# Studies on Pyrrolidinones. Synthesis of 2-(5-Oxo-2-pyrrolidinyl)-1,3,4-oxadiazoles and 2-(5-Oxo-2-pyrrolidinyl)benzimidazoles [1]

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The condensation of pyroglutamic acids with 1,2-phenylenediamine leads to 2-(5-oxo-2-pyrrolidinyl)benzimidazoles and the cyclization of disilylated diacylhydrazines derived from the same acids gives 2-(5-oxo-2-pyrrolidinyl)-1,3,4-oxadiazoles. These compounds show weak antifungal activity.

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1,3,4-Oxadiazole derivatives have been reported to show a broad range of biological activities [2]; for example, compound **1**, a bioisotere of carbamate **3**, is a potent fungicide [3]. Interestingly, benzimidazoles **2** [4] and **3** [5] also show fungicide properties. On the other hand, many pyrrolidinones such as **4** [6], **5** [7], and **6** [8] have been reported to be active in the same field. These observations prompted us to study the synthesis of products **7** and **8**, which possess a lactam ring linked to an oxadiazole or a benzimidazole ring, with a view to comparing their biological properties.

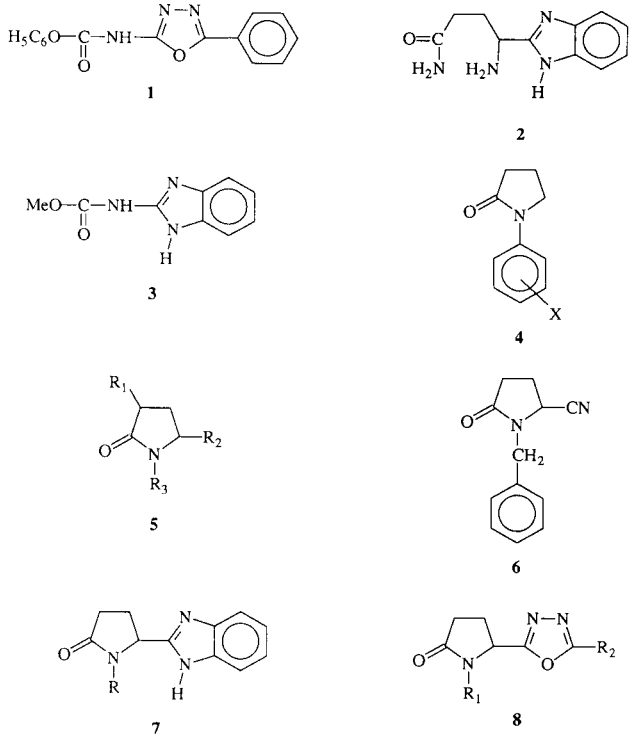
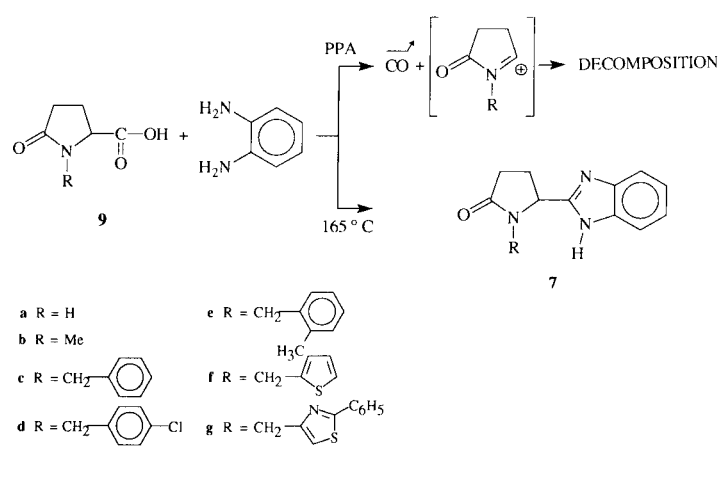



FIGURE 1

A - Benzimidazoles **7**.

In a first attempt to obtain these benzimidazoles, pyroglutamic acids **9** [9] and *o*-phenylenediamine were heated in polyphosphoric acid, but a decarbonylation occurred giving rise to acyliminium salts [10]. However, by heating (165-220°) a melt of the pyroglutamic acids **9** in *o*-phenylenediamine [11], a blue color, turning yellow at the end of the reaction was observed and compounds **7** were obtained in fair yields (Scheme 1).

Scheme 1




Physical properties of the benzimidazoles **7** are reported in Tables 1 and 2.

Table 1

Synthesis s of Benzimidazoles **7**

| Nb | R | M.p., °C (Solvent) | Reaction Time (Minutes) 165° | 220° | Yield, [a] % | Formula | Analysis, % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| **7a** | H | > 260 $C_2H_5OH$ | 20 | 60 | 93 | $C_{11}H_{11}N_3O$ | 65.66<br>65.27 | 5.51<br>5.72 | 20.88<br>20.96 |
| **7b** | $CH_3$ | > 260 $C_2H_5OH/H_2O$ | 120 | 25 | 57 | $C_{12}H_{13}N_3O$ | 66.96<br>66.59 | 6.09<br>5.85 | 19.52<br>19.86 |
| **7c** | $CH_2$-Ph | 239 $C_2H_5OH$ | 45 | 15 | 65 | $C_{18}H_{17}N_3O$ | 74.21<br>74.02 | 5.88<br>6.17 | 14.42<br>14.52 |
| **7d** | $CH_2$-Ph-*p*-Cl | 215 $C_2H_5OH/H_2O$ | 150 | 40 | 58 | $C_{18}H_{16}N_3OCl$ | 66.36[b]<br>65.80 | 4.95<br>4.98 | 12.90<br>12.58 |
| **7e** | $CH_2$-Ph-*o*-$CH_3$ | 263 $C_2H_5OH/H_2O$ | 120 | 20 | 64 | $C_{19}H_{19}N_3O$ | 74.73<br>74.53 | 6.27<br>6.34 | 13.76<br>13.58 |
| **7f** | $CH_2$-$C_4H_3S$ | 190 $CH_3CN$ | 30 | 10 | 45 | $C_{16}H_{15}N_3OS$ | 64.62<br>64.54 | 5.08<br>5.06 | 14.13<br>14.23 |
| **7g** | $CH_2$-$C_3HNS$-Ph | 233 $CH_3OH/H_2O$ | 150 | 15 | 53 | $C_{21}H_{18}N_4OS$ | 67.36<br>67.29 | 4.85<br>4.80 | 14.96<br>15.02 |

[a] Crude Yield; [b] we did not succeed in obtaining a better analysis.

Table 2

Spectral Properties of Benzimidazoles **7**

| Nb | R | IR (nujol) $cm^{-1}$ | $^1H$ NMR (Solvent) ppm |
|---|---|---|---|
| **7a** | H | 1595 (C=C arom.); 1690 (C=O); 3180-3400 (N-H) | (DMSO $d_6$): 2.0-2.6 (m, 4H); 4.7-5.0 (m, 1H), 7.0-7.7 (m, 4H); 8.10 (s, 1H); 8.40 (s, 1H) |
| **7b** | $CH_3$ | 1590 (C=C arom.); 1690 (C=O) | (DMSO $d_6$): 2.0-2.9 (m, 4H); 2.65 (s, 3H); 4.7-5.2 (m, 1H); 7.0-7.6 (m, 4H); 8.50 (s, 1H) |
| **7c** | $CH_2$-Ph | 1590 (C=C arom.); 1690 (C=O) | ($CDCl_3$): 2.0-2.9 (m, 4H); 3.70 (d, J = 14.9 Hz, 1H); 4.8-5.1 (m, 1H); 5.05 (d, J = 14.9 Hz, 1H); 6.9-7.8 (m, 9H); 9.9 (s, 1H) |
| **7d** | $CH_2$-Ph-*p*-Cl | 1595 (C=C arom.); 1695 (C=O) | ($CDCl_3$): 2.1-2.9 (m, 4H); 3.67 (d, J = 14.4 Hz, 1H); 5.06 (d, J - 14.4 Hz, 1H); 4.8-5.15 (m, 1H), 7.1-8.0 (m, 9H) |
| **7e** | $CH_2$-Ph-*o*-$CH_3$ | 1595-1600 (C=C arom.); 1690 (C=O) | ($CDCl_3$): 2.21 (s, 3H); 2.3-2.9 (m, 4H); 3.9 (d, J = 14.8 Hz, 1H); 4.9-5.2 (m, 1H); 5.1 (d, J = 14.8 Hz, 1H); 6.9-7.9 (m, 9H) |
| **7f** | $CH_2$-$C_4H_3S$ | 1590 1605 (C=C arom.); 1690 (C=O) | ($CDCl_3$): 2.0-2.8 (m, 4H); 4.01 (d, J = 15.0 Hz, 1H); 5.15 (d, J = 15.0 Hz, 1H); 4.8-5.2 (m, 1H); 6.85 (s, 1H); 6.92 (s, 1H); 7.1-7.5 (m, 4H); 7.5-7.9 (m, 2H) |
| **7g** | $CH_2$-$C_3HNS$-Ph | 1595-1610 (C=C arom. ); 1700 (C=O) | ($CDCl_3$): 2.1-2.7 (m, 4H); 4.31 (d, J = 15.0 Hz, 1H); 4.81 (d, J = 15.0 Hz, 1H); 5.0-5.3 (m, 1H); 7.1-7.4 (m, 4H); 7.8-8.1 (m, 2H) |

Table 3

Physical Properties of New Pyroglutamic Hydrazides **12** and Diacylhydrazines **10**

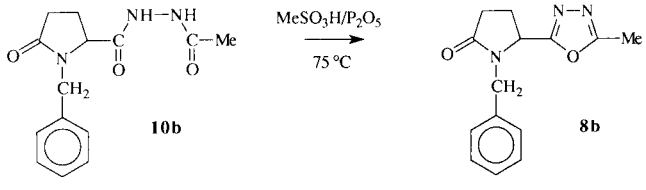
| Nb | $R_1$ | $R_2$ | M.p., °C | Yield, % | Formula | Analysis, % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|---|
| **12c** | $CH_2$-Ph-*o*-Cl | | [a] | 96[b] | $C_{12}H_{14}N_3O_2Cl$ | [a] | [a] | [a] |
| **12d** | $CH_2$-Ph-*p*-$CH_3$ | | 152 | 98[b] | $C_{13}H_{17}N_3O_2$ | 63.12<br>63.37 | 6.93<br>7.03 | 16.99<br>16.74 |
| **10a** | $CH_3$ | $CH_3$ | 172 | 89[b] | $C_8H_{13}N_3O_3$ | 48.22<br>48.06 | 6.58<br>6.69 | 21.10<br>21.09 |
| **10c** | $CH_2$-Ph | $CH_2$-O-Ph-*p*-Cl | 175 | 75[b] | $C_{20}H_{20}N_3O_4Cl$ | 59.83<br>59.88 | 5.03<br>5.07 | 10.47<br>10.31 |
| **10d** | $CH_2$-Ph | Ph-3,4,5-$(OCH_3)_3$ | 160 | 46 | $C_{22}H_{25}N_3O_6$ | 61.82<br>61.51 | 5.90<br>5.97 | 9.83<br>10.14 |
| **10e** | $CH_2$-Ph | Ph-*p*-Cl | 144 | 67 | $C_{19}H_{18}N_3O_3Cl.H_2O$ | 58.54<br>58.22 | 5.17<br>5.14 | 10.78<br>10.60 |
| **10f** | $CH_2$-Ph-*o*-Cl | $CF_3$ | 208 | 72[b] | $C_{14}H_{13}N_3O_3F_3Cl$ | 46.23<br>46.19 | 3.60<br>3.55 | 11.55<br>11.46 |
| **10g** | $CH_2$-Ph-*p*-$CH_3$ | $CH_2$-$C_4H_3S$ | 210 | 77[b] | $C_{19}H_{21}N_3O_3S$ | 61.44<br>61.44 | 5.70<br>5.78 | 11.31<br>11.27 |

[a] Hygroscopic, not purified before next step; [b] Crude yield.

B - Oxadiazole **8**.

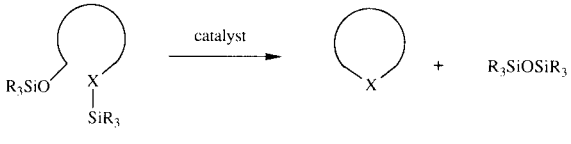
To date, the main reaction used for the synthesis of 1,3,4-oxadiazoles is the dehydration of diacylhydrazines, performed either thermally [12], or with the aid of an acidic dehydrating agent, such as sulfuric acid [13], acetic anhydride [14], phosphorus oxychloride [15], polyphosphoric acid (PPA) [16], or polyphosphate ester (PPE) [17]. In the pyroglutamic acid series, we have previously shown [18] that the best dehydrating agent for the synthesis of oxadiazole **8b** is the mixture methanesulfonic acid/phosphoric anhydride (Scheme 2).

Scheme 2



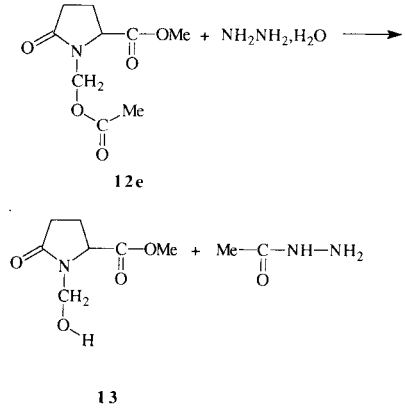

In this work, we chose to use the heterocyclization induced by silyl groups, recently developed in our laboratory (Scheme 3) [19], because these reactions can accommodate acid sensitive compounds, and because an aqueous treatment is not required; this method generally gives very good yields in the synthesis of oxadiazoles, and can be realized by using very different catalysts such as triflic acid, iron trichloride, fluoride ion, palladium over carbon, or azaisobutyronitrile [20].

Scheme 3




The starting materials, diacylhydrazines **10a-g** were prepared by reaction of the pyroglutamic hydrazides **12a-e** with acetic anhydride, or acyl chlorides, as already reported for diacylhydrazine **10b** [18]. The hydrazides **12a-d** were obtained from the action of hydrazine monohydrate on pyroglutamic esters **11a-d** (Scheme 4) [21] as previously described for the preparation of hydrazides **12a-b** [21a-b]. Interestingly, the reaction of hydrazine monohydrate with acetate **12a** [22] at 0° only afforded methyl *N*-hydroxymethylpyroglutamate **13** [22] and acetic hydrazide (Scheme 5).

Scheme 5




Physical properties of the new compounds **10** and **12** are reported in Tables 3 and 4; some hydrazides **10** are highly hygroscopic and have been acylated without complete purification.

Scheme 6 shows the synthesis of oxadiazoles **8**. The cyclization was performed one-pot by refluxing the diacylhydrazines **10** in hexamethyldisilazane (HMDS), in the presence of tetrabutylammonium fluoride or trifluoromethanesulfonic acid. In cases where formation of the intermediate

Scheme 4

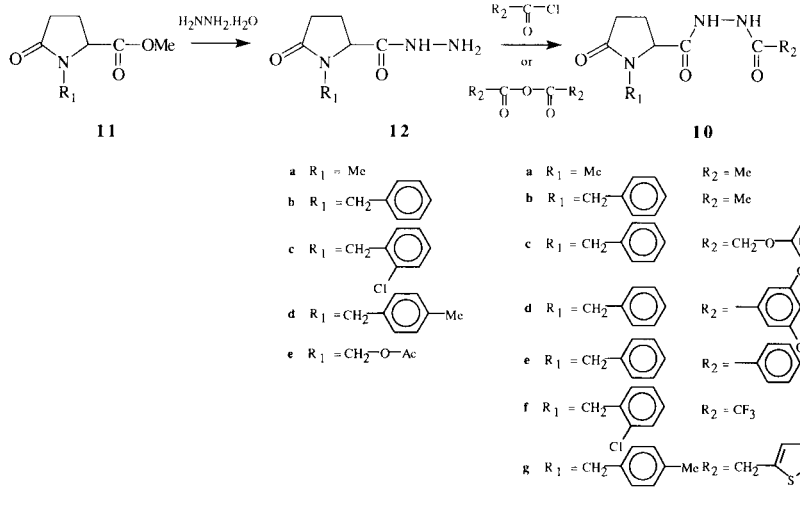


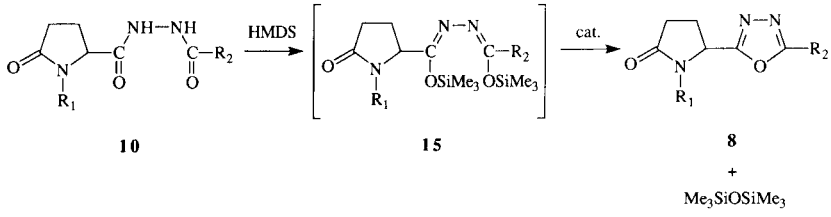
Table 4

Spectral Properties of New Pyroglutamic Hydrazides **12** and Diacylhydrazines **10**

| Nb | $R_1$ | $R_2$ | IR (nujol) $cm^{-1}$ | $^1H$ NMR (Solvent) ppm |
|---|---|---|---|---|
| **12c** | $CH_2$-Ph-*o*-Cl | | 1655-1685 (C=O); 3290 (N-H) | ($CDCl_3$): 1.29 (s, 2H) [a]; 1.9-2.95 (m, 4H); 2.3-1.8 (m, 1H) [a]; 3.75-4.15 (m, 1H); 4.23 (d, J = 14.9 Hz, 1H); 4.96 (d, J = 14.9 Hz, 1H); 7.26 (s, 4H) |
| **12d** | $CH_2$-Ph-*p*-$CH_3$ | | 1655-1685 (C=O); 3260-3300 (N-H) | ($CDCl_3$): 1.7-2.8 (m, 4H); 2.29 (s, 3H); 3.78 (d, J=14.4Hz, 1H); 3.95 (m, 1H); 3.1-5.3 (m, 2H); 4.96 (d, J = 14.4 Hz, 1H); 6.9-7.3 (m, 1H) [a]; 7.07 (s, 4H) |
| **10a** | $CH_3$ | $CH_3$ | 1655-1700-1710 (C=O); 3200 (N-H) | ($CDCl_3$/$DMSOd_6$; 70/30): 1.55-2.45 (m, 4H); 1.95 (s, 3H); 2.74 (s, 3H); 4.0-4.35 (m, 1H) |
| **10c** | $CH_2$-Ph | $CH_2$-O-Ph-*p*-Cl | 1490-1510 (C=C arom.); 1690 (C=O); 3050-3175 (N-H) | ($CDCl_3$): 2.0-2.6 (m, 4H); 3.8-4.15 (m, 1H);3.91 (d, J = 14.8 Hz, 1H); 4.50 (s, 2H); 5.09 (d, J = 14.8 Hz, 1H); 6.86 (d, J = 9.0 Hz, 2H); 7.22 (s, 5H); 7.26 (d, J = 9.0 Hz, 2H); 8.2-9.7 (m, 2H) [a] |
| **10d** | $CH_2$-Ph | Ph-3,4,5-$(OCH_3)_3$ | 1140 (C-O); 1600-1540-1515 (C=C arom.); 1715-1675 (C=O); 3260 (N-H) | ($CDCl_3$): 2.0-2.7 (m, 4H); 3.83 (s, 3H); 3.91 (s, 6H); 3.7-4.1 (m, 1H); 3.91 (d, J = 15.0 Hz, 1H); 5.08 (d, J = 15.0 Hz, 1H); 7.25-7.50 (m, 7H) |
| **10e** | $CH_2$-Ph | Ph-*p*-Cl | 1485-1510 (C=C arom.); 1625-1655-1690-1710 (C=O); 3215-3420 (N-H) | ($CDCl_3$): 1.5-2.7 (m, 4H); 3.82 (d, J = 15.3 Hz, 1H); 3.9-4.25 (m, 1H); 5.01 (d, J = 15.3 Hz, 1H); 7.13 (s, 5H); 7.28 (d, J = 8.6 Hz, 2H); 7.68 (d, J = 8.6 Hz, 2H); 9.8-10.3 (m, 2H) [a] |
| **10f** | $CH_2$-Ph-*o*-Cl | $CF_3$ | 1670-1685-1755 (C=O); 3180-3260 (N-H) | ($CD_3OD$): 1.95-2.6 (m, 4H); 3.9-4.25 (m, 1H); 4.07 (d, J = 15.0 Hz, 1H); 5.09 (d, J = 15.0 Hz, 1H); 7.33 (s, 4H) |
| **10g** | $CH_2$-Ph-*p*-$CH_3$ | $CH_2$-$C_4H_3S$ | 1630-1660-1710 (C=O); 3160-3210 (N-H) | ($CDCl_3$/$DMSOd_6$; 70/30): 1.9-2.5 (m, 4H); 2.36 (s, 3H); 3.81 (d, J = 14.9 Hz, 1H); 3.84 (s, 2H); 3.9-4.25 (m, 1H); 5.05 (d, J = 14.9 Hz, 1H); 6.8-7.3 (m, 7H) |

(a) These peaks disappear upon addition of deuterium oxide.

Scheme 6




**10** **15** **8** + $Me_3SiOSiMe_3$

disilylated compound **14** was more difficult to achieve, imidazole was added to the reaction medium; this catalyst yields *in situ* to *N*-trimethylsilylimidazole, a very potent silylating agent [23].

Although the yields in oxadiazoles are generally good, oxadiazole **8g** formed after refluxing for 36 hours could not be purified; oxadiazoles **8e** and **8f** have not been obtained under these one-pot conditions. We studied more precisely the reaction conditions and catalysts for compound **8e**:

-addition of a solvent, chlorobenzene, allowed the solubilization of the diacylhydrazine **10e** and thus made the silylation easier; by use of trimethylsilyl trifluoromethanesulfonate or tetrabutylammonium fluoride, oxadiazole **8e** was thus obtained in 33 and 69% yield, respectively.

-disilylated compound **14e** could be obtained by reflux of the diacylhydrazine **10e** with chlorotrimethylsilane in triethylamine; it has been thermally cyclized (200-250°) under vacuum during a distillation attempt, affording the oxadiazole **8e** in 62% yield.

Refluxing the diacylhydrazine **10f** in HMDS in the presence of a catalytic amount of tetrabutylammonium fluoride only yielded the bis-silyl derivative **14f**. Cyclization of this isolated intermediate could be achieved by reflux with trifluoromethanesulfonic acid as a catalyst giving the oxadiazole **8f** in 70% yield.

In order to obtain oxadiazoles in one step from the corresponding pyroglutamic derivatives, we considered the action of a carboxylic acid on a pyroglutamic hydrazide in the presence of a silylating agent and a cyclization catalyst. This was tried with compound **10d** (HMDS/165°/several hours) but, although a mixture of silylated compounds was obtained, methanolysis only yielded the starting materials.

Table 5

Synthesis of Oxadiazoles **8**

| Nb | $R_1$ | $R_2$ | M.p., °C (solvent) | B.p. °C (mm) | Reaction Time (hours) | Purification Method [a] | Yield % | Formula | Analysis, % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **8a** | $CH_3$ | $CH_3$ | 80 $CH_2Cl_2$ | 145 (0.25) | 30 | A | 81 | $C_8H_{11}N_3O_2$ | 53.03 | 6.12 | 23.19 |
| | | | | | | | | | 52.93 | 6.12 | 22.86 |
| **8b** | $CH_2$-Ph | $CH_3$ | 86[b] $CH_3OH$ | 180 (0.15) | 48 | A | 75 | | | | |
| **8c** | $CH_2$-Ph | $CH_2$-O-Ph-*p*-Cl | 109 $C_2H_5OH$ | | 21 | B | 63 | $C_{20}H_{18}N_3O_3Cl$ | 62.58 | 4.73 | 10.95 |
| | | | | | | | | | 62.28 | 4.50 | 10.98 |
| **8d** | $CH_2$-Ph | Ph-3,4,5-$(OCH_3)_3$ | 127 $C_2H_5OH$ | | 3 | C | 83 | $C_{22}H_{23}N_3O_5$ | 64.54 | 5.66 | 10.26 |
| | | | | | | | | | 64.57 | 5.63 | 10.14 |
| **8e** | $CH_2$-Ph | Ph-*p*-Cl | 138 $C_2H_5OH$ | | 24 | D | 69 | $C_{19}H_{16}N_3O_2Cl$ | 64.50 | 4.56 | 11.88 |
| | | | | | | | | | 64.63 | 4.36 | 11.88 |
| **8f** | $CH_2$-Ph-*o*-Cl | $CF_3$ | oil | 150 (0.20) | 3[c] | A | 81[d] | $C_{14}H_{11}N_3O_2F_3Cl$ | 48.64 | 3.21 | 12.15 |
| | | | | | | | | | 48.88 | 3.45 | 12.01 |

[a] A = Vacuum Distillation; B = Crystallization from Ethanol; C = Crystallization from Ethanol and Activated Charcoal Workup; D = Crystallization from Chlorobenzene. [b] Lit [18] 86°. [c] Catalyst: $CF_3SO_3H$. [d] From the corresponding Bis Trimethylsilyl Diacyl Hydrazide

Table 6

Spectral Properties of New Oxadiazoles **8**

| Nb | $R_1$ | $R_2$ | IR (nujol) $cm^{-1}$ | $^1H$ NMR ($CDCl_3$) ppm |
|---|---|---|---|---|
| **8a** | $CH_3$ | $CH_3$ | 1585 (C=N); 1685 (C=O) | 2.15-2.75 (m, 4H); 2.55 (s, 3H); 2.81 (s, 3H); 4.7-5.0 (m, 1H) |
| **8c** | $CH_2$-Ph | $CH_2$-O-Ph-*p*-Cl | 1440-1450-1580 (C=C arom.); 1605 (C=N) | 1.95-2.9 (m, 4H); 4.16 (d, J = 14.6 Hz, 1H); 4.69 (d, J = 14.6 Hz, 1H); 4.65-5.0 (m, 1H); 5.07 (s, 2H); 6.7-7.55 (m, 4H); 7.20 (s, 5H) |
| **8d** | $CH_2$-Ph | Ph-3,4,5-$(OCH_3)_3$ | 1125 (C-O); 1490-1570 (C=C arom.); 1590 (C=N); 1665 (C=O) | 2.2-2.5 (m, 4H); 3.93 (s, 9H); 4.17 (d, J = 14.8 Hz, 1H); 4.75-5.0 (m, 1H); 4.80 (d, J = 14.8 Hz); 7.13 (s, 2H); 7.18 (s, 5H) |
| **8e** | $CH_2$-Ph | Ph-*p*-Cl | 1490-1565 (C=C arom.); 1590 (C=N); 1685 (C=O) | 2.1-2.95 (m, 4H); 4.27 (d, J = 14.5 Hz, 1H); 4.7-5.05 (m, 1H); 4.71 (d, J = 14.5 Hz, 1H); 7.18 (s, 5H); 7.47 (d, J = 9 Hz, 2H); 7.83 (d, J = 9 Hz, 2H) |
| **8f** | $CH_2$-Ph-*o*-Cl | $CF_3$ | 1475-1560 (C=C, arom.); 1585 (C=N); 1705 (C=O) | 2.1-2.8 (m, 4H); 4.48 (d, J = 15.7 Hz, 1H); 4.88 (d, J = 15.7 Hz, 1H); 4.7-5.1 (m, 1H); 7.22 (s, 4H) |

Physical properties of the new oxadiazoles **8** are reported in Tables 5 and 6.

Antifungic activities of the various products prepared was tested *in vitro*, against the following fungi: *Rhyzoctonia solani, Botrytis cinerea, Phytophtora infestans, Fusarium oxysporum, Colletotrichum lindemuthianum, Phaeosphaeria nodorum, Cercosporella herpotrichoïdes,* and *Ustilago zeae.*

(5-Oxo-2-pyrrolidinyl)-1,3,4-oxadiazoles show more antifungic activity than 2-(5-oxo-2-pyrrolidinyl)benzimidazoles, although it is still weak. The more potent compound we synthesized in these series is oxadiazole **8e**. Intermediate compounds (pyroglutamic esters, hydrazides and diacylhydrazines) were also screened and in general they have very weak properties.

Antitumor activity was also looked for in these compounds, but unsuccessfully [24].

## EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a Perkin Elmer 700 spectrometer, the nmr spectra on a Hitachi Perkin Elmer R-600 at 60 MHz, using tetramethylsilane as an internal reference. Elemental analyses were performed by the Central Microanalytical Department of CNRS in Thiais, France.

### Benzimidazoles **7a-g**.

All the benzimidazoles **7a-g** were prepared according to the same procedure for which a typical example is given below (see also the reaction time and yields in Table 1). Physical properties (mp, ir, nmr) and the elemental analysis are given in Tables 1 and 2.

2-[*N*-(4-Chlorobenzyl)-5-oxo-2-pyrrolidinyl]benzimidazole (**7d**).

A mixture of 2.4 g (9.26 mmoles) of *N*-(4-chlorobenzyl)pyroglutamic acid (**9d**) and 1.0 g (9.26 mmoles) of *o*-phenylenediamine was heated at 165° for 2.5 hours (the reaction medium became blue), and then at 220° for 40 minutes (the reaction medium became yellow). After cooling, the residue was dissolved in ethanol, and dichloromethane was added. The mixture was neutralized with diluted sodium hydroxide, washed with water, dried over sodium sulfate, worked up with activated charcoal and crystallized with ether (58% crude yield). The residue was recrystallized from a mixture water/ethanol for analysis.

Pyroglutamic Hydrazides **12a-e**.

All the pyroglutamic hydrazides **12a-e** were prepared according to the same procedure for which a typical example is given below. Physical properties (mp, ir, nmr) and the elemental analysis of the new compounds are given in Tables 3 and 4.

[*N*-(4-Methylbenzyl)pyroglutamoyl]hydrazine (**12d**).

Hydrazine monohydrate (7.9 g, 155 mmoles) was slowly added with cooling to a solution of 25.0 g (101 mmoles) of methyl *N*-(4-methylbenzyl)pyroglutamate in 50 ml of methanol. The solution was refluxed for 3 hours and filtered. The filtrate was concentrated and filtered. The solids were combined (24.7 g, 98% yield) and used without further purification for the next step. A small amount of this product was recrystallized from ethanol for analysis.

Diacylhydrazines **10a,c-g**.

Physical properties (mp, ir, nmr) and the elemental analysis of the new compounds are given in Tables 3 and 4.

($N_1$-Acetyl-$N_2$-(*N*-methylpyroglutamoyl))hydrazine (**10a**).

*N*-Methylpyroglutamic hydrazide (**12a**) (40.0 g, 0.25 mole) was fractionally added with cooling to 100.0 ml (1.06 moles) of acetic anhydride. The reaction mixture was stirred at room temperature for 13 hours and filtered. The solid was washed with ether and then dried in the air for several days. Diacylhydrazine **10a** was thus obtained in 89% yield and used without further purification for the cyclization reaction. A small amount of this product was recrystallized from ethanol for analysis.

($N_1$-(4-Chlorophenoxyacetyl)-$N_2$-(*N*-benzylpyroglutamoyl))hydrazine (**10c**).

A solution of 4-chlorophenoxyacetyl chloride (17.4 g, 85 mmoles) in 40 ml of anhydrous dichloromethane was slowly added to 20.0 g (85 mmoles) of *N*-benzylpyroglutamic hydrazide (**12b**) and 8.6 g (85 mmoles) of triethylamine in solution in 100 ml of anhydrous dichloromethane. The reaction mixture was stirred for 15 hours. A small amount of solid was removed by filtration. Dichloromethane (100 ml) was added and the solution was washed with water, dried over sodium sulfate, concentrated, and precipitated with acetone. The resulting solid was filtered and washed with ether. Diacylhydrazine **10c** was thus obtained in 75% yield and used without further purification for the cyclization reaction. A small amount of this product was recrystallized from ethanol for analysis.

($N_1$-(3,4,5-Trimethoxybenzoyl)-$N_2$-(*N*-benzylpyroglutamoyl))hydrazine (**10d**).

A solution of 3,4,5-trimethoxybenzoyl chloride (16.5 g, 71 mmoles) and *N*-benzylpyroglutamic hydrazide (16.6 g, 71 mmoles) (**12b**) in 90 ml of pyridine was refluxed for 3 hours and stirred at room temperature overnight. The pyridine was evaporated, the residue dissolved in dichloromethane and washed with diluted hydrochloric acid, with an aqueous solution of sodium bicarbonate and then with water until neutralization. The solution was dried over sodium sulfate, and then concentrated. The product was crystallized from acetone at 0° overnight. The resulting solid was filtered, washed with acetone and recrystallized from ethanol. Analytically pure diacylhydrazine **10d** was thus obtained in 46% yield.

($N_1$-(4-Chlorobenzoyl)-$N_2$-(*N*-benzylpyroglutamoyl))hydrazine (**10e**).

A solution of 4-chlorobenzoyl chloride (13.8 g, 79 mmoles) in 90 ml of anhydrous dichloromethane was slowly added at 0° to 18.0 (77 mmoles) of *N*-benzylpyroglutamic hydrazide (**12b**) and 7.8 g (132 mmoles) of triethylamine in solution in 165 ml of anhydrous dichloromethane. The reaction mixture was stirred overnight. The resulting solid was filtered. After concentration of the filtrate a second fraction of crystalline compound was filtered. The combined solids were washed with carbonated water. The product was dissolved in THF, dried over sodium sulfate and crystallized from THF. Analytically pure monohydrated diacylhydrazine **10e** was thus obtained in 67% yield.

($N_1$-(Trifluoroacetyl)-$N_2$-(*N*-(2-chlorobenzyl)pyroglutamoyl))hydrazine (**10f**).

A solution of trifluoroacetic anhydride (19.4 ml, 138 mmoles) in 100 ml of anhydrous dichloromethane was slowly added to a solution of 35.0 g (131 mmoles) of *N*-(2-chlorobenzyl)pyroglutamic hydrazide (**12c**) in 200 ml of anhydrous dichloromethane. The reaction mixture was stirred for 48 hours. The resulting solid was filtered, washed with ether, and dried under vacuum. Diacylhydrazine **10f** was thus obtained in 72% yield and used without further purification for the cyclization reaction. A small amount of this product was recrystallized from ethanol, and then from dichloromethane for analysis.

($N_1$-(2-Thiopheneacetyl)-$N_2$-(*N*-(4-methylbenzyl)pyroglutamoyl))-hydrazine (**10g**).

A solution of 2-thiopheneacetyl chloride (6.7 g, 42 mmoles) in 50 ml of anhydrous dichloromethane was slowly added with cooling to 10.0 g (40 mmoles) of *N*-(4-methylbenzyl)pyroglutamic hydrazide (**12d**) and 4.1 g (41 mmoles) of triethylamine in solution in 125 ml of anhydrous dichloromethane. The reaction mixtuer was stirred for 17 hours. The resulting solid was filtered. After concentration of the filtrate and crystallization with ether, a second fraction of crystalline compound was filtered. The concentration, crystallization, and filtration steps were repeated twice. The combined solids were washed with an aqueous solution of sodium hydroxide. Traces of the starting hydrazide were removed by washing with THF. Diacylhydrazine **10g** was thus obtained in 77% yield and used without further purification for the cyclization reaction. A small amount of this product was treated with activated charcoal in ethanol, washed with ether and recrystallized twice from ethanol for analysis.

1,3,4-Oxadiazoles **8a-f**.

The oxadiazoles **8a-d** were prepared according to the same

procedure for which a typical example is given below. For the syntheses of 2-(*N*-benzyl-5-oxo-2-pyrrolidinyl)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole (**8d**), 0.05 g of imidazole was added to the reaction medium. Physical properties (mp, ir, nmr) and the elemental analysis of the new compounds are given in Tables 5 and 6.

2-(*N*-Methyl-5-oxo-2-pyrrolidinyl)-5-methyl-1,3,4-oxadiazole (**8a**).

A mixture of 6.0 g (30 mmoles) of ($N_1$-acetyl-$N_2$-(*N*-methylpyroglutamoyl))hydrazine (**10a**), 7.8 g (48 mmoles) of hexamethyldisilazane (HMDS) and 0.05 g of tetrabutylammonium fluoride trihydrate was heated at 130° for 13 hours under nitrogen. The remaining HMDS and the obtained hexamethyldisiloxane were evaporated and the residue worked up as described in Table 5 and recrystallized in the suitable solvent (see Table 5).

2-(*N*-Benzyl-5-oxo-2-pyrrolidinyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole (**8e**).

a) A solution of 4.0 g (10 mmoles) of ($N_1$-(4-chlorobenzoyl)-$N_2$-(*N*-benzylpyroglutamoyl))hydrazine (**10e**), 4.4 g (27 mmoles) of hexamethyldisilazane (HMDS), 0.05 g of tetrabutylammonium fluoride trihydrate and 0.05 g of imidazole in 10 ml of chlorobenzene was heated at 130° for 24 hours under nitrogen. The solid was filtered and washed with ether. By concentrations of the filtrate and filtrations, 3 new fractions were obtained. The total yield of oxadiazole **8e** was 69%. The product was recrystallized from ethanol.

b) Oxadiazole **8e** was obtained in 33% by the same procedure with trimethylsilyl trifluoromethanesulfonate (3 drops) instead of tetrabutylammonium fluoride trihydrate; 35% of the starting diacylhydrazine **10e** was also obtained during the crystallization.

c) A solution of 10.0 g (27 mmoles) of ($N_1$-(4-chlorobenzoyl)-$N_2$-(*N*-benzylpyroglutamoyl))hydrazine (**10e**) in 50 ml of triethylamine was refluxed. A solution of 14 ml (18 mmoles) of chlorotrimethylsilane in 20 ml of triethylamine was slowly added. The reaction medium was refluxed for 17 hours. The triethylamine hydrochloride was filtered under nitrogen and washed with anhydrous toluene. The solvents were evaporated and the residue, heated at 250° for a few minutes. By fractionated crystallization from ethanol, 5.9 g of oxadiazole **8e** (62%) and 1.1 g of diacylhydrazine **10e** (11%) were obtained.

Bistrimethylsilyl($N_1$-trifluoroacetyl-$N_2$-(*N*-(2-chlorobenzyl)pyroglutamoyl))hydrazine (**14f**).

A solution of 25.0 g (68 mmoles) of ($N_1$-(trifluoroacetyl)-$N_2$-(*N*-(2-chlorobenzyl)pyroglutamoyl))hydrazine (**10f**) and 0.05 g of tetrabutylammonium fluoride trihydrate in 33.3 g (206 mmoles) of hexamethyldisilazane was refluxed under nitrogen for 36 hours. The reaction mixture was distilled under vacuum. Bissilylated compound **14f** was thus obtained in 85% yield ($bp_{0.35}$ = 185°); $^1$H-nmr (deuteriochloroform): δ (ppm) 0.20 (s, 9H), 0.29 (s, 9H), 1.95-2.8 (m, 4H), 4.10 (d, J = 15.6 Hz, 1H), 4.05-4.3 (m, 1H), 5.03 (d, d, J = 15.6 Hz, 1H), 7.23 (s, 4H).

2-(*N*-(2-Chlorobenzyl)-5-oxo-2-pyrrolidinyl)-5-trifluoromethyl-1,3,4-oxadiazole (**8f**).

A mixture of 6.0 g (12 mmoles) of bistrimethylsilyl ($N_1$-trifluoroacetyl-$N_2$-(*N*-(2-chlorobenzyl)pyroglutamoyl)hydrazine (**14f**) and 0.2 ml of trifluoromethanesulfonic acid was heated at 140° for 3 hours, the obtained hexamethyldisiloxane being removed by distillation as soon as it is formed. Oxadiazole **8f** was distilled under vacuum ($bp_{0.20}$ = 150°) and thus obtained in 81% yield.

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