Synthesis of *cis*-4-Methyl-3-phenylpyrrolidines as Potential Dopaminergic Agonists

A. Michael Crider* [1a], Susan C. Sylvestri [1a], Kathryn D. Tschappat [1b], Ronald M. Dick [1a], and W. Greg Leader [1a]

School of Pharmacy, Northeast Louisiana University, Monroe, LA 71209
and
College of Pharmacy, University of Toledo, Toledo, OH 43606

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cis-3-(3,4-Dihydroxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine (**23**) was synthesized and evaluated for dopaminergic activity. The synthesis of **23** involved selective 4-acylation of the 3-phenylpyrrolidine-2,5-dione **15** and *cis*-addition of hydrogen to a 4-methyl-3-phenyl-3-pyrroline **4**. Pharmacological evaluation of **23** showed that introduction of a *cis*-4-methyl group into the 3-phenylpyrrolidine nucleus decreases dopaminergic activity.

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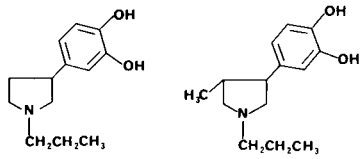
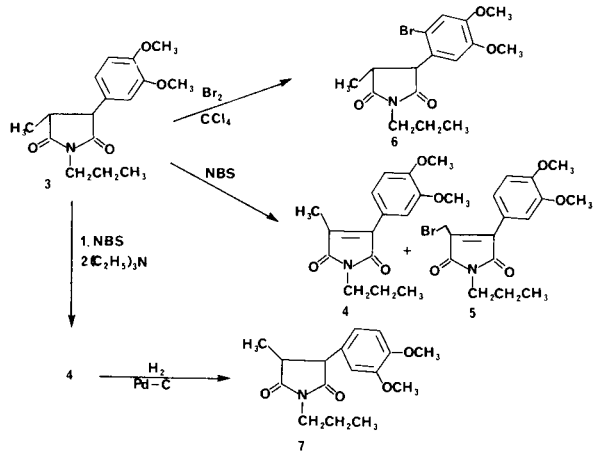
Introduction.

Previously, the synthesis and dopaminergic activity of 3-(3,4-dihydroxyphenyl)-1-(*n*-propyl)pyrrolidine (**1**) were reported [2]. Although **1** demonstrated significant activity in various tests to determine dopaminergic activity, the compound exhibited a short duration of action. A subsequent study showed that *trans*-3-(3,4-dihydroxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine (**2**) was virtually inactive as a dopamine agonist [3]. Steric effects of the *trans*-4-methyl group at dopamine receptors may be responsible for the reduced activity of **2**. Recent reports indicate that central dopamine receptors prefer flat molecules [4]. Thus, the present study was performed to synthesize *cis*-3-(3,4-dihydroxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine (**23**) for comparison of its dopaminergic activity with the *trans* diastereoisomer **2**. Since **23** is a more planar structure than **2**, the former compound was expected to exhibit some dopaminergic activity.



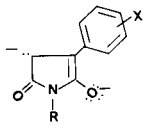
Results and Discussion.

Our first attempt to prepare *cis*-3-(3,4-dihydroxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine (**23**) involved the attempted preparation of the key intermediate **7** (Scheme I) utilizing a procedure that was successful for the synthesis of *cis*-1,4-dimethyl-3-phenylpyrrolidine-2,5-dione [3]. However, bromination of **3** with *N*-bromosuccinimide gave predominately the allyl bromide **5**. Apparently, **3** is initially brominated at the benzylic 3-position. During the course of the reaction the 3-bromo derivative readily undergoes dehydrohalogenation to yield **4**, which is brominated at the allylic position to give **5**. Bromination of **3** with bromine in carbon tetrachloride gave only *trans*-3-[(2-bromo-4,5-dimethoxy)phenyl]-4-methyl-1-(*n*-propyl)-pyrrolidine-2,5-dione (**6**). The presence of two distinct singlets at δ 6.50 and δ 7.00, respectively, in the nmr spectrum of **6** supports the assigned structure.



Scheme I

An alternate route for the synthesis of **23** involved the synthesis of 3-(3,4-dimethoxyphenyl)-4-ethoxalyl-1-(*n*-propyl)pyrrolidine-2,5-dione (**20**) (Scheme III) as a key intermediate. Selective acylation at the 4-position of the ring was achieved following a reported method by Hauck and Fan [5]. These workers postulated that the 4-alkylations or acylations proceeded through a dianion in which reaction occurred at the more nucleophilic 4-position. The required 1-alkyl-3-phenyl-pyrrolidine-2,5-diones were prepared by a described method [2] or as shown in Scheme II. Using Hauck's procedure, selective 4-acylation of the dianion **12** (R = CH_3 or $CH_2CH_2CH_3$ and X = 3-OCH_3 or 3,4-OCH_3)



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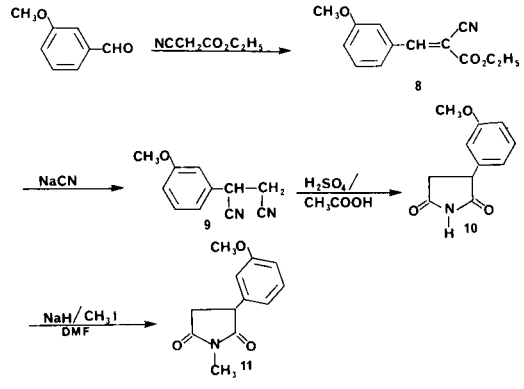
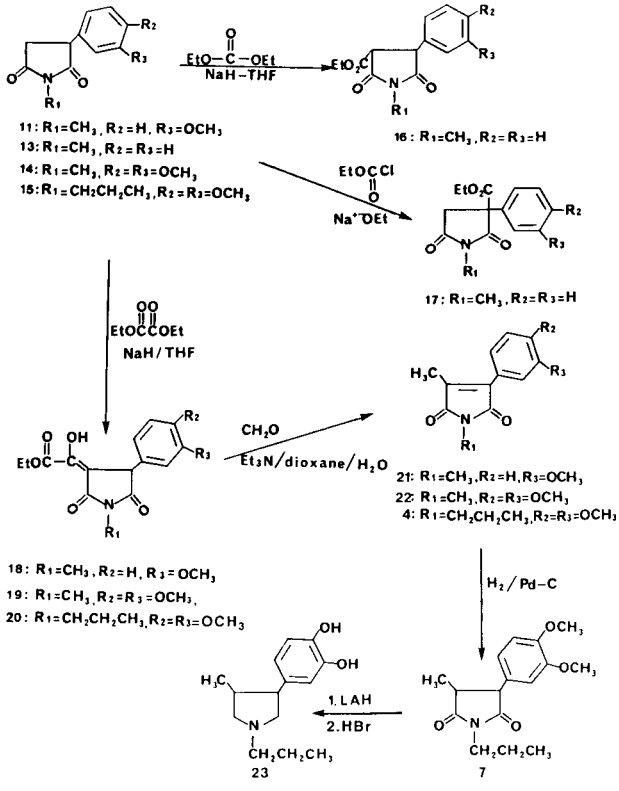
was accomplished with either diethyl carbonate or diethyl oxalate and two equivalents of sodium hydride in tetrahydrofuran (Scheme III). The 4-ethoxalyl derivatives existed almost exclusively in their enol forms. The C_3-H for these compounds appeared as singlets at δ 4.7-4.8 in the nmr spectra.



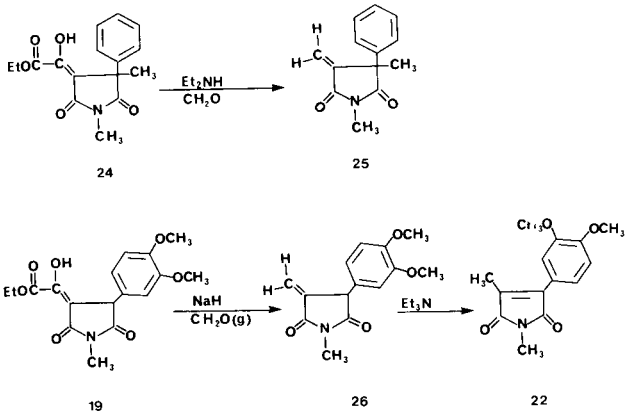
Scheme II



Scheme III

The position of the acylation is readily determined by examination of the nmr spectra. Acylation of 1-methyl-3-phenylpyrrolidine-2,5-dione (**13**) utilizing one equivalent of sodium ethoxide afforded the 3-ethoxycarbonyl derivative **17** (Scheme III). The C_4 protons were found as doublets $J_{AB}(gem)$ = 18 Hz [6] at δ 3.05 and δ 3.70, respectively, while the isomeric *trans*-4-ethoxycarbonyl-1-methyl-3-phenylpyrrolidine-2,5-dione (**16**) exhibited doublets at δ 3.85, $J_{AX}(trans)$ = 6 Hz [3] and δ 4.45, $J_{AX}(trans)$ = 6 Hz for the C_3-H and C_4-H, respectively.

In an earlier report, conversion of the 4-ethoxalylpyrrolidine-2,5-dione **24** to a 4-methylene derivative **25** (Scheme IV) using aqueous formaldehyde and diethylamine was described [7]. Since the 3-position is disubstituted, **25** is unable to isomerize to a 3-pyrroline. Attempted conversion of 4-ethoxalyl-3-phenylpyrrolidine-2,5-diones **18-20** to 3-phenyl-3-pyrrolines **4, 21-22** was unsuccessful utilizing our previously reported method. When 3-(3,4-dimethoxyphenyl)-4-ethoxalyl-1-(methyl)pyrrolidine-2,5-dione (**19**) was treated with gaseous formaldehyde and sodium hydride in tetrahydrofuran following the method of McMurry [8], 3-(3,4-dimethoxyphenyl)-1-methyl-4-(methylene)pyrrolidine-2,5-dione (**26**) was obtained in low yield. Compound **26** readily undergoes isomerization to the 3-pyrroline **22** in the presence of a catalytic amount of triethylamine (Scheme IV). Substitution of triethylamine for diethylamine in aqueous formaldehyde-dioxane converted **18-20** to the desired 3-pyrrolines **4,21-22** in moderate yields (Scheme III).



Scheme IV

The target compound **23** of this investigation was prepared as shown in Scheme III. Catalytic hydrogenation of **4** proceeded with *cis*-addition of hydrogen to the double bond to yield **7**. The nmr spectrum of **7** exhibits doublets at δ 4.10, J_{AB} = 10 Hz for the C_3-H and at δ 0.92 for the C_4-CH_3, respectively. The C_4-CH_3 is shielded by the 3-phenyl group in **7** and appears at a higher field position than in the corresponding *trans* diastereoisomer **2**, in which the C_4-CH_3 group is found at δ 1.40 [3]. Lithium

aluminum hydride reduction of **7** followed by methyl ether cleavage of the intermediate pyrrolidine readily afforded **23**. The C_4-methyl group of **23** is found in the nmr spectrum upfield at δ 0.66.

Evaluation of **23** for dopaminergic activity (Table I) showed weak activity in comparison studies with apomorphine. Compound **23** increased locomotor activity and produced stereotyped behavior in reserpinized rats. However, **23** was considerably less potent than the known dopamine agonist apomorphine. Similar to apomorphine, **23** completely reversed reserpine-induced catalepsy in rats. Previously, *trans*-3-(3,4-dihydroxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine (**2**) was reported to be inactive in most dopaminergic tests when compared with apomorphine [3]. Apparently, incorporation of a *cis*-4-methyl group into **1** decreases dopaminergic activity while a *trans*-4-methyl eliminates activity. This appears to be in agreement with the report that dopamine receptors prefer flat structures [4]. Thus, it appears that substitution at the 4-position of 3-(3,4-dihydroxyphenyl)-1-(*n*-propyl)pyrrolidine (**1**) sterically hinders binding to dopamine receptors.

Table I

Behavioral Effects of Apomorphine and **23** [a]

Treatment [b]	Catalepsy [c]	Stereotypy [d,e]	Locomotor Activity [e]
Control	4	0	498.9 ± 116.4
Apomorphine	0 [f,g]	9 [g]	3620.0 ± 314.8 [g]
23	0 [h]	4.9 ± 0.96 [h]	1551.1 ± 280.9 [h]

[a] Assessed in rats (n = 10) pretreated with reserpine (5 mg/kg) 17 to 20 hours prior to testing. [b] Compounds were administered by intraperitoneal injections with 0.01 *M* sodium bisulfite solution as the vehicle. [c] See reference [2]. [d] Rats were pretreated with reserpine (5mg/kg) and were scored (see text) before the administration, and at the time of peak effect, of the dopamine agonists. [e] Mean ± SEM. [f] Number of animals = 11. [g] Administered at a dose of 2 mg/kg, intraperitoneally. [h] Administered at a dose of 100 mg/kg, intraperitoneally.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. The ir spectra were recorded as potassium bromide pellets or as liquid films with a Nicolet 5MX FT spectrophotometer. The nmr spectra were recorded on 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. Mass spectra were recorded on a Finnigan MAT TSQ 4510 spectrometer. Analytical data were obtained from Desert Analytics, Tucson, Arizona.

Catalepsy.

This was assessed in reserpinized rats by a reported method [2].

Stereotypy and Locomotor Activity.

These effects were measured simultaneously in reserpinized male rats after intraperitoneal injection of vehicle, test compound, or apomorphine. Stereotypy was ranked as previously described [10] in the following manner: 0 = no activity; 1,2,3 = sniffing; 4,5,6 = licking; 7,8,9 = gnawing. Locomotor activity was measured for thirty minutes after injection of vehicle, test compound, or apomorphine using a Stoelting activity monitor.

4-Bromomethyl-3-(3,4-dimethoxyphenyl)-1-*n*-propyl-3-pyrroline-2,5-dione (**5**).

A solution of *trans*-3-(3,4-dimethoxyphenyl)-4-methyl-1-(*n*-propyl)-pyrrolidine-2,5-dione (**3**) [2] (4.0 g, 13.7 mmoles) and *N*-bromosuccinimide (2.44 g, 13.7 mmoles) in carbon tetrachloride (200 ml) was refluxed for 7 hours. Considerable evolution of hydrogen bromide gas was observed during the reflux period. The mixture was cooled, filtered, and evaporated to afford a light yellow oil. Trituration with 2-propanol gave 1.01 g (17%) of a yellow solid, mp 108-110°. Several recrystallizations from 2-propanol produced an analytical sample of yellow crystals, mp 113-115°; ir (potassium bromide): 1780, 1720 (C=O, imide), 1640 (C=C) cm^{-1}; nmr (deuteriochloroform): δ 0.93 (t, 3H, J = 8 Hz, CH_3), 1.63 (m, 2H, CH_2CH_3), 3.56 (t, 2H, J = 8 Hz, N-CH_2), 3.95 (s, 6H, OCH_3), 4.37 (s, 2H, CH_2Br), 7.30 (m, 3H, ArH).

Anal. Calcd. for $C_{16}H_{18}BrNO_4$: C, 52.19; H, 4.93; N, 3.80. Found: C, 52.49; H, 4.90; N, 3.82.

trans-3-[(2-Bromo-4,5-dimethoxy)phenyl]-4-methyl-1-(*n*-propyl)pyrrolidine-2,5-dione (**6**).

A solution of **3** (5.0 g, 17.0 mmoles) in carbon tetrachloride (70 ml) was treated dropwise with bromine (2.7 g, 17.0 mmoles) in carbon tetrachloride (20 ml) over a period of 1 hour. The dark red mixture was refluxed for 20 hours, cooled, and washed with water (2 x 75 ml). The carbon tetrachloride layer was dried (sodium sulfate), filtered, and evaporated to afford a yellow oil. Trituration with petroleum ether (bp 39-55°) gave a solid which was recrystallized from 95% ethanol to yield 4.1 g (56%) of a light yellow solid, mp 112-114°; ir (potassium bromide): 1780, 1710 (C=O, imide) cm^{-1}; nmr (deuteriochloroform): δ 0.93 (t, J = 7 Hz, 3H, $CH_2CH_2CH_3$), 1.20-1.80 (m, including d, J = 7 Hz, C_4-CH_3 at 1.43, 5H), 2.87 (m, 1H, C_4-H), 3.40-3.76 (m, 3H, N-CH_2 and C_3-H), 3.80 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.50 (s, 1H, ArH), 7.00 (s, 1H, ArH); ms: (m/e) 369 (M^+), 371 (M^+ +2), 290 (M^+ -Br).

Anal. Calcd. for $C_{16}H_{20}BrNO_4$: C, 51.90; H, 5.46; N, 3.78. Found: C, 52.01; H, 5.49; N, 3.74.

Ethyl 2-Cyano-3-(3-methoxyphenyl)acrylate (**8**).

A mixture of *m*-methoxybenzaldehyde (39.5 g, 290 mmoles), ethyl cyanoacetate (32.7 g, 290 mmoles), and piperidine (3.8 ml) in toluene (350 ml) was heated to reflux. Water was removed *via* a Dean Stark trap. Heating was continued until the theoretical volume of water was removed. The solvent was evaporated to afford a yellow solid. Recrystallization from 95% ethanol gave 58.2 g (87%) of **8**, mp 53-54° [lit [11] mp 56°]; ir (potassium bromide): 2250 (C≡N), 1740 (C=O), 1620 (C=C) cm^{-1}; nmr (unisol-d): δ 1.33 (t, 3H, J = 8 Hz, CH_2CH_3), 3.80 (s, 3H, OCH_3), 4.40 (q, 2H, CH_2CH_3), 7.27 (m, 4H, ArH), 8.16 (s, 1H, CH=C).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.51; H, 5.68; N, 6.06. Found: C, 67.27; H, 5.80; N, 5.84.

3-Cyano-3-(3-methoxyphenyl)propanenitrile (**9**).

Ethyl 2-cyano-3-(3-methoxyphenyl)acrylate (**8**) (4.30 g, 190 mmoles) was dissolved in a mixture of chloroform (400 ml) and 95% ethanol (300 ml) and a solution of sodium cyanide (9.6 g, 200 mmoles) in water (50 ml) was added. The mixture was refluxed for 80 hours, cooled, and acidified with concentrated hydrochloric acid to *p*H 1. The solvents were evaporated and the residue was partitioned between chloroform (300 ml) and water (200 ml). The chloroform layer was separated, washed with water (2 x 100 ml), dried (sodium sulfate), filtered, and evaporated to yield a dark brown solid. Recrystallization from 95% ethanol yielded 27.0 g (76%) of **9**, mp 83-84°; ir (potassium bromide): 2290 (C≡N) cm^{-1}; nmr (dimethyl sulfoxide-d_6): δ 3.32 (d, 2H, J = 6 Hz, CH_2CN), 3.80 (s, 3H, J = 6 Hz, OCH_3), 4.68 (t, 1H, J = 6 Hz, CHCN), 7.19 (m, 4H, ArH).

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.94; H, 5.42; N, 15.05. Found: C, 70.81; H, 5.49; N, 14.77.

3-(3-Methoxyphenyl)pyrrolidine-2,5-dione (**10**).

A mixture of **9** (41.6 g, 223 mmoles), acetic acid (270 ml) and 78% sulfuric acid (40 ml) was refluxed for 1 hour, cooled, and evaporated under reduced pressure. The resulting brown oil was triturated with water to yield a yellow solid. Recrystallization from 95% ethanol gave 23.6 g (52%) of a yellow-crystalline solid, mp 105-106°; ir (potassium bromide): 1780, 1730 (C=O) cm^{-1}; nmr (dimethyl sulfoxide-d_6): δ 3.33 (m, 2H, C_4-CH_2), 3.70 (s, 3H, OCH_3), 4.13 (m, 1H, C_3-H), 6.96 (m, 4H, ArH).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.37; H, 5.41; N, 6.83. Found: C, 64.39; H, 5.49; N, 6.62.

3-(3-Methoxyphenyl)-1-(methyl)pyrrolidine-2,5-dione (**11**).

A 50% mineral oil dispersion of sodium hydride (4.4 g, 92 mmoles) was washed with hexanes (3 x 30 ml), suspended in dimethylformamide (100 ml) and charged into a reaction flask under a nitrogen atmosphere. A solution of **10** (18.8 g, 92 mmoles) in dimethylformamide (50 ml) was added dropwise. After the addition had been completed, the reaction mixture was heated at 80° for 2 hours. The reaction mixture was cooled to room temperature and iodomethane (13.1 g, 92 mmoles) in dimethylformamide (30 ml) was added dropwise. The mixture was heated to 80° for 17 hours, cooled to room temperature, and treated slowly with absolute ethanol (5 ml). The solvents were evaporated under reduced pressure to yield an oil. The oil was partitioned between water (200 ml) and chloroform (200 ml). The chloroform phase was washed with water (100 ml), separated, and dried (sodium sulfate). Evaporation of the solvents gave an oil which upon trituration with 2-propanol gave a white solid. Recrystallization from 2-propanol gave 12.9 g (64%) of a white solid, mp 72-74° [lit [12] mp 73-75°]; ir (potassium bromide): 1780, 1700 (C=O) cm^{-1}; nmr (unisol-d): δ 3.00 (s, 3H, N-CH_3), 3.15 (m, 2H, ring CH_2), 3.77 (s, 3H, OCH_3), 4.06 (m, 1-H, C_3-H), 6.93 (m, 4H, ArH).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.73; H, 5.99; N, 6.39. Found: C, 65.76; H, 5.96; N, 6.25.

3-(3,4-Dimethoxyphenyl)-1-(methyl)pyrrolidine-2,5-dione (**14**).

Compound **14** was prepared in a similar manner as described for **11** to give in 54% yield (2-propanol) a white solid, mp 79-81° [lit [13]]; ir (potassium bromide): 1785, 1695 (C=O, imide) cm^{-1}; nmr (deuteriochloroform): δ 2.53-3.43 (m, including s at 3.07, N-CH_3, 5H), 3.87-4.07 (m, including s at 3.87, OCH_3, 7H), 6.77 (m, 3H, ArH).

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.63; H, 6.08; N, 5.62. Found: C, 62.39; H, 6.25; N, 5.79.

trans-4-Ethoxycarbonyl-1-methyl-3-phenylpyrrolidine-2,5-dione (**16**).

A 50% mineral oil dispersion of sodium hydride (10.6 g, 220 mmoles) was washed with hexane (3 x 20 ml) and suspended into a reaction flask in tetrahydrofuran (70 ml) under a nitrogen atmosphere. The suspension was heated to reflux and a mixture of **13** [9] (18.9 g, 100 mmoles) and diethyl carbonate (26.0 g, 220 mmoles) in tetrahydrofuran (70 ml) was added dropwise. The reaction mixture was refluxed for 36 hours, cooled, acidified with glacial acetic acid, and evaporated to afford a yellow oil. The oil was partitioned between chloroform (250 ml) and water (250 ml). The chloroform layer was separated, washed with water (100 ml), dried (sodium sulfate), filtered, and evaporated under reduced pressure. Trituration of the resulting oil with hexane afforded a solid. Recrystallization from diethyl ether gave 9.7 g (37%) of a white solid, mp 74-75°; ir (potassium bromide): 1800, 1720 (C=O, imide), 1760 (C=O, ester) cm^{-1}; nmr (deuteriochloroform): δ 1.30 (t, J = 8 Hz, 3H, CH_2, CH_3), 3.10 (s, 3H, N-CH_3), 3.85 (d, J = 6 Hz, 1H, C_3-H), 4.26 (q, J = 8 Hz, 2H, CH_2CH_3), 4.45 (d, J = 6 Hz, 1H, C_4-H), 7.26 (m, 5H, ArH).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.80; N, 5.36. Found: C, 64.31; H, 5.51; N, 5.28.

3-Ethoxycarbonyl-1-methyl-3-phenylpyrrolidine-2,5-dione (**17**).

Sodium metal (1.27 g, 0.055 g-atom) was charged into a reaction flask under nitrogen and absolute ethanol (35 ml) was added dropwise. The reaction mixture was cooled to 50° and **13** [9] (9.45 g, 50 mmoles) in anhydrous toluene (110 ml) was added. The reaction mixture was heated until the temperature reached 110°. Approximately 75 ml of ethanol-toluene azeotrope was removed *via* a Dean-Stark trap. The reaction mixture was cooled to room temperature and ethyl chloroformate (5.42 g, 50 mmoles) in anhydrous toluene (45 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature, refluxed for 1 hour, cooled, and treated with 10% sodium bicarbonate (40 ml). The toluene phase was separated and the aqueous layer was extracted with additional toluene (50 ml). The combined toluene extracts were dried (sodium sulfate), filtered, and evaporated to afford an oil. Fractional distillation gave 4.89 g (37%) of a colorless oil, bp 160-162° (0.6 mm); ir (film): 1785, 1750 (imide and ester) cm^{-1}; nmr (deuteriochloroform): δ 1.17 (t, J = 8 Hz, 3H, CH_2CH_3), 3.02 (s, 3H, N-CH_3), 3.05 (d, J = 18 Hz, 1H, C_4-H), 3.71 (d, J = 18 Hz, 1H, C_4-H), 4.20 (q, J = 8 Hz, 2H, CH_2CH_3), 7.40 (s, 5H, ArH).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.80; N, 5.36. Found: C, 64.61; H, 5.72; N, 5.31.

General Procedure for the Synthesis of 4-Ethoxalyl Derivatives **18-20**.

4-Ethoxalyl-3-(3-methoxyphenyl)-1-(methyl)pyrrolidine-2,5-dione (**18**).

A 50% mineral oil dispersion of sodium hydride (5.23 g, 109 mmoles) was washed with hexane (3 x 25 ml) and suspended in tetrahydrofuran (80 ml) and heated to reflux under a nitrogen atmosphere. The suspension was treated with a mixture of diethyl oxalate (15.9 g, 109 mmoles) and **11** (12.0 g, 55 mmoles) in tetrahydrofuran (180 ml). The reaction mixture was refluxed for 27 hours, cooled, and acidified with glacial acetic acid. Removal of solvents gave a viscous dark red oil. The oil was partitioned between chloroform (250 ml) and water (50 ml). The chloroform layer was separated and washed an additional four times with water (50 ml). After drying (sodium sulfate), the chloroform was evaporated to give a dark red oil. The oil was chromatographed on silica gel using a solvent system of chloroform-ethyl acetate (30%) to afford a solid. Recrystallization from ethyl acetate-hexane gave 2.0 g (11%) of a white solid, mp 99-100°; ir (potassium bromide): 1785, 1695 (C=O, imide), 1750 (C=O, ester), 1650 (C=C-OH) cm^{-1}; nmr (deuteriochloroform): δ 1.07 (t, J = 8 Hz, 3H, CH_2CH_3), 3.10 (s, 3H, N-CH_3), 3.80 (s, 3H, OCH_3), 4.07 (q, J = 8 Hz, 2H, OCH_2CH_3), 4.77 (s, 1H, C_3-H), 6.80 (m, 4H, ArH).

Anal. Calcd. for $C_{16}H_{17}NO_6$: C, 60.17; H, 5.38; N, 4.39. Found: C, 60.08; H, 5.19; N, 4.18.

3-(3,4-Dimethoxyphenyl)-4-ethoxalyl-1-(methyl)pyrrolidine-2,5-dione (**19**).

Compound **19** was obtained in the same manner as described for **18** to yield a light yellow solid (ethyl acetate) in 42% yield, mp 120-122°; ir (potassium bromide): 1785, 1695 (C=O, imide), 1755 (C=O, ester), 1650 (C=C-OH) cm^{-1}; nmr (deuteriochloroform): δ 1.03 (t, 3H, CH_2CH_3), 3.10 (s, 3H, N-CH_3), 3.83 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.73 (s, 1H, C_3-H), 6.76 (br s, 3H, ArH).

Anal. Calcd. for $C_{17}H_{19}NO_7$: C, 58.44; H, 5.49; N, 4.01. Found: C, 58.86; H, 5.65; N, 3.97.

3-(3,4-Dimethoxyphenyl)-4-ethoxalyl-1-(*n*-propyl)pyrrolidine-2,5-dione (**20**).

Compound **20** was prepared in a similar manner. Flash chromatography of the crude reaction product on silica gel using an ethyl acetate-hexane (50%) solvent system afforded 2.65 g (40%) of a yellow solid. An analytical sample was prepared by recrystallization from diethyl ether to give a white solid, mp 90-92°; ir (potassium bromide): 1780, 1700 (C=O, imide), 1750 (C=O, ester); nmr (deuteriochloroform): δ 0.90 (t, J = 8 Hz, 3H, $CH_2CH_2CH_3$), 1.11 (t, J = 8 Hz, 3H, OCH_2CH_3), 1.61 (m, 2H, $CH_2CH_2CH_3$), 3.57 (t, J = 8 Hz, N-CH_2), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.11 (q, J = 8 Hz, 2H, OCH_2CH_3), 4.76 (s, 1H, C_3-H), 6.78 (m, 3H, ArH).

Anal. Calcd. for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.42; H, 6.15; N, 3.73.

3-(3,4-Dimethoxyphenyl)-1-methyl-4-(methylene)pyrrolidine-2,5-dione (**26**).

Using a reported procedure [8], sodium hydride (126 mg, 3.0 mmoles)

was washed with hexane (3 x 20 ml) and suspended in tetrahydrofuran (15 ml). A solution of **19** (1.0 g, 3.0 mmoles) in tetrahydrofuran (10 ml) was added in a dropwise manner. During the addition, hydrogen evolution was noted. After stirring for 0.5 hour, anhydrous gaseous formaldehyde, generated by thermal cracking of paraformaldehyde, was passed into the reaction mixture by means of nitrogen gas for ten minutes. The reaction mixture was filtered through a celite pad and the solvent was evaporated under reduced pressure. The residue was dissolved in methylene chloride (50 ml) and washed with saturated sodium bicarbonate solution (50 ml). The methylene chloride layer was separated, dried (sodium sulfate), and evaporated to yield a yellow oil. Flash chromatography on silica gel using ethyl acetate-hexane (80%) (500 ml), followed by elution of the product with ethyl acetate-hexane (50%) (100 ml) gave 191 mg (26%) of pure product [Rf = 0.2 ethyl acetate-hexane (50%)]. An analytical sample was prepared by recrystallization from diethyl ether to afford a white solid, mp 104-105°; nmr (deuteriochloroform): δ 3.09 (s, 3H, N-CH_3), 3.82 (s, 6H, OCH_3), 4.34 (s, 1H, C_5-H), 5.52 (d, J = 2 Hz, 1H, C=CH), 6.48 (d, J = 2 Hz, 1H, C=CH), 6.78 (m, 3H, ArH).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 68.18; H, 5.77; N, 5.27.

General Procedure for the Reaction of Ethoxalyl Derivatives **18-20** with Triethylamine and Formaldehyde. 3-(3,4-Dimethoxyphenyl)-4-methyl-1-*n*-propyl-3-pyrroline-2,5-dione (**4**).

A mixture of **20** (7.0 g, 18.5 mmoles), triethylamine (7 ml) and 40% aqueous formaldehyde (7 ml) in dioxane (120 ml)-water (120 ml) was stirred overnight at room temperature. The reaction mixture was acidified with 6*N* hydrochloric acid. The solvents were evaporated under reduced pressure and the residue was dissolved in diethyl ether (100 ml). The diethyl ether was washed with saturated sodium bicarbonate (1 x 50 ml), water (1 x 50 ml), dried (sodium sulfate), filtered, and evaporated to yield a yellow oil. Flash chromatography on silica gel using hexane-ethyl acetate (50%) gave 2.48 g (54%) of a yellow solid. Recrystallization from petroleum ether (bp 39-55°) gave an analytical sample, mp 88.5-90°; ir (potassium bromide); 1770, 1710 (C=O, imide), 1620 (C=C) cm^{-1}; nmr (deuteriochloroform): δ 0.90 (t, J = 8 Hz, 3H, CH_2CH_3), 1.62 (m, 2H, CH_2CH_3), 2.19 (s, 3H, C_4-CH_3), 3.50 (t, J = 8 Hz, N-CH_2), 3.90 (s, 6H, OCH_3), 7.05 (m, 3H, ArH).

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.41; H, 6.63; N, 4.84. Found: C, 66.48; H, 6.69; N, 4.73.

1,4-Dimethyl-3-(3-methoxyphenyl)-3-pyrroline-2,5-dione (**21**).

Compound **21** was prepared in a similar fashion to give a light yellow solid (ethanol-water) in 47% yield, mp 104-106°; ir (potassium bromide): 1770, 1700 (C=O, imide) cm^{-1}; nmr (deuteriochloroform): δ 2.20 (s, 3H, C_4-CH_3), 3.07 (s, 3H, N-CH_3), 3.84 (s, 3H, OCH_3), 7.26 (m, 4H, ArH).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.66; N, 6.06. Found: C, 67.35; H, 5.58; N, 5.98.

3-(3,4-Dimethoxyphenyl)-1,4-dimethyl-3-pyrroline-2,5-dione (**22**).

In a similar manner **22** was obtained as dark yellow crystals (2-propanol) in 18% yield based on **14**, mp 145-147°; ir (potassium bromide): 1770, 1700 (C=O, imide) cm^{-1}; nmr (deuteriochloroform): δ 2.19 (s, 3H, C_4-CH_3), 3.05 (s, 3H, N-CH_3), 3.91 (s, 6H, OCH_3), 6.98 (m, 3H, ArH).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.07; H, 5.86; N, 5.27.

Isomerization of **26** to **22**.

A mixture of **26** (13.1 mg) and triethylamine (1 drop) in ethanol (10 ml) was stirred overnight at room temperature. The bright yellow solution was evaporated to yield a yellow solid. The solid was washed with diethyl ether and dried to yield 5.5 mg of **22**, mp 138-141°; [Rf = 0.4 compared with **26**, Rf = 0.24, ethyl acetate-hexane (50%)]. The Rf for **22** was identical with authentic **22** prepared from **19**, aqueous formaldehyde, and triethylamine; nmr (deuteriochloroform): δ 2.19 (s, 3H, C_4-CH_3), 3.05 (s, 3H, N-CH_3), 3.91 (s, 6H, OCH_3), 6.98 (m, 3H, ArH). The nmr spectrum was also identical with that of authentic **22**.

cis-3-(3,4-Dimethoxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine-2,5-dione (**7**).

A mixture of **4** (1.68 g, 6.0 mmoles) and 0.5 g of 10% palladium on carbon in ethanol (200 ml) was shaken on a Parr hydrogenator at an initial pressure of 46 psi. After the theoretical amount of hydrogen had been absorbed, the catalyst was filtered and the solvent was removed under reduced pressure to yield a white solid. Recrystallization from diethyl ether gave 0.93 g (55%) of a white crystalline solid, mp 121-123°; ir (potassium bromide): 1780, 1700 (C=O, imide) cm^{-1}; nmr (deuteriochloroform): δ 0.92 (d, J = 8 Hz, 3H, C_4-CH_3), 0.96 (t, J = 8 Hz, 3H, CH_2CH_3), 1.60 (m, 2H, CH_2CH_3), 3.13 (m, 1H, C_4-H), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.10 (d, J = 10 Hz, 1H, C_3-H), 6.66 (m, 3H, ArH).

Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.28; N, 4.81. Found: C, 66.06; H, 7.27; N, 4.69.

cis-3-(3,4-Dihydroxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine Hydrobromide (**23**).

cis-3-(3,4-Dimethoxyphenyl)-4-methyl-1-(*n*-propyl)-pyrrolidine-2,5-dione (**7**) (6.36 g, 21.8 mmoles) in tetrahydrofuran (150 ml) was added to a suspension of lithium aluminum hydride (4.97 g, 131 mmoles) in tetrahydrofuran (150 ml) under nitrogen and the mixture was refluxed overnight. The reaction mixture was cooled and water was carefully added to decompose the excess lithium aluminum hydride. The reaction mixture was filtered, evaporated under reduced pressure, and the resulting residue was partitioned between methylene chloride (250 ml) and water (100 ml). The methylene chloride layer was separated, dried (sodium sulfate), filtered, and evaporated to yield an oil. The oil was flash chromatographed (methylene chloride, 98: methanol, 2: ammonium hydroxide, 0.5) to give 4.22 g (74%) of an oil. The oil was dissolved in 48% hydrobromic acid (45 ml) and refluxed for 3 hours under a nitrogen atmosphere. Evaporation of the solvent followed by azeotroping with absolute ethanol gave 4.4 g of **23**. Recrystallization from 2-propanol-diethyl ether gave 3.05 g (44%) based on **7** of a gray solid, mp 167-170°. An analytical sample was prepared by an additional recrystallization from 2-propanol-diethyl ether to yield a brown crystalline solid, mp 169-172°; ir (potassium bromide): 3300 (OH) cm^{-1}; nmr (deuterium oxide) δ 0.66 (d, 3H, J = 8 Hz, C_4-CH_3), 0.97 (t, J = 8 Hz, 3H), 1.47-3.82 (m, 10H), 6.73 (m, 3H, ArH).

Anal. Calcd. for $C_{14}H_{22}BrNO_2$: C, 53.16; H, 7.03; N, 4.43. Found: C, 53.28; H, 7.01; N, 4.29.

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