Nitroimidazoles. VI [1]. Syntheses of 1-Methyl-2-(1,3,4-thiadiazol-2-yl)-5-nitroimidazole and 1-Methyl-2-(1,3,4-oxadiazol-2-yl)-5-nitroimidazole

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Starting from readily available 1-methyl-5-nitroimidazole-2-carboxylic acid hydrazide (**1**), 1-methyl-2-(1,3,4-thiadiazol-2-yl)-5-nitroimidazole (**4**) and 1-methyl-2-(1,3,4-oxadiazol-2-yl)-5-nitroimidazole (**10**) were prepared. The reaction of **1** with formic acid gave 1-(1-methyl-5-nitroimidazole-2-carboxyl)-2-(formyl)hydrazine (**8**) in high yield. Refluxing of the latter with phosphorus pentasulfide in xylene yielded compound **4** in 50% yield. Reaction of compound **8** with phosphorus pentoxide afforded compound **10** in 60% yield.

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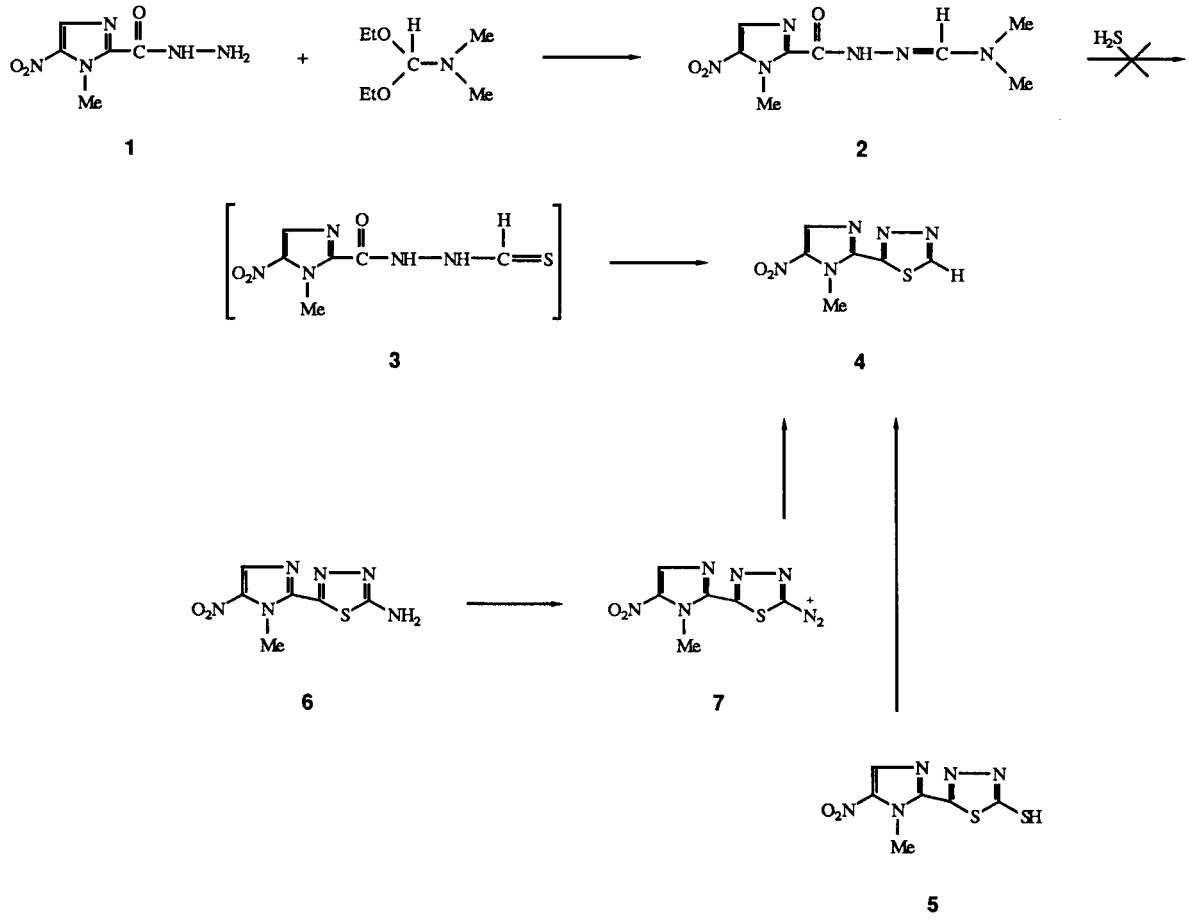
The considerable biological importance of nitroimidazoles has stimulated much work on this heterocycle [2-5]. It was also shown that substituted nitroimidazolylthiadiazoles and nitroimidazolyloxadiazoles have antiprotozoal activity [6-8]. The syntheses of 1-methyl-2-(2-pyridyl)nitroimidazoles, 1-methyl-2-(2-oxazolyl)-5-nitromidazole and 1-methyl-2-(2-methyl-4-thiazolyl)-nitroimidazoles have recently been reported [9-11]. We would like to report the syntheses of the title compounds as possible effective drugs against tropical diseases [12].

The synthesis of 1-methyl-2-(1,3,4-thiadiazol-2-yl)-5-nitroimidazole (**4**) was studied according to the method for the preparation of 2-phenyl-1,3,4-thiadiazole [13] (Scheme I).

The reaction of 1-methyl-5-nitroimidazole-2-carboxylic acid hydrazide (**1**) [14] with dimethylformamide diethylacetal gave 1-methyl-5-nitroimidazole-2-carboxamide-*N*-[amino(dimethylamino)methylene] (**2**) in high yield. However the reaction of **2** with hydrogen sulfide did not give 1-(1-methyl-5-nitroimidazole-2-carboxyl)-2(thioformyl)hy-

Scheme I



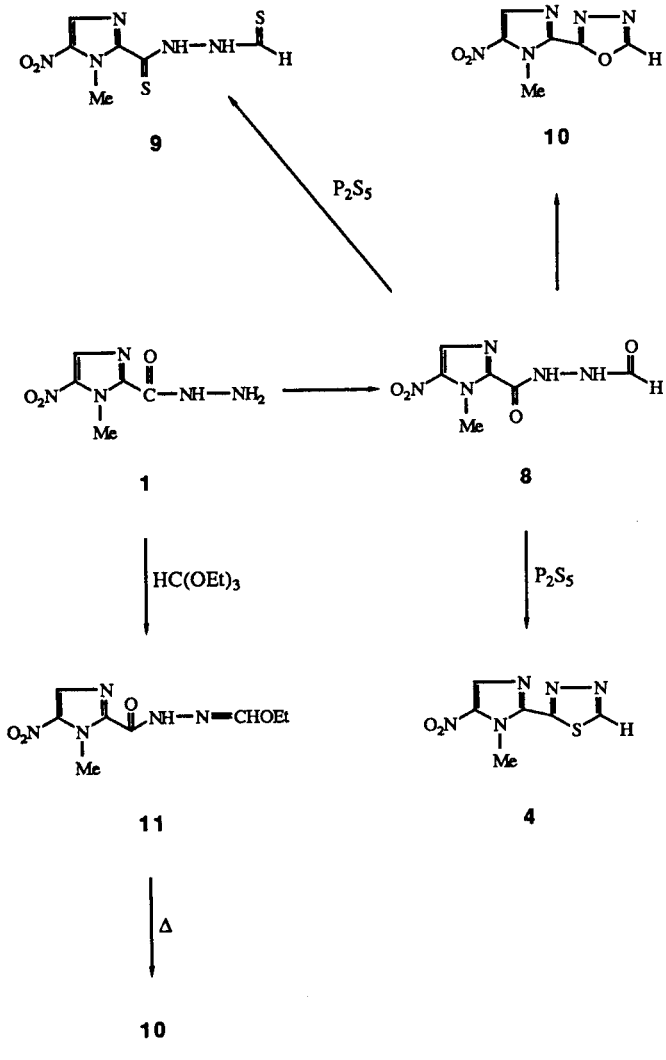
drazine (**3**).

Oxidation of 5-(1-methyl-5-nitroimidazol-2-yl)1,3,4-thiadiazole-2-thiol (**5**) [15] with dilute nitric acid gave compound **4** in poor yield.

Diazotization of 2-amino-5-(1-methyl-5-nitroimidazol-2-yl)-1,3,4-thiadiazole (**6**) [15] afforded the diazonium salt **7**. Reduction of **7** with hypophosphorous acid gave compound **4** in poor yield (Scheme I).

Finally compound **4** could be synthesized in relatively good yield according to Scheme II.

Scheme II



Refluxing of compound **1** with formic acid for 15 minutes gave 1-(1-methyl-5-nitroimidazole-2-carboxyl)-2-(formyl)hydrazine (**8**) in high yield. Refluxing 0.085 mole of compound **8** with 0.1 mole phosphorus pentasulfide in xylene gave 1-(methyl-5-nitroimidazole-2-thiocarboxyl)-2-(thioformyl)hydrazine (**9**) which could not be converted to compound **8** under different experimental conditions. However refluxing 0.085 mole of compound **8** with 0.05 mole phosphorus pentasulfide gave compound **4** in 50% yield. In addition 1-methyl-2-(1,3,4-oxadiazol-2-yl)-5-nitroimidazole (**10**) was also formed in 10% yield.

The usual reaction for the formation of 1,3,4-oxadiazole, namely the reaction of compound **1** with ethyl orthoformate, did not give the desired compound **10**. In the latter reaction ethyloxyformaldehyde 1-methyl-5-nitroimidazole-2-carboxylhydrazone (**11**) was formed. Heating compound **11** up to its melting point gave compound **10** in only 10% yield. However compound **11** could be obtained in 60% yield through refluxing of compound **8** with phosphorus pentoxide in xylene.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. Uv spectra were recorded using a Perkin-Elmer Model 550 SE. The ir spectra were obtained using a Perkin-Elmer Model 781 spectrograph (potassium bromide disks). The ^{1}H nmr spectra were recorded on a Varian T-60A 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.

1-Methyl-5-nitroimidazole-2-carboxamide-*N*-[amino(dimethylamino)methylene] (**2**).

A mixture of compound **1** (185 mg, 1 mmole) [14] 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 230 mg (95%) of compound **2**, mp 186-188°; ir (potassium bromide): ν 3295 (NH), 3130 (H-C_4 imidazole), 1682 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): 3.0 (s, 6H, CH_3), 4.50 (s, 3H, CH_3), 7.83 (s, 1H) and 7.90 ppm (s, 1H); ms: m/e (%) 240 (M^+, 100), 196 (9), 154 (13), 140 (30), 127 (16), 123 (13), 86 (17), 71 (41), 57 (16), 43 (99), 41 (83) and 32 (57).

Anal. Calcd. for $C_8H_{12}N_6O_3$: C, 40.00; H, 5.04; N, 34.98. Found: C, 39.91; H, 4.96; N, 34.87.

Oxidation of 5-(1-Methyl-5-nitroimidazole-2-yl)-1,3,4-thiadiazole-2-thiol (**5**).

A solution of compound **5** [12] (243 mg, 1 mmole) in 10% nitric acid (15 ml) was refluxed for ½ hour. The solution was neutralized with aqueous sodium bicarbonate solution and extracted with chloroform. The chloroform was dried (sodium sulfate), filtered and evaporated. The residue was purified by tlc on silica gel using chloroform-ethyl acetate (80:20) as the eluent to give 21 mg (10%) of compound **4**; mp 158-160°; uv (methanol): λ max 337 (log ϵ = 4.8); ir (potassium bromide): ν 3120 (H-C_4 imidazole), 3065 (H-C_5 thiadiazole), 1530 and 1360 cm^{-1} (NO_2); ^{1}H nmr (deuteriochloroform): 3.65 (s, 3H, CH_3), 8.17 (s, 1H, H-C_4 imidazole) and 9.35 ppm (s, 1H, H-C_5 thiadiazole); ms: m/e (%) 211 (M^+, 85), 184 (75), 181 (100), 165 (19), 157 (34), 151 (27), 138 (14), 116 (37), 112 (43), 97 (27), 85 (34), 83 (16), 70 (60), 54 (73), 53 (52), 52 (80), and 45 (55).

Anal. Calcd. for $C_6H_5N_5O_2S$: C, 34.13; H, 2.39; N, 33.17. Found: C, 34.25; H, 2.43; N, 33.25.

Diazotization of 2-Amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole (**6**).

To a stirring solution of 50% hypophosphorous acid (20 ml) at 0-5° a mixture of compound **6** (2.26 g, 0.01 mole) and sodium

nitrite (2.07 g, 0.03 mole) was gradually added. After addition was complete, the mixture was let to stand in refrigerator overnight. To the mixture 50% hypophosphorous acid (10 ml) was added and stirred at room temperature for 10 hours. The mixture was neutralized with concentrated aqueous sodium hydroxide at 0° and extracted with chloroform. The chloroform was dried (sodium sulfate), filtered and evaporated. The residue was purified by tlc on silica gel using chloroform-ethyl acetate (80:20) as eluent to give 422 mg (20%) of compound **4**, mp 158-160°.

1-(1-Methyl-5-nitroimidazole-2-carboxyl)-2-(formyl)hydrazine (**8**).

A solution of compound **1** [14] (1.85 g, 0.01 mole) in formic acid (25 ml) was refluxed for 1 hour. The solvent was evaporated. The residue in water (10 ml) was neutralized with sodium bicarbonate and the precipitate was filtered and crystallized from methanol to give 2.09 g (98%) of compound **8**, mp 164-165°; ir (potassium bromide): ν 1675, 1720 cm^{-1} (carbonyl); ^1H nmr (deuteriochloroform): 4.3 (s, 3H, CH_3), 8.1 (s, 1H, H_4) and 8.15 ppm (s, 1H, HCO); ms: m/e (%) 213 (M^+, 94), 186 (46), 185 (100), 154 (95), 108 (46), 107 (94), 81 (37), 80 (64) and 32 (71).

Anal. Calcd. for $C_6H_7N_5O_4$: C, 33.81; H, 3.31; N, 32.86. Found: C, 33.65; H, 3.43; N, 32.71.

1-(1-Methyl-5-nitroimidazole-2-thiocarboxyl)-2-(thioformyl)hydrazine (**9**).

To a solution of compound **8** (18.1 g, 0.085 mole) in xylene (900 ml) phosphorus pentasulfied (22.2 g, 0.1 mole) was added. The mixture was refluxed for ½ hour and filtered. The solvent was evaporated and the residue was crystallized from methanol to give 19.8 g (95%) of compound **9**, mp 253-255°; ir (potassium bromide): ν 1470, 1240 (C=S), 1530, 1360 cm^{-1} (NO_2); ms: m/e (%) 245 (M^+, 46), 244 (47), 243 (100), 213 (39), 197 (19), 167 (65), 156 (35), 121 (32), 80 (39), 70 (31), 59 (28), 52 (58) and 42 (99).

Anal. Calcd. for $C_6H_7N_5O_2S_2$: C, 29.38; H, 2.88; N, 28.56. Found: C, 29.43; H, 2.95; N, 28.55.

1-Methyl-2-(1,3,4-thiadiazol-2-yl)-5-nitroimidazole (**4**).

To a solution of compound **8** (18.1 g, 0.085 mole) in xylene (900 ml) phosphorus pentasulfide (11.0 g, 0.05 mole) was added. The mixture was refluxed for ½ hour and filtered. The solvent was evaporated and the residue was crystallized from methanol to give 8.97 (50%) of compound **4**, mp 158-160°. The filtrate was evaporated and the residue was purified by preparative tlc on silica gel using chloroform-ethyl acetate (80:20) as the eluent to give 1.66 g (10%) of 1-methyl-2-(1,3,4-oxadiazol-2-yl)-5-nitroimidazole (**10**), mp 178-180°; ir (potassium bromide): ν 3120 ($H\text{-}C_4$ imidazole), 3090 (H-C oxadiazole) 1530, 1365 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): 4.56 (s, 3H, CH_3), 8.14 (s, 1H, H_4) and 8.60 ppm (s, 1H, $H\text{-}C_2$ oxadiazole); ms: m/e (%) 195 (M^+, 98), 165 (100), 154 (24), 81 (32), 80 (25), 69 (29), 54 (40), 52 (46) and 42 (96).

Anal. Calcd. for $C_6H_5N_5O_3$: C, 36.93; H, 2.58; N, 35.89. Found: C, 36.99; H, 2.47; N, 35.94.

1-Methyl-2-(1,3,4-oxadiazol-2-yl)-5-nitroimidazole (**10**).

Method A.

To a solution of compound **8** (18.1 g, 0.085 mole) in xylene (900 ml), phosphorus pentoxide (7.1 g, 0.05 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 9.96 g (60%) of compound **10**, mp 178-180°.

Method B.

Compound **11** (2.41 g, 0.01 mole) was heated at 125° for 1 hour. The mixture was dissolved in chloroform and purified by preparative tlc on silica gel using chloroform-methanol (95:5) as the eluent to give 0.2 g (10%) of compound **10** mp 178-180°.

Ethoxyformaldehyde 1-Methyl-5-nitroimidazole-2-carboxylhydrazone (**11**).

A mixture of compound **1** (370 mg, 2 mmoles) and ethyl orthoformate (2.5 ml) was heated up to the boiling point. After cooling the precipitate was filtered and crystallized from ether to give 241 mg (50%) of compound **11**, mp 124-125; ir (potassium bromide): ν 3355 (NH), 3138 ($H\text{-}C_4$ imidazole), 1705 (C=O) and 1635 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): 1.43 (t, 3H, CH_3), 4.36 (q, 2H, CH_2), 4.50 (s, 3H, CH_3), 6.76 (s, 1H, HC=N) and 7.96 ppm (s, 1H, H_4); ms: m/e (%) 241 (M^+, 54), 226 (25), 212 (23), 196 (99), 185 (35), 154 (97), 140 (55), 127 (100), 123 (29), 108 (32), 97 (34), 80 (80), 68 (38), 54 (45), 53 (42) and 42 (63).

Anal. Calcd. for $C_8H_{11}N_5O_4$: C, 39.84; H, 4.60; N, 29.04. Found: C, 39.67; H, 4.71; N, 28.95.

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