SYNTHESIS OF 1-METHYL-2-(2-OXAZOLYL)-5-NITROIMIDAZOLE

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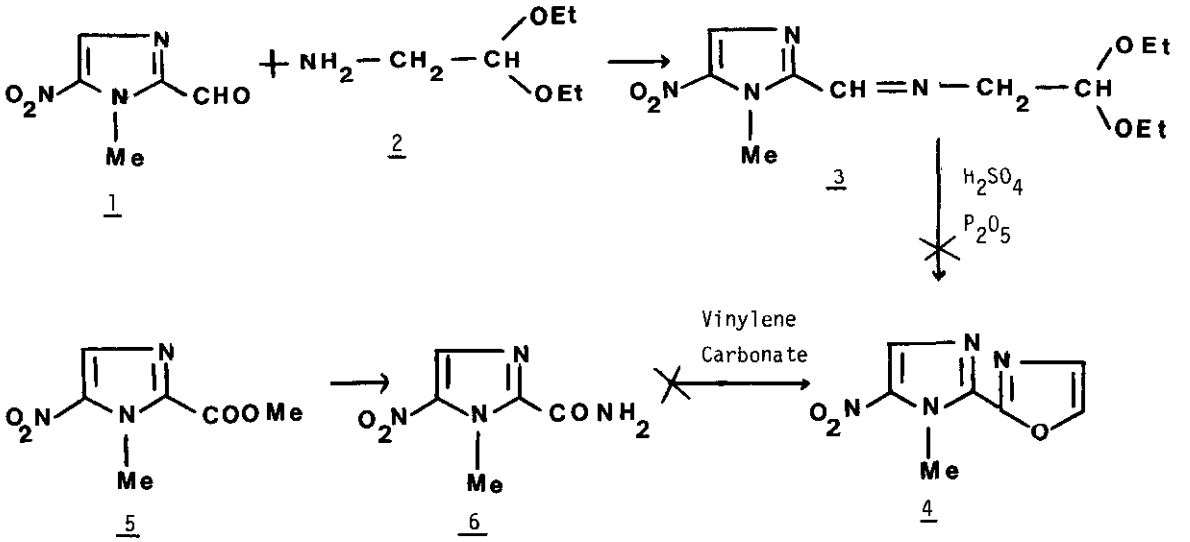
Abstract- 1-Methyl-2-(2-oxazolyl)-5-nitroimidazole (4) was prepared from methyl 1-methyl-5-nitroimidazole-2-carboxylate (5). The reaction of compound 5 with 2-aminoethanol gave N-(2-hydroxyethyl)-1-methyl-5-nitroimidazole-2-carboxamide (7). Treatment of 7 with thionyl chloride gave 8 which was cyclized to afford 9 by treatment with a base. Oxidation of 9 with nickel peroxide afforded compound 4.

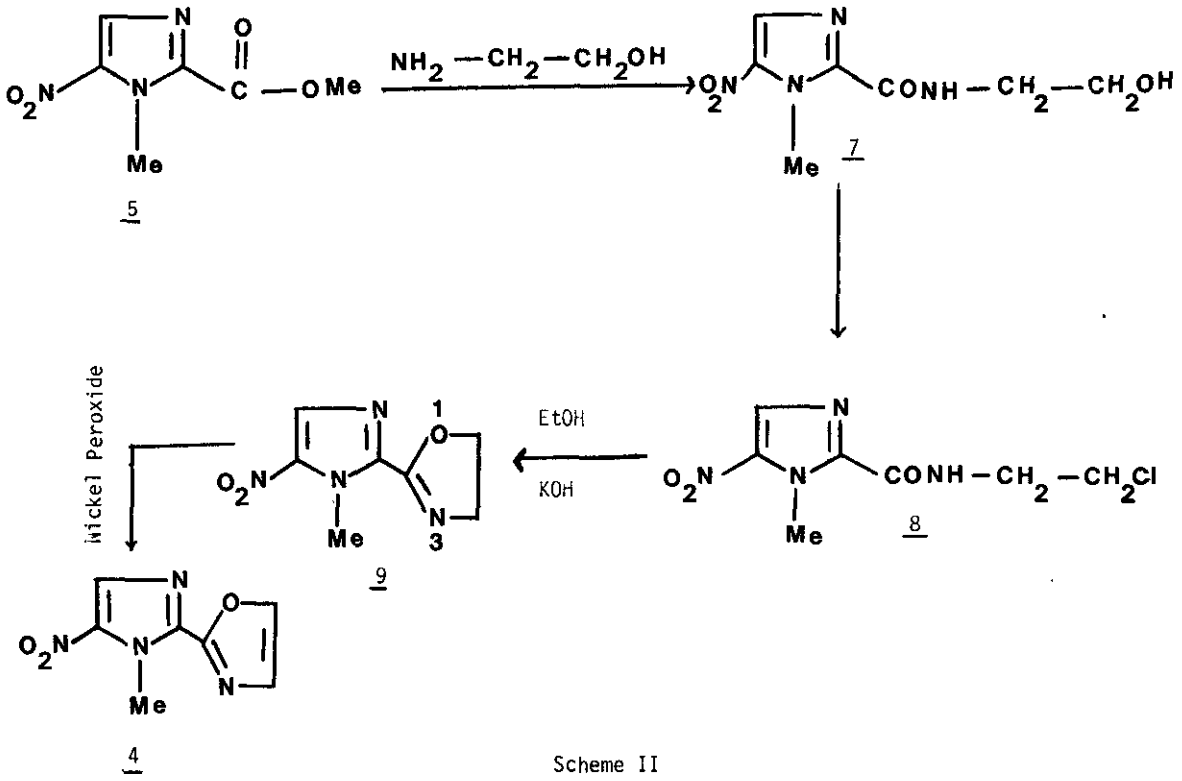
The considerable biological importance of nitroimidazole has stimulated much work on this heterocycle[1-5]. We would like to report the synthesis of the title compound which may be effective against tropical diseases.[6]

The synthesis of 1-methyl-2-(2-oxazolyl)-5-nitroimidazole (4) was attempted according to the published methods for the preparation of 2-aryloxazole[7-8] (Scheme I).



Scheme I

Reaction of 1-methyl-2-formyl-5-nitroimidazole (1) with aminoacetaldehyde diethyl acetal afforded 1-methyl-5-nitroimidazole-2-carboxyaldehyde 2,2-diethoxyethylimine (3). However, the reaction of 3 with sulfuric acid did not give the desired compound 4. The reaction of 1-methyl-5-nitroimidazole-2-carboxylate (5) with ammonia gave 1-methyl-5-nitroimidazole-2-carboxamide (6)[9]. However, the reaction of 6 with vinylene carbonate did not afford 4. Finally compound 4 could be synthesized by the route shown in Scheme II.



Scheme II

Reaction of compound 5 with 2-aminoethanol gave N(2-hydroxyethyl)-1-methyl-5-nitroimidazole-2-carboxamide (7) in good yield. Reaction of compound 7 with thionyl chloride afforded N(2-chloroethyl)-1-methyl-5-nitroimidazole-2-carboxamide (8) which was cyclized to 2-(1-methyl-5-nitroimidazol-2-yl)oxazoline (9). Oxidation of 9 with nickel peroxide[10] gave compound 4.

EXPERIMENTAL

Melting points were taken on Kofler hot stage microscope. The uv spectra were taken on a Varian Techtron 635 spectrometer. The ir spectra were obtained on a Perkin-Elmer 267 spectrograph, nmr and ms spectra were run on a Varian T-60 A and MS-311 spectrometers. Tetramethylsilane was used as an internal standard for nmr. Ms were taken at 70 eV.

1-Methyl-5-nitroimidazole-2-carboxyaldehyde 2,2-Diethylimine (3)

A solution of 1-methyl-5-nitroimidazole-2-carboxyaldehyde (1, 1.55 g, 0.01 mol), aminoacetaldehyde diethyl acetal (1.33 g, 0.01 mol) in toluene (70 ml) was refluxed under Dean and Stark apparatus for 4 h. The solvent was removed under the reduced pressure and the residue was distilled to give compound 3 (2.4 g, 89%); bp 148-152 °C (4 mm Hg); ^{1}H nmr ($CDCl_3$) δ 1.18 (t, 6H, CH_3), 3.67 (m, 6H, CH_2O and CH_2N), 4.33 (s, 3H, CH_3N), 4.82 (t, 1H. $CH(OC_2H_5)_2$), 8.01 (s, 1H, H4), 8.33 (s, 1H, CH=N), Anal. Calc. for $C_{11}H_{18}N_4O_4$: C, 48.88, H, 6.71; N, 20.73. Found: C, 48.95; H, 6.58; N, 2065.

1-Methyl-5-nitroimidazole-2-carboxamide (6)

To a stirring solution of methyl 1-methyl-5-nitroimidazole-2-carboxylate (5, 1.85 g, 0.01 mol) in methanol (12 ml), a saturated solution of ammonia (12 ml) was added. The solution was refluxed for 5 min and cooled. The precipitate was collected by filtration and recrystallized from acetone to give 6 (1.56 g, 92%); mp 221-22°C (ref. 9, mp 222-224°C); ir (KBr) 3340, 3170 (NH_2), 3125 (H-C4 imidazole), 1690 (C=O), 1620 (NH_2), 1325 and 1535 cm^{-1} (NO_2); ms m/z (relative intensity) 170 (M^+, 25), 140 (M^+-NO, 100), 123 (37), 110 (22), 97 (27), 81 (97), 71 (19), 67 (25), 54 (93), 44 (84) and 42 (71).

N(2-Hydroxyethyl)-1-methyl-5-nitroimidazole-2-carboxamide (7)

To a stirring solution of methyl 1-methyl-5-nitroimidazole-2-carboxylate (5, 1.85 g, 0.01 mol) in tetrahydrofuran (20 ml) at ambient temperature, a solution of 2-aminoethanol (0.01 g, 0.01 mol) in tetrahydrofuran (20 ml) was added dropwise. The reaction mixture was stirred until the spot of the starting 5 was disappeared on tlc and then evaporated. The resulting crystalline residue was recrystallized from ether to give 7 (2.0 g, 93%); mp 88-90°C; ir (KBr) 3350 (OH), 3260 (NH), 3115 (H-C4 imidazole), 1650 (C=O), 1540 and 1365 cm^{-1} (NO_2); ^{1}H nmr ($CDCl_3$) δ 3.75 (m, 4H, CH_2), 4.43 (s, 3H, CH_3) 7.90 (s, 1H, H4); ms m/z (relative intensity) 214 (M^+, 3), 196 (8), 184 (69), 183 (93), 154 (100), 141 (8), 127 (8), 108 (11), 80 (7); Anal. Calcd. for $C_7H_{10}N_4O_4$: C, 39.26; H, 4.71; N, 26.16. Found: C, 39.41; H, 4.65; N, 26.08.

N(2-Chloroethyl)-1-methyl-5-nitroimidazole-2-carboxamide (8)

A stirring mixture of compound 7 (2.14 g, 0.01 mol) and thionyl chloride (20 ml) was refluxed for 2 h. The solvent was removed under reduced pressure. To the residue, ice-water was added and neutralized with sodium bicarbonate solution to give a precipitate. The precipitate was filtered and crystallized from ether to give compound 8 (1.63 g, 70%), mp 107-108°C; ir (KBr) 3322 (NH), 3140 (H-C4 imidazole) and 1668 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 3.75 (m, 4H, CH_2), 4.47 (s, 3H, CH_3-N) 7.90 (s, 1H, H4); ms m/z (relative intensity) 234 (M^++2, 27 232 (M^+, 87), 197 (95), 196 (91), 184 (72), 183 (99), 175 (53), 169 (37), 155 (68), 154 (100), 138 (23), 137 (20), 127 (50), 108 (88), 81 (57), 80 (88), 68 (54), 63 (64), 54 (50), 53 (57), 42 (55); Anal. Calcd. for $C_7H_9ClN_4O_3$: C, 36133; H, 3.90; N, 24.09. Found: C, 36.01; H, 3.98; N, 23.98.

2-(1-Methyl-5-nitroimidazol-2-yl)oxazoline (9)

To a stirring solution of compound 8 (2.32 g, 0.01 mol) in ethanol (40 ml) at 75°C a solution of potassium hydroxide (0.56 g) in ethanol (10 ml) was added dropwise. The reaction mixture was cooled to give 9 (1.47 g, 75%), mp 148-150°C; ir (KBr) 3118 (H-C4 imidazole, 1648 (C=N), 1530 and 1365 cm^{-1} (NO_2); ^1H nmr ($CDCl_3$) δ 4.33 (m, 4H, CH_2), 4.40 (s, 3H, CH_3N), 8.07 (s, 1H, H4); ms m/z (relative intensity) 196 (M^+, 25), 166 (M^+-NO, 100), 136 (14), 122 (15), 97 (25), 79 (27), 54 (24); Anal. Calcd. for $C_7H_8N_4O_3$: C, 42.86; H, 4.11; N, 28.56. Found: C, 42.69; H, 4.30; N, 28.39.

1-Methyl-2-(2-oxazolyl)-5-nitroimidazole (4)

To a stirring solution of compound 9 (196 mg, 1 mmol) in benzene (14 ml), nickel peroxide[10] (4 g) was added. The mixture was refluxed for 15 min and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by tlc on silica gel using chloroform:methanol (97:3) as an eluent to give compound 4 (48.5 mg, 25%), mp 173-175°C; ir (KBr) 3120 (H-C4 imidazole), 1528 and 1363 cm^{-1} (NO_2); ^1H nmr ($CDCl_3$) δ 4.53 (s, 3H, N-CH_3), 7.40 (d, 1H, H4-oxazole, $J_{4,5}$ = 1 Hz), 7.88 (d, 1H, H5-oxazole, $J_{4,5}$ = 1 Hz), 8.10 (s, 1H, H4); ms m/z (relative intensity) 194 (M^+, 100), 164 (98), 95 (83), 81 (36), 77 (68), 66 (45), 54 (98), 52 (98); Anal. Calcd. for $C_7H_6N_4O_3$: C, 43.31; H, 3.21; N, 28.86. Found: C, 43.16; H, 3.05; N, 28.69.

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