

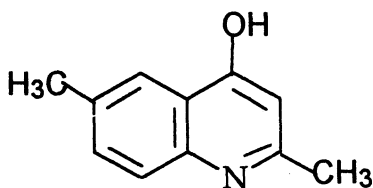
## Synthesis and Antimicrobial Properties of 2-Substituted Mercapto-4,8-Dimethyloxazolo(4,5-C)Quinolines

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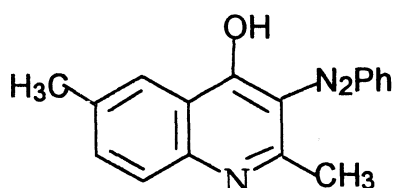
2-Mercapto-4,8-dimethyloxazolo(4,5-c)quinoline (IIa) was produced by the condensation of 3-amino-4-hydroxy-2,6-dimethyl quinoline (Ic) with carbon disulphide in alkaline medium. The reaction of IIa with alkyl and aralkyl halides offered the corresponding thioethers (IIb-k). The compounds synthesised were characterised by their analytical and spectral analyses. A few selected compounds were screened for their antimicrobial properties.

### INTRODUCTION

A large number of oxazoloquinolines are found to possess antimicrobial<sup>1-4</sup>, anti-allergic<sup>5</sup> and herbicidal<sup>6</sup> properties. A few of these derivatives are also proved to exhibit optical brightening<sup>7,8</sup> properties. In continuation of our interest in the synthesis of nitrogen heterocycles, we now report the synthesis and biological properties of the title compounds. 4-Hydroxy-2,6-dimethylquinoline (Ia) was prepared by the condensation of *p*-toluidine with ethylacetoacetate in the presence of polyphosphoric acid. It was coupled with benzenediazonium chloride to yield 4-hydroxy-2,6-dimethyl-3-phenylazoquinoline (Ib) which was later reduced by sodium dithionite to give 3-amino-4-hydroxy-2,6-dimethylquinoline (Ic). Reaction of Ic with carbon disulphide in methanolic potassium hydroxide to afford 2-mercapto-4,8-dimethyloxazolo(4,5-c)quinoline (IIa). Reaction of IIa with various alkyl/aralkyl halides in the presence of methanolic potassium hydroxide produced the title compounds. They were characterised by their analytical and spectral data.

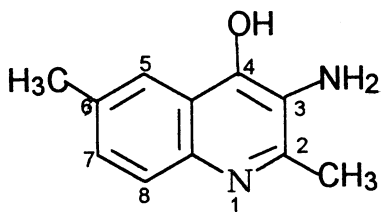


Ia

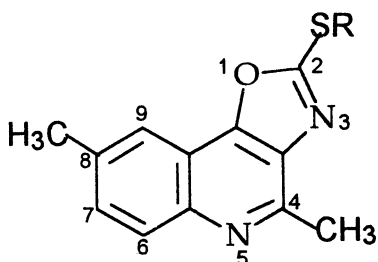


Ib

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Ic



II

IIa, R = H

IIb-k, R = alkyl / aralkyl

### EXPERIMENTAL

All the melting points are uncorrected. Purity of the compounds was checked by TLC. The elemental analyses were carried out on Carlo-Erba Model EA 1108 CHNS—O elemental analyser. The IR spectra (KBr) were taken on Shimadzu FTIR-8101M spectrophotometer. The PMR spectra were recorded at 200 MHz on Varian Gemini instrument using TMS as the internal reference in  $\delta$  ppm. The mass spectra were taken on JEOL-D300 instrument at 70 eV. The physical and analytical data are given in the table.

1. *4-Hydroxy-2,6-dimethyl quinoline (Ia)*: *p*-Toluidine (5.35 g, 0.05 mol) was added to polyphosphoric acid prepared by stirring a mixture of phosphorus pentoxide (20 g) in phosphoric acid (12 mL) at 100°C. The mixture was stirred for 5 min and ethyl acetoacetate (6.65 g, 0.05 mol) was added and again stirred for 10 min. The reaction mixture was slowly heated and maintained at 140°C for 2 h. It was cooled to ambient temperature and 1 N hydrochloric acid (50 mL) was added and the mixture was neutralised with conc. sodium hydroxide solution. The crude product precipitated was collected and purified from ethyl alcohol. Yield 5.65 g (65%). m.p. 273–74°C. NMR (CDCl<sub>3</sub>,  $\delta$  ppm): 2.3 (s, 3H, 2-CH<sub>3</sub>)<sup>4</sup>, 2.45 (s, 3H, 6-CH<sub>3</sub>), 5.95 (s, 1H, 3-H), 7.5 (m, 2H, Ar—H), (s, 1H, Ar—H), 11.45 (br, s, 1H, OH). Mass (m/z): 173 (M<sup>+</sup>, 100), 158 (M—CH<sub>3</sub>, 5), 144 (M—CHO, 50), 130(13), 115(10).

2. *4-Hydroxy-2,6-dimethyl-3-phenylazoquinoline (Ib)*: A mixture of Ia (8.65 g, 0.05 mol), 5N sodium hydroxide solution (100 mL) and water (20 mL) was cooled to 5°C. This was treated with benzenediazonium chloride solution (from 6 g, 0.06 mol aniline) which was kept at 5°C. The reaction mixture was neutralised with ice-cold solution of 5N hydrochloric acid. The red phenylazo derivative was collected and dried. It was recrystallised from alcohol. Yield 8.3 g (60%). m.p. 175–76°C, NMR (CDCl<sub>3</sub>,  $\delta$  ppm): 2.5 (s, 3H, 2-CH<sub>3</sub>), 2.8 (s, 3H, 6-CH<sub>3</sub>), 7.3–7.8 (m, 8H, Ar—H), 8.2 (br, s, 1H, OH). Mass (m/z): 277 (M<sup>+</sup>, 85), 262 (M—CH<sub>3</sub>, 8),

248 (M—CHO, 13), 172 (M—PhN<sub>2</sub>, 97), 144 (172—CO, 16), 105 (PhN<sub>2</sub>, 30). 77 (C<sub>6</sub>H<sub>5</sub>, 100).

3. *3-Amino-4-hydroxy-2,6-dimethylquinoline (Ic)*: A mixture of Ib (2.7 g, 0.01 mol), sodium dithionite (9 g), alcohol (15 mL), water (30 mL) and liquor ammonia (30 mL) was refluxed for  $\frac{1}{2}$  h, until the colour of solution was changed to yellow. It was filtered hot. The filtrate on cooling gave the amino compound. It was purified from alcohol. Yield 0.94 g (50%). m.p. 302–04°C (decomp). NMR (CDCl<sub>3</sub>,  $\delta$  ppm): 2.4 (s, 3H, 2-CH<sub>3</sub>), 2.55 (s, 3H 6-CH<sub>3</sub>), 7.4 (m, 2H, Ar—H), 7.9 (s, 1H, Ar—H), 3.3–4.0 (broad hump may be due to OH and NH<sub>2</sub>). Mass (m/Z): 188 (M<sup>+</sup>, 100), 173 (M—CH<sub>3</sub>, 13), 160 (M—CO, 18), 145 (160-CH<sub>3</sub>, 13), 132 (160-H<sub>2</sub>CN, 10).

TABLE-I  
CHARACTERISTICS OF THE TITLE COMPOUNDS

Compd. No.	R	m.p. (°C)	Yield (%)	Mol. formula	Elemental analyses %, Found (Calcd.)			
					C	H	N	S
IIa	H	>300	74	C <sub>12</sub> H <sub>10</sub> N <sub>2</sub> O <sub>5</sub>	62.52 (62.60)	4.32 (4.34)	12.13 (12.17)	13.85 (13.91)
IIb	CH <sub>3</sub>	142–44	53	C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> OS	63.75 (63.93)	4.88 (4.91)	11.45 (11.47)	13.07 (13.11)
IIc	C <sub>2</sub> H <sub>5</sub>	260–61	60	C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> OS	65.02 (65.11)	5.39 (5.42)	10.79 (10.85)	12.35 (12.40)
IId	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	170–71	66	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> OS	66.11 (66.17)	5.84 (5.88)	10.27 (10.29)	11.73 (11.76)
IIe	C <sub>4</sub> H <sub>9</sub>	209–10	49	C <sub>16</sub> H <sub>18</sub> N <sub>2</sub> OS	67.08 (67.13)	6.27 (6.29)	9.77 (9.79)	11.14 (11.18)
IIf	CH <sub>2</sub> CH <sub>2</sub> =CH <sub>2</sub>	165–66	58	C <sub>15</sub> H <sub>15</sub> N <sub>2</sub> OS	66.54 (66.66)	5.48 (5.55)	10.32 (10.37)	11.78 (11.85)
IIg	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	143–45	48	C <sub>19</sub> H <sub>16</sub> N <sub>2</sub> OS	71.11 (71.25)	5.04 (5.00)	8.82 (8.75)	10.08 (10.00)
IIh	CH <sub>2</sub> COC <sub>6</sub> H <sub>5</sub>	185–86	56	C <sub>20</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> S	68.90 (68.96)	4.58 (4.59)	8.02 (8.04)	9.16 (9.19)
IIi	CH <sub>2</sub> CO—C <sub>6</sub> H <sub>4</sub> Cl( <i>p</i> )	154–56	67	C <sub>20</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> SCl	62.77 (62.74)	3.89 (3.92)	7.27 (7.32)	8.34 (8.37)
IIj	CH <sub>2</sub> COC <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> ( <i>p</i> )	145–46	76	C <sub>20</sub> H <sub>15</sub> N <sub>3</sub> O <sub>4</sub> S	61.16 (61.06)	3.86 (3.81)	10.71 (10.68)	8.16 (8.14)
IIk	CH <sub>2</sub> COC <sub>6</sub> H <sub>4</sub> Br( <i>p</i> )	162–63	57	C <sub>20</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> SBr	56.01 (56.22)	3.54 (3.51)	6.60 (6.55)	7.46 (7.49)

Satisfactory analyses for halogens were also obtained. Compounds IIa–c and f–h were purified from ethanol, IId, e from acetone and IIi–k from methanol.

4. *2-Mercapto-4-8-dimethyl(4,5-c)quinoline (IIa)*: A mixture of Ic (1.88 g, 0.01 mol), carbon disulphide (30 mL), potassium hydroxide (1.12 g, 0.02 mol),

methanol (40 mL) and water (10 mL) was refluxed for 24 h. It was cooled and acidified with dil. acetic acid. The precipitated solid was collected by filtration and washed with cold water. It was purified by dissolving in aq. potassium hydroxide and regenerated by acidification after carbon treatment. Yield 1.7 (g, 74%). m.p. > 300°C.

5. *2-Substituted mercapto-4,8-dimethyloxazolo(4,5-c)quinolines* (IIb–k) (General Procedure): Compound IIa (0.01 mol) was dissolved in methanol (20 mol) containing potassium hydroxide (0.015 mol) and the appropriate halide (0.01 mol) was added dropwise. The reaction mixture was refluxed for 4 h and later it was cooled and poured into crushed ice. The solid separated was collected by filtration and washed with cold water. The product was recrystallised from suitable solvent (Table). IIb: NMR (CDCl<sub>3</sub>,  $\delta$  ppm): 2.55 (s, 3H, 4-CH<sub>3</sub>), 2.85 (s, 3H, 8-CH<sub>3</sub>), 2.95 (s, 3H, —SCH<sub>3</sub>), 7.55 (d, 1H, 7-H), 7.85 (s, 1H, 9-H), 8.05 (d, 1H, 6-H)<sup>11</sup>. Mass (m/Z): 240 (M<sup>+</sup>, 90), 229 (M—CH<sub>3</sub>, 7), 211 (M—SH, 58), 201 (229-CO, 29), 105 (C<sub>7</sub>H<sub>7</sub>N, 100).

## RESULTS AND DISCUSSION

The IR spectrum of IIa shows absorption bands at 1590–1570 cm<sup>-1</sup>, 1040–1030 cm<sup>-1</sup>, 1360–1350 cm<sup>-1</sup> which are assignable to oxazole ring. A sharp peak at 2750 cm<sup>-1</sup> may be due to SH stretching vibrations. The PMR spectrum of IIa in CDCl<sub>3</sub> and DMSO-d<sub>6</sub> displays a broad single  $\delta$  10.6 ppm which may be assignable to —SH group. The singlets at  $\delta$  2.45 and  $\delta$  2.9 are due to the methyl protons at C-4 and C-8 positions respectively. The aromatic protons resonate at  $\delta$  7.3–8.0. The mass spectrum of IIa contains peak at m/Z 230 (M<sup>+</sup>, 100), 201 (M—CHO, 25), 197 (M—SH, 9), 193 (M—HCNS, 8), 119 (30), 91 (32). Most of IR absorptions of alkyl/aralkyl derivatives are similar to the mercaptooxazoloquinoline except for the bands around 2800 and 1430 cm<sup>-1</sup> (—S—CH<sub>2</sub>—), 1340 cm<sup>-1</sup> (—S—CH<sub>3</sub>) and 3000 cm<sup>-1</sup> (allylic). The chemical shifts in the PMR spectra of these compounds indicate the presence of aromatic protons at around  $\delta$  6.9–8.0 as multiplets. The singlets<sup>4</sup> at  $\delta$  2.55 and 2.95 are attributable to the methyl protons at C-4 and C-8 carbon atoms respectively. The characteristic peaks for other protons in the side chain are also present. The mass spectra of these derivatives also indicate similar type of fragmentation of quinoline unit. The loss of substituent upon sulphur is common in many of these compounds. The other prominent peaks are observed at m/Z 229, 211, 201, 105.

### Antibacterial activity

The compounds (IIa, b, c, f, h) were screened for their antimicrobial activity<sup>9</sup> against *Escherichia coli*, *Klebsiella pneumonia* (gram negative), *Bacillus polymixa* and *Bacillus subtilis* (gram positive). They were found to be ineffective against all the bacteria tested except IIc which registered a moderate activity against *E. coli* and *B. subtilis*.

### Antifungal activity

These compounds were also screened for their antifungal activity<sup>10</sup> against

*Fusarium oxysporum* and *Curvularia lunata*. Compounds IIa, IIb registered a moderate activity and IIc registered more than 60% inhibition at a dose level of 120 µg/mL against both the fungi employed. Compound IIc showed lower activity even at 600 µg/mL dose level against *F. oxysporum* and registered no activity against *C. lunata*. The compound IIh was found to be inactive against both the fungi at all the dose levels.

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