Synthesis and Dopaminergic Activity of *trans*-4-Methyl-3-phenylpyrrolidines

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trans-3-(3,4-Dihydroxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine (**13**) and *trans*-3-(3-Hydroxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine (**14**) were synthesized and evaluated for dopaminergic activity. The stereochemical assignments of **13** and **14** were determined by nmr. Both **13** and **14** were either inactive or weakly active in most dopaminergic tests.

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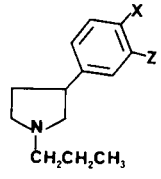
Introduction.

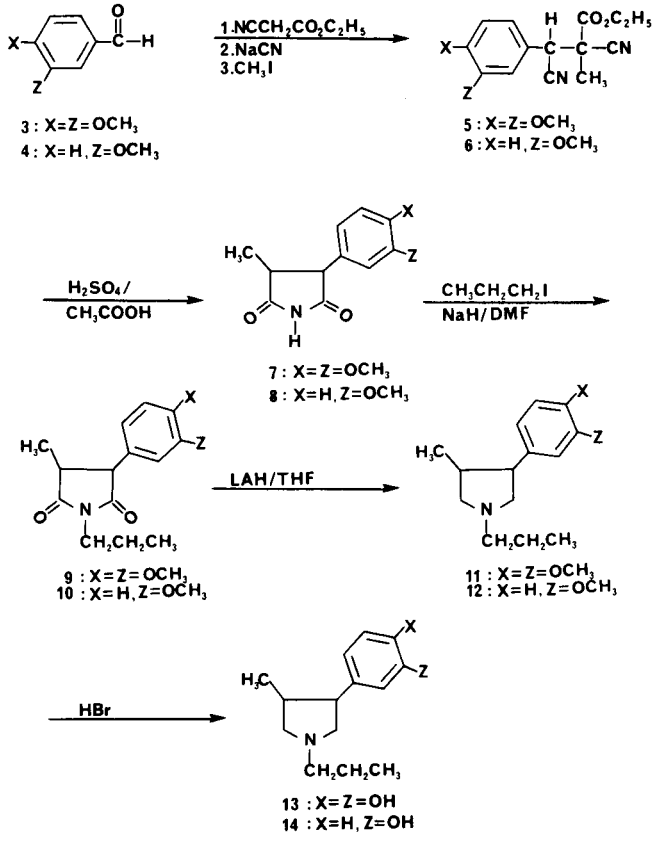
In a previous study, the synthesis and biological activity of 3-(3,4-dihydroxyphenyl)-1-(*n*-propyl)pyrrolidine (**1**) were reported [2]. The compound produced behavioral and biochemical changes characteristic of central dopaminergic stimulation. These included: reversal of the reserpine syndrome, stereotypic behavior, contralateral rotation following unilateral 6-hydroxydopamine lesion of the substantia nigra, reduction in the rate of dopamine turnover and inhibition of prolactin release. Although **1** acts as an effective dopaminergic agonist, the duration of action of this compound is relatively brief.



1: X=Z=OH
2: X=H, Z=OH

As a continuation of our previous study, the effect of substitution at the 4-position of the pyrrolidine ring on dopaminergic activity was investigated. This approach follows other studies in which substitution on the heterocyclic ring of dopaminergic agonists may greatly influence biological activity [3,4]. A methyl group was incorporated at the 4-position of the ring for the following reasons: (1) a methyl substituent enhances the lipophilic character of the molecule and thus may enhance the ability of the molecule to reach its site of action; and (2) by virtue of its relatively small size, a methyl substituent should be more readily accommodated by dopamine receptors than larger alkyl groups.

The purpose of this study was to synthesize 3-(3,4-dihydroxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine (**13**) and



Scheme I

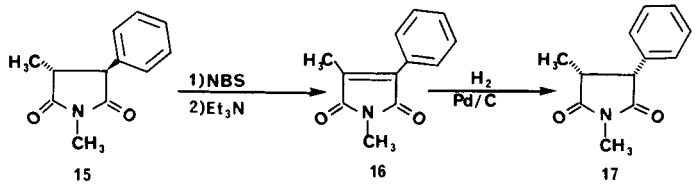
3-(3-hydroxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine (**14**) for evaluation as dopaminergic agonists. Compound **14** is closely related in structure to 3-(3-hydroxyphenyl)-1-(*n*-propyl)pyrrolidine (**2**) which has been shown to exhibit weak activity as a dopamine autoreceptor agonist [5]. Selectively acting dopamine autoreceptor agonists may have therapeutic potential in the treatment of hyperdopaminergic states such as schizophrenia [6,7].

Results and Discussion.

The reaction sequence (Scheme I) for the requisite 4-methyl-3-phenylpyrrolidines **13** and **14** involved preparation of the intermediate 4-methyl-3-phenylpyrrolidine-2,5-diones **7** and **8** utilizing the methods of Miller [8] and Hauck [9]. Knoevenagel condensation of the appropriately substituted benzaldehyde and ethyl cyanoacetate followed by addition of sodium cyanide and alkylation with methyl iodide gave the 2,3-dicyanopropanoates **5** and **6**. Acid catalyzed ring closure of **5** and **6** yielded the 4-methyl-3-phenylpyrrolidine-2,5-diones **7** and **8** as predominately the *trans* diastereoisomers. The presence of only one diastereoisomer was confirmed by nmr. The C_4-methyl groups for recrystallized **7** and **8** appeared as doublets centered at δ 1.23. The presence of the minor diastereoisomers (less than 5% by nmr) in crude **7** and **8** was observed by noting the presence of upfield doublets (C_4-methyl) centered at δ 0.73 and δ 0.70, respectively. In *trans* **7** and **8** the C_4-methyl group is deshielded by the 3-phenyl group and appears downfield from the C_4-methyl group, which is shielded by the 3-phenyl group in the corresponding *cis* diastereoisomers. The C_3-H in **7** and **8** is coupled to the C_4-H and should appear as a doublet with $J_{ax\ (cis)} \simeq$ 9-12 Hz and $J_{ax\ (trans)} \simeq$ 4-7 Hz [10-12]. However, the C_3-H is obscured by the aromatic ring methoxy groups making assignment of the chemical shifts and determination of the coupling constants difficult.

As a means of supporting the assigned stereochemistry of **7** and **8**, 1,4-dimethyl-3-phenylpyrrolidine-2,5-dione (**15**) was synthesized by the method of Miller [8] and the nmr spectrum was examined. The nmr spectral properties of **15** had been previously reported by Hauck [9], although the stereochemistry was not given. Following Miller's procedure, a mixture of diastereoisomers was obtained with the major diastereoisomer comprising about 91% (by nmr) of the crude product. A single recrystallization from diethyl ether gave a pure compound that exhibited a doublet at δ 1.33 for the C_4-methyl group and a doublet at δ 3.47, J_{ax} = 6.5 Hz, for the C_3-H. It is apparent from the nmr spectrum that **15** is predominately formed utilizing the literature method. The C_4-methyl group is deshielded by the 3-phenyl group and appears at approximately the same chemical shift position as the C_4-methyl group in *trans* **7** and **8**.

Further evidence for the stereochemical assignment was obtained by the synthesis of **17** (Scheme II). Bromination of **15** with *N*-bromosuccinimide gave the intermediate 3-bromo derivative which was directly dehydrohalogenated using triethylamine to yield the 1,4-dimethyl-3-phenyl-3-pyrroline-2,5-dione (**16**). Catalytic hydrogenation of **16** gave almost exclusively a *cis* addition of hydrogen to the double bond to afford *cis*-1,4-dimethyl-3-phenylpyrrolidine-2,5-dione (**17**). The nmr spectrum for **17** showed a much lower field position for the C_4-methyl group than the corresponding *trans* diastereoisomer **15**. The C_4-methyl appeared as a doublet at δ 0.88, and the C_3-H appeared as a doublet centered at δ 4.19, J_{ax} = 10 Hz.



Scheme II

Efforts to synthesize *cis* **13** and **14** by bromination of **9** and **10** with *N*-bromosuccinimide gave mixtures of products. It was anticipated that the intermediate 3-bromo derivatives of **9** and **10** could be dehydrohalogenated and the resulting 3-pyrroline reduced to give *cis* **11** and **12** as described for the synthesis of **17** (Scheme II). However, this route does not appear to be feasible for the synthesis of *cis* **13** and **14**.

The target compounds **13** and **14** were evaluated for dopaminergic activity and the results are given in Table I. Compounds **13** and **14** were both completely inactive in reversing reserpine-induced catalepsy and inducing stereotypy, typical effects of dopamine agonists such as

Table I

Behavioral Effects of 4-Methyl-3-phenylpyrrolidines [a]

Treatment [b]	Catalepsy	Stereotypy	Rotational Behavior [c]
Control	3	0	[d]
Apomorphine	0 [e,f]	3 [e,f]	0.25 mg/kg
1	0 [f,g]	3 [f,g]	10 mg/kg
13	3 [g]	0 [g]	50 mg/kg
14	3 [g]	0 [g]	[d]

[a] Catalepsy and stereotypy were assessed in rats (n = 6) pretreated with reserpine (5 mg/kg) and were scored (see text) before the administration, and at the time of peak effect, of the dopamine agonists. [b] Compounds were administered by intraperitoneal injections with 0.01 *M* sodium bisulfite solution as the vehicle. [c] Minimal effective dose. [d] No rotation either spontaneously or in response to vehicle administration. [e] Apomorphine was administered at a dose of 2 mg/kg, intraperitoneally. [f] See reference [2]. [g] Administered at a dose of 100 mg/kg, intraperitoneally.

apomorphine. The catechol **13** did produce contralateral turning in 6-hydroxydopamine lesioned rats. However, it was considerably less potent than **1**. The 4-methyl group may sterically hinder the binding of **13** and **14** to dopamine receptors. Further work is in progress to prepare the *cis* diastereoisomers of **13** and **14** and compare their dopaminergic activity with the corresponding *trans* diastereoisomers.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The ir spectra were recorded as potassium bromide pellets or as liquid films with a Perkin-Elmer 137 spectrophotometer. The nmr spectra were recorded on a Varian EM 360A spectrometer or a JEOL FX 90Q spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (1%) or in the case of deuterium oxide sodium 2,2-dimethyl-2-silapentane-5-sulfonate. Analytical data were obtained from Micro-Analysis, Inc. Wilmington, DE and MicAnal, Tucson, Arizona.

Catalepsy.

This was assessed using a reported method [2], by the length of time a reserpinized rat maintained an abnormal posture with its front paws over a bar (2 centimeters diameter) 7 centimeters from bench level. Catalepsy was scored in control reserpinized rats, and in experimental animals, just prior to drug administration and at the peak of effect of the experimental compound as follows: 0-9 seconds = 0; 10 seconds-2.5 minutes = 1; 2.6-5.0 minutes = 2; 5.1-10 minutes = 3; 10.1-20 minutes = 4; > 20 minutes = 5.

Stereotypy.

This was scored as previously described [2] at the peak effect of the experimental compound as follows: animals indistinguishable from vehicle-treated controls = 0; discontinuous sniffing and continuous locomotor activity = 1; continuous sniffing and discontinuous locomotor activity = 2; continuous sniffing and discontinuous biting, licking or gnawing = 3; continuous compulsive biting, licking, or gnawing with no locomotor activity = 4.

Rotational Behavior.

The left substantia nigra was lesioned following a reported procedure [2]. Apomorphine (0.12-2.0 mg/kg) or test compound (10-100 mg/kg) was administered and the rotational behavior recorded.

Ethyl 2,3-Dicyano-3-(3,4-dimethoxyphenyl)-2-methylpropanoate (**5**).

The synthesis of this compound was accomplished using the method of Miller and coworkers [8]. A mixture of 3,4-dimethoxybenzaldehyde (**3**) (100.0 g, 0.602 mole), ethyl cyanoacetate (68.0 g, 0.602 mole), and piperidine (2 ml) in ethanol (400 ml) was stirred vigorously as the temperature increased to 53°. After the temperature of the thick yellow slurry had cooled to 35°, sodium cyanide (32.4 g, 0.662 mole) was added and the mixture was heated at 60° for 0.5 hour. After cooling to 40°, iodomethane (94.0 g, 0.662 mole) was added and the mixture was refluxed for 17 hours, cooled to 30°, and acidified with concentrated hydrochloric acid. The inorganic precipitate (sodium iodide) was removed by filtration and the filtrate was evaporated under reduced pressure to afford an oil. The oil was dissolved in chloroform (300 ml) and was washed with water (3 x 50 ml). The chloroform phase was dried (sodium sulfate), filtered, and evaporated to yield an oil which solidified upon stirring. Recrystallization from 95% ethanol gave 106 g (58%) of a white crystalline solid, mp 89-91°; ir (potassium bromide): 2270 (C≡N), 1750 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 1.17 and 1.33 (t, 3H, J = 8 Hz, $CO_2CH_2CH_3$), 1.53 and 1.87 (s, 3H, CH_3), 3.90 (s, 6H, OCH_3), 3.95 (s, 1H, CH), 4.29 (q, 2H, J = 8 Hz, $CO_2CH_2CH_3$), 6.77-7.06 (m, 3H, ArH).

Anal. Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.55; H, 6.01; N, 9.27. Found: C, 63.64; H, 5.94; N, 9.16.

trans-3-(3,4-Dimethoxyphenyl)-4-methylpyrrolidine-2,5-dione (**7**).

Compound **7** was prepared by a previously reported procedure [2]. A mixture of **5** (63.0 g, 0.208 mole), glacial acetic acid (500 ml), and 78% sulfuric acid (65 ml) was refluxed for 2 hours and the solvent was evaporated under reduced pressure. The resulting oil solidified upon trituration with water. Recrystallization from 95% ethanol gave 18 g (35%) of a white crystalline solid, mp 205-206°; ir (potassium bromide): 3140 (NH), 1785, 1730 (C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 1.23 (d, 3H, J = 8 Hz, CH_3), 2.93 (m, 1H, C_4-H), 3.58 (d, 1H, C_3-H), 3.73 (s, 6H, OCH_3), 6.82 (m, 3H, ArH).

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.63; H, 6.08; N, 5.62. Found: C, 62.67; H, 6.19; N, 5.73.

trans-3-(3-Methoxyphenyl)-4-methylpyrrolidine-2,5-dione (**8**).

Ethyl 2,3-dicyano-3-(3-methoxyphenyl)-2-methylpropanoate (**6**) was prepared as described for **5** from *m*-methoxybenzaldehyde (**4**) (100 g, 0.74 mole), ethyl cyanoacetate (83 g, 0.74 mole), piperidine (5 ml), sodium cyanide (39.6 g, 0.81 mole), and iodomethane (115 g, 0.81 mole) in ethanol (400 ml) to yield 54 g of a dark red oil, bp 150-190° (1.8 mm); ir (film): 2270 (C≡N), 1755 (C=O) cm^{-1}. A mixture of crude oil, glacial acetic acid (500 ml) and 78% sulfuric acid (55 ml) was refluxed for 2 hours, cooled, and evaporated under reduced pressure. Trituration of the resulting oil with water gave a solid which was collected by filtration and recrystallized from ethanol to yield 24 g (15% based on **4**) of white crystalline solid, mp 166-167°; ir (potassium bromide): 1790, 1740 (C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 1.23 (d, 3H, J = 8 Hz, C_3-H), 2.40-3.27 (m, 1H, C_4-H), 3.75 (s, 3H, OCH_3), 3.78 (d, 1H, C_3-H), 6.50-7.40 (m, 4H, ArH).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.73; H, 5.99; N, 6.39. Found: C, 66.00; H, 6.06; N, 6.21.

trans-3-(3,4-Dimethoxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine-2,5-dione (**9**).

A total of 3.47 g (0.072 mole) of a 50% mineral oil dispersion of sodium hydride was washed with hexane (3 x 30 ml), suspended in dimethylformamide (100 ml), and added to a reaction flask under a nitrogen atmosphere. The stirred suspension was treated dropwise with **7** (18.0 g, 0.072 mole) in dimethylformamide (200 ml), heated at 80° for 2 hours, and cooled to 30°. A solution of *n*-propyl iodide (12.3 g, 0.072 mole) in dimethylformamide (50 ml) was added and the mixture was heated at 80° for 19 hours. The reaction mixture was cooled, treated with absolute ethanol (15 ml), and evaporated under reduced pressure to afford a dark red oil. Trituration of the oil with water gave a solid which was recrystallized from 2-propanol to give a 12.4 g (60%) of a yellow solid, mp 83-84°; ir (potassium bromide): 1785, 1710 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 0.93 (m, 3H, $NCH_2CH_2CH_3$), 1.40 (d, 3H, J = 7 Hz, CH_3), 1.53-1.86 (m, 2H, $NCH_2CH_2CH_3$), 2.83 (m, 1H, C_4-H), 3.50 (m, 3H, $NCH_2CH_2CH_3$ and C_3-H), 3.86 (s, 6H, OCH_3), 6.43-7.96 (m, 3H, ArH).

Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.28; N, 4.81. Found: C, 65.74; H, 7.23; N, 4.75.

trans-3-(3-Methoxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine-2,5-dione (**10**).

Compound **10** was prepared from **8** (23.0 g, 0.105 mole), *n*-propyl iodide (17.8 g, 0.105 mole), and sodium hydride (5.04 g, 0.105 mole, 50% mineral oil dispersion) in dimethylformamide (325 ml) in the same manner as described for the synthesis of **9**. Vacuum distillation gave 15.0 g (56%) of a yellow oil, bp 159-160° (0.25 mm); ir (film): 1790, 1710 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 0.97 (m, 3H, $NCH_2CH_2CH_3$), 1.33-2.33 (m, including d at 1.47, J = 8 Hz, 5H, $NCH_2CH_2CH_3$ and CH_3), 2.57-3.20 (m, 1H, C_4-H), 3.57 (m, 2H, $NCH_2CH_2CH_3$), 3.83 (s, 4H, OCH_3 and C_3-H), 6.67-7.43 (m, 4H, ArH).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.93; H, 7.34; N, 5.36. Found: C, 68.88; H, 7.41; N, 5.25.

trans-3-(3,4-Dimethoxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine (**11**).

This compound was prepared from **9** by a previously reported pro-

cedure [2] to give in 67% yield a clear, colorless oil, bp 149-157° (1.1 mm); ir (film): 3010, 2825, 1610, 1265, 1235 cm^{-1}; nmr (deuteriochloroform): δ 0.70-1.1 (m, 6H, CH_3 and $NCH_2CH_2CH_3$), 1.17-1.85 (m, 3H, $NCH_2CH_2CH_3$ and C_4-H), 1.87-3.37 (m, 6H, ring CH_2, $NCH_2CH_2CH_3$, and C_3-H), 3.83 (d, 6H, OCH_3), 6.73 (s, 3H, ArH).

An analytical sample was prepared by formation of the hydrochloride salt. Recrystallization from absolute ethanol-diethyl ether gave a white crystalline solid, mp 106-107°.

Anal. Calcd. for $C_{16}H_{26}ClNO_2$: C, 64.09; H, 8.74; Cl, 11.83; N, 4.67. Found: C, 63.96; H, 8.89; Cl, 11.81; N, 4.60.

trans-3-(3-Methoxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine (**12**).

Compound **12** was prepared from **10** by the same method described for **11** to afford in 66% yield a clear, colorless oil, bp 104-105° (0.1 mm); nmr (deuteriochloroform): δ 0.53-3.33 (m, 16H), 3.87 (s, 3H, OCH_3), 6.57-7.38 (m, 4H, ArH).

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.20; H, 9.93; N, 6.00. Found: C, 76.94; H, 10.08; N, 5.73.

The hydrochloride salt of **12** was prepared and recrystallized from absolute ethanol-diethyl ether to yield a white crystalline solid, mp 122-124°.

Anal. Calcd. for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.97; N, 5.19. Found: C, 66.96; H, 9.14; N, 5.07.

trans-3-(3,4-Dihydroxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine (**13**).

A solution of **11** (4.50 g, 0.017 mole) in 48% aqueous hydrobromic acid (45 ml) was refluxed for 3 hours under a nitrogen atmosphere. The solvent was evaporated and the resulting oil was azeotroped with absolute ethanol (4 x 10 ml). Trituration of the oil with absolute ethanol-diethyl ether gave a solid which was recrystallized from absolute ethanol-diethyl ether to afford 2.5 g (47%) of a beige solid of **13** hydrobromide, mp 146-148°; ir (potassium bromide): 3280 (OH) cm^{-1}; nmr (deuterium oxide) δ 0.37-1.15 (m, 6H, CH_3 and $NCH_2CH_2CH_3$), 1.33-2.10 (m, 3H, $NCH_2CH_2CH_3$ and C_4-H), 2.13-4.35 (m, 6H, ring CH_2, C_3-H, and $NCH_2CH_2CH_3$), 6.9 (m, 3H, ArH).

Anal. Calcd. for $C_{14}H_{22}BrNO_2$: C, 53.16; H, 7.03; N, 4.43. Found: C, 53.01; H, 6.98; N, 4.44.

trans-3-(3-Hydroxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine (**14**).

Compound **14** was prepared as described for **13** from **12** (5.0 g, 0.021 mole) and 48% aqueous hydrobromic acid (50 ml). Work up in the normal manner gave 4.4 g (68%) of beige crystals of **14** hydrobromide, mp 127-129°; ir (potassium bromide): 3125 (OH) cm^{-1}; nmr (deuterium oxide): δ 0.33-4.17 (m, 16H, aliphatic CH_2 and CH_3, ring CH_2 and ring), 6.67-7.60 (m, 4H, ArH).

Anal. Calcd. for $C_{14}H_{22}BrNO$: C, 56.00; H, 7.40; N, 4.67. Found: C, 56.22; H, 7.33; N, 4.39.

trans-1,4-Dimethyl-3-phenylpyrrolidine-2,5-dione (**15**).

A mixture of α-methyl-β-phenylsuccinic acid [8] (17.0 g, 0.082 mole) and 40% aqueous methylamine (5.06 g, 0.163 mole) was heated to 210°. Water was removed during heating *via* a Dean-Stark trap. The residue was dissolved in diethyl ether and cooled to yield 9.79 g (59%) of a white solid, mp 62-64° [lit [8] bp 132-133° (0.5 mm)].

An analytical sample was prepared by recrystallization of a small sample from petroleum ether (bp 39-55°) to give a white crystalline solid, mp 62-64°; ir (potassium bromide): 1780, 1720 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 1.33 (d, 3H, J = 8 Hz, C_4-CH_3), 2.96 (m, 1H, C_4-H), 2.98 (s, 3H, N-CH_3), 3.47 (d, 1H, $J_{ax\ (trans)}$ = 6.5 Hz), 7.16 (m, 5H, ArH).

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.88; H, 6.44; N, 6.89. Found: C, 71.07; H, 6.44; N, 6.81.

1,4-Dimethyl-3-phenyl-3-pyrroline-2,5-dione (**16**).

A mixture of **15** (5.0 g, 0.025 mole) and *N*-bromosuccinimide (4.36 g, 0.025 mole) in carbon tetrachloride (250 ml) was refluxed for 24 hours. The reaction mixture was filtered to remove the precipitated succinimide and the solvent was evaporated under reduced pressure to yield a yellow oil. The oil was dissolved in tetrahydrofuran (150 ml) and triethylamine (2.48 g, 0.025 mole) was added. The mixture was stirred at room temperature for 1 hour and filtered to remove the triethylamine hydrobromide. Evaporation of the solvent gave a yellow oil that solidified upon trituration with petroleum ether. Recrystallization from 2-propanol-water gave 2.19 g (44%) of a light yellow solid, mp 73.5-75.5°; ir (potassium bromide) 1775, 1700 (C=O) cm^{-1}; nmr (deuteriochloroform) δ 2.19 (s, 3H, C-CH_3), 3.08 (s, 3H, N-CH_3), and 7.49 (m, 5H, ArH).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.36; H, 5.42; N, 6.88.

cis-1,4-Dimethyl-3-phenylpyrrolidine-2,5-dione (**17**).

A mixture of **16** (1.5 g, 0.007 mole) and 0.5 g of 10% palladium on carbon in 95% ethanol (100 ml) was shaken overnight on a Parr hydrogenator at an initial pressure of 51 psi. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure to afford a white solid. Recrystallization from petroleum ether (bp 39-55°) gave 734 mg (49%) of a white crystalline solid, mp 88-89°; ir (potassium bromide): 1780, 1700 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 0.88 (d, 3H, J = 8 Hz, C_4-CH_3), 3.11 (s, 3H, N-CH_3), 3.21 (m, 1H, C_4-H), 4.19 (d, 1H, $J_{ax\ (cis)}$ = 10 Hz, C_3-H), 7.17 (m, 5H, ArH).

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.88; H, 6.44; N, 6.89. Found: C, 71.07; H, 6.22; N, 6.80.

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