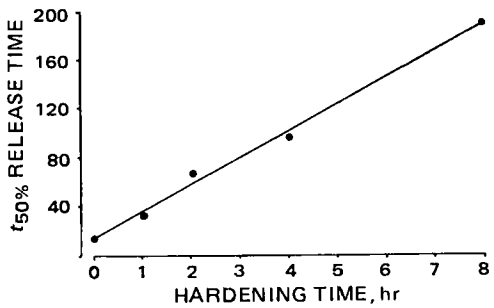


**Figure 8**—*The $t_{50\%}$ release time as a function of hardening time of the microcapsules.*

## SUMMARY AND CONCLUSIONS

This study was undertaken to investigate the feasibility of microencapsulation of clofibrate, to collect the microcapsules in the form of a free-flowing powder, and to evaluate the dissolution characteristics of the microcapsules obtained. From the results, the following conclusions are drawn:

1. Microencapsulation of clofibrate can be successfully achieved by simple coacervation.
2. Free-flowing discrete microcapsules can be obtained by treatment with 2-propanol.
3. After an initial surge, dissolution of clofibrate from microcapsules under sink conditions followed apparent zero-order release rates until nearly 90% of the drug was released. The dissolution pattern observed can be explained by a model in which the capsule wall limits dissolution from a saturated solution of the clofibrate formed inside the microcapsule.
4. The release rates of the microcapsules were related directly to the hardening time of the microcapsules. A linear correlation was found between the hardening time and the *in vitro* $t_{50\%}$ release time of the microcapsules.
5. Hardening of microcapsules up to 8 hr did not result in a loss of clofibrate, but longer hardening times caused rupture of some of the microcapsules with subsequent loss of clofibrate.

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ˣ To whom inquiries should be directed.

# Synthesis of Potential Mescaline Antagonists

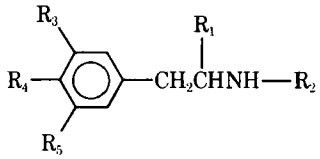
**FRANK DeSANTIS, Jr. *, and KARL A. NIEFORTH ˣ**

**Abstract** □ 1-[2-(3,4,5-Trimethoxyphenyl)ethyl]-3-pyrroline, 2-(3,4,5-trimethoxybenzyl)-1,2,3,6-tetrahydropyridine, *N*-*n*-propylmescaline, *N*-cyclopropylmethylmescaline, and *N*-allylmescaline were synthesized as potential mescaline antagonists. The ability of these compounds to antagonize mescaline-induced disruption of swim behavior is also given.

**Keyphrases** □ 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 □ 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




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

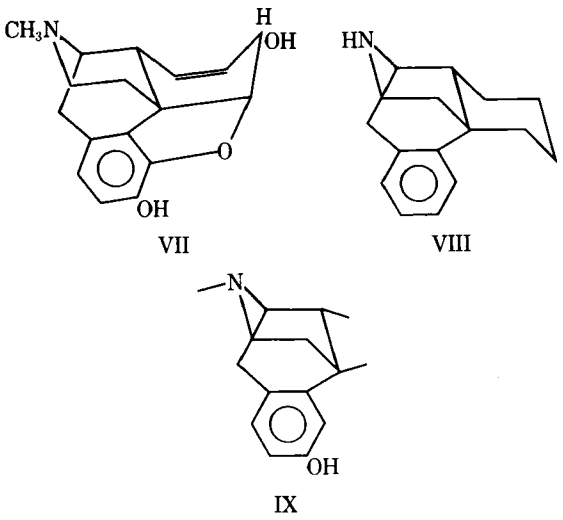
II: $R_1 = CH_3$, $R_2 = R_3 = R_4 = R_5 = H$

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

IV: $R_1 = H$, $R_2 = n\text{-}C_3H_7$, $R_3 = R_4 = R_5 = OCH_3$

V: $R_1 = H$, $R_2 = CH_2$—  , $R_3 = R_4 = R_5 = OCH_3$

VI: $R_1 = H$, $R_2 = CH_2$—$CH$=$CH_2$, $R_3 = R_4 = R_5 = OCH_3$



VII VIII

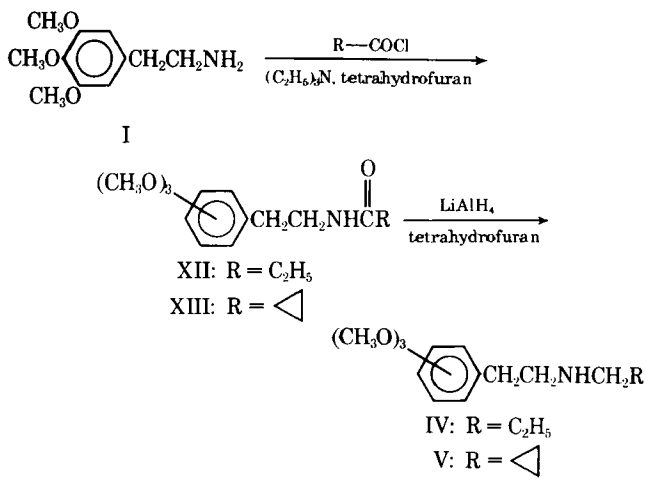


IX

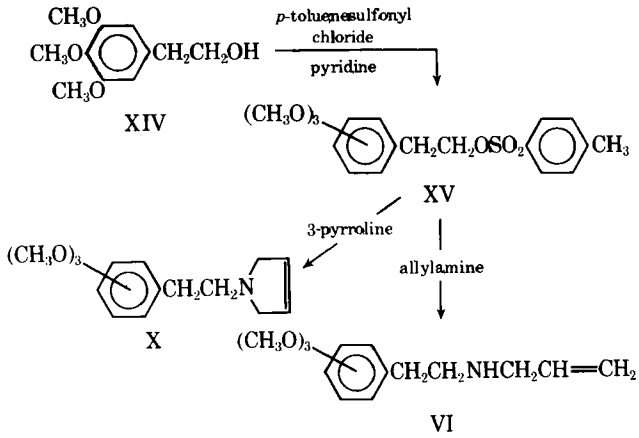
*N*-methyl group of morphine (VII) with certain short chain alkyl groups produced compounds that acted as antagonists (2). Similar manipulations in the morphinan (VIII) (3–5) and benzomorphan (IX) (6, 7) series also produced narcotic antagonists.

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 (III) in which the double bond of the allyl group is tied back to the methyl group of the isopropyl side chain. Compound III is a hallucinogen with twice the potency of mescaline (10).




*Scheme I*




*Scheme II*

## 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 XII (*N*-propionyl) and XIII (*N*-cyclopropylcarbonyl). The amides were reduced with lithium aluminum hydride to the secondary amines, IV and V, respectively.

Compounds VI and X were synthesized by utilizing Scheme II. 2-(3,4,5-Trimethoxyphenyl)ethanol (XIV), which was previously prepared (12), was converted to the *p*-toluenesulfonate ester (XV). Compounds VI and X were synthesized by displacing the *p*-toluenesulfonate of XV with allylamine and 3-pyrroline, respectively.

Scheme III was utilized for the synthesis of XI. Compound XVI (3,4,5-trimethoxybenzaldehyde) was allowed to react with 2-bromopyridine 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)-pyridine (XIX).

Compound XIX was converted to the methiodide salt (XX) and reduced with sodium borohydride to *N*-methyl-2-(3,4,5-trimethoxybenzyl)-1,2,3,6-tetrahydropyridine (XXI). Compound XXI was *N*-demethylated by initial reaction with 2,2,2-trichloroethyl chloroformate and subsequent reduction of the resultant unisolated carbamate (XXII) with zinc and acetic acid to XI.

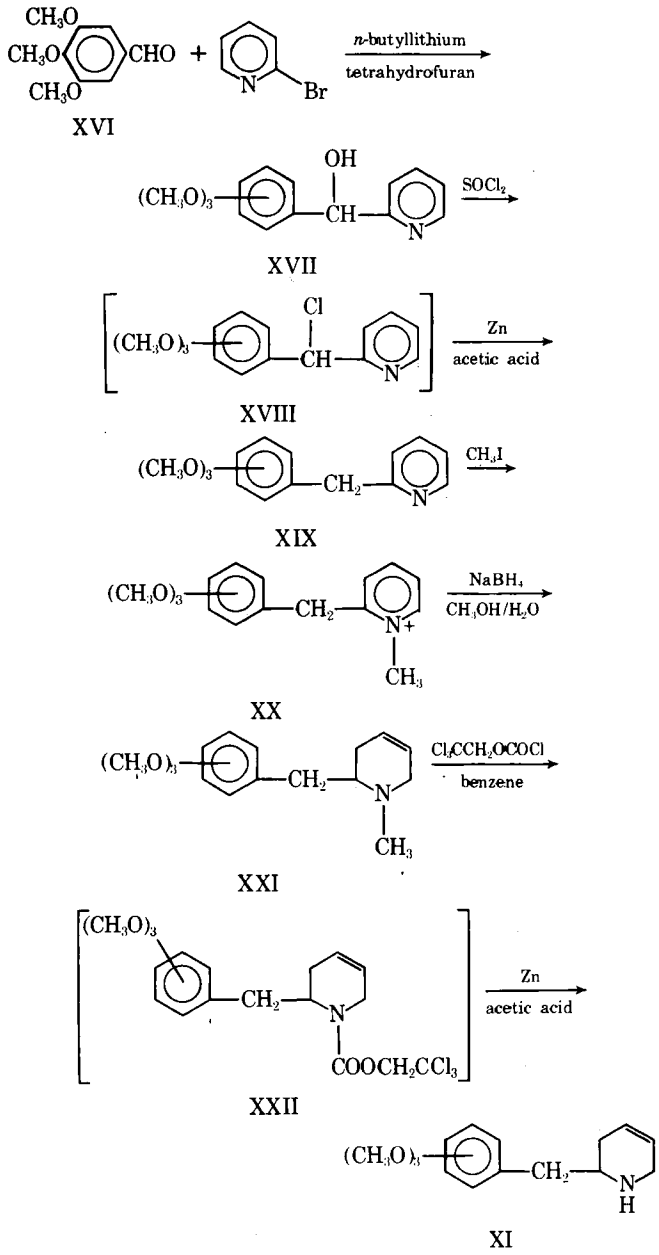
**Pharmacology**—Charles River CD-1 male mice, 4–6 weeks old, were used. All drugs were given as hydrochloride salts dissolved in normal saline and were administered intraperitoneally.

The $LD_{50}$'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).

The ability of the test compounds to antagonize mescaline-induced disruption of swim behavior was determined by the use of the swimming maze outlined in Fig. 1 (14). The maze was constructed of Plexiglas and painted black on the outside. The walls of the maze were 25.4 cm (10 in.) high, and the maze was filled with water at 30° to a depth of 10.2 cm (4 in.). A mouse was placed in the water at the "start"

**Table I—Toxicity Study of Mescaline and Synthetic Derivatives**

| Compound | $LD_{50}$ with Confidence Limit ($p$ = 0.05), mg/kg | Highest Dose without Overt Effects, mg/kg |
|---|---|---|
| I | 346 (292–410) | — |
| IV | 450 (418–484) | 150 |
| V | 399 (366–475) | 150 |
| VI | 363 (323–408) | 100 |
| X | 346 (292–410) | 100 |
| XI | 238 (218–261) | 100 |




XVI XVII XVIII XIX XX XXI XXII XI

*Scheme III*

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.

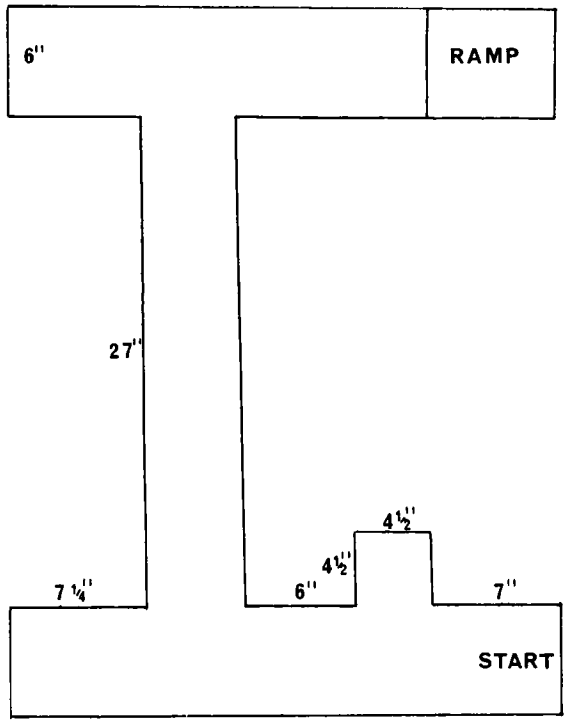



**Figure 1**—*Swimming maze.*

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 as 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

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

| Compound | $n$[a] | Dose of Compound, mole/kg (mg/kg)[b] | Performance 20 min after Saline[c] Time[d] | Performance 20 min after Saline[c] Errors[e] | Performance 20 min after Compound Time[d] | Performance 20 min after Compound Errors[e] | $t$ Test[f] Time | $t$ Test[f] Errors |
|---|---|---|---|---|---|---|---|---|
| I | 20 | $3.03 \times 10^{-4}$ (75) | 7.10 ± 0.50 | 0.65 ± 0.15 | 22.9 ± 6.00 | 3.30 ± 1.01 | S | S |
| IV | 13 | $3.47 \times 10^{-4}$ (100) | 8.81 ± 0.72 | 0.92 ± 0.20 | 7.77 ± 0.61 | 0.69 ± 0.20 | IS | IS |
| V | 13 | $3.47 \times 10^{-4}$ (100) | 7.42 ± 0.66 | 0.46 ± 0.17 | 7.27 ± 0.60 | 0.54 ± 0.21 | IS | IS |
| VI | 13 | $3.33 \times 10^{-4}$ (100) | 6.96 ± 0.36 | 0.38 ± 0.17 | 7.23 ± 0.49 | 0.62 ± 0.21 | IS | IS |
| X | 13 | $3.34 \times 10^{-4}$ (100) | 5.88 ± 0.24 | 0.08 ± 0.09 | 11.23 ± 1.55 | 1.46 ± 0.38 | S | S |
| XI | 13 | $3.34 \times 10^{-4}$ (100) | 5.88 ± 0.29 | 0.31 ± 0.13 | 34.30 ± 10.1 | 14.5 ± 1.41 | S | S |

[a] Number of animals in group. [b] Weight based on hydrochloride salt. [c] Each animal was given a volume of saline equal to the volume of drug it would receive. [d] Average number of seconds ± $SE$ for group of mice to swim maze. [e] Average number of errors ± $SE$ made by group of mice in that period of time. [f] Student $t$ 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.

**Table III—Effect of Test Compounds on Mescaline-Induced Disruption of Mouse Swim Behavior**

| Compound | $n^a$ | Performance 20 min after Saline[b] | | Performance 20 min after Mescaline plus Test Compound | | *t* Test[f] | | *t* Test[g] | |
|---|---|---|---|---|---|---|---|---|---|
| | | Time[c] | Errors[d] | Time[c] | Errors[d] | Time | Errors | Time | Errors |
| IV | 13 | 6.00 ± 0.36 | 0.08 ± 0.02 | 11.38 ± 2.30 | 1.08 ± 0.02 | S | S | $p < 0.1$ | $p < 0.1$ |
| V | 13 | 6.23 ± 0.33 | 0.15 ± 0.24 | 16.31 ± 4.90 | 1.38 ± 0.49 | $p < 0.1$ | S | IS | $p < 0.1$ |
| VI | 13 | 7.00 ± 0.58 | 0.69 ± 0.25 | 8.73 ± 1.69 | 0.69 ± 0.30 | IS | IS | S | S |
| X | 11 | 5.20 ± 0.36 | 0.31 ± 0.13 | 25.18 ± 6.15 | 2.55 ± 0.81 | S | S | IS | IS |
| XI | 13 | 6.04 ± 0.19 | 0.08 ± 0.07 | 20.04 ± 6.39 | 1.92 ± 0.91 | S | S | IS | IS |

[a] Number of animals in group. [b] Each animal was given a total volume of saline in one dose that equalled the total volume of test compound and mescaline it would receive. [c] Average number of seconds ± *SE* for group of mice to swim maze. [d] Average number of errors ± *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 in swim behavior, and IS ($p > 0.2$) means no disruption in swim behavior. [g] Student *t* test comparing mescaline *versus* mescaline + test compound; S ($p < 0.05$) means antagonism of mescaline response, $p < 0.1$ means a lowering of mescaline response, and IS ($p > 0.2$) 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 significant disruption of 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*-*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 hallucinogen potency in animals as related to humans.

## EXPERIMENTAL[1]

***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 (0.031 mole) of triethylamine dissolved in anhydrous tetrahydrofuran (Scheme I). To this solution was added dropwise 2.86 g (0.031 mole) of propionyl chloride dissolved in 20 ml of anhydrous tetrahydrofuran with stirring on an ice bath. A white precipitate began to form immediately. After addition was complete, the mixture was stirred for 1 hr at room temperature.

The white precipitate was then removed by filtration and washed with two 20-ml portions of tetrahydrofuran. The combined filtrate and washings were concentrated *in vacuo* to yield a semisolid residue which solidified upon addition of petroleum ether. The solid was collected and recrystallized from hexane to yield 6.5 g (85%) of product, mp 70–72°. The IR spectrum showed a peak at 3320 $cm^{-1}$, indicative of an amino group, and a peak at 1640 $cm^{-1}$, indicative of a carbonyl group of an amide.

*Anal.*—Calc. for $C_{14}H_{21}NO_4$: C, 62.89; H, 7.92; N, 5.24. Found: C, 62.76; H, 7.91; N, 5.00.

***N*-Cyclopropylcarbonylmescaline (XIII)**—The procedure used to make XII was followed for the synthesis of similar quantities of XIII (Scheme I). Compound XIII was prepared in 53% 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.

*Anal.*—Calc. for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.53; N, 5.02. Found: C, 64.89; H, 7.51; N, 4.83.

***N*-*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 3.00 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 (0.0187 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 dropwise additions 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 2450 $cm^{-1}$, indicative of $NH_2^+$. The NMR spectrum (dimethyl sulfoxide-$d_6$) showed peaks at $\delta$ 0.8 (t, 3H, methyl), 1.6 (m, 2H, methylene $\alpha$ to methyl), 2.5–3.2 (b, 6H, benzylic and two methylenes $\alpha$ to nitrogen), 3.5 (s, 3H, *p*-methoxy), 3.7 (s, 6H, *m*-methoxy), 6.5 (s, 2H, aromatic), and 9.3 (b, 2H, $NH_2^+$).

*Anal.*—Calc. for $C_{14}H_{24}ClNO_3$: C, 58.02; H, 8.35; N, 4.83. Found: C, 57.87; H, 8.19; N, 4.84.

***N*-Cyclopropylmethylmescaline Hydrochloride (V)**—The procedure used to prepare IV was followed for the synthesis of similar quantities of V (Scheme I). 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 $NH_2^+$. The NMR spectrum (dimethyl sulfoxide-$d_6$) showed peaks at $\delta$ 0.4 (b, 4H, cyclopropyl methylenes), 1.1 (m, 1H, CH), 2.6–3.2 (b, 6H, benzylic and two methylenes $\alpha$ to nitrogen), 3.6 (s, 3H, *p*-methoxy), 3.8 (s, 6H, *m*-methoxy), 6.6 (s, 2H, aromatic), and 9.4 (b, 2H, $NH_2^+$).

*Anal.*—Calc. for $C_{15}H_{24}ClNO_3$: C, 59.69; H, 8.02; N, 4.64. Found: C, 59.54; H, 7.86; N, 4.50.

**2-(3,4,5-Trimethoxyphenyl)ethyl *p*-Toluenesulfonate (XV)**—In a three-necked flask fitted with a condenser, drying tube, and mechanical stirrer were placed 3.5 g (0.0165 mole) of 2-(3,4,5-trimethoxyphenyl)ethanol (XIV) and 5.2 g (0.066 mole) of pyridine (Scheme II). The solution was stirred and cooled on an ice–salt bath while 3.0 g (0.0182 mole) of *p*-toluenesulfonyl chloride was added in small portions. After addition, the mixture was stirred on the ice bath for 1 hr.

[1] IR spectra were determined on a Beckman Microspec model 1485 using potassium bromide pellets for solids and neat for liquids. NMR spectra were determined on the Hitachi Perkin-Elmer model R-24 spectrometer using tetramethylsilane as the internal standard when deuterochloroform was the solvent and as an external standard when deuterodimethyl sulfoxide was the solvent. The letter abbreviations used are: s, singlet; 2s, two singlets; d, doublet; 2d, two doublets; t, triplet; m, multiplet; and b, broad. Mass spectra were determined using an A.E.I. Scientific Mg-902 double-focusing spectrometer. Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Microanalyses were performed by Baron Consulting Co., Orange, Conn.

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 ($CDCl_3$) showed peaks at δ 2.4 (s, 3H, $CH_3$), 2.9 (t, 2H, benzylic), 3.8 (2s, 9H, methoxy), 4.2 (t, 2H, methylene), 6.3 (s, 2H, phenyl), and 7.5 (2d, 4H, tolyl aromatic).

*Anal.*—Calc. for $C_{18}H_{22}O_6S$: C, 58.99; H, 6.05. Found: C, 59.34; H, 6.05.

***N*-Allylmescaline Hydrochloride (VI)**—In a three-necked flask fitted with a reflux condenser, drying tube, and mechanical stirrer were placed 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 vacuo*. 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 1.3 g (42%), mp 172–173°. The IR spectrum showed a broad peak from 2850 to 2350 $cm^{-1}$, indicative of $NH_2^+$. The NMR spectrum (dimethyl sulfoxide-$d_6$) showed peaks at δ 3.1–3.8 (b, 6H, methylenes), 3.6 (s, 3H, *p*-methoxy), 3.8 (s, 6H, *m*-methoxy), 5.3 (m, 2H, vinylic methylene), 5.8 (m, 1H, CH), 6.5 (s, 2H, aromatic), and 9.6 (b, 2H, $NH_2$).

*Anal.*—Calc. for $C_{14}H_{22}ClNO_3$: C, 60.09; H, 7.40; N, 4.83. Found: C, 59.95; H, 7.37; N, 4.58.

**1-[2-(3,4,5-Trimethoxyphenyl)ethyl]-3-pyrroline Hydrochloride (X)**—In a three-necked flask fitted with a mechanical stirrer, dropping funnel, and drying tube, under nitrogen atmosphere, were placed 4.0 g (0.011 mole) of XV and 50 ml of anhydrous tetrahydrofuran (Scheme II). While the solution was stirring, 3.45 g (0.05 mole) of 3-pyrroline[2] was added dropwise through the dropping funnel. After addition, the dropping funnel was replaced with a reflux condenser and the yellow solution which formed was refluxed for 3 hr. The solution was then cooled to room temperature and concentrated *in vacuo*.

To the residue was added 75 ml of ether, and the insoluble matter was filtered. The same isolation procedure used for VI was then followed. The yield of X was 1.1 g (35%), mp 176–177° (ethanol–ethyl acetate). The IR spectrum showed a broad peak centered at 2500 $cm^{-1}$, indicative of $>NH^+$. The NMR spectrum (dimethyl sulfoxide-$d_6$) showed peaks at δ 3.1 (m, 4H, ethylene), 3.6 (s, 3H, *p*-methoxy), 3.8 (s, 6H, *m*-methoxy), 4.1 (s, 4H, pyrroline methylenes), 5.9 (s, 2H, vinylic), 6.6 (s, 2H, aromatic), and 12.3 (b, 1H, NH).

*Anal.*—Calc. for $C_{15}H_{22}ClNO_3$: C, 60.09; H, 7.40; N, 4.83. Found: C, 59.95; H, 7.42; N, 4.57.

**3,4,5-Trimethoxyphenyl-2-pyridylcarbinol (XVII)**—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 thermometer, were placed 80 ml (0.16 mole) of 2 *M* *n*-butyllithium in hexane[3] and 50 ml of anhydrous tetrahydrofuran (Scheme III). The stirrer was started, and the temperature was reduced to −40°. A 50-ml solution of 17.5 g (0.11 mole) of 2-bromopyridine in anhydrous tetrahydrofuran was added dropwise while the temperature was maintained below −30°.

After addition, the dark-red mixture which formed was stirred at from −30 to −40° for 30 min. A 200-ml solution of 20.0 g (0.10 mole) of 3,4,5-trimethoxybenzaldehyde (XVI) in anhydrous tetrahydrofuran was added dropwise while the temperature of the reaction was maintained below −25°. After addition, the reaction was allowed to warm to −15° and was stirred at that temperature for 1 hr. Water (100 ml) was then added to the clear yellow solution.

The reaction mixture was made acidic with 10% HCl and washed with three 50-ml portions of ether. The acid layer was made basic (pH 8) with ammonia gas and extracted with three 75-ml portions of chloroform. The chloroform was dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield 20.3 g (73%), mp 95–99°, of crude product; this product was used in the subsequent reaction without further purification. Several recrystallizations were attempted which failed to improve the melting point. An analytical sample was obtained (mp 104–106°) by passing 1 g of crude product through a silica gel column. The column was initially eluted with petroleum ether–ethyl acetate (1:1) and subsequently with ethyl acetate–methanol (1:1). The latter eluant contained the desired product. The IR spectrum showed a peak at 3100 $cm^{-1}$, indicative of hydroxyl. The NMR spectrum ($CDCl_3$) showed peaks at δ 3.8 (s, 9H, methoxy), 5.4 (b, 1H, OH exchanged by $D_2O$), 5.6 (s, 1H, CH), 6.6 (s, 2H, aromatic), 7.0–7.8 (m, 3H, 3CH, 4CH, and 5CH), and 8.5 (d, 1H, 6CH).

*Anal.*—Calc. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.08. Found: C, 65.32; H, 6.37; N, 4.93.

**2-(3,4,5-Trimethoxybenzyl)pyridine (XIX)**—In a three-necked flask fitted with a condenser, drying tube, mechanical stirrer, thermometer, and dropping funnel was dissolved 26.0 g (0.095 mole) of XVII in 400 ml of anhydrous benzene (Scheme III). The solution was stirred and cooled to 0° using an ice–salt bath. A 50-ml solution of 22.0 g (0.114 mole) of thionyl chloride in anhydrous benzene was added dropwise while the temperature of the reaction was kept below 20°. After addition, the resultant reddish solution was warmed to room temperature and stirred for 1 hr.

While the solution was cooled on an ice bath, 150 ml of 25% NaOH was added slowly. The aqueous layer was washed with three 80-ml portions of chloroform. The organic layers were combined, dried over anhydrous sodium sulfate, and filtered. The solution was concentrated *in vacuo* to yield a dark-reddish oil (XVIII), which was dissolved in 125 ml of acetic acid and transferred to a three-necked flask fitted with a condenser, drying tube, and mechanical stirrer. While the solution was stirred, 17.0 g of zinc dust was added in portions and the mixture was refluxed for 4 hr.

After cooling to room temperature, the mixture was filtered of inorganic salts and the solution was concentrated *in vacuo*. To the residue was added 75 ml of 25% NaOH, and the resultant aqueous mixture was extracted with three 80-ml portions of chloroform. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The residue was distilled, yielding 11.5 g (47%) of XIX, bp 157–160°/0.2 mm. The NMR spectrum ($CDCl_3$) showed peaks at δ 3.8 (s, 9H, methoxy), 4.1 (s, 2H, benzylic), 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 vacuo*, yielding a solid (XX) which was recrystallized from acetone. The yield of product varied from 64 to 71%, mp 151–153°.

*Anal.*—Calc. for $C_{16}H_{20}INO_3$: C, 47.89; H, 5.02; N, 3.49. Found: C, 47.90; H, 5.10; N, 3.30.

***N* - Methyl-2-(3,4,5,-trimethoxybenzyl)-1,2,3,6-tetrahydropyridine (XXI)**—In a three-necked flask equipped with a condenser, dropping funnel, magnetic stirrer, and thermometer was dissolved 2.0 g (0.05 mole) of sodium borohydride in aqueous methanol (57% v/v). This solution was cooled to 0°, and 10.0 g (0.025 mole) of XX in aqueous methanol (33% v/v) at 0° was added (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 vacuo*. The residue was distilled to yield 6.0 g (87%) of product, bp 154–155°/0.27 mm. The NMR spectrum ($CDCl_3$) showed peaks at δ 2.0 (m, 2H, $3CH_2$), 2.3 (m, 1H, 2CH), 2.4 (s, 3H, methyl), 2.7 (m, 2H, benzylic), 3.0 (m, 2H, $6CH_2$), 3.8 (s, 9H, methoxy), 5.6 (m, 2H, vinylic), and 6.4 (s, 2H, aromatic); mass spectrometry: M, 277.1675. Calc. for $C_{16}H_{23}NO_3$, 277.1675. The picrate was prepared for chemical analysis and had a melting point of 168.5–170°.

*Anal.*—Calc. for $C_{22}H_{26}N_4O_{10}$: C, 52.17; H, 5.17; N, 11.06. Found: C, 51.90; H, 5.15; N, 10.90.

**2-(3,4,5-Trimethoxybenzyl)-1,2,3,6-tetrahydropyridine Hydrochloride (XI)**—In a three-necked flask fitted with a reflux condenser, drying tube, and mechanical stirrer were placed 4.0 g (0.014 mole) of XXI, 3.5 g (0.017 mole) of 2,2,2-trichloroethyl chloroformate, 1.0 g of potassium carbonate, and 50 ml of anhydrous benzene (Scheme III). The mixture was then stirred and refluxed for 24 hr. After the reaction was cooled and filtered, it was extracted twice with 20 ml of 10% hydrochloric acid. The benzene layer was then dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield

[2] Available from Aldrich Chemical Co. as a 3:1 mixture of 3-pyrroline and 1-pyrroline.

[3] Alpha Chemical Co.

6.8 g of a yellow oil (XXII). The IR spectrum showed a peak at 1700 $cm^{-1}$, indicative of the carbonyl of a carbamate.

The crude oil, without further purification, was reduced by dissolving it in 50 ml of acetic acid and transferred to a three-necked flask fitted with a mechanical stirrer, reflux condenser, and drying tube. After gradual addition of 3.0 g of zinc dust, the mixture was stirred at room temperature for about 60 hr. The zinc mixture was filtered, and the acetic acid was reduced in volume *in vacuo* almost to completion. The residue was made basic with 25% NaOH and extracted with three 30-ml portions of ether. The ether extracts were combined, dried over anhydrous sodium sulfate, and filtered. Hydrogen chloride gas was passed through the ether solution, forming a white precipitate. The precipitate was filtered and recrystallized from ethyl acetate–ethanol (1:1) to yield 2.2 g (51%) of product, decomposition at 230–232°. The IR spectrum showed a broad peak from 2800 to 2600 $cm^{-1}$, indicative of $NH_2^+$. The NMR spectrum (dimethyl sulfoxide-$d_6$) showed peaks at $\delta$ 2.3 (m, 2H, $3CH_2$), 3.0 (m, 2H, benzylic), 3.6 (m, 3H, 2CH and $6CH_2$), 3.8 (s, 3H, *p*-methoxy), 3.9 (s, 6H, *m*-methoxy), 5.9 (m, 2H, vinylic), 6.8 (s, 2H, aromatic), and 9.9 (b, 2H, $NH_2$).

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* Present address: Vick Divisions Research, Vick Chemical Co., Mt. Vernon, NY 10553

‡ To whom inquiries should be directed.


# Dissolution Behavior and Bioavailability of Phenytoin from a Ground Mixture with Microcrystalline Cellulose


**KEIJI YAMAMOTO *, MASAHIRO NAKANO *, TAKAICHI ARITA *‡, YOSHIKAZU TAKAYAMA *, and YOSHINOBU 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 pharmacopeial 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 excretion patterns of the metabolite were determined in two subjects. The ground mixtures significantly 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


When a relatively insoluble drug is administered orally, the rate of absorption and/or the extent of bioavailability are controlled by its dissolution rate in the GI fluids (1). Therefore, efforts have been made to increase the dissolution rate of poorly soluble drugs (2–5).

In an earlier study (6), a ground mixture of griseofulvin and microcrystalline cellulose significantly im-