in lessening the ventricular fibrillation induced in anesthetized dogs by immersion tank hypothermia was measured. Quinidine was the reference drug used and the active compounds are listed in Table IX.

(20) E. T. Angelakos and A. H. Hegnauer, *J. Pharmacol. Exptl. Therap.*, **127**, 137 (1959).

**Acknowledgment.**—The authors thank Dr. R. E. Bowman for many helpful discussions, Mr. F. H. Oliver for the microanalyses, Miss E. M. Tanner for the physical measurements, Dr. Vandenbelt for the n.m.r. spectra, and Drs. Corne, Chen, and Wheelock, and Mr. C. Schneider for the pharmacological testing.

# New Analgesic N-Substituted Carboxamides

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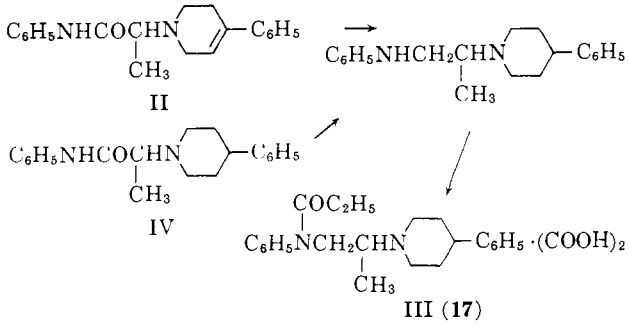
A series of N-substituted propionanilides was synthesized as potential analgesics. The most active compound, N-[1-methyl-2-(4-hydroxy-4-phenylpiperidino)ethyl]propionanilide oxalate (**27**), was approximately 150 times more active than morphine by the artery-clip assay method in mice.

In the course of our search for new, potent analgesics, we have synthetized a group of N-substituted carboxamides (I), mainly N-substituted propionanilides, which are structurally related to methadone in that the quaternary carbon atom and a phenyl group of methadone are replaced with a tertiary nitrogen. During the course of our work, two potent analgesics, phenampromid and diampromid,[1] were reported. Both compounds are N-substituted propionanilides. Similar compounds were described later by Shigematsu[2] and by Carabateas.[3] Among our compounds, **1** and **2** of Table I were described in a recent patent.[4]

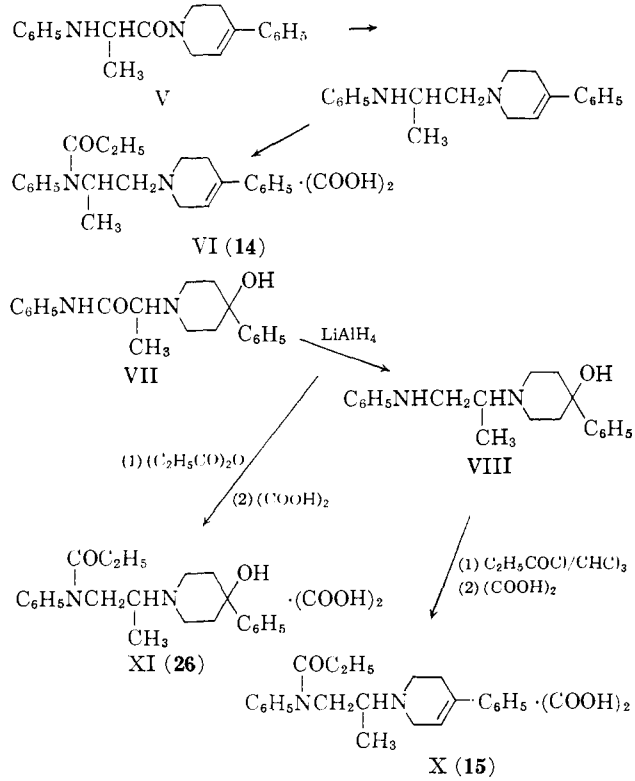
The compounds reported here are listed in Table I and may be represented by the generic formula $R^1$-$C_6H_4(CH_2)_nN(COR^2)CHR^3CHR^4$+B (I). The isomerically pure compounds were prepared readily by reduction of the corresponding amides, with lithium aluminum hydride followed by acylation. When α-(1,2,3,6-tetrahydro-4-phenyl-1-pyridyl)propionanilide (II) was reduced in this way, followed by propionylation, the product isolated as the oxalate was unexpectedly the saturated compound (III). The latter was also synthesized by reducing α-(4-phenylpiperidino)propionanilide (IV), followed by propionylation and formation of the oxalic acid salt.

Salts (III), prepared by both routes, were identical by mixture melting point determination and gave identical ultraviolet spectra which showed two maxima at 257.5 mμ (ε 1050) and 264 mμ (ε 832).




III (**17**)

In contrast, the reduction of 1-(α-anilinopropionyl)-1,2,3,6-tetrahydro-4-phenylpyridine (V), an isomer of II, gave the unsaturated compound VI. In support of the unsaturated structure was a strong absorption maximum at 244.5 mμ (ε 14,600),[5] indicating the presence of a double bond conjugated with the aromatic ring. It is reported that a double bond in the systems ArC=CCO— or ArC=CN—[6] may be reduced with lithium aluminum hydride, but such a reduction of the double bond in the grouping $C_6H_5C{=}CCH_2$— has not been described previously.




(1) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **81**, 1518 (1959); *J. Org. Chem.*, **25**, 1033 (1960); *ibid.*, **26**, 476, 485 (1961).

(2) N. Shigematsu, *Yakugaku Zasshi*, **81**, 423 (1961); *ibid.*, **81**, 815 (1961); N. Sugimoto, K. Okumara, N. Shigematsu, and G. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **10**, 1061 (1962); G. Hayashi, N. Shigematsu, and Y. Kowa, *Yakugaku Zasshi*, **81**, 62 (1963).

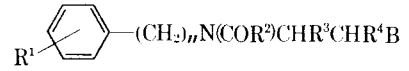
(3) P. M. Carabateas, W. F. Wetterau, and L. Grumbach, *J. Med. Chem.*, **6**, 355 (1963).

(4) O. E. Fancher and S. Hayao, U. S. Patent 3,037,982 (June 5, 1962).

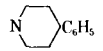
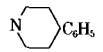
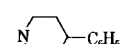
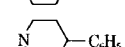
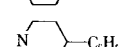
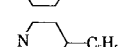
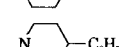
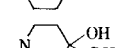
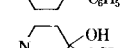
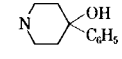
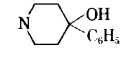
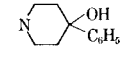
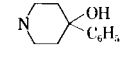
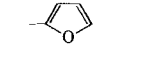
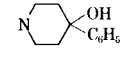
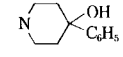
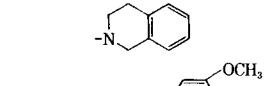
(5) α-Methylstyrene has $\lambda_{max}^{EtOH}$ 243 mμ (ε 11,500); A. E. Gillam and E. S Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," 2nd Ed., Edward Arnold Ltd., London, 1957, p. 277.

(6) W. G. Brown, *Org. Reactions*, **6**, 480 (1951).

Table I



| No. | R¹ | R² | R³ | R⁴ | B | n | Formula | M.p., °C. | Calcd., % | | | Found, % | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | C | H | N | C | H | N |
| 1 | H | $C_2H_5$ | $CH_3$ | H |  | 0 | $C_{22}H_{29}N_3O \cdot C_2H_2O_4$[a] | 150–152 dec. | 65.3 | 7.03 | 9.52 | 65.1 | 7.03 | 9.68, 9.57 |
| 2 | H | $C_2H_5$ | H | $CH_3$ |  | 0 | $C_{22}H_{29}N_3O \cdot C_2C_2O_4$ | 172.5–173.5 dec. | 65.3 | 7.03 | 9.52 | 65.0 | 7.21 | 9.54 |
| 3 | H | $C_2H_5$ | H | $CH_3$ |  | 1 | $C_{23}H_{31}N_3O \cdot C_2H_2O_4$ | 131–133 dec. | 65.9 | 7.25 | 9.23 | 65.6 | 7.20 | 9.46 |
| 4 | H | $C_2H_5$ | H | $CH_3$ |  | 0 | $C_{22}H_{28}ClN_3O \cdot C_2H_2O_4$ | 162–163 | 60.5 | 6.30 | 8.83 | 60.4 | 6.53 | 8.74 |
| 5 | H | $C_2H_5$ | H | $CH_3$ |  | 0 | $C_{22}H_{28}ClN_3O \cdot C_2H_2O_4$ | 108–109 dec. | | | 8.83 | | | 8.74 |
| 6 | H | $C_2H_5$ | H | $CH_3$ |  | 0 | $C_{23}H_{31}N_3O \cdot C_2H_2O_4$ | 175–176 dec. | 66.0 | 7.25 | 9.23 | 65.8 | 7.18 | 9.30 |
| 7 | *p*-$CH_3O$ | $C_2H_5$ | H | $CH_3$ |  | 0 | $C_{23}H_{31}N_3O_2 \cdot C_4H_4O_4$[b] | 132–133.5 | 65.2 | 7.04 | 8.45 | 64.5 | 6.81 | 8.46 |
| 8 | *m*-$CH_3O$ | $C_2H_5$ | H | $CH_3$ |  | 0 | $C_{23}H_{31}N_3O_2 \cdot C_2H_2O_4$ | 143–144 | 63.6 | 7.00 | 8.91 | 63.6 | 6.82 | 9.05 |
| 9 | *o*-$CH_3O$ | $C_2H_5$ | H | $CH_3$ |  | 0 | $C_{23}H_{31}N_3O_2 \cdot C_2H_2O_4$ | 166.5–168.5 dec. | 63.6 | 7.01 | 8.91 | 64.0 | 7.13 | 8.87 |
| 10 | H | $C_2H_5$ | H | $CH_2$ |  | 0 | $C_{17}H_{27}N_3O \cdot 2C_2H_2O_4$ | 209 dec. | 53.8 | 6.61 | 5.97 | 53.4 | 6.52 | 5.91 |
| 11 | H | $C_6H_5$ | H | $CH_2$ |  | 0 | $C_{21}H_{27}N_3O \cdot 2C_2H_2O_4$ | 203–203.5 dec. | 58.0 | 5.99 | 8.12 | 57.9 | 5.88 | 8.18 |
| 12 | H | $C_2H_5$ | H | $CH_3$ |  | 0 | $C_{24}H_{32}N_3O \cdot 2C_2H_2O_4$ | 216 dec. | 60.1 | 6.62 | 7.52 | 59.4 | 6.46 | 7.79 |
| 13 | H | $C_2H_5$ | H | $CH_3$ |  | 0 | $C_{29}H_{35}N_3O \cdot C_2H_2O_4$ | 216–216.5 dec. | 70.0 | 6.96 | 7.92 | 69.9 | 7.05 | 7.96 |
| 14 | H | $C_2H_5$ | $CH_3$ | H |  | 0 | $C_{23}H_{28}N_2O \cdot C_2H_2O_4$ | 159–160 dec. | 68.4 | 6.84 | 6.39 | 68.2 | 6.65 | 6.32 |
| 15 | H | $C_2H_5$ | H | $CH_3$ |  | 0 | $C_{23}H_{28}N_2O \cdot C_2H_2O_4$ | 193.5–194.5 dec. | 68.5 | 6.84 | 6.39 | 68.4 | 6.73 | 6.39 |
| 16 | H | $C_2H_5$ | $CH_3$ | H |  | 0 | $C_{23}H_{30}N_2O \cdot C_2H_2O_4$ | 152–153 dec. | 68.2 | 7.28 | 6.36 | 67.7 | 7.24 | 6.46 |
| 17 | H | $C_2H_5$ | H | $CH_3$ |  | | $C_{23}H_{30}N_2O \cdot C_2H_2O_4$ | 186–187 dec. | 68.2 | 7.28 | 6.36 | 67.8 | 7.30 | 6.48 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 18 | H | $C_2H_5$ | $CH_3$ | H |  | 1 | $C_{24}H_{32}N_2O \cdot C_2H_2O_4$ | 142–144 dec. | 68.7 | 7.49 | 6.17 | 67.9 | 7.56 | 6.05 |
| 19 | H | $C_2H_5$ | H | $CH_3$ |  | 1 | $C_{24}H_{32}N_2O \cdot C_2H_2O_4$ | 149–151 dec. | 68.7 | 7.49 | 6.17 | 68.2 | 7.49 | 6.33 |
| 20 | H | $C_6H_5$ | $CH_3$ | H |  | 0 | $C_{27}H_{30}N_2O \cdot C_2H_2O_4$ | 160–161 dec. | 71.4 | 6.55 | 5.74 | 71.1 | 6.45 | 5.88 |
| 21 | H | $C_6H_5$ | H | $CH_3$ |  | 0 | $C_{27}H_{30}N_2O \cdot C_2H_2O_4$ | 198–199 dec. | 71.4 | 6.55 | 5.74 | 71.1 | 6.55 | 5.92 |
| 22 | *p*-$CH_3O$ | $C_2H_5$ | H | $CH_3$ |  | 0 | $C_{24}H_{32}N_2O_2 \cdot C_4H_4O_4$ | 145–146 | 67.5 | 7.25 | 5.65 | 67.4 | 7.18 | 5.72 |
| 23 | *o*-$CH_3O$ | $C_2H_5$ | H | $CH_3$ |  | 0 | $C_{24}H_{32}N_2O_2 \cdot C_2H_2O_4$ | 120.5–121.5 dec. | 66.4 | 7.23 | 5.96 | 65.8 | 7.24 | 5.75 |
| 24 | H | $C_6H_5$ | H | $C_6H_5$ |  | 0 | $C_{26}H_{28}N_2O \cdot HCl$[c] | 198.5–200 dec. | 74.2 | 6.90 | | 73.6 | 6.74 | |
| 25 | H | $C_2H_5$ | H | $C_6H_5$ |  | 0 | $C_{28}H_{32}N_2O \cdot C_2H_2O_4$ | 174–175.5 dec. | 71.7 | 6.77 | 5.58 | 71.1 | 6.30 | 5.57 |
| 26 | H | $C_2H_5$ | H | $CH_3$ |  | 0 | $C_{23}H_{30}N_2O_2 \cdot C_2H_2O_4$ | 103–105 dec. | 65.8 | 7.01 | 6.14 | 65.3 | 7.10 | 6.07 |
| 27 | H | $C_2H_5$ | $CH_3$ | H |  | 0 | $C_{23}H_{30}N_2O_2 \cdot C_2H_2O_4$ | 165.5–167 dec. | 65.8 | 7.01 | 6.14 | 65.6 | 6.91 | 6.19 |
| 28 | | | | | | | $C_{23}H_{30}N_2O_2 \cdot HCl$[d] | 215–217 dec. | 68.5 | 7.69 | 6.95 | 68.1 | 7.80 | 7.03 |
| 29 | | | | | | | $C_{23}H_{30}N_2O_2 \cdot CH_3I$[e] | 72–84 dec. | 56.7 | 6.50 | 5.51 | 56.3 | 6.64 | 5.54 |
| 30 | H | $C_2H_5$ | H | $CH_3$ |  | 1 | $C_{24}H_{32}N_2O_2 \cdot C_2H_2O_4$ | 142–144 dec. | 66.4 | 7.23 | 5.96 | 65.9 | 7.14 | 6.07 |
| 31 | H | $C_2H_5$ | $CH_3$ | H |  | 2 | $C_{25}H_{34}N_2O_2 \cdot HCl$ | 189–191 dec. | 69.7 | 8.13 | 6.50 | 69.3 | 7.98 | 6.62 |
| 32 | H | $OC_2H_5$ | $CH_3$ | H |  | 0 | $C_{23}H_{30}N_2O_3 \cdot NH_2SO_3H$[f] | 185–185.5 | 57.6 | 6.89 | 8.76 | 57.6 | 6.96 | 8.65 |
| 33 | H | $C_6H_{11}$ | $CH_3$ | H |  | 0 | $C_{27}H_{36}N_2O_2 \cdot C_2H_2O_4$ | 165.5–167 dec. | | | 5.49 | | | 5.41 |
| 34 | H |  | $CH_3$ | H |  | 0 | $C_{25}H_{28}N_2O_3 \cdot HCl$ | 200–202 dec. | 68.1 | 6.58 | 6.36 | 67.8 | 6.86 | 6.28 |
| 35 | H |  | $CH_3$ | H |  | 0 | $C_{33}H_{41}N_3O_3 \cdot 2C_2H_2O_4$ | 196–198 | 62.8 | 6.43 | 5.95 | 62.6 | 6.34 | 6.12 |
| 36 | H | $C_2H_5$ | H | $CH_3$ |  | 0 | $C_{21}H_{26}N_2O \cdot C_2H_2O_4$ | 145.5–147 dec. | 67.0 | 6.80 | 6.80 | 66.3 | 6.57 | 6.83 |
| 37 | H | $C_2H_5$ | H | H |  | 0 | $C_{23}H_{32}N_2O_3 \cdot C_2H_2O_4$ | 149–150 dec. | 63.4 | 7.18 | 5.92 | 63.6 | 7.27 | 5.93 |
| 38 | H | $C_2H_5$ | H | $CH_3$ | $N(CH_2CH{=}CH_2)_2$ | 0 | $C_{18}H_{26}N_2O \cdot HCl$[g] | 156–157 dec. | 67.0 | 8.37 | 8.68 | 66.1 | 8.80 | 8.68 |

[a] Oxalate. [b] Maleate. [c] Calcd.: HCl, 8.68. Found: HCl, 8.67. [d] Calcd.: HCl, 9.08. Found: HCl, 9.04. [e] Methiodide. [f] Sulfamate. [g] Calcd.: HCl, 11.3. Found: HCl, 11.4.

Reduction of α-(4-hydroxy-4-phenylpiperidino)propionanilide (VII) with lithium aluminum hydride gave the corresponding amine (VIII) which showed near infrared absorption (in chloroform) at 1.47 (OH) and 1.56 μ (NH). Propionylation of VIII and formation of the oxalic salt gave IX.

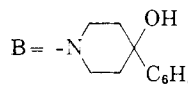
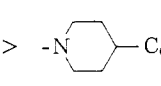
The near-infrared absorption of IX (free base) at 1.47 μ confirmed the presence of an OH group. However, heating VIII in chloroform with propionyl chloride for 7 hr. resulted in dehydration to give X. Absorption at 240.8 mμ (ε 16,800)[5] showed the presence of a styrene-like double bond.

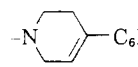
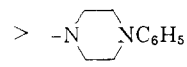
**Pharmacology.**—The most active compound in this series is N-[1-methyl-2-(4-hydroxy-4-phenylpiperidino)ethyl]propionanilide oxalate (**27**) which is 150 times more active than morphine sulfate and about 1000 times more active than (+)-propoxyphene hydrochloride. These conclusions are based on the $ED_{50}$ values determined by the artery-clip[7] method after subcutaneous administration in mice. The structure–activity relationships in this series may be summarized as follows (referring to I).

$R^1 = H > R^1 = OCH_3$ (*o*, *m*, *p*); $n = 0 > 1 > 2$

$R^2 = C_2H_5 >$  $> OC_2H_5 > C_6H_{11}$ and $C_6H_5$

$R^3 = CH_3$, $R^4 = H > R^3 = H$, $R^4 = CH_3$

B =  >  >

 > 

Selected analgesic results are given in Table II. These compounds, though in different degrees, led to the development of dependence and were antagonized by nalorphine. For example, **27** produced less tolerance development and was less antagonized by nalorphine than was **16**. The abstinence symptoms in monkeys[8] addicted to 3 mg./kg. of morphine sulfate were completely suppressed 12–14 hr. after withdrawal by 0.2 mg./kg. of **16**. Additional pharmacological details will be published elsewhere.

## Experimental[9]

The detailed procedures are intended as models for the preparation of the compounds in Table I.

**N-[2-(4-Phenylpiperidino)propyl]propionanilide Oxalate (III). Method A. (a) Synthesis of II.**—1,2,3,6-Tetrahydro-4-phenylpyridine (31.8 g., 0.2 mole), α-bromopropionanilide (45.0 g., 0.2 mole), 2-propanol (230 ml.), and anhydrous sodium carbonate (21.2 g., 0.2 mole) were heated under reflux for 15 hr. with vigorous stirring, then were filtered and cooled. The solid that separated was collected, washed with ether, and dried in air, m.p. 138–139°, yield 45.9 g. It was recrystallized from aqueous acetone to give a pale yellow powder (39 g.) of m.p. 139–140°.

TABLE II

ANALGESIC ACTIVITY

| Compd. | $ED_{50}$ (95% confidence limits) Base, mg./kg., s.c.[a] | $LD_{50}$ base, mg./kg., s.c. | Therapeutic index |
|---|---|---|---|
| **16** | 0.20 (0.14–0.29) | 86.0[b] | 430.0 |
| **17** | 0.48 (0.37–0.63) | 251.0[b] | 556.0 |
| **26** | 0.155 (0.076–0.32) | 94.6[c] | 610.0 |
| **27** | 0.021 (0.015–0.035) | 89.5[b] | 4260.0 |
| **32** | 0.088 (0.058–0.13) | 71.0[b] | 807.0 |
| **34** | 0.045 (0.028–0.065) | 91.7[b] | 2040.0 |
| **30** | 7.5 (5.35–10.5) | 45.5[b] | 6.1 |
| **18** | 29.5 (23.6–36.5) | 117.0[b] | 4.0 |
| **19** | 17.5 (14.6–20.0) | 54.2[b] | 3.10 |
| **1** | 35.5 (23.4–54.0) | 480.0[c] | 13.5 |
| (+)-Propoxyphene hydrochloride[d] | 22.5 (27.6–18.4) | 118.0[c] | 5.25 |
| Morphine sulfate | 3.10 (2.68–3.60) | 390.0[c] | 126.0 |

[a] Determined by the method of J. F. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949), using at least four dose levels of 20 mice/dose. [b] Determined by the method of W. Thompson, *Bacteriol. Rev.*, **11**, 115 (1947), with the tables of C. Brown, *Federation Proc.* **20**, 169 (1961), using a minimum of four dose levels of 2 mice/dose. [c] Same as footnote *b* except that 5 mice/dose were used. [d] Darvon®.

*Anal.* Calcd. for $C_{20}H_{22}N_2O$: N, 9.15. Found: N, 9.10.

**(b) Reduction of II.**—The above amide (34.5 g., 0.112 mole) in 150 ml. of tetrahydrofuran was added dropwise during 30 min. to a slurry of lithium aluminum hydride (6.4 g., 0.17 mole) in 150 ml. of tetrahydrofuran. The mixture was refluxed for 6 hr. and decomposed with 6 ml. of water, 6 ml. of 20% NaOH, and 18 ml. of water. The dried filtrate was concentrated *in vacuo* to a dark brown sirup which distilled to give 17.6 g. of **1-(2-anilinoethyl-1-methyl)-4-phenylpiperidine**, b.p. 191–192° (0.3 mm.), $\lambda_{max}^{CHCl_3}$ 1.56 μ (NH).

*Anal.* Calcd. for $C_{20}H_{24}N_2$: N, 9.60. Found: N, 9.54.

**(c) Propionylation.**—The above amine (14.9 g., 0.05 mole) and 30 ml. of propionic anhydride were kept at 25° for 2 days. The dark solution was concentrated *in vacuo* and the residue dissolved in ether. The cooled solution (ice-water bath) was shaken with aqueous NaOH. The ether layer was dried and treated with anhydrous oxalic acid (4.6 g., 0.05 mole) to give a tan salt (17.1 g.) which was recrystallized from methanol–ether to give 13.8 g. of colorless III, m.p. 185–186° dec., $\lambda_{max}^{CH_3OH}$ 257.5 mμ (ε 1050) and 264 mμ (ε 832).

*Anal.* Calcd. for $C_{23}H_{30}N_2O \cdot C_2H_2O_4$: N, 6.36. Found: N, 6.35.

The melting point of a mixture with a sample from method B (m.p. 186–187° dec.) was not depressed. The ultraviolet spectra of two samples were identical.

**Method B. (a) Synthesis of IV.**—4-Phenylpiperidine (51.0 g., 0.316 mole), α-bromopropionanilide (72 g., 0.315 mole), absolute ethanol (250 ml.), and anhydrous sodium carbonate (33.5 g., 0.316 mole) were stirred under reflux for 22 hr. The mixture was filtered while hot and the inorganic salt was rinsed with absolute ethanol. The clear filtrate was heated to boiling, and water was added to cloudiness. A colorless solid separated and was collected by filtration, m.p. 117–120°, yield 77.9 g. (80%). A sample was recrystallized from aqueous methanol to give needles of m.p. 123–124°; $\lambda_{max}^{CHCl_3}$ 2.88 (NH), 5.91 (amide C=O), and 6.5 μ (amide II).

*Anal.* Calcd. for $C_{29}H_{24}N_2O$: N, 9.09. Found: N, 9.08.

**(b) 1-(2-Anilinoethyl-1-methyl)-4-phenylpiperidine.**—α-(4-Phenylpiperidino)propionanilide (76.0 g., 0.246 mole) was reduced with lithium aluminum hydride as before. The reaction mixture was processed by standard procedures to give a dark brown liquid, which distilled as a pale yellow liquid at 182–191° (0.15–0.2 mm.), yield 60.2 g. (83.3%).

**(c) Propionylation.**—The above amine (32.5 g., 0.11 mole) was propionylated as before and converted to the oxalate salt. The colorless salt was collected, washed with ether, and dried in air, m.p. 186° dec., yield 45.1 g. (92%). It was recrystallized from aqueous methanol–ether to give 39.7 g. of a colorless powder (**17**), m.p. 186–187° dec.

(7) C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).

(8) Private communication from G. Deneau and M. H. Seevers, Department of Pharmacology, School of Medicine, University of Michigan, Ann Arbor, Mich.

(9) All melting points were measured in a Büchi apparatus (Switzerland) and are corrected. Infrared spectra were measured with a Perkin-Elmer Infracord Model 137 and Perkin-Elmer 237 grating infrared spectrophotometer. Near infrared and ultraviolet spectra were measured with a Warren Spectracord 4000. Titrations were done with a Sargent recording titrator Model D.

**1-(2-Anilinopropyl)-1,2,3,6-tetrahydro-4-phenylpyridine.**—The reaction mixture (0.2-mole run) in benzene obtained from α-bromopropionyl chloride and 4-phenyl-1,2,3,6-tetrahydropyridine under Schotten–Baumann conditions was stirred with 0.4 mole of aniline under reflux for 24 hr. Aniline hydrobromide was filtered, washed with benzene, and the dark benzene solution was concentrated *in vacuo* to give a tan solid mass of amide V which, after trituration with water and ether, melted at 120–127°, yield 40.5 g. (66%).

The amide (74.4 g., 0.24 mole) was reduced with lithium aluminum hydride under conditions identical with those for the reduction of II. The dark brown liquid distilled as a pale yellow viscous liquid of b.p. 192–201° (0.4 mm.), yield 47.9 g. (67.4%).

**N-[1-Methyl-2-(1,2,3,6-tetrahydro-4-phenyl-1-pyridyl)-ethyl]propionanilide Oxalate (VI).**—The above amine (47.9 g., 0.164 mole) was propionylated as usual. Anhydrous oxalic acid (15.3 g., 0.17 mole) was added to the crude amide to give a light tan sticky gum which slowly solidified on scratching. The solid was collected, washed with ether, and dried in air, m.p. 150–156°, yield 60.1 g. (83.5%). It was recrystallized twice from methanol–ether (Norit) to give 39.1 g. of a colorless powder (**14**) of m.p. 159–160° dec., $\lambda_{max}^{CH_3OH}$ 244.5 mμ (ε 14,600). Mixed with **16** (m.p. 152–153°), the m.p. was 141–151° (with bubbling).

**1-(2-Anilino-1-methylethyl)-4-hydroxy-4-phenylpiperidine (VIII).**—α-(4-Hydroxy-4-phenylpiperidino)propionanilide (VII, 45.0 g., 0.14 mole) was reduced with lithium aluminum hydride as before. The amber sirup distilled at 202–215° (0.25 mm.); yield 30.3 g.; $\lambda_{max}^{CHCl_3}$ 2.79 (OH), 2.99 (NH), and 8.59 μ (CO stretching of tertiary alcohol), but no carbonyl band around 6 μ. The near infrared spectrum ($CHCl_3$) showed bands at 1.47 and 1.56 μ due to OH and NH, respectively.

*Anal.* Calcd. for $C_{20}H_{26}N_2O$: N (basic), 4.52. Found: N (basic), 4.51 (titration).

**N-[2-(4-Hydroxy-4-phenylpiperidino)propyl]propionanilide (IX).**—Amine VIII (30.0 g.) was dissolved in 50 ml. of hot benzene, and propionic anhydride (25 ml.) was added. The light amber solution was refluxed for 1 hr., and the solvent was removed *in vacuo*. The residue was taken up in ether, washed with sodium hydroxide solution, and dried ($MgSO_4$). The filtrate was treated with 8.7 g. (0.1 mole) of anhydrous oxalic acid to give a light tan sticky gum which gradually solidified on scratching. This was collected by suction, washed with ether, and air-dried, yield 43.9 g. It was recrystallized from methanol–ether to give a solid which was collected, washed with ether, and dried *in vacuo*, m.p. 103–105° dec., yield 31.7 g. (**26**).

A small sample was converted to the free base, extracted with ether, and dried. Removal of the solvent *in vacuo* gave a sirup whose near infrared spectrum ($CHCl_3$) showed an OH band at 1.47 μ, but no NH band at 1.56 μ.

**N-[2-(1,2,3,6-tetrahydro-4-phenyl-1-pyridyl)propyl]propionanilide Oxalate (X).**—Amine VIII (28.7 g., 0.09 mole), propionyl chloride (37.0 g., 0.4 mole), and 100 ml. of chloroform were refluxed for 1.5 hr. and left overnight. The solvent and excess acid chloride were removed *in vacuo* to leave an amber sirup which was dissolved in a small amount of methanol and made basic with sodium hydroxide solution. The free base was extracted with ether and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a sirup. The infrared spectrum ($CHCl_3$) showed an ester band at 5.79 (m) and amide band at 6.10 μ (s). Esterification seemed to be incomplete. It was again dissolved in 100 ml. of chloroform, and 15 ml. of propionyl chloride was added. The solution was refluxed for 5.5 hr. and left overnight. The reaction mixture was worked up as before. The infrared spectrum of the free base ($CHCl_3$) showed a weak ester band at 5.80, a strong amide band at 6.10 μ, but no OH band. The sirup was dissolved in ether, filtered, and treated with anhydrous oxalic acid (9.0 g., 0.1 mole) to give a sticky gum which soon solidified on scratching, yield 37.3 g. It was recrystallized from methanol–ether to give 19.7 g. of a colorless solid (**15**), m.p. 193.5–194.5° dec., $\lambda_{max}^{MeOH}$ 240.8 mμ (ε 16,800).

**N-[1-Methyl-2-(4-hydroxy-4-phenylpiperidino)ethyl]propionanilide (27). A. 1-(α-Anilinopropionyl)-4-hydroxy-4-phenylpiperidine.**—A toluene solution of α-bromopropionyl chloride (68.6 g., 0.4 mole) was added slowly with stirring to an ice-cold suspension of 4-phenyl-4-piperidinol (70.8 g., 0.4 mole) in 750 ml. of toluene and 130 ml. of 20% sodium hydroxide. Stirring was continued overnight. The layers were separated, and the dried toluene layer was concentrated *in vacuo* to half its volume. This concentrate and aniline (74.4 g., 0.8 mole) were heated under reflux with stirring for 16 hr. The solvent was removed *in vacuo* to leave a solid mixture of amide and aniline hydrobromide. This was suspended in water and left overnight. The amide was collected, washed with water, and dried. The solid was triturated in ether and again collected and dried, yield 112.9 g. (87%), m.p. 147.5–148.5°.

*Anal.* Calcd. for $C_{20}H_{24}N_2O_2$: N, 8.64. Found: N, 8.65.

**B. 1-(2-Anilinopropyl)-4-hydroxy-4-phenylpiperidine.**—The above amide (113 g., 0.35 mole) was reduced with lithium aluminum hydride as before. The reduction was repeated since the infrared spectrum still showed absorption at 6.1 μ. The crude amine was distilled using a short-path column, b.p. 195–210° (0.2–0.3 mm.), yield 39.5 g. (36.6%). No amide absorption (6.1 μ) appeared in the spectrum of this product.

*Anal.* Calcd. for $C_{20}H_{26}N_2O$: N, 9.03. Found: N, 9.04.

**C. N-2-(4-Hydroxy-4-phenylpiperidino)-1-methylethyl]-propionanilide Oxalate.**—A solution of the above compound (39 g., 0.125 mole) was treated with propionic anhydride as before and converted to the oxalate salt. The salt was collected and recrystallized twice from a methanol–ether solution, yield 41 g. (72%), m.p. 165.5–167.0° dec.

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