Syntheses of Substituted 1-Methyl-2-(1,3,4-thiadiazol-2-yl)-4-nitropyrroles and 1-Methyl-2-(1,3,4-oxadiazol-2-yl)-4-nitropyrroles [1]

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Starting from readily available ethyl-4-nitropyrrole-2-carboxylate (**1**), substituted 1-methyl-2-(1,3,4-thiadiazol-2-yl)-4-nitropyrroles and 1-methyl-2-(1,3,4-oxadiazol-2-yl)-4-nitropyrroles were prepared. The reaction of **1** with diazomethane gave ethyl 1-methyl-4-nitropyrrole-2-carboxylate (**2**). Reaction of compound **2** with hydrazine hydrate afforded the corresponding hydrazide **3**. The reaction of **3** with formic acid yielded 1-(1-methyl-4-nitropyrrole-2-carboxyl)-2-(formyl)hydrazine (**7**). Refluxing of the latter with phosphorus pentasulfide in xylene yielded compound **6** in 40% yield. Reaction of compound **7** with phosphorus pentoxide afforded compound **9**. Reaction of compound **3** with 1,1'-carboxyldiimidazole in the presence of triethylamine yielded 2-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-oxadiazoline-4(*H*)-5-one (**11**). Refluxing compound **3** with cyanogen bromide in methanol gave compound **12**. Compound **13** could be obtained through the reaction of compound **3** with carbon disulfide in basic medium. Alkylation of compound **13** afforded the correspanding alkylthio derivative **14**. Reaction of 1-methyl-4-nitropyrrole-2-carboxylic acid (**15**) with thiosemicarbazide and phosphorus oxychloride gave 2-amino-5-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-thiadiazole (**16**). Sandmeyer reaction of compound **16** yielded 2-chloro-5-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-thiadiazole (**17**). Refluxing of the latter with thiourea afforded 2-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-thiadiazoline-4(*H*)-5-thione (**18**). Alkylation of compound **18** gave the corresponding alkylthio derivative **19**. Oxidation of the latter with hydrogen peroxide in acetic acid yielded 2-(1-methyl-4-nitro-2-pyrrolyl)-5-methylsulfonyl-1,3,4-thiadiazole (**20**).

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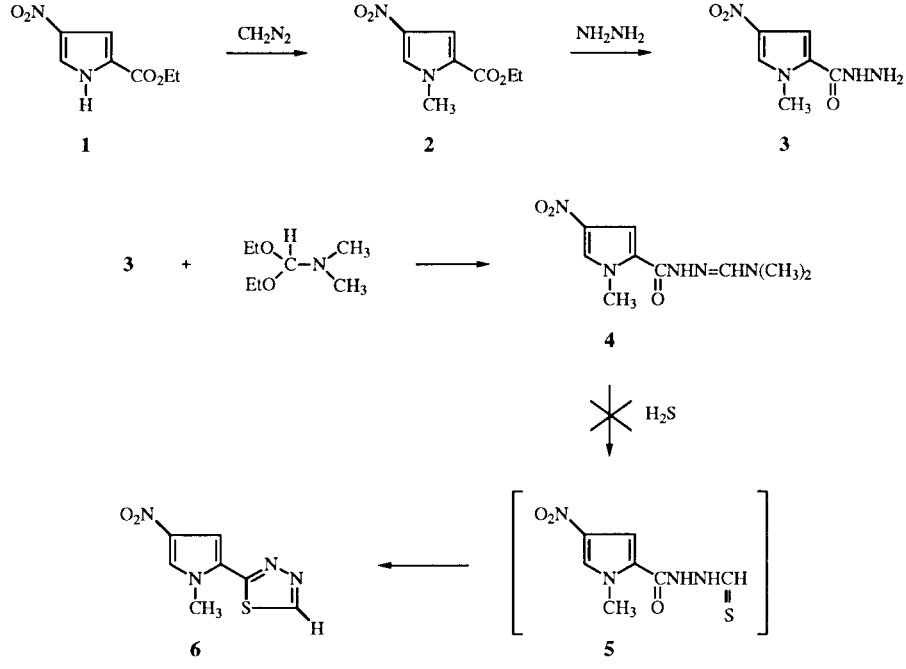
The considerable biological importance of nitroimidazoles has stimulated much work on this heterocycles [2-5]. It was also shown that 5-nitropyrrole-2-sulfonamides and 3-chloro-4-(3-chloro-2-nitrophenyl)pyrrole have antifungal and antibacterial activity [6-7]. We would like to report the syntheses of the title compounds as possible effective drugs against tropical diseases [8].

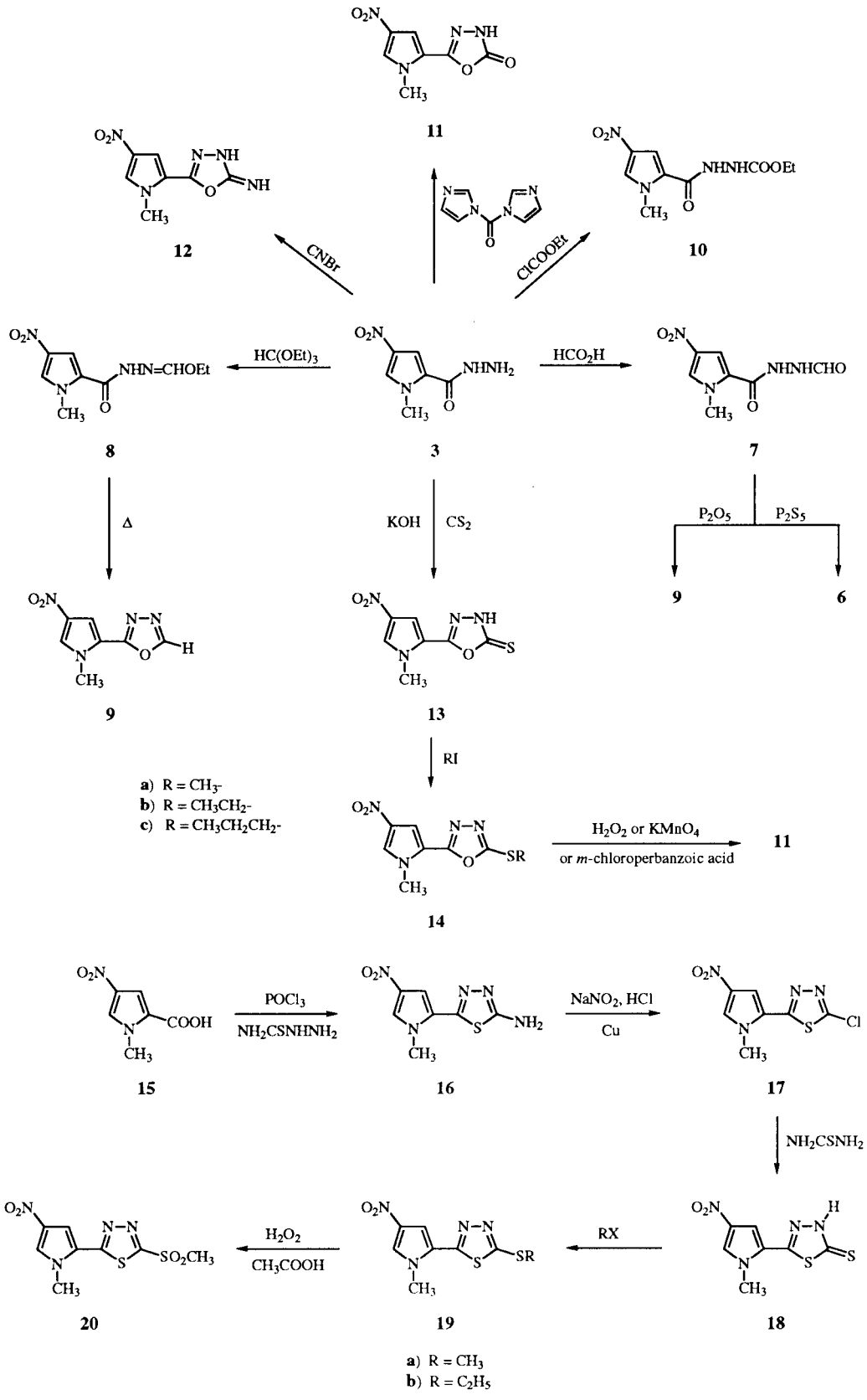
The synthesis of 1-methyl-2-(1,3,4-thiadiazol-2-yl)-4-nitropyrrole (**6**) was studied according to the method for the preparation of 2-phenyl-1,3,4-thiadiazole [9] (Scheme 1).

The reaction of ethyl 4-nitropyrrole-2-carboxylate (**1**) [10] with diazomethane in ether afforded ethyl 1-methyl-

Scheme 1



Scheme 2


11
12
10
CNBr
ClCOOEt
HC(OEt)3
HCO2H
8
3
7
Δ
KOH
CS2
P2O5
P2S5
9
6
9
13
RI
a) R = CH3-
b) R = CH3CH2-
c) R = CH3CH2CH2-
H2O2 or KMnO4
or m-chloroperbanzoic acid
11
14
POCl3
NH2CSNHNH2
NaNO2, HCl
Cu
15
16
17
NH2CSNH2
H2O2
CH3COOH
RX
20
19
18
a) R = CH3
b) R = C2H5

4-nitropyrrole-2-carboxylate (**2**). Addition of hydrazine hydrate to compound **2** gave 1-methyl-4-nitropyrrole-2-carboxylic acid hydrazide (**3**) in high yield. The reaction of compound **3** with dimethylformamide diethylacetal yielded 1-methyl-4-nitropyrrole-2-carboxamide-*N*-[amino(dimethylamino)methylene] (**4**) in moderate yield. However the reaction of **4** with hydrogen sulfide did not give 1-(1-methyl-4-nitropyrrole-2-carboxyl)-2-(thioformyl)hydrazine (**5**).

Compound **6** could be synthesized in relatively good yield according to Scheme 2.

Refluxing compound **3** with formic acid for 30 minutes gave 1-(1-methyl-4-nitropyrrole-2-carboxyl)-2-(formyl)-hydrazine (**7**) in high yield. Refluxing 0.085 mole of compound **7** with 0.05 mole phosphorus pentasulfide gave compound **6** in 40% yield. In addition 1-methyl-2-(1,3,4-oxadiazol-2-yl)-4-nitropyrrole (**9**) was also formed in 10% yield.

The usual reaction for the formation of 1,3,4-oxadiazole, namely the reaction of compound **3** with ethyl orthoformate, did not give the desired compound **9**. In the latter reaction ethoxyformaldehyde 1-methyl-4-nitropyrrole-2-carboxyhydrazone (**8**) was formed. Heating compound **8** up to its melting point gave compound **9** in 35% yield. Compound **9** could also be obtained in 50% yield through refluxing of compound **7** with phosphorus pentoxide in xylene.

For the preparation of 2-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-oxadiazolin-4(*H*)-5-one (**11**) hydrazide **3** was reacted with ethyl chloroformate in triethylamine. In this reaction, the intermediate **10** was isolated. Compound **10** could not be converted to compound **11** under different experimental conditions. However, compound **11** could be obtained through the reaction of compound **3** with 1,1'-carbonyldiimidazole in the presence of triethylamine. The infrared spectrum of compound **11** had a strong absorption at 1765 cm^{-1} (potassium bromide disk) supporting the keto structure **11**, at least in the solid state. The 2-amino-5-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-oxadiazole (**12**) resulted from the action of cyanogen bromide on **3** [11].

In the infrared, 2-amino-5-phenyl-1,3,4-oxadiazole absorbs strongly at 3279, 3129, 1652 and 1600 cm^{-1}. The 3279, 3129 and 1600 are assigned to NH_2 and the band at 1652 to endocyclic C=N- [11]. However, in substituted 4(*H*)-5-imino-1,3,4-oxadiazoline the exocyclic C=N absorbs at 1680 to 1710 cm^{-1} [12]. Compound **12** had absorption at 1675 and 3400 cm^{-1} supporting the imino structure **12**.

The 2-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-oxadiazoline-4(*H*)-5-thione (**13**) was obtained by reaction of compound **3** with carbon disulfide under basic condition [13]. This compound could be in equilibrium with 2-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-oxadiazole-5-thiol. Compound **13** had maximum absorption at 3125 (NH dimer), 1320 (C=S dimer) and 1635 (endocyclic C=N). These bands are similar to the one reported for 5-thione derivatives [14]. Reaction of compound **13** with alkyl iodide under basic condition afforded 2-(1-methyl-4-nitro-2-pyrrolyl)-5-alkylthio-1,3,4-oxadiazole (**14**). Oxidation of compound **14** with hydrogen peroxide, potassium permangenate or *m*-chloroperbenzoic acid did not give the corresponding sulfone. In this reaction compound **11** was obtained.

Reaction of 1-methyl-4-nitropyrrole-2-carboxylic acid (**15**) with phosphorus oxychloride and thiosemicarbazide under the condition reported previously [15] afforded 2-amino-5-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-thiadiazole (**16**). Diazotization of compound **16** with sodium nitrite in hydrochloric acid in the presence of copper gave 2-chloro-5-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-thiadiazole (**17**). Reaction of thiourea with **17** afforded 2-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-thiadiazoline-4(*H*)-5-thione (**18**) [16]. Reaction of compound **18** with alkyl iodide in the alkaline medium afforded 2-alkylthio-5-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-thiadiazole (**19**). Oxidation of the latter (R = CH_3) with hydrogen peroxide in acetic acid yielded 2-(1-methyl-4-nitro-2-pyrrolyl)-5-methylsulfonyl-1,3,4-thiadiazole (**20**).

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The uv spectra were recorded using a Perkin-Elmer Model 550 SE spectrometer. The ir spectra were obtained using a Perkin-Elmer Model 781 spectrograph (potassium bromide disks). The ^1H nmr spectra were recorded on a Bruker FT-80 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. The mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 ev.

Ethyl 1-Methyl-4-nitropyrrole-2-carboxylate (**2**).

To a suspension of compound **1** (1.84 g, 0.01 mole) in dry ether (10 ml) diazomethane in ether (0.1 mole) was added. The progress of the reaction was followed by tlc on silica gel. After the reaction was complete, it was filtered. The solvent was evaporated and the residue was crystallized from acetone to give 1.78 g (97%) of compound **2**, mp 109-110°; ir (potassium bromide): ν 3140 (pyrrole), 1695 (C=O) 1540, 1320 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): 1.40 (t, 3H, CH_3), 4.05 (s, 3H, N-CH_3), 4.46 (q, 2H, CH_2), 7.15 (d, 1H, aromatic, $J_{3,5}$ = 2 Hz) and 7.33 ppm (d, 1H, aromatic, $J_{3,5}$ = 2 Hz).

Anal. Calcd. for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.05; N, 14.14. Found: C, 48.58; H, 5.21; N, 14.01.

1-Methyl-4-nitropyrrole-2-carboxylic Acid Hydrazide (**3**).

To a solution of compound **2** (1.98 g, 0.01 mole) in ethanol (20 ml) hydrazine hydrate (2.5 g, 0.05 mole) was added. After 15 minutes the precipitate was filtered and crystallized from ethanol to give compound **3** (1.58 g, 86%), mp 228-230°; ir

(potassium bromide): ν 3310, 3120 (NH_2 and NH), 1635 (C=O) 1540, 1320 cm^{-1} (NO_2): ms: m/z (%) 184 (M^+, 97), 154 (38), 107 (96), 98 (58), 80 (51), 72 (53), 57 (87) and 43 (72).

Anal. Calcd. for $C_6H_8N_4O_3$: C, 39.13; H, 4.35; N, 30.43. Found: C, 39.30; H, 4.45; N, 30.61.

1-Methyl-4-nitropyrrole-2-carboxamide-*N*-[amino(dimethylamino)methylene] (**4**).

A mixture of compound **3** (184 mg, 1 mmole) and dimethylformamide diethylacetal (147 mg, 1 mmole) was allowed to stand at room temperature for 5 minutes.

The product was crystallized from ethyl acetate to give compound **4** (143 mg, 60%), mp 167-168°; ^1H nmr (deuteriochloroform): 2.95 (s, 6H, CH_3), 3.98 (s, 3H, N-CH_3), 7.18 (d, 1H, aromatic), and 7.67 ppm (d, 1H, aromatic); ms: m/z (%) 239 (M^+, 100), 195 (26), 169 (41), 153 (96), 123 (19), 114 (26), 107 (95), 70 (54) and 43 (99).

Anal. Calcd. for $C_9H_{13}N_5O_3$: C, 45.19; H, 5.44; N, 29.29. Found: C, 45.23; H, 5.35; N, 29.21.

1-(1-Methyl-4-nitropyrrole-2-carboxyl)-2-(formyl)hydrazine (**7**).

A solution of compound **3** (1.84 g, 0.01 mole) in formic acid (25 ml) was refluxed for 30 minutes. After cooling the precipitate was filtered to give 1.84 g (84%) of compound **7**, mp 248-250°; ir (potassium bromide): ν 3300, 3120 (NH), 1690, 1650 (C=O), 1525, 1320 cm^{-1} (NO_2); ms: m/z (%) 212 (M^+, 98), 184 (96), 154 (99), 138 (92), 107 (100), 91 (89), 80 (93), 65 (91), 52 (91) and 43 (90).

Anal. Calcd. for $C_7H_8N_4O_4$: C, 39.63; H, 3.77; N, 26.41. Found: C, 39.62; H, 3.62, N, 26.30.

1-Methyl-2-(1,3,4-thiadiazol-2-yl)-4-nitropyrrole (**6**).

To a solution of compound **7** (2.12 g, 0.01 mole) in xylene (220 ml) phosphorus pentasulfide (1.4 g, 0.006 mole) was added. The mixture was refluxed for 45 minutes and filtered. The solvent was evaporated. To the residue dimethyl sulfoxide (10 ml) was added and filtered. The precipitate was crystallized from chloroform to give 194 mg (10%) of **9**, mp 188-189°; ir (potassium bromide): ν 3125 (aromatic), 1560, 1350 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): 4.26 (s, 3H, N-CH_3), 7.76 (d, 1H, H_3 pyrrole, $J_{3,5}$ = 2 Hz) and 9.10 ppm (s, 1H, oxadiazole); ms: m/z (%) 194 (M^+, 100), 152 (60), 147 (30), 106 (35) and 91 (20).

Anal. Calcd. for $C_7H_6N_4O_3$: C, 43.30; H, 3.09; N, 28.87. Found: C, 43.15; H, 2.96; N, 28.92.

The mother liquid was evaporated and the residue was chromatographed on silica gel (small column) using chloroform as eluent to give 0.84 g (40%) of compound **6**, mp 176-178°; ir (potassium bromide): ν 3125 (pyrrole), 3065 (H-C_5 thiadiazole), 1560 and 1350 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): 4.17 (s, 3H, N-CH_3), 7.30 (2d, 2H, $H_{2,5}$ pyrrole) and 9.83 ppm (s, 1H, H_5, thiadiazole); ms: m/z (%) 210 (M^+, 98), 195 (44), 183 (55), 163 (81), 137 (31), 121 (17), 96 (98), 79 (100), 59 (98) and 58 (67).

Anal. Calcd. for $C_7H_6N_4O_2S$: C, 40.00; H, 2.86; N, 26.67. Found: C, 39.96; H, 2.73; N, 26.59.

Ethoxyformaldehyde 1-Methyl-4-nitropyrrole-2-carboxyhydrazone (**8**).

A mixture of compound **3** (368 mg, 2 mmoles) and ethyl orthoformate (2.5 ml) was heated up to boiling point. After cooling the precipitate was filtered and crystallized from chloroform to give 360 mg (75%) of compound **8**, mp 169-170°; ir (potassium bromide): ν 3210 (NH), 3110 (C-H) pyrrole, 1650 (C=O), 1615 (C=N), 1560 and 1310 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): 1.42 (t, 3H, CH_3), 4.22 (q, 2H, CH_2), 4.0 (s, 3H, CH_3), 6.76 (s, 1H, HC=N), 7.39 (d, 1H, H_3, $J_{3,5}$ = 1.9 Hz), 7.68 (d, 1H, H_5 pyrrole, $J_{3,5}$ = 1.9 Hz) and 8.90 ppm (bs, 1H, NH).

Anal. Calcd. for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.00; N, 23.33. Found: C, 44.91; H, 5.15; N, 23.21.

1-Methyl-2-(1,3,4-oxadiazol-2-yl)-4-nitropyrrole (**9**).

Method A.

Compound **8** (240 mg, 1 mmole) was heated at 170-175° for 30 minutes. The residue was purified by preparative tlc on silica gel using chloroform ethyl acetate (90:10) as the eluent to give 68 mg (35%) of compound **9**, mp 188-189°.

Method B.

To a solution of compound **7** (1.8 g, 0.0085 mole) in xylene (90 ml), phosphorus pentoxide (0.71 g, 0.005 mole) was added. The mixture was refluxed for 2 hours and filtered. The solvent was evaporated and the residue was crystallized from chloroform to give 0.97 g (50%) of compound **9**, mp 188-189°.

1-(1-Methyl-4-nitropyrrole-2-carbonyl)-2-ethoxycarbonylhydrazine (**10**).

To a stirring solution of compound **3** (184 mg, 1 mmole) and triethylamine (101 mg, 1 mmole) in acetonitrile (5 ml) at 0° ethyl chloroformate (108.5 mg, 1 mmole) was added. The stirring was continued at 0° for 1 hour and at room temperature for 7 hours. The solvent was evaporated and the residue was crystallized from ethanol to give 205 mg (80%) of **10**; mp 183-185°; ir (potassium bromide): 3290, 3240 (NH), 3140 (H-C of pyrrole), 1730 (C=O ester), 1665 (C=O), 1525 and 1320 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): 1.33 (t, 3H, CH_3), 3.99 (s, 3H, NCH_3), 4.31 (q, 2H, CH_2); 7.37 (d, 1H, H_3 pyrrole, $J_{3,5}$ = 1.87 Hz) and 7.71 ppm (d, 1H, H_5 pyrrole, $J_{3,5}$ = 1.87 Hz).

Anal. Calcd. for $C_9H_{12}N_4O_5$: C, 42.19; H, 4.69; N, 21.87. Found: C, 42.02; H, 4.78; N, 21.69.

2-(1-Methyl-4-nitro-2-pyrrolyl)-1,3,4-oxadiazolin-4(*H*)-5-one (**11**).

To a stirring solution of compound **3** (184 mg, 1 mmole) and triethylamine (0.15 ml) in tetrahydrofuran (25 ml) at 0° was added 1,1'-carbonyldiimidazole (225.2 mg, 1.39 mmoles). The stirring was continued for 5 hours. Triethylamine (0.1 ml) and 1,1'-dicarbonyldiimidazole (130 mg, 0.8 mmole) were added and stirring was continued at room temperature overnight. The solvent was evaporated and the residue was purified by preparative tlc on silica gel using chloroform-ethanol (90:10) as the eluent to give 126 mg (60%) of **11**, mp 212-214° (ethanol); uv (methanol): λ_{max} 325 (log ε = 3.63) 261 nm (log ε = 4.17); ir (potassium bromide): ν 3310 (weak, NH), 3130 (H-C pyrrole), 1760 (C=O), 1625 (C=N), 1530 and 1320 (NO_2); ^1H nmr (deuteriochloroform): 4.00 (s, 3H, NCH_3), 7.33 (d, 1H, H_3 pyrrole, $J_{3,5}$ = 1.8 Hz) and 7.73 ppm (d, 1H, H_5 pyrrole, $J_{3,5}$ = 1.8 Hz); ms: m/z (%) 210 (M^+, 68), 194 (20), 166 (25), 164 (17), 153 (76), 137 (10), 124 (20), 120 (12), 107 (100), 93 (13), 79 (66), 78 (13), 66 (28), 64 (24), 52 (29) and 51 (19).

Anal. Calcd. for $C_7H_6N_4O_4$: C, 40.00; H, 2.86; N, 26.67. Found: C, 40.12; H, 2.98; N, 26.78.

4(*H*)-5-Imino-2-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-oxadiazoline (**12**).

A solution of compound **3** (350 mg, 1.9 mmoles) and cyanogen bromide (225 mg, 2.12 mmoles) in methanol (7.5 ml) was refluxed for half an hour. The solvent was evaporated and the residue was crystallized from ethanol to give 310 mg (78%) of compound **12**, mp 252-255°; uv (methanol): λ_{max} 330 (log ε = 3.58) and 270 nm (log ε = 4.12) ir (potassium bromide): ν 3400 (NH), 3140 (HC pyrrole), 1675 (exocyclic C=N), 1620 (endocylic C=N), 1525 and 1320 cm^{-1} (NO_2); ms: m/z (%) 209 (M^+, 100), 166 (88), 133 (11), 120 (10), 107 (34), 79 (34), 74 (30) and 57 (11).

Anal. Calcd. for $C_7H_7N_5O_3$: C, 40.19; H, 3.35; N, 33.49. Found: C, 40.03; H, 3.21; N, 33.54.

2-(1-Methyl-4-nitro-2-pyrrolyl)-1,3,4-oxadiazoline-4(*H*)-5-thione (**13**).

To a solution of compound **3** (696 mg, 3.78 mmoles) in ethanol (20 ml) at 0° was added carbon disulfide (684 mg, 9 mmoles) and potassium hydroxide (224 mg, 4 mmoles). The mixture was refluxed for 7 hours. The solvent was evaporated. The residue was dissolved in water and acidified with dilute hydrochloric acid. The precipitate was filtered and crystallized from ethanol-water to give 513 mg (60%) of **13**, mp 233-235°; uv (methanol): λ_{max} 296 (log ε = 4.3) and 234 nm (log ε = 4.17); ir (potassium bromide): ν 3125 (NH dimer) 3090 (H-C pyrrole), 1635 (C=N), 1530 and 1370 (NO_2), 1320 cm^{-1} (C=S dimer); ^1H nmr (deuteriochloroform): 4.04 (s, 3H, NCH_3), 7.50 (d, 1H, H_3 pyrrole, $J_{3,5}$ = 1.98 Hz) and 7.80 ppm (d, 1H, H_5 pyrrole, $J_{3,5}$ = 1.98 Hz); ms: m/z (%) 226 (M^+, 100), 166 (83), 153 (29), 120 (14), 107 (15) and 79 (33).

Anal. Calcd. for $C_7H_6N_4O_3S$: C, 37.17; H, 2.65; N, 24.78. Found: C, 37.20; H, 2.88; N, 24.61.

2-(1-Methyl-4-nitro-2-pyrrolyl)-5-methylthio-1,3,4-oxadiazole (**14a**).

To a stirring solution of compound **13** (226 mg, 1 mmole) in ethanol (15 ml) and sodium hydroxide (1N, 1 ml) methyl iodide (0.5 ml) was added dropwise. After half an hour the precipitate was filtered and crystallized from ethyl acetate to give 214 mg (89%) of **14a**, mp 224-226°; uv (methanol): λ_{max} 272.5 (log ε = 4.36) and 218 nm (log ε = 4.13); ir (potassium bromide): ν 3135 (H-C pyrrole), 1615 (C=N), 1530 and 1325 cm^{-1} (NO_2): ^1H nmr (deuteriochloroform): 2.78 (s, 3H, SCH_3), 4.11 (s, 3H, NCH_3), 7.32 (d, 1H, H_3 pyrrole, $J_{3,5}$ = 1.85 Hz) and 7.64 ppm (d, 1H, H_5 pyrrole, $J_{3,5}$ = 1.85 Hz); ms: m/z (%) 240 (M^+, 30), 193 (14), 169 (39), 153 (100), 151 (27), 137 (12), 123 (14), 107 (66), 91 (18), 79 (15), 75 (56) and 64 (10).

Anal. Calcd. for $C_8H_8N_4O_3S$: C, 40.00; H, 3.33; N, 23.33. Found: C, 39.88; H, 3.45; N, 23.46.

2-(1-Methyl-4-nitro-2-pyrrolyl)-5-ethylthio-1,3,4-oxadiazole (**14b**).

This compound was prepared similar to **14a** in 83% yield, mp 165-167° (ethanol); uv (methanol) λ_{max} 273.5 (log ε = 4.34), 218 nm (log ε = 4.08); ir (potassium bromide): ν 3115 (HC pyrrole), 1610 (C=N), 1530 and 1320 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): 1.53 (t, 3H, CH_3), 3.32 (q, 2H, CH_2), 4.11 (s, 3H, NCH_3), 7.31 (d, 1H, H_3 pyrrole, $J_{3,5}$ = 2 Hz) and 7.65 ppm (d, 1H, H_5 pyrrole, $J_{3,5}$ = 2 Hz); ms: m/z (%) 254 (M^+, 42), 193 (12), 169 (36), 153 (100), 151 (14), 121 (13), 107 (58), 91 (19), 89 (38) and 79 (11).

Anal. Calcd. for $C_9H_{10}N_4O_3S$: C, 42.52; H, 3.94; N, 22.05. Found: C, 42.67; H, 4.05; N, 22.16.

2-(1-Methyl-4-nitro-2-pyrrolyl)-5-*n*-propylthio-1,3,4-oxadiazole (**14c**).

This compound was made from compound **13** and ethyl bromide similar to **14a** in 80% yield, mp 129-131°; uv (methanol): λ_{max} 275 (log ε = 4.05); 218 nm (log ε = 3.67); ^1H nmr (deuteriochloroform): 1.10 (t, 3H, CH_3), 1.89 (m, 2H, CH_2), 3.29 (t, 2H, SCH_2), 4.12 (s, 3H, NCH_3), 7.28 (d, 1H, H_3 pyrrole, $J_{3,5}$ = 1.85 Hz) and 7.66 ppm (d, 1H, H_5 pyrrole, $J_{3,5}$ = 1.85 Hz); ms: m/z (%) 268 (M^+, 37), 226 (35), 169 (15), 166 (15), 153 (100), 151 (12), 121 (16), 107 (46), 91 (19), 79 (10) and 74 (22).

Anal. Calcd. for $C_{10}H_{12}N_4O_3S$: C, 44.78; H, 4.48; N, 20.90. Found: C, 44.83; H, 4.59; N, 20.81.

5-Amino-2-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-thiadiazole (**16**).

A mixture of acid **15** (17 g, 0.1 mole), thiosemicarbazide (9.1 g, 0.1 mole), phosphorus oxychloride (35 ml) was refluxed gently for half an hour. After cooling, water was added (100 ml). The mixture was refluxed for 4 hours and filtered. The solution was neutralized with potassium hydroxide. The precipitate was filtered and crystallized from ethanol-water to give 12.4 g (55%) of **16**, mp 248-250°; uv (methanol): λ_{max} 292 (log ε = 3.8); ir (potassium bromide): ν 3475, 3340 (NH_2), 3200, 3120 (aromatic), 1610 (C=N), 1520 and 1310 cm^{-1} (NO_2); ms: m/z (%) 225 (M^+, 100), 183 (39), 169 (21), 152 (17), 137 (34), 135 (74), 123 (74), 121 (33), 96 (33), 90 (37), 79 (73), 77 (75), 64 (38), 51 (19), 45 (38).

Anal. Calcd. for $C_7H_7N_5O_2S$: C, 37.33; H, 3.11; N, 31.11. Found: C, 37.18; H, 3.02; N, 31.28.

5-Chloro-2-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-thiadiazole (**17**).

To a stirring mixture of copper powder (0.5 g) hydrochloric acid 37% (28 ml) and water at 0° an homogenous mixture of compound **16** (2.25 g, 0.01 mole) and sodium nitrite (2.25 g) was gradually added. After stirring for 30 minutes at 0° and 2 hours at room temperature it was warmed to 45° and stirring was continued for 15 minutes. The mixture was neutralized with sodium hydroxide and extracted with chloroform. The solvent was dried, filtered and evaporated. The residue was crystallized from ether to give 1.47 g (60%) of **17**, mp 110-112°; uv (methanol): λ_{max} 292 (log ε = 3.90); ir (potassium bromide): ν 3120 (aromatic), 1550, 1350 cm^{-1} (NO_2); ms: m/z (%) 246 (42), 244 (M^+, 100), 227 (18), 198 (22), 197 (51), 183 (80), 169 (15), 151 (18), 138 (40), 121 (39), 93 (50), 79 (70), 64 (39), 53 (36) and 46 (39).

Anal. Calcd. for $C_7H_5ClN_4O_2S$: C, 34.36; H, 2.04; N, 22.90. Found: C, 34.24; H, 1.93; N, 22.98.

2-(1-Methyl-4-nitro-2-pyrrolyl)-1,3,4-thiadiazoline-4(*H*)-5-thione (**18**).

A stirring solution of compound **17** (244.5 mg, 1 mmole) and thiourea (228 mg, 3 mmoles) in ethanol (15 ml) was refluxed. The progress of the reaction was followed on tlc until the reaction was complete. After cooling the precipitate was filtered and recrystallized from ethanol to give 218 mg (90%) of **18**, mp 224-226°; uv (methanol): λ_{max} 345 (log ε = 3.21); ^1H nmr (deuteriochloroform): 3.46 (bs, 1H, NH), 3.92 (s, 3H, NCH_3), 7.20 (d, 1H, H_5 pyrrole) and 8.20 (d, 1H, H_3 pyrrole); ms: m/z (%) 242 (M^+, 100), 183 (24), 166 (18), 151 (10), 137 (10), 121 (15),

96 (10), 76 (10) and 59 (15).

Anal. Calcd. for $C_7H_6N_4O_2S_2$: C, 34.71; H, 2.48; N, 23.14. Found: C, 34.57; H, 2.63; N, 23.03.

2-(1-Methyl-4-nitro-2-pyrrolyl)-5-methylthio-1,3,4-thiadiazole (**19a**).

Starting from compound **18** and methyl iodide this compound was made similar to **14a** in 95% yield, mp 170-171° (ethyl acetate); uv (methanol): λ_{max} 307 (log ε = 4.10); ^{1}H nmr (dimethyl sulfoxide-d_6): 2.80 (s, 3H, SCH_3), 4.01 (s, 3H, NCH_3), 7.27 (d, 1H, H_3 pyrrole, $J_{3,5}$ = 1.8 Hz) and 8.20 (d, 1H, H_5 pyrrole, $J_{3,5}$ = 1.8 Hz); ms: m/z (%) 256 (m, 100), 240 (18), 223 (10), 209 (12), 183 (80), 169 (64), 151 (15), 138 (15), 123 (39), 121 (22), 105 (36), 91 (82), 79 (47), 67 (17), 53 (11) and 46 (32).

Anal. Calcd. for $C_8H_8N_4O_2S_2$: C, 37.50; H, 3.12; N, 21.87. Found: C, 37.63; H, 3.28; N, 21.72.

5-Ethylthio-2-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-thiadiazole (**19b**).

Starting from compound **18** and ethyl iodide this compound was made similar to **14a** in 60% yield, mp 180-181°; uv (methanol): λ_{max} 305 (log ε = 4.07); ^{1}H nmr (deuteriochloroform): 1.53 (t, 3H, CH_3), 3.35 (q, 2H, CH_2), 4.11 (s, 3H, NCH_3), 7.18 (d, 1H, H_3 pyrrole) and 7.63 ppm (d, 1H, H_5 pyrrole).

Anal. Calcd. for $C_9H_{10}N_4O_2S_2$: C, 40.00; H, 3.70; N, 20.74. Found: C, 40.12; H, 3.57; H, 20.86.

2-(1-Methyl-4-nitro-2-pyrrolyl)-5-methylsulfonyl-1,3,4-thiadiazole (**20**).

To a stirring solution of compound **19a** (256 mg, 1 mmole) in acetic acid (3 ml) hydrogen peroxide (30%, 3 ml) was added. The stirring was monitored by tlc. After the reaction was complete (3 hours) water (6 ml) was added and extracted with ether (3 x 10 ml). The ether was washed with sodium bicarbonate solution and then water. It was dried (sodium sulfate) filtered and evaporated. The residue was crystallized from ethanol to give 173 mg (60%) of **20**, mp 178-180°; nmr (deuteriochloroform): 3.17 (s, 3H, CH_3), 4.15 (s, 3H, NCH_3), 7.27 (d, 1H, H_3 pyrrole, $J_{3,5}$ = 1.6 Hz) and 7.68 (d, 1H, H_5 pyrrole, $J_{3,5}$ = 1.6 Hz); ms: m/z (%) 288 (M^+, 9), 272 (53), 257 (24), 229 (16), 217 (15), 202 (17), 183 (33), 169 (100), 163 (18), 155 (19), 151 (65), 138 (18), 137 (32), 125 (40), 123 (67), 121 (85), 105 (43), 91 (26), 79 (58), 64 (24), 53 (34) and 46 (15).

Anal. Calcd. for $C_8H_8N_4O_4S_2$: C, 33.33; H, 2.78; N, 19.44. Found: C, 33.16; H, 2.61; N, 19.29.

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REFERENCES AND NOTES

[1] A preliminary account of this work was presented in 16th ISOCS, Merseburg, Germany, July 1994.

[2] K. Akimoto and Y. Munezuka, H. Ota; *Jpn. Kokai Tokkyo Koho*, JP 02, 212, 486 (1990); *Chem. Abstr.*, **114**, 101995f (1991).

[3] E. Nishiwaki, H. Lee, T. Matsumoto, K. Toyooka, H. Sakurai and M. Shibuya, *Tetrahedron Letters*, **31**, 1299 (1990).

[4] A. Shafiee, M. Anaraki, S. Sadrai and F. Kamal, *J. Sci. Islamic Repub. Iran*, **1**, 44 (1989).

[5] A. Shafiee, A. Lavasani, B. Pirrouzzadeh, B. Mafakhari and F. Kamal, *ibid.*, **1**, 197 (1990).

[6] G. A. Carter, G. W. Dawson, and J. L. Garraway, *Pestic. Sci.*, **6**, 43 (1975); *Chem. Abstr.*, **82**, 16536a (1975).

[7] M. Gorman and D. H. Lively, *Antibiotics*, **2**, 433 (1967).

[8] G. T. Seaborg, *Science*, **223**, 9 (1984).

[9] H. Eilingsfeld, *Chem. Ser.*, **98**, 1308 (1965); *Chem. Abstr.*, **62**, 16232d (1965).

[10] M. Lee, D. M. Coulter, and J. W. Lown, *J. Org. Chem.*, **53**, 1855 (1988).

[11] W. R. Sherman, *J. Org. Chem.*, **26**, 88 (1961).

[12] J. F. Giudicelli, J. Menin, and H. Najer, *Bull. Soc. Chim. de France*, 4568 (1968).

[13] V. J. Ram, and A. J. Vlietinck, *J. Heterocyclic Chem.*, **25**, 253 (1988).

[14] C. Ainsworth, *J. Am. Chem. Soc.*, **78**, 4475 (1956).

[15] I. Lalezari and A. Shafiee, *J. Heterocyclic Chem.*, **8**, 835 (1971).

[16] J. Sandstrom and I. Wennerback, *Acta Chem. Scand.*, **20**, 57 (1966); *Chem. Abstr.*, **64**, 15716c (1966).