SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF N-METHYL PIPERIDINE ANALGESICS

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Abstract

Pain is probably the immediate stimulus for more visits to the Physician's office than all other complaints combined. Since pain serves as an alert to injury, it is often the first harbinger of disease. Piperidine has been extensively utilized for the synthesis of a wide range of therapeutic agents in general and analgetics in particular for the mitigation of pain. In a similar attempt, the N-methyl piperidine molecule was derivatized with various phenacyl halides and the resultant quaternary derivatives were explored extensively for analgesic activity using the tail flick test. Spectrophotometric techniques such as UV, IR, Proton NMR and Mass (EI) were also utilized to confirm the structures of the newly-synthesized compounds. All the compounds exhibited analgesic activity and particularly 1-[3', 4'-dihydroxyphenacyl)-N-methylpiperidinium bromide showed approximately one twentieth the analgesic activity of morphine.

Introduction

The continued search for molecules that possess the sedative-hypnotic properties of the barbiturates but show a better pharmacological ratio has taken many directions [1].

The discovery of the analgesic properties of meperidine represented a major advance in the analgesic field because it demonstrated that partial similarity to the morphine structure can lead to opiate analgesic activity [2, 3]. Many N-substituted meperidine analogues have since been prepared with varying degrees of analgesic potency and side effects. Janssen pioneered the development of fentanyl and by relatively minor chemical modifications produced a series of potent analgesics with different pharmacokinetic properties for different clinical applications [4]. Fentanyl itself is about 500 times as potent as pethidine and has a significantly improved therapeutic ratio. Some of the 4,4-disubstituted piperidines, alfentanyl, sufentanyl and carfentanyl are even more potent. The incorporation of N-phenethyl substituent may have been made because of the observation that this moiety confers high activity to morphine [5] and enkephalin [6]. In the course of the present investigation, N-methyl piperidine molecule was quaternized with phenacyl halides keeping in view the utility of the N-methyl function in case of pethidine, bemidone and prodine etc.,

Keywords: N-methylpiperidine; Phenacyl halide; Analgesics

and at the same time the N-phenacyl group, partially similar to N-phenethyl moiety which is present in fentanyl and carfentanyl.

Despite the absence of any substituent on piperidine nucleus other than nitrogen, the newly synthesized quaternary derivatives displayed significant analgesic activity.

Experimental Section

All melting points were determined in a capillary tube and were uncorrected. The ultraviolet spectra were measured in methanol on a Pye-Unicam SP-800G ultraviolet spectrometer with graphic printer PR-1. The infrared spectra were scanned on JASCO A-302 infrared spectrometer in KBr discs. Electron impact EI mass spectra were determined on a Finnigan spectrometer. Proton NMR spectra were determined on a Bruker AM-300 spectrometer with TMS as internal reference and coupling constants are in Hz. The purity of the samples was checked on TLC (silica gel).

General Procedure

1-(3', 4'-Dihydroxyphenacyl)-N-methylpiperidinium bromide (1)

Equimolar quantities of different phenacyl halides (α-bromo-3',4'-dihydroxy-acetophenone, α-bromo-4'-methoxy acetophenone and α-bromo-4'-nitroacetophenone) and N-methylpiperidine were dissolved separately in 30 ml of acetone. The reaction mixture was vigorously stirred at room temperature for 50 minutes, followed by refluxing until completion of the reaction for different time periods for different phenacyl halides, and was monitered by TLC in different systems of $CHCL_3$: MeOH. The resulting precipitate was collected by filtration, washed and recrystallized from appropriate solvent to give the different quaternary ammonium salts. All the compounds were synthesized by the route given in Scheme 1.

NMR (D_2O): δ 7.48 (1H, dd, J=8.42, 2.26 Hz, H-13), 7.42 (1H, d, J=2.22 Hz, H-9), 6.94 (1H, d, J=8.41 Hz, H-12), 3.73 (2H, m, H-2), 3.59 (2H, m, H-6), 3.31 (3H, s, N-CH_3), 1.47-1.93 (6H, m, H-3, H-4, H-5).

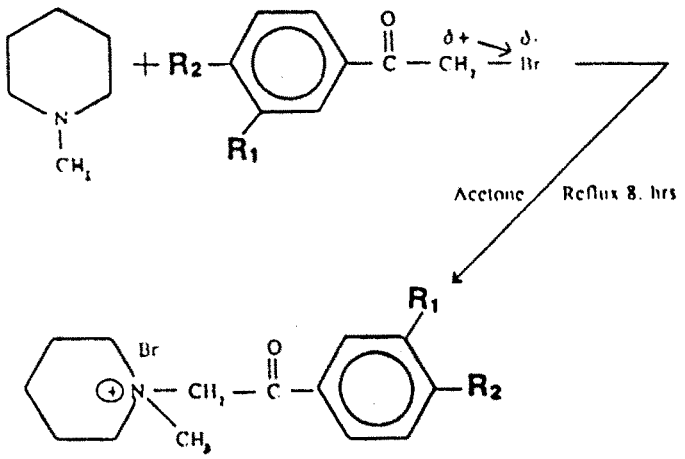
EIMS m/z M^{+2} = 252 other important peaks at 119 and 98.

UV (λ_{max}nm): 318, 285, 236 and 207 nm.

IR (υ, cm^{-1}): 3050 (OH), 3060 (Ar. CH), 2900 (Alip. CH) 1680 (C=O carbonyl ketone), 1580, 1490 (Arm. C=C), 1390 (CH_3).

1-(4'-Methoxyphenacyl)-N-methylpiperidinium bromide (II)

This compound was synthesized according to the method previously reported, and was similarly obtained from corresponding phenacyl halide. The spectral data is as follows:



Scheme 1

S. No.	R_1	R_2	Solubility	M.P.	Yield	Mol.Formula	Mol.Wt.
1	OH	OH	DMSO/H_2O	242°C	62%	$C_{14}H_{20}BrNO_3$	330
2	H	OCH_3	DMSO/H_2O	241°C	82%	$C_{15}H_{22}BrNO_2$	328
3	H	NO_2	DMSO/H_2O	245°C	73%	$C_{14}H_{19}BrNO_3$	343

NMR (D_2O): δ 7.98 (2H, d, J=9.03 Hz, H-9, H-13), 7.11 (2H, d, J=9.05 Hz, H-10, H-12), 3.91 (3H, s, Ar-OCH_3), 3.74 (2H, m, H-2) 3.63 (2H, m, H-6), 3.34 (3H, s, N-CH_3), 2.14-3.01 (6H, m, H-3, H-4, H-5).
EIMS m/z M^{+1} = 249 other diagnostic peaks at 231, 151, 137 and 100.
UV (λ_{max}nm): 286, 233, 202 and 193.
IR (ν, cm^{-1}): 3010 (Ar. CH), 2895 (Alip. CH), 1600 (carbonyl, ketone C=O) 1500, 1485 (C=C), 1350, (CH_3) 750, 810 (C=C).

1-(4'-Nitrophenacyl)-N-methylpiperidinium bromide (III)

The same procedure was also adopted for the synthesis of this compound and the spectral data is given below:
NMR (D_2O): δ 8.34 (2H, d, J=8.64 Hz, H-9, H-13), 8.71 (2H, d, J=7.84 Hz, H-10, H-12), 3.78 (2H, m, H-2), 3.53 (2H, m, H-6), 3.21 (2H, s, N-CH_3), 1.99-2.69 (6H, m, H-3, H-4, H-5).
EIMS m/z M^{+1} = 264 other prominent peaks are 165, 152, 122, 112 and 100.
UV (λ_{max}nm): 261 and 201 nm.
IR (ν, cm^{-1}): 3080 (Ar. CH), 2980 (Alip. CH), 1690 (carbonyl ketone C=O), 1510-1320 (NO_2), 850 (C=C).

Pharmacology

The analgesic properties of these compounds were evaluated by the tail flick test [7]. The basal reaction time of each mouse was determined using the tail withdrawal response when one third of the tail was 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 120 minutes after the administration of a compound. Morphine (10 mg/kg) was used as a standard drug in the case of a control group which was always run together with the compound treated group. Pharmacological data for all the three compounds are represented in Tables I-III.

Table I. The values represent the difference from basal values and show the delay in producing the tail flick reaction after immersion for compound no.I [1-(3, 4-Dihydroxyphenyl)-N-methylpiperdinium bromide].

	Analgesia TFLD or mean increase in latency±S.EM (s) after drug 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: I	50 mg	0.44±0.084	0.45±0.055	0.19±0.050	0.51±0.058
	75 mg	1.48±0.076	2.11±0.054	2.29±0.063	2.19±0.030
	100 mg	1.28±0.028	1.23±0.088	1.25±0.026	1.31±0.030
Morphine HCl	10 mg	44.44±0.528	58.25±1.092	61.85±1.158	61.37±1.154

N=5 $p<0.05$ (All the observations were highly significant from corresponding control.)

Table II. The values represent the difference from basal values and show the delay in producing the tail flick reaction after immersion for compound no.II 1-(4-Methoxyphenyl)-N-methylpiperidinium bromide.

	Analgesia TFLD or mean increase in latency±S.EM (s) after drug 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	0.09±0.074*	-0.10±0.089*	0.11±0.088*	0.17±0.055
	75 mg	0.84±0.089	0.35±0.055	0.15±0.055	0.57±0.084
	100 mg	0.94±0.045	0.95±0.089	0.55±0.084	0.87±0.110
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 except*.)
*(Insignificant observations)

Table III. The values represent the difference from basal values and show the delay in producing the tail flick reaction after immersion for compound no. III (1-(4-Nitrophenacyl)-N-methylpiperdinium bromide.

Treatment	Dose mg/kg (1/m)	Analgesia TFLD or mean increase in latency±S.EM (s) after drug administration +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: III	50 mg	0.16±0.055	0.45±0.055*	0.95±0.071*	0.07±0.084
	75 mg	0.34±0.114*	-0.05±0.055	-0.25±0.055	0.27±0.055*
	100 mg	0.24±0.114	0.95±0.134	0.85±0.084*	1.47±0.100*
Morphine HCl	10 mg	44.44±0.526	58.25±1.092	61.85±11.158	61.37±1.154

N=5 $p<0.05$ (*Significant difference from corresponding control group)

Discussion

With a view to studying the analgesic activity of N-methylpiperidine derivatives having neither a phenyl nor hydroxyl group at the piperidine nucleus, which are essentially present in almost all the piperidine class of analgetics, attempts were made to incorporate phenacyl function at the nitrogen of piperidine, making it a quaternary centre. This quaternary centre is at a distance of two carbon atoms from the phenyl ring of phenacyl moiety.

Among the three derivatives, the most significant activity was shown by the compound (I) which has OH group at the third and fourth position of the phenyl ring. This part of molecule partially resembles the structure of adrenaline. Hence it can be postulated that interaction with adrenergic receptors is contributing to this sort of activity.

As a result of this project, it is expected that new derivatives could be designed which can exhibit analgesic effects.

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