SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF MANNICH BASES OF 3, 4-DIHYDRO-8-METHOXY-2H-1, 2, 4-TRIAZINO[3, 4-b] BENZOTHIAZOLE-3, 4-DIONE.  

S. P. VARTALE*, V. N. BHOSALE, S. V. KHANSOLE, P. A. KULKARNI and J. S. JADHAVa  

Department of Chemistry, Yeshwant Mahavidyalaya, NANDED - 431602 (M. S.) INDIA  
Department of Chemistry, N. S. B. College, NANDED - 431601 (M. S.) INDIA.  

ABSTRACT  

2-Hydradzino-6-methoxy benzothiazole (1) in methanol on reaction with diethyl oxalate in the presence of pyridine afforded 3, 4-dihydro-8-methoxy-2H-as-triazino[3, 4-b]-benzothiazole-3, 4-dione (2). The latter on further reaction with formaldehyde and different heteryl amines such as morpholine, pyrrolidine and pipyridine afforded Mannich bases (3,5). The newly synthesized compounds were subjected to evaluation for antibacterial activity.  

Key words: 3, 4-Dihydro-8-methoxy-2H-as-triazino [3, 4-b] benzothiazole-3, 4-dione, 2-Hydradzino-6-methoxy benzothiazole, Mannich bases, Antibacterial activity.  

INTRODUCTION  

A survey of literature reveals that very little work has been carried on the synthesis and chemistry of as-triazines fused with benzothiazole system1. In present work, 3,4-dihydro-8-methoxy-2H-as-triazino [3,4-b]- benzothiazole-3,4-dione2 (2) was prepared by refluxing 2-hydradzino-6-methoxy benzothiazole (1) in methanol with diethyl oxalate in the presence of pyridine for four hours with 75% yield.  

In view of the high antibacterial activity reported3-5, for the Mannich bases derived from aza heterocycles and the sedative and tranquilizing properties6 exhibited by Mannich bases derived from as- triazoles, it was considered appropriate to prepare a few Mannich bases from the parent lactam compound (2). Authors have come across only one reference1 on the Mannich bases derived from as-triazines condensed with benzothiazole system. In view of this lacuna, the preparation of some Mannich bases (3-5) was undertaken.  

* Author for correspondence; E-mail: drspv@rediffmail.com
EXPERIMENTAL

3, 4-Dihydro-8-methoxy-2H-1, 2, 4-triazino[3, 4-b]benzothiazole-3, 4-dione (2) was prepared by refluxing a mixture of 2-hydrazino-6-methoxy-benzothiazole (1.95 g; 0.01 mole), methanol (20 mL), pyridine (0.5 mL) and diethyl oxalate (6 mL) on water bath for 4 hours. Insoluble product obtained was filtered, washed with water and then with ethanol. It was crystallized from dioxane to give 1.86 of (2).

3,4-Dihydro-2-N-methyl morpholino/pyrrolidino/piperidino-8-methoxy-2H-1, 2, 4-triazino [3, 4-b]benzothiazole-3, 4-dione (3-5) were prepared by refluxing (2) (0.249 g; 0.001 mole), dioxane (5 mL), formaldehyde (1 mL) and morpholine/pyrrolidine/piperidine (0.002 mole) on water bath independently at 60°C for one hour and mixture was kept over night. The product was recrystallized from ethanol to give (3-5).

3,4-Dihydro-2-N-hydroxy methyl-8-methoxy-1, 2, 4-triazino[3, 4-b]benzothiazole-3, 4-dione (6) was prepared by heating a mixture of (2) (0.74 g; 0.003 mole), dioxane (7 mL) formaldehyde (1 mL) on water bath for 1 hour. The product isolated as in (2) was recrystallized from benzene to give 0.52 g of (6).

Compound (3)/(4)/(5) were also synthesized by heating a mixture of (6) (0.249 g; 0.001 mole), dioxane (3 mL) and morpholine/pyrrolidine/piperidine (0.002 mole) on water bath for 2 hours and mixture was kept over night independently. A separated solid compound was crystallized from ethanol to give (3)/(4)/(5). The TLC and mixed melting points of these compounds are similar to that synthesized by earlier methods. Physical and spectral data of synthesized compounds are given in Table 1.

Table 1 : Physical and spectral data of Mannich bases of 3, 4-dihydro-8-methoxy-2H-1, 2, 4-triazino[3, 4-b]benzothiazole-3, 4-dione

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Mass</th>
<th>Yield (%)</th>
<th>m. p. (°C)</th>
<th>(^1)H NMR (DMSO-d(_6)) in δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>249</td>
<td>75</td>
<td>309</td>
<td>3.8 (s, 3H, OCH(_3)), 7.3-7.6 (m, 3H, Ar-H), 11.6 (s, 1H, NH, exch. with D(_2)O)</td>
</tr>
<tr>
<td>3</td>
<td>348</td>
<td>78</td>
<td>180</td>
<td>2.8 (t, 4H, -NCH(_2)_2), 3.7(t, 4H, -OCH(_2)_2), 3.9 (s, 3H, -OCH(_3)_3), 4.9 (s, 2H, -NCH(_2)N-), 6.9-7.1 (m, 3H, Ar-H)</td>
</tr>
</tbody>
</table>

Cont…
Three Manich bases of (2) were prepared by condensing 3, 4-dihydro-8-methoxy-2H-as-triazino[3, 4-b] benzothiazole-3, 4-dione (2) indioxane with cyclic secondary amines such as morpholine, pyrrolidine, piperidine and formaldehyde independently at 50-60°C.
These Mannich bases (3-5) were also prepared by stepwise reaction through the formation of 3, 4-dihydro-2-N-hydroxy methyl-8-methoxy-as-triazino [3, 4-b] benzothiazole-3, 4-dione (6). IR spectra of compounds (3-5) showed the absence of absorption band at 3180 cm\(^{-1}\) due to-NH stretching indicates the formation of Mannich bases (3-5). PMR spectrum of compound (3) exhibits peaks at \(\delta 2.79\) as triplet, \(\delta 3.69\) as triplet, \(\delta 3.87\) as singlet and \(\delta 4.93\) as singlet which can be assigned to –NCH\(_2\), -O-CH\(_2\), -O-CH\(_3\) and –CH\(_2\) protons respectively. Mass spectrum of (3) exhibits molecular ion peak at 348 which corresponds to its molecular weight.

**RESULTS AND DISCUSSION**

All the newly synthesized compounds were evaluated for their antibacterial activity against gram positive species *S. aureus*, *B. Substilis* and gram negative species *E. coli*, *S. typhi* by paper disc diffusion methods. All the synthesized compounds exhibited zone of inhibition of 10-14 mm in diameter where as standard streptomycin exhibited zone of inhibition of 18 and 22 mm in diameter and penicillin inhibited zone of inhibition of 15 and 16 mm in diameter against *E. Coli* and *S. typhi*, respectively. DMF was used as a solvent for dissolving the compounds. The data of antibacterial activity of the synthesized compounds are given in Table 2.

**Table 2 : Antibacterial activity of Mannich bases of 3, 4-dihydro-8-methoxy-2H-1, 2, 4-triazino[3, 4-b]benzothiazole-3, 4-dione by disc diffusion method.**

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th><em>S. aureus</em></th>
<th><em>B. Substilis</em></th>
<th><em>E. Coli</em></th>
<th><em>S. Typhi</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>12</td>
<td>12</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>12</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>18</td>
<td>22</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Penicillin</td>
<td>---</td>
<td>---</td>
<td>15</td>
<td>16</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENT

Authors are grateful to Dr. N. V. Kalyankar, Principal, Yeshwant Mahavidyalaya, Nanded for providing laboratory facilities and the Director, Indian Institute of Chemical Technology, Hyderabad for providing spectral data and UGC, Western Regional office, Pune for financial assistance under minor research project.

REFERENCES

2. J. S. Jadhav, S. P. Vartale and S. V. Kuberkar, Indian J. Pharma. Sci. (Communicated)

Accepted : 21.07.2008