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# Synthesis of 4-Hydroxypiperidine Derivatives and Their Screening for Analgesic Activity

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Six substituted phenacyl derivatives of 4-hydroxypiperidine were prepared and their structures were confirmed through spectroscopic techniques. These newly synthesized derivatives were also screened for analgesic activity by chemical and thermal methods. Only halogenated phenacyl derivatives demonstrated more or less protection against acetic acid induced writhing in mice where as rest of three derivatives were found inactive when screened by this chemical method. Similarly all the six derivatives were proved inactive by tail flick test.

**Key words** : Hydroxypiperidine, Substituted Phenacyl Halide, Analgesic

## INTRODUCTION

The preparation of *N*-phenacyl derivatives of alkylated and arylated piperidinols was reported (Mailey and Day, 1957), but were not evaluated for possible biological activity. *Kugita et al.* (1963 and 1965) carried out the synthesis and analgesic activity of 3-alkyl-3-phenylpiperidine derivatives. The highest analgesic activity of this series of compounds, observed with 1-phenacyl-3-(3-hydroxyphenyl)-3-methylpiperidine (HCl), was equal to that of meperidine and twice that of codeine, but the duration of its activity was shorter than that of codeine or morphine. Similarly, 1-phenacyl-3-(3-hydroxyphenyl)-2,3-dimethylpiperidine (HBr) also showed powerful analgesic activity and its acute toxicity was greatly lowered.

Hameed et al.(1992 and 1993) reported the synthesis and analgesic screening of a few substituted phenacyl derivatives of *N*-methylpiperidine.

The superior therapeutic index of *N*-phenacyl group in 3-alkyl-3-phenylpiperidine derivatives in general and analgesic activity showed by the para methoxyphenacyl derivative of *N*-methylpiperidine in particular encouraged us to undertake the synthesis and evaluation of analgesic activity of four different methoxy substituted phenacyl derivatives of 4-hydroxypiperidinol (Saeed *et al.* 1996). Among these, only 2',4',-dimethoxy substituted phenacyl derivative showed more or less protection against acetic acid induced writhing whereas all the four derivatives were proved inactive by tail flick test.

Although recent findings were not very much encouraging yet we are going to report synthesis and evaluation of further more six substituted phenacyl derivatives of 4-hydroxypiperidine.

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## MATERIALS AND METHODS

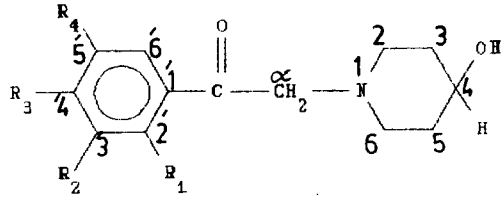
Melting points were determined on Buchi-535 melting point apparatus and are uncorrected. The $^1$H-NMR spectra were recored on Brucker AM 400 spectrometer operating at 400 MHz. The chemical shifts are reported in $\delta$ (ppm) and coupling constants in Hz. IR and UV spectra were measured on JASCO IRA-I and Pye-Unicam SP-800 spectrometers respectively. Mass spectra were recorded on Finnigan MAT 112 and purity of the products were checked on TLC plates coated with silica gel $PF^{254}$ and the spots were visualized under ultraviolet light at 254 nm or by spraying iodine vapours.

### Synthesis of 4-hydroxypiperidine derivatives

Equimolar quantities of 4-hydroxypiperidine (Aldrich) and substituted phenacyl halides (Aldrich) were dissolved in acetone, mixed together in a round bottom flask and refluxed on water-bath until completion of the reaction.

Conversion of reactants into product was monitored by T.L.C. in different combinations of $CH_3Cl$-MeOH. When almost all the reactants changed to product, the resulting precipitate was collected by filtration, washed with cold acetone and recrystallized from approp-

**Table I.** Substituted phenacyl derivatives of 4-hydroxypiperidine and their physical data



| Compound | R1 | R2 | R3 | R4 | Colour/Shape | M.P.(°C) | Mol.Form. | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| II | H | H | $CH_3$ | H | Brown Gummy Matter | - | $C_{14}H_{20}BrNO_2$ | 72 |
| III | H | OH | OH | H | Ash White cryst. | 148-150 | $C_{13}H_{18}ClNO_4$ | 78 |
| IV | H | H | Ph | H | Colourless needles | 212-215 | $C_{19}H_{22}BrNO_2$ | 70 |
| V | H | H | Br | H | Colourless rods | 216-218 | $C_{13}H_{17}Br_2NO_2$ | 72 |
| VI | H | H | Cl | H | Light yellow plates | 238-240 | $C_{13}H_{17}BrClNO_2$ | 65 |
| VII | H | H | F | H | Colourless powder | 246-248 | $C_{13}H_{17}ClNO_2$ | 63 |

riate solvent. The physical properties of these derivatives are presented in Table I.

### 1-(4'-Methylphenacyl)-4-hydroxypiperidinium bromide (II)

$^1$H-NMR ($CD_3OD$, 400 MHz) δ: 7.94 (2H, d, J=8.30 Hz, H-2',6'), 7.36 (2H, d, J=8.30 Hz, H-3',5'), 6.02 (2H, s, H-α), 3.12 (3H, m, H-2,6), 2.43 (3H, s, Ar-$CH_3$), 2.05 (1H, m, H-4) and 1.76 ((4H, m, H-3,5).

**EIMS *m/z* (relative int., %):** 233 ($M^+$-HBr, $C_{14}H_{19}NO_2$, 1), 135 (19), 120 (2), 114 (100), 105 (1), 91 (25), 84 (3), 76 (1) and 56 (90). IR $\nu_{max}$ ($CHCl_3$) $cm^{-1}$: 3400, 2850, 1655, 1590, 1235 and 825. UV $\lambda_{max}$ (MeOH) nm: 256, 202 and 193.

### 1-(3',4'-Dihydroxyphenacyl)-4-hydroxypiperidinium chloride (III)

$^1$H-NMR ($CD_3OD$, 400 MHz) δ: 7.45 (1H, dd, J=8.82 2.18 Hz, H-6'), 7.43 (1H, d, J=2.18 Hz, H-2'), 6.87 (1H, d, J=8.82 Hz, H-5'), 6.16 (2H, s, H-α), 3.29 (4H, m, H-2,6), 2.11 (1H, m, H-4) and 1.90 ((4H, m, H-3, 5).

**EIMS *m/z* (relative int., %):** 251 ($M^+$-HCl, $C_{13}H_{17}NO_4$, 1), 137 (4), 123 (2), 114 (100), 100 (8), 84 (3), 81 (2) and 56 (7). IR $\nu_{max}$ (KBr) $cm^{-1}$: 3440, 2950, 1665, 1590, 1300, 1200 and 810 UV $\lambda_{max}$ (MeOH) nm: 234, 222 and 208.

### 1-(4'-Phenylphenacyl)-4-hydroxypiperidinium bromide (IV)

$^1$H-NMR ($CD_3OD$, 400 MHz) δ: 8.11 (2H, d, J=8.65 Hz, H-2',6'), 7.85 (2H, d, J=8.65 Hz, H-3',5'), 7.70 (2H, dd, J=8.45, 1.45 Hz, H-2", 6"), 7.49 (2H, dt, J= 8.45, 1.50 Hz, H-3",5"), 7.42 (1H, dd, J=8.45, 1.45 Hz, H-4"), 6.23 (2H, s, H-α) 3.15 (4H, m, H-2,6), 2.17 (1H, m, H-4) and 1.89 (4H, m, H-3,5).

**EIMS *m/z* (relative int., %):** 295 ($M^+$-HBr, $C_{19}H_{21}NO_2$, 2), 181 (2), 114 (100), 100 (4), 84 (2), 80 (7) and 56 (3). IR $\nu_{max}$ (KBr) $cm^{-1}$: 3350, 2900, 1680, 1600, 1380 and 780 UV $\lambda_{max}$ (MeOH) nm: 289, 265 and 203.

### 1-(4'-Bromophenacyl)-4-hydroxypiperidinium bromide (V)

$^1$H-NMR ($CD_3OD$, 400 MHz) δ: 7.94 (2H, d, J=8.80 Hz, H-2',6'), 7.76 (2H, d, J=8.80 Hz, H-3',5'), 6.12 (2H, s, H-α), 3.09 (4H, m, H-2,6), 2.14 (1H, m, H-4), and 1.73 (4H, m, H-3,5). EIMS *m/z* (relative int., %): 299 ($M^+$-Br, $C_{13}H_{17}ClNO_2$, 2), 183 (2), 114 (100), 82 (14), 80 (15), 70 (3) and 56 (3). IR $\mathbf{n}_{max}$ (KBr) $cm^{-1}$: 3350, 2900, 1680, 1570, 1390, 1060 and 800. UV $\lambda_{max}$ (MeOH) nm: 261, 203 and 194.

### 1-(4'-Chlorophenacyl)-4-hydroxypiperidinium bromide (VI)

$^1$H-NMR ($CD_3OD$, 400 MHz) δ: 8.02 (2H, d, J=8.83 Hz, H-2',6'), 7.60 (2H, t, J=8.83 Hz, H-3',5'), 6.39 (2H, s, H-α), 3.36 (4H, m, H-2,6), 2.15 (1H, m, H-4), and 1.81 (4H, m, H-3,5).

**EIMS *m/z* (relative int., %):** 254 ($M^+$-Br, $C_{13}H_{17}ClNO_2$, 1), 139 (13), 114 (100), 101 (2), 84 (3), 82 (11) and 56 (6). IR $\nu_{max}$ (KBr) $cm^{-1}$: 3300, 2900, 1675, 1565, 1250, 1045 and 820 UV $\lambda_{max}$ (MeOH) nm: 256, 230 and 203.

### 1-(4'-Fluorophenacyl)-4-hydroxypiperidinium chloride (bromide) (VII)

$^1$H-NMR ($CD_3OD$, 400 MHz) δ: 8.11 (2H, dd, J= 9.03 5.28 Hz, H-2',6'), 7.32 (2H, t, J=9.03 Hz, H-3',5'), 6.18 (2H, s, H-α), 3.22 (4H, m, H-2,6), 2.15 (1H, m, H-4), and 1.90 (4H, m, H-3,5).

**EIMS *m/z* (relative int., %):** 237 ($M^+$-HCl, $C_{13}H_{16}FNO_2$, 1), 123 (7), 114 (100), 101 (15), 100 (6), 96 (2), 84 (6) 82 (3) and 56 (18). IR $\nu_{max}$ (KBr) $cm^{-1}$: 3300,

2900, 1675, 1580, 1230, 1050 and 840 UV $\lambda_{max}$ (MeOH) nm: 250, 204 and 192.

### Analgesic activity

Analgesic activity of compounds was tested as antinociceptive effect against chemical and thermal stimuli.

Female mice of NMRI strain weighing between 18-22 gms were used in the writhing test and those for thermal test were mice of either sex weighing between 20-30 gms. (The animals were maintained under standard colony coonditions i.e., 12 hrs. light and 12 hrs. dark, temperature 21±2°C, fed with balanced diet and water ad libitum).

### Chemical method (Writhing test)

A group of 5 mice were injected i.p. 0.6% acetic acid 15 minutes after administration of compound and the number of writhing movements were noted in control mice (Wc) and in the treated mice (Wx) (Bentley *et al.*, 1983).

$$\% \text{ IAAISR} = 100 - [\frac{Wx}{Wc} 100]$$

% IAAISR=Percent inhibition of acetic acid induced stretching response

### Thermal method (Tail flick test)

The procedure used was a modification of Distasi *et al.*, (1988). The basal reaction time of each mouse in a group of five was determined using the tail withdrawal response when one third of the tail was immersed in a water-bath at 55°C. The cut-off time for immersion was 30 seconds. The reaction time was evaluated at +30, +60, +90, +120 minutes after the administration of compound. Morphine HCl (10 mg/kg) and aspirin (300 mg/kg) were used as standard drugs in case of a control group which was always run parallel to the compound treated group.

**Table II.** Results of analgesic activity of 4-hydroxypiperidine.HCl (I) and its derivatives (II-VII)

| Compound | Dose ($mg \cdot kg^{-1}$) | Mean Writhing | % Inhibation |
|---|---|---|---|
| Acetic acid (0.6%) | 15 $ml \cdot kg^{-1}$ | ±S.E.M. 8.50±0.35 | - |
| I | 50 | inactive | - |
| | 100 | inactive | - |
| II | 50 | inactive | - |
| | 100 | inactive | - |
| III | 50 | inactive | - |
| | 100 | inactive | - |
| IV | 50 | inactive | - |
| | 100 | 4.40±0.24 | 48 |
| V | 50 | 6.00±0.31 | 33 |
| | 100 | 4.60±0.24 | 49 |
| VI | 50 | 4.40±0.24 | 48 |
| | 100 | 3.20±0.20 | 65 |
| VII | 50 | 6.10±0.30 | 38 |
| | 100 | 2.45±0.24 | 70 |
| Aspirin | 300 | 1.30±0.53 | 77 |
| Morphine HCl | 10 | 0 | 100 |

## RESULTS

Table II presents the results of antinociceptive activity of substituted *N*-phenacyl derivatives of 4-hydroxypiperidine along with their parent compounds (I).

Compound **I** is the starting material of substituted phenaycl derivatives of 4-hydroxypiperidine and found devoid of analgesic activity at tested doses when screened by writhing test as well as tail flick test.

Among the compounds of this series (**II-VII**). *para* halogenated derivatives (**V-VII**) exhibited maximum percent inhibition of writhing at 50-100 mg/kg doses. Compounds with chloro (Cl) and fluoro (F) substituents showed almost same level of protection against acetic acid induced writhing. Compound **IV** was inactive at 50 mg/kg dose whereas, exhibited 48% inhibition when tested at 100 mg/kg dose. Rest of two compounds (**II** and **III**) of this series showed no analgesic activity at tested doses.

## DISCUSSION

Analgesic activity of 4-hydroxypiperidine (HCl) and its derivatives was determined by measuring the inhibition of acetic acid induced writhing and the delay in response to noxious heat stimuli in mice (tail flick test).

Although piperidine derivatives understudy did not show any promising analgesic activity yet it is hoped that halogen substituted phenacyl derivatives which were active in writhing test might demonstrate any other therapeutic effect.

Since writhing test is used to detect both weak and strong analgesics, while the tail flick test is sensitive to the strong, opiate like analgesics (8). It has been well established that not all compounds exhibiting potent antinociceptive activity in acetic acid induced writhing assay are analgesic agents of potential clinical use [6]. Other types of drugs besides analgesics which inhibit writhing, are antihistaminics, parasympathomimetics, sympthomimetics, CNS stimulants and adrenergic blocking agents [9].

It is hoped that further exploration of the pharmacological properties of these derivatives will provide deep insight. In depth studies on a few derivatives are currently in progress.

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