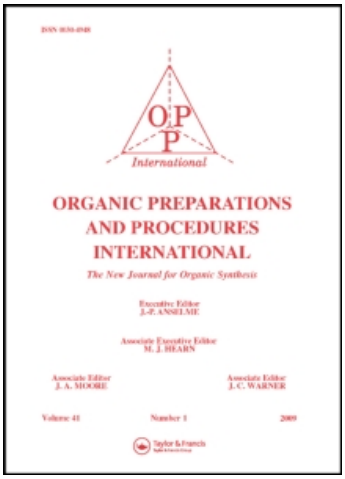


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# SYNTHESIS OF N-METHYLATED QUINOLONES

J. N. Domínguez[a]; J. Charris[a]
[a] Universidad Central de Venezuela Facultad de Farmacia, Laboratorio Síntesis Orgánica, Caracas, VENEZUELA

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## SYNTHESIS OF N-METHYLATED QUINOLONES

*Submitted by* J. N. Domínguez* and J. Charris
(03/18/93)

*Universidad Central de Venezuela*
*Facultad de Farmacia , Laboratorio Síntesis Orgánica*
*Caracas 1051, VENEZUELA*

Quinolones have received considerable attention as useful antibacterial agents.[1] Over the last few years, we have endeavored to develop new compounds of potential antimalarial activity. Although recent emphasis has been placed on vaccine development, this approach has not yet contributed to the control of this endemia.[2] The need for new drugs which are effective against drug-resistant parasites is obvious. We now report a methodology for the rapid synthesis of new N-methylated quinolones.

The starting 2-methylthio-3-cyanoquinolones **1**, easily prepared in high yields from the corresponding anilines with ketene dithioacetal,[3] were treated with methyl iodide and potassium carbonate in refluxing DMF to give the N-methylquinolones **2**; their structure was established from the spectral

data (Table 2). Further evidence[4] was necessary to confirm the structure as *quinolone* instead of *quinoline* during the alkylation process. Treatment of the quinolones **1** with methyl iodide and potassium carbonate in refluxing acetone, afforded a mixture of quinolones and 4-methoxyquinolines. Two methyl signals at δ 4.6 and 4.2 with intensities 3:1 respectively were assigned to the OMe and NMe. Treatment of **2** with hydrazine hydrate in refluxing pyridine, gave the expected 3-amino-9-methyl-1H-pyrazolo[3,4-b]quinolones **3**.

**TABLE 1.** Mps, Yields and Elemental Analyses from **2a-d** to **4a-d**

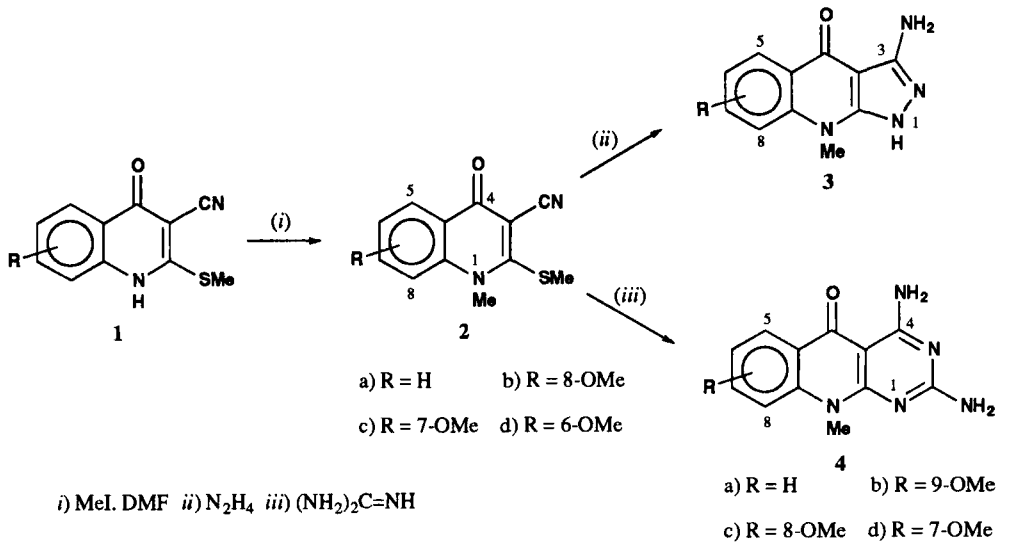
| Cmpd | mp. (°C) | Yields (%) | Elemental Analyses Calcd. (Found) | | | |
|---|---|---|---|---|---|---|
| | | | C | H | N | S |
| **2a** | 197-198 | 86 | 62.59 (62.34) | 4.38 (4.31) | 12.16 (12.25) | 13.92 (14.25) |
| **2b** | 228 | 80 | 59.98 (59.83) | 4.65 (4.75) | 10.76 (10.71) | 12.32 (12.29) |
| **2c** | 215-216 | 83 | 59.98 (59.99) | 4.65 (4.57) | 10.76 (10.85) | 12.72 (12.27) |
| **2d** | 244-245 | 85 | 59.98 (60.13) | 4.65 (4.65) | 10.76 (10.85) | 12.32 (12.17) |
| **3a** | 278-280 | 92 | 61.67 (61.90) | 4.71 (4.75) | 26.16 (25.93) | |
| **3b** | 244-245 | 95 | 59.01 (59.24) | 4.95 (4.98) | 22.94 (23.01) | |
| **3c** | 272-273 | 78 | 59.01 (59.19) | 4.95 (4.96) | 22.94 (22.87) | |
| **3d** | 257-258 | 78 | 59.01 (58.93) | 4.95 (4.87) | 22.94 (22.72) | |
| **4a** | 360 (dec.) | 85 | 59.74 (59.44) | 4.60 (4.59) | 29.03 (28.93) | |
| **4b** | 298 | 77 | 57.56 (57.65) | 4.83 (4.80) | 25.82 (25.87) | |
| **4c** | 348-350 | 73 | 57.56 (57.46) | 4.83 (4.67) | 25.82 (25.80) | |
| **4d** | 320-322 | 82 | 57.56 (57.48) | 4.83 (4.67) | 25.82 (25.90) | |

Similarly, derivatives **4** were obtained by treatment of **2** with guanidine hydrochloride and potassium carbonate in refluxing DMF, which afforded the corresponding 2,4-diamino-10-methylpyrimido [4,5-b]quinolones **4.** Their structures were established on the basis of the spectral data (Table 2).

**TABLE 2.** Spectral Data for Compounds **2a-d, 3a-3d** and **4a-d**

| Cmpd. | IR($cm^{-1}$) | $^1H$ NMR[a] (δ) MS m/z |
|---|---|---|
| **2a** | 2250 (CN), 1620 (CO) | 2.7 (s, 3H, SMe), 4.2 (s, 3H, NMe), 7.4-8.4 (m, 4H, Ar)[b] |
| **2b** | 2204 (CN), 1620 (CO) | 2.9 (s, 3H, SMe), 4.2 (s, 3H, NMe), 4.6 (s, 3H, OMe), 7.7-8.4 (m, 3H, Ar) |
| **2c** | 2212 (CN), 1622 (CO) | 3 (s, 3H, SMe), 4.2 (s, 3H, NMe), 4.6 (s, 3H, OMe), 7.4-7.8 (m, 2H, C8, C6, Ar), 8.8 (d, 1H, C5, Ar) |
| **2d** | 2205 (CN), 1625 (CO) | 2.9 (s, 3H, SMe), 4.2 (s, 3H, NMe), 4.6 (s, 3H, OMe), 7.7-8.2 (m, 3H, Ar) |
| **3a** | 3303, 3132, 2914 ($NH_2$) 1650, 1618 (CO) | 3.8 (s, 3H, NMe), 6-6.6 (br, 2H, $NH_2$, $D_2O$), 7.2-8 (m, 3H, Ar), 8.6 (d, 1H, Ar);[b] $M^+$ 244 (57%) |
| **3b** | 3496, 3276, 2994 ($NH_2$) 1660, 1620 (CO) | 4.2 (s, 3H, NMe), 4.3 (s, 3H, OMe), 7.4-7.8 (m, 2H, Ar), 8.1-8.3 (m, 1H, Ar); $M^+$ 2.14 (63%) |
| **3c** | 3407, 3290, 3140 ($NH_2$) 1650, 1629 (CO) | 3.9 (s, 3H, NMe), 4.2 (s, 3H, OMe), 7.1-7.6 (m, 2H, C8, C6, Ar), 8.6 (d, 1H, C5, Ar) |
| **3d** | 3334, 3094 ($NH_2$) 1652, 1627 (CO) | 4.1 (s, 3H, NMe), 4.2 (s, 3H, OMe), 7.7-8.2 (m, 3H, Ar) |
| **4a** | 3400, 3300, 3108 ($NH_2$) 1662, 1621 (CO) | 4.2 (s, 3H, NMe), 6.5-7.5 (br, 2H, $NH_2$, $D_2O$), 7.7-8.7 (m, 4H, Ar); $M^+$ 271 (68%) |
| **4b** | 3424, 3400, 2965 ($NH_2$) 1656, 1620 (CO) | 4.2 (s, 3H, NMe), 4.4 (s, 3H, OMe), 7.6-8.6 (m, 7H, Ar, $NH_2$, $D_2O$); $M^+$ 241 (92%) |
| **4c** | 3470, 3321, 3138 ($NH_2$) 1658, 1629 (CO ) | 4.2 (s, 6H, NMe, OMe), 7.2-7.5 (m, 2H, C7, C9, Ar), 8.5 (d, 1H, C6, Ar) |
| **4d** | 3472, 3400, 2961 ($NH_2$) 1653, 1620 (CO) | 4.1 (s, 3H, NMe), 4.2 (s, 3H, OMe), 7.9 (m, 3H, Ar), 8.6 (br, 2H, $NH_2$) |

a) In a mixture of $CDCl_3$ and trifluoroacetic acid (TFA) unless otherwise indicated. b) In DMSO-$d_6$.



## EXPERIMENTAL SECTION

Melting points were taken using a Thomas micro hot stage apparatus and are uncorrected . $^1$H NMR spectra (60 MHz) were recorded using a Varian 360 SL spectrometer and are reported in ppm (δ) downfield from TMS as internal standard. Infrared spectra were determined as KBr pellets on a Shimadzu model 435 V-03 spectrophotometer. Mass spectra were recorded on a Hewlett Packard 5995 Mass spectrometer. Chemical analyses were determined by Galbraith Laboratories, Inc., Knoxville, TN. All solvents were distilled and dried with the usual desiccants.

**General Procedure for the Synthesis of Quinolones 2-4.**- To a refluxing solution of 1 mmol of **1** in 10 mL of DMF containing 2 mmol of potassium carbonate, was added dropwise 4 mmol of methyl iodide. The reflux was continued for 2 hrs and the mixture was allowed to cool to RT. It was then poured slowly into ca. 20 g of ice-water. The precipitated solid was collected, washed with water and crystallized from methanol to give the quinolone **2** (Table 1). Each derivative **2** (1.3 mmol) was treated separately with hydrazine hydrate (2 mmol) in refluxing pyridine (5 mL) for 4 hrs or with guanidine hydrochloride (2 mmol) and potassium carbonate (2.6 mmol) in refluxing DMF (10 mL) for 5 hrs. In both cases, the mixtures were cooled and poured into water; the solids thus obtained were collected and crystallized from ethanol to give yellow crystals of **3** or **4** respectively.

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4. X-ray Crystal structure determination of compounds **4** and **5** established that the methyl group is N-bonded (unpublished results).

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