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Synthesis, spectral studies and antimicrobial study of aminomethylated derivatives of 7-azaspiro [4.5] decane-6, 8-Dione

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ABSTRACT

Ten amino-alkylated Mannich bases of 7-azaspiro[4.5]decane-6,8-dione with intact imide moiety are 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: ***B.subtilis***, ***E.coli*** and ***K.pneumoniae***. Mannich bases are found more potent than their parent sulphonamide.

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

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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. Interest in Mannich bases has been quite striking and wide ranged considering the enormous domain of the applications involving variant biological, pharmaceutical and industrial nature [1]. Glutarimide moiety with the intact imide group is acting as the carrier molecule (vector), which transports biologically active substituents (functional groups) through cell membranes [2]. Glutarimide (2, 6-piperidinedione) has been found in a number of antibiotics with the antiviral and fungicidal activity [3-8]. In addition, the 2, 6-piperidinedione moieties constitute an important center in several new anticancer drugs, which have recently been introduced into experimental chemotherapy [9]. It is also a structural part of a number of molecules with interesting biochemical activities [10]. The sulphonamide is well known antibacterial [11, 12], antitubercular [13], anti-inflammatory [14], carbonic inhibitory [15], insecticidal [16]. Prompted by these observations, the aminoalkylation of 7-azaspiro[4.5]decane-6,8-dione moieties with sulphonamides and secondary amines are presented in this paper. In addition the antimicrobial activity of the synthesized compound is also reported.

EXPERIMENTAL

All the m.p. was 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 (50 mL) 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

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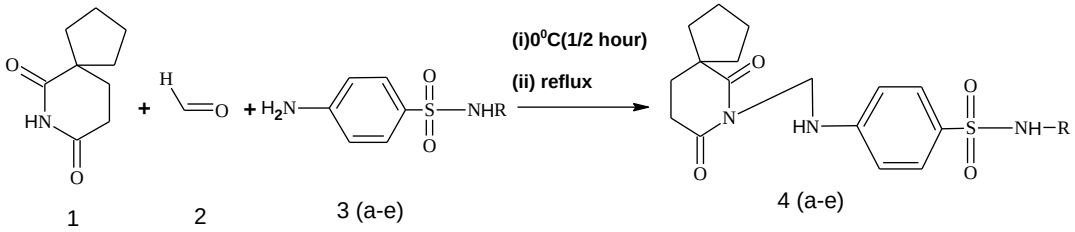
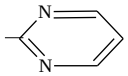
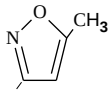
formaldehyde solution (37%, v/v) was added slowly with constant stirring. The reaction mixture was stirred at 70-75^{0}C for 3.0 to 8.5 hours, depending upon the secondary amine. The remaining portion of formaldehyde solution was added in two installments after 1 and 2 hours, respectively. The reaction 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).

Scheme 1. Synthesis of Mannich bases from sulphonamides



Where

(3a-4a);R= 

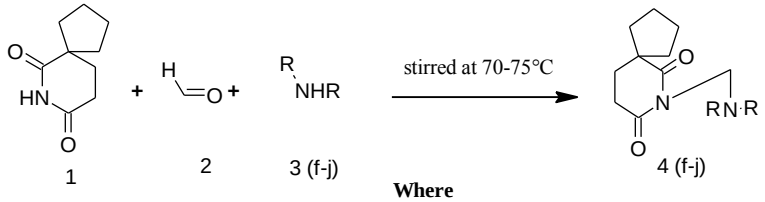
(3b-4b);R= 

(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

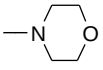


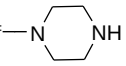
Where

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

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

(3h-4h);R= 

(3i-4i);R= 

(3j-4j);R= 

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RESULTS 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 *E.coli, B.subtils and K.Pneumoniae ,* 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 : Antibacterial Screening results of Mannich Bases 4a – 4j

Comp No.	*E.coli* (Zone of inhibition in mm)					*K.pneumonae* (Zone of inhibition in mm)					*B.subtilis* (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	9.0	11.0	12.0	13.0	11.0	9.5	11.5	15.0	16.0	13.0	11.6	11.6	11.6	11.6	11.6
4b	8.0	9.0	10.0	13.0	10.0	10.5	12.0	15.0	16.5	13.5	10.5	11.5	12.2	13.0	11.8
4c	7.5	10.5	10.5	13.5	10.5	10.5	12.0	13.0	15.5	12.5	13.2	13.2	13.2	13.2	13.2
4d	8.5	14.0	14.0	15.0	12.0	10.0	12.0	13.0	14.0	12.0	13.5	14.5	15.2	16.0	14.8
4e	10.5	12.5	12.5	15.5	12.5	11.0	11.0	12.0	15.0	12.0	15.6	15.6	15.6	15.6	15.6
4f	9.5	11.5	11.5	11.5	10.5	11.5	11.5	11.5	11.5	11.5	8.0	9.5	10.5	14.0	10.5
4g	8.5	10.5	10.5	13.5	10.5	10.5	10.5	12.5	12.5	11.5	7.5	8.5	8.5	9.5	8.5
4h	10.5	10.5	10.5	10.5	10.5	11.6	11.6	11.6	11.6	11.6	7.5	7.5	7.5	7.5	7.5
4i	8.0	10.0	11.0	12.0	10.0	10.5	11.5	11.5	12.5	11.5	9.5	10.5	10.5	11.5	10.5
4j	11.0	11.0	11.0	11.0	11.0	11.5	11.5	11.5	11.5	11.5	10.5	12.0	12.0	13.5	12.0
3a	9.0	10.0	10.0	12.0	10.3	8.0	8.5	8.5	9.0	8.5	-	-	-	-	-
3b	7.5	8.5	9.0	10.0	8.75	-	-	-	-	-	10.0	10.0	10.0	10.0	10.0
3c	7.0	9.0	9.5	10.0	8.87	9.0	9.0	9.0	9.0	9.0	11.5	11.5	11.5	11.5	11.5
3d	8.0	12.0	13.0	11.0	11.0	9.5	9.5	10.0	10.0	9.75	-	-	-	-	-
3e	10.0	11.0	12.0	13.5	11.6	-	-	-	-	-	12.0	13.0	14.0	14.0	13.3

Table-1 reflects that in *E-coli* amongst all synthesized Mannich bases showing antibacterial activity, Mannich base **4e** was found to be most potent fallowed by **4c, 4f, 4g, 4h** were at par and showed significant antibacterial activity. Compound **4b** was found to be significantly active over others against *K.Pneumonie* fallowed by **4a** and **4c**. *B.Subtilis* was significantly inhibited by Mannich base 4e fallowed by **4d** and **4c** over other Mannich bases.

It was found that the all compounds were highly active at concentration 320mg/ml. All the Mannich bases showing better antibacterial activity to the corresponding sulphonamides.

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

7-azaspiro[4.5]decane-6,8-dionemethylsulphadizene(4a) : $C_{20}H_{23}N_5O_4S$, mp206-210, 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)3010v(C-H) of tetramethyline ring ,2345v(NH)of gluterimide moiety,3327*v*NHof 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,

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838out of plane C-H in disubstituted aromatic ring,^{1}H NMR2.46(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<groupe,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): $C_{16}H_{21}N_3O_4S$, mp210-212, yield74%, 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, 3350v_{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 NMR2.50(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}HNMR2.52(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 NMR2.64(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 NMR2.66(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

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(gluterimidomoiety), 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 NMR2.66(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(gluterimidomoiety), 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,850out of plane C-H in disubstituted aromatic ring,^{1}H NMR2.62(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 NMR2.60(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 NMR2.66(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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