+, Se isotope pattern]. IR: $\upsilon = 1710$ (C=O); 2200 (CN) cm^{-1}. ^{77}Se NMR: $\delta = 453.9$ ppm.

ANTIMICROBIAL SCREENING

The compounds were tested using the disc-diffusion method[23,24] with a 5% compound solution in DMSO. Filter paper discs (Whatman No. 3 filter paper, 5 mm diameter) were saturated with these solutions. The saturated filter paper discs were placed on the surface of solidified Nutrient agar dishes seeded by the test bacteria and Czapek·s Dox agar dishes seeded by the test fungi. The inhibition zones were measured in mm at the end of an incubation period of 48 h (at 37°C for the bacteria and 28°C for the fungi).

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