PRELIMINARY REPORT

NEUROPHARMACOLOGICAL ACTIONS OF SOME NEWLY SYNTHESIZED MANNICH BASES

S. K. TONGIA AND C.P. TRIVEDI

Department of Pharmacology,
M.G.M. Medical College, Indore - 452 001

and

S. V. MATKAR, R. S. CHOUHAN AND R. KAUSHAL
Department of Chemistry,
Holkar Science College, Indore - 452 003

(Received on October 9, 1980)

Summary : Benzamido (alkyl) methyl pyrrolidine Mannich bases were synthesized and subjected to certain neuropharmacological studies. All the bases reduced the pentobarbitone sleeping time and rota-rod grip of rats. The Mannich bases II, III and V raised the minimal electro-shock seizure threshold of rats. The TAB-induced pyrexia was not reduced by the bases I and III in rabbits. None of the bases showed any significant analgesic activity.

Key words : Mannich bases pentobarbitone sleeping time rotarod-grip time TAB induced pyrexia minimal electroshock threshold

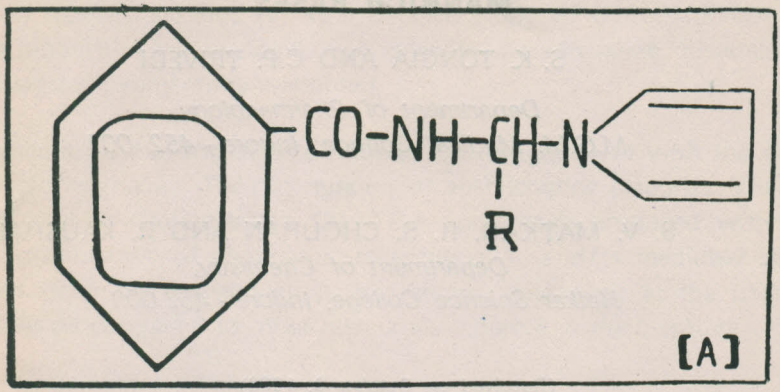
INTRODUCTION

The brain biogenic amines, noradrenaline, dopamine, 5-hydroxytryptamine, histamine, and acetylcholine, which are known to be involved in the central nervous system as neuratransmitters (2) in various physiological processes, sleep, wakefulness, motor activity, temperature regulation (3,4) and pain perception (5) possess in common a C-C-N linkage of Mannich bases in their structural configuration. The Mannich bases also have either a C-C-N or N-C-N linkage.

In view of the probability of competition between a compound with C-C-N linkage and a compound with N-C-N linkage for receptor sites in the brain; five Mannich bases of benzamide, synthezized through Mannich reaction were investigated for certain neuropharmacological properties.

MATERIAL AND METHODS

The Mannich bases of the general structure (A) were prepared by refluxing a mixture of benzamide, pyrrolidine and respective aldehyde in 25 *ml* of methanol containing 3–4 drops of hydrochloric acid for two and half hr on water bath. The excess of methanol



was distilled off and residue on chilling at ice temperature gave the desired new Mannich bases. They were suitably recrystallized (1, 8). The details of preparation including the analytical results are recorded in Table I.

TABLE I : Benzamido (alkyl) methyl pyrrolidines
(Benzamide 0.01 mol + pyrrolidine 0.0125 mol + respective aldehyde).

Ref. No.	*R. (Mol propn)*	*Mannich base formula*	*yield%*	*Crystalization solvent*	*MP C O*	*Analytical results** *C: (C:*	*H: H:*	*N** N)*
I	H (0.0125)	Benzamidosmethyl pyrrolidine $C_{12}H_{12}N_2O$	47	Alcohol+acetone	154	71.86 (72.00	6.22 6.00	13.92 14.00)
II	$-CH_3$ (0.02)	Benzamido (methyl) methyl pyrrolidine $C_{13}H_{14}N_2O$	43	Alcohol+isopropanol	129	73.00 (72.89	7.00 6.54	13.26 13.08)
III	$-C_2H_5$ (0.0125)	Benzamido (ethyl) methyl pyrrolidine $C_{14}H_{16}N_2O$	52	Alcohol	137	73.52 (73.68	7.44 7.01	12.09 12.28)
IV	$-C_3H_7$ (0.10125)	Benzamido (propyl) methyl pyrrolidine $C_{15}H_{18}N_2O$	63	Acetone+benzene	121	73.95 (74.38	7.85 7.43	11.42 11.57)
V	$-C_6H_{13}$ (0.0125)	Benzamido (hexyl) $C_{18}H_{24}N_2O$	69	Acetone+benzene	132	76.00 (76.05	8.95 8.45	9.62 9.85)

*The C, H and N values in the upper columns indicate observed values and those in the lower columns are theoretical values.

**The nitrogen was estimated by the modified semimicro Kjeldahl bromate-bromide method (8).

The Mannich bases were dissolved in a solvent system comprising of 1/10 by volume of dimethylformamide (DMF) and 9/10 by volume of distilled water, the pH of which ranged between 6.5 to 7.0. Pentobarbitone sodium and TAB vaccine were also used. All drugs were injected intraperitoneally. The study was done in albino rats and rabbits. The test compounds were administered in doses of 10 *mg/kg* as these doses were found to be effective and nontoxic in preliminary studies.

Pentobarbitone sleeping time :

Male albino rats weighing between 100–200 g were employed and divided in six groups of ten each. Five groups received the test compounds intraperitoneally in the doses of 10 *mg/kg* of body weight half an hr before the administration of 35 *mg/kg* of pentobarbitone. The sixth group serving as control, received 35 *mg/kg* pentobarbitone with the solvent. The sleeping time was calculated after observing the time interval between the loss of righting reflex and its reappearance.

Rota-rod grip time :

The motor (muscular) power of albino rat was tested through rota-rod techniques, devised in the laboratory. The rats were placed on the rod which was kept rotating at a fixed speed. The time interval between the placing of the rat and its falling from the rod was recorded and termed as grip time. Fifteen rats divided into 5 groups of 3 each were employed for the test. All the rats of each group were injected intraperitoneally with the test compounds in 10 *mg/kg* dose. The grip time of each animal was recorded in three successive trials half an hr before and then after 45 min and three hr of the injection of the test compounds. Each animal served as its own control.

Minimal electroshock threshold seizure :

The rats were divided into 6 groups of 5 each. One group serving as control received the solvent intraperitoneally and the other 5 groups were administered with 5 test compounds intraperitoneally at dose of 10 *mg/kg* using a Techno-Convulsiometer. A current of increasing intensity starting from 10 mA and then increasing gradually was delivered for 0.2 sec through the ear-electrodes.

TAB induced pyrexia :

Pyrexia (105°f) was induced in 15 rabbits by injecting 0.4 *ml* of TAB vaccine intraperitoneally. Rectal temperature was recorded by clinical thermometer before and after administration of compounds.

TABLE II : Effect of the test compounds on three parameters.
Values are the Mean ± Standard deviation.
(P values = 0.01 or 0.05)

Preliminary tests		*Mannich bases number* I	II	III	IV	V
1. Pentobarbitone sleeping time in male rats (min)	Before injection of test compound (control)	128 ±9.0	128 ±9.0	128 ±9.0	128 ±9.0	128 ±9.0
	After injection (test)	81.5 ±5.4	62.0 ±2.27	90.0 ±5.87	90.0 ±20.24	112.0 ±4.5
2. Rotarod grip time in male rats (sec)	Before injection (self control)	37.0 ±3.44	48.0 ±5.33	44.0 ±4.54	29.0 ±3.65	30.0 ±4.45
	After injection (test)	22.0 —41.0% ±2.50	26.0 —46.0% ±3.82	23.0 —46.0% ±3.33	18.0 —38.0% ±2.60	15.0 —50.0% ±2.70
3. Minimal Electroshock Threshold seizure in male rats (mA)	Before injection (self control)	—	11.65	14.85	—	17.0
	After injection (test)	—	15.50 33.0% ±0.83	17.63 18.8% ±1.23	—	22.5 32.3% ±0.73

RESULTS AND DISCUSSION

Table II summarizes the effects of drugs on various CNS parameters. All the bases caused marked reduction in the PB sleeping time of the rats. The maximum reduction (51.5%) was obtained with methyl substituted base II. The rota-rod experiments also demonstrated a marked reduction in the grip time of the rats. However, hexyl substituted Mannich base V was most active in this test. The three compounds methyl, ethyl and hexyl substituted bases increased the MES threshold (6) of the rats. The changes shown with all the above tests by the Mannich base used in the studies were highly significant. Though these compounds caused a slight reduction in the TAB induced pyrexia but the results were not significant.

It is evident that the Mannich bases reduced the PB sleeping time and rota-rod grip time. However, anticonvulsant property is possessed by II, III and V Mannich bases only. Decrease in PB sleeping time and increase in the MES threshold is similar to amphetamine like activity (7). However, the decrease in the rota-rod grip time and TAB pyrexia does not agree fully, with this inference and further studies are required to explore and correlate the various findings.

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