

# New Compounds: Some 3,4,5-Trimethoxyphenyl Analogs of Analgesics

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**Abstract** □ Starting from 3,4,5-trimethoxybenzoic acid, the syntheses of the 3,4,5-trimethoxyphenyl analogs of meperidine hydrochloride and ketobemidone hydrochloride are described.

**Keyphrases** □ Meperidine HCl, 3,4,5-trimethoxyphenyl analogs—synthesis □ Ketobemidone HCl, 3,4,5-trimethoxyphenyl analogs—synthesis □ NMR spectrometry—structure □ IR spectrophotometry—structure

A number of naturally occurring compounds having action on the CNS possess a 3,4,5-trimethoxyphenyl group. For the past 15 years, a considerable amount of work on 3,4,5-trimethoxyphenyl compounds of possible psychotropic activity has been done (1). Many of these compounds have little chemical relationship except the possession of 3,4,5-trimethoxyphenyl groups. One laboratory reported previously on the synthesis of some 3,4,5-trimethoxyphenyl analogs of antihistamines (2) and anticonvulsants (3). Since analgesics are known to have a distinct effect upon the CNS, the drugs selected for the present studies were the important synthetic substitutes for the narcotic analgesic morphine. They are meperidine hydrochloride<sup>1</sup> and ketobemidone hydrochloride.<sup>2</sup>

The synthetic routes are shown in Scheme I. The 3,4,5-trimethoxybenzoic acid (I) was reduced to the corresponding alcohol according to the procedure reported by DiFazio (4). This alcohol was converted to 3,4,5-trimethoxybenzyl chloride (II) following the procedure of Drake and Tuemmler (5). It remained stable without any change in color in an evacuated desiccator over sodium hydroxide pellets for more than 6 months at room temperature, in contrast to a previous report by Tsao (6) that this product slowly darkens even when stored in the refrigerator. Acetone has been reported (4, 7) to be the best of several solvents tried for the conversion of II to 3,4,5-trimethoxyphenylacetone nitrile (III). By reaction in dimethyl sulfoxide (DMSO) at 55–60°, the desired nitrile was obtained in approximately the same yield but the reaction time was decreased from 10 days (acetone) to 3 hr. Alkylation of III followed by treatment of the resulting product with hydrogen chloride gave  $\alpha,\alpha$ -bis(2-dimethylaminoethyl)-(3,4,5-trimethoxyphenyl)acetone nitrile dihydrochloride (IV). Pyrolysis of IV at its melting point to cause evolution of trimethylamine and give the cyclized product V failed. Only a black residue which did not melt when tested up to 350° was obtained. Therefore, III was alkylated with 2,2'-dichloro-*N*-methyldiethylamine to obtain the

cyclized product V. Sodium amide or *n*-butyllithium worked equally well as the base for this condensation reaction.

Hydrolysis of V according to the method reported by Eisleb (8) failed. Several attempts, using either acid or alkali at elevated temperatures under pressure, did not yield the desired product. Finally, refluxing V with an excess of 2.2 *M* ethanolic sulfuric acid for 4 days and then hydrolyzing the imino ester gave the desired ethyl ester VIII. It is known that the carboxyl group on a quaternary carbon atom reacts sluggishly, probably because the alkyl groups dominate so much space in the neighborhood of the carboxyl group that they tend to block the intermediate ionic addition complex (9). Similar steric hindrance of the 4-cyano group in V is the probable reason for the failure in facile hydrolysis of the nitrile. Compound VIII was also prepared by condensation of 2,2'-dichloro-*N*-methyldiethylamine with ethyl 3,4,5-trimethoxyphenylacetate (VII) in the presence of sodium ethoxide.

Compound V reacted with ethylmagnesium bromide only at low temperatures. Addition of ethylmagnesium bromide at 0° and then stirring the reaction mixture at 20° for 24 hr. gave the intermediate ketimine, which finally was hydrolyzed to the corresponding ketone by warming with dilute acid. Similar trials at higher temperatures did not yield any product. It appears, therefore, that the intermediate magnesium adduct of the ketimine is unstable above 20°. A similar observation was reported recently by Muren (10).

## EXPERIMENTAL

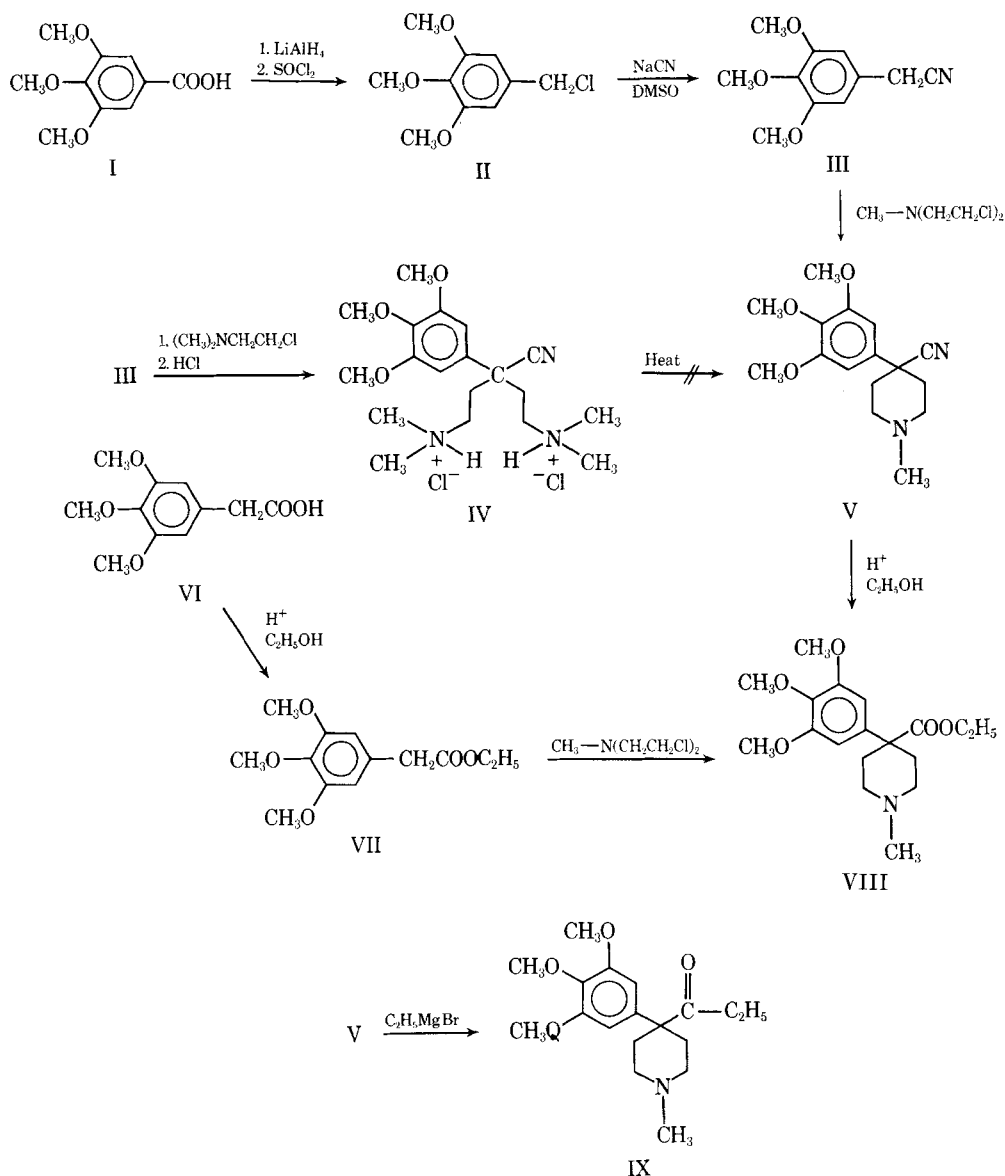
All melting points were determined with a Thomas-Hoover melting-point apparatus and are uncorrected. IR spectra were recorded with Beckman model 8 or Perkin-Elmer 237B grating IR spectrophotometers. NMR spectra were determined with Varian Associates A-60 and A-60D instruments, using tetramethylsilane or 3-(trimethylsilyl)propanesulfonic acid sodium salt as the internal standard. Unless otherwise specified, all NMR spectra were obtained with approximately 15% concentrations; s refers to singlet, d to doublet, t to triplet, q to quadruplet, and m to multiplet. Microanalyses were performed by Micro-Analysis, Inc., Wilmington, Del., and M-H-W Laboratories, Garden City, Mich.

**3,4,5-Trimethoxyphenylacetone nitrile (III)**—3,4,5-Trimethoxybenzyl chloride (II) was prepared according to the method reported by Drake and Tuemmler (5). A mixture of 2.18 g. (0.0101 mole) of II, 0.49 g. (0.010 mole) of sodium cyanide, and 190 ml. of DMSO was heated with magnetic stirring for 3 hr. at 55–60°. Subsequently, the mixture was cooled, diluted with four times its volume of water, and then extracted with three 100-ml. portions of ether. The combined pale-yellow ethereal extracts were washed with 6 *N* hydrochloric acid and with water, and then they were dried over anhydrous magnesium sulfate. Removal of the ether under vacuum yielded a pale-yellow oil, which crystallized upon cooling to provide 1.2 g. (58%) of yellow needles, m.p. 75–76°.

**$\alpha,\alpha$  - Bis(2 - dimethylaminoethyl) - (3,4,5 - trimethoxyphenyl)acetone nitrile dihydrochloride (IV)**—Sodium amide was freshly prepared, starting with 7.5 g. (0.33 g. atom) of sodium and about 400

<sup>1</sup> Marketed as Demerol hydrochloride by Winthrop Laboratories, N. Y.; 4-carbomethoxy-1-methyl-4-phenylpiperidine hydrochloride.

<sup>2</sup> Named Cliradon hydrochloride and used experimentally as an analgesic; ethyl 4-(*m*-hydroxyphenyl)-1-methyl-4-piperidyl ketone hydrochloride.



Scheme 1

ml. of anhydrous liquid ammonia, according to the procedure of Hancock and Cope (11). The ammonia was allowed to evaporate as the reaction flask achieved room temperature. Then 150 ml. of dry benzene and 15 g. (0.072 mole) of III were added. The mixture was stirred with heating for 1 hr. and then was cooled. Next, 21 g. (0.14 mole) of 2-chloro-*N,N*-dimethylethylamine hydrochloride was added with stirring, and the reaction mixture was stirred and heated at reflux for 24 hr. It was cooled, 100 ml. of water was added, and the two layers were separated. The aqueous layer was extracted with benzene. The combined benzene extracts were dried, and the solvent was removed under vacuum to yield a red residue, which was dissolved in anhydrous ether. Dry HCl gas was bubbled into the ethereal solution, whereupon a copious pale-yellow solid precipitated; yield 18.4 g. (60.6%). Decolorization with activated carbon<sup>3</sup> and four recrystallizations from hot absolute ethanol gave a white solid, the dihydrochloride, m.p. 270°.

*Anal.*—Calcd. for C<sub>19</sub>H<sub>31</sub>N<sub>2</sub>O<sub>3</sub>·2HCl: C, 54.03; H, 7.87; Cl, 16.79; N, 9.95; O, 11.36. Found: C, 54.27; H, 7.79; Cl, 16.47; N, 9.83; O, 11.51.

**4-Cyano-4-(3,4,5-trimethoxyphenyl)-1-methylpiperidine (V)**—A mixture of 2.07 g. (0.0100 mole) of III, 1.07 g. (0.0274 mole) of sodium amide,<sup>4</sup> and 1.92 g. (0.0100 mole) of 2,2'-dichloro-*N,N*-

methyldiethylamine hydrochloride (12) in 50 ml. of toluene was refluxed for 12 hr. with stirring. It was cooled and decomposed with water. The organic layer was separated and extracted with three 20-ml. portions of 10% hydrochloric acid. The acidic extracts were combined, made alkaline with 40% aqueous sodium hydroxide solution, and then extracted with ether. After the ethereal layer was dried over magnesium sulfate, the ether was removed under vacuum to obtain 1.5 g. (52%) of V as an oily residue. This was redissolved in ether, and dry hydrogen bromide gas was bubbled in to precipitate a dark solid. This solid was separated and recrystallized four times from hot absolute ethanol with decolorization (Norite) to yield a white granular powder, the hydrobromide of V, m.p. 244.5°. The IR spectrum showed a broad ammonium band (2700–2250 cm.<sup>-1</sup>) and a nitrile peak (2242 cm.<sup>-1</sup>). The NMR spectrum (D<sub>2</sub>O) showed peaks of  $\delta$  values: 2.45 (t, 4 $\beta$ H, piperidine ring); 3.18 (s, 3H, N—CH<sub>3</sub>); 3.60 (t, 4 $\alpha$ H, piperidine ring); 4.0 (d, 9H, methoxys); and 7.05 (s, 2H, aromatic).

*Anal.*—Calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>·HBr: C, 51.76; H, 6.24; Br, 21.52; N, 7.55; O, 12.93. Found: C, 52.42; H, 6.43; Br, 21.36; N, 7.48; O, 12.85.

**4-Carbethoxy-4-(3,4,5-trimethoxyphenyl)-1-methylpiperidine (VIII)**—*Method A*—To an ice-cold solution of 2.9 g. (0.010 mole) of V in 210 ml. of absolute ethanol, previously dried according to the procedure of Vogel (13), was added dropwise 30 ml. of concentrated sulfuric acid. This reaction mixture was stirred mag-

<sup>3</sup> Norite, American Norit Co., Jacksonville, Fla.

<sup>4</sup> Gray powder, Fisher Scientific Co., Fairland, N. J.

netically and heated at reflux for 4 days. After being cooled, it was poured upon 300 g. of ice and the resulting aqueous solution was boiled for 5 hr. and cooled. The solution was made alkaline with 40% aqueous sodium hydroxide solution, and the resulting turbid solution was extracted with ether. The ethereal extract was dried over magnesium sulfate and the ether was removed under vacuum to obtain 1.7 g. (50%) of an oily residue (VIII). The IR spectrum (film) of this oil showed a strong peak for ester carbonyl (1718  $\text{cm}^{-1}$ ), ester C—O—C stretch (1316 and 1066  $\text{cm}^{-1}$ ), and complete absence of any nitrile peak. The NMR spectrum ( $\text{CCl}_4$ ) showed peaks of  $\delta$  values: 1.18 (t, 3H, C—CH<sub>3</sub>); 2.34 (m, 11H, 8 piperidine ring and 3 N—CH<sub>3</sub>); 3.75 (d, 9H, methoxys); 4.12 (q, 2H, CH<sub>2</sub> of ethyl); and 6.64 (s, 2H, aromatic). This oily free base (VIII) was dissolved in dry ether, and dry HCl gas was bubbled in to produce a white granular precipitate. This hydrochloride was separated, decolorized (Norite), and recrystallized twice from absolute ethanol and ether, m.p. 198–199°.

*Anal.*—Calcd. for  $\text{C}_{18}\text{H}_{27}\text{NO}_5 \cdot \text{HCl}$ : C, 57.82; H, 7.55; Cl, 9.48; N, 3.75; O, 21.40. Found: C, 57.83; H, 7.47; Cl, 9.58; N, 3.91; O, 21.28

*Method B*—Sodium ethoxide was prepared by reacting 1.5 g. (0.065 g. atom) of sodium with 100 ml. of absolute ethanol. Most of the alcohol was distilled and 100 ml. of dry toluene was added, of which 50 ml. was distilled to ensure complete removal of ethanol. Then 7.6 g. (0.030 mole) of ethyl 3,4,5-trimethoxyphenylacetate (VII) was added, and the reaction mixture was warmed for 1 hr. and cooled. Next 4.7 g. (0.030 mole) of 2,2'-dichloro-*N*-methyl-diethylamine was added, and the mixture was stirred and heated for 24 hr. under an atmosphere of dry nitrogen. The contents were cooled and diluted with water. The organic layer was separated and extracted with dilute hydrochloric acid. The acidic aqueous layer was made alkaline with 40% sodium hydroxide solution and extracted with ether. The ethereal extract was dried over sodium sulfate, and the ether was evaporated to obtain 3.5 g. (35%) of oily residue (VIII). The IR spectrum of this oil was identical with that of the oily free base obtained by Method A.

**Ethyl 4-(3,4,5-Trimethoxyphenyl)-1-methyl-4-piperidyl Ketone (IX)**—A solution of 0.58 g. (0.0020 mole) of V in 20 ml. of dry benzene was added to a solution of ethylmagnesium bromide prepared by reacting 0.44 g. (0.0040 mole) of ethyl bromide with 0.096 g. (0.0040 g. atom) of magnesium in 10 ml. of dry ether under an atmosphere of dry nitrogen. During the addition, the reaction was maintained at 0° and, after the addition, was stirred for 24 hr. at 20°. The reaction mixture was decomposed with 10 ml. of 3 *N* hydrochloric acid and heated for 1 hr. on a steam bath while the organic layer was allowed to evaporate. The mixture was cooled and made alkaline with 3 *N* sodium hydroxide solution. The resulting turbid solution was extracted with chloroform. The combined extracts were dried and the chloroform was evaporated. The residual oil, on TLC examination (basic alumina; ethyl acetate–benzene, 7:3, as the developing solvent), showed two distinct spots. The spot with the lower  $R_f$  value proved to be the desired ketone

(IX), which was isolated by chromatography using ethyl acetate–benzene (7:3) on a basic alumina<sup>5</sup> column. The eluting solvents were evaporated under reduced pressure; the residual oil, 0.27 g. (42%), was dissolved in minimal ether and treated with ethereal HCl. The precipitate obtained was decolorized (Norite) once and recrystallized twice from chloroform–hexane so as to yield a white fluffy powder, m.p. 226–228° (dec.). The IR spectrum of this hydrochloride showed a broad ammonium band, complete absence of a nitrile band, and the presence of a carbonyl band (1699  $\text{cm}^{-1}$ ). The NMR spectrum of the hydrochloride salt ( $\text{CDCl}_3$ ) showed peaks of  $\delta$  values: 0.93 (t, 3H, CH<sub>3</sub>); 2.55 (m, 13H, 8 piperidine ring, 3 N—CH<sub>3</sub> and 2 CH<sub>2</sub> of ethyl); 3.86 (d, 9H, methoxys); and 6.44 (s, 2H, aromatic).

*Anal.*—Calcd. for  $\text{C}_{18}\text{H}_{27}\text{NO}_4 \cdot \text{HCl}$ : C, 60.41; H, 7.89; N, 3.91. Found: C, 60.56; H, 7.88; N, 4.01.

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<sup>5</sup> Basic Alumina AG10, 100-200 mesh, Bio-Rad Laboratories, Richmond, Calif.