

## Synthesis, Characterisation and Antimicrobial Screening of Aminobenzylated Mannich Bases of Acetamide and Urea

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The compound N-(1-piperidino-4-methylbenzyl)acetamide (**1a**), N-(1-piperidino-4-chlorobenzyl)acetamide (**1b**), N,N'-bis (1-piperidino-4-methylbenzyl)urea (**2a**) and N,N'-bis (1-piperidino-4-chlorobenzyl)urea (**2b**) have been synthesised by condensing piperidine and acetamide/urea with 4-methylbenzaldehyde/4-chlorobenzaldehyde. The compounds have been characterised on the basis of microanalytical, IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR and mass spectral data and screened for their antimicrobial activity against gram-positive and gram-negative bacteria.

### INTRODUCTION

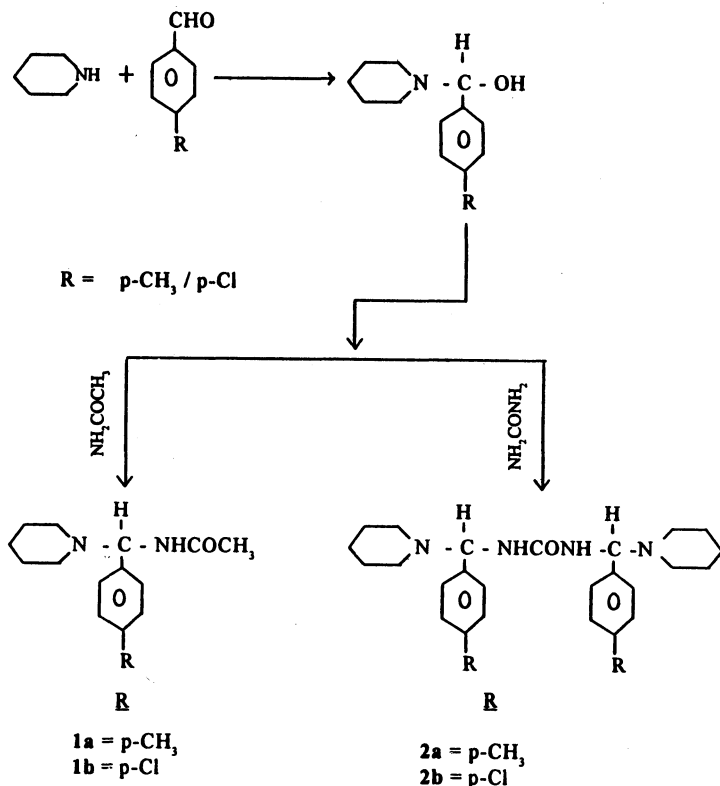
Several aminomethylated Mannich bases using formaldehyde have been reported to have good biological activities and complexation characteristics with transition metals<sup>1-3</sup>. The role of these compounds as intermediates in the synthesis of other compounds has been extensively studied<sup>4,5</sup>. Only a few Mannich reactions employing benzaldehyde are reported<sup>6,7</sup>. It is known<sup>8</sup> that benzaldehyde reacts with a secondary amine to form an intermediate N-aminophenyl carbinol which condenses with a compound containing active hydrogen to form N-aminobenzylated Mannich base. Recently we have reported N-amino benzylated urea derivatives<sup>9</sup>. In continuation of our work, in the present communication, we report a series of compounds (**1a-2b**) derived from piperidine, *p*-methyl or *p*-chlorobenzaldehyde and acetamide/urea.

### EXPERIMENTAL

The compounds are all stable colourless solids. Melting points reported were determined in open capillary tubes and are uncorrected. IR spectra in KBr medium were recorded on a Perkin-Elmer 983 spectrometer. Only principal sharply defined IR peaks are reported.  $^1\text{H}$  NMR spectra were taken on a Jeol GSX 400/Varian EM-390 (90 MHz) and  $^{13}\text{C}$  NMR on a Jeol GSX 400 spectrometer in  $\text{CDCl}_3$  with  $\text{SiMe}_4$  as internal standard (chemical shifts in  $\delta$ , ppm) and mass spectra on Jeol D-300 spectrometer.

**N-(1-piperidino-4-methylbenzyl)acetamide (1a):** Acetamide (4.40 g, 0.075

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mol) was added to piperidine (4.3 mL, 0.05 mol) and stirred to get a clear solution. 4-Methyl benzaldehyde (6.0 mL, 0.05 mol) was added dropwise to the solution and the mixture was stirred for 2 h in ice bath. The resulting solution was kept at room temperature for about a week with occasional stirring. The solid separated was collected and washed with excess water to remove unreacted acetamide and piperidine followed by carbon tetrachloride to remove any unreacted benzaldehyde. It was dried and crystallised from methanol; yield 14.27 g (58%), m.p. 170°C; (Found: C, 73.42; H, 8.82; N, 11.44. C<sub>15</sub>H<sub>22</sub>N<sub>2</sub>O requires C, 73.17; H, 8.94; N, 11.38%); IR: 3342  $\nu$ (NH), 1647  $\nu$ (C=O), 1160  $\text{cm}^{-1}$   $\nu$ (piperidine CNC); <sup>1</sup>H NMR:  $\delta$  1.4–1.65 (m, 6H, piperidine  $\beta$ ,  $\gamma$ -H), 2.15 (t, 3H, CH<sub>3</sub>), 2.30–2.65 (br, 3H, p-CH<sub>3</sub> and 4H, piperidine  $\alpha$ -H), 5.80 (br, 1H, NH), 6.55 (s, 1H, CH), 7.35–7.7 (m, 4H, Ar-H); MS (m/z, %): 245 (M<sup>+</sup> - 1, 45), 120 (CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>CH=NH<sub>2</sub><sup>+</sup>, 100), 91 (CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub><sup>+</sup>, 25), 84 (C<sub>5</sub>H<sub>10</sub>N<sup>+</sup>, 58).

**N-(1-piperidino-4-chlorobenzyl)acetamide (1b):** The compound was prepared according to the procedure above using acetamide (4.4 g, 0.075 mol), piperidine (4.3 mL, 0.05 mol) and *p*-chlorobenzaldehyde (7.0 g, 0.05 mol), yield 10.66 g (40%), m.p. 184°C; (Found: C, 63.34; H, 7.10; N, 10.6; Cl, 13.38. C<sub>14</sub>H<sub>19</sub>ClN<sub>2</sub>O requires C, 63.04; H, 7.13; N, 10.51; Cl, 13.3%); IR: 3305  $\nu$ (NH), 1645  $\nu$ (C=O), 1155  $\text{cm}^{-1}$   $\nu$ (piperidine CNC); <sup>1</sup>H NMR:  $\delta$  1.25–1.50 (br, 6H, piperidine  $\beta$ ,  $\gamma$ -H), 2.05 (t, 3H, CH<sub>3</sub>), 2.4–2.75 (br, 4H, piperidine  $\alpha$ -H), 5.65 (br, 1H, NH), 6.82 (s, 1H, CH), 7.5–7.22 (m, 4H, Ar-H).

**N,N'-bis(1-piperidino-4-methylbenzyl)urea (2a):** To a solution of urea (6.0 g, 0.1 mol) in 20 mL water, was added ice-cooled piperidine (6.5 mL, 0.01 mol) and stirred for 1 h. Then 4-methylbenzaldehyde (9.0 mL, 0.075 mol) was added dropwise during the next 15 min. The resulting mixture was stirred for 3 h at 5°C in ice bath and left for a day at room temperature. The resultant residue was filtered, washed repeatedly with water and finally recrystallised from 1 : 1 (v/v) chloroform-methanol mixture; yield 23.87 g (55%), m.p. 146–150°C; (Found: C, 74.91; H, 8.76; N, 12.98. C<sub>27</sub>H<sub>38</sub>N<sub>4</sub>O requires C, 74.65; H, 8.76; N, 12.80%); IR: 3394 ν(NH), 1664 ν(C=O), 1165 cm<sup>-1</sup> ν(piperidine CNC); <sup>1</sup>H NMR: δ 1.2–1.6 (m, 12H, 2 piperidine β,γ-H), 2.25–2.70 (br, 6H, 2CH<sub>3</sub> and 8H, 2 piperidine α-H), 5.58–5.70 (br, 2H, 2NH), 6.5–6.7 (d, 2H, 2CH), 7.05–7.5 (m, 8H, 2 Ar-H); MS (m/z, %): 434 (M<sup>+</sup>, 6), 188 (C<sub>5</sub>H<sub>10</sub>N—C<sup>+</sup>H—C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>, 100) 91 (CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub><sup>+</sup>, 36), 84 (C<sub>5</sub>H<sub>10</sub>N<sup>+</sup>, 62).

**N,N'-bis(1-piperidino-4-chlorobenzyl)urea (2b):** It was prepared according to the procedure used above employing urea (6.0 g, 0.1 mol), piperidine (6.9 mL, 0.08 mol) and *p*-chlorobenzaldehyde (10.53 g, 0.075 mol) as white crystalline solid; yield 15.2 g (32%), m.p. 168°C; (Found: C, 63.42; H, 6.76; N, 11.68; Cl, 14.76. C<sub>25</sub>H<sub>32</sub>Cl<sub>2</sub>N<sub>4</sub>O requires C, 63.17; H, 6.73; N, 11.78; Cl, 14.93%); IR: 3350 ν(NH), 1656 ν(C=O), 1158 cm<sup>-1</sup> ν(piperidine CNC); <sup>1</sup>H NMR: δ 1.3–1.75 (br, 12H, 2 piperidine β,γ-H), 2.45–2.85 (m, 8H, 2 piperidine α-H), 5.5–5.7 (br, 2H, 2NH), 6.6–6.8 (d, 2H, 2CH), 7.5–7.8 (m, 8H, 2Ar-H).

**Antimicrobial Activity:** The compounds were tested *in vitro* for their antimicrobial activity against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* by filter pape disc method<sup>10</sup> with necessary modifications. All the test chemicals were dissolved in DMSO. Filter paper disc of 0.6 mm diameter containing 100 μg of the test compound per disc was prepared, dried and placed on the surface of bacteria seeded agar plates. It was incubated at 37°C for 24 h. The antimicrobial activity was determined<sup>11</sup> using the following relationship:

$$\text{Activity (\%)} = \frac{Y - 0.6}{X - 0.6} \times 100$$

where X (mm) was the diameter of the inhibition zone by tetracycline and Y (mm) was the diameter of the inhibition zone by the sample.

Acetamine derivatives **1a** and **1b** showed comparatively high antibacterial activity whereas urea derivatives **2a** and **2b** showed moderate activity against *E. coli* and *P. aeruginosa* (Table-1).

TABLE-1  
ANTIMICROBIAL ACTIVITY (%) OF COMPOUNDS(1a–2b) AT 100 μg/DISC

Compound	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>
<b>1a</b>	60	69	45
<b>1b</b>	65	74	54
<b>2a</b>	45	49	38
<b>2b</b>	48	56	32
Tetracycline	100	100	100

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