New Analgesic Drugs Derived from Phencyclidine

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Several esters of 1-(1-phenylcyclobexyl)-4-piperidinol (3), 1-(1-phenylcyclobexyl)-4-phenyl-4-piperidinol (10) and its propionate (11), and 1-(1-phenylcyclobexyl)-4-phénylpiperidine (13) were prepared and characterized. The new compounds, which are derived from phencyclidine, exerted analgesic activity in mice. The most potent is 10, which is twice as active as morphine. The antinociceptive activity of 10, 11, and 13 could be well correlated with their potency in the mouse vas deferens bioassay, and both were completely reversed by naloxone.

Phencyclidine [1-(1-phenylcyclobexyl)piperidine, PCP], now a major drug of abuse,6 held initially the promise of a safe general anesthetic. Indeed, the drug is unique in its lack of depressant effect on the heart and respiration.3ab Its use, precluded in man on account of the acute psychotic syndrome it precipitates, is still practiced with success in veterinary medicine.65 PCP has also been accredited with the exertion of analgesia,6,5 but no precise data are available on this particular aspect. We assumed that a proper manipulation of the PCP structure might change the balance between its antinociceptive and psychotomimetic properties in favor of the former. This is not unreasonable, in view of the successful precedence offered by ketamine.8

(1) Taken from the Ph.D. dissertation of Y.L., 1980.
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caused potentiation of twitches (which was concentration dependent).

Table I. 4-Substituted 1-(1-Phenylcyclohexyl)piperidines

<table>
<thead>
<tr>
<th>no.</th>
<th>R</th>
<th>R₁</th>
<th>mp, °C</th>
<th>formula</th>
<th>recryst. yield, %</th>
<th>anal.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>H</td>
<td></td>
<td>154-155</td>
<td>C₉H₁₂NO₂</td>
<td>A 62</td>
<td>C, H, N</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td></td>
<td>146-148</td>
<td>C₉H₁₂NO₂</td>
<td>A 85</td>
<td>C, H, N</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td></td>
<td>114-115</td>
<td>C₁₂H₂₃N₂O₂</td>
<td>A 60</td>
<td>C, H, N</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td></td>
<td>167-168</td>
<td>C₁₂H₂₃NO₂</td>
<td>E 75</td>
<td>C, H, N</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td></td>
<td>195-196</td>
<td>C₁₂H₂₃NO₂</td>
<td>B 72</td>
<td>C, H, N</td>
</tr>
<tr>
<td>10</td>
<td>OH</td>
<td></td>
<td>103-105</td>
<td>C₁₀H₁₃NO</td>
<td>E 60</td>
<td>C, H, N</td>
</tr>
<tr>
<td>11</td>
<td>C₂H₄CO₂</td>
<td></td>
<td>214-215</td>
<td>C₁₂H₂₃NO₂</td>
<td>B 60</td>
<td>C, H, N</td>
</tr>
<tr>
<td>13</td>
<td>H</td>
<td></td>
<td>131-132</td>
<td>C₁₂H₂₃N₂</td>
<td>C 57</td>
<td>C, H, N</td>
</tr>
</tbody>
</table>

a Reference 13.  b A = ethyl acetate; B = acetone; C = ethyl acetate-ethanol; D = benzene; E = petroleum ether-hexane.

Table II. Analgesic Activity, Analytical Data, and Acute Toxicity

<table>
<thead>
<tr>
<th>compd</th>
<th>hot-plate test</th>
<th>writhing test</th>
<th>ED₅₀, mg/kg sc</th>
<th>IC₅₀, μM</th>
<th>rel potency</th>
<th>LD₅₀, mg/kg sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>f</td>
<td>i</td>
<td>2.8 (2.2-3.4)</td>
<td>i</td>
<td>5.0</td>
<td>37.5 (28.2-49.8)</td>
</tr>
<tr>
<td>3</td>
<td>g</td>
<td>i</td>
<td>11.2 (7.5-16.6)</td>
<td>i</td>
<td>2.3</td>
<td>nt</td>
</tr>
<tr>
<td>4</td>
<td>7.5 (4.7-12.0)</td>
<td>i</td>
<td>5.2 (3.1-8.4)</td>
<td>i</td>
<td>0.5</td>
<td>74.0 (57.1-96.2)</td>
</tr>
<tr>
<td>5</td>
<td>15.0 (8.8-25.6)</td>
<td>i</td>
<td>24.5 (14.4-41.6)</td>
<td>i</td>
<td>1.1</td>
<td>&gt;300k</td>
</tr>
<tr>
<td>6</td>
<td>45.0h</td>
<td>i</td>
<td>16.5 (11.1-24.5)</td>
<td>i</td>
<td>1.3</td>
<td>&gt;300k</td>
</tr>
<tr>
<td>7</td>
<td>40.0h</td>
<td>i</td>
<td>9.3 (5.4-15.8)</td>
<td>i</td>
<td>0.7</td>
<td>nt</td>
</tr>
<tr>
<td>8</td>
<td>40.0h</td>
<td>i</td>
<td>14.5 (8.0-26.1)</td>
<td>i</td>
<td>2.0</td>
<td>nt</td>
</tr>
<tr>
<td>10</td>
<td>1.3 (0.9-2.0)</td>
<td>i</td>
<td>0.27 (0.18-0.40)</td>
<td>i</td>
<td>0.082 ± 0.008</td>
<td>1.2</td>
</tr>
<tr>
<td>11</td>
<td>12.1 (8.6-16.9)</td>
<td>i</td>
<td>5.8 (3.7-8.9)</td>
<td>i</td>
<td>0.73 ± 0.042</td>
<td>3.1</td>
</tr>
<tr>
<td>13</td>
<td>56.0 (43.4-72.2)</td>
<td>i</td>
<td>42.0 (30.4-57.9)</td>
<td>i</td>
<td>7.5 ± 0.40</td>
<td>&gt;300k</td>
</tr>
<tr>
<td>morphine</td>
<td></td>
<td>i</td>
<td>2.5 (1.6-3.7)</td>
<td>i</td>
<td>0.50 ± 0.058</td>
<td>1.1</td>
</tr>
</tbody>
</table>

a Tested subcutaneously as water-soluble hydrochloride salts.  b Effect of the compounds on the mouse vas deferens according to ref 17.  c Values refer to the potency of the compounds to produce hyperactivity in mice. Untreated mice were taken as the control group (potency = 1).  d Numbers in parentheses are 95% confidence limits by probit analysis; data refer to the free base; nt = not tested.  e Concentration which produces 50% inhibition of twitches plus or minus SEM.  f Not active up to 9 mg/kg sc; higher doses produced ataxia.  g Not active up to 25 mg/kg sc; higher doses produced ataxia.  h Approximate ED₅₀.  i Concentrations up to 1.0 μM caused no change in twitches; higher concentrations (up to 100 μM) caused potentiation of twitches (which was concentration dependent).  j No change in twitches was observed up to 100 μM.  k No acute toxicity up to 300 mg/kg sc.  l Reference 25.

which has retained the anesthetic profile of the parent structure but lost much of its psychotomimetic activity. Some of the structural modifications we sought borrowed elements from the well-known analgesic prodine. The relationship between PCP and its new congeners is shown in Table I.

While this work was in progress, disclosure was made of a group of analgesics derived from the structurally related (1-phenylcyclohexyl)dimethylamine.

Chemistry. The synthesis of the new compounds was carried out according to Scheme I. 1-(1-Phenylcyclohexyl)-4-piperidinol (3) was obtained by us in 45% yield,

but silylation of its precursor 2 prior to reaction with PhMgBr increased its yield to 77%. The piperidinol 3 was further esterified to compounds 4-6 and 8 (Table I) with the corresponding acyl chlorides. The 4-aminobenzoate 7 was prepared by transesterification.

1-(1-Phenylcyclohexyl)-4-piperidone (9) was obtained from the alcohol 3 by the Oppenauer oxidation. Attempts to oxidize 3 with chromic trioxide in various media (AcOH,
H₂SO₄, or pyridine) failed. The piperidone 9 and pheno-
nephrin gave 1-(1-phenycyclohexyl)-4-phenyl-4-
piperidinol (10), which with propionic anhydride gave the
propionate 11. In addition, the deoxy analogous 13 was
prepared from 4-phenylpiperidine and cyclohexanone
cyanohydrin (Scheme II).

**Pharmacology.** The mouse hot-plate and the
wringing tests (using 0.6% acetic acid ip) were used to
assess the analgesic activity of the compounds. In the hot-plate
test, PCP did not produce any significant change in latency
up to 9 mg/kg sc, while higher doses produced marked
ataxia. In the wringing test a steep dose-response relation-
ship with an ED₅₀ of 2.5 mg/kg sc was observed. Among
the 4-monosubstituted derivatives of PCP, only 4,
5, and 13 produced analgesia in both tests, while 6–8 exhib-
ited analgesia only in the wringing test (Table II).

The 4,4-disubstituted derivatives of PCP, 10 and 11, and
exerted analgesic activity in both tests. 10 was found to
be the most potent in this series (almost twice as potent
as morphine; Table II). The analgesic activities of 10, 11,
and 13 were completely antagonized by 2 mg/kg naloxone
sc (in the hot-plate test).

In order to assess the opiate-like activity of the new
compounds, the mouse vas deferens preparation was used.
Opioids were shown to inhibit the contractions induced by
electrical-field stimulation of the vas deferens of mice by
inhibiting noradrenaline release. 

We have also found that the pA₂ values of naloxone
in antagonizing the inhibitory effect of the various com-
ounds were as follows: normorphine, 8.60; 10, 8.76; 11,
8.74; 13, 8.71. However, the regression lines did not have a
uniform slope and, therefore, one cannot state with
certainty that a single competitive mechanism is involved
in the antagonism with naloxone, even though the pA₂
values are very close.

For compounds 10, 11, and 13, showed a concentra-
tion-dependent inhibition of contractions; all other com-
pounds showed concentration-dependent increases in
twitch height (Table II). The maximal inhibition produced by
10, which was six times as potent as morphine, 11 and
13 could be reversed by 20–50 nM naloxone; the same
concentration range was needed to antagonize the effect
of morphine in this bioassay.

We have also found that the pA₂ values of naloxone
in antagonizing the inhibitory effect of the various com-
ounds were as follows: normorphine, 8.60; 10, 8.76; 11,
8.74; 13, 8.71. However, the regression lines did not have a
 uniform slope and, therefore, one cannot state with
certainty that a single competitive mechanism is involved
in the antagonism with naloxone, even though the pA₂
values are very close.

For compounds 10, 11, and 13, and morphine, a good cor-
relation was obtained between the relative analgesic po-
tency (hot-plate test) and the relative potency of the in-
hibitory effect in the mouse vas deferens (r = 0.95). When
morphine was omitted from the calculation of the re-
gression line, correlation was even better (r = 0.99).

It has been suggested that the psychotogenic effect of PCP
is associated with induction of hyperactivity in mice and rats. 

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14) (a) G. Wooll and A. D. MacDonald, J. Pharmacol. Exp. Ther., 80, 300 (1944); (b) J. I. Szekely, Z. Dunni-Kovacs, E. Migelez,
19) Y. Itzhak, B. A. Weissman, S. Cohen, and A. Kalir, “New De-
rivatives of PCP as Analgesics,” Abstracts of the 46th Meeting

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Experimental Section

MELTING POINTS: The melting points were determined on a Fisher apparatus and were uncorrected.

**Infrared Spectra:** (CHCl₃) were taken on a Per-
kin-Elmer spectrophotometer Model 137 B. Analytical results
were within ±0.3% of the theoretical values.

1-[(1-Phenylcyclohexyl)-4-piperidinol (3) was prepared by
modification of the published procedure. A solution of 28 g (0.35
mol) of the 4-hydroxypiperidinocyclohexylcarbonitrile (2) in
200 mL of pyridine was treated with 50 mL of hexamethyldisilazane
and 30 mL of trimethylchlorosilane. After stirring for 1 h at room
temperature, the solvent was removed, and the residue was taken
into CHCl₃, filtered, concentrated, and crystallized from pe-
troleum ether to give 30 g of crystals, mp 90 °C. A solution
containing 28 g (0.14 mol) of this nitrile in 200 mL of benzene
was added to PhMgBr (prepared from 47 g of bromobenzene and
8 g of Mg in 250 mL of ether), refluxed for 5 h, left overnight at
ambient temperature, and then poured into ice-NH₄Cl. The
organic layer was separated and washed with water, and the base
which solidified was recrystallized from benzene–ethanol (5:1) to
give 20 g of 3: mp 116–118 °C (lit.12 mp 117–118 °C).

**ESTERS 4.** The corresponding aromatic acid was refluxed
for 1 h with a considerable excess of freshly distilled thionyl chloride:

After concentration, the residue was treated with dry benzene and
then distilled again. The residue was treated with 400
mL of pyridine was treated with
30 mL of trimethylchlorosilane. After stirring for 1 h at room
temperature, the solvent was removed, and the residue was taken
into CHCl₃, filtered, concentrated, and crystallized from pe-
troleum ether to give 30 g of crystals, mp 90 °C. A solution
containing 28 g (0.14 mol) of this nitrile in 200 mL of benzene
was added to PhMgBr (prepared from 47 g of bromobenzene and
8 g of Mg in 250 mL of ether), refluxed for 5 h, left overnight at
ambient temperature, and then poured into ice-NH₄Cl. The
organic layer was separated and washed with water, and the base
which solidified was recrystallized from benzene–ethanol (5:1) to
give 20 g of 3: mp 116–118 °C (lit.12 mp 117–118 °C).

**4-Aminobenzoate 7** was prepared as follows: 2.6 g (0.01 mol)
was heated with 0.15 g of sodium (0.065 g-atom) in
30 mL of toluene for 2 h, then a solution of 1.5 g (0.01 mol) of methyl
4-aminobenzoate was prepared by hydrolysis of the
amide with an excess of concentrated HCl. The residue was precipi-
tated from water, washed with methanol, and recrystallized from
acetone.

1-[(1-Phenylcyclohexyl)-4-piperidyl acetic acid (8) was prepared
from 8 g (0.1 mol) of acetyl chloride and 6 g (0.023 mol) of 3 in
dry benzene. After refluxing for 2 h, the solvents were removed,
and the product was converted into its HCl salt and recrystallized
from acetone.

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85–86 °C; IR 1720 (C=O) cm⁻¹. Further elution of the column with CHCl₃ (300 mL) and then CH₃OH (200 mL) yielded about 8 g of the starting material 3.

1-(1-Phenylcyclohexyl)-4-phenyl-4-piperidinol (10). A solution of 5 g (0.019 mol) of the ketone 9 in 10 mL of benzene was added dropwise to phenylithium (from 6.3 g of bromobenzene and 0.56 g of lithium ribbon in 40 mL of ether). After 1 h of reflux, the mixture was poured into ice-water-AcOH, ammonia was added, and the basic substance was extracted with benzene, dried, and concentrated. The residue was recrystallized: yield 5.0 g (77%).

1-(1-Phenylcyclohexyl)-4-phenyl-4-piperidyl Propionate (11). A solution of 2 g of the piperidinol 10 in 3 mL of pyridine was refluxed for 5 h with 5 mL of propionic anhydride, diluted with 50 mL of CHCl₃, washed with aqueous NaHCO₃, dried, and concentrated, and converted to the hydrochloride, which was recrystallized from acetone: IR 1750 cm⁻¹.

Pheny1piperidino)cyclohexanecarbonitrile (12). A solution of 2 g of the piperidinol 10 in 3 mL of pyridine was refluxed for 5 h with 5 mL of propionic anhydride, diluted with 50 mL of CHCl₃, washed with aqueous NaHCO₃, dried, and concentrated, and converted to the hydrochloride, which was recrystallized from acetone: IR 1750 cm⁻¹.

1-(1-Phenylcyclohexyl)-4-phenylpiperidine (13). 1-(4-Phenylpiperidino)cyclohexanecarbonitrile (12) was prepared from 24.5 g (0.152 mol) of 4-phenylpiperidine (Aldrich) and 18.7 g (0.15 mol) of cyclohexanone cyanhydrin by refluxing azeotropically in 60 mL of benzene for 3 h. The residue was recrystallized from methanol–ethanol (1:1), mp 106–107 °C. A solution of 12 g (0.044 mol) of 12 in 50 mL of benzene was added dropwise to PhMgBr (from 2.0 g of Mg and 12.5 g of bromobenzene in 20 mL of ether). The mixture was decomposed after 2 h of reflux and then treated as described for 3.

Pharmacology. All compounds as hydrochloride salts were dissolved in saline or twice distilled water (for bioassay). Male ICR mice weighing approximately 30 g were used for bioassay. Male ICR mice weighing 25–30 g were injected sc with the compound tested (ED₅₀ from the anesthetic assay) and three with saline (controls). Each group was transferred to a cage, and counts were recorded at 6-min intervals. The counts at the peak effect of each compound was divided by the value found for its control group (taken as 1.0). At least nine mice were tested for each compound. (The tests were carried out between 8:00 and 12:00).

Acknowledgment. We thank Dr. Y. Sarne and Mrs. O. Keren for their suggestions for the bioassay.

Oxazepam Esters. 3. Intrinsic Activity, Selectivity, and Prodrug Effect

Gábor Maksay,* Éva Pálosi, Zsuzsanna Tegyey, and László Ötvös


Antimetrazol and muscle-relaxant activities of 11 aliphatic esters of oxazepam were studied as a function of time in mice. The esters given intravenously retained antimitrazol activity, while muscle-relaxant activity was generally decreased. The administration of a dose equivalent to the antimitrazol ED₅₀ resulted in constant oxazepam brain levels for most esters; therefore, the intrinsic anticonvulsant activity of the intact ester is insignificant. The dimethylphenylpropionyl ester appeared to antagonize the effect of oxazepam, since it elevated the free oxazepam level required to achieve the ED₅₀ in the antimitrazol assay. The administration of doses equivalent to the muscle-relaxant ED₅₀ values resulted in no correlation with total brain benzodiazepine levels, suggesting that changes in the selectivity of action are the consequence of different sites of action.

Oxazepam (7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-1H,1,4-benzodiazepin-2-one) is a widely used centrally acting drug.² Although it had been concluded that 3-substitution diminished the activity of 1,4-benzodiazepines,³ several 3-substituted derivatives of oxazepam were synthetized and investigated.⁴ The hemisuccinate ester of oxazepam and its enantiomers were extensively...