WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 8, 1921-1926. Research Article ISSN 2277– 7105

SYNTHESIS OF MANNICH BASES AND SCREENING FOR ANTI-MICROBIAL ACTIVITY

Dr. Ravi Malhotra*

Director HIMT Greater Noida, UP.

Article Received on
11 June 2015,

Revised on 02 July 2015,
Accepted on 23 July 2015

***Correspondence for Author**
Dr. Ravi Malhotra
Director HIMT Greater Noida, UP.

ABSTRACT

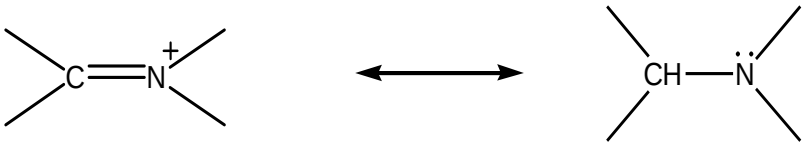
In an attempt to develop new analeptics mannich bases are synthesized in which main nucleus remained camphor while different secondary amines are added as subsituents. It is observed that existing analeptic (doxapram) have close resemblance with our newly synthesized series in one way or another as compound shows promising results in our studies ; as respiratory and circulatory stimulant have substituent piperidine which is very close to substituent morpholine in doxapram. The IR and NMR studies were conducted for the confirmation of the chemical structure of the final product. But in present studies we have concentrated on its anti – microbial activity.

KEY WORDS: mannich bases, piperidine, biological evaluation, camphor, formaldehyde.

INTRODUCTION

Mannich bases of heterocyclic ring derivatives were reported to exhibit a wide range of CNS activities such as potentiation of pentobarbitone induced necrosis[1] analgesic[2,3] anticonvulsant[4-8], antidepressant[9] and antiinflammatory activity.[10] A mannich base is a beta-amino-ketone, which is formed in the reaction of an amine, formaldehyde (or an aldehyde) and acid.[11] The Mannich base is an end product in the Mannich reaction, which is nucleophilic addition reaction of a non-enolizable aldehyde and any primary or secondary amine to produce resonance stabilized imine (iminium ion or imine salt). The addition of a carbanion from a CH acidic compound (any enolizable carbonyl compound, amide, carbamate, hydantoin or urea) to the imine gives the Mannich base.[12]

The substitution of an-hydrogen atom of a ketone by the CR2 – NR2 group since reaction proceeds through the attack of iminium ion



Mannich base of camphor have not been reported in the literature so far & therefore it was thought worth while to modify the camphor molecule to improve its physical & biological properties, camphor has been studied widely for its topical & systemic effects but till date it is only being used due to its topical effects. The literature reveals its use as respiratory & circulatory stimulants. Beside this camphor in combination has been used as counter irritant & antipruretic. Doxapram is ketonic in nature & also possesses morpholine as substituent while the compound studied in our laboratories contains piperidine. So it has shown promising results as respiratory & circulatory stimulant. The Mannich bases of camphor were obtained on treatment with paraformaldehyde and various secondary amines and were screened for their analeptic and antimicrobial activity. It is observed that existing analeptics do not have not close resemblance with our new synthesized series of compounds like- secondary amine.

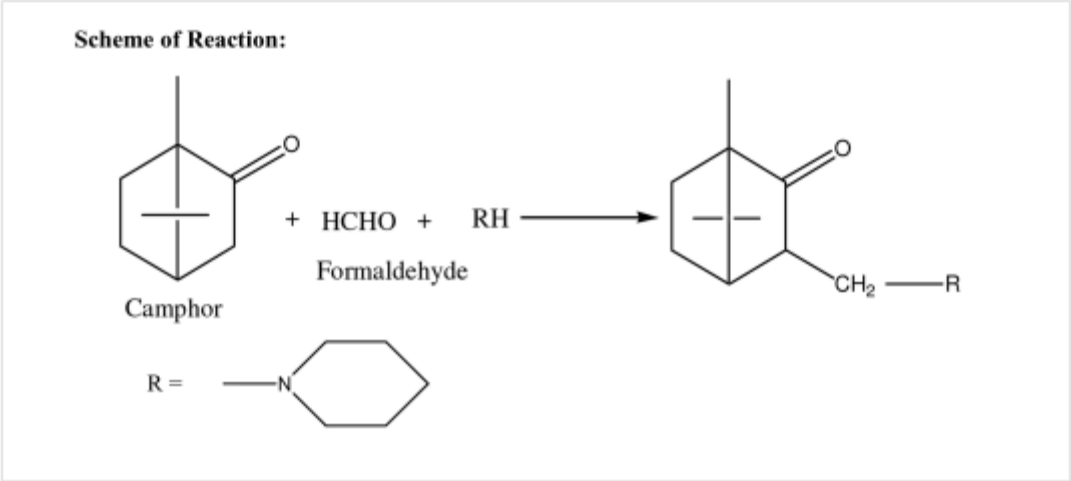
MATERIAL AND METHODS

Chemicals: I) Camphor (GDH), I) Secondary amines, III) Hydrochloric acid (A.R. Grade) IV)Methanol (S.D.S) V), Acetone (S.D.S.), VI)Silica Gel „G" (E. MERCK)

Equipment: I) Magnetic Stirrer II) Water Condenser III) U.V.(simadzu) IV) FT I.R. V.) N.M.R. Spectrometer)

Method: A mixture of one mole of secondary amine hydrochloride, one mole of camphor& equal weight of paraformadehyde, as that of camphor were mixed in 200ml of methanol. The mixture was made acidic with AR grade HCl. The pH was set between 2-3. The reaction was carried out at 50^0C using water condenser. After that excess solvent was evaporated .The crystallized mass was filtered off & further purification was done by repeated washings with solvent. NMR and IR Studies were conducted.

Scheme of Reaction



Antimicrobial activity: The antimicrobial activity of some selected compounds were determined using cup plate method[14].The in vitro antibacterial activity was carried our against 24 hr old culture of Esherichia coli. Micrococus luteus ad Staphylococcus aureus. The fungi used were Aspergellius flavus, Aspergillus niger and Curvuliaria lunata. The compounds were tested at a concentration of 0.001 mol/ml in dimethy1 formamide against all the organisms. Chloramphenicol (0.001 mole/mL) and flucanazole (0.001 mole/mL) were used as standard for antibacterial and antifungal activity respective.

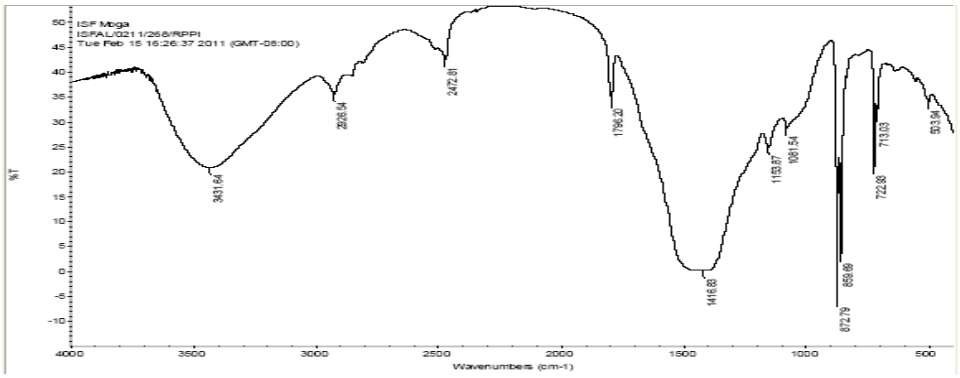
RESULT AND DISCUSSION

ISF Analytical Laboratory (ISFAL)
ISF College of Pharmacy, Ferozepur Road, Moga, Punjab 142 001
Ph. +91 1636-324200 Mobile: +91 97793 00464 Fax: +91 1636-236564
e-mail: isfal.lab@gmail.com Website: www.isfcp.org

CERTIFICATE OF ANALYSIS

Sample Name: RPPi Sample No.: RPPi Report No.: ISFAL/0211/267
Date of Receipt: 15-Feb-11 Date of manufacture: NA Date of expiry: NA
Name of the Manufacturer: NA Batch number: NA Batch size: NA

FTIR Analysis



Report: In the opinion of the undersigned, the sample complies/does not comply the test as per pharmacopoeia.
Note: Party asked for above tests only.

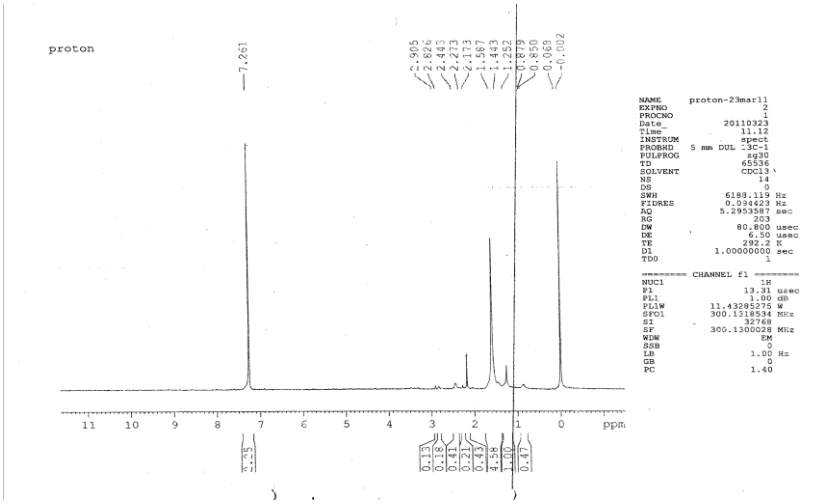
Analyst:_____ Date:_____ Person In-Charge of Testing:_____

Graph: 1

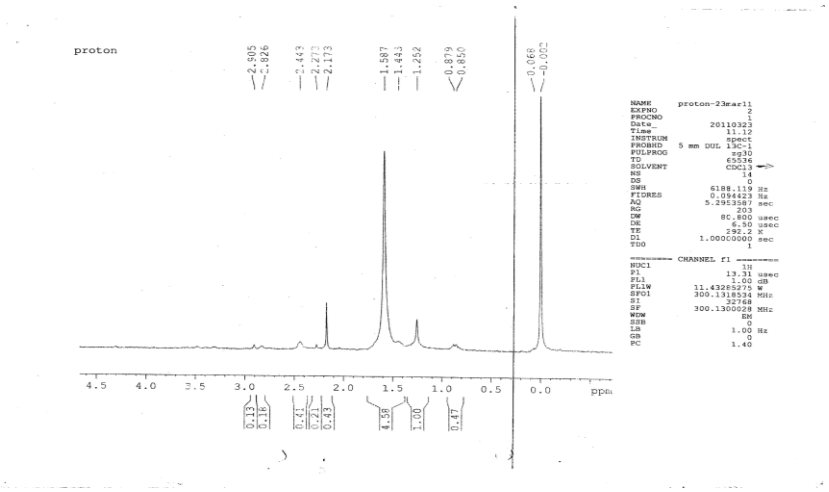
FT-IR interpretation of compound RPPi(Piperidine)

S.No.			Observed	Expected
1	Sec amine N-H		3431.64	3200-3500
2	Ar C-H		2926.54	2850-2960
3	-C=C-		2472.81	2100-2660
4	-C=O		1796.26	1600-1900
5	Ar-C=C-		1416.83	1500-1600
6	-C-O		1153.87	1000-1300
7	-C-O		1081.54	1000-1300
8	-C-H (aromatic), -NH		872.79	(900-700), (1600-900)
9	-C-H (aromatic), -NH		859.69	(900-700), (1600-900)
10	-C-H (disubstituted ortho), -NH		722.93	(770-735), (600-900)
11	-C-H (monosubstituted Ar compound), -NH Disubstituted Ar. Compound)		713.03	(710-680), (600-900)

NMR-IIT DELHI)



Graph 2



Interpretation of NMR

(1) 1.8 is due to @ where electronegative atom N (nitrogen) has deshielded the neighboring proton (triplet)

(2) 2.5 is due to (6) the free methyl group attached to the aromatic ring

(3) 3.34 may be due to water because DMSO has great affinity to water (even if it is present in trace amount and sample is stored over molecular sieve). Water proton gives characteristic peak (sharp) at around 3.35 or around 4.08 (broad). This can be minimized by adding few drops of D2O

(4) 7.8 may be due to aromatic proton the peak is strongest (intense) due to highest no of equivalence electron in the compd. (aromatic equivalent proton)

(5) 4.7 is due to aromatic proton.

(6) 9.61 is due to methyline proton attached at bridged system.

NMR shows - Keto proton,Keto Group Aromatic Proton,NH in aromatic ring and Aliphatic proton

Table No. 1: Microbiological activity of Piperidine compound no. 6

MIC- Minimum inhibitory concentration Table

Microorganism	Compound NO.6	Ciprofloxacin
Escherchia coli	25.0	3.9
Pseudomonas aeruginosa	12.5	3.9
Bacillus cereus	25.0	7.8
Bacillus subtilis	25.0	3.9
Klebsiella aeruginosa	50.0	15.6

The concentration is in ug/ml

The Mannich bases using camphor as substrate and utilizing secondary amine hydrochloride and paraformaldehyde in acidic pH in methanol medium were synthesized by aminomethylation. The resulted reaction mixture was concentrated and cooled for crystallization. The solubility of synthesized Mannich bases, camphor and amine hydrochlorides were taken into consideration during crystallization and removal of unreacted substances. The compounds were further purified by washing with a solvent in which it showed poor solubility. The thin layer chromatography (TLC) using Silicagel „G" as adsorbant & solvent system saturated with ammonia and Dragendroff"s reagent as detecting reagent, were performed to check the purity of compound. The entire synthesized compounds were T.L.C. pure.

CONCLUSION

The compound RPPi showed anti-microbial activity (refer Table 1). The compound also showed protection of mice from leptazole induced convulsion.

REFERENCES

1. Sarangapani M., Reddy N. A., Jayamma Y., Reddy V. M., Indian Drugs, 1998; 35: 336—343.
2. Sarangapani M., Reddy V. M., Indian Drugs, 1999; 36: 357—362.
3. Sarangapani M., Reddy V. M., Indian J. Pharm. Sci., 1996; 58: 147—149.
4. Sarangapani M., Reddy V. M., Indian J. Pharm. Sci., 1997; 59: 105—109.
5. Popp F. D., Parson R., Donigan B. E., J. Heterocycl. Chem., 1980; 17: 1329—1330.
6. Popp F. D., Parson R., Donigan B. E., J. Pharm. Sci., 1980; 69: 1235—1237.
7. Pajouhesh H., Parson R., Popp F. D., J. Pharm. Sci., 1983; 72: 318—321.
8. Popp F. D., Pajouhesh H., J. Pharm. Sci., 1982; 71: 1052—1054.
9. Singh G. S., Singh T., Lakhan R., Indian J. Chem., 1997; 36B: 951—954.
10. Lingaiah N., Narendra R., Dattatray A. M., Indian J. Chem., 1998; 37B: 1254—1257.
11. March, Jerry, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (3rd ed.), New York: Wiley, 1985; ISBN 0-471-85472-7.
12. V. J. Belinelo, G. T. Reis, G. M. Stefani, D. L. Ferreira-Alves and D. Piló-Veloso. "Synthesis of 6a,7b-dihydroxyvouacapan-17b-oic acid derivatives. Part IV: mannich base derivatives and its activities on the electrically stimulated Guinea-pig ileum preparation" (open access). Journal of the Brazilian Chemical Society, 2002; 13: 830–837. doi:10.1590/S0103-50532002000600016.
13. R. Silverstein, F. X Webster "Infrared spectrometry "Spectrometric Identification of Organic Compounds, 6th edition: 1998; 71-76.
14. Saundane A R, Rudresh K, Sathyanarayna N D & Hiremath S P, Indian J Pharm Sci, 1998; 60: 379.