DESIGN, SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF N-METHYL PIPERIDINE DERIVATIVES

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SUMMARY: Piperidine is among the most important heterocyclic compounds which exhibits its therapeutic activity due to its conformationally flexible nature. Molecular modifications of meperidine and morphine like compounds led to the synthesis of analgesics having antagonistic properties with specific reference to Drug-Receptor Interaction. During the course of present investigations attempts were made to synthesize quaternary derivatives of N-methyl piperidine with various phenacylhalides and extensively explored for possible analgesic activity.

Spectrophotometric studies such as UV, IR, Mass (EI) and proton NMR were carried out to confirm the structures of newly synthesized derivatives in order to correlate the Structure-Activity Relationship (SAR).

Key Words: N-methyl piperidine, analgesic activity .

INTRODUCTION

The accentuated interest in the piperidine class of opiate analgesics continues to be expressed in the pharmaceutical community; the synthesis and biological properties of these agents have been the subject of on going investigations (1).

Extensive molecular dissection of the morphine molecule over the past several decades led to a host of molecules which showed narcotic analgesic activity even though they possessed but faint suggestion of the structural features present in morphine itself (4). Thus both cyclic molecules such as meperidine and acyclic compounds such as methadone were found to be effective as analgesics.

The opioid activity of methadone is abolished by an N-phenethyl group and does not depend upon the presence of a phenolic OH group (3). As a part of continuing effort to develop therapeutically advantageous analgesics, we initiated a research programme to quaternize the N-methyl piperidine molecule with various phenacyl halides and evaluated the resultant derivatives for possible analgesic activity. Despite the absence of any substituent on piperidine nucleus other than nitrogen, newly synthesized quaternary derivatives of N-methyl piperidine exhibited significant analgesic activity. This unexpected result prompted us to investigate the analgesic properties of a new series of derivatives.

The relevant chemical and pharmacological results obtained with these compounds will be presented in the series of papers. The purpose of this paper is to describe a simple and convenient method of synthesis and spectrophotometric data for structure elucidation, as well as some relevant analgesic properties in mice of a selected group of three typical compounds of Structure 1.

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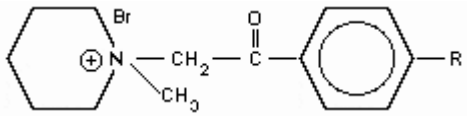


Structure 1

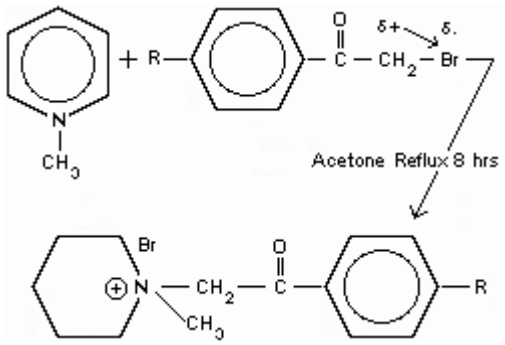
S. No.	Compound	R
1	I	CH_3
2	II	Cl
3	III	Br

EXPERIMENTAL

All melting points were determined in a capillary tube and uncorrected. Infrared (ir) spectra were recorded in potassium bromide (KBr) on JASCO IRA-2Ultraviolet (uv) absorption were determined in methanol on Pye-Unicam SP-800 spectrometer. Mass spectra were recorded on Finnigan MAT 112 and 312 double focusing mass spectrometer, connected to PDP 11/34 computer system. Proton NMR spectra were obtained in D_2O on Bruker AM 300 spectrometer.

1-(4-methylphenyl)-N-methyl piperidinium bromide (I)

N-methyl piperidine and 2-Bromo-4'-methyl acetophenone were dissolved in acetone separately in two conical flask, then they were mixed together in round bottom flask and contents were refluxed on water bath for about six hours, on cooling, a solid colored compound separated out. Filtered and re-crystallized in appropriate solvent to give 80% yield as brown solid as depicted in Figure 1.



S. No.	R	Solubility	M. P. (°C)	Yield (%)	Mol. Formula	Mol. Wt.
1	CH_3	CH_3OH/H_2O	240-242	80	$(C_{14}H_{22}NO)Br$	312
2	Cl	CH_3OH/H_2O	245-246	74	$(C_{14}ClH_{19}NO)Br$	332
3	Br	CH3OH	244-246	67	$(C_{14}BrH_{19}NO)Br$	377

nmr (D_2O): δ 7.92 (2H, d, J=8.54 Hz, H-9, H-13), 7.74 (2H, d, J=8.22 Hz, H-10, H-12), 3.76 (2H, m, H-2), 3.65 (2H, m, H-6), 3.48 (3H, s, N-CH3), 2.54 (3H, s, Ar-CH3), 1.98-2.26 (4H, m, H-3, H-5), 1.81 (2H, m, H-4). eims m/z M^{+1}=233 other important peaks at 119, 98 and 91. IR (KBr) ν_{max}: 2990 (Alip. CH), 1690 (carbonyl, ketone C=O), 1360 (CH3), 800 (C=C). $UV_{\lambda max}$ (MeOH): 260, 202 and 194 nm

1-(4-Chlorophenacyl)-N-methyl piperidinium bromide (II)

It was synthesized by the procedure as for compound No. I. nmr (D_2O) δ 8.00 (2H, d, J=8.91 Hz, H-9, H-13), 7.64 (2H, d, J=7.92 Hz, H-10, H-12), 3.89 (2H, m, H-2), 3.69 (2H, m, H-6), 3.43 (3H, s, N-CH3), 1.97-1.78 (6H, m, H-3, H-4, H-5). eims m/z M^{+1}=253 other prominent peaks at 194, 153, 139 and 98. IR (KBr) ν_{max} 3100 (Arom. CH), 2900 (Alip. CH), 1690 (carbonyl ketone C=O), 1590, 1480 (C=C aromatic) 1395 (CH3), 785 and 830 (C=C), $UV_{\lambda max}$ (MeOH): 259 and 201 nm.

1-(4-Bromophenacyl)-N-methyl piperidinium bromide (III)

Same method was also adopted to synthesize this compound. The structure is elucidated by means of spectral studies which is as follows. nmr (D_2O): δ 8.01 (2H, d, J=8.42 Hz, H-9, H-13), 7.43 (2H, d, J=7.92 Hz, H-11, H-13), 3.81 (2H, m, H-2), 3.62 (2H, m, H-6), 3.48 (3H, s, N-CH3), 1.98 (4H, m, H-3, H-5), 1.70 (2H, m, H-4). eims m/z M^{+1}=298 other diagnostic peaks at 198, 183, 155 and 98. IR (KBr) ν_{max}: 3100 (Arm. CH), 1600 (carbonyl, ketone C=O), 1580 and 1480 (Arom. C=C), 1380 (CH3), 850 (C=C). $UV_{\lambda max}$ (MeOH): 418, 263, 202 nm.

PHARMACOLOGY

The analgesic properties of these compounds were evaluated by Tail flick test (2). The basal reaction time of each mouse was determined using the tail withdrawal response when one third of the tail immersed in a water bath at 51°C. The cut-off time for immersion was 180 seconds. The reaction time was evaluated +30, +60, +90 and

Table 1: The values represent the difference from basal values and show the delay to produce the tail flick reflection after immersion for compound No. I [1-(4-Methylphenacyl)-N-methylpiperidinium bromide].

		Analgesia TFLD or mean increase in latency after drug ±S.E.M (s) administration			
Treatment	Dose mg/kg (1/M)	+30	+60	+90	+120
Water for injection	0.3 ml	0.06±0.128	0.35±0.110	0.35±0.055	0.33±0.013
Compound No:1	50 mg	0.26±0.046	0.85±0.089	0.85±0.148	0.97±0.122
	75 mg	0.34±0.089	2.15±0.255	2.25±0.259	3.07±0.249
	100 mg	1.94±0.286	1.75±0.228	2.85±0.110	2.57±0.217
Morphine HCl	10 mg	44.44±0.526	58.25±1.092	61.85±1.158	61.37±1.154
	N=5	p<0.05 (All the observations are significant)			

120 minutes after the administration of a compound. Morphine (10 mg/kg) was used as a standard drug in case of a control group which was always run together with the compound treated group. Pharmacological data for all the three compounds is represented in Tables 1, 2 and 3.

RESULTS AND DISCUSSION

On the basis of analgesic receptor theory as postulated by Portoghese (5) apart from anionic and Cationic sites of binding along with a support cavity on the receptor and anchoring groups on the phenyl nucleus plays a significant role in making a drug to interact with the respective receptor surface. Morphine being a standard compound, attempts are made to correlate the activity of compounds No. I-III with that of Morphine. The prepared compounds while fulfilling all the conditions of the receptor requirement exhibited less significant activity as that of morphine. The reason being the incorporation of a phenacyl function in

Table 2: The values represent the difference from basal values and show the delay to produce the tail flick reflection after immersion for compound No. II [1-(4-Chlorophenacyl)-N-methylpiperidinium bromide].

		Analgesia TFLD or mean increase in latency after drug ± S.E.M (s) administration			
Treatment	Dose mg/kg (1/M)	+30	+60	+90	+120
Water for injection	0.3 ml	0.06±0.128	0.35±0.110	0.35±0.055	0.33±0.013
Compound No:II	50 mg	-0.16±0.055	0.07±0.055	-0.03±0.009	-0.09±0.052
	75 mg	1.14±0.228*	0.69±0.91*	0.19±0.050*	-0.01±0.109
	100 mg	0.4±0.081*	0.21±0.076	-0.15±0.053	0.41±0.076*
Morphine HCl	10 mg	44.44±0.526	58.25±1.092	61.85±1.158	61.37±1.154
	N=5	p<0.05 (*Significant difference from corresponding control group)			

Table 3: The values represent the difference from basal values and show the delay to produce the tail flick reflection after immersion for compound No. III [1-(4-Bromophenacyl)-N-methylpiperidinium bromide].

		Analgesia TFLD or mean increase in latency after drug ± S.E.M (s) administration				
Treatment	Dose mg/kg (oral)	+30	+60	+90	+120	+150
Water for injection	0.3 ml	0.06±0.128	0.35±0.110	0.35±0.055	0.33±0.013	0.31±0.045
Compound No:III	50 mg	0.24±0.037	0.45±0.069*	-0.03±0.030	0.25±0.043*	-0.13±0.057
	75 mg	0.58±0.030*	0.57±0.048*	0.35±0.048*	0.15±0.041*	-0.15±0.075
	100 mg	0.16±0.052	0.17±0.046	0.11±0.078	-0.07±0.033	0.05±0.089
Morphine HCl	10 mg	44.44±0.526	58.25±1.092	61.85±1.158	61.37±1.154	67.25±0.879
	N=5	p<0.05 (*Significant difference from corresponding control group)				

place of an alkyl group. For the compounds having desired analgesic activity and less addiction liability, we synthesized three different substituents containing compounds at para-position of the phenyl nucleus of phenacyl halide derivative.

The most significant activity is observed in a compound having methyl function at the para-position with the dose level of 50, 75 and 100 mg/kg. The incorporation of methyl group could be proved to a certain extent the efficacy of methyl function, the activity of which can be compared with that of N-methyl function on the piperidine nucleus. However when the methyl group is displaced from the nitrogen atom of the piperidine to that of phenacyl function, resulted in decrease in analgesic activity. Among the three compounds No. 1 having methyl group showed significant activity to that of two other compounds having bromo and chloro group at the para-position of the phenyl of the phenacyl piperidinium compounds. This difference in activity can be attributed to the electron donating and electron withdrawing effects of the compounds, which may be expected to produce hindrance to interact with the receptor at the electronic level.

These results also confirm the importance of methyl group on pethidine and morphine analogs. This work is still in progress to test the efficacy of these compounds as potential anesthetic agent.

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