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**Meldrum's Acid in Organic Synthesis. V. Versatile One-pot Synthesis of Indolepropionic Esters *via* Simultaneous Condensation of Three Different Carbon Components, Indole, Aldehydes and Meldrum's Acid<sup>1)</sup>**

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When an acetonitrile solution of Meldrum's acid (1), indole (5), and an aliphatic or aromatic aldehyde (8) in the presence of a small amount of proline (except in the case of acetaldehyde) was allowed to stand at 30°C, a simultaneous condensation of three different carbon components occurred readily to give a 5-(1*H*-indol-3-ylalkyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (11) in high yield. The reaction proceeded regardless of the nature of the aldehyde. An ethanolysis of 11 with loss of acetone and carbon dioxide took place smoothly in boiling ethanol-pyridine (1:10) containing a small amount of copper powder to give an ethyl  $\beta$ -alkylindolepropionate (2). These two reactions, the condensation and the ethanolysis, were combined in a one-pot procedure, which may provide an efficient and convenient synthetic method for various ethyl indolepropionates (2).

**Keywords**—Meldrum's acid; indole; aldehyde; condensation of three different carbon components; one-pot synthesis; ethanolysis; indolepropionic ester

Until recently, Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione (1),<sup>2,3)</sup> has received little attention, except for its use as a substitute for acyclic malonic esters. However, 1 is now known to be very versatile because of its unusual reactivities due to its great acidity ( $pK_a$  4.97)<sup>4)</sup> compared with usual acyclic malonic esters ( $pK_a$  13.7 for ethyl malonate), steric rigidity, and marked tendency to regenerate acetone.

Recently, several reports have described advantages of some derivatives of 1 over their acyclic analogs. Dauben<sup>5)</sup> reported an efficient and simple synthesis of  $\delta$ -damascone based on the use of isopropylidene Meldrum's acid as a dienophile. Trost<sup>6)</sup> and Bloch<sup>7)</sup> showed that bromo Meldrum's acids are useful as mild brominating agents. Danishefsky<sup>8)</sup> synthesized a highly activated cyclopropane derivative of 1. We reported a general and versatile synthesis of  $\beta$ -keto esters from 1 *via* acyl Meldrum's acids.<sup>9)</sup> In the present paper, we report another remarkable example, a versatile and efficient one-pot synthesis of various ethyl indolepropionates (2), of the synthetic usefulness of 1, which is readily accessible from malonic acid and acetone on a relatively large scale.<sup>2)</sup>

During the course of our synthetic work on an antitumor indole alkaloid, ellipticine (3), and its analogs, the need for an efficient synthetic method for indolepropionic esters (2) substituted at the  $\beta$ -position became evident. Indolepropionic acid (4) and its esters are readily prepared by the condensation of indole (5) and acrylic acid (6),<sup>10)</sup> but crotonic acid and methacrylic acid gave no condensation products with indole. So far, there is no general and practical method for the synthesis of 2. Recently, we synthesized ethyl  $\beta$ -methyl-1*H*-indole-3-propionate (2a) from a Mannich base (7) of indole and ethyl malonate, but the yield was still unsatisfactory.<sup>11)</sup>

Since the  $\alpha$ -protons of 1 are extraordinarily acidic, it is expected that 1 can react with an electrophile even in the absence of a strong base. Actually, various aldehydes (8) react with 1 to give 9,<sup>3,12)</sup> and in some cases a further reaction takes place, namely the Michael addition of a second molecule of 1 as a nucleophile with 9 occurs in the presence<sup>13)</sup> and absence<sup>14)</sup> of a weak base to give 10. If another appropriate nucleophile is present in this reaction system, it may react with 9 in place of the second molecule of 1.

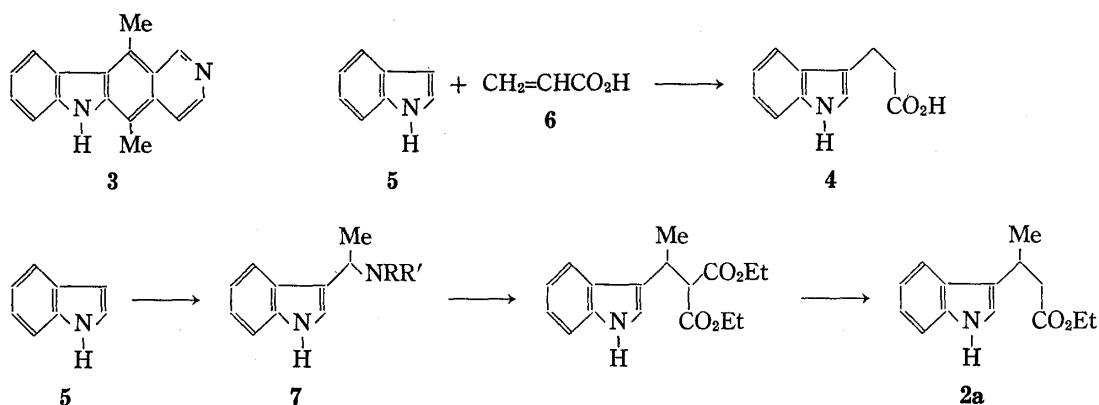


Chart 1

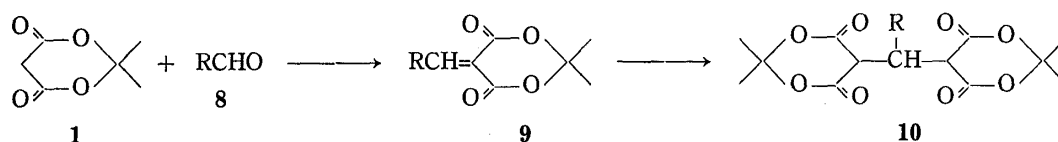
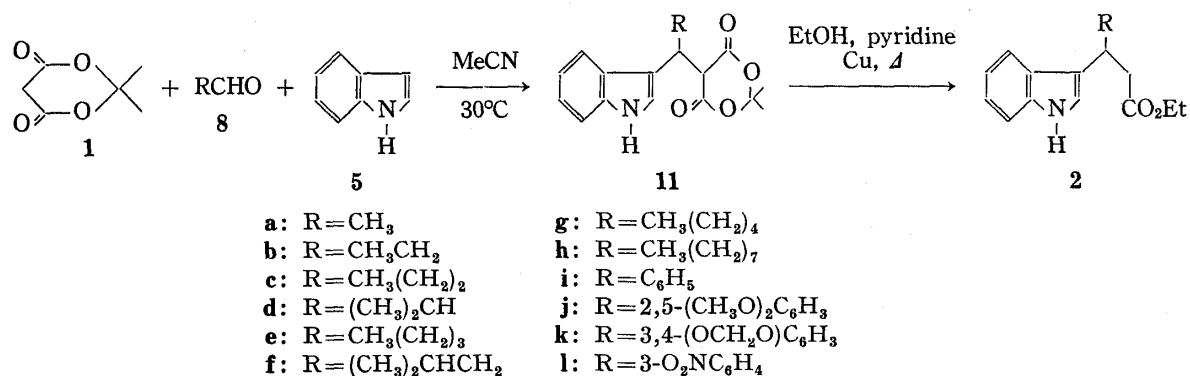


Chart 2

When an acetonitrile solution of a mixture of 1, acetaldehyde (8a), and indole (5) (1 : 2 : 1 eq) was allowed to stand at 30°C for 7 h, a new simultaneous condensation of three different carbon components occurred quite smoothly. After evaporation of the solvent, the resulting crystals were washed with hexane to give 11a in a nearly pure state almost quantitatively.<sup>15)</sup> Acyclic malonic esters instead of 1 were completely unreactive under similar conditions. Since this condensation was accelerated by addition of a small amount of proline, various aliphatic aldehydes (8b—h; 2 eq) with straight and branched chains and aromatic aldehydes (8i—l; 1 eq) with electron-donating and electron-withdrawing substituents were condensed with 1 and 5 (1 eq each) in the presence of proline (0.05 eq). The reaction proceeded quite smoothly regardless of the nature of the aldehyde to give various condensation products (11) in 80—96% yields.<sup>16)</sup> The crude products were pure enough for the next reaction, but recrystallization for the solid products (11a, g—l) and chromatography for the oily products (11b—f) were employed in order to obtain pure 11.

The reaction of equimolar amounts of 1 and benzaldehyde (8i) is known to give the 2:1 product (10i) in 93% yield.<sup>14)</sup> The addition of 5 (1 eq) as presented here, however, changed the product completely from 10i to 11i, clearly indicating that 5 is much more reactive than 1 in the Michael reaction with 9.



- |  |   |
|--|---|
| a: $\text{R}=\text{CH}_3$                  | g: $\text{R}=\text{CH}_3(\text{CH}_2)_4$                      |
| b: $\text{R}=\text{CH}_3\text{CH}_2$       | h: $\text{R}=\text{CH}_3(\text{CH}_2)_7$                      |
| c: $\text{R}=\text{CH}_3(\text{CH}_2)_2$   | i: $\text{R}=\text{C}_6\text{H}_5$                            |
| d: $\text{R}=(\text{CH}_3)_2\text{CH}$     | j: $\text{R}=2,5-(\text{CH}_3\text{O})_2\text{C}_6\text{H}_3$ |
| e: $\text{R}=\text{CH}_3(\text{CH}_2)_3$   | k: $\text{R}=3,4-(\text{OCH}_2\text{O})\text{C}_6\text{H}_3$  |
| f: $\text{R}=(\text{CH}_3)_2\text{CHCH}_2$ | l: $\text{R}=3-\text{O}_2\text{NC}_6\text{H}_4$               |

Chart 3

The direct ethanolysis of **11** to **2** was next examined. Meldrum's acid (**1**) and its monoalkyl derivatives are labile in acidic solution,<sup>17)</sup> and when heated with phenols and cyclohexanols, **1** gave malonic acid monoesters in good yields.<sup>18)</sup> On the other hand, they are rather stable in alkaline solution because their enolate anions resist the nucleophilic attack of hydroxide anion.<sup>4)</sup>

In fact, compounds **11** were almost inert to ethanolysis in the presence and absence of a strong base such as sodium ethoxide, potassium hydroxide, and potassium cyanide, while in the presence of a strong acid such as *p*-toluenesulfonic acid and sulfuric acid **11** disappeared rather rapidly, but gave only a complex product mixture. After several unsuccessful attempts, the most satisfactory results were obtained by ethanolysis in pyridine.

When **11** was heated in ethanol-pyridine (1:10), the ethanolysis took place quite smoothly with liberation of acetone followed by gradual decarboxylation to give **2** in a high yield. Addition of a small amount of copper powder accelerated this decarboxylation.

Finally, an efficient and convenient one-pot synthetic method for ethyl indolepropionates (**2**) was established, and a typical example (the synthesis of **2a**) is as follows: an acetonitrile solution of **1**, **8a** and **5** (1:2:1) was allowed to stand at 30°C for 7 h, and then the solvent was evaporated off *in vacuo* to leave a solid, which, without further purification, was dissolved in ethanol-pyridine (1:10) containing a small amount of copper powder and heated under reflux for 3 h. After removal of the solvent and the copper, the residue was distilled under reduced pressure to give ethyl  $\beta$ -methyl-1*H*-indole-3-propionate (**2a**) in 80% yield.

Similarly, various ethyl indolepropionates (**2b—g, i—l**) were synthesized in 62—87% overall yields. Purification of undistillable products (**2i—l**) derived from aromatic aldehydes (**8i—l**) was carried out by column chromatography on silica gel.<sup>19)</sup>

In summary, the Meldrum's acid procedure presented here may provide an efficient and versatile method for the synthesis of various indolepropionic esters as well as a remarkable example of the novel Mannich-type condensation of three different carbon components.

### Experimental

**General Procedures for the Preparation of 5-(1*H*-Indol-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-diones (11)—a.** For **11a**: An MeCN solution (4 ml) of indole (**5**; 234 mg; 2 mmol), acetaldehyde (**8a**: 176 mg; 4 mmol), and 2,2-dimethyl-1,3-dioxane-4,6-dione (**1**: 288 mg; 2 mmol) was allowed to stand at 28—30°C for 7 h. After evaporation of the solvent, the residual colorless crystals were washed with hexane to give almost pure **11a**.

b) For **11b—f**: An MeCN solution (4 ml) of **5** (234 mg; 2 mmol), an aldehyde (**8b—f**: 4 mmol), **1** (288 mg; 2 mmol), and L-proline (12 mg; 0.1 mmol) was stirred at 28—30°C for 24—28 h. After evaporation of the solvent, the residue was passed through a short column of silica gel to give almost pure **11b—f**.

c) For **11g—j**: An MeCN solution (4 ml) of **8g, h** (4 mmol) or **8i, j** (2 mmol), **5** (2 mmol), **1** (2 mmol), and proline (12 mg; 0.1 mmol) was treated as described above. After 18—28 h, the solvent was evaporated off *in vacuo*, and the residue was crystallized by addition of EtOH and collected by filtration to give almost pure **11g—j**.

d) For **11k, l**: **8k, l** (2 mmol) was treated as described above. Colorless crystals precipitated from the reaction mixture were collected by filtration and washed with a small amount of EtOH to give almost pure **11k, l**.

Yields and physical data are as follows.

5-[1-(1*H*-Indol-3-yl)ethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11a**): Yield 98%, mp 119—120°C (dec.) (EtOH). IR  $\nu_{\max}^{\text{Nujol}}$  cm<sup>-1</sup>: 3400, 1770, 1735. NMR (CDCl<sub>3</sub>)  $\delta$ : 1.32 (3H, s), 1.59 (3H, s), 1.65 (3H, d, *J*=7 Hz), 3.28 (1H, d, *J*=3 Hz), 4.18—4.52 (1H, m). *Anal.* Calcd for C<sub>16</sub>H<sub>17</sub>NO<sub>4</sub>: C, 66.88; H, 5.96; N, 4.88. Found: C, 67.48; H, 6.13; N, 4.69.

5-[1-(1*H*-Indol-3-yl)propyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11b**): Yield 88%, viscous oil. IR  $\nu_{\max}^{\text{neat}}$  cm<sup>-1</sup>: 3400, 1770, 1735. MS *m/e*: 301 (M<sup>+</sup>), 199, 170, 158, 149, 84 (base). NMR (CDCl<sub>3</sub>)  $\delta$ : 1.62 (3H, s), 3.80 (1H, d, *J*=3 Hz), 3.92—4.30 (1H, m), 7.1—7.5 (4H, m), 7.6—7.85 (1H, m), 8.2 (1H, s).

5-[1-(1*H*-Indol-3-yl)butyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11c**): Yield 93%, viscous oil. IR  $\nu_{\max}^{\text{neat}}$  cm<sup>-1</sup>: 3400, 1770, 1735. MS *m/e*: 315 (M<sup>+</sup>), 213, 170 (base), 156. NMR (CDCl<sub>3</sub>)  $\delta$ : 0.94 (3H, t, *J*=6 Hz), 1.21 (3H, s), 1.61 (3H, s), 3.77 (1H, d, *J*=3 Hz), 4.02—4.21 (1H, m), 7.0—7.45 (4H, m), 7.6—7.9 (1H, m), 8.5 (1H, s).

5-[1-(1*H*-Indol-3-yl)-2-methylpropyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11d**): Yield 96%, viscous oil. IR  $\nu_{\max}^{\text{neat}}$  cm<sup>-1</sup>: 3400, 1770, 1735. MS *m/e*: 315 (M<sup>+</sup>), 213, 170 (base). NMR (CDCl<sub>3</sub>)  $\delta$ : 0.84 (3H, d, *J*=

6 Hz), 1.09 (3H, s), 1.21 (3H, d,  $J=6$  Hz), 1.60 (3H, s), 3.70 (1H, d,  $J=3$  Hz), 3.92 (1H, d,  $J=3$  Hz), 7.05—7.45 (4H, m), 7.6—7.9 (1H, m), 8.25 (1H, s).

5-[1-(1*H*-Indol-3-yl)pentyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11e**): Yield 83%, viscous oil. IR  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 3450, 1770 (sh), 1740. NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.85 (3H, t,  $J=6$  Hz), 1.15 (3H, s), 1.66 (3H, s), 3.79 (1H, d,  $J=3$  Hz), 3.9—4.3 (1H, m), 7.1—7.4 (4H, m), 7.6—7.8 (1H, m), 8.50 (1H, s).

5-[1-(1*H*-Indol-3-yl)-3-methylbutyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11f**): Yield 90%, viscous oil. IR  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 3450, 1770 (sh), 1740. NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.93 (6H, d,  $J=6$  Hz), 1.17 (3H, s), 1.59 (3H, s), 3.75 (1H, d,  $J=3$  Hz), 3.9—4.4 (1H, m), 7.1—7.4 (4H, m), 7.6—7.85 (1H, m), 8.40 (1H, s).

5-[1-(1*H*-Indol-3-yl)hexyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11g**): Yield 80%, mp 98—100°C (EtOH). IR  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 3400, 1780, 1740. NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.85 (3H, t,  $J=6$  Hz), 1.19 (3H, s), 1.60 (3H, s), 3.77 (1H, d,  $J=3$  Hz), 4.00—4.38 (1H, dt,  $J=3, 9$  Hz), 7.1—7.45 (4H, m), 7.6—7.85 (1H, m), 8.30 (1H, s). *Anal.* Calcd for  $\text{C}_{20}\text{H}_{25}\text{NO}_4$ : C, 69.95; H, 7.33; N, 4.88. Found: C, 70.04; H, 7.30; N, 4.12.

5-[1-(1*H*-Indol-3-yl)nonyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11h**): Yield 83%, mp 95—99°C (EtOH). *Anal.* Calcd for  $\text{C}_{23}\text{H}_{31}\text{NO}_4$ : C, 71.66; H, 8.11; N, 3.63. Found: C, 71.71; H, 8.11; N, 3.44.

5-[1*H*-Indol-3-yl(phenyl)methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11i**): Yield 92%, mp 141—143°C (dec.) (EtOH). *Anal.* Calcd for  $\text{C}_{21}\text{H}_{19}\text{NO}_4$ : C, 72.19; H, 5.48; N, 4.01. Found: C, 72.02; H, 5.43; N, 4.11.

5-[(2,5-Dimethoxyphenyl)-1*H*-indol-3-ylmethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11j**): Yield 88%, mp 138—139°C (dec.) (EtOH). *Anal.* Calcd for  $\text{C}_{23}\text{H}_{23}\text{NO}_6$ : C, 67.46; H, 5.66; N, 3.42. Found: C, 67.54; H, 5.70; N, 3.36.

5-[(1,3-Benzodioxol-5-yl)-1*H*-indol-3-ylmethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11k**): Yield 92%, mp 159—162°C (dec.) (EtOH). *Anal.* Calcd for  $\text{C}_{22}\text{H}_{19}\text{NO}_6$ : C, 67.17; H, 4.87; N, 3.56. Found: C, 66.97; H, 4.89; N, 3.40.

5-[1*H*-Indol-3-yl-(3-nitrophenyl)methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11l**): Yield 87%, mp 174°C (dec.) (EtOH). *Anal.* Calcd for  $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_6$ : C, 63.95; H, 4.60; N, 7.10. Found: C, 63.74; H, 4.54; N, 6.84.

**One-pot Synthesis of Ethyl  $\beta$ -Methyl-1*H*-indole-3-propionate (2a)**—An MeCN solution (120 ml) of **5** (11.7 g; 0.1 mol), **8a** (8.8 g; 0.2 mol), and **1** (14.4 g; 0.1 mol) was allowed to stand at 25—30°C for 4.5—7 h. Removal of the solvent by evaporation *in vacuo* left crystals of **11a**, which were dissolved in pyridine (200 ml). Ethanol (20 ml) and copper powder (2.5 g) were added to the solution, and the mixture was heated under reflux for 3 h. After removal of the solvent *in vacuo*, the residual oil was dissolved in ether and separated from the copper powder by decantation. The ether solution was washed with 2 *N* HCl and  $\text{H}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$ , and concentrated to leave an oil, which was subjected to vacuum distillation to give a colorless oil, **2a** (18.5 g; 80%),<sup>11</sup> bp 179—181°C (2 Torr). IR  $\nu_{\text{max}}^{\text{neat}}$   $\text{cm}^{-1}$ : 3400, 1720. NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.30 (3H, t,  $J=7$  Hz), 1.40 (3H, d,  $J=6$  Hz), 2.30—3.05 [2H, octet (AB portion of ABX),  $J_{\text{AB}}=15$  Hz,  $J_{\text{AX}}=8$  Hz,  $J_{\text{BX}}=6$  Hz], 3.35—3.95 (1H, m), 4.10 (2H, q,  $J=7$  Hz), 6.9—7.45 (4H, m), 7.5—7.8 (1H, m), 8.0 (1H, s).

The following ethyl indolepropionates were synthesized in a similar manner.

Ethyl  $\beta$ -Ethyl-1*H*-indole-3-propionate (**2b**): Yield 65%, bp 166—169°C (0.6 Torr). MS *m/e* relative intensity (%): 245 ( $\text{M}^+$ , 30), 216 (40), 174 (15), 158 (100), 143 (30), 130 (15).

Ethyl  $\beta$ -Propyl-1*H*-indole-3-propionate (**2c**): Yield 62%, bp 160—162°C (0.4 Torr). MS *m/e* relative intensity (%): 259 ( $\text{M}^+$ , 45), 216 (60), 172 (100), 143 (40), 130 (60).

Ethyl  $\beta$ -(1-Methylethyl)-1*H*-indole-3-propionate (**2d**): Yield 64%, bp 160—164°C (0.3 Torr). MS *m/e* relative intensity (%): 259 ( $\text{M}^+$ , 25), 216 (100), 174 (25), 172 (30), 143 (40), 130 (15).

Ethyl  $\beta$ -Butyl-1*H*-indole-3-propionate (**2e**): Yield 68%, bp 165—170°C (0.3 Torr). MS *m/e* relative intensity (%): 273 ( $\text{M}^+$ , 50), 216 (85), 186 (100), 143 (40), 130 (70).

Ethyl  $\beta$ -(2-Methylpropyl)-1*H*-indole-3-propionate (**2f**): Yield 68%, bp 174—177°C (0.3 Torr). MS *m/e* relative intensity (%): 273 ( $\text{M}^+$ , 50), 216 (65), 186 (75), 143 (45), 130 (100).

Ethyl  $\beta$ -Pentyl-1*H*-indole-3-propionate (**2g**): Yield 63%, bp 182—186°C (0.2 Torr). MS *m/e* relative intensity (%): 287 ( $\text{M}^+$ , 50), 216 (95), 200 (100), 174 (20), 143 (45), 130 (80).

Ethyl  $\beta$ -Phenyl-1*H*-indole-3-propionate (**2l**): Yield 85%, mp 96—98°C (65% EtOH). *Anal.* Calcd for  $\text{C}_{19}\text{H}_{19}\text{NO}_2$ : C, 77.79; H, 6.53; N, 4.77. Found: C, 77.69; H, 6.51; N, 4.75.

Ethyl  $\beta$ -(2,5-Dimethoxyphenyl)-1*H*-indole-3-propionate (**2j**): Yield 86%, hard oil. MS *m/e* relative intensity (%): 353 ( $\text{M}^+$ , 40), 266 (100), 130 (80). The corresponding carboxylic acid,  $\beta$ -(2,5-dimethoxyphenyl)-1*H*-indole-3-propanoic acid, mp 186—187°C (45% EtOH). *Anal.* Calcd for  $\text{C}_{19}\text{H}_{19}\text{NO}_4$ : C, 70.14; H, 5.89; N, 4.31. Found: C, 70.03; H, 5.91; N, 4.27.

Ethyl  $\beta$ -(1,3-Benzodioxol-5-yl)-1*H*-indole-3-propionate (**2k**): Yield 86%, hard oil. The corresponding carboxylic acid,  $\beta$ -1,3-benzodioxol-5-yl-1*H*-indole-3-propanoic acid, mp 167—168°C (30% EtOH). *Anal.* Calcd for  $\text{C}_{18}\text{H}_{15}\text{NO}_4$ : C, 69.89; H, 4.89; N, 4.53. Found: C, 69.80; H, 4.84; N, 4.48.

Ethyl  $\beta$ -(3-Nitrophenyl)-1*H*-indole-3-propionate (**2l**): Yield 70%, mp 138—139°C (EtOH). *Anal.* Calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_4$ : C, 67.44; H, 5.36; N, 8.28. Found: C, 67.46; H, 5.27; N, 8.23.

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