bolic changes would be expected to result in altered UV spectra and, therefore, fluorescence excitation spectra. No such changes were observed in the dog. Moreover, TLC of serum extracts showed that the major component (>85%) was similar to I, confirming the measurement of intact drug. Thus, the method possesses adequate sensitivity and specificity for drug absorption studies in animals.

Based on fluorometric and TLC analyses, less than 1% of the dose was excreted in urine as intact I by the dog during the 24-hr collection interval. Extensive metabolism and/or biliary secretion are indicated.

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Conformationally Constrained Analogs of Mescaline II

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

Abstract □ The synthesis of methyl-2-(3,4,5-trimethoxyphenyl)-2-(2-piperidyl) acetate is described. In addition, preliminary pharmacological data comparing the compound with mescaline are given.

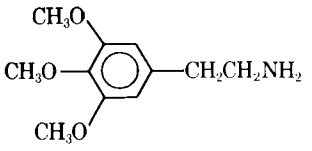
Keyphrases □ Mescaline—synthesis of conformationally constrained analog, methyl-2-(3,4,5-trimethoxyphenyl)-2-(2-piperidyl) acetate, IR and NMR spectra □ Methyl-2-(3,4,5-trimethoxyphenyl)-2-(2-piperidyl) acetate—analog of mescaline, synthesis, IR and NMR spectra

In an earlier publication (1), the synthesis of several conformationally constrained analogs of mescaline (I) was reported. This article reports the synthesis of methyl -2-(3,4,5-trimethoxyphenyl) -2- (2-piperidyl) acetate (II) as a modified mescaline analog. Compound II possesses the trimethoxyphenyl ring and the two-carbon chain of mescaline. The nonmethoxy analog of II, methylphenidate[1] (III), is a known central nervous system stimulant (2). It was anticipated that II would possess stimulant properties like mescaline and methylphenidate.

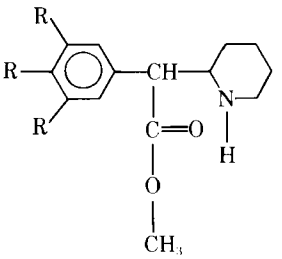
DISCUSSION

The synthetic route utilized for II was basically the same as that employed by Hartmann and Panizzon (3) for the synthesis of methylphenidate (Scheme I). The starting material, 3,4,5-trimethoxyphenylacetonitrile (IV), was synthesized according to the procedure of Telang and Smith (4).

Compound IV was reacted with 2-chloropyridine, using sodium hydride as the base, to form 2-(3,4,5-trimethoxyphenyl)-2-(2-pyridyl)acetonitrile (V). Compound V was hydrolyzed with sulfuric acid to form the amide VI. Methanolysis of VI gave the methyl ester VII. Catalytic hydrogenation of VII afforded the desired product II.



I



II: R = —OCH_3

III: R = —H

EXPERIMENTAL[2]

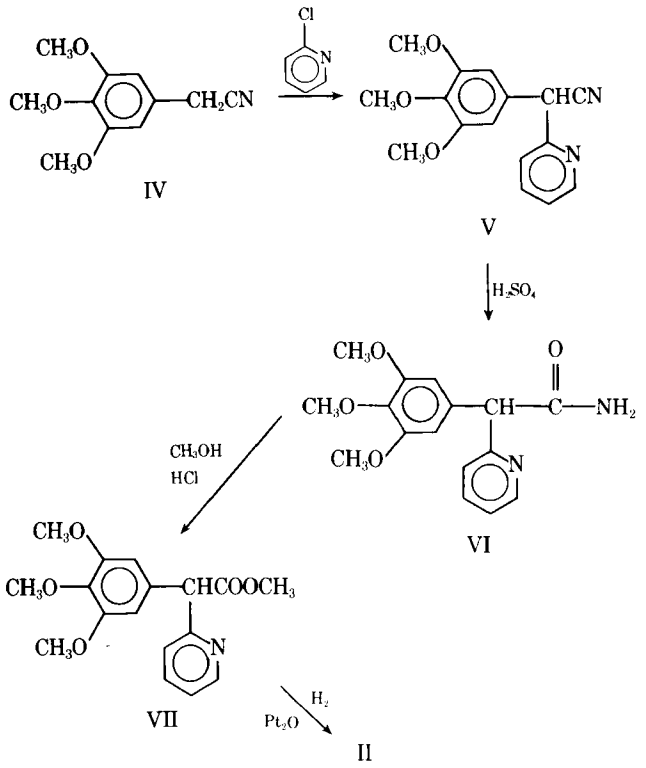
Pharmacology—The spontaneous activity of the test compound was compared to amphetamine, methylphenidate, and mescaline by means of activity chambers according to the procedure of Wolters *et al.* (1). The response of amphetamine, methylphenidate, and mescaline was reported previously (1).

The test compound 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 activity was comparable to mescaline, although the stereotyped behavior of mescaline scratching was not observed with the test compound at this dose.

Chemistry *2- (3,4,5-Trimethoxyphenyl) -2- (2-pyridyl)acetonitrile Hydrochloride (V-HCl)*—A solution of 75 ml of anhydrous dimethylformamide and 11.0 g (0.0531 mole) of IV was cooled to 0°. Then 3.0 g (0.060 mole) of sodium hydride was added. After the cessation of hydrogen evolution, a solution of 6.07 g (0.053 mole) of 2-chloropyridine in 50 ml of dimethylformamide was added drop-

[1] Ritalin Hydrochloride, Ciba Pharmaceutical Co., Summit, N.J.

[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, 2s = 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 I

wise and the reaction mixture was stirred for an additional hour. The mixture was allowed to equilibrate to room temperature and was stirred for an additional 12 hr.

Approximately 1.5 liters of water was added to the mixture, and the organic phase was separated and extracted with ether. Then the ether phase was extracted with several 25-ml portions of 10% hydrochloric acid. The combined acid extract was neutralized with 10% sodium hydroxide and extracted exhaustively with ether. The ether extract was evaporated on a steam bath to yield 8.9 g (61%) of viscous oil, and the oil was dissolved in anhydrous ether. Dry hydrogen chloride was bubbled into the ether solution to yield 10 g (59%) of crude product.

After recrystallization from a mixture of ethanol and anhydrous ether, the product melted at 162–180°. Additional recrystallizations did not appreciably reduce the melting-point range. The IR spectrum showed a peak at 2250 cm^{-1}, indicative of a nitrile group. The NMR spectrum of the free base gave the following: δ 3.9 (2s, 9H, methoxys), 6.5 (s, 1H, —CH), 7.1 (2s, 2H, aromatic), 7.5 (b, 3H, pyridine ring), and 8.2 (b, 1H, pyridine ring).

Anal.—Calc. for $C_{16}H_{16}N_2O_3 \cdot HCl$: C, 59.91; H, 5.34; N, 8.73. Found: C, 59.76; H, 5.50; N, 8.54.

2-(3,4,5-Trimethoxyphenyl)-2-(2-pyridyl)acetamide (VI)—To 35 ml of concentrated sulfuric acid was added 6.59 g (0.0232 mole) of V. The resulting solution was allowed to stand for 12 hr at room temperature. The reaction mixture was poured into crushed ice and neutralized with sodium carbonate, and the product was extracted with chloroform. The chloroform was removed on a steam bath, and the residue was recrystallized from ethyl acetate to yield 5.01 g (72%) of product, mp 144–146°.

The IR spectrum showed a peak at 1700 cm^{-1}, indicative of amide carbonyl. The NMR spectrum gave the following: δ 3.8 (s, 9H, methoxys), 5.0 (s, 1H, —CH), 6.8 (s, 2H, aromatic), 7.6 (b, 3H, pyridine ring, and 2H, amide), and 8.6 (b, 1H, pyridine ring).

Anal.—Calc. for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.59; H, 6.11; N, 9.08.

Methyl-2-(3,4,5-trimethoxyphenyl)-2-(2-pyridyl) Acetate (VII)—Hydrogen chloride gas was bubbled into a solution of 5.01 g (0.0166 mole) of VI and 150 ml of anhydrous methanol for 6 hr. After most of the methanol was removed, sodium carbonate was added to form the free base. The precipitate was filtered and recrystallized from 50% ethanol and then from ether, yielding 2.79 g (53%) of product, mp 101–104°.

The IR spectrum showed a carbonyl peak at 1740 cm^{-1}. The NMR spectrum gave the following: δ 3.8 (s, 3H, methoxys), 3.9 (s, 9H, methoxys), 5.2 (s, 1H, —CH), 6.8 (s, 2H, aromatic), 7.5 (b, 3H, pyridine ring), and 8.6 (b, 1H, pyridine ring).

Anal.—Calc. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.26; H, 6.21; N, 4.25.

Methyl-2-(3,4,5-trimethoxyphenyl)-2-(2-piperidyl) Acetate Hydrochloride (II-HCl)—A mixture of 1.34 g (0.00423 mole) of VII, 10 ml of acetic acid, and 5 mg of platinum oxide was shaken with hydrogen (initial pressure of 55 psi) in a Parr hydrogenator for 20 hr. The platinum oxide was removed by filtration. The filtrate was diluted with three times its volume of water, and sodium carbonate was added to precipitate the free base, which was extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, and the hydrochloride salt was made from the dried ether solution in the usual manner.

The crude product was recrystallized from methyl ethyl ketone, yielding 0.69 g (45%) of product, mp 202–203°. The NMR spectrum of the free base gave the following: δ 1.8 (b, 9H, piperidine ring), 3.6 (b, 1H, —NH), 3.8 (s, 3H, methoxys), 3.9 (2s, 9H, methoxys), 4.0 (b, 1H, —CH), and 6.6 (2s, 2H, aromatic).

Anal.—Calc. for $C_{17}H_{25}NO_5 \cdot HCl$: C, 56.76; H, 7.28; N, 3.89. Found: C, 56.84; H, 7.16; N, 4.00.

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