4-Anilidopiperidine Analgesics I: Synthesis and Analgesic Activity of Certain Ring-Methylated 1-Substituted 4-Propananilidopiperidines

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Abstract In view of the potency-enhancing effect of methyl substitution of the piperidine ring of the 4-phenylpiperidine analgesics and the alkylene chain of the acyclic basic anilide analgesics, the 1-methyl, 1-benzyl, and 1-phenylethyl derivatives of 2-methyl-, 3-methyl-, and 2,5-dimethyl-4-propananilidopiperidine were prepared. The analgesic activity of these compounds indicates that 3-methylation has the greatest effect in enhancing analgesic potency whereas 2-methyl and 2,5-dimethyl substitution is detrimental to analgesic activity.

Keyphrases 4-Anilidopiperidine analgesics—synthesis and activity of ring-methylated 1-substituted 4-propananilidopiperidines Analgesics, potential—synthesis of ring-methylated 1-substituted 4-propananilidopiperidines, structure–activity relationships Structure–activity relationships—4-anilidopiperidines and analgesic activity, effect of ring methylation

Fentanyl (I, R = C₆H₅CH₂CH₂) is a potent narcotic analgesic which possesses a rapid onset and short duration of action (1). Its pharmacological profile is very similar to other morphinomimetic compounds, except that fentanyl is a considerably more potent narcotic analgesic (2). Structurally, fentanyl may be characterized as a 4-anilidopiperidine derivative. This class of synthetic narcotic analgesics exhibits structural features also found in the acyclic basic anilide analgesics (II) and the 4-phenylpiperidine analgesics (III).

In general, studies of structure–activity relationships in the 4-anilidopiperidine class (3–6) indicate that structural requirements for analgesic activity are similar to those established for both the acyclic basic anilides and the 4-phenylpiperidines. One aspect of the structure–activity relationships of the 4-anilidopiperidines

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1 Fentanyl citrate, Sublimaze, McNeil Laboratories, Inc.
These considerations prompted this study of the effect of ring methylation in conjunction with 1-substitution on the analgesic activity of the 4-propananilidopiperidines. The 1-substituted 2-methyl analogs (IV) possess structural features shown to confer high analgesic activity on the acyclic basic anilides. The 1-substituted 3-methyl-4-propananilidopiperidines (V) and 2,5-dimethyl-4-propananilidopiperidines (VI) exhibit structural features important for potent analgesic activity in the 4-phenylpiperidine class.

SYNTHESIS

Literature schemes for the synthesis of 4-anilidopiperidines usually proceed through the 1-substituted 4-piperidines with the formation of the Schiff base with aniline, followed by reduction and subsequent acylation of the 4-anilino moiety (5, 8). In this study, however, the desired 4-anilidopiperidines were most readily accessible via the appropriate 4-anilinopyridines (XI, Scheme I). These key intermediates were prepared according to literature procedures (9) via nucleophilic displacement of chloride by aniline from the appropriate 4-chloropyridine N-oxides (IX) or 4-chloropyridine hydrochlorides (X). Syntheses of X proved to be more facile than the preparation of IX, and treatment of X with aniline hydrochloride gave higher yields of the desired 4-anilinopyridines.

The propananilidopiperidines (XII, Scheme II) were obtained by heating the 4-anilinopyridines (XI) in propionic anhydride. Hydrogenation of the pyridine ring in XII was achieved using 10% palladium-on-charcoal in glacial acetic acid in a catalyst to a compound ratio of 1:3. The use of platinum oxide as a catalyst in this conversion proved unsatisfactory because of partial pyridine ring reduction and reduction of the aniline ring.

Scheme I

\[ R = (a) \text{CH}_3, (b) \text{C}_6\text{H}_5\text{CH}_2, \text{or (c) C}_6\text{H}_5\text{CH}_2\text{CH}_2 \]

Scheme II

The ring-methylated 4-propananilidopiperidines obtained from the reduction of the 4-anilinopyridines proved very difficult to purify. Preparation of the 1-benzyl-4-propananilopiperidine provided products that could be easily purified by adsorption chromatography. The other two series of 1-substituted 4-propananilidopiperidines were conveniently prepared by catalytic hydrolysis of the 1-benzyl derivatives in the presence of either formic or phenylacetic aldehyde.

The synthetic procedures employed for the preparation of the ring-methylated 4-anilidopiperidines of this study undoubtedly gave rise to diastereomeric mixtures of the products. Isomeric mixtures were indicated in certain cases by separation during chromatographic purification. However, in all cases that this was observed the isomers were combined to give homogeneous products with regard to elemental analyses. The results with adsorption chromatography will be of value in future studies of the isomers of these compounds.

ANALGESIC ACTIVITY

The analgesic activity of the ring-methylated 4-anilidopiperidines prepared in this study was determined in rats by the D'Amour-Smith (10) tail-flick method. The compounds were tested as the hydrochloride salts and were dissolved in normal saline immediately prior to intraperitoneal injection. The E\text{D}_{50} value for the compound studied is defined as the dose of the drug which, in 50% of the animals tested, increased the reaction time by 50% at 40 min. postinjection. Compounds were deemed inactive if the rats did not exhibit significant analgesia at dose levels of 100 mg./kg.

EXPERIMENTAL

4-Anilino-2-methylpyridine (Xla)—A mixture of 8.2 g. (0.05 mole) of 4-chloro-2-methylpyridine hydrochloride (Xa) [prepared by standard procedures by treatment of 2-methylpyridine N-oxide (VIIa) with phosphorus oxychloride] and 10.3 g. (0.08 mole) of aniline hydrochloride was placed in a sealed vessel and heated for 4 hr. at 130°. The resulting tarry material was purified by steam distillation. After 800 ml. of distillate had been collected, the residue was filtered and the filtrate was treated with charcoal and filtered through diatomaceous earth. The filtrate was extracted with chloroform and the chloroform was dried (sodium sulfate) and evaporated in vacuo, leaving 5.2 g. (56%) of Xla as white crystals, m.p. 146–147°; NMR (CDCl\textsubscript{3}) \( \delta \) 8.40 (d, 1, C-6 H), 7.45–7.85 (m, 5, N—C\textsubscript{6}H\textsubscript{5}) 7.28 (s, 1, C-3 H), 7.20 (d, 1, C-5 H), 6.78 (broad s, 1, N—H), and 2.30 (s, 3, C-2 CH\textsubscript{3}).

1 All melting points were determined on a Thomas-Hoover melting-point apparatus and are uncorrected. The IR spectra for all compounds were as expected. The NMR spectra were taken using a C-60HL Jeolco instrument, using tetramethylsilane as the internal standard. Elemental analyses were performed by Chemilabs, Inc., Tempe, Ariz. Hydrochloride salts of amine oxides were formed by dissolving the amine oxide in dilute aqueous hydrochloric acid and evaporating in vacuo.

2 Celite.
4-(N-Propanal-3-2-methylpyridine) (XIIb)—A 20.3-g. (0.110 mole) sample of 4-amino-3-methylpyridine (XIIb) dissolved in 100 ml of propionic anhydride was stirred and heated at 80° for 12 hr.

Purification by the procedure described for XIIa gave 21.1 g. (80%) of a light-yellow oil; NMR (CDCl3): δ 8.63 (d, 1, C-6 H), 8.70 (s, 1, C-2 H), 7.55–7.80 (m, 5, N—C6H4), 7.35 (d, 1, C-5 H), 2.45 (m, 2, COCH2CH2), and 1.20 (t, 3, COCH2CH3). The hydrochloride salt of XIIb was formed in the usual way and recrystallized from ethanol–ether, m.p. 136°–137°.

5-Benzyl-2-methyl-4-(N-propanal-3-2-methylpyridine) (Vb)—A 9.6-g. (0.04 mole) sample of XIIb was dissolved in 100 ml of glacial acetic acid and 4.0 g. of 10% palladium-on-charcoal was added to the solution. The mixture was hydrogenated for 24 hr. at 75°. After filtration, the catalyst was removed and the solution was refluxed for 1 hr. 0.01 mole of 4-(N-propanal-3-2-methylpyridine) (Ve) was added. The mixture was refluxed for 1 hr. and the solution was concentrated in vacuo.

The residue was added to a saturated solution of ammonium carbonate and extracted with chloroform. The chloroform extract was then dried (Na2SO4) and concentrated in vacuo to yield 0.21 g. of a yellow oil, which was then passed through a column of silica gel (m.p. 212°–213°). The pircate of Ve was recrystallized from ethanol, m.p. 205°–204°.

5-Benzyl-2-methyl-4-(N-propanal-3-2-methylpyridine) (Ve)—A 4.0-g. (0.02 mole) sample of Ve was dissolved in 100 ml of glacial acetic acid and 4.0 g. of 10% palladium-on-charcoal was added to the solution. The mixture was hydrogenated for 24 hr. at 75°. After filtration, the catalyst was removed and the solution was refluxed for 1 hr. 0.01 mole of 2-methyl-4-(N-propanal-3-2-methylpyridine) (Vc) was added. The mixture was refluxed for 1 hr. and the solution was concentrated in vacuo to yield 0.02 g. of a yellow oil, which was then passed through a column of silica gel (m.p. 212°–213°). The pircate of Vc was recrystallized from ethanol, m.p. 164°–166°.

1,3-Dimethyl-4-(N-propanal-3-2-methylpyridine) (Va)—A mixture of 4.0 g. (0.012 mole) of Ve and 0.13 g. (0.005 mole) of formaldehyde solution (37%) was treated according to the procedure described in the preparation of IVa to yield 2.9 g. (82%) of Ve as a clear oil. NMR (CDCl3): δ 7.10–7.65 (m, 5, N—C6H4), 4.24–4.75 (m, 1, C-4 H), 2.23 (s, 3, N—CH3), and 1.10 (d, 3, C-3 CH3). The hydrochloride salt of Ve was prepared and recrystallized from ethanol–ether, m.p. 154°–156°.

4-Chloro-2,5-dimethylpyridine (Xc)—A 154.5-g. (0.88-mole) sample of 2,5-dimethylpyridine N-oxide hydrochloride was prepared by standard procedures and added to 475 g. (3.10 moles) of phosphorus oxychloride. The reaction was heated to 120° for 1 hr. and then refluxed for 4 hr. The solution was allowed to cool and poured into ice. The solution was basified (potassium carbonate) and extracted with ether, and the etheral extracts were dried (sodium sulfate) and concentrated in vacuo, leaving an impure liquid which was distilled at 100–110° (1 mm) to give 89.7 g. (72%) of Ve; NMR (CDCl3): δ 7.90–7.75 (m, 5, N—C6H4), 7.15 (t, 3, C=CH2), 2.53 (s, 3, CH3), and 2.40 (s, 3, CH2). The hydrochloride salt of Ve was recrystallized from ethanol, m.p. 240°–241°.

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Table I—Analogic Activities of 4-Propananilidopiperidines

<table>
<thead>
<tr>
<th>1-Substituent</th>
<th>2-CH₃ (IV)</th>
<th>3-CH₃ (V)</th>
<th>2-CH₃, 5-CH₃ (VI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) CH₃</td>
<td>Inactive</td>
<td>14.34</td>
<td>Inactive</td>
</tr>
<tr>
<td>(b) C₆H₅CH₂</td>
<td>Inactive</td>
<td>36.67</td>
<td>65.14</td>
</tr>
<tr>
<td>(c) C₆H₅CH₂CH₂</td>
<td>0.665</td>
<td>0.004</td>
<td>0.803</td>
</tr>
</tbody>
</table>

* The ED₅₀ of fentanyl hydrochloride as determined in these studies was 0.04 mg./kg. \( \alpha = 0.05 \).

b The activity of these compounds which is possibly related to the mode of binding of the molecules at the analgesic receptor.

A meaningful interpretation of the nature of the interaction of the 4-propananilidopiperidines with the analgesic receptor is rather difficult to derive from the analgesic activities given in Table I. In addition to reflecting differences in receptor affinities, these results also reflect differences in distribution and metabolism of the various compounds. These latter factors can result in significant differences in biophase concentrations and, hence, apparent differences in analgesic activities (11).

Introduction of a ring methyl into the 4-propananilidopiperidines results in chiral molecules. In view of the reported stereoselectivity of the narcotic analgesic receptor (12), it is anticipated that separation of the geometric and optical isomers of the compounds in this study will provide even more potent compounds and will afford pertinent information with regard to the nature of the drug–receptor interaction. Studies on stereostructure–activity relationships for the ring-methylated 4-propananilidopiperidines are currently underway in these laboratories.

REFERENCES


RESULTS AND DISCUSSION

Analogic activities of the ring-methylated 4-propananilidopiperidines prepared in this study are given in Table I. The results of analogic activities of the 4-propananilidopiperidines in this study are in accord with previous findings of structure–activity relationships for morphinomimetic compounds in that phenethylation of a basic nitrogen in these agents provides compounds of the highest analgesic activity. The results further indicate that 3-methylation of the piperidine ring of the 4-propananilidopiperidines significantly enhances analogic activity, whereas 2-methylation and 2,5-dimethylation lead to a significant reduction in analogic activity. It is interesting to correlate the effect of 1-substitution on the analogic activities of the 4-propananilidopiperidines.

In the fentanyl (I) and the 2,5-dimethylated (VI) series, potency is observed to decrease in the order C₆H₅CH₂CH₂ > C₆H₅CH₂ > C₆H₅CH₂CH₂, whereas in the 3-methylated series (V) the dependence of analogic activity on the 1-substituent is in the order C₆H₅CH₂CH₂ > C₆H₅CH₂ > C₆H₅CH₂CH₂. These relationships suggest that introduction of a methyl substituent in the piperidine ring of the 4-propananilidopiperidine analogs results in a fundamental alteration of the analogic ac-

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