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Synthesis, characterization and Antibacterial Screening of aminomethylated derivatives of 7-azaspiro[4.5]decane-6,8-dione

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Abstract

Novel series of Mannich bases of 7-azaspiro[4.5]decane-6,8-dione with intact imide moiety were synthesized for the first time from various sulfonamides and secondary amines. The structural characterization is made using elemental and spectral studies. All the newly synthesized Mannich bases are introduced for antimicrobial activity against the bacteria ***S.aureus****,* ***S.typhi*** *and* ***P.aruginosa****. Mannich bases are found more potent than their parent sulphonamide.*

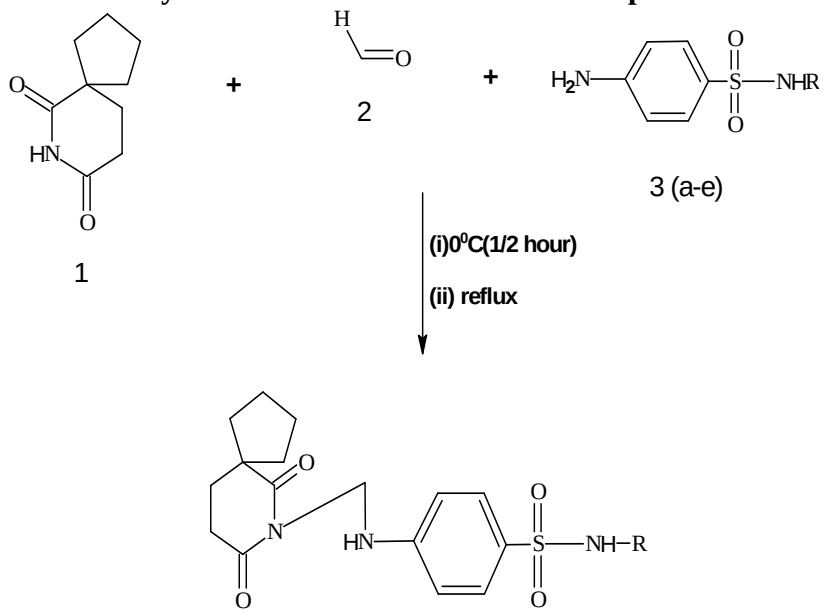
Key words: 7-azaspiro[4.5]decane-6,8-dione, sulfonamides, Mannich bases, antimicrobial activity.

INTRODUCTION

The ever-increasing attractiveness of the Mannich reaction and convenience of Mannich bases has been fluctuated by the ubiquitous nature of nitrogen in them as well as by the potential of multi-component Mannich reaction to generate diversity [1]. Mannich reaction offers a judicious method for introduction of basic aminoalkyl chain in various drugs/compounds. Further a considerable amount of work has been reported on synthesis and pharmacological activity of various Mannich bases for analgesic, anti-inflammatory, anesthetic and antimicrobial activity as well as intermediates in drug synthesis [2-4]. Glutarimide moiety with the intact imide group is acting as the carrier molecule (vector), which transports biologically active substituents (functional groups) through cell membranes [5]. Glutarimide (2, 6-piperidinedione) has been found in a number of antibiotics with the antiviral and fungicidal activity [6-11]. In addition, the

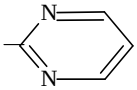
2, 6-piperidinedione moieties constitute an important center in several new anticancer drugs, which have recently been introduced into experimental chemotherapy [12]. It is also a structural part of a number of molecules with interesting biochemical activities [13]. The sulphonamide is well known antibacterial [14-16], antitubercular [17], anti-inflammatory [18], carbonic inhibitory [19], insecticidal [20]. Keeping in view the unique features of these compounds 7-azaspiro [4.5] decane-6, 8-dione as a substrate and sulphonamide as amine component were condensed via Mannich reaction. A series of Mannich bases were synthesized with different sulphonamides/ secondary amines **(Scheme 1&2)**. The synthesized Mannich bases were characterized by elemental analysis and spectral studies-UV, IR and ^{1}H NMR and screened for *in-vitro* antibacterial activity gram-positive and gram-negative bacteria at arbitrarily chosen concentrations.

Scheme 1. Synthesis of Mannich bases from sulphonamides

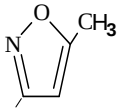


Where

(3a-4a);R =



(3b-4b);R =

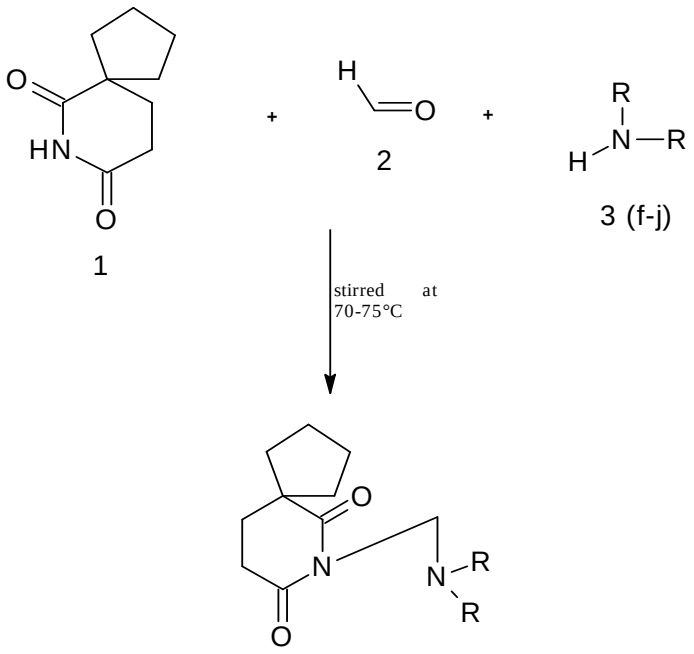


(3c-4c);R = —H

(3d-4d)R = —$COCH_3$

(3e-4e)R = —C=NH.NH_2

Scheme 2: Synthesis of Mannich bases from secondary amines

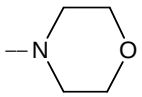


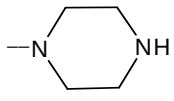
Where

(3f-4f); R = $-N(C_2H_4OH)_2$

(3g-4g); R = $-N(C_6H_5)_2$

(3h-4h); R = $-N(CH_3)_2$

(3i-4i); R = 

(3j-4j); R = 

MATERIALS AND METHODS

All the m.p. were determined using Thomas Hoover capillary melting point apparatus. The purity of the Mannich bases was confirmed by TLC analysis using chloroform / methanol mixture (90:10) as mobile phase and silica gel-G (chromatographic grade) as stationary phase. The antimicrobial screening was performed using paper disc method. Mullar Hinton Agar was taken as media for cultivation of bacteria. The inhibitory effect of the samples were measured against

the bacteria after incubation for 24 hours at 37^0C.The experiments were run in triplicate and the mean of readings were recorded.

Synthesis of Mannich bases from primary amines:
Mannich bases of 7-azaspiro[4.5]decane-6,8-dione were prepared by taking 7-azaspiro[4.5]decane-6,8-dione (0.01mol) dissolved in 20 mL of ethanol with sulfonamide (0.01mol) and 2.5 mL (0.01mol) of formaldehyde solution (37%, v/v) was added slowly with constant stirring.

The pH of the mixture was adjusted to 3.5 by adding 0.5 mL of 1 mol L^{-1} HCl. The mixture was kept at efficient ice cooling for half an hour, and then refluxed on water bath. Reflux time varied with the sulfonamide used. The refluxed mixture was kept at 0^0C for four days when crystalline product was obtained. The product was re-crystallized from dry distilled ethanol and dioxane-water (1:1) (**scheme-1**).

Synthesis of Mannich bases from secondary amines:
Secondary amine (0.01mol) was added to an ethanolic solution (50mL) of 7-azaspiro [4.5] decane-6, 8-dione (0.01 mol) in a flat bottom flask. Amount of 0.4 mL (0.015mol) of formaldehyde solution (37%, v/v) was added slowly with constant stirring. The reaction mixture was stirred at 70-75^{0}C for 3.0 to 8.5 hours, depending upon the secondary amine. The remaining portion of formaldehyde solution was added in two installments after 1 and 2 hours, respectively. The reaction mixture was kept overnight in the refrigerator. Next day, the excess of solvent was distilled off from the reaction mixture under reduced pressure. It was again kept for crystallization in the refrigerator. The products obtained were purified by re-crystallization from dry distilled ethanol (**Scheme-2**).

RESULT AND DISCUSSION

The synthesized Mannich bases were analyzed for elemental analysis and results were found to be in full agreement with calculated values. The anticipated structure is in agreement with the spectral data–UV, IR and ^{1}HNMR. The Mannich bases were screened for their biological significance. They were evaluated for antibacterial activity against pathogenic strains of ***S.aureus***, ***S.typhi*** and ***P.aeruginosa*** at varying concentrations 20, 40, 80, 160 mg/ml using paper disc method. All the reported compounds exhibit remarkable *in vitro* activity against these pathogens. Their activity was also compared with parent sulphonamides. All the observations are given in Table-1.

Table-1 reflects that in ***S.aureus*** amongst all synthesized Mannich bases showing antibacterial activity, Mannich base **4a** was found to be most potent fallowed by **4e, 4d, 4j** were at par and showed significant antibacterial activity. On comparison with parent sulphonamide results indicated that Mannich base **4a, 4b**, and **4d** are superior to the corresponding sulphonamides. Mannich base **4e** was found to be significantly active over others against ***S.typhi*** fallowed by **4d** and **4c**.results shows that all the Mannich bases are superior to the corresponding sulphonamide except **4d.**

Mannich base **4e** fallowed by **4d** and **4c** over other Mannich bases significantly inhibited ***P.aeruginosa***. It was found that the all compounds were highly active at concentration 160mg/ml. All the Mannich bases showing better antibacterial activity to the corresponding sulphonamides.

Table – 1: Antibacterial screening results of Mannich Bases(4a-4j) and Sulphonamides (3a-3e)

Comp. No.	***S.*aureus (Zone of inhibition in mm)**					***S.*typhi (Zone of inhibition in mm)**					***P.*aeruginosa (Zone of inhibition in mm)**				
	Concentration in mg/mL					**Concentration in mg/mL**					**Concentration in mg/mL**				
	20	**40**	**80**	**160**	**Avg**	**20**	**40**	**80**	**160**	**Avg**	**20**	**40**	**80**	**160**	**Avg**
4a	10.4	12.4	12.4	15.4	12.4	11.0	11.0	11.0	11.0	11.0	11.6	11.6	11.6	11.6	11.6
4b	10.0	11.0	11.0	13.0	11.0	11.0	11.0	11.0	11.1	11.0	11.8	11.8	11.8	11.8	11.8
4c	9.2	10.2	11.2	14.2	11.2	11.0	11.5	11.5	12.0	11.5	13.2	13.2	13.2	13.2	13.2
4d	11.5	11.5	11.5	11.5	11.5	12.0	12.5	12.5	13.0	12.5	14.8	14.8	14.8	14.8	14.8
4e	10.0	12.0	13.5	15.5	12.0	12.0	13.0	13.5	15.5	13.5	15.6	15.6	15.6	15.6	15.6
4f	10.0	11.0	11.0	13.0	11.0	11.5	11.5	11.5	11.5	11.5	9.5	9.5	11.5	11.5	10.5
4g	9.0	10.0	11.0	15.0	11.0	7.5	9.0	10.0	13.5	10.0	7.5	8.5	8.5	9.5	8.5
4h	8.5	9.5	10.5	13.5	10.5	10.0	10.0	10.0	10.0	10.0	7.5	7.5	7.5	7.5	7.5
4i	9.0	11.0	12.0	13.0	11.0	8.0	9.0	10.0	13.0	10.0	9.5	10.0	11.0	11.5	10.5
4j	11.5	11.5	11.5	11.5	11.5	8.0	8.5	11.0	12.5	10.0	9.5	11.5	12.0	15.0	12.0
3a	9.5	9.0	10.0	10.0	9.77	10.0	10.0	10.0	10.0	10.0	11.6	11.0	11.5	12.0	11.5
3b	-	-	-	-	-	9.5	9.5	9.5	9.5	9.5	10.5	10.5	10.5	10.5	10.5
3c	11.0	11.0	11.0	11.0	11.0	-	-	-	-	-	-	-	-	-	-
3d	-	-	-	-	-	13.0	13.0	13.0	13.0	13.0	12.5	12.5	12.5	12.5	12.5
3e	12.0	12.0	12.0	12.0	12.0	-	-	-	-	-	13.0	13.5	13.5	14.0	13.5

Physical and spectral characteristics of compounds (4a-4j):

7-azaspiro[4.5]decane-6,8-dionemethylsulphadizene(4a) : $C_{20}H_{23}N_5O_4S$, mp 206-210, yield 72%, C(%)-55.20(55.93), H(%)-5.30(5.40), N(%)-16.30(16.31), UV-217 (gluterimidomoiety), 219 (sulphoxide group), 260 (Sulphonamide), IR(KBr) 3010*v* (C-H) of tetramethyline ring , 2345*v* (NH) of gluterimide moiety, 3327*v* (NH) of SO_2NH, 3010*v* (=C-H) of aromatic ring , 2910*v*(as) C-H in CH_2,2340*v*$CH_2N<$group, 1340v_{as} (S=O) in SO_2NH, 1149*v* (C-H) in disubstituted aromatic ring, 838out of plane C-H in disubstituted aromatic ring, ^{1}H NMR 2.46 (d, 2H, CH_2); 6.30 (S, 1H, NH) ; 6.86 (m, ArH) ; 11.08 (S, 1H, SO_2NH).

7-azaspiro[4.5]decane-6,8-dionemethylsulphamethoxazole(4b) : $C_{20}H_{24}N_4O_5S$, mp 146 - 150, yield 80%, C(%)-55.60(55.54), H(%)-5.62(5.59), N(%)-12.92(12.95), UV-219(gluterimidomoiety), 218(sulphoxidegroup), 258 (Sulphonamide), IR (KBr) 3016*v* (C-H) of tetramethylinering , 2350*v*(NH) of gluterimide moiety, 3330*v* (NH) of SO_2NH, 3015*v* (=C-H) of aromatic ring, 2920*v* (as) C-H in CH_2, 2330*v* $CH_2N<$group, 1350v_{as} (S=O)in SO_2NH, 1120*v*(C-H) in disubstituted aromatic ring, 850out of plane C-H in disubstituted aromatic ring, ^{1}H NMR 2.48 (d, 2H, CH_2); 6.32 (S, 1H, NH) ;6.86(m,ArH) ; 11.04 (S, 1H, SO_2NH).

7-azaspiro[4.5]decane-6,8-dionemethylsulphanilamide(4c) : $C_{16}H_{21}N_3O_4S$, mp 210-212, yield 74%, C(%)-54.64(55.68), H(%)-6.10(6.02), N(%)-11.88(11.96), UV-216 (gluterimidomoiety) , 220 (sulphoxide group), 262 (Sulphonamide), IR(KBr) 3020*v* (C-H) of tetramethyline ring, 2360*v* (NH) of gluterimide moiety, 3350*v* (NH) of SO_2NH, 3030*v* (=C-H) of aromatic ring ,2915$v_{(as)}$ C-H in CH_2, 2360*v*$CH_2N<$group, 1360v_{as}(S=O) in SO_2NH, 1110*v*(C-H) in disubstituted aromatic ring,850out of plane C-H in disubstituted aromatic ring, ^{1}H NMR 2.50 (d, 2H, CH_2); 6.88 (S, 1H, NH); 6.60 (m, ArH); 10.62 (S, 1H, SO_2NH).

7-azaspiro[4.5]decane-6,8-dionemethylsulphamacetamide(4d): $C_{18}H_{23}N_3O_5S$, mp188-192, yield 75%, C(%)-54.08(54.95), H(%)-5.80(5.89), N(%)-10.80(10.68), UV-214 (gluterimidomoiety), 219(sulphoxidegroup), 259(Sulphonamide), IR(KBr) 3012*v*(C-H) of tetramethylline ring , 2335*v* (NH) of gluterimide moiety, 3355$v_{NH}$of SO_2NH, 3020*v* (=C-H) of aromatic ring ,2922$v_{(as)}$C-H in CH_2,2380*v*$CH_2N<$group,1346v_{as} (S=O) in SO_2NH, 1112*v*(C-H) in disubstituted aromatic ring,830out of plane C-H in disubstituted aromatic ring,^{1}HNMR 2.52 (d, 2H, CH_2); 6.32 (S,1H,NH) ;6.88 (m,ArH) ; 11.12 (S,1H,SO_2NH).

7-azaspiro[4.5]decane-6,8-dionemethylsulphaguanidine(4e) : $C_{17}H_{23}N_5O_4S$, mp208-214, yield 71%, C(%)-51.80(51.89), H(%)-5.86(5.89), N(%)-17.60(17.80), UV-222 (gluterimido-moiety), 219(sulphoxide group), 261 (Sulphonamide), IR(KBr) 3022*v* (C-H) of tetramethyline ring , 2348*v*(NH) of gluterimide moiety, 3335*v* (NH) of SO_2NH, 3023*v* (=C-H) of aromatic ring ,2912$v_{(as)}$ C-H in CH_2, 2343*v* $CH_2N<$ group, 1341v_{as} (S=O) in SO_2NH, 1120*v* (C-H) in disubstituted aromatic ring, 830 out of plane C-H in disubstituted aromatic ring, ^{1}H NMR 2.64 (d, 2H, CH_2); 6.34 (S, 1H, NH) ;6.82 (m, ArH); 11.12 (S, 1H, SO_2NH).

7-azaspiro[4.5]decane-6,8-dionemethyldiethanolamine(4f) : $C_{14}H_{24}N_2O_4$, mp198-202, yield 81%, C(%)-59.08(59.13), H(%)-8.54(8.51), N(%)-9.56(9.85), UV-203(sec amine), 219(gluterimidomoiety), IR(KBr) 3016*v*(C-H) of tetramethyline ring, 2350*v*(NH) of gluterimidemoiety, 3015*v* (=C-H) of aromatic ring , 2920*v*(as) C-H in CH_2, 2330*v* $CH_2N<$ group,

1120*v* (C-H)in disubstituted aromatic ring, 850 out of plane C-H in disubstituted aromatic ring, ^{1}H NMR-2.66 (d, 2H, CH_2); 6.80 (m, ArH) .

7-azaspiro[4.5]decane-6,8-dionemethyldimethylamine(4g) : $C_{22}H_{24}N_2O_2$, mp120-125, yield 80%, C(%)-75.88(75.83), H(%)-6.98(6.94), N(%)-8.08(8.04), UV-203 (sec amine) , 219 (gluterimido- moiety), IR(KBr) 3018*v* (C-H) of tetramethyline ring , 2356*v* (NH) of gluterimidemoiety, 3015*v* (=C-H) of aromatic ring , 2920*v*(as) C-H in CH_2, 2330*v* $CH_2N<$ group, 1120*v* (C-H)in disubstituted aromatic ring, 850out of plane C-H in disubstituted aromatic ring, ^{1}H NMR 2.66 (d, 2H, CH_2); 6.86(m, ArH) .

7-azaspiro[4.5]decane-6,8-dionemethyldiphenylamine(4h) : $C_{12}H_{20}N_2O_2$, mp112-116, yield 68%, C(%)-64.12(64.26), H(%)-8.92(8.99), N(%)-12.46(12.49), UV-203(sec amine) , 219 (gluterimido-moiety), IR(KBr) 3014*v* (C-H) of tetramethyline ring , 2360*v* (NH) of gluterimide moiety, 3015*v* (=C-H) of aromatic ring, 2920*v*(as) C-H in CH_2, 2330*v* $CH_2N<$ group, 1120*v* (C-H) in disubstituted aromatic ring, 850 out of plane C-H in disubstituted aromatic ring, ^{1}H NMR 2.62 (d, 2H, CH_2); 6.88 (m, ArH) .

7-azaspiro[4.5]decane-6,8-dionemethylmorpholine(4i): $C_{14}H_{22}N_2O_3$, mp168-172, yield 72%, C(%)-64.12(64.26), H(%)-8.92(8.99), N(%)-12.46(12.49), UV-203(sec amine), 219 (gluterimidomoiety), IR(KBr) 3026*v* (C-H) of tetramethyline ring, 2345*v* (NH) of gluterimide moiety, 3015*v* (=C-H) of aromatic ring, 2920*v*(as) C-H in CH_2, 2330*v* $CH_2N<$ group, 1120*v* (C-H) in disubstituted aromatic ring, 850 out of plane C-H in disubstituted aromatic ring, ^{1}H NMR-2.60(d, 2H,CH_2); 6.90(m, ArH) .

7-azaspiro[4.5]decane-6,8-dionemethylpiperazine(4j) : $C_{12}H_{20}N_2O_2$, mp160-165, yield 84%, C(%)-63.14(64.26), H(%)-8.78(8.74), N(%)-15.88(15.88), UV-203(sec amine), 219 (gluterimidomoiety), IR(KBr) 3033*v* (C-H) of tetramethyline ring, 2355*v* (NH) of gluterimide moiety, 3015*v* (=C-H) of aromatic ring, 2920*v*(as) C-H in CH_2,2330*v* $CH_2N<$ group, 1120*v* (C-H) in disubstituted aromatic ring, 850out of plane C-H in disubstituted aromatic ring,^{1}H NMR-2.66 (d, 2H, CH_2); 6.94(m, ArH) .

CONCLUSION

The newly synthesized Mannich bases appeared to be very potent and outstanding antibacterial agents with promising activity and are found safer. This shows that the newly prepared and novel Mannich bases could be used as useful drug .The results discussed here in will prove helpful to those who are engrossed in the synthesis of potential Mannich bases as drugs with minimum side effects and also having comparatively low cost. Thus our results are valuable in constructing pharmacologically imperative heterocyclic as a new exotic drug. Efforts are continuing to synthesize new amino methyl derivatives of various active hydrogen compounds, that the derived compounds may have enhanced pharmacological activity.

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