Synthesis of Potential Mescaline Antagonists

FRANK DeSANTIS, Jr.* and KARL A. NIEFORTH

Abstract Mescaline antagonists, potential—synthesized and screened for effect on mescaline-induced CNS stimulation. Antagonists, mescaline, potential—synthesized and screened for effect on mescaline-induced CNS stimulation. Mescaline-induced effect of various mescaline antagonists evaluated. Structure-activity relationships—various mescaline antagonists screened for effect on mescaline-induced CNS stimulation.

The method presently used to counteract the hallucinogenic effects of mescaline (I) and other hallucinogens is administration of drugs that indirectly counteract the hallucinogenic effects, such as tranquilizers and sedatives (1). The object of this research was to synthesize compounds that would antagonize the effects of mescaline through a direct competitive mechanism. The compounds would ideally have little or no effect of their own but, when given in conjunction with mescaline, would mitigate the central nervous system (CNS) stimulation.

It has been well documented that replacement of the

![Structure](attachment:structure.png)

REFERENCES

8. Ibid., 61, 1586 (1972).
13. Ibid., 52, 1145 (1963).

ACKNOWLEDGMENTS AND ADDRESSES

Received February 18, 1975, from the *College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, NY 11439, the **Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada, and the School of Pharmacy, University of Georgia, Athens, GA 30602 Accepted for publication December 10, 1975. *Recipient of a Lederle Pharmacy Faculty Award. To whom inquiries should be directed.
N-methyl group of morphine (VII) with certain short chain alkyl groups produced compounds that acted as antagonists (2). Similar manipulations in the morphinan (VIII) (3–5) and benzomorphan (IX) (6, 7) series also produced narcotic antagonists.

In the amphetamine series (II), compounds more closely related to mescaline, N-allylation produced a compound that antagonized amphetamine-induced motor activity in mice (8). Therefore, the N-n-propyl (IV), N-cyclopropylmethyl (V), and N-allyl (VI) derivatives of mescaline were prepared as potential mescaline antagonists. These three alkyl groups were chosen because small N-alkyl groups generally produced the most active narcotic antagonists (9).

1-[2-(3,4,5-Trimethoxyphenyl)ethyl]-3-pyrroline (X) and 2-(3,4,5-trimethoxybenzyl)-1,2,3,6-tetrahydropyridine (XI), also synthesized, may be considered N-allyl derivatives of mescaline in which the relative spatial position of the double bond of the allyl group is more rigid with respect to nitrogen than in the acyclic amines. Compound XI may also be considered as an N-allyl derivative of 3,4,5-trimethoxyamphetamine (11) in which the double bond of the allyl group is tied back to the methyl group of the isopropyl side chain. Compound XI is a hallucinogen with twice the potency of mescaline (10).

RESULTS AND DISCUSSION

Synthesis—Scheme I was used to prepare the N-n-propyl (IV) and N-cyclopropylmethyl (V) derivatives of mescaline. The procedure of Lundstrom and Agurell (11) was employed to synthesize mescaline (I). Mescaline was acylated with the suitable acid chloride to form amides XI (N-propionyl) and XI (N-cyclopropylcarbonyl). The amides were reduced with lithium aluminum hydride to the secondary amines, IV and V, respectively.

Scheme III was employed for the synthesis of XI. Compound XVI (3,4,5-trimethoxybenzaldehyde) was allowed to react with 2-bromo-1-pyridine in the presence of n-butyllithium to form the corresponding carbinol (XVII). The carbinol was converted with thionyl chloride to the benzyl chloride (XVIII). Compound XVIII was reduced without purification with zinc and acetic acid to 2-(3,4,5-trimethoxybenzyl)-1,2,3,6-tetrahydropyridine (XIX).

Pharmacology—Charles River CD-1 male mice, 4–6 weeks old, were used. All drugs were given as hydrochloride salts dissolved in normal saline and were administered intraperitoneally.

The LD₅₀'s with confidence limits of the test compounds and of mescaline were determined using the procedure of Weil (13) (Table I). Also listed in Table I is the highest dose of each test compound given in this study that did not cause any overt effect (tremors, hyperactivity, or convulsions).
position and was allowed to swim to the ramp. After it climbed onto the ramp, it was lifted from the maze, placed in a sawdust-filled box, and dried by an IR heat lamp located 0.9 m (3 ft) above the box.

A group of mice was trained to swim the maze by conditioning every 2 hr for 2–3 consecutive days. Swimming times and numbers of incorrect turns were recorded. A trained mouse by definition was able to swim the maze in 4–7 sec with no more than one error. Any mouse that did not learn to swim the maze acceptably within 3 days was eliminated.

Table II contains the swim maze results of individual doses of mescaline (75 mg/kg) and the five test compounds (100 mg/kg). Disruption of swim behavior was defined as a significant \( p < 0.05 \) increase in both the average number of seconds and errors generated by a group of mice 20 min after injection of drug as compared to performance 20 min after injection of saline. The data for each group (treatment versus saline) were analyzed using the Student t test. The group of mice given mescaline showed swim behavior disruption and hyperactivity, indicated by an increased exploring tendency. The hindleg scratching response, typical of mescaline, was also present. Compounds IV–VI did not cause disruption of swim behavior, hyperactivity, or scratching. Compounds X and XI disrupted swim behavior and produced signs of hyperactivity without scratching.

The effect of each test compound on swim behavior when given with mescaline is described in Table III. Disruption of swim behavior was defined as before. Antagonism of mescaline-induced disruption of swim behavior was measured by a significant \( p < 0.05 \) decrease in both the average number of seconds and errors generated by a group of mice 20 min after injection of mescaline plus test compound compared to performance 20 min after injection of mescaline alone (Table III). The Student t test was again used to analyze the data (mescaline plus test compound versus saline and versus mescaline).

Of the compounds that did not disrupt swim behavior, IV and VI

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**Table II—Effect of Mescaline and Test Compounds on Mouse Swim Behavior**

<table>
<thead>
<tr>
<th>Compound</th>
<th>n</th>
<th>Dose of Compound, mole/kg (mg/kg)</th>
<th>Performance 20 min after Saline</th>
<th>Performance 20 min after Compound</th>
<th>t Test f</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time d</td>
<td>Errors e</td>
<td>Time d</td>
</tr>
<tr>
<td>I</td>
<td>20</td>
<td>3.08 x 10^-4, (75)</td>
<td>7.10 ± 0.50</td>
<td>0.65 ± 0.15</td>
<td>22.9 ± 6.00</td>
</tr>
<tr>
<td>IV</td>
<td>13</td>
<td>3.47 x 10^-4 (100)</td>
<td>8.81 ± 0.72</td>
<td>0.92 ± 0.20</td>
<td>7.77 ± 0.61</td>
</tr>
<tr>
<td>V</td>
<td>13</td>
<td>3.47 x 10^-4 (100)</td>
<td>7.42 ± 0.66</td>
<td>0.46 ± 0.17</td>
<td>7.27 ± 0.60</td>
</tr>
<tr>
<td>VI</td>
<td>13</td>
<td>3.33 x 10^-4 (100)</td>
<td>6.96 ± 0.36</td>
<td>0.38 ± 0.17</td>
<td>7.23 ± 0.49</td>
</tr>
<tr>
<td>X</td>
<td>13</td>
<td>3.34 x 10^-4 (100)</td>
<td>5.88 ± 0.24</td>
<td>0.08 ± 0.09</td>
<td>11.23 ± 1.55</td>
</tr>
<tr>
<td>XI</td>
<td>13</td>
<td>3.34 x 10^-4 (100)</td>
<td>5.88 ± 0.29</td>
<td>0.31 ± 0.13</td>
<td>34.30 ± 10.1</td>
</tr>
</tbody>
</table>

aNumber of animals in group. bWeight based on hydrochloride salt. cEach animal was given a volume of saline equal to the volume of drug it would receive. dAverage number of seconds ± SE for group of mice to swim maze. eAverage number of errors ± SE made by group of mice in that period of time. fStudent t test to compare saline versus drug; S (p < 0.05) means disruption in swim behavior, and IS (p > 0.2) means no disruption in swim behavior.

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Figure 1—Swimming maze.
Table III—Effect of Test Compounds on Mescaline-Induced Disruption of Mouse Swim Behavior

<table>
<thead>
<tr>
<th>Compound</th>
<th>Performance 20 min after Saline</th>
<th>Performance 20 min after Mescaline plus Test Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time</td>
<td>Errors</td>
</tr>
<tr>
<td>IV</td>
<td>13</td>
<td>6.00 ± 0.36</td>
</tr>
<tr>
<td>VI</td>
<td>13</td>
<td>6.23 ± 0.33</td>
</tr>
<tr>
<td>X</td>
<td>11</td>
<td>5.20 ± 0.36</td>
</tr>
<tr>
<td>XI</td>
<td>13</td>
<td>6.04 ± 0.19</td>
</tr>
</tbody>
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<th>Performance 20 min after Saline</th>
<th>Performance 20 min after Mescaline plus Test Compound</th>
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<td>X</td>
<td>11</td>
<td>5.20 ± 0.36</td>
</tr>
<tr>
<td>XI</td>
<td>13</td>
<td>6.04 ± 0.19</td>
</tr>
</tbody>
</table>

a Number of animals in group. b Each animal was given a total volume of saline in one dose that equaled the total volume of test compound and mescaline it would receive. c Average number of seconds by mescaline effect on mescaline response. d Number of seconds ± SE made by group of mice in that period of time. e Each animal was first given the test compound (100 mg/kg as hydrochloride salt) followed immediately by mescaline (75 mg/kg as hydrochloride salt). f Student t test comparing saline versus mescaline + test compound; S (p < 0.05) means disruption by mescaline and S (p > 0.2) means no disruption in swim behavior. g Student t test comparing mescaline + test compound; S (p < 0.05) means antagonism of mescaline response, p < 0.1 means a lowering of mescaline response, and 1.5 (p > 0.2) means no effect on mescaline response.

were the only ones that reduced the mescaline-induced disruption of swim behavior. Compound VI appeared more effective than IV since there was no significant difference in swim behavior of the test animals dosed with saline and the swim behavior of the same animals subsequently dosed with mescaline plus VI (Table III). On the other hand, there was a slight increase in swim behavior when comparing mescaline plus IV to saline, but the disruption was not as great as with mescaline alone. Also, the group of mice that received mescaline plus VI showed no signs of scratching, while the group that received mescaline plus IV did exhibit the hindleg scratch response.

Compound V, when given alone, showed no disruption of swim behavior (Table II). However, when given with mescaline, V was not capable of reducing the mescaline response. The hindleg scratching response also was observed when V was given with mescaline. Compounds X and XI did not reduce the mescaline response as was anticipated since both compounds disrupted mouse swim behavior when given alone. The group of mice receiving X plus mescaline exhibited the hindleg scratch response of mescaline. However, the group of mice receiving XI plus mescaline did not exhibit this response.

Other studies will have to be completed to demonstrate that N-allyl- (VI) and N-propylmescaline (IV) antagonize the hallucinogenic as well as the swim maze effects of mescaline. Recently, Pinder et al. (15) reported excellent correlation between induced hyperthermia in rabbits and psychotomimetic activity in humans. Although similar correlations were described previously, there is still no test system that suitably defines hallucinogenic potency in animals as related to humans.

**EXPERIMENTAL**

**N-Propionylmescaline (XII)**—In a three-necked flask fitted with a mechanical stirrer, dropping funnel, and reflux condenser equipped with a drying tube were placed 6.3 g (0.0284 mole) of I and 3.14 g (0.0284 mole) of lithium aluminum hydride and 30 ml of anhydrous tetrahydrofuran. The mixture was stirred and heated to reflux as 5.0 g (0.0277 mole) of XII dissolved in 50 ml of anhydrous tetrahydrofuran was added dropwise (Scheme I). After addition, the reaction mixture was stirred and refluxed overnight. After cooling to room temperature, the reaction was quenched with successive addition of 1.6 ml of water, 1.3 ml of 20% NaOH, and 5.8 ml of water.

The white precipitate which formed was removed by filtration and washed with additional tetrahydrofuran. The combined filtrate and washings were concentrated in vacuo. The oily residue was dissolved in ether, dried over anhydrous sodium sulfate, and filtered. Hydrogen chloride gas was bubbled into the ether solution to form the hydrochloride salt. The precipitate was filtered to yield a semisolid residue of an amino group, and a peak at 3320 cm⁻¹, indicative of a carbonyl group of an amide.

**N-Cyclopropylcarbonylmescaline (XIII)**—The procedure used to make XII was followed for the synthesis of similar compounds of XIII (Scheme I). Compound XIII was prepared in 93% yield, mp 96-98°, after recrystallization from benzene-petroleum ether (1:1). The IR spectrum showed a peak at 3310 cm⁻¹, indicative of an amino group, and a peak at 1620 cm⁻¹, indicative of a carbonyl group of an amide.

**N-Propylmescaline Hydrochloride (IV)**—In a three-necked flask fitted with a mechanical stirrer, dropping funnel, and reflux condenser equipped with a drying tube were placed 3.0 g (0.1496 mole) of lithium aluminum hydride and 50 ml of anhydrous tetrahydrofuran. The mixture was stirred and heated to reflux as 5.0 g (0.0277 mole) of XII dissolved in 50 ml of anhydrous tetrahydrofuran was added dropwise (Scheme I). After addition, the reaction mixture was stirred and refluxed overnight. After cooling to room temperature, the reaction was quenched with successive addition of 1.6 ml of water, 1.3 ml of 20% NaOH, and 5.8 ml of water.

The white precipitate which formed was removed by filtration and washed with additional tetrahydrofuran. The combined filtrate and washings were concentrated in vacuo. The oily residue was dissolved in ether, dried over anhydrous sodium sulfate, and filtered. Hydrogen chloride gas was bubbled into the ether solution to form the hydrochloride salt. The precipitate was filtered to yield 2.1 g (39%) of IV as the hydrochloride. After recrystallization from ethyl acetate-ethanol (1:1), the melting point of the product was 174-175°. The IR spectrum showed a broad peak from 2750 to 2500 cm⁻¹, indicative of NH₂⁺. The NMR spectrum (dimethyl sulfoxide-d₆) showed peaks at δ 0.8 (t, 3H, methyl), 1.6 (m, 2H, methylene α to methyl), 2.5-3.2 (b, 6H, benzyl), and 3.5 (a, 3H, p-methoxy), 3.7 (s, 6H, m-methoxy), 6.5 (s, 2H, aromatic), and 9.3 (b, 2H, NH₂⁻).

**N-Cyclopropylmethylmescaline Hydrochloride (V)**—The procedure used to prepare IV was followed for the synthesis of similar quantities of V (Scheme D). Compound V was prepared in 34% yield, mp 185-187°, after recrystallization from ethyl acetate-ethanol (1:1). The IR spectrum showed a broad peak from 2750 to 2400 cm⁻¹, indicative of NH₂⁺. The NMR spectrum (dimethyl sulfoxide-d₆) showed peaks at δ 0.4 (b, 4H, cyclopropyl methylene), 1.1 (m, 1H), 1.8-2.2 (b, 6H, aromatic), and 3.6 (b, 3H, p-methoxy), 3.8 (s, 6H, m-methoxy), 6.6 (s, 2H, aromatic), and 9.4 (b, 2H, NH₂⁻).

**N-[2-(3,4,5-Trimethoxyphenethyl)ethyl] p-Toluenesulfonate (XIV)**—In a three-necked flask fitted with a condenser, drying tube, and mechanical stirrer was placed 3.5 g (0.0165 mole) of 2-(3,4,5-trimethoxyphenethyl)ethanol (XIV) and 5.2 g (0.066 mole) of pyridine (Scheme II). The solution was stirred and cooled on an ice–salt bath until a yellow solid of 2-(3,4,5-trimethoxyphenethyl)ethanol was precipitated. After addition, the mixture was stirred on the ice bath for 1 hr.
The mixture was then diluted with 20 ml of cold 10% HCl and filtered, and the filter cake was washed with excess 10% HCl to yield 4.7 g (85%) of crude product, mp 88-91°. Recrystallization from ethanol gave the product, mp 92-93°. The NMR spectrum (CDCl₃) showed peaks at δ 2.4 (s, 3H, CH₃), 2.9 (t, 2H, benzylic), 3.8 (2s, 9H, methoxy), 4.2 (2H, aromatic), 6.3 (2s, 2H, phenyl), and 7.5 (2d, 4H, tolylic aromatic). Anal.—Calc. for C₂₃H₂₂O₇: C, 56.35; H, 4.35; N, 3.30.

N-Allylcysteine Hydrochloride (VI)—In a three-necked flask fitted with a reflux condenser, drying tube, and mechanical stirrer, 4.0 g (0.0109 mole) of XV and 75 ml of allylamine (Scheme II). The solution was stirred and refluxed for 2 hr. After cooling to room temperature, the solution was concentrated in vucuo. To the residue was added 50 ml of ether, and the insoluble matter was filtered. The ether layer was then dried over anhydrous sodium sulfate and filtered.

Hydrogen chloride gas was passed through the ether solution to yield the hydrochloride salt, which was collected and recrystallized from ethanol-ethyl acetate (1:1). The yield of product was 1.2 g (42%), mp 172-173°. The IR spectrum showed a broad peak from 2850 to 2350 cm⁻¹, indicative of NH₃⁺. The NMR spectrum (dimethyl sulfoxide-d₆) showed peaks at δ 3.1-3.8 (b, 6H, methylene), 3.6 (3H, p-methoxy), 3.8 (2s, 6H, m-methoxy), 5.3 (2H, vinylic), 5.8 (ms, 1H, CH₃), 6.5 (s, 2H, aromatic), and 9.6 (b, 2H, NH₂).

Anal.—Calc. for C₂₃H₂₂O₇N₂: C, 59.95; H, 6.05. Found: C, 59.4; H, 6.05.

N-Allylcysteine Hydrochloride (VI)—In a three-necked flask fitted with a reflux condenser, drying tube, and mechanical stirrer, 4.0 g (0.0109 mole) of XV and 75 ml of allylamine (Scheme II). The solution was stirred and refluxed for 2 hr. After cooling to room temperature, the solution was concentrated in vucuo. To the residue was added 50 ml of ether, and the insoluble matter was filtered. The ether layer was then dried over anhydrous sodium sulfate and filtered.

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Anal.—Calc. for C₂₃H₂₂O₇N₂: C, 59.95; H, 6.05. Found: C, 59.4; H, 6.05.

3,4,5-Trimethoxyphenyl-2-pyridylcarbinol (XVI) was prepared for chemical analysis and had a melting point of 168.5-170°. This solution was cooled to 0°, and 10.0 g (0.025 mole) of XX in anhydrous methanol (33% v/v) was added at 0° (Scheme III). After addition, the solution was stirred for an additional 0.5 hr. A 100-ml portion of water was then added, and the mixture was extracted with three 50-ml portions of chloroform. The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vucuo to yield 6.0 g (87%) of product, bp 154-155°/0.27 mm. The NMR spectrum (CDCl₃) showed peaks at δ 2.0 (m, 2H, 3CH₂), 2.3 (m, 1H, 2CH), 2.4 (s, 3H, methyl), 2.7 (m, 2H, benzylic), 3.0 (2H, 6H, 2CH, and 5CH), and 8.5 (d, 1H, 6CH). The methiodide salt was used for analytical purposes and also in subsequent reactions. The salt was prepared by dissolving the free amine (XIX) in methanol (approximately 15-20 times the weight of the free amine), and to this mixture was added methyl iodide (~2.5 times the weight of the free amine). The solution was then stirred at room temperature for 1 hr, followed by refluxing for 2 hr. After cooling to room temperature, the solution was concentrated in vucuo, yielding a solid (XX) which was recrystallized from acetone. The yield of product varied from 64 to 71%, mp 151-153°.

Anal.—Calc. for C₂₃H₂₆N₄O₁₀: C, 52.17; H, 5.17; N, 11.06. Found: C, 51.90; H, 5.15; N, 10.90.

3,4,5-Trimethoxyphenyl-2-pyridylcarbinol (XVI)—In a 1-liter three-necked flask, placed in an acetone-dry ice bath under nitrogen atmosphere and fitted with a mechanical stirrer, dropping funnel, and drying tube, under nitrogen atmosphere, 3.45 g (0.0109 mole) of XXI and 3.45 g (0.05 mole) of 3-pyrrolidine was added dropwise through the dropping funnel. After addition, the dark-red mixture which formed was stirred at that temperature for 1 hr. After addition, the resultant reddish solution was warmed to room temperature for 1 hr, followed by refluxing for 2 hr. After cooling to room temperature, the mixture was filtered of inorganic salts and the solution was concentrated in vucuo. To the residue was added 75 ml of 25% NaOH, and the resultant aqueous mixture was extracted with three 50-ml portions of chloroform. The organic extract was combined, dried over anhydrous sodium sulfate, filtered, and evaporated in vucuo. The residue was distilled, yielding 11.5 g (47%) of XIX, bp 167-169°/0.2 mm. The NMR spectrum (CDCl₃) showed peaks at δ 3.8 (s, 9H, methoxy), 4.1 (2H, benzyl), 6.5 (s, 2H, aromatic), 7.0-7.8 (m, 3H, 3CH, 4CH, and 5CH), and 8.5 (d, 1H, 6CH).

The methiodide salt was used for analytical purposes and also in subsequent reactions. The salt was prepared by dissolving the free amine (XIX) in methanol (approximately 15-20 times the weight of the free amine), and to this mixture was added methyl iodide (~2.5 times the weight of the free amine). The solution was then stirred at room temperature for 1 hr, followed by refluxing for 2 hr. After cooling to room temperature, the solution was concentrated in vucuo, yielding a solid (XX) which was recrystallized from acetone. The yield of product varied from 64 to 71%, mp 151-153°.

Anal.—Calc. for C₂₃H₂₆N₄O₁₀: C, 52.17; H, 5.17; N, 11.06. Found: C, 51.90; H, 5.15; N, 10.90.
Dissolution Behavior and Bioavailability of Phenytoin from a Ground Mixture with Microcrystalline Cellulose

KEIJI YAMAMOTO *, MASAIRO NAKANO *, TAKAICHI ARITA **, YOSHIKAZU TAKAYAMA *, and YOSINOBU NAKAI 

**Abstract** The ground mixture of phenytoin and microcrystalline cellulose was prepared by grinding in a vibrational ball mill. The X-ray diffraction patterns indicated the amorphous nature of the ground mixture. Comparative studies were made concerning the in vitro dissolution and in vivo absorption of fine phenytoin powder, phenytoin sodium powder, and the ground mixture. The ground mixture showed a greater dissolution rate than the fine powder and attained supersaturation in the pharmaceutical disintegration media at pH 1.2 and 7.4. In vivo absorption studies of each preparation were carried out in five subjects, using a crossover design, by measuring the urinary excretion rate of a main metabolite, 5-(p-hydroxyphenyl)-5-phenylhydantoin. The blood levels of phenytoin and the corresponding urinary excetration patterns of the metabolite were determined in two subjects. The ground mixture signficantly improved the bioavailability of phenytoin. The drug was completely and rapidly absorbed after oral administration of the ground mixture. The vibrational ball milling technique for a poorly water-soluble drug with microcrystalline cellulose provides a promising way of improving the in vivo drug absorption.

**Keyphrases** Phenytoin—dissolution and bioavailability, ground mixture with microcrystalline cellulose compared to fine powder. Dissolution—phenytoin, ground mixture with microcrystalline cellulose. Bioavailability—phenytoin, ground mixture with microcrystalline cellulose. Dosage forms—phenytoin and microcrystalline cellulose ground mixture, dissolution and bioavailability, compared to fine powder. Cellulose, microcrystalline—ground mixture with phenytoin, effect on dissolution and bioavailability. Anticonvulsant agents—phenytoin, dissolution and bioavailability, ground mixture with microcrystalline cellulose.