# Syntheses of Substituted 2-(1-Methyl-5-nitro-2-benzimidazolyl)quinolines [1]



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Reaction of *N*-methyl-2-amino-4-nitroaniline (**1**) with lactic acid afforded 2-(1-hydroxyethyl)-1-methyl-5-nitrobenzimidazole (**2**). Oxidation of compound **2** with chromic acid in acetic acid gave 2-acetyl-1-methyl-5-nitrobenzimidazole (**3**). Reaction of compound **3** with substituted 2-aminobenzaldehyde (**4**) under basic conditions yielded substituted 2-(1-methyl-5-nitro-2-benzimidazolyl)quinolines (**5**). Condensation and cyclization of *o*-aminoacetophenone (or substituted *o*-aminobenzophenones) with compound **3** under acetic condition afforded compound **7**. Condensation and cyclization of compound **1** with indole-3-carboxaldehyde (**11**) in ethanol in the presence of excess nitrobenzene gave 3-(1-methyl-5-nitro-2-benzimidazolyl)indole (**12**).

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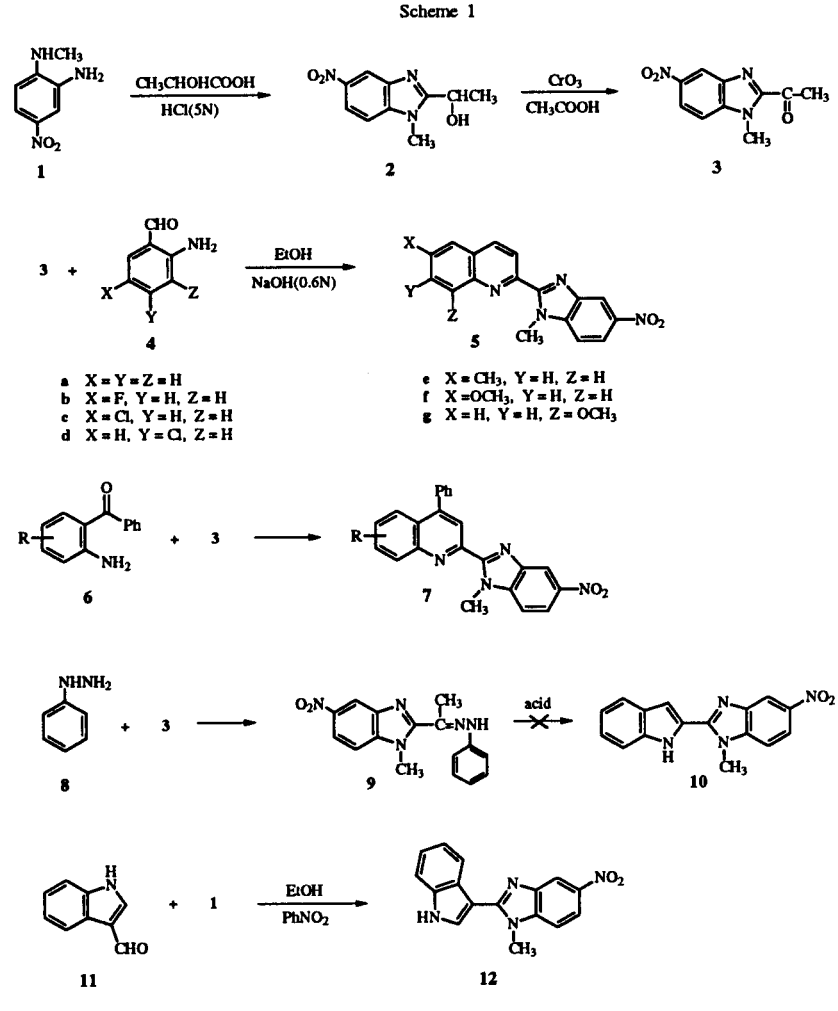
The considerable biological importance of benzimidazole derivatives has stimulated much work on this heterocycle [2-7]. We would like to report the syntheses of the title compounds as possible effective drugs against tropical diseases [8].

The most common approach employed to synthesize substituted quinolines are the condensation of lithiumaryl with 2-chloroquinoline, condensation of an aldehyde with aniline and subsequent condensation cyclization of the intermediate with propiolic acid or maleic acid and par-

Scheme 1



aldehyde [9] and the condensation-cyclization of an aniline with α,β-unsaturated aldehyde (Skraup synthesis) [10]. The first two reactions failed in our case and the latter reaction was not feasible because of the unavailability of the starting α,β-unsaturated aldehyde. However, we could synthesize the desired compounds according to Friedlander's method [10, 11] (see Scheme 1).

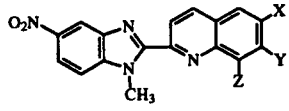
Reaction of substituted-2-nitrobenzaldehyde with sodium dithionite gave substituted-2-aminobenzaldehyde (**4**). 2-(1-Hydroxyethyl)-1-methyl-5-nitrobenzimidazole (**2**) was prepared by modified Philip's method [12]. Oxidation of compound **2** with chromic acid in acetic acid gave 2-acetyl-1-methyl-5-nitrobenzimidazole (**3**) [13]. Reaction of compound **4** with **3** in basic medium afforded the desired compounds, namely substituted 2-(1-methyl-5-nitro-2-benzimidazolyl)quinolines (**5**), in moderate yield (see Table 1).

Reaction of substituted 2-aminobenzophenone (or acetophenone) **6** with compound **3** in basic medium did not give substituted 2-(1-methyl-5-nitro-2-benzimidazolyl)-4-phenyl (or methyl) quinolines **7**. However, these compounds could be synthesized in acid medium in high yield.

For the preparation of 2-(1-methyl-5-nitro-2-benzimidazolyl)indole (**10**) compound **3** was reacted with hydrazine and 2-acetyl-1-methyl-5-nitrobenzimidazole phenylhydrazone (**9**) was obtained. Fischer indole synthsis for the preparation of compound **10** through the reaction of compound **9** with polyphosphoric acid, zinc chloride or boron trifluoride failed. In addition, reaction of indole-2-carboxylic acid with **1** under Philips's condition did not give the desired compound. However, reaction of compound **1** with indole-3-carboxaldehyde (**11**) in ethanol with excess nitrobenzene afforded 3-(1-methyl-5-nitro-2-benzimidazolyl)indole (**12**). Indole-2-carboxaldehyde was unstable under the above condition and did not give compound **10**.

The structure of all compounds were confirmed by elemental analysis, ir, nmr and mass spectroscopy.

Table 1




| Compound No. | X | Y | Z | Mp°C [a] (%) | Yield | Formula | %C Calcd. | %C Found | %H Calcd. | %H Found | %N Calcd. | %N Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | H | H | H | 312-314 | 45 | $C_{17}H_{12}N_4O_2$ | 67.11 | 67.23 | 3.95 | 4.04 | 18.42 | 18.58 |
| **5b** | F | H | H | 312-315 | 73 | $C_{17}H_{11}FN_4O_2$ | 63.35 | 63.18 | 3.42 | 3.57 | 17.39 | 17.22 |
| **5c** | Cl | H | H | 279-281 | 32 | $C_{17}H_{11}ClN_4O_2$ | 60.27 | 60.38 | 3.25 | 3.15 | 16.54 | 16.67 |
| **5d** | H | Cl | H | 315-317 | 58 | $C_{17}H_{11}ClN_4O_2$ | 60.27 | 60.15 | 3.25 | 3.18 | 16.54 | 16.45 |
| **5e** | $CH_3$ | H | H | 292-295 | 60 | $C_{18}H_{14}N_4O_2$ | 67.92 | 67.79 | 4.40 | 4.56 | 17.61 | 17.77 |
| **5f** | $OCH_3$ | H | H | 294-296 | 60 | $C_{18}H_{14}N_4O_3$ | 64.67 | 64.53 | 4.19 | 4.32 | 16.77 | 16.88 |
| **5g** | H | H | $OCH_3$ | 270-272 | 65 | $C_{18}H_{14}N4O_3$ | 64.67 | 64.79 | 4.19 | 4.26 | 16.77 | 16.07 |

a) All compounds were crystallized from chloroform.

## 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. 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 spectra 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.

2-(1-Hydroxyethyl)-1-methyl-5-nitrobenzimidazole (**2**).

A solution of *N*-methyl-2-amino-4-nitroaniline (3.17 g, 0.019 mole), lactic acid (9.63 g, 0.107 mole) and hydrochloric acid (5*N*, 30 ml) was refluxed. The progress of the reaction was followed by tlc (silica gel, chloroform:ethyl acetate, 80:20) until the reaction was complete (about 8 hours). The solution was filtered and made basic with ammonia. The precipitate was filtered and crystallized from alcohol-water (1:1) to give 3.15 g (75%) of compound **2**, mp 145-150° (lit 13, mp 145-155°); ir (potassium bromide): ν 3230 (OH), 1550 and 1380 $cm^{-1}$ ($NO_2$); $^1H$ nmr (deuteriochloroform): 8.2 (q, 1H, $H_6$), 7.4 (d, 1H, $H_4$), 7.3 (d, 1H, $H_7$), 5.2 (q, 1H, HC-O), 3.9 (6, 3H, N-$CH_3$), 2.9 (s, 1H, OH) and 1.7 ppm (d, 3H, $CH_3$).

*Anal.* Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.30; H, 4.98; N, 19.00. Found: C, 54.46; H, 4.79; N, 18.88.

6-Chloro-2-(1-Methyl-5-nitro-2-benzimidazolyl)quinoline (**5c**).

To a stirring suspension of 2-acetyl-1-methyl-5-nitrobenzimidazole (**3**, 438 mg, 2 mmoles) [13], 2-amino-5-chlorobenzaldehyde (311 mg, 2 mmoles) in 100 ml of ethanol a solution of sodium hydroxide (0.4 g, 0.01 mole) in 20 ml of water was added dropwise. After addition was complete the stirring was continued for 4 hours. The precipitate was filtered and crystallized from chloroform to give 237 mg (35%) of **5c**, mp 279-282°; uv (tetrahydrofuran): λ max 279 (log ε = 4.42), 347 nm (log ε = 4.32); $^1$H nmr (trifluoroacetic acid): 8.88 (d, 1H, $H_4$ benzimidazole, $J_{4,6}$ = 1.9 Hz), 8.76 (d, 1H, $H_4$ quinoline, $J_{3,4}$ = 8.5 Hz), 8.67 (q, $H_7$ quinoline, $J_{5,7}$ = 1.9 Hz $J_{7,8}$ = 7.8 Hz), 8.39 (d, 1H, $H_5$ quinoline, $J_{5,7}$ = 1.9 Hz), 8.24 (q, $H_6$ benzimidazole, $J_{4,6}$ = 1.9 Hz, $J_{6,7}$ = 8.5 Hz), 8.07 (q, 3H, $H_7$ benzimidazole and $H_{3,5}$ quinoline); ms: m/z (%) 338 ($M^+$, 100), 292 (M-$NO_2$, 41), 257(M-($NO_2$+Cl), 10), 162 (22), 126 (12), 77 (27), 75 (28), 65 (21) and 50 (14).

*Anal.* Calcd. for $C_{17}H_{11}ClN_4O_2$: C, 60.27; H, 3.25; N, 16.54. Found: C, 60.38; H, 3.15; N, 16.67.

Compounds **5a** to **5g** were prepared similarly (Table 1).

2-(1-Methyl-5-nitro-2-benzimidazolyl)-4-phenylquinoline (**7**, R = H).

To a solution of compound **3** (657 mg, 3 mmoles) and 2-aminobenzophenone (768.3 mg, 3.9 mmoles) in acetic acid (10 ml) concentrated sulfuric acid (3 drops) was added. The solution was refluxed for 22 hours. After cooling it was added to ice (35 g) and neutralized with ammonia. The precipitate was filtered and crystallized from methanol to give 456 mg (40%) of **7** (R = H), mp 252-255°; uv (tetrahydrofuran): λ max 277 (log ε = 4.68), 338 nm (log ε = 4.48); $^1$H nmr (deuteriochloroform): 8.80 (d, 1H, $H_4$ benzimidazole, $J_{4,6}$ = 1.8 Hz); 8.50 (s, 1H, $H_3$ quinoline), 8.37-7.66 (m, 6H, aromatic), 7.57 (s, 5H, phenyl) and 4.56 ppm (s, 3H, $CH_3$); ms: m/z (%) 380 ($M^+$, 100), 334 (M-$NO_2$, 56), 230 (18), 204 (4-phenylquinoline, 37), 176 (1-methyl-5-nitrobenzimidazole, 21), 167 (22), 76 (28), 63 (20) and 41 (26).

*Anal.* Calcd. for $C_{23}H_{16}N_4O_2$: C, 72.63; H, 4.21; N, 14.74. Found: C, 72.81; H, 4.35; N, 14.86.

2-(1-Methyl-5-nitro-2-benzimidazolyl)-7-methyl-4-phenylquinoline (**7**, R = 7-$CH_3$).

This compound was prepared similarly to **7** (R = H) in 35% yield; mp 267-270°; uv (tetrahydrofuran): λ max 244 (log ε =4.45), 277 (log ε = 4.69), 341 nm (log ε = 4.49); $^1$H nmr (deuteriochloroform): 8.75 (d, 1H, $H_4$ benzimidazole, $J_{4,6}$ = 1.8 Hz), 8.44 (s, 1H, $H_3$ quinoline), 8.30 (q, 1H, $H_6$ benzimidazole, $J_{4,6}$ = 1.8 Hz, $J_{6,7}$ = 8.7 Hz), 8.0 (q, 1H, $H_6$ quinoline), 7.9 (d, 1II, $H_7$ benzimidazole, $J_{6,7}$ = 8.7 Hz), 7.56 (s, 5H, phenyl), 7.47-7.30 (d, 2H, $H_5$ and $H_8$ quinoline), 4.56 (s, 3H, N-$CH_3$) and 2.61 ppm (s, 3H, $CH_3$); ms: m/z (%) 394 ($M^+$, 62), 348 (M-$NO_2$, 21), 246 (100), 242 (25), 229 (26), 217 (42), 203 (42), 189 (44), 174 (33), 165 (15), 152 (14), 129 (16), 115 (16), 104 (26), 91 (27), 88 (26), 77 (33) and 63 (27).

*Anal.* Calcd. for $C_{24}H_{18}N_4O_2$: C, 73.10; H, 4.57; N, 14.21. Found: C, 73.01; H, 4.38; N, 14.35.

6-Chloro-2-(1-methyl-5-nitro-2-benzimidazolyl)-4-phenylquinoline (**7**, R = 6-Cl).

This compound was prepared similarly to **7** (R = H) in 30% yield, mp 312-314°; uv (tetrahydrofuran): λ max 282 (log ε = 4.60), 355 nm (log ε = 4.43); $^1$II nmr (deuteriochloroform): 8.82 (d, 1H, $H_4$ benzimidazole, $J_{4,6}$ = 1.8 Hz), 8.60 (q, 1H, $H_6$ benzimidazole, $J_{4,6}$ = 1.8 Hz, $J_{6,7}$ = 9 Hz), 8.37 (s, 1H, $H_3$ quinoline), 8.18 (m, 4H, aromatic), 7.6 (s, 5H, phenyl) and 4.56 ppm (s, 3H, N-$CH_3$); ms: m/z (%) 414 ($M^+$, 9), 368 (M-$NO_2$, 4), 266 (23), 204 (28), 176 (21), 130 (18), 103 (50), 77 (100), 62 (56), 50 (42) and 38 (22).

*Anal.* Calcd. for $C_{23}H_{15}ClN_4O_2$: C, 66.59; H, 3.62; N, 13.51. Found: C, 66.42; H, 3.73; N, 13.69.

2-Acetyl-1-methyl-5-nitrobenzimidazole Phenylhydrazone (**9**).

To a solution of compound **3** (109.5 mg, 0.5 mmole) in ethanol (1.5 ml), phenylhydrazine (108 mg, 1 mmole) and acetic acid (2 drops) were added. The mixture was refluxed for 3 hours. After cooling the precipitate was filtered and recrystallized from ethanol to give 100 mg (65%) of compound **9**, mp 218-220°; ir (potassium bromide): ν 3300 (NH), 1610, 1485 (aromatic), 1530 and 1380 cm$^{-1}$ ($NO_2$).

*Anal.* Calcd. for $C_{16}H_{15}N_5O_2$: C, 62.14; H, 4.85; N, 22.65. Found: C, 62.01; H, 4.67; N, 22.49.

3-(1-Methyl-5-nitro-2-benzimidazolyl)indole (**12**).

A solution of compound **1** (501 mg, 3 mmoles), and indole-3-carboxaldehyde (725 mg, 5 mmoles) in ethanol (5 ml) and nitrobenzene (4 ml) was refluxed for 36 hours. After cooling the precipitate was filtered, washed with cold acetone (3 x 5 ml) and recrystallized from acetone to give 526 mg (60%) of **12**, mp 314-317°; uv (methanol): λ max 291 (log ε = 4.0), 250 nm (log ε = 4.07); ir (potassium bromide): ν 3410 (NH), 1560 and 1330 cm$^{-1}$ ($NO_2$); ms: m/z (%) 292 ($M^+$, 100), 246 (M-$NO_2$, 55), 142 (13), 116 (indole, 17), 89 (11) and 63 (17).

*Anal.* Calcd. for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.11; N, 19.18. Found: C, 65.60; H, 4.25; N, 19.36.

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REFERENCES AND NOTES

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