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Starting from readily available pyroglutamic esters **1**, some new 1,2,4-triazole-3-thione derivatives, bonded to a pyrrolidinone ring were synthesized and are characterized by their spectral data.

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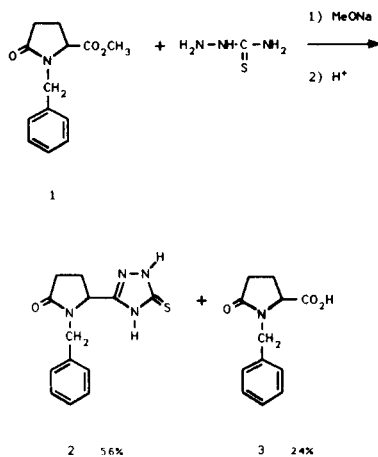
1,2,4-Oxadiazole-3-thione derivatives are reported to show a broad spectrum of biological activities. Some of these compounds have been shown to exhibit bactericide [1], fungicide [2], antiviral [3] and herbicide [4] properties. It is also reported in the literature that some 1,3,4-thiadiazoles linked to the nitrogen of a lactam type heterocycle possess phytosanitary activity [5]. These observations, and our interest in pyroglutamic acid chemistry [6], prompted us to undertake the synthesis of an, as yet, unreported series of 1,2,4-oxadiazole thione derivatives linked to a lactam ring with possible fungicide and herbicidal properties.

Three different reactions were used to obtain the starting materials 5-(5-oxo-2-pyrrolidinyl)-1,2,4-triazole-3-thione.

#### Method A (Scheme 1).

The condensation [7] of methyl *N*-benzylpyroglutamate (**1**) [8] with thiosemicarbazide and sodium methylate afforded compound **2a**, without isolation of intermediate acyl thiosemicarbazide. The cyclization produced water, thus a part of the ester was transformed into *N*-benzylpyroglutamic acid **3**. To limit this formation, a low boiling point solvent (methanol) was chosen to effect the reaction.

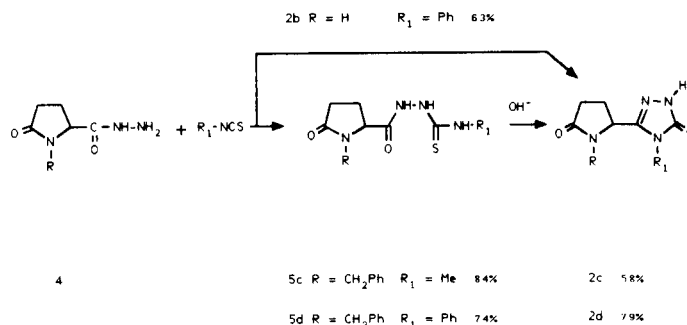
#### Scheme 1



#### Method B-C (Scheme 2).

The condensation [9] of hydrazides **4** [10] with isothiocyanates afforded the acyl thiosemicarbazides **5** which either spontaneously cyclized thermally to the triazole **2b** [11] (Method B) or had to be treated with alkali [12] to produce compounds **2c,d** (Method C).

#### Scheme 2



#### Method D (Scheme 3).

Aniline reacted rapidly, at high temperature, in a melt with oxadiazolethione **6** [10a] giving an acylthiosemicarbazide [13] which cyclized thermally to the triazolethione **2b** [11]. With *N*-methylaniline, the reaction product cannot be cyclized and acylthiosemicarbazide **5e** was obtained.

#### Scheme 3

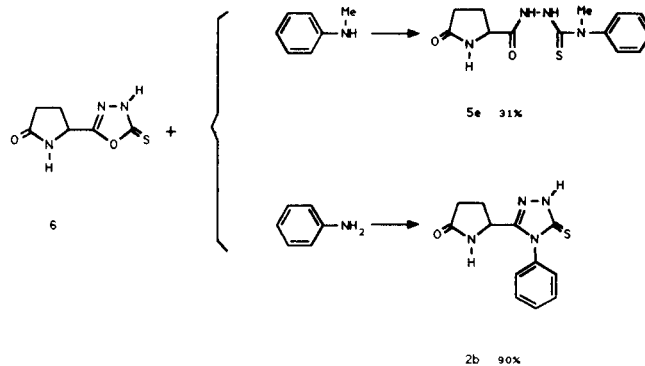


Table 1  
Physical Data of New Compounds

Compound No.	R	R <sub>1</sub>	R <sub>2</sub>	Yield % (method)	Reaction Time/°C	MP (°C) (Solvent)	Molecular formula	Analysis (%) Calcd./ (Found)
								C H N
2a	CH <sub>2</sub> Ph	H		57 (A)		>260 (MeOH)	C <sub>13</sub> H <sub>14</sub> N <sub>4</sub> O <sub>5</sub>	56.93 (56.99) 5.11 (5.18) 20.44 (20.44)
2b	H	Ph		63 (B) 90 (D)	13 h/80° 5 mm/180°	>260 (acetone/H <sub>2</sub> O)	C <sub>12</sub> H <sub>12</sub> N <sub>4</sub> O <sub>5</sub>	55.36 (55.55) 4.65 (4.68) 21.52 (21.30)
2c	CH <sub>2</sub> Ph	Me		58 (C, H <sub>2</sub> O/NaOH)	13 h/65°	206 (EtOH)	C <sub>14</sub> H <sub>16</sub> N <sub>4</sub> O <sub>5</sub>	58.32 (57.91) 5.59 (5.52) 19.43 (19.43)
2d	CH <sub>2</sub> Ph	Ph		79 (C, H <sub>2</sub> O/NaOH)	100°/2 h	260-262 (EtOH)	C <sub>19</sub> H <sub>18</sub> N <sub>4</sub> O <sub>5</sub>	65.12 (65.04) 5.17 (5.27) 15.98 (15.73)
5c	CH <sub>2</sub> Ph	Me		84 (C)	3 h/80°	198 (EtOH)	C <sub>14</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S	54.88 (54.64) 5.92 (6.00) 18.30 (18.54)
5d	CH <sub>2</sub> Ph	Ph		74 (C)	24 h/80°	132-134 (EtOH/H <sub>2</sub> O)	C <sub>19</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub> S 1/2H <sub>2</sub> O; 1/2EtOH	59.98 (60.01) 6.04 (5.92) 13.99 (14.02)
5e	H			31 (D)	5 mm/80°	182 (EtOH)	C <sub>13</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub> S	53.40 (53.02) 5.52 (5.28) 19.16 (19.55)
7a	H	Ph	Me	55 (E)	20 h/20°	178 (MeCN)	C <sub>14</sub> H <sub>14</sub> N <sub>4</sub> O <sub>5</sub>	56.91 (57.01) 5.14 (5.12) 20.42 (20.30)
7b	CH <sub>2</sub> Ph	H	Me	100 (E)	5 mm/20°	141 (CH <sub>2</sub> Cl <sub>2</sub> /ether)	C <sub>14</sub> H <sub>16</sub> N <sub>4</sub> O <sub>5</sub>	58.33 (58.06) 5.56 (5.48) 19.44 (19.42)
7c	CH <sub>2</sub> Ph	H	Et	85 (E)	1 h/20°	136 (MeOH/ether)	C <sub>15</sub> H <sub>18</sub> N <sub>4</sub> O <sub>5</sub>	59.60 (59.84) 5.96 (6.14) 18.54 (18.60)
7d	CH <sub>2</sub> Ph	H	Bu	46 (E)	24 h/20°	134 (MeOH/ether)	C <sub>17</sub> H <sub>22</sub> N <sub>4</sub> O <sub>5</sub>	61.81 (62.03) 6.67 (6.54) 16.97 (17.12)
7e	CH <sub>2</sub> Ph	Me	CH <sub>2</sub> CO <sub>2</sub> H	58 (E)	2 h/100°	150-151 (EtOH)	C <sub>16</sub> H <sub>18</sub> N <sub>4</sub> O <sub>3</sub> S 1/2H <sub>2</sub> O	54.27 (54.63) 5.39 (5.33) 15.76 (15.74)
8	CH <sub>2</sub> Ph	H		44	10 mm/20°	167-168 (MeOH/ether)	C <sub>14</sub> H <sub>16</sub> N <sub>4</sub> O <sub>3</sub> S	52.48 (52.32) 5.03 (5.16) 17.49 (17.38)

Table 2  
IR, UV and <sup>1</sup>H-NMR Spectral Data of New Compounds

Compound No.	IR (Nujol) cm <sup>-1</sup>	UV (MeOH) λ <sub>max</sub> (ε × 10 <sup>4</sup> )(nm)	<sup>1</sup> H-NMR (Solvent) (ppm)
<b>2a</b>	3100 (NH), 1660 (C=O), 1590, 1500 (C=C, C=N), 1320 (C=S)	203 (2), 255 (1.7)	(DMSO-d <sub>6</sub> ): 2.1-2.8 (m, 4H) 3.86 (d, J = 16.2 Hz, 1H), 4.74 (d, J = 16.2 Hz, 1H), 4.36-4.80 (m, 1H) 7-7.5 (m, 5H), 13-13.8 (s, broad, 1H) [a]
<b>2b</b>	3200 (NH), 1675 (C=O), 1595, 1555, 1500 (C=C, C=N), 1320 (C=S)	201 (1.4), 255 (1)	(Deuterium oxide with 5% NaOD): 1.7-2.5 (m, 4H), 4.5-4.8 (m, 1H), 7.1-7.7 (m, 5H)
<b>2c</b>	3100 (NH), 1660 (C=O), 1570, 1490 (C=C, C=N), 1320 (C=S)	204 (2.4), 255 (1.8)	(Deuteriochloroform with 5% DMSO-d <sub>6</sub> ): 1.8-2.8 (m, 4H), 3.28 (s, 3H), 3.97 (d, J = 14.7 Hz, 1H), 4.4-4.8 (m, 1H), 4.95 (d, J = 14.7 Hz, 1H), 6.0-7.5 (s, broad, 1H) [a], 6.9-7.6 (m, 5H)
<b>2d</b>	3130 (NH), 1645 (C=O), 1595, 1570, 1500, (C=C, C=N)	203 (2.6), 258 (1.3)	(Deuteriochloroform with 5% DMSO-d <sub>6</sub> ): 1.7-2.7 (m, 4H), 3.90 (d, J = 14.7 Hz, 1H), 4.2-4.7 (m, 1H), 5.12 (d, J = 14.7 Hz, 1H), 5.4-6.7 (s, broad, 1H) [a], 6.8-7.6 (m, 10H)
<b>5c</b>	3340-3160 (NH), 1700-1690, 1655 (C=O), 1370 (C=S)	204 (2.5), 243 (1.5)	(Deuterium oxide with 5% NaOD): 1.6-2.8 (m, 4H), 2.95 (s, 3H), 3.6-4.2 (m, 1H), 3.90 (d, J = 15 Hz, 1H), 7.1-7.4 (m, 5H) [b]
<b>5d</b>	3270 (NH), 1700-1675, 1645 (C=O), 1345 (C=S)	204 (3.6), 233 (1.3), 266 (1.4)	(Deuterium oxide with 5% NaOD): 1.6-2.4 (m, 2H), 2.4-2.9 (m, 2H), 3.87 (d, J = 15.2 Hz, 1H), 3.8-4.2 (m, 1H), 4.96 (d, J = 15.2 Hz, 1H), 6.8-7.7 (m, 10H) [c]
<b>5e</b>	3230 (NH), 1700, 1670 (C=O) 1595-1580 (C=C), 1350 (C=S)	203 (2.1), 252 (1.4)	(Deuteriochloroform with 5% DMSO-d <sub>6</sub> ): 2.2-2.7 (m, 4H), 3.62 (s, 3H), 4-4.4 (m, 1H), 7.38, 7.42 (s, 5H), 7.1-7.4 (s, broad, 1H) [a], 7.6-7.9 (s, broad, 1H) [a], 9.7-10 (s, broad, 1H) [a]
<b>7a</b>	3200 (NH), 1700 (C=O), 1650, 1590, 1510, 1490 (C=C, C=N)	204 (2), 240 (0.4)	(Deuteriochloroform): 2-2.5 (m, 4H), 2.62 (s, 3H), 4.4-4.9 (m, 1H), 7.2-7.7 (m, 5H), 7.2-7.7 (s, 1H) [a]
<b>7b</b>	3100 (NH), 1630 (C=O), 1525-1490 (C=C, C=N)	204 (2), 238 (0.4)	(Deuteriochloroform): 2.08-2.92 (m, 4H), 2.60 (s, 3H), 3.88 (d, J = 13.8 Hz, 1H), 4.90 (d, J = 13.8 Hz, 1H), 4.57-4.93 (m, 1H), 7.12 (s, 5H), 12 (s, 1H) [a]
<b>7c</b>	3100 (NH), 1645 (C=O), 1525 (C=C, C=N)	204 (2.1), 238 (0.4)	(Deuteriochloroform): 1.37 (t, J = 7.2 Hz, 3H) 2-2.9 (m, 4H), 3.17 (q, J = 7.2 Hz, 2H), 3.88 (d, J = 14.3 Hz, 1H), 4.90 (d, J = 14.3 Hz, 1H), 4.57-4.83 (m, 1H), 7.20 (s, 5H), 12.27 (s, 1H) [a]
<b>7d</b>	3100 (NH), 1640 (C=O), 1525 (C=C, C=N)	204 (2.1), 238 (0.4)	(Deuteriochloroform): 0.60-1.07 (m, 3H), 1.10-1.95 (m, 4H), 2.05-2.83 (m, 4H), 3.10 (t, J = 7.1 Hz, 2H), 3.86 (d, J = 15 Hz, 1H), 4.89 (d, J = 15 Hz, 1H), 4.53-4.90 (m, 1H), 7.97 (s, 5H), 12.8 (s, 1H) [a]
<b>7e</b>	1680 (C=O), 1490 (C=C, C=N) 1185 (C-O)	204 (2.1), 250 (0.3)	(Deuteriochloroform with 10% DMSO-d <sub>6</sub> ): 1.8-3 (m, 4H), 3.17 (s, 3H), 3.97 (s, 2H), 4.08 (d, J = 14.7 Hz, 1H), 4.75 (d, J = 14.7 Hz, 1H), 6.8-7.4 (m, 5H), 6.8-7.4 (s, 2H) [a]
<b>8</b>	1640 (C=O), 1585-1500 (C=C, C=N) 1150, 1325 (SO <sub>2</sub> )	201 (1.9)	(Deuteriochloroform with 10% DMSO-d <sub>6</sub> ): 2.07-2.83 (m, 4H), 3.20 (s, 3H), 3.81 (d, J = 15.2 Hz, 1H), 4.92 (d, J = 15.2 Hz, 1H), 4.73-4.93 (m, 1H), 7.17 (s, 5H), 11.5 (s, 1H) [a]

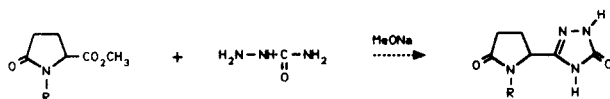
[a] These peaks disappear upon addition of deuterium oxide.

[b] Fifteen minutes after the addition of sodium deuterioxide, parts of the <sup>1</sup>H-nmr spectrum of **2c** appear.

[c] Solvated ethanol: 1.33 and 3.75 ppm.

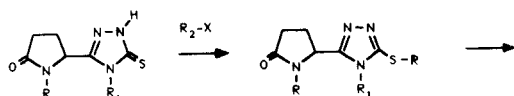
Following the method of Pesson and Dupin [14], we tried to obtain some 1,2,4-triazol-2-one by reacting pyrroglutamic esters with semicarbazide, but we never succeeded in purifying the very insoluble products obtained (Scheme 4).

Scheme 4



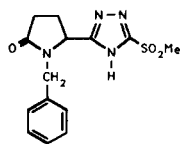
The thioethers **7** were prepared by reaction of thione **2** and appropriate alkyl halides in sodium hydroxyde [11a], lower yields being obtained in alcoholic sodium ethylate [15]. The sulfone **8** was prepared by reaction of thione **7b** with potassium permanganate in aqueous sulfuric acid (44%); for this compound, erratic results were obtained when performing the reaction in acetic acid, with potassium permanganate [16,11b] or hydrogen peroxide [11b], by using potassium permanganate in excess, or activated with copper sulfate [17].

Scheme 5



2

7a	R = H	R <sub>1</sub> = Ph	R <sub>2</sub> = Me
b	R = CH <sub>2</sub> Ph	R <sub>1</sub> = H	R <sub>2</sub> = Me
c	R = CH <sub>2</sub> Ph	R <sub>1</sub> = H	R <sub>2</sub> = Et
d	R = CH <sub>2</sub> Ph	R <sub>1</sub> = H	R <sub>2</sub> = n-Bu
e	R = CH <sub>2</sub> Ph	R <sub>1</sub> = Me	R <sub>2</sub> = CH <sub>2</sub> CO <sub>2</sub> H



8

The physical properties and yields for the new compounds are given in Table I. All the newly synthesized compounds gave satisfactory spectral data, and the structures, particularly the position of the alkylations, were assigned on the results of the oxidation reaction and on the basis of elemental analysis, uv (methanol), ir (nujol) and <sup>1</sup>H nmr spectral data, given in Table 2.

New compounds were tested *in-vitro* against a variety of fungi; the antitumor effects of these products were tested *in-vivo* against P-388 leukemia in mice, according to a typical NCI protocol [18]. These compounds have no activity under the testing conditions.

## EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a "Perkin-Elmer 700" spectrometer, the nmr spectra on a "Hitachi Perin-Elmer R-600" at 60 MHz, using tetramethylsilane as an internal reference, and the uv spectra on "Beckman uv 5240" (10<sup>-4</sup> mole l<sup>-1</sup>, in methanol). Elemental analyses were performed by the "Central Microanalytical Department" of CNRS in Vernaison, France.

5-(5-Oxo-1-benzyl-2-pyrrolidiny)-1,2,4-triazole-3-thione (**2a**) (Method A).

Methyl 1-benzylpyrroglutamate [8] (25 g, 0.107 mole) and sodium methoxide (7.02 g, 0.13 mole) were dissolved in methanol (150 ml). The mixture was refluxed for 6 hours. The solid which precipitated after cooling was filtered away (thiosemicarbazide, 2.25 g, 22.5%). Hydrochloric acid was added to the remaining solution (pH 6). After filtration, a yield of 57% of triazole **2a** was obtained. Hydrochloric acid was added to the solution (pH 1). After filtration, *N*-benzylpyrroglutamic acid (5.6 g, 24%, mp 122°) was obtained (mp lit [8] 123°).

4-Phenyl-5-(5-oxo-2-pyrrolidiny)-1,2,4-triazole-3-thione (**2b**) (Method B).

A mixture of pyrroglutamic hydrazide [10] (40 g, 0.29 mole), phenyl isothiocyanate (52.3 g, 0.39 mole) and ethanol (200 ml) was heated under reflux for 13 hours. The triazole which precipitated after cooling was filtered and recrystallized from acetone/water (50/50). The yield was 63%.

1-(1-Benzylpyrroglutamoyl)-4-methyl thiosemicarbazide (**5c**), and 4-Methyl-5-(5-oxo-1-benzyl-2-pyrrolidiny)-1,2,4-triazole-3-thione (**2c**) (Method C).

A mixture of 1-benzylpyrroglutamic hydrazide (50 g, 0.21 mole), methyl isothiocyanate (15 g, 0.21 mole) and ethanol (200 ml) was heated under reflux for 3 hours. The acylthiosemicarbazide **5c** which precipitated after cooling was filtered and recrystallized from ethanol (yield 84%).

A mixture of acylthiosemicarbazide **5c** (30.5 g, 0.10 mole), sodium methylate (7 g, 0.13 mole) and methanol (150 ml) was heated under reflux for 13 hours. The excess solvent was removed by vacuum evaporation, and the residue was dissolved in water and acidified with hydrochloric acid. The triazole **2c** was filtered and recrystallized from ethanol.

The acylthiosemicarbazide **5d** (solvent: 1/2 water: 1/2 ethanol) was obtained following the same procedure as for **5c**. The triazole **2d** was obtained by heating 0.054 mole of compound **5d** in sodium hydroxide (2*N*, 275 ml).

4-Phenyl-5-(5-oxopyrrolidiny)-1,2,4-triazole-3-thione (**2b**) (Method D).

A mixture of oxadiazole **6** [10a] (18.5 g, 0.10 mole) and aniline (30 ml) was refluxed. After cooling, ether was added then the precipitate was recrystallized from water. The resulting compound was the same as for method B.

1-Pyrroglutamoyl-4-methyl-4-phenyl Thiosemicarbazide (**5e**).

This compound was obtained following method D, by using *N*-methylaniline at 150°.

3-Alkylthio-1,2,4-triazoles (**7a-e**) (Method E).

A mixture of thione **2** (0.02 mole), sodium hydroxide (0.02 mole

for **7a-d**, 0.04 mole for **7e**) and the appropriate alkyl halide (0.021 mole) was stirred in 100 ml of water (time and temperature, see Table 1). The resulting thioether was collected by filtration or extraction with methylene chloride (acidification with hydrochloric acid for **7e**), dried and recrystallized from suitable solvent.

5-(5-Oxo-1-benzyl-2-pyrrolidinyl)-3-methylsulfonyl-1,2,4-triazole (**8**).

A solution of potassium permanganate (5.5 g, 0.035 mole in water (80 ml) was dropped into a solution of thioether **7b** (5 g, 0.017 mole) in water (10 ml) and sulfuric acid (2 ml). After 10 minutes, the mixture was discolored with sodium bisulfite. The resulting triazole was treated with Darco in methanol and crystallized from ether.

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