Synthesis of Novel Analgesic Agents IV: 1,2-Dialkyl-3-aryl Piperidazines and 1,2,3-Trialkyl-3-aryl Piperidazines

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Abstract □ Several members of both 1,2-dialkyl- and 1,2,3-trialkyl-3-aryl piperidazines were synthesized and investigated for analgesic activity. None possessed significant analgesic activity.

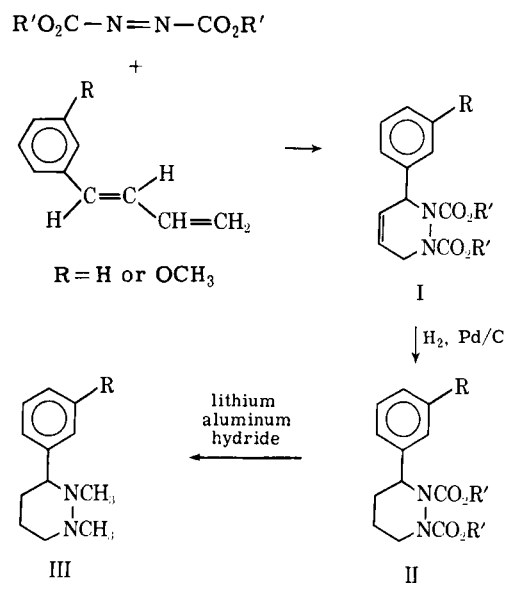
Keyphrases □ 3-Aryl piperidazines, 1,2-dialkyl and 1,2,3-trialkyl—synthesized as potential analgesics, screened □ Piperidazines, 3-substituted—syntheses of series of 1,2-dialkyl and 1,2,3-trialkyl substituted, screened as possible analgesics □ Analgesics, potential—synthesis of 1,2-dialkyl- and 1,2,3-trialkyl-3-aryl piperidazines, screened

Recently, in the search for synthetic analgesic agents, attention was focused on compounds based on the pyrazolidine and piperidazine nuclei (1–3). Both nuclei contain two contiguous, basic nitrogen atoms; a possible advantage of this characteristic was discussed in a previous paper (3). This study has now been extended to the 3-substituted piperidazines, and the preparation and analgesic activity of the title compounds are the subjects of this paper.

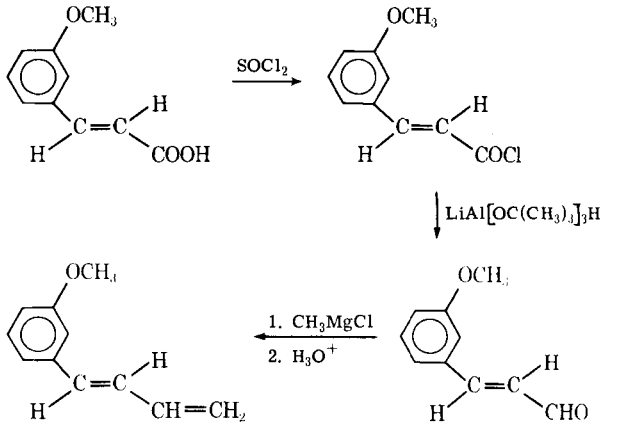
SYNTHESIS

1,2-Dialkyl-3-aryl Piperidazines—The Diels–Alder reaction of dienes with azodicarboxylates provides a ready means of obtaining the $\Delta^{4,5}$-dehydropiperidazine ring. By employing this reaction with 1-aryl 1,3-butadienes, compounds having Structure I can be made easily (4, 5) (Scheme I).

By following the method of Baranger and Levisalles (4), 1,2-dicarbethoxy-3-phenyl-1,2,3,6-tetrahydropyridazine (*Ia*, R = H, R′ = C_2H_5) was prepared from 1-phenyl-1,3-butadiene and diethyl azodicarboxylate. In a similar way, 1,2-dicarbomethoxy-3-phenyl-1,2,3,6-tetrahydropyridazine (*Ib*, R = H, R′ = CH_3) and 1,2-dicarbomethoxy-3-(*m*-methoxyphenyl)-1,2,3,6-tetrahydropyridazine (*Ic*, R = OCH_3, R′ = CH_3) were also prepared in good yield. The diene, 1-phenyl-1,3-butadiene, used in the first two syntheses was prepared from *trans*-cinnamaldehyde by the method of Grummit and Becker (6). 1-(*m*-Methoxyphenyl)-1,3-butadiene was obtained in several steps from *m*-methoxycinnamic acid. The first step involved the conversion of the acid to its acid chloride by means of thionyl chloride (Scheme II). The *m*-methoxycinnamoyl chloride was then reduced to *m*-methoxycinnamaldehyde by means of lithium tri(*tert*-butoxy)aluminum hydride in diglyme at −70° in a manner similar to the reduction of cinnamoyl chloride (7). Conversion of the *m*-methoxycinnamaldehyde to 1-(*m*-methoxyphenyl)-1,3-butadiene was accomplished by a method adapted from Grummit and Becker (6).



Scheme I



Scheme II

Catalytic hydrogenation of 1,2,3,6-tetrahydropyridazines leads to saturation of the $\Delta^{4,5}$-double bond. In the present work, catalytic hydrogenation was successfully effected with 10% palladium-on-charcoal as the catalyst. In this way, 1,2-dicarbethoxy-3-phenylpiperidazine (*IIa*), 1,2-dicarbomethoxy-3-phenylpiperidazine (*IIb*), and 1,2-dicarbomethoxy-3-(*m*-methoxyphenyl)piperidazine (*IIc*) were obtained from the corresponding tetrahydropyridazines.

Lithium aluminum hydride reduction of *IIa* afforded 1,2-dimethyl-3-phenylpiperidazine (*IIIa*). Likewise, reduction of *IIc* with lithium aluminum hydride produced 1,2-dimethyl-3-(*m*-methoxyphenyl)piperidazine (*IIIb*).

Demethylation of *IIIb* with 48% aqueous hydrobromic acid afforded the corresponding *m*-hydroxy analog (IX). Compounds *IIIa*, *IIIb*, and IX represent the potential analgesic agents having a central tertiary carbon atom.

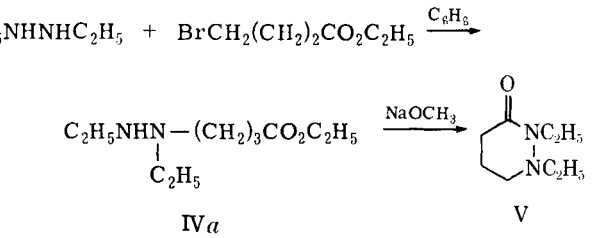
1,2,3-Trialkyl-3-aryl Piperidazines—Numerous examples of the mercuric acetate oxidation of saturated nitrogen heterocycles to cyclic enamines have been reported (8). A noteworthy example is the oxidation of 1,2-dimethyl-3-phenylpyrazolidine in boiling absolute alcohol to afford 1,2-dimethyl-3-phenyl-3-pyrazoline (9). An analogous oxidation of the six-membered homologous piperidazines would be expected to afford the corresponding $\Delta^{3,4}$-dehydro compounds. Alkylation of the iminium salts derived from these enehydrazines with alkyl Grignard reagents should give 1,2,3-trialkyl-3-aryl piperidazines.

Attempts to oxidize 1,2-dimethyl-3-phenylpiperidazine (*IIIa*) with mercuric acetate under various conditions were not successful. Refluxing *IIIa* with mercuric acetate in 5% aqueous acetic acid for 1.5 hr. yielded a small amount of orange-colored crystals. The IR spectrum showed the presence of an N—H stretching band at 2.92 μ and a carbonyl stretching band at 5.98 μ. The NMR spectrum showed the absence of a vinyl proton in the olefinic

region, indicating that the solid could not be the expected product. The product was not investigated further. When the oxidations were conducted in refluxing glacial acetic acid or in refluxing absolute alcohol, only intractable tars were obtained. However, stirring III*a* with mercuric acetate in 5% aqueous acetic acid at room temperature afforded a poor yield of a mixture consisting of III*a* (major component) and 1,2-dimethyl-3-phenyl-1,2,5,6-tetrahydropyridazine (VII*a*) (minor component). The latter compound was detected by its NMR spectrum, which exhibited an olefinic proton signal at δ 5.26. Because of these unrewarding results, this synthetic approach was abandoned.

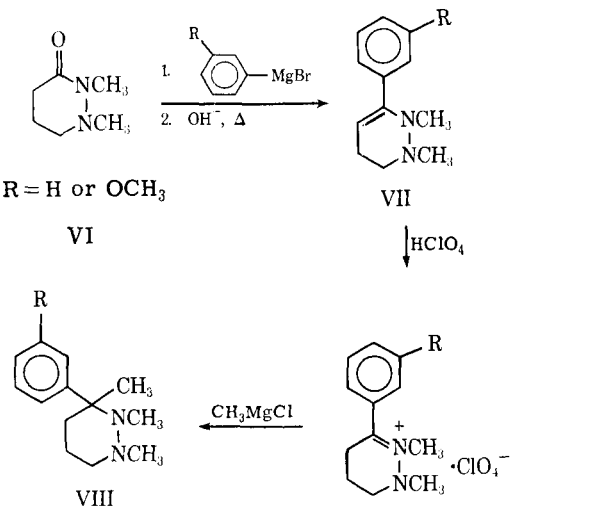
Recently, this laboratory (10) reported the synthesis of 1,2-dialkyl-3-aryl 3-pyrazolines by the reaction of aryl Grignard reagents with 1,2-dialkyl 3-pyrazolidinones. Based on these results, it seemed plausible that the reaction of Grignard reagents with 1,2-dialkyl 3-piperidazinones would lead to the desired dehydropiperidazines.

The synthesis of a model compound, 1,2-diethyl-3-piperidazinone (V), was investigated. A successful two-step route was developed (Scheme III). Treatment of two equivalents of 1,2-diethylhydrazine with one equivalent of ethyl 4-bromobutanoate gave ethyl 4-(1,2-diethylhydrazino)butanoate (IV*a*). Cyclization of IV*a* by means of a catalytic amount of sodium methoxide produced 1,2-diethyl-3-piperidazinone (V) in good yield. In a similar manner, ethyl 4-(1,2-dimethylhydrazino)butanoate (IV*b*) was obtained from 1,2-dimethylhydrazine and ethyl 4-bromobutanoate. Ring closure of IV*b* afforded 1,2-dimethyl-3-piperidazinone (VI).



Scheme III

By following the method of Kornet and Tan (10), VI was stirred for 137 hr. with a 2.5-fold excess of phenylmagnesium bromide in tetrahydrofuran. Steam distillation of the adduct in the presence of barium hydroxide produced 1,2-dimethyl-3-phenyl-1,2,5,6-tetrahydropyridazine (VII*a*) (Scheme IV). Similar treatment of VI with *m*-methoxyphenylmagnesium bromide afforded 1,2-dimethyl-3-(*m*-methoxyphenyl)-1,2,5,6-tetrahydropyridazine (VII*b*).



Scheme IV

These 1,2,5,6-tetrahydropyridazines were obtained as colorless liquids. The IR spectra exhibited the C=C—N absorption at 6.11 μ, and the NMR spectra displayed a vinyl proton triplet at δ 5.25–5.26. A few hours after preparation, the liquids became pale yellow and darkened upon prolonged standing, even under a nitrogen atmosphere. Because of this instability, the liquids were converted into the corresponding perchlorates. The perchlorates of both compounds were obtained as pale-yellow crystals. Charcoal treatment during recrystallization always resulted in dark-brown crystals.

Treatment of the perchlorate of VII*a* with a 14-fold excess of methylmagnesium chloride in tetrahydrofuran at reflux temperature for 100 hr. resulted in the formation of 1,2,3-trimethyl-3-phenylpiperidazine (VIII*a*). The alkylation was incomplete after refluxing overnight, as evidenced by the presence of the olefinic proton signal at δ 5.26 in the NMR spectrum of the distilled product mixture. Similarly, 1,2,3-trimethyl-3-(*m*-methoxyphenyl)piperidazine (VIII*b*) was obtained from VII*b* and methylmagnesium chloride. These two compounds are representatives of potential analgesics containing a central quaternary carbon atom.

Attempted demethylation of VIII*b* with 48% aqueous hydrobromic acid resulted only in intractable tars.

ANALGESIC ACTIVITY

The analgesic activity was determined as previously described (3). The compounds examined included III*a*, III*b*, VIII*a*, VIII*b*, and IX. None of these exhibited significant analgesic activity.

EXPERIMENTAL[1]

1-Phenyl-1,3-butadiene—This compound was prepared by the method of Grummit and Becker (6), 46.7% yield, b.p. 99–100° (15 mm.) [lit. (6) 72–75% yield, b.p. 78–81° (8 mm.)]; IR (film): 6.14 (diene C=C) μ.

***m*-Methoxycinnamoyl Chloride**—A mixture of 50.0 g. (0.28 mole) of *m*-methoxycinnamic acid and 25 ml. (~0.336 mole) of thionyl chloride was refluxed for 3 hr. The excess thionyl chloride was removed under reduced pressure. Anhydrous benzene was added to the residue, and the resulting solution was again evaporated under reduced pressure. This process was repeated three more times. The remaining residue solidified upon scratching. After recrystallization from ligroin (b.p. 66–75°), 41.0 g. of tan-colored crystals was obtained, m.p. 40–41.5° [lit. (11) b.p. 170–175° (15 mm.)]. The mother liquor was evaporated under reduced pressure, and the residue was recrystallized from ligroin (b.p. 66–75°) to afford an additional 7.8 g. of tan-colored crystals, m.p. 39–39.5°; IR (KBr): 5.98 (acid chloride C=O) and 6.13 (C=C) μ; NMR ($CDCl_3$): δ 7.78 (d, 1, J = 15.5 Hz., C=CH—COCl), 6.86–7.52 (m, 4, ArH), 6.58 (d, 1, J = 15.5 Hz., Ar—CH=C), and 3.83 (s, 3, OCH_3). The total yield was 88.7%.

***m*-Methoxycinnamaldehyde**—The method of Brown and Subba Rao (7) for the preparation of cinnamaldehyde was adapted to synthesize this aldehyde. *m*-Methoxycinnamoyl chloride (48.8 g., 0.248 mole) was dissolved in 125 ml. of dried and freshly distilled diglyme (12) and placed in a reaction flask. The flask was flushed with dry nitrogen and cooled to ~−75° in a dry ice–acetone bath. To the cooled solution was added dropwise over 90 min. a solution of 62.97 g. (0.248 mole) of lithium tri(*tert*-butoxy)aluminum hydride in 250 ml. of dried and freshly distilled diglyme. The rate of addition was regulated in such a manner that the temperature of the reaction mixture was always below −70°. The cooling bath was removed, and the mixture was allowed to warm to room temperature. The contents were poured onto 500 g. of crushed ice, and the resulting mixture was filtered through a phase-separating filter paper by suction. The filter was washed with ether, and the filtrate was extracted three times with 100-ml. portions of ether. The combined ether solution was dried, filtered, and concentrated under reduced pressure. The residue was distilled and afforded 20.67 g. (51.4%) of a pale-yellow oil, b.p. 106° (0.15 mm.) [lit. (13) b.p. 87–89° (0.0005 mm.)]; IR (film): 5.97 (aldehyde C=O) and 6.14 (C=C) μ; NMR ($CDCl_3$): δ 9.78 (d, 1, J = 7.5 Hz., CHO), 6.32–

[1] Melting points were determined with a Fisher-Johns apparatus. All melting points are corrected, whereas boiling points are uncorrected. IR spectra were obtained on a Beckman IR-8 spectrophotometer. NMR spectra were determined on a Varian A-60A spectrometer, using tetramethylsilane as the internal reference for solutions in organic solvents. Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland. Magnesium sulfate was employed as the drying agent.

7.22 (m, 6, ArH, including one ArCH—C=C doublet at 7.53, J = 16 Hz., and the C=C*H*—CHO signal as two doublets at 6.87 and 6.60, J = 7.5 Hz.), and 3.86 (s, 3, OCH_3).

1-(*m*-Methoxyphenyl)-1,3-butadiene—This diene was prepared in a manner similar to that described for the preparation of 1-phenyl-1,3-butadiene (6). From a mixture of 20.0 g. (0.123 mole) of *m*-methoxycinnamaldehyde and 43.5 ml. (0.126 mole) of 2.85 *M* methylmagnesium chloride in tetrahydrofuran, which was diluted with 45 ml. of anhydrous ether, there was obtained 15.34 g. of a cloudy oil, b.p. 114–118° (1.8 mm.). The product was dried with anhydrous potassium carbonate, decanted, and again distilled into a receiver containing 75 mg. of *N*-phenyl-β-naphthylamine to afford 12.90 g. (67.3%) of a colorless oil, b.p. 90–93° (0.70 mm.); $n_D^{24.8}$ 1.6010; IR (film): 6.11 (diene C=C) μ; NMR ($CDCl_3$): δ 3.87 (s, 3, OCH_3).

Anal.[2]—Calc. for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 81.35, 80.75; H, 7.35, 7.50.

1,2-Dicarbethoxy-3-phenyl-1,2,3,6-tetrahydropyridazine (I*a*)—A solution of 15.1 g. (0.087 mole) of diethyl azodicarboxylate in 25 ml. of dry benzene was added dropwise to a solution of 11.3 g. (0.087 mole) of 1-phenyl-1,3-butadiene in 25 ml. of dry benzene, with stirring, at reflux temperature under a nitrogen atmosphere. After the addition was complete, the reaction mixture was refluxed for 3 hr. and then allowed to stand overnight at room temperature. The solvent was removed under reduced pressure, and the residue was distilled to afford 14.32 g. (54.3%) of a viscous yellow oil, b.p. 148–150° (2.3 mm.). The oil solidified upon standing, m.p. 45–46° [lit. (4) yield 88%, m.p. 47–48°]; IR (film): 5.86 (urethan C=O) and 6.11 (C=C) μ; NMR ($CDCl_3$): δ 7.12–7.79 (m, 5, ArH), 5.75–7.05 (m, 3, Ar—C*H*—C*H*=C*H*), 3.32–4.83 (m, 6), 1.28 (t, 3, C—CH_3), and 0.78 (t, 3, C—CH_3).

1,2-Dicarbomethoxy-3-phenyl-1,2,3,6-tetrahydropyridazine (I*b*)—This compound[3] was obtained, in a manner similar to that described for I*a*, from 30.7 g. (0.21 mole) of dimethyl azodicarboxylate and 27.8 g. (0.21 mole) of 1-phenyl-1,3-butadiene in 112 ml. of dry benzene. Distillation afforded 32.88 g. (56.7%) of a viscous yellow oil, b.p. 158–160° (1.3 mm.); $n_D^{24.0}$ 1.5295; IR (film): 5.85 (urethan C=O) and 6.11 (C=C) μ; NMR ($CDCl_3$): δ 7.33–7.90 (m, 5, ArH), 5.84–6.45 (m, 3, Ar—C*H*—C*H*=C*H*), and 3.17–5.02 (m, 8, including singlets at 3.88 and 3.27 due to the NCO_2CH_3 protons).

Anal.—Calc. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.73; H, 5.78; N, 10.04.

1,2-Dicarbomethoxy-3-(*m*-methoxyphenyl)-1,2,3,6-tetrahydropyridazine (I*c*)—This compound was obtained, in a manner similar to that described for I*a*, from 11.68 g. (0.08 mole) of dimethyl azodicarboxylate and 12.95 g. (0.08 mole) of 1-(*m*-methoxyphenyl)-1,3-butadiene in 43 ml. of dry benzene. Distillation of the reaction product gave 14.88 g. (60.8%) of a viscous yellow oil, b.p. 169° (0.50 mm.); $n_D^{26.2}$ 1.5344; IR (film): 5.85 (urethan C=O) and 6.11 (C=C) μ; NMR ($CDCl_3$): δ 6.83–7.66 (m, 4, ArH), 5.75–6.38 (m, 3, Ar—C*H*—C*H*=C*H*), and 3.20–4.91 [m, 11, including a singlet at 3.86 ($ArOCH_3$ and NCO_2CH_3) and a singlet at 3.33 (NCO_2CH_3)].

Anal.—Calc. for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.85; H, 5.86; N, 9.13.

1,2-Dicarbethoxy-3-phenylpiperidazine (II*a*)—A solution of 14.32 g. (0.047 mole) of I*a* in 71 ml. of 95% ethanol was hydrogenated overnight over 0.57 g. of 10% palladium-on-charcoal catalyst at an initial pressure of 56 p.s.i. at room temperature in a Parr apparatus. The mixture was filtered, and the solvent was removed under reduced pressure. Absolute alcohol was added to the residue, and the resulting solution was evaporated under reduced pressure to ensure complete removal of water. The residue was distilled and afforded 12.57 g. (87.4%) of a colorless viscous oil, b.p. 152–154° (0.30 mm.), $n_D^{23.0}$ 1.5100 [lit. (14) b.p. 210–212° (15 mm.), $n_D^{20.0}$ 1.5164]; IR (film): 5.86 (urethan C=O), no absorption at 6.11 (C=C) μ; NMR ($CDCl_3$): δ 7.19–7.76 (m, 5, ArH), 5.34–5.68 (m, 1, ArCH), 2.87–4.56 (m, 6), and 1.01–2.39 (m, 10, including two C—CH_3 triplets at 1.17 and 1.28).

1,2-Dicarbomethoxy-3-phenylpiperidazine (II*b*)—A solution of 27.0 g. (0.098 mole) of I*b* in 150 ml. of 95% ethanol was hydrogenated for 3 hr. at room temperature over 1.2 g. of 10% palladium-on-charcoal catalyst at an initial pressure of 56 p.s.i. in a Parr apparatus. The mixture was filtered, and the solvent was removed under reduced pressure. Benzene was added to the residue, and the resulting solution was evaporated under reduced pressure. The residue was distilled and produced 25.39 g. (93.3%) of a colorless viscous oil, b.p. 153–154° (0.40 mm.); $n_D^{24.1}$ 1.5270; IR (film): 5.86 (urethan C=O) μ, no absorption at 6.11 (C=C) μ; NMR ($CDCl_3$): δ 7.30–7.86 (m, 5, ArH), 5.44–5.74 (m, 1, Ar—CH), 2.92–4.44 (m, 8, including NCO_2CH_3 singlets at 3.88 and 3.65), and 1.36–2.45 (m, 4, ArC—C*H*$_2$—C*H*$_2$).

Anal.—Calc. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.46; H, 6.68; N, 10.03.

1,2-Dicarbomethoxy-3-(*m*-methoxyphenyl)piperidazine (II*c*)—This compound was obtained, in a manner similar to that described for II*b*, from 13.46 g. (0.044 mole) of I*c* in 70 ml. of 95% ethanol over 0.55 g. of 10% palladium-on-charcoal catalyst at room temperature at an initial pressure of 56 p.s.i. Distillation of the reaction product gave 10.90 g. (80.4%) of a colorless viscous oil, b.p. 175° (0.70 mm.); $n_D^{23.2}$ 1.5330; IR (film): 5.86 (urethan C=O) μ, no absorption at 6.11 (C=C) μ; NMR ($CDCl_3$): δ 6.90–7.70 (m, 4, ArH), 5.48–5.85 (m, 1, Ar—CH—N), 3.02–4.52 [m, 11, including singlets at 3.94 ($ArOCH_3$ and NCO_2CH_3) and 3.75 (NCO_2CH_3)], and 1.38–2.42 (m, 4, Ar—CH—C*H*$_2$—C*H*$_2$).

Anal.—Calc. for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.54; H, 6.58; N, 9.07.

1,2-Dimethyl-3-phenylpiperidazine (III*a*)—A solution of 39.78 g. (0.13 mole) of II*a* in 40 ml. of anhydrous ether was added dropwise to a stirred suspension of 14.78 g. (0.39 mole) of lithium aluminum hydride in 185 ml. of anhydrous ether over 2 hr. After the addition was complete, the mixture was stirred at room temperature for 18 hr., cooled in an ice bath, and decomposed with 40% aqueous potassium hydroxide solution. The ether was decanted, and the inorganic sludge was extracted with four 35-ml. portions of ether. The combined ether solution was dried, filtered, and evaporated under reduced pressure. Distillation of the residue afforded 23.05 g. (93.3%) of a colorless liquid, b.p. 136–137° (12 mm.); $n_D^{24.6}$ 1.5343; IR (film): no absorption at 5.86 (urethan C=O) μ; NMR ($CDCl_3$): δ 7.18–7.60 (s with shoulders, 5, ArH), 3.52–3.84 (m, 1, Ar—CH), 2.74–3.10 (m, 2, NCH_2), 2.57 (s, 3, NCH_3), 2.19 (s, 3, NCH_3), and 1.43–2.10 (m, 4, Ar—CH—C*H*$_2$—C*H*$_2$).

Anal.—Calc. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.72; H, 9.43; N, 14.63.

A hydrochloride derivative was prepared and recrystallized from absolute ethanol–ether, m.p. 170–171.5°.

Anal.—Calc. for $C_{12}H_{19}ClN_2$: C, 63.55; H, 8.46; N, 12.36. Found: C, 63.52; H, 8.55; N, 12.36.

1,2-Dimethyl-3-(*m*-methoxyphenyl)piperidazine (III*b*)—This compound was obtained, in a manner similar to that described for III*a*, from 10.0 g. (0.032 mole) of II*c* and 3.64 g. (0.096 mole) of lithium aluminum hydride in 95 ml. of anhydrous ether. The addition required 1 hr., and the duration of stirring was 18 hr. at room temperature. After workup and distillation, 4.61 g. (65.5%) of a colorless oil was obtained, b.p. 102–104° (0.15 mm.); $n_D^{24.5}$ 1.5365; IR (film): no absorption at 5.86 (urethan C=O) μ; NMR ($CDCl_3$): δ 6.83–7.65 (m, 4, ArH), 3.53–4.24 (m, 4, Ar—C*H*—N and the OCH_3 protons as a singlet at 3.89), and 1.39–3.18 (m, 12, including the NCH_3 singlets at 2.61 and 2.24).

Anal.—Calc. for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 71.01; H, 9.17; N, 12.69.

A picrate derivative was prepared and recrystallized from absolute alcohol, m.p. 145.5–146.5°.

Anal.—Calc. for $C_{13}H_{23}N_5O_8$: C, 50.78; H, 5.16; N, 15.58. Found: C, 50.82; H, 4.99; N, 15.76.

Ethyl 4-Bromobutanoate—This compound was obtained by modifying the procedure of Avison and Morrison (15). To 180 ml. of 48% aqueous hydrobromic acid was added dropwise 129 g. (1.50 moles) of γ-butyrolactone, with stirring and ice cooling. After the addition was complete, the solution was refluxed for 16 hr. and cooled in an ice bath. Two hundred milliliters of water was added cautiously. The mixture was extracted once with 200 ml. of ether and four times with 50-ml. portions of ether. The combined ether solution was extracted once with 50 ml. of water, dried, and filtered, and the ether was removed under reduced pressure. After the residue was dried thoroughly by dissolution in benzene and repeated evaporation under reduced pressure, the residual 4-bromobutyric acid was obtained as a yellow-brown oil (72.5 g.). To this crude acid

[2] A satisfactory analysis could not be obtained for this compound; however, the adduct obtained from this diene and dimethyl azodicarboxylate gave satisfactory analytical data.

[3] *Reference 5* gives only NMR data for this compound; other physical constants and analytical data are not reported.

was added carefully 70 ml. of thionyl chloride. The mixture was refluxed for 2 hr., and the excess thionyl chloride was removed under reduced pressure. The remaining oil was treated cautiously with 50 ml. of absolute alcohol with ice bath cooling and frequent shaking. When the reaction subsided, the solution was allowed to warm up to room temperature. After an additional 2 hr., it was poured into 75 ml. of ice water. The mixture was extracted once with 100 ml. of ether and twice with 75-ml. portions of ether. The combined ether solution was dried, filtered, and concentrated under reduced pressure. Distillation of the residue yielded 73.2 g. (87.3%) of a colorless oil, b.p. 102–104° (28 mm.) [lit. (15) b.p. 83–85° (13 mm.)]; IR (film): 5.78 (ester C=O) μ; NMR ($CDCl_3$): δ 4.21 (q, 2, OCH_2), 3.50 (t, 2, $Br—CH_2$), 1.87–2.75 (m, 4, CH_2), and 1.27 (t, 3, $C—CH_3$).

Ethyl 4-(1,2-Diethylhydrazino)butanoate (IV*a*)—To a solution of 17.6 g. (0.20 mole) of 1,2-diethylhydrazine in 50 ml. of dry benzene was added dropwise a solution of 19.5 g. (0.10 mole) of ethyl 4-bromobutanoate in 17 ml. of dry benzene with stirring and cooling. After the addition was complete, the reaction mixture was refluxed for 3 hr. An oil layer separated after 20 min. of reflux. The mixture was allowed to stand overnight at room temperature. The benzene layer was separated, and the oil layer was extracted with two 15-ml. portions of benzene. The combined benzene extract was dried, filtered, and concentrated under reduced pressure. Distillation of the residue produced 10.04 g. (49.7%) of a colorless oil, b.p. 133–135° (28 mm.); $n_D^{22.2}$ 1.4400; IR (film): 5.76 (ester C=O) μ; NMR ($CDCl_3$): δ 4.14 (q, 2, OCH_2), 1.52–3.83 (m, 11), and 0.88–1.49 (m, 9, three overlapping triplets due to the $N—C—CH_3$ and $O—C—CH_3$ protons).

Anal.—Calc. for $C_{10}H_{22}N_2O_2$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.47; H, 11.04; N, 13.99.

Ethyl 4-(1,2-Dimethylhydrazino)butanoate (IV*b*)—To a solution of 24.0 g. (0.40 mole) of 1,2-dimethylhydrazine in 200 ml. of dry benzene was added dropwise a solution of 39.0 g. (0.20 mole) of ethyl 4-bromobutanoate in 40 ml. of dry benzene with stirring and cooling. After completion of the addition, the mixture was stirred overnight, refluxed for 6 hr., and allowed to stand for 2 days in the refrigerator. The oil layer, which separated during the stirring, solidified. The benzene layer was decanted, and the solid was repeatedly extracted with benzene. The benzene extracts were combined and concentrated under reduced pressure. Distillation of the residue gave 26.56 g. (76.3%) of a colorless oil, b.p. 94–96° (9 mm.); $n_D^{25.2}$ 1.4360; IR (film): 5.17 (ester C=O) μ; NMR ($CDCl_3$): δ 4.15 (q, 2, OCH_2), 1.56–2.76 (m, 13, including two NCH_3 singlets at 2.43 and 2.55), and 1.26 (t, 3, $C—CH_3$).

Anal.—Calc. for $C_8H_{18}N_2O_2$: C, 55.15; H, 10.41; N, 16.08. Found: C, 55.05; H, 10.06; N, 16.04.

1,2-Diethyl-3-piperidazinone (V)—A solution of 5.05 g. (0.025 mole) of IV*a* in 41 ml. of hexane was refluxed for 1 hr. under a Dean–Stark tube. Only 0.05 ml. of water was collected. The mixture was cooled, the Dean–Stark tube was removed, and 100 mg. of sodium methoxide was added. The mixture was refluxed for 23 hr., cooled, diluted with 40 ml. of ether, dried, and filtered. The solvents were removed under reduced pressure, and the residue was distilled to yield 2.92 g. (74.9%) of a colorless oil, b.p. 139–141° (28 mm.); $n_D^{23.1}$ 1.4739; IR (film): 6.09 (amide C=O) μ; NMR ($CDCl_3$): δ 3.54 (q, 2, $CO—NCH_2$), 1.68–3.28 (m, 8, including a quartet due to the $N—CH_2—CH_3$ protons at 2.93), 1.17 (t, 3, $NCH_2—CH_3$), and 1.12 (t, 3, $NCH_2—CH_3$).

Anal.—Calc. for $C_8H_{16}N_2O$: C, 61.51; H, 10.22; N, 17.93. Found: C, 61.38; H, 10.47; N, 17.78.

1,2-Dimethyl-3-piperidazinone (VI)—This compound was prepared, in a manner similar to that described for V, from 26.5 g. (0.152 mole) of IV*b* and 600 mg. of sodium methoxide in 135 ml. of hexane. Distillation of the product afforded 15.38 g. (78.8%) of a colorless oil, b.p. 100–104° (9 mm.); $n_D^{22.5}$ 1.4332; IR (film): 6.10 (amide C=O) μ; NMR ($CDCl_3$): δ 1.73–3.35 (m, 12, including two NCH_3 singlets at 3.09 and 2.66).

Anal.—Calc. for $C_6H_{12}N_2O$: C, 56.23; H, 9.44; N, 21.86. Found: C, 56.31; H, 9.50; N, 22.11.

***m*-Bromoanisole**—To a stirred solution of 50 g. (0.29 mole) of *m*-bromophenol in 159 ml. of 2 *N* NaOH was added dropwise 27.6 ml. (0.29 mole) of dimethyl sulfate at 40–45°. When the addition was complete, the mixture was stirred for 5 min. An 80-ml. portion of 2 *N* NaOH was added in one lot, and then 18.3 ml. (0.145 mole) of dimethyl sulfate was added dropwise as before, except that the temperature was allowed to rise to 50°. Stirring was continued for 30 min. at 50°, and the pH of the mixture was tested frequently to make sure that it remained on the alkaline side. The mixture was cooled, and the organic layer was extracted three times with 50-ml. portions of ether. The combined ether extract was dried and filtered, and the ether was removed under reduced pressure. Distillation of the residue produced 54.3 g. (100%) of a colorless oil, b.p. 85–87.5° (9 mm.) [lit. (16) b.p. 210–211° (752 mm.)]; IR (film): 9.58 (ether C—O—C) μ; NMR ($CDCl_3$): δ 6.71–7.50 (m, 4, ArH) and 3.79 (s, 3, OCH_3).

1,2-Dimethyl-3-phenyl-1,2,5,6-tetrahydropyridazine (VII*a*)—Phenylmagnesium bromide was prepared by dissolving 29.67 g. (0.189 mole) of bromobenzene in 60 ml. of tetrahydrofuran and adding 30 ml. of this solution to 4.54 g. (0.189 g. atom) of magnesium. As soon as the reaction began, the remaining bromobenzene solution was added dropwise. After the addition was complete, the mixture was refluxed for 20 min. This Grignard reagent was cooled to room temperature, and a solution of 7.00 g. (0.054 mole) of VI in 20 ml. of dry tetrahydrofuran was added dropwise. The mixture was stirred for 137 hr. at room temperature and decomposed with saturated aqueous ammonium chloride. The tetrahydrofuran was decanted, the inorganic sludge was extracted with three 20-ml. portions of tetrahydrofuran, and the combined tetrahydrofuran solution was concentrated under reduced pressure. The remaining residue was subjected to steam distillation in the presence of excess barium hydroxide. Approximately 250 ml. of distillate was collected. The distillate was covered with 30 ml. of ether and saturated with solid potassium hydroxide with ice bath cooling and stirring. The ether was separated, and the aqueous phase was extracted three times with 25-ml. portions of ether. The combined ether solution was dried, filtered, and concentrated under reduced pressure. Distillation of the residue gave 2.52 g. (24.8%) of a colorless oil, b.p. 125–127.5° (10 mm.); $n_D^{24.2}$ 1.5680; IR (film): 6.12 (C=C—N) μ; NMR ($CDCl_3$): δ 7.23–7.83 (m, 5, ArH), 5.26 (t, 1, J = 4 Hz., vinyl H), 2.99 (t, 2, $N—CH_2$), 2.57 (s, 6, NCH_3), and 1.74–2.32 (m, 2, $C=CH—CH_2$). The oil darkened on standing, even under a nitrogen atmosphere.

A perchlorate derivative was prepared. Recrystallization from absolute alcohol afforded pale-yellow crystals, m.p. 104–106°. An analytical sample was obtained from twice-recrystallized material, m.p. 102–105°.

Anal.—Calc. for $C_{12}H_{17}ClN_2O_4$: C, 49.91; H, 5.95; N, 9.70. Found: C, 49.97; H, 6.06; N, 9.79.

1,2-Dimethyl-3-(*m*-methoxyphenyl)-1,2,5,6-tetrahydropyridazine (VII*b*)—This compound was obtained, in a manner similar to that described for VII*a*, from 14.33 g. (0.11 mole) of VI in 36 ml. of dry tetrahydrofuran and *m*-methoxyphenylmagnesium bromide [prepared from 72.0 g. (0.385 mole) of *m*-bromoanisole and 9.24 g. (0.385 g. atom) of magnesium in 122 ml. of dry tetrahydrofuran by the procedure described for the preparation of phenylmagnesium bromide]. The mixture was stirred for 125 hr. at room temperature. After workup, about 1000 ml. of steam distillate was collected. Extraction of this distillate and distillation of the residue afforded 5.52 g. (23.0%) of a colorless oil, b.p. 109.5–112° (0.12 mm.); $n_D^{23.7}$ 1.5613; IR (film): 6.11 (C=C—N) μ; NMR ($CDCl_3$): δ 6.68–7.41 (m, 4, ArH), 5.25 (t, 1, J = 4 Hz., vinyl H), 3.82 (s, 3, OCH_3), 2.97 (t, 2, NCH_2), 2.57 (s, 3, NCH_3), 2.54 (s, 3, NCH_3), and 1.92–2.38 (m, 2, $C=CH—CH_2$). The oil darkened on standing, even under a nitrogen atmosphere.

Anal.—Calc. for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.56; H, 8.24; N, 12.77.

A perchlorate derivative was prepared. Recrystallization from absolute alcohol afforded pale-yellow crystals. An analytical sample was obtained from twice-recrystallized material, m.p. 104–105.5°.

Anal.—Calc. for $C_{13}H_{19}ClN_2O_5$: C, 48.99; H, 6.01; N, 8.79. Found: C, 49.01; H, 6.20; N, 8.88.

1,2,3-Trimethyl-3-phenylpiperidazine (VIII*a*)—A solution of 33.1 ml. (0.096 mole) of 2.85 *M* methylmagnesium chloride in tetrahydrofuran was diluted with 18 ml. of dry tetrahydrofuran. To the resulting solution was added portionwise 1.85 g. (0.0064 mole) of the perchlorate salt of VII*a* over 4 min. The mixture was refluxed for 100 hr., cooled, decomposed with saturated aqueous ammonium chloride, and evaporated to dryness under reduced pressure. The residue was suspended in 35 ml. of ether and made strongly alkaline with 40% aqueous potassium hydroxide and the ether was decanted. The sludge was extracted with three 25-ml. portions of ether. The combined ether solution was dried, filtered, and concentrated under reduced pressure. Then the residue was

distilled and produced 0.5 g. (38.5%) of a yellow oil, b.p. 80–83° (0.27 mm.); $n_D^{25.1}$ 1.5165; IR (film): no absorption at 6.12 (C=C—N) μ; NMR ($CDCl_3$): δ 6.95–7.73 (m, 5, ArH) and 0.67–3.10 (m, including two NCH_3 singlets at 2.27 and 2.40, and a C—CH_3 singlet at 1.30). The oil was converted into the picrate which was purified by recrystallization from absolute alcohol. The yellow solid melted at 162–163.5°.

Anal.—Calc. for $C_{19}H_{23}N_5O_7$: C, 52.65; H, 5.35; N, 16.16. Found: C, 52.84; H, 5.30; N, 16.14.

1,2,3-Trimethyl-3-(*m*-methoxyphenyl)piperidazine (VIII*b*)—This compound was obtained in a manner similar to that described for VIII*a* from 5.80 g. (0.0182 mole) of the perchlorate salt of VII*b* and 94.1 ml. (0.273 mole) of 2.85 *M* methylmagnesium chloride in tetrahydrofuran. The mixture was refluxed for 120 hr. After workup, the product was distilled to afford 1.86 g. (36.8%) of a yellow oil, b.p. 110–113° (0.30 mm.); $n_D^{24.3}$ 1.5323; IR (film): no absorption at 6.11 (C=C—N) μ; NMR ($CDCl_3$): δ 6.54–7.48 (m, 4, ArH), 3.77 (s, 3, OCH_3), and 0.76–3.37 (m, 15, including singlets at 2.38, 2.26, and 1.26 due to NCH_3, NCH_3, and C—CH_3 protons, respectively).

Anal.—Calc. for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found: C, 71.88; H, 9.33; N, 11.81.

The picrate derivative was recrystallized from absolute alcohol, m.p. 128.5–130.5°.

Anal.—Calc. for $C_{20}H_{25}N_5O_8$: C, 51.83; H, 5.44; N, 15.11. Found: C, 51.84; H, 5.33; N, 15.07.

A methiodide derivative was also prepared and recrystallized from isopropyl alcohol, m.p. 174.5–176.5°.

Anal.—Calc. for $C_{15}H_{25}IN_2O$: C, 47.88; H, 6.70; N, 7.44. Found: C, 47.90; H, 6.75; N, 7.62.

1,2-Dimethyl-3-(*m*-hydroxyphenyl)piperidazine (IX)—A solution of 2.0 g. (0.009 mole) of III*b* in 9.7 ml. of 48% aqueous hydrobromic acid was refluxed for 1 hr. under a nitrogen atmosphere. The mixture was evaporated to dryness under reduced pressure. The residue was suspended in 5 ml. of water, made alkaline with solid potassium carbonate, and saturated with solid sodium chloride. The mixture was extracted with three 10-ml. portions of chloroform. The combined chloroform solution was dried, filtered, and concentrated under reduced pressure. Distillation of the residue afforded 1.12 g. (60.5%) of a viscous liquid, b.p. 140–142° (0.10 mm.), which solidified in the receiver. The solid was sublimed at 85° (0.05 mm.) and afforded the pure product, m.p. 50–52°; IR (KBr): 2.93 (phenolic OH) μ; NMR ($CDCl_3$): δ 6.62–7.70 (m, 5, ArH and ArOH) and 1.26–4.34 (m, 13, including two NCH_3 singlets at 2.64 and 2.25).

Anal.—Calc. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 70.01; H, 8.73; N, 13.61.

The methiodide derivative was recrystallized from absolute alcohol, m.p. 215–218° dec.

Anal.—Calc. for $C_{13}H_{21}IN_2O$: C, 44.84; H, 6.08; N, 8.04. Found: C, 44.95; H, 6.26; N, 8.16.

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