acid, base, and enzymatic degradations of I which involve the loss of the 3-position substituent.

When taking into consideration the work of Jones *et al.* (1), it is believed that the polarographic method should be generally applicable to all cephalosporins containing a leaving group at the 3-position. Those free leaving groups containing a thiol functionality should also be amenable to polarographic determination *via* oxidative mercurous salt formation.

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ACKNOWLEDGMENTS AND ADDRESSES

Received September 13, 1972, from the *Lilly Research Laboratories, Indianapolis, IN 46206*

Accepted for publication January 24, 1973.

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

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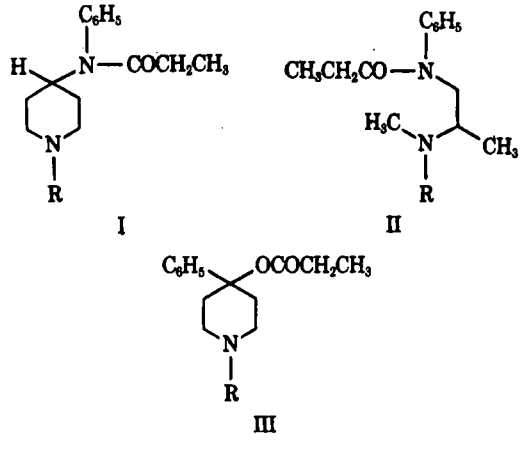
Abstract □ In view of the potency-enhancing effect of methyl substitution of the piperidine ring of the 4-phenylpiperidine analgesics and the alkylene chain of the acyclic basic anilide analgesics, the 1-methyl, 1-benzyl, and 1-phenylethyl derivatives of 2-methyl-, 3-methyl-, and 2,5-dimethyl-4-propananilidopiperidine 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.

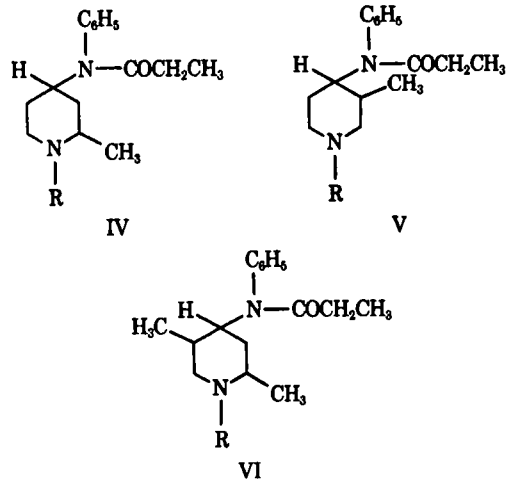
Keyphrases □ 4-Anilidopiperidine analgesics—synthesis and activity of ring-methylated 1-substituted 4-propananilidopiperidines □ Analgesics, potential—synthesis of ring-methylated 1-substituted 4-propananilidopiperidines, structure–activity relationships □ Structure–activity relationships—4-anilidopiperidines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

Fentanyl[1] (I, R = $C_6H_5CH_2CH_2$) 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 that has not as yet been reported is the effect of piperidine ring methylation in this class. It is well established that methylation of the piperidine ring of the 4-phenylpiperidine analgesics (*e.g.*, the prodines) results in a significant increase in analgesic activity. In addition, introduction of a methyl substituent on the alkylene chain of the acyclic basic anilides provides for compounds of high analgesic activity. In this regard, however, it is important to note that the increase in analgesic activity in these analogs is highly dependent on the position of the methyl substituent relative to the basic nitrogen. In the 4-phenylpiperidines, 3-methylation and 2,3-, 2,5-, and 3,5-dimethylation result in high analgesic activities (7). Other methyl substitution patterns in this class generally reduce analgesic activity. In the acyclic basic anilide analgesics, methyl substitution α to the basic nitrogen affords the greatest enhancement of analgesic activity (3).



[1] Fentanyl citrate, Sublimaze, McNeil Laboratories, Inc.



IV V VI

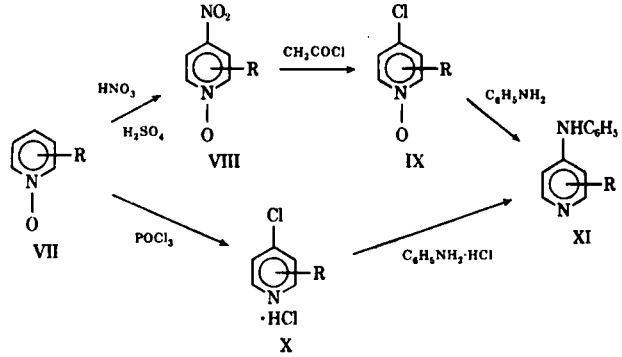
R = (*a*) CH_3, (*b*) $C_6H_5CH_2$, or (*c*) $C_6H_5CH_2CH_2$

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-piperidones 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.

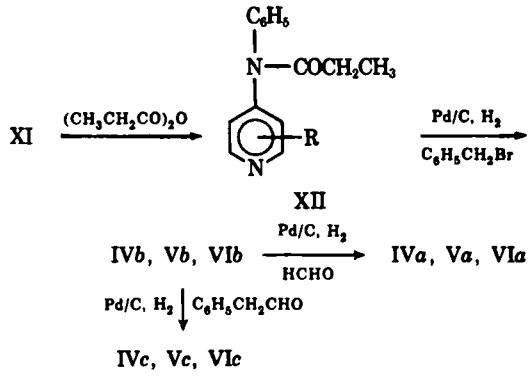
The propananilides (XII, Scheme II) were obtained by heating the 4-anilinopyridines (XI) in propionic anhydride. Hydrogenation of the pyridine ring in XII was achieved using 10% palladium-on-charcoal in glacial acetic acid in a catalyst to a compound ratio of 1:3. The use of platinum oxide as a catalyst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



VII VIII IX X XI

R = (*a*) 2-CH_3, (*b*) 3-CH_3, (*c*) 2-CH_3, 5-CH_3

Scheme I



XI XII IV*b*, V*b*, VI*b* IV*a*, V*a*, VI*a* IV*c*, V*c*, VI*c*

Scheme II

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

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 ED_{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[2]

4-Anilino-2-methylpyridine (XI*a*)—A mixture of 8.2 g. (0.05 mole) of 4-chloro-2-methylpyridine hydrochloride (X*a*) [prepared by standard procedures by treatment of 2-methylpyridine *N*-oxide (VII*a*) 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[3]. The filtrate was extracted with chloroform and the chloroform was dried (sodium sulfate) and evaporated *in vacuo*, leaving 5.2 g. (56%) of XI*a* as white crystals, m.p. 146–147°; NMR ($CDCl_3$): δ 8.40 (d, 1, C-6 H), 7.45–7.85 (m, 5, N—C_6H_5), 7.28 (s, 1, C-3 H), 7.20 (d, 1, C-5 H), 6.78 (broad s, 1, N—*H*), and 2.50 (s, 3, C-2 CH_3).

[2] 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 Chemlytics, Inc., Tempe, Ariz. Hydrochloride salts of amine oxides were formed by dissolving the amine oxide in dilute aqueous hydrochloric acid and evaporating *in vacuo*.

[3] Celite.

Anal.—Calc. for $C_{15}H_{13}N_3$: C, 78.26; H, 6.52; N, 15.22. Found: C, 78.21; H, 6.67; N, 14.64.

4-(*N*-Propananilido-2-methylpyridine) (XII*a*)—An 18.4-g. (0.10-mole) sample of XI*a* was dissolved in 100 ml. of propionic anhydride and heated at 80° for 12 hr. The excess propionic anhydride was removed *in vacuo*, and the dark residue was purified in 10-g. quantities by passage through a 1000 × 25-mm. chromatographic column packed with 190 g. of silica gel. Elution was carried out with ethyl acetate and 30-ml. fractions were collected. Fractions 11–20 were found to contain the product. This procedure gave 19.5 g. (81%) of XII*a* as a light oil; NMR ($CDCl_3$): δ 8.40 (d, 1, C-6 H), 7.40–7.85 (m, 5, N—C_6H_5), 7.31 (s, 1, C-3 H), 7.25 (d, 1, C-5 H), 2.54 (s, 3, C-2 CH_3), 2.48 (m, 2, $COCH_2CH_3$), and 1.25 (t, 3, $COCH_2CH_3$). The hydrochloride salt was prepared by standard procedures and recrystallized from ethanol–ether, m.p. 152°.

Anal.—Calc. for $C_{15}H_{16}N_2O \cdot HCl$: C, 65.10; H, 6.15; N, 10.13. Found: C, 64.91; H, 6.22; N, 9.64.

1-Benzyl-2-methyl-4-(*N*-propananilido)piperidine (IV*b*)—A 15.6-g. (0.064-mole) sample of XII*a* was dissolved in 150 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°. The catalyst was removed by filtration, and the filtrate was carefully basified with sodium hydroxide and then extracted with chloroform. The chloroform extract was dried (sodium sulfate) and concentrated *in vacuo*, giving a viscous oil. This oil was dissolved in acetonitrile, and 13.3 g. (0.078 mole) of benzyl bromide was added. The solution was refluxed for 11 hr. followed by concentration *in vacuo*. The residual oil was taken up in a saturated solution of potassium carbonate and extracted with chloroform. The chloroform extract was dried (sodium sulfate) and concentrated *in vacuo* to yield a yellow oil, which was then passed through a 500 × 25-mm. chromatographic column packed with 90 g. of silica gel. Elution with ethyl acetate gave 10.5 g. (48%) of IV*b* as a clear oil; NMR ($CDCl_3$): δ 7.20–7.75 (m, 10, N—C_6H_5 and N—$CH_2C_6H_5$), 4.50–5.05 (m, 1, C-4 H), 3.15 and 4.33 (*AB* quartet, 2, N—$CH_2C_6H_5$), and 0.80–1.45 (m, 6, $COCH_2CH_3$ and C-2 CH_3). The picrate of IV*b* was recrystallized from ethanol, m.p. 210–212°.

Anal.—Calc. for $C_{22}H_{28}N_2O \cdot C_6H_3N_3O_7$: C, 59.46; H, 5.50; N, 12.38. Found: C, 59.72; H, 5.40; N, 12.36.

1-(2-Phenylethyl)-2-methyl-4-(*N*-propananilido)piperidine (IV*c*)—A 3.0-g. (0.009-mole) sample of IV*b* was mixed with 1.44 g. (0.012 mole) of phenylacetaldehyde and 0.5 g. of 10% palladium-on-charcoal in ethanol and hydrogenated for 4 hr. at room temperature. The reaction mixture was filtered and concentrated *in vacuo*, leaving a dark oil. The oil was purified by passing it through a 500 × 25-mm. chromatographic column packed with 90 g. of silica gel. Elution with ethyl acetate provided 2.24 g. (71%) of IV*c* as an oil; NMR ($CDCl_3$): δ 7.20–7.85 (m, 10, N—C_6H_5 and N—$CH_2CH_2C_6H_5$), 4.33–4.80 (m, 1, C-4 H), and 0.80–1.50 (m, 6, $COCH_2CH_3$ and C-2 CH_3). The oil formed a picrate which was recrystallized from ethanol, m.p. 207–208°.

Anal.—Calc. for $C_{23}H_{30}N_2O \cdot C_6H_3N_3O_7$: C, 60.09; H, 5.74; N, 12.08. Found: C, 59.90; H, 5.75; N, 12.12.

1,2-Dimethyl-4-(*N*-propananilido)piperidine (IV*a*)—A mixture of 2.0 g. (0.006 mole) of IV*b*, 0.90 g. (0.01 mole) of 37% formaldehyde solution, and 0.5 g. of 10% palladium-on-charcoal was hydrogenated for 4 hr. The reaction mixture was filtered, concentrated *in vacuo*, and passed through a 250 × 20-mm. chromatographic column packed with silica gel. Elution with ethyl acetate gave 1.2 g. (79%) of viscous oil; NMR ($CDCl_3$): δ 7.20–7.75 (m, 5, N—C_6H_5), 4.50–5.00 (m, 1, C-4 H), 2.07 (s, 3, N—CH_3), and 0.80–1.50 (m, 6, $COCH_2CH_3$ and C-2 CH_3). The oil formed a picrate which was recrystallized from ethanol, m.p. 194–196.5°.

Anal.—Calc. for $C_{16}H_{24}N_2O \cdot C_6H_3N_3O_7$: C, 53.98; H, 5.56; N, 14.31. Found: C, 54.00; H, 5.68; N, 14.76.

4-Anilino-3-methylpyridine (XI*b*)—A mixture of 7.2 g. (0.05 mole) of 4-chloro-3-methylpyridine *N*-oxide (IX*b*), prepared by standard procedures from the 4-nitro derivative (VIII*b*) (9), and 9.3 g. (0.10 mole) of aniline was heated in a sealed vessel at 130° for 4 hr. The deep-violet tar obtained from this procedure was purified as described in the synthesis of XI*a*, leaving a green crystalline solid which was recrystallized from ethanol–water (1:3) to yield 3.51 g. (38%) of product, m.p. 119–120° [lit. (9) m.p. 122°].

4-(*N*-Propananilido)-3-methylpyridine (XII*b*)—A 20.3-g. (0.11-mole) sample of 4-anilino-3-methylpyridine (XI*b*) dissolved in 100 ml. of propionic anhydride was stirred and heated at 80° for 12 hr. Purification by the procedure described for XII*a* gave 21.1 g. (80%) of a light-yellow oil; NMR ($CDCl_3$): δ 8.63 (d, 1, C-6 H), 8.70 (s, 1, C-2 H), 7.55–7.80 (m, 5, N—C_6H_5), 7.35 (d, 1, C-5 H), 2.45 (m, 2, $COCH_2CH_3$), and 1.20 (t, 3, $COCH_2CH_3$). The hydrochloride salt of XII*b* was formed in the usual way and recrystallized from ethanol–ether, m.p. 136–137°.

Anal.—Calc. for $C_{15}H_{16}N_2O \cdot HCl$: C, 65.09; H, 6.15; N, 10.12. Found: C, 64.94; H, 6.25; N, 9.98.

1-Benzyl-3-methyl-4-(*N*-propananilido)piperidine (V*b*)—A 9.6-g. (0.04-mole) sample of XII*b* 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, basification, and concentration, the residual oil was refluxed with 11.9 g. (0.07 mole) of benzyl bromide in acetonitrile. The oil obtained by this procedure was purified as described for IV*b*, yielding 7.8 g. (58%) of V*b* as a clear oil; NMR ($CDCl_3$): δ 7.45 (s, 5, $CH_2C_6H_5$), 7.30–7.80 (m, 5, N—C_6H_5), 4.45–4.80 (m, 1, C-4 H), 3.55 (s, 2, N—$CH_2C_6H_5$), and 1.10 (d, 3, C-3 CH_3). The hydrochloride salt of V*b* was prepared and recrystallized from ethanol–ether, m.p. 202.5–204°.

Anal.—Calc. for $C_{22}H_{28}N_2O \cdot HCl \cdot H_2O$: C, 67.59; H, 7.99; N, 7.17. Found: C, 67.83; H, 7.55; N, 7.02.

1-(2-Phenylethyl)-3-methyl-4-(*N*-propananilido)piperidine (V*c*)—A 4.0-g. (0.012-mole) sample of V*b* was mixed with 1.0 g. (0.016 mole) of phenylacetaldehyde and treated according to the procedure described for the synthesis of IV*c*, resulting in 3.32 g. (79%) of V*c* as a clear oil; NMR ($CDCl_3$): δ 7.42 (s, 5, N—$CH_2CH_2C_6H_5$), 7.30–7.77 (m, 5, N—C_6H_5), 4.40–4.80 (m, 1, C-4 H), and 1.10 (d, 3, C-3 CH_3). The hydrochloride salt of V*c* was prepared and recrystallized from ethanol–ether, m.p. 164–166°.

Anal.—Calc. for $C_{23}H_{30}N_2O \cdot HCl$: C, 71.38; H, 8.08; N, 7.24. Found: C, 71.01; H, 8.24; N, 6.95.

1,3-Dimethyl-4-(*N*-propananilido)piperidine (V*a*)—A mixture of 4.0 g. (0.012 mole) of V*b* and 0.13 g. (0.015 mole) of formaldehyde solution (37%) was treated according to the procedure described in the preparation of IV*a* to yield 2.6 g. (82%) of V*a* as a clear oil; NMR ($CDCl_3$): δ 7.10–7.65 (m, 5, N—C_6H_5), 4.24–4.75 (m, 1, C-4 H), 2.23 (s, 3, N—CH_3), and 1.10 (d, 3, C-3 CH_3). The picrate of V*a* was prepared in the usual manner, m.p. 164°.

Anal.—Calc. for $C_{16}H_{24}N_2O \cdot C_6H_3N_3O_7$: C, 53.98; H, 5.56; N, 14.31. Found: C, 54.04; H, 5.56; N, 14.73.

4-Chloro-2,5-dimethylpyridine (X*c*)—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 ethereal extracts were dried (sodium sulfate) and concentrated *in vacuo*, leaving an impure liquid which was distilled at 40–50° (1 mm.) to give 89.7 g. (72%) of X*c*; NMR ($CDCl_3$): δ 8.60 (s, 1, C-6 H), 7.15 (s, 1, C-3 H), 2.50 (s, 3, CH_3), and 2.40 (s, 3, CH_3). The hydrochloride of X*c* was prepared, m.p. 240–241°.

Anal.—Calc. for $C_7H_8ClN \cdot HCl$: C, 47.21; H, 5.09; N, 7.69. Found: C, 47.29; H, 5.55; N, 7.74.

4-Anilino-2,5-dimethylpyridine (XI*c*)—Following the procedure used to prepare XI*a*, 81.6 g. (0.63 mole) of aniline hydrochloride and 80.1 g. (0.45 mole) of X*c*·HCl reacted to yield XI*c* as a gray solid. Recrystallization from dioxane yielded 61.2 g. (49%) of a white solid, m.p. 145°; NMR ($CDCl_3$): δ 7.05–7.90 (m, 6, C-3 H and N—C_6H_5), 2.50 (s, 3, CH_3), and 2.40 (s, 3, CH_3).

Anal.—Calc. for $C_{13}H_{14}N_2$: C, 78.78; H, 7.07; N, 14.14. Found: C, 78.70; H, 7.15; N, 14.16.

4-(*N*-Propananilido)-2,5-dimethylpyridine (XII*c*)—A 29.7-g. (0.15-mole) sample of XI*c* was heated in 150 ml. of propionic anhydride for 12 hr. at 80°. The reaction was worked up as described for XII*a* to give 31.7 g. (83%) of XII*c* as an oil which solidified on standing at room temperature. Recrystallization of this solid from ether gave white crystals, m.p. 87–89°; NMR ($CDCl_3$): δ 8.15 (s, 1, C-6 H), 7.20–7.55 (m, 5, N—C_6H_5), 7.13 (s, 1, C-3 H), 2.57 (s, 3, C-2 CH_3), 2.26 (s, 3, C-5 CH_3), 2.33 (m, 2, $COCH_2CH_3$), and 1.16 (t, 3, $COCH_2CH_3$).

Anal.—Calc. for $C_{16}H_{18}N_2O$: C, 75.79; H, 7.09; N, 11.02. Found: C, 75.53; H, 6.90; N, 10.77.

1-Benzyl-4-(*N*-propananilido)-2,5-dimethylpiperidine (VI*b*)—A solution of 10.1 g. (0.04 mole) of XII*c* in 120 ml. of glacial acetic acid was hydrogenated and then treated with 8.5 g. (0.05 mole) of

Table I—Analgesic Activities of 4-Propananilidopiperidines

1-Substituent	ED_{50}, mg./kg.[a,b] 2-CH_3 (IV)	3-CH_3 (V)	2-CH_3, 5-CH_3 (VI)
(*a*) CH_3	Inactive	14.34	Inactive
(*b*) $C_6H_5CH_2$	Inactive	36.67	65.14
(*c*) $C_6H_5CH_2CH_2$	0.665	0.004	0.803

[a] The ED_{50} of fentanyl hydrochloride as determined in these studies was 0.04 mg./kg. [b] Significance level: $\alpha = 0.05$.

benzyl bromide, as previously described for the preparation of IV*b*, to yield 7.3 g. (52%) of VI*b* as a clear oil; NMR ($CDCl_3$): δ 7.20–7.75 (m, 10, N—C_6H_5 and N—$CH_2C_6H_5$), 4.30–4.75 (m, 1, C-4 H), 2.95–4.20 (*AB* quartet, 2, N—$CH_2C_6H_5$), and 0.80–1.40 (m, 9, C-2 CH_3, C-5 CH_3 and $COCH_2CH_3$). The oil formed a picrate which was recrystallized from ethanol, m.p. 209–210°.

Anal.—Calc. for $C_{23}H_{30}N_2O \cdot C_6H_3N_3O_7$: C, 60.09; H, 5.74; N, 12.08. Found: C, 59.71; H, 5.68; N, 11.81.

1-(2-Phenylethyl)-2,5-dimethyl-4-(*N*-propananilido)piperidine (VI*c*)—A solution of 1.0 g. (0.008 mole) of phenylacetaldehyde and 2.0 g. (0.006 mole) of VI*b* was hydrogenated over 10% palladium-on-charcoal. The product was purified, as previously described in the preparation of IV*c*, to provide 1.16 g. (53%) of VI*a* as a clear oil; NMR ($CDCl_3$): δ 7.35–7.75 (m, 10, N—C_6H_5 and N—$CH_2CH_2C_6H_5$), 4.30–4.75 (m, 1, C-4 H), and 0.80–1.40 (m, 9, C-2 CH_3, C-5 CH_3 and $COCH_2CH_3$). The oil formed a hydrochloride salt which was recrystallized from ethanol–ether, m.p. 235.5–237°.

Anal.—Calc. for $C_{24}H_{32}N_2O \cdot HCl$: C, 71.88; H, 8.30; N, 6.99. Found: C, 71.70; H, 8.24; N, 6.96.

4-(*N*-Propananilido)-1,2,3-trimethylpiperidine (VI*a*)—Two grams (0.006 mole) of VI*b* and 0.9 g. (0.01 mole) of formaldehyde were hydrogenated. The product was purified, as previously described in the preparation of IV*a*, to yield 1.28 g. (78%) of VI*a* as a clear oil; NMR ($CDCl_3$): δ 7.20–7.75 (m, 5, N—C_6H_5), 4.30–4.75 (m, 1, C-5 H), 2.07 (s, 3, N—CH_3), and 0.80–1.40 (m, 9, C-2 CH_3, C-5 CH_3 and $COCH_2CH_3$). The oil formed a picrate which was recrystallized from ethanol, m.p. 242–244°.

Anal.—Calc. for $C_{17}H_{26}N_2O \cdot C_6H_3N_3O_7$: C, 54.86; H, 5.81; N, 13.91. Found: C, 55.86; H, 5.95; N, 14.13.

RESULTS AND DISCUSSION

Analgesic activities of the ring-methylated 4-propananilidopiperidines prepared in this study are given in Table I. The results of analgesic 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 analgesic activity, whereas 2-methylation and 2,5-dimethylation lead to a significant reduction in analgesic activity. It is interesting to correlate the effect of 1-substitution on the analgesic activities of the 4-propananilidopiperidines. In the fentanyl (I) and the 2,5-dimethylated (VI) series, potency is observed to decrease in the order $C_6H_5CH_2CH_2 > C_6H_5CH_3 > CH_3$, whereas in the 3-methylated series (V) the dependence of analgesic activity on the 1-substituent is in the order $C_6H_5CH_2CH_2 > CH_3 > C_6H_5CH_2$. These relationships suggest that introduction of a methyl substituent in the piperidine ring of the 4-propananilidopiperidine analgesics results in a fundamental alteration of the analgesic 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.

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ACKNOWLEDGMENTS AND ADDRESSES

Received October 12, 1972, from the *Department of Medicinal Chemistry, University of Mississippi, University, MS 38677*

Accepted for publication January 16, 1973.

Abstracted from a thesis submitted by D. B. Hale to the Graduate School, University of Mississippi, in partial fulfillment of the Master of Science degree requirements.

The authors acknowledge the assistance of Dr. R. L. Mikeal, Department of Health Care Administration, University of Mississippi, in the statistical analysis of the pharmacological results of this study. They also acknowledge the financial assistance of the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, in carrying out this study. In addition, the authors acknowledge the generous gift of fentanyl citrate supplied by McNeil Laboratories, Inc.

• National Defense Education Act, Title IV Fellow, 1970–1972.

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