using either film former. The skin temperature of the animal and the use of a liquid crystal thermographic tape did not prove to be useful evaluative tools because additional factors may interfere with obtaining a true reading.

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Conformationally Constrained Analogs of Mescaline

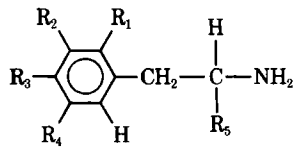
ROBERT J. WOLTERS [x], A. J. BEJ, and N. S. TANNER

Abstract □ The syntheses of 3-(3,4,5-trimethoxyphenyl)piperidine, 2-(3,4,5-trimethoxybenzyl)piperidine, and 2-(3,4,5-trimethoxyphenyl)morpholine are described. In addition, preliminary pharmacological data comparing these compounds with mescaline are given.

Keyphrases □ Mescaline—synthesis of conformationally constrained analogs, pharmacological data □ Hallucinogens—synthesis of conformationally constrained analogs of mescaline, pharmacological data

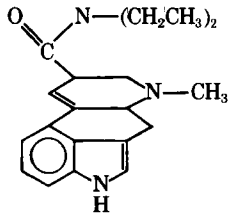
Recent years have seen extensive research in the synthesis of hallucinogens. Most of these compounds have been related to mescaline (I) and methoxyamphetamines (II) rather than to the more complex lysergic acid diethylamide (lysergide, LSD) (III) and tetrahydrocannabinol (IV) analogs (1). The latter two compounds are fairly rigid molecules; however, mescaline's side chain is conformationally mobile.

Most modifications of mescaline have been on the aromatic ring (1–3). However, Walters and Cooper (4) prepared *trans*-2-(3,4,5-trimethoxyphenyl)cyclopropylamine (V) in which the side chain was placed in a cyclopropyl ring. This analog produced mescaline-like activity. Later, Cooper (5) synthesized VI, the *cis*-isomer of V, and Trager and Huitric (6) prepared two related compounds, *cis*- and *trans*-2-(3,4,5-trimethoxyphenyl)cyclohexylamine (VII and VIII) by placing the side chain in a cyclohexyl ring.



I: $R_1 = R_5 = H$, $R_2 = R_3 = R_4 = OCH_3$

II: R_1, R_2, R_3, R_4 = H or OCH_3, $R_5 = CH_3$



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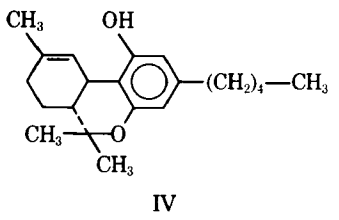
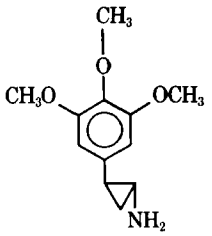


IV

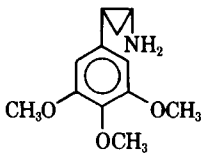
The purpose of this investigation was to impose conformational restraint on the aliphatic side chain of mescaline by placing it in various heterocyclic ring systems, namely piperidine and morpholine. This report discusses the synthesis of 3-(3,4,5-trimethoxyphenyl)piperidine (IX), 2-(3,4,5-trimethoxybenzyl)-piperidine (X), and 2-(3,4,5-trimethoxyphenyl)morpholine (XI).

DISCUSSION

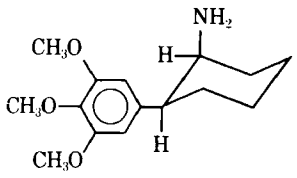
The procedure of Telang and Smith (7) was employed to synthesize 3,4,5-trimethoxyphenylacetonitrile (XII). Compound XII was



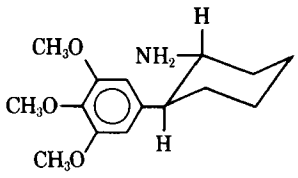
V



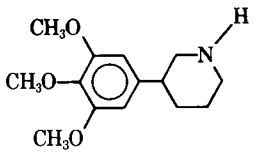
VI



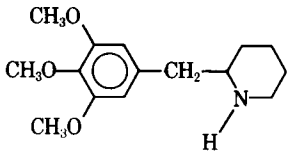
VII



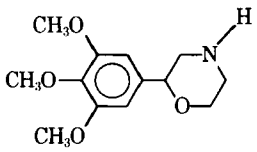
VIII



IX



X



XI

reacted with 3-bromopropionitrile and the resulting dinitrile (XIII) was hydrolyzed with sodium hydroxide solution to form the dicarboxylic acid (XIV). The glutarimide (XV) was synthesized by heating XIV with urea. Reduction of XV with lithium aluminum hydride afforded the desired compound, 3-(3,4,5-trimethoxyphenyl) piperidine (IX) (Scheme I).

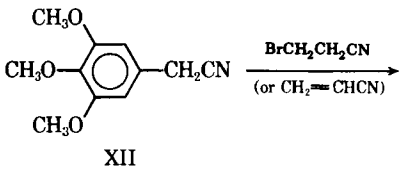
In an alternative procedure, XIII was synthesized *via* the Michael reaction by reacting XII with acrylonitrile in the presence of sodium. The yield by this method was low, 10–15% compared to a 50% yield obtained by the first method.

For the synthesis of 2-(3,4,5-trimethoxybenzyl)piperidine (X), 3,4,5-trimethoxybenzoic acid (XVI) was reacted with 2-pyridyl lithium to yield 3,4,5-trimethoxyphenyl 2-pyridyl ketone (XVII). Compound XVII was reacted with hydrazine to form the hydrazone (XVIII). Then XVIII was reduced by the Wolff–Kishner reaction to yield 2-(3,4,5-trimethoxybenzyl)pyridine (XIX). Catalytic hydrogenation of XIX afforded the desired Compound X (Scheme II).

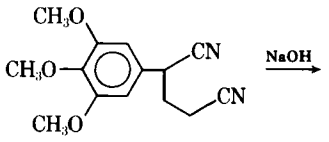
The synthetic route for the morpholine derivative is shown in Scheme III. The starting material, β-hydroxymescaline (XX), was synthesized according to the procedure of Friedman *et al.* (8). Compound XX was reacted with chloroacetyl chloride to form the *N*-acetyl chloride (XXI) followed by cyclization with base, yielding the morpholone (XXII). Reduction of XXII with lithium aluminum hydride or Red Al [sodium dihydro-bis(2-methoxyethoxy)-aluminate] afforded the desired Compound XI.

PHARMACOLOGY

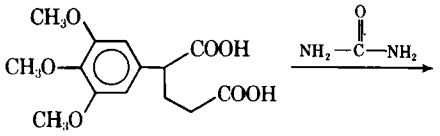
The spontaneous activity of Male Cox (SW) mice, 20–30 g, was determined and recorded by means of activity chambers[1]. Following 3 days of acclimation in a 12-hr light–12-hr dark cycle, the mice were randomly selected for pairing and assignment to an activity chamber (two mice per chamber). Pairing was done with animals from the same cage to avoid interaction in the activity chamber. Saline or the test compounds (50 mg/kg) were randomly assigned and administered intraperitoneally to each group. The animals were placed in the chambers and their activity was measured during 1-min periods at 5, 10, 20, 30, 40, 50, 60, 75, 90, 105, and 120 min following drug administration and was recorded as counts per minute. In addition, amphetamine (5 mg/kg), methylphenidate (10 mg/kg), and mescaline (50 mg/kg) were used as standards for comparison. The data for each time period (treatment *versus* control) were analyzed using the Student *t* test.



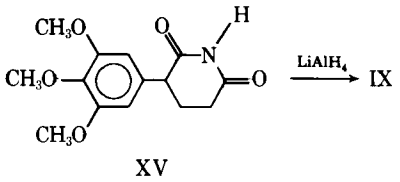
XII



XIII



XIV



XV

Scheme I

The saline-treated mice were recorded with an initial high activity, possibly due to exploratory behavior, after which the activity decreased markedly. The amphetamine and methylphenidate treatments significantly increased activity to a level greater than that of saline or mescaline. The activity of methylphenidate treatment decreased with time more rapidly than did amphetamine. Mescaline was associated with an activity level that was less than that of saline initially and decreased only slightly during the study period.

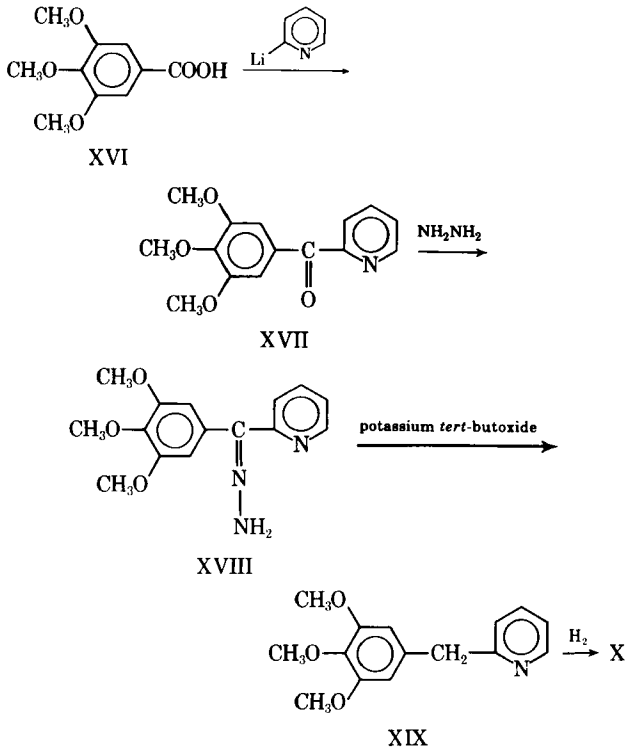
The compounds at the 50-mg/kg dosage induced locomotor activity corresponding to that of saline in the first 40 min. Beyond 40 min the rate of decrease in activity was more gradual than with saline. The tendency toward the mescaline characteristic was XI > X > IX. The stereotyped behavior of mescaline, scratching, was not observed with the test compounds at this dose.

EXPERIMENTAL[2]

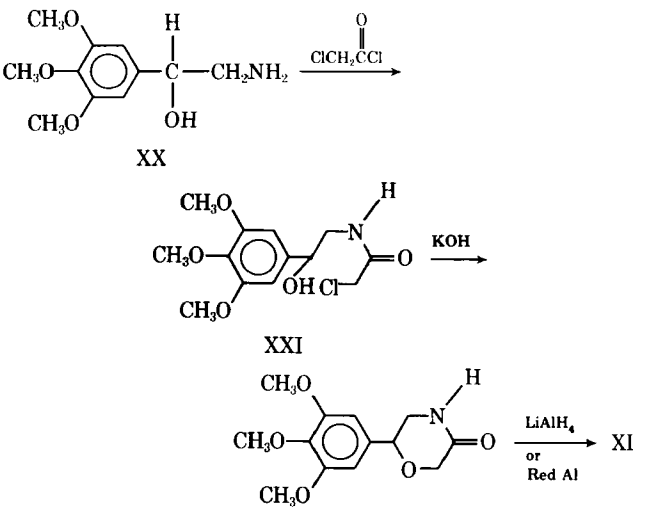
2-(3,4,5-Trimethoxyphenyl)glutaronitrile (XIII)—*Method A*—The procedure of Sugimoto and Kugita (9) was modified in the preparation of XIII. To a flask heated in an oil bath to 110° were added 8.00 g (0.0386 mole) of XII and 0.20 g (0.00087 g-atom) of sodium, and the temperature of the bath was increased to 120°. Subsequently, 1.20 g (0.0226 mole) of acrylonitrile was added dropwise. After the addition was completed, the mixture was allowed to cool, treated with 1 ml of acetic acid, extracted with ethyl acetate, and distilled. The third fraction gave 1.42 g (14%) of prod-

[1] Woodard Research Corp., Herndon, Va.

[2] IR spectra were determined on a Perkin-Elmer model 337 spectrophotometer using potassium bromide pellets. NMR spectra were determined on the Varian model A-60A using tetramethylsilane as the internal standard and deuterochloroform as the solvent in approximately 30% concentration. The letter abbreviations used follow: s = singlet, 2 s = two singlets, t = triplet, m = multiplet, and b = broad. Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Microanalyses were performed by Alfred Bernhardt Mikroanalytishes Laboratorium, Fritz-Pregel-Strasse, West Germany.



Scheme II



Scheme III

uct, bp 190–200°/0.22 mm. After recrystallization the product had a melting point of 94.5–96°. The IR spectrum showed a peak at 2250 cm^{-1}, indicative of nitriles.

Anal.—Calc. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.77. Found: C, 64.52; H, 6.34; N, 10.93.

Method B—A solution of 9.00 g (0.043 mole) of XII and 125 ml of anhydrous dimethylformamide was cooled in an ice bath treated with 2.5 g (0.052 mole) of sodium hydride in an oil dispersion. After cessation of hydrogen evolution, 5.85 g (0.0436 mole) of 3-bromopropionitrile was added dropwise. When the addition was completed, the ice bath was removed and the mixture was stirred at room temperature for 15 hr. About 2 liters of water was added to the reaction mixture, and the product was extracted with ether. The ether layer was concentrated and the precipitate was filtered and recrystallized from ether to yield 5.67 g (50%) of product, mp 94–95°. The melting point of a mixture of this product with a sample obtained by Method A was undepressed. The IR spectra were identical.

2-(3,4,5-Trimethoxyphenyl)glutaric Acid (XIV)—The procedure of Elvidge *et al.* (10) was adopted for this preparation. A mixture of 6.09 g (0.0234 mole) of XIII and 12 g of sodium hydroxide in 35 ml of water and 18 ml of ethanol was refluxed for 2.5 hr. After the solution attained room temperature, it was acidified to pH 2 with 10% hydrochloric acid and the precipitate was filtered and air dried to yield 5.4 g (77%) of crude product. On recrystallization from water, the melting point of the product varied between 80 and 90°, depending on the rate of heating. The IR spectrum showed a broad peak from 3600 to 3350 cm^{-1}, indicative of a hydroxyl group, and a peak at 1740 cm^{-1}, indicative of a carbonyl group.

Anal.—Calc. for $C_{14}H_{18}O_7$: C, 56.37; H, 6.08. Found: C, 56.22; H, 6.11.

3-(3,4,5-Trimethoxyphenyl)glutarimide (XV)—The procedure of Degutis and Sukeliene (11) was adopted for this preparation. A flask containing 6.24 g (0.0202 mole) of XIV and 3.0 g (0.64 mole) of urea was placed in an oil bath preheated to 135°. The temperature was raised to 165–170° and, after 1.5 hr, the reaction mixture was poured into 30 ml of 10% sodium bicarbonate solution and heated on a steam bath for 20 min. The solid which separated was filtered and recrystallized from methyl ethyl ketone, yielding 1.99 g (36.6%) of product, mp 185–187°. The IR spectrum showed a peak at 3200 cm^{-1}, indicative of NH, and a doublet at 1700 cm^{-1}, indicative of a carbonyl group. The NMR spectrum showed peaks at δ 2.6 (b, 4H, methylene), 3.6 (s, 1H, CH), 3.8 (s, 9H, methoxy), 6.4 (s, 2H, aromatic), and 8.3 (b, 1H, NH).

Anal.—Calc. for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.32; H, 6.29; N, 4.98.

3-(3,4,5-Trimethoxyphenyl)piperidine Hydrochloride (IX)—The procedure of Rice and Scott (12) was adopted for reduction of XV. To a mixture of 125 ml of anhydrous tetrahydrofuran and 3.5 g (0.075 mole) of lithium aluminum hydride was added 2.16 g (0.00774 mole) of XV, and the mixture was refluxed for 4 hr. The excess lithium aluminum hydride was decomposed by the dropwise addition of ice water. The solid which separated was removed by filtration and washed twice with ethyl acetate. The combined filtrate and washings were concentrated *in vacuo*. The oily residue was dissolved in benzene and extracted with 10% hydrochloric acid, followed by neutralization by the addition of sodium carbonate and extraction of the product with benzene. The benzene layer was dried over anhydrous magnesium sulfate and filtered. Dry hydrogen chloride was bubbled into the benzene solution to yield 1.45 g (59.5%) of product. Recrystallization from *n*-propanol gave the product, mp 215–216°. The NMR spectrum of the free base showed peaks at δ 2.1 (b, 8H, methylene), 3.1 (s, 1H, CH), 3.8 (2 s, 9H, methoxy), 4.6 (b, 1H, NH), and 6.3 (s, 2H, aromatic).

Anal.—Calc. for $C_{14}H_{21}NO_3$·HCl: C, 58.43; H, 7.71; N, 4.87. Found: C, 58.26; H, 7.52; N, 4.79.

3,4,5-Trimethoxyphenyl 2-Pyridyl Ketone (XVII)—The procedure of Boykin *et al.* (13) was adopted in the synthesis of XVII. The requisite 2-pyridyl lithium (from a solution of 31.6 g of 2-bromopyridine in 100 ml of anhydrous ether and 3.7 g of lithium) was prepared by the method of Wibaut *et al.* (14). Under nitrogen at −45°, 21.2 g (0.100 mole) of XVI was added to 2-pyridyl lithium along with 200 ml of anhydrous ether. The mixture was stirred for 1 hr and allowed to equilibrate to room temperature. The ketone (XVII) was extracted from the ether layer with 10% hydrochloric acid and neutralized with a 10% sodium hydroxide solution. The precipitate which separated was filtered and air dried to yield 14.6 g (53.5%) of product, mp 108.5–110°, after recrystallization from ether. The IR spectrum showed a peak at 1660 cm^{-1}, indicative of carbonyls.

Anal.—Calc. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.91; H, 5.65; N, 5.31.

3,4,5-Trimethoxyphenyl 2-Pyridyl Ketone Hydrazone (XVIII)—The procedure of Boyer *et al.* (15) was adopted for the synthesis of XVIII. Compound XVIII was prepared in 66% yield with a melting point of 158–160° after recrystallization from ethanol. The IR spectrum showed a doublet at 3380 and 3280 cm^{-1}, attributed to the hydrazone.

Anal.—Calc. for $C_{15}H_{17}N_3O_3$: C, 62.72; H, 5.95; N, 14.62. Found: C, 62.68; H, 6.13; N, 14.79.

2-(3,4,5-Trimethoxybenzyl)pyridine Hydrochloride (XIX)—The Cram *et al.* (16) modification of the Wolff–Kishner reaction was utilized to reduce XVIII. To a solution of 8.0 g (0.073 mole) of

potassium *tert*-butoxide and 50 ml of dimethyl sulfoxide was slowly added, over 10 hr, 8.00 g (0.0278 mole) of XVIII. The solution was allowed to stand overnight. Then 200 ml of benzene was added and the product was extracted with 10% hydrochloric acid, neutralized with 10% sodium hydroxide, and reextracted with benzene. The solvent was removed and the residue was chromatographed on 400 g of a neutral alumina column, 3 cm in diameter. The column was first eluted with 50% petroleum ether–benzene solution until the first band was completely eluted and discarded. The column was then eluted with a 90% benzene–10% chloroform solution to elute XIX. The hydrochloride salt was made in the usual manner and recrystallized from methyl ethyl ketone, yielding 2.09 g (29.1%) of product, mp 250–252°. The NMR spectrum of the free base showed peaks at δ 3.9 (2 s, 9H, methoxy), 5.7 (b, 2H, CH_2), 6.8 (s, 2H, aromatic), 7.7 (b, 2H, pyridine ring), and 8.2 (b, 2H, pyridine ring).

Anal.—Calc. for $C_{15}H_{17}NO_3$·HCl: C, 60.91; H, 6.14; N, 4.74. Found: C, 60.82; H, 6.26; N, 4.35.

2-(3,4,5-Trimethoxybenzyl)piperidine (X)—A mixture of 1.80 g (0.00694 mole) of XIX, 10 ml of acetic acid, and 5 mg of platinum oxide was shaken with hydrogen (initial pressure of 55 psi) for 20 hr. The mixture was filtered, the filtrate was diluted with 50 ml of water, and the cloudy dispersion was extracted with ether. The aqueous phase was neutralized with sodium carbonate and the product was extracted with ether. The hydrochloride salt was made in the usual manner and recrystallized from methanol, yielding 1.81 g (74.3%) of product, mp 250–252°. The base melted at 59–60°. The NMR spectrum showed peaks at δ 2.6 (b, 6H, methylene), 2.9 (b, 4H, methylene), 3.5 (b, 1H, CH), 3.9 (2 s, 9H, methoxy), 4.2 (b, 1H, NH), and 6.4 (s, 2H, aromatic).

Anal.—Calc. for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.73; N, 5.28. Found: C, 67.85; H, 8.59; N, 5.40.

1 - (3,4,5 - Trimethoxyphenyl) - 2 - chloracetamidoethanol) (XXI)—The procedure of Fodor *et al.* (17) was adopted to synthesize XXI. To a solution of 5.00 g (0.0220 mole) of XX [synthesized by the published method (8)] in 125 ml of 1,2-dichloroethane was added a solution of 1.3 g (0.032 mole) of sodium hydroxide in 25 ml of water. The mixture was placed in an ice bath and, after the mixture had equilibrated, 3.5 g (0.031 mole) of chloroacetyl chloride was added dropwise over 1 hr. The ice bath was removed and the mixture was stirred for 3 hr. The layers were separated and the organic phase was washed successively with 20 ml of water, 20 ml of 10% sodium hydroxide, two 20-ml portions of 10% hydrochloric acid, and 20 ml of water. The organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was removed *in vacuo* and the solid residue was recrystallized from benzene, yielding 4.56 g (68.6%) of product, mp 109–110°. The IR spectrum showed peaks at 3450, 3250, and 1650 cm^{-1}, indicative of a hydroxyl proton, an amide proton, and a carbonyl group, respectively. The NMR spectrum showed peaks at δ 3.5 (b, 2H, N—CH_2), 3.9 (2 s, 9H, methoxy), 4.1 (s, 1H, OH), 4.1 (s, 2H, Cl—CH_2), 5.9 (s, 1H, CH), 6.6 (s, 2H, aromatic), and 7.2 (b, 1H, NH).

Anal.—Calc. for $C_{13}H_{18}ClNO_5$: C, 51.41; H, 5.97; N, 4.61. Found: C, 51.41; H, 6.02; N, 4.53.

2-(3,4,5-Trimethoxyphenyl)-5-morpholone (XXII)—To a solution of 3.57 g (0.0118 mole) of XXI in 125 ml of ethanol was added dropwise a solution of 0.90 g (0.017 mole) of potassium hydroxide in 4.5 ml of water. During the addition of potassium hydroxide, the pH of the ethanolic solution was not allowed to exceed 11. The precipitate that separated during the addition was removed by filtration. The solvent was removed *in vacuo* and the residue was recrystallized from methyl ethyl ketone to yield 2.29 g (72.5%) of product, mp 159–160°. The NMR spectrum showed peaks at δ 3.6 (b, 2H, N—CH_2), 3.9 (2 s, 9H, methoxy), 4.4 (s, 2H, O—CH_2), 4.8 (t, 1H, CH), 6.7 (s, 2H, aromatic), and 7.7 (b, 1H, NH).

Anal.—Calc. for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.49; H, 6.50; N, 5.29.

2-(3,4,5-Trimethoxyphenyl)morpholine Hydrochloride (XI)—*Method A*—The procedure of Rice and Scott (12), as previously described for the reduction of XV, was adopted for the reduction of XXII using 1.0 g (0.0037 mole) of XXII and 0.50 g (0.013 mole) of lithium aluminum hydride. The product, after recrystallization from methyl ethyl ketone, yielded 0.47 g (43%), mp 216–219°.

Method B—The procedure of Cerny *et al.* (18) was adopted to reduce XXII. A solution of 0.90 g (0.0034 mole) of XXII in 25 ml of anhydrous benzene was added dropwise to 2.5 g (0.012 mole) of Red Al in 25 ml of anhydrous benzene cooled to 0°. After the addition was completed, the flask was allowed to warm to room temperature and the solution was refluxed for 4 hr. The excess Red Al was decomposed with 6 ml of water and the resulting mixture was filtered. The filtrate was extracted with two 15-ml portions of 10% hydrochloric acid, neutralized with 10% sodium hydroxide, and reextracted with ether. The hydrochloride salt of the product was made in the usual manner from the dried ethereal solution, yielding 0.67 g (69%) of product, mp 214–218°. The analytical sample had a melting point of 222.5–224°. The IR spectra of the hydrochloride salt from Methods A and B were identical. The NMR spectrum of the free base showed peaks at δ 3.2 [b, 4H, N—$(CH_2)_2$], 3.9 (2 s, 9H, methoxy), 4.2 (b, 2H, O—CH_2), 4.5 (b, 1H, CH), 5.0 (b, 1H, NH), and 6.7 (s, 2H, aromatic).

Anal.—Calc. for $C_{13}H_{19}NO_4$·HCl: C, 53.89; H, 7.00; N, 4.83. Found: C, 53.92; H, 7.03; N, 4.76.

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