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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. JADHAV[a]

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

ABSTRACT

2-Hydrazino-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-Hydrazino-6-methoxy benzothiazole, Mannich bases, Antibecterial 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 system[1]. In present work, 3,4-dihydro-8-methoxy-2H-as-triazino [3,4-b]- benzothiazole-3,4-dione[2] **(2)** was prepared by refluxing 2-hydrazino-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 reported[3-5], for the Mannich bases derived from aza heterocycles and the sedative and tranquilizing proerties[6] 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 reference[1] 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 60^0C 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)**.

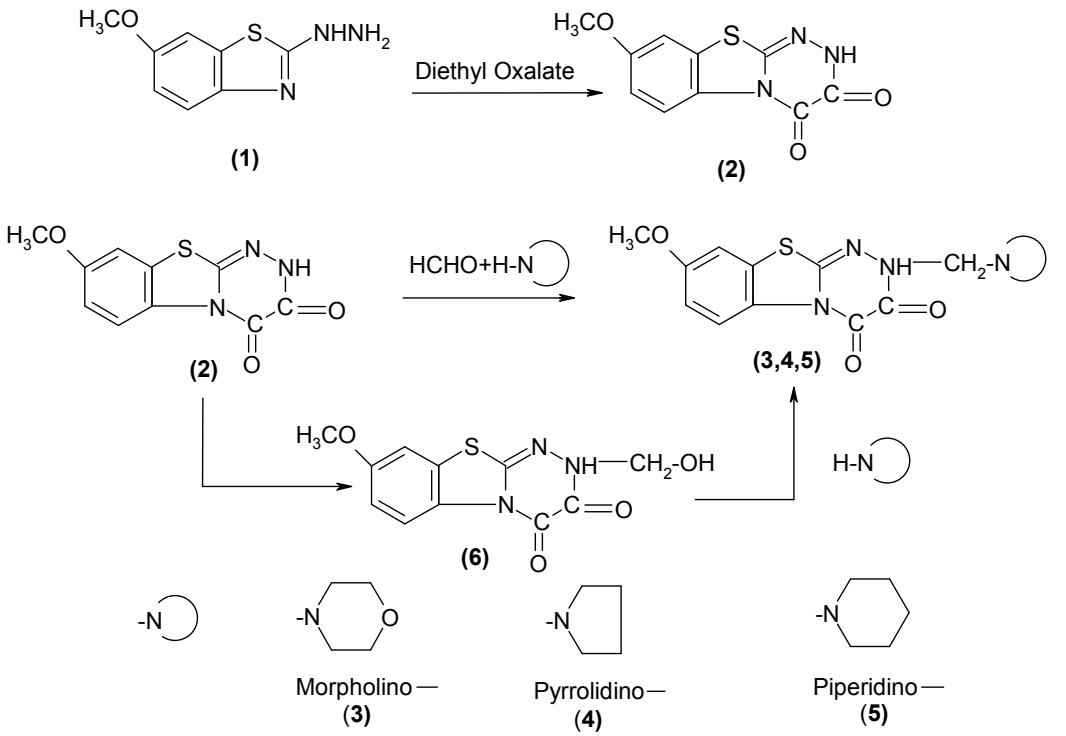
Compound **(3)/(4)/(5)** were also synthesized by heating a mixture of **(6)** (0.249 g; 0.001 mole), dioxane (3 mL) and morpholine/pyrrolidine/piperidine (0.002 mole) on water bath for 2 hours and mixture was kept over night independently. A separated solid compound was crystallized from ethanol to 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

Comp. No.	Mass	Yield (%)	m. p. (^{o}C)	^{1}H NMR (DMSO-d_6) in δ (ppm)
2	249	75	309	3.8 (s, 3H, OCH_3), 7.3-7.6 (m, 3H, Ar-H), 11.6 (s, 1H, NH, exch. with D_2O)
3	348	78	180	2.8 (t, 4H, -NCH_2-), 3.7(t, 4H, -OCH_2-), 3.9 (s, 3H, -OCH_3), 4.9 (s, 2H, -NCH_2N-), 6.9-7.1 (m, 3H, Ar-H)

Cont…

Comp. No.	Mass	Yield (%)	m. p. (^oC)	^1H NMR (DMSO-d_6) in δ (ppm)
4	332	63	284	2.1 (q, 4H, -CH_2-), 2.8 (t, 4H-NCH_2-), 3.7 (s, 3H, -OCH_3), 4.5(s, 2H, -NCH_2N-), 6.9-7.3(m, 3H, Ar-H)
5	346	67	225	1.9 (q, 4H, -CH_2-), 2.2(q, 2H, -CH_2), 3.0 (t, 4H, -NCH_2-), 3.8(s, 3H, -OCH_3), 4.7 (s, 2H, -NCH_2N-), 7.0-7.2(m, 3H, Ar-H)
6	279	62	270	3.6(s, 3H, OCH_3), 4.4(s, 1H, -OH exch. with D_2O), 5.0(s, 2H, -NCH_2O-), 7.1-7.4(m, 3H, Ar-H)



Scheme 1

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^{0}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 δ2.79 as triplet, δ3.69 as triplet, δ3.87 as singlet and δ4.93 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[7]. 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.

Comp. No.	Diameter of zone of inhibition in 25 µg/disc (mm.)			
	S. aureus	***B. Substilis***	***E. Coli***	***S. Typhi***
2	12	12	13	14
3	10	12	10	10
4	10	10	12	10
5	10	10	11	10
6	14	10	10	10
Streptomycin	18	22	---	---
Penicillin	---	---	15	16

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