Synthesis of Novel Analgesic Agents III: 1,2-Dialkyl-4-aryl and 1,2,4-Trialkyl-4-aryl Piperidazines

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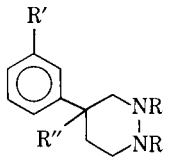
Abstract □ Several members of both 1,2-dialkyl-4-aryl and 1,2,4-trialkyl-4-aryl piperidazines were synthesized and investigated for analgesic activity. The most potent compound was 1,2-dimethyl-4-*n*-propyl-4-(*m*-hydroxyphenyl)piperidazine.

Keyphrases □ Piperidazines, 1,2-dialkyl-4-aryl and 1,2,4-trialkyl-4-aryl—synthesis, screened for analgesic activity □ 1,2-Dialkyl-4-aryl piperidazines—synthesis, screened for analgesic activity □ 1,2,4-Trialkyl-4-aryl piperidazines—synthesis, screened for analgesic activity □ Analgesic agents, potential—1,2-dialkyl-4-aryl and 1,2,4-trialkyl-4-aryl piperidazines

McElvain and Clemens (1) synthesized potent piperidine analgesics which contain alkyl and aryl substituents in the 4-position. The most potent compounds contain a *meta*-hydroxyl substituent in the aromatic ring. When the hydroxyl group is in the *ortho*- or *para*-position, the analgesic activity disappears. The 3-alkyl-3-aryl piperidines were studied by Kugita *et al.* (2) and exhibited excellent activity.

This laboratory reported (3, 4) the synthesis and analgesic activity of a number of 3- and 4-aryl pyrazolidines and 3-alkyl-3-aryl and 4-alkyl-4-aryl pyrazolidines. In a continuation of the search for new analgesic agents, several 4-substituted piperidazines, represented by Structure I, were synthesized and evaluated for their analgesic activity. An advantage of these compounds, which contain two contiguous basic nitrogen atoms, is that they embody the nitrogen to quaternary carbon distances found in both the 3- and 4-substituted piperidines.



I: R = CH_3 or C_2H_5
R′ = H, OH, or OCH_3
R″ = H or alkyl

SYNTHESIS

It was reported (5, 6) that the reaction between 1,2-dialkyl hydrazines and succinic anhydride leads first to acid hydrazides which, on heating, undergo dehydration with the formation of 3,6-piperidazinediones. By using appropriately substituted succinic anhydrides, this reaction provides a route to the synthesis of the title compounds. Reaction between aryl succinic anhydrides and 1,2-dialkyl hydrazines should afford 1,2-dialkyl-4-aryl piperidazine-3,6-diones (II).

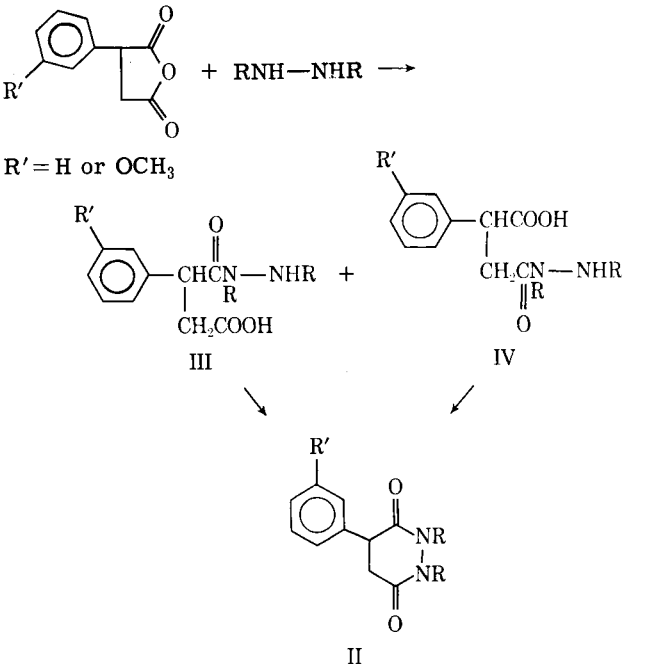
The first step of this reaction probably results in a mixture of the corresponding α-hydrazide (III) and the α'-hydrazide (IV) (Scheme I). Because of the presence of the phenyl ring, the carbonyl carbon atom alpha to that bearing the aryl substituent is probably more susceptible to nucleophilic attack than the other carbonyl carbon. Therefore, it is more likely that III constitutes the major component in the product mixture. No attempts, however, were made to determine the composition of this product mixture because cyclization of III and IV would result in II. A similar ring opening of α-substituted and α,α'-disubstituted succinic anhydrides by ammonia and amines was studied (7). This study showed that when the α-substituent was phenyl, the mixture consisted of 77% of the α-amide and 23% of the α'-amide.

Cyclization of III and IV occurred when the hydrazide mixture was subjected to distillation under reduced pressure. The product (II), however, was always contaminated with the starting aryl succinic anhydride, as indicated by IR spectroscopy. Purification of II was accomplished by refluxing the distillation product with a hydroalcoholic sodium bicarbonate solution. Extraction with ether and workup yielded pure II in a moderate yield. Compounds having Structure II are key intermediates for Compounds I (Scheme II).

Treatment of 1,2-diethylhydrazine with phenylsuccinic anhydride afforded 1,2-diethyl-4-phenylpiperidazine-3,6-dione (II*a*). The phenylsuccinic anhydride was obtained in the usual way by dehydration of commercially available phenylsuccinic acid with acetyl chloride (8). Similarly, 1,2-dimethyl-4-phenylpiperidazine-3,6-dione (II*b*) was prepared. Reaction between 1,2-dimethylhydrazine and *m*-methoxyphenylsuccinic anhydride gave 1,2-dimethyl-4-(*m*-methoxyphenyl)piperidazine-3,6-dione (II*c*). The *m*-methoxyphenylsuccinic acid was synthesized from *m*-methoxybenzaldehyde by a procedure analogous to that described for the preparation of phenylsuccinic acid from benzaldehyde (9, 10). Dehydration of the acid to *m*-methoxyphenylsuccinic anhydride was accomplished by means of acetic anhydride (11).

Reduction of 1,2-dimethyl-4-phenylpiperidazine-3,6-dione with lithium aluminum hydride produced 1,2-dimethyl-4-phenylpiperidazine (V*a*) (Scheme II). In a similar way, the *m*-methoxyphenyl analog (V*b*) was obtained. These compounds represent the potential analgesic agents having a central tertiary carbon atom.

Alkylation of II using sodium hydride as the base in tetrahydrofuran resulted in the monoalkylation products (VI). As expected, alkylation occurred at carbon atom 4 of the ring (Scheme II). Treat-



Scheme I

ment of II*a* with sodium hydride and methyl iodide in tetrahydrofuran gave 1,2-diethyl-4-methyl-4-phenylpiperidazine-3,6-dione (VI*a*). This reaction proceeded almost quantitatively. Reduction of the latter compound with lithium aluminum hydride in tetrahydrofuran afforded 1,2-diethyl-4-methyl-4-phenylpiperidazine (VII*a*). The overall yield starting from II*a* was 68.8%.

Likewise, 1,2-dimethyl-4-*n*-propyl-4-phenylpiperidazine-3,6-dione (VI*b*) was obtained from II*b* and *n*-propyl bromide. Reduction of dione VI*b* with lithium aluminum hydride afforded 1,2-dimethyl-4-*n*-propyl-4-phenylpiperidazine (VII*b*). Also, 1,2-dimethyl-4-*n*-propyl-4-(*m*-methoxyphenyl)piperidazine-3,6-dione (VI*c*) was prepared. Reduction of this compound produced 1,2-dimethyl-4-*n*-propyl-4-(*m*-methoxyphenyl)piperidazine (VII*c*). Compounds possessing Structure VII represent potential analgesic agents having a central quaternary carbon atom.

Demethylation of V*b* and VII*c* with 48% aqueous hydrobromic acid proceeded readily and resulted in the formation of the corresponding *m*-hydroxyphenyl analogs, VIII and IX, respectively.

ANALGESIC ACTIVITY

The analgesic activity of Compounds V*a*, V*b*, VII*a*, VII*b*, VIII, and IX was determined in CRCD mice by the hot-plate method (12). Ten animals were used at every dose level, and the compounds were administered intraperitoneally. The only compound[1] having significant activity was IX. At a dose of 100 mg./kg. (as base), IX caused no fatalities and all of the animals exhibited analgesia. The time of peak effect was 15 min. after drug administration, and the only overt effect noted was slight ataxia. The LD_{50} value for this drug was 172 mg./kg. By comparison, codeine phosphate (as salt, LD_{50} = 130 mg./kg.) exhibited similar activity at the same dose level except that the overt effect was a slight depression. Because of these preliminary results, IX will be tested further as a potential analgesic agent.

EXPERIMENTAL[2]

Phenylsuccinic Anhydride—To 25.0 g. (0.129 mole) of phenylsuccinic acid was added 27.8 ml. (0.387 mole) of acetyl chloride. The semidry mixture was carefully heated, whereupon the mixture became a homogeneous solution. The solution was refluxed for 4.5 hr., cooled, and concentrated under reduced presure. Distillation of the residue afforded 20.77 g. (91.7%) of a viscous oil, b.p. 154–159° (0.40 mm.), m.p. 49–51° (after recrystallization from ether–ligroin) [lit. b.p. 196° (16 mm.) (13), m.p. 53–54° (8)]; IR (film): 5.37 and 5.58 μ (anhydride C=O); NMR ($CDCl_3$): δ 7.40–7.92 (m, 5, ArH), 4.60 and 4.44 (two d, 1, methine H), and 2.89–3.91 (m, 2, methylene H).

Diethyl *m*-Methoxybenzalmalonate—The procedure used for the preparation of this malonate was similar to that described by Allen and Spangler (9) for ethyl benzalmalonate. From 100.0 g. (0.74 mole) of *m*-methoxybenzaldehyde, 113.6 g. (0.71 mole) of ethyl malonate in 225 ml. of benzene in the presence of 2.2 g. of benzoic acid, and 4.5 ml. of piperidine, there was obtained 180 g. (93.7%) of a colorless oil, b.p. 150–154° (0.28 mm.) [lit. (14) b.p. 130.5–133° (0.02 mm.)]; $n_D^{24.0}$ 1.5429; IR (film): 5.78 (ester C=O) and 6.13 μ (C=C); NMR ($CDCl_3$): δ 7.73 (s, 1, C=CH), 6.82–7.50 (m, 4, ArH), 4.35 (q, 2, OCH_2), 4.32 (q, 2, OCH_2), 3.80 (s, 3, OCH_3), 1.33 (t, 3, C—CH_3), and 1.29 (t, 3, C—CH_3).

Ethyl 3-(*m*-Methoxyphenyl)-3-cyanopropanoate—This compound was prepared by a procedure adapted from Allen and Johnson (10). From 72.7 g. (0.261 mole) of diethyl *m*-methoxybenzalmalonate in 643 ml. of absolute alcohol and 17.9 g. (0.276 mole) of potassium cyanide in 32 ml. of water, a viscous oil (44.97 g., 73.9%) was obtained, b.p. 142–144° (0.55 mm.); $n_D^{24.0}$ 1.5090 [lit. (11) b.p. 164–166° (0.6 mm.), $n_D^{21.5}$ 1.5100]; IR (film): 4.47 (C≡N) and 5.78 μ (ester C=O); NMR ($CDCl_3$): δ 6.78–7.59 (m, 4, ArH), 4.00–4.51 (m, 3, Ar—CH—CN and OCH_2 quartet at 4.21), 3.82 (s, 3, OCH_3), 2.99 and 2.85 [two d, 2, Ar—C(CN)—CH_2], and 1.25 (t, 3, C—CH_3).

***m*-Methoxyphenylsuccinic Acid**—A mixture of 26.4 g. (0.115 mole) of ethyl 3-(*m*-methoxyphenyl)-3-cyanopropanoate and 85 ml. of concentrated hydrochloric acid was stirred and refluxed for 16 hr. and then cooled. The solid cake was broken up and collected on a filter cloth. The crude tan-colored product was washed with 50 ml. of ice water. After drying in a vacuum desiccator, 18.1 g. (70.3%) of crude acid was obtained, m.p. 173–179°. A sample for analysis was prepared by recrystallization from water, m.p. 174.5–176° dec. [lit. (11) m.p. 177–178° dec.]; IR (KBr): 3.44 (OH) and 5.92 μ (C=O); NMR (dimethyl sulfoxide-d_6): δ 6.80–7.56 (m, 4, ArH), 3.67–4.12 (m, 4, ArCH and one OCH_3 singlet at 3.79), and 2.34–3.33 (m, 2).

Anal.—Calc. for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 59.32; H, 5.56.

***m*-Methoxyphenylsuccinic Anhydride**—A mixture of 6.72 g. (0.03 mole) of *m*-methoyxphenylsuccinic acid and 9.18 g. (0.09 mole) of acetic anhydride was refluxed for 3 hr. The solution was cooled and the excess acetic anhydride was removed under reduced pressure. The remaining residue was distilled, yielding 4.60 g. (74.4%) of a colorless oil, b.p. 157–160° (0.30 mm.) [lit. (11) b.p. 185–195° (1 mm.)]; $n_D^{23.9}$ 1.5490; IR (film): 5.36 and 5.61 μ (anhydride C=O); NMR ($CDCl_3$): δ 6.74–7.56 (m, 4, ArH), 4.40 and 4.24 (two d, 1, ArCH), and 2.79–3.96 (m, 5, including one OCH_3 singlet at 3.82).

1,2-Diethyl-4-phenylpiperidazine-3,6-dione (II*a*)—To a stirred solution of 10.47 g. (0.059 mole) of phenylsuccinic anhydride in 40 ml. of tetrahydrofuran was added dropwise a solution of 5.71 g. (0.065 mole) of 1,2-diethylhydrazine in 10 ml. of tetrahydrofuran with ice bath cooling. The solution was stirred overnight at room temperature and refluxed for 6 hr. After the solution was cooled and the solvent was removed under reduced pressure, the remaining residue was distilled and afforded 10.37 g. of a crude product, b.p. 174–177° (1.5 mm.). The product was dissolved in 10 ml. of ethanol, and the resulting solution was refluxed with 60 ml. of 5% aqueous sodium bicarbonate for 1 hr. The alcohol was removed under reduced pressure, and the aqueous solution was saturated with sodium chloride. The mixture was then extracted three times with 20-ml. portions of chloroform. The combined chloroform solution was dried, filtered, and concentrated under reduced pressure. Distillation of the residue afforded 6.72 g. (46.2%) of a semisolid oil, b.p. 143–145° (0.18 mm.); $n_D^{23.1}$ 1.5477; IR (film): 5.98 μ (amide C=O); NMR ($CDCl_3$): δ 7.21 (s, 5, ArH), 2.76–4.30 (m, 7), 1.12 (t, 3, C—CH_3), and 0.72 (t, 3, C—CH_3).

Anal.—Calc. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.34; H, 7.39; N, 11.53.

1,2-Dimethyl-4-phenylpiperidazine-3,6-dione (II*b*)—This compound was prepared, in a manner similar to that described for II*a*, from 20.6 g. (0.117 mole) of phenylsuccinic anhydride and 7.80 g. (0.13 mole) of 1,2-dimethylhydrazine in 120 ml. of tetrahydrofuran. A crude product weighing 22.02 g. (b.p. 164–170° at 0.15 mm.) was obtained. This product was refluxed for 1 hr. with 125 ml. of a 5% aqueous sodium bicarbonate solution and worked up to yield 11.90 g. (42.0%) of a semisolid oil, b.p. 147–148° (0.13 mm.); $n_D^{23.5}$ 1.5628; IR (film): 5.98 μ (amide C=O); NMR ($CDCl_3$): δ 7.12–7.69 (m, 5, ArH), 3.98 (t, 1, ArCHCO), 3.31 (s, 3, NCH_3), 3.15 (s, 3, NCH_3), and 2.98 (d, 2, CH_2).

Anal.—Calc. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.98; H, 6.52; N, 12.77.

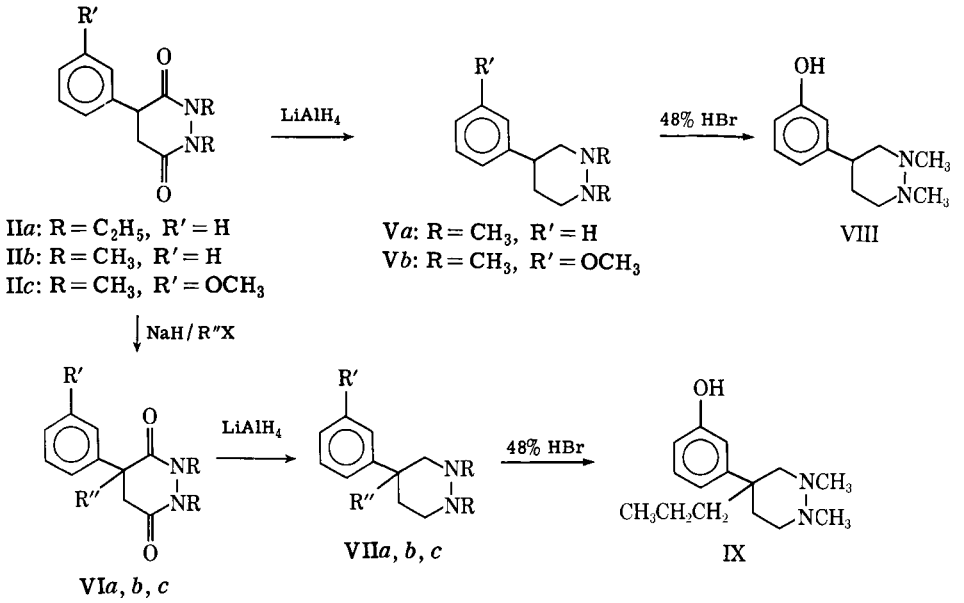
1,2-Dimethyl-4-(*m*-methoxyphenyl)piperidazine-3,6-dione (II*c*)—This compound was obtained, in a manner similar to that described for II*a*, from 22.68 g. (0.11 mole) of *m*-methoxyphenylsuccinic anhydride and 7.26 g. (0.121 mole) of 1,2-dimethylhydrazine in 110 ml. of tetrahydrofuran. A crude product weighing 24.0 g. (b.p. 185–186° at 0.20 mm.) was obtained. This product was refluxed for 2 hr. with 150 ml. of a 5% aqueous sodium bicarbonate solution and worked up to afford 8.05 g. (29.5%) of a semisolid oil, b.p. 168–169° (0.08 mm.); $n_D^{25.1}$ 1.5672; IR (film): 6.02 μ (amide C=O); NMR ($CDCl_3$): δ 6.68–7.51 (m, 4, ArH), 3.95 (t, 1, methine H), 3.77 (s, 3, OCH_3), 3.26 (s, 3, NCH_3), 3.12 (s, 3, NCH_3), and 2.92 (d, 2, CH_2).

Anal.—Calc. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.08; H, 6.66; N, 11.23.

1,2-Diethyl-4-methyl-4-phenylpiperidazine-3,6-dione (VI*a*)—Sodium hydride (50% mineral oil dispersion, 1.33 g., 0.028 mole)

[1] This compound was solubilized in isotonic saline by means of dilute hydrochloric acid; the pH of a 1% solution was 2.7.

[2] Melting points were obtained with a Fisher-Johns melting-point apparatus. A Mel-Temp apparatus was used for melting-point determinations in a sealed tube. All melting points are corrected whereas boiling points are uncorrected. IR data were recorded on a Beckman IR-8 spectrophotometer. NMR spectra were determined with a Varian A-60A spectrometer using tetramethylsilane as the internal reference. Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland. Magnesium sulfate was employed as the drying agent.



Scheme II—For Compounds VI and VII: (a) $R = C_2H_5$, $R' = H$, $R'' = CH_3$; (b) $R = CH_3$, $R' = H$, $R'' = n\text{-}C_3H_7$; *and* (c) $R = CH_3$, $R' = OCH_3$, $R'' = n\text{-}C_3H_7$

was washed three times with hexane and once with tetrahydrofuran and then was suspended in 35 ml. of tetrahydrofuran. To this suspension was added dropwise a solution of 6.00 g. (0.024 mole) of II*a* in 10 ml. of tetrahydrofuran with stirring at 40°. Hydrogen evolution was observed. The reaction mixture was refluxed for 90 min. and cooled, and a solution of 5.11 g. (0.036 mole) of methyl iodide in 10 ml. of tetrahydrofuran was added dropwise. The mixture was again refluxed for 20 hr., cooled, and decomposed with saturated aqueous ammonium chloride solution. The tetrahydrofuran was decanted, and the inorganic sludge was extracted with three 20-ml. portions of tetrahydrofuran. The combined tetrahydrofuran extracts were evaporated under reduced pressure. The residue was dissolved in 50 ml. of ether, dried, and filtered, and the ether was removed under reduced pressure. A yellow semicrystalline material (6.86 g., m.p. 102–117°) was obtained. NMR analysis indicated a purity of 95%. A sample for analysis was prepared by sublimation of the crude product at 70° (0.30 mm.). The sublimate, m.p. 110.5–115.5°, was recrystallized from ligroin to give colorless crystals, m.p. 118–118.5°; IR (KBr): 6.02 μ (amide C=O); NMR ($CDCl_3$): δ 7.34 (s, 5, ArH), 3.72–4.67 (m, 2, $COCH_2$), 2.47–3.42 (m, 4, NCH_2), 1.46 (s, 3, Ar—C—CH_3), 1.12 (t, 3, N—C—CH_3), and 0.22 (t, 3, N—C—CH_3).

Anal.—Calc. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.33; H, 7.75; N, 10.86.

1,2-Dimethyl-4-*n*-propyl-4-phenylpiperidazine-3,6-dione (VI*b*)—This compound was prepared, in a manner similar to that described for VI*a*, from 11.9 g. (0.054 mole) of II*b*, 3.22 g. (0.067 mole) of sodium hydride (50% mineral oil dispersion), and 13.28 g. (0.108 mole) of *n*-propyl bromide in 125 ml. of tetrahydrofuran. After workup of the reaction mixture, a viscous oil was obtained which afforded, upon distillation, 7.98 g. (55.4%) of a colorless oil, b.p. 149–152° (0.30 mm.); $n_D^{25.5}$ 1.5415; IR (film): 6.00 μ (amide C=O); NMR ($CDCl_3$): δ 7.34 (s, 5, ArH), and 0.53–3.41 (m, 15, including two NCH_3 singlets at 3.25 and 2.72).

Anal.—Calc. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.22; H, 7.71; N, 10.76.

1,2-Dimethyl-4-*n*-propyl-4-(*m*-methoxyphenyl)piperidazine-3,6-dione (VI*c*)—This compound was prepared in a manner similar to that described for VI*a* from 8.05 g. (0.032 mole) of II*c*, 1.92 g. (0.040 mole) of sodium hydride (50% mineral oil dispersion), and 7.90 g. (0.064 mole) of *n*-propyl bromide in 80 ml. of tetrahydrofuran. After workup of the reaction mixture, a viscous oil was obtained which yielded, upon distillation, 5.22 g. (56.3%) of a semisolid oil, b.p. 165–167° (0.18 mm.); $n_D^{25.1}$ 1.5450; IR (film): 6.01 μ (amide C=O); NMR ($CDCl_3$): δ 6.54–7.54 (m, 4, ArH) and 0.56–4.13 (m, 18, including one OCH_3 singlet at 3.84 and two NCH_3 singlets at 3.28 and 2.79).

Anal.—Calc. for $C_{16}H_{22}N_2O_3$: C, 66.19; H, 7.64; N, 9.65. Found: C, 65.96; H, 7.91; N, 9.67.

1,2-Dimethyl-4-phenylpiperidazine (V*a*)—A solution of 6.71 g. (0.03 mole) of II*b* in 25 ml. of tetrahydrofuran was added dropwise to a stirred suspension of 2.31 g. (0.06 mole) of lithium aluminum hydride in 50 ml. of tetrahydrofuran. After the addition was complete, the reaction mixture was refluxed for 20 hr. and decomposed with 40% aqueous potassium hydroxide with ice bath cooling. The tetrahydrofuran was decanted, and the inorganic sludge was extracted three times wtih 15-ml. portions of tetrahydrofuran; then the combined tetrahydrofuran solution was dried. After removal of the solvent under reduced pressure, the residue was distilled to afford 3.84 g. (67.3%) of a yellow oil, b.p. 142–145° (9 mm.). Redistillation of the product yielded 3.51 g. of a pale-yellow oil, b.p. 78–79° (0.10 mm.); $n_D^{24.1}$ 1.5518; IR (film): no absorption at 5.98 μ (amide C=O); NMR ($CDCl_3$): δ 7.31 (s, 5, ArH) and 1.65–3.27 (m, 13, including a singlet at 2.52 due to the NCH_3 protons).

Anal.—Calc. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.81; H, 9.51; N, 14.62.

A picrate derivative was prepared and recrystallized from absolute alcohol, m. p. 135–137.5°.

Anal.—Calc. for $C_{18}H_{21}N_5O_7$: C, 51.55; H, 5.05; N, 16.70. Found: C, 51.57; H, 4.96; N, 16.64.

1,2-Dimethyl-4-(*m*-methoxyphenyl)piperidazine (V*b*)—This compound was obtained, in a manner similar to that described for V*a*, from 7.19 g. (0.028 mole) of II*c* and 2.12 g. (0.056 mole) of lithium aluminum hydride in 70 ml. of tetrahydrofuran. The reaction mixture was refluxed for 21 hr. Workup and distillation afforded 4.43 g. (71.9%) of a pale-yellow oil, b.p. 109–111° (0.10 mm.); $n_D^{25.1}$ 1.5541; IR (film): no absorption at 6.02 μ (amide C=O); NMR ($CDCl_3$): δ 6.54–7.54 (m, 4, ArH), 3.79 (s, 3, OCH_3), and 1.51–3.54 (m, 13, including a singlet at 2.52 due to the NCH_3 protons).

Anal.—Calc. for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.74; H, 9.31; N, 12.65.

The picrate derivative was recrystallized from absolute alcohol, m.p. 163.5–165.5°.

Anal.—Calc. for $C_{19}H_{23}N_5O_8$: C, 50.78; H, 5.16; N, 15.58. Found: C, 50.91; H, 5.16; N, 15.70.

1,2-Diethyl-4-methyl-4-phenylpiperidazine (VII*a*)—This compound was prepared, in a manner similar to that described for V*a*, from 6.04 g. (0.022 mole) of VI*a* and 1.30 g. (0.034 mole) of lithium aluminum hydride in 50 ml. of tetrahydrofuran. The reaction mixture was refluxed for 20 hr. Distillation of the crude product gave 3.84 g. (71.9%) of a pale-yellow oil, b.p. 91–92° (0.25 mm.); $n_D^{28.0}$ 1.5230; IR (film): no absorption at 6.02 μ (amide C=O); NMR ($CDCl_3$): δ 7.02–7.45 (m, 5, ArH), 1.24–3.25 (m, 13, including the

Ar—C—CH_3 singlet at 1.33), 1.05 (t, 3, N—C—CH_3), and 1.02 (t, 3, N—C—CH_3).

Anal.—Calc. for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41; N, 12.06. Found: C, 77.58; H, 10.38; N, 12.00.

A hydrochloride derivative was prepared. The salt was recrystallized two times from isopropyl alcohol–hexane with charcoal treatment to yield white needles, m.p. 186–188° (sealed tube).

Anal.—Calc. for $C_{15}H_{25}ClN_2$: C, 67.02; H, 9.37; N, 10.42. Found: C, 66.92; H, 9.29; N, 10.51.

1,2-Dimethyl-4-*n*-propyl-4-phenylpiperidazine (VII*b*)—This compound was synthesized, in a manner similar to that described for V*a*, from 6.41 g. (0.024 mole) of VI*b* and 1.82 g. (0.048 mole) of lithium aluminum hydride in 75 ml. of tetrahydrofuran. The reaction mixture was refluxed for 26 hr. Workup and distillation gave 3.37 g. (60.5%) of a colorless oil, b.p. 99–102° (0.20 mm.); $n_D^{24.2}$ 1.5304; IR (film): no absorption at 6.00 μ (amide C=O); NMR ($CDCl_3$): δ 7.34 (s, 5, ArH), and 0.54–3.18 (m, 19, including two singlets at 2.45 and 2.42).

Anal.—Calc. for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41; N, 12.06. Found: C, 77.58; H, 10.30; N, 12.25.

A methiodide derivative was prepared and recrystallized from isopropyl alcohol, m.p. 204.5–206°.

Anal.—Calc. for $C_{16}H_{27}IN_2$: C, 51.34; H, 7.27; N, 7.48. Found: C, 51.18; H, 7.34; N, 7.60.

1,2-Dimethyl-4-*n*-propyl-4-(*m*-methoxyphenyl)piperidazine (VII*c*)—This compound was obtained, in a manner similar to that described for V*a*, from 4.72 g. (0.016 mole) of VI*c* and 1.21 g. (0.032 mole) of lithium aluminum hydride in 50 ml. of tetrahydrofuran. The reaction mixture was refluxed for 25 hr. Workup and distillation produced 3.50 g. (83.5%) of a colorless oil, b.p. 124–124.5° (0.18 mm.); $n_D^{23.8}$ 1.5328; IR (film): no absorption at 6.01 μ (amide C=O); NMR ($CDCl_3$): δ 6.67–7.52 (m, 4, ArH), 3.84 (s, 3, OCH_3), and 0.57–3.32 (m, 19, including two singlets at 2.46 and 2.42).

Anal.—Calc. for $C_{16}H_{26}N_2O$: C, 73.24; H, 9.99; N, 10.68. Found: C, 73.21; H, 9.82; N, 10.83.

1,2-Dimethyl-4-(*m*-hydroxyphenyl)piperidazine (VIII)—A solution of 2.33 g. (0.0106 mole) of V*b* in 11.4 ml. of 48% aqueous hydrobromic acid was refluxed for 1 hr. under a nitrogen atmosphere. The dark mixture was evaporated to dryness under reduced pressure and the residue was suspended in 5 ml. of water. The mixture was made alkaline, saturated with solid potassium carbonate, and extracted with three 15-ml. portions of chloroform. The combined chloroform solution was dried and filtered. After removal of the chloroform under reduced pressure, 1 g. (47.4%) of a red-brown powder was obtained. Sublimation of the powder at 150° (0.10 mm.) gave a nearly white sublimate, m.p. 147–167°. Recrystallization from chloroform–hexane gave a white powder, m.p. 175–177° dec. (sealed tube); IR (KBr): 2.95 μ (phenolic OH); NMR ($CDCl_3$): δ 6.38–7.37 (m, 5, ArH and ArOH), 2.47–3.50 (m, 11, including a singlet due to the NCH_3 protons at 2.55), and 1.50–2.10 (m, 2).

Anal.—Calc. for $C_{12}H_{18}N_2O_4 \cdot 0.25\ H_2O$: C, 68.37; H, 8.84; N, 13.29. Found: C, 68.20; H, 8.67; N, 13.17.

1,2-Dimethyl-4-*n*-propyl-4-(*m*-hydroxyphenyl)piperidazine (IX)—This compound was obtained, in a manner similar to that described for VIII, from 2.48 g. (0.009 mole) of VII*c* and 10 ml. of 48% aqueous hydrobromic acid. The mixture was refluxed for 1 hr. under a nitrogen atmosphere, worked up, and distilled to afford 0.45 g. (24.7%) of a viscous liquid, b.p. 170–171° (0.45 mm.). The liquid solidified, m.p. 43–45°; IR (KBr): 2.96 μ (phenolic OH); NMR ($CDCl_3$): δ 6.50–7.47 (m, 5, ArH and ArOH), and 0.54–3.13 (m, 19, including a singlet due to the NCH_3 protons at 2.46).

Anal.—Calc. for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.61; H, 9.66; N, 11.24.

Derivatization afforded the methiodide which was recrystallized from isopropyl alcohol, m.p. 195–196.5°.

Anal.—Calc. for $C_{16}H_{27}IN_2O$: C, 49.24; H, 6.97; N, 7.18. Found: C, 49.25; H, 6.99; N, 7.29.

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