

## Articles

### New Practical Synthesis of Tenidap

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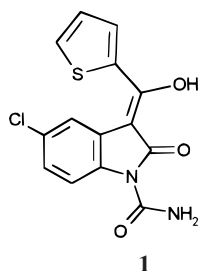
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#### Abstract:

The development of a new, practical synthesis to tenidap is described. *N,O*-Dialkoxy(aryloxy)carbonylation of 5-chloro-2-oxo-2,3-dihydroindole, followed by removal of the *O*-alkoxy(aryloxy)carbonyl group gave 1-[alkoxy(aryloxy)carbonyl]-5-chloro-2-oxo-2,3-dihydroindoles in good yields. The latter compounds were thenoylated in the 3-position. The role of DMAP in the acylation reaction is discussed. The structures of the thenoylated products and their enolate salts were investigated both in solution and solid phases. Ammonolysis of 5-chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-1-phenoxy-carbonyl-2,3-dihydroindole afforded the corresponding 1-carbamoyl derivative (tenidap) in high yield. The corresponding 1-ethoxy- and 1-methoxycarbonyl derivatives could not be similarly transformed to tenidap; loss of the alkoxy-carbonyl moiety occurred instead of carbamoylation.

#### Introduction

Oxindoles constitute a new class of drugs for the treatment of rheumatoid arthritis and osteoarthritis exhibiting cyclooxygenase inhibiting activity and cytokine modulating properties. An outstanding example of these antirheumatic oxindoles, tenidap **1** ((*Z*)-5-chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-dihydroindole-1-carboxamide) was discovered and developed by Pfizer, and regulatory approval was granted for its sodium salt in several countries.<sup>1,2</sup> Despite the very high market expectations, finally it was not launched because of serious side effects.



The methods previously described for the synthesis of tenidap are shown in Scheme 1. Two routes (a and b) were elaborated starting from 5-chloro-2-oxindole (**2**)<sup>3,4</sup> just differing in the sequence of the introduction of the substituents. According to method a, thenoylation of **2** with thiophen-2-carbonyl chloride to **3**<sup>4</sup> is followed by *N*-carbamoylation, with chlorosulfonylisocyanate and subsequent hydrolysis.<sup>5</sup> According to route b, 1-carbamoyl derivative **4** was prepared in the first step by the reaction of **2** with chlorosulfonylisocyanate<sup>5</sup> and subsequent hydrolysis. Thenoylation of compound **4** afforded tenidap **1**.<sup>5,6</sup> Intermediate **4** was also obtained by cyclisation of urea **5** in very low yield (route c).<sup>6</sup> Considering the published yields of the above procedures, route b seems to represent the only practical approach to tenidap **1**.

We were interested in a new patentable manufacturing synthesis of tenidap **1**, avoiding the use of the inconvenient chlorosulfonylisocyanate in the course of the procedure. Here we report a new synthesis of tenidap **1**, satisfying these criteria.<sup>7</sup>

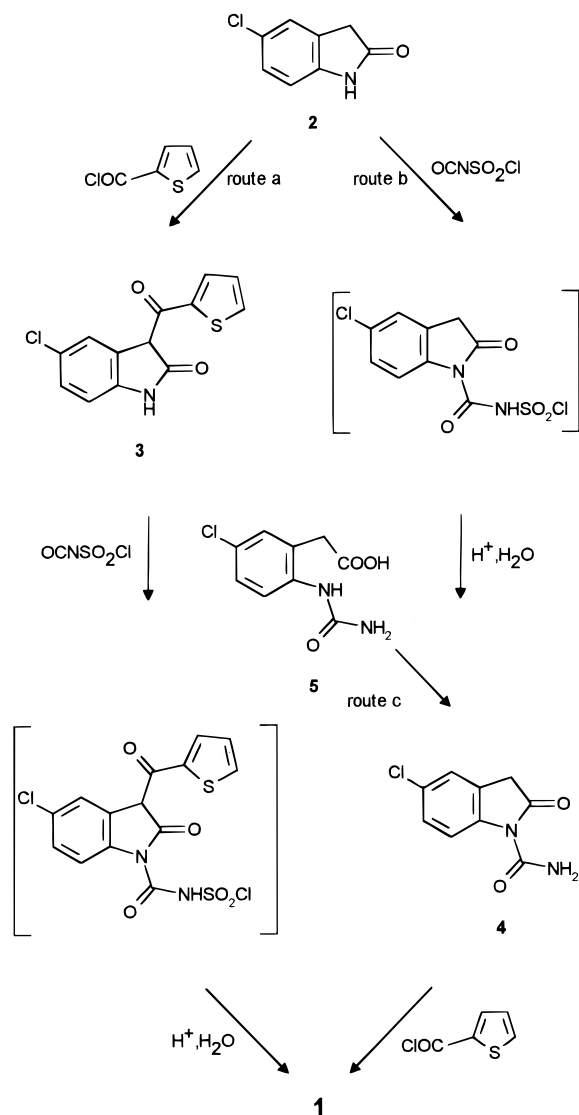
#### Results and Discussion

Our strategy for the new synthesis was to use the appropriate *N*-carboxylate as the precursor of the *N*-carbamoyl functionality, that is to introduce the *N*-carbamoyl moiety via alkoxy(aryloxy)carbonylation of the oxindole nitrogen followed by treatment with ammonia. Compounds **3** and **4** could also not be used for patent reasons. Therefore the *N*-carbamoyl group of tenidap **1** would have to be introduced in the last step of synthesis by ammonolysis of a key *N*-carboxylate intermediate **7** (Scheme 2) prepared by thenoylation of **6**.

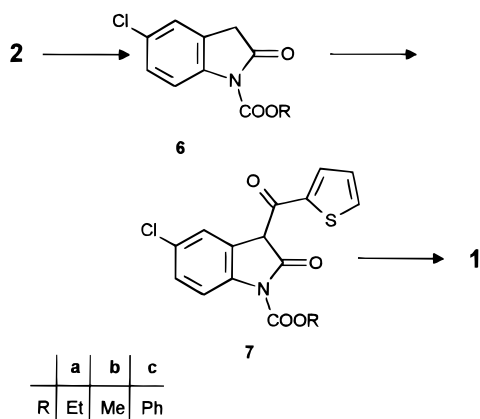
- (1) (a) Robinson, C. *Drugs Future* **1990**, *15*, 898. (b) *Drugs Future* **1993**, *18* (9), 875.  
 (2) Robinson R. P.; Reiter, L. A.; Barth, W. E.; Campeta, A. M.; Cooper, K.; Cronin, B. J.; Destito, R.; Donahue, K. M.; Falkner, F. C.; Fiese, E. F.; Johnson, D. L.; Kuperman, A. V.; Liston, T. E.; Malloy, D.; Martin, J. J.; Mitchell, D. Y.; Rusek, F. W.; Shamblin, S. L.; Wright, C. F. *J. Med. Chem.* **1996**, *39*, 10.

- (3) Junge, H. (BASF AG). Ger Offen. 21 58955, May 30, 1973; *Chem. Abstr.* **1973**, *79*, 66169z.  
 (4) Kadin, S. B. (Pfizer Inc.). EPA 153,818, February 4, 1985; *Chem. Abstr.* **1986**, *104*, 88427u.  
 (5) Crawford, Th. Ch. (Pfizer Inc.). EPA 155,828, March 15, 1985; *Chem. Abstr.* **1986**, *104*, 109466y.  
 (6) Kadin, S. B. (Pfizer Inc.). EPA 156,603, March 15, 1985; *Chem. Abstr.* **1986**, *104*, 109468a.  
 (7) Blaskó, G.; Lukács, G.; Reiter, J.; Flórián, E.; Porcs-Makkay, M.; Mezei, T.; Simig, G. (Egis Pharmaceuticals Ltd.). WO 97 36,895, April 3, 1997; *Chem. Abstr.* **1997**, *127*, 318879z.

Scheme 1



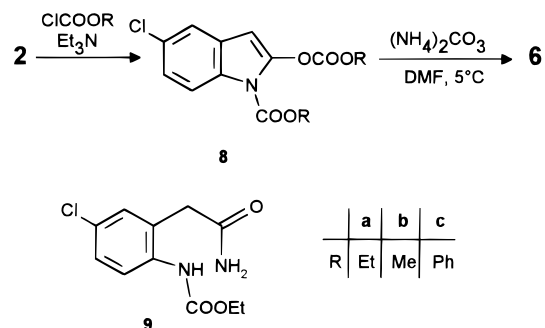
Scheme 2



First we addressed the task of preparing *N*-alkoxy-(aryloxy)carbonyloxindoles **6**.<sup>8</sup> Reaction of 2-oxindole with

(8) During the compilation of our manuscript the protection of the amide nitrogen of indol-2-ones with Boc and benzyloxycarbonyl group was reported using (Boc)<sub>2</sub>O and benzyl chloroformate, respectively, in THF in the presence of Na<sub>2</sub>CO<sub>3</sub> or NaHCO<sub>3</sub> at room temperature: Rajeswaran, W. G.; Cohen, L. A. *Tetrahedron* **1998**, *54*, 11375.

Scheme 3



an equivalent of ethyl chloroformate in the presence of triethylamine in THF is reported to give the corresponding 1-ethoxycarbonyl derivative after chromatographic separation.<sup>9</sup> The low yield (20%) can be attributed to simultaneous formation of *N,O*-diethoxycarbonylated product as indicated by our experiments. *N,O*-Diethoxycarbonylation of some 3-substituted 2-oxindoles with excess of ethyl chloroformate was reported.<sup>10</sup> Consequently we decided to carry out the synthesis of compounds **6** in a new two-step sequence starting from readily available 5-chloro-2-oxindole (**2**).<sup>3,4</sup>

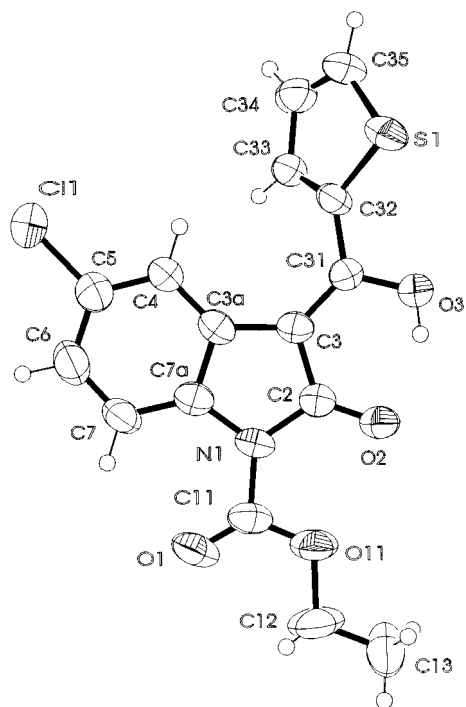
In the first step, oxindole **2** was treated with 2.2 equiv of ethyl chloroformate in the presence of triethylamine in THF to afford **8a** in excellent yield (Scheme 3). The corresponding methyl and phenyl esters (**8b** and **8c**) were obtained similarly. In the second step, selective *O*-dealkyl(aryl)oxycarbonylation of compounds **8** was accomplished with 1 equiv of ammonium carbonate in DMF under mild conditions to furnish **6** in good yield.

When applying more vigorous reaction conditions, different byproducts were formed, depending on the structure of the carbamate moiety. Thus, longer treatment of **8a** with ammonium carbonate at ambient temperature resulted in the formation of a ring-opened byproduct **9** (10% after 24 h), indicating attack of ammonia at the oxindole carbonyl group of initially formed **6a** (an ill omen regarding the introduction of the *N*-carbamoyl group via ethoxycarbonyl intermediate!). Heating **8a** with 2 equiv of ammonium carbonate at 80–90 °C in DMF for 5 h, **9** was obtained as the single product (79%). Similar result was obtained with ammonium acetate at 0–5 °C for 5 h. Although formation of byproduct **4** was observed after prolonged reaction of **8c** with ammonium carbonate in DMF at ambient temperature, elevated temperatures led to the formation of compounds **2** and **4**, demonstrating that in this case the carbamate carbonyl group of **6c** is attacked by ammonia more readily than the oxindole carbonyl.

Thenoylation of compounds **6** with thiophen-2-carbonyl chloride in the presence of 2.2 equiv of 4-(dimethylamino)-

(9) Caramella, P.; Coda Corsico, A.; Corsaro, A.; Del Monte, D.; Marinone Albini, F. *Tetrahedron* **1982**, *38*, 173.

(10) (a) Beccalli, E. M.; Marchesini, A. *Synthesis* **1992**, 265. (b) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Synthesis* **1992**, 891. (c) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Tetrahedron* **1992**, *48*, 5359. (d) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Tetrahedron* **1993**, *49*, 4741. (e) Beccalli, E. M.; Marchesini, A. *Synthetic Comm.*, **1993**, *23*, 2945. (f) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Tetrahedron* **1994**, *50*, 12697. (g) Beccalli, E. M.; Marchesini, A.; Pilati, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 579. (h) Beccalli, E. M.; Marchesini, A. *Org. Prep. Proced. Int.* **1995**, *27*, 113. (i) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Tetrahedron* **1996**, *52*, 3029.



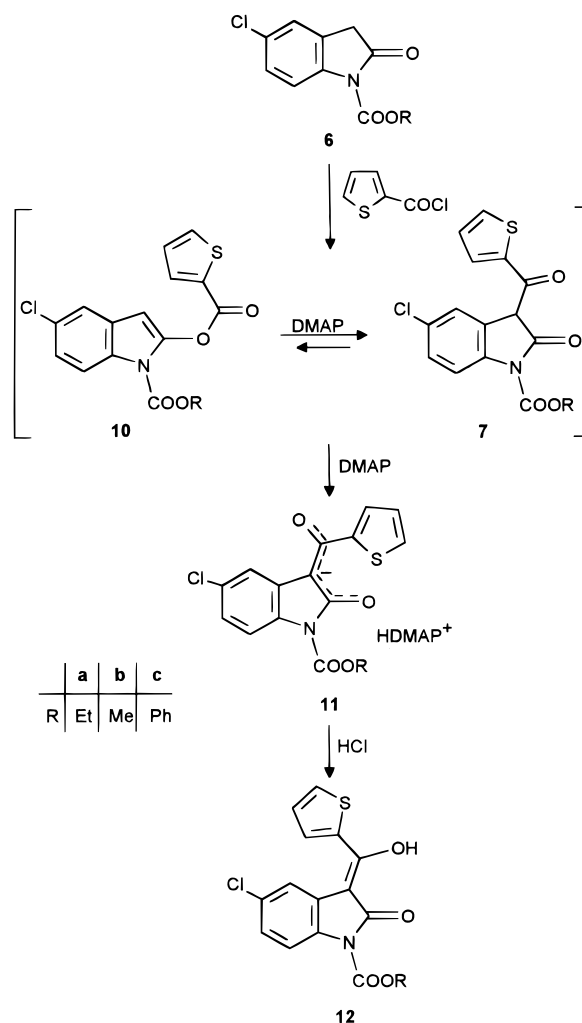
**Figure 1.** ORTEP drawing of **12a**. Thermal ellipsoids have been drawn at the 50% probability level.

pyridine (DMAP) in DMF followed by an acidic workup provided compounds **12** in good yield, which are the enolic forms of the required key intermediates **7**. The *Z* enol structure was assigned to compounds **12** based on  $^1\text{H}$  NMR studies where significant NOE between oxindole C4 and thiophene C3 hydrogens was detected. The X-ray structure analysis has shown that compound **12a** exhibits the *Z* enol structure also in the crystalline form (Figure 1).

It is suggested in the patent literature<sup>5,6</sup> that this thenoylation can be carried out also in the presence of various amines in addition to DMAP, for example, trialkylamines, *N*-methylmorpholine, *N*-methylpiperidine, etc. In our hands thenoylation of compounds **6** in the presence of 2.2 equiv of triethylamine did not give the required 3-thenoyl derivatives **12** in good yield, that is, DMAP cannot be replaced by triethylamine. However, treatment of **6c** with thiophen-2-carbonyl chloride in the presence of 1.1 equiv of triethylamine afforded *O*-thenoyl derivative **10c** (53%), while the same reaction with 1.1 equiv DMAP as the amine component gave a mixture of the starting compound **6c** and the required 3-thenoyl derivative **12c** (Scheme 4). The rearrangement of *O*-thenoyl derivative **10c** in the presence of 1.1 equiv DMAP gave *C*-thenoyl derivative **12c** in good yield.

These results suggest that formation of enols **12** by thenoylation of oxindoles **6** involves a multistep reaction sequence: *O*-thenoylation to compounds **10** followed by rearrangement, affording 3-thenoyl derivatives **7** (the keto form of the final products **12**). *O*-Thenoylation can be carried out both in the presence of triethylamine and DMAP; however, the rearrangement takes place smoothly only in the presence of DMAP. Because of the  $\beta$ -keto amide structure of compound **7**, the rearrangement **10** to **7** should be reversible in the presence of base, in principle. Despite this fact the reaction can be accomplished; the equilibrium

**Scheme 4**



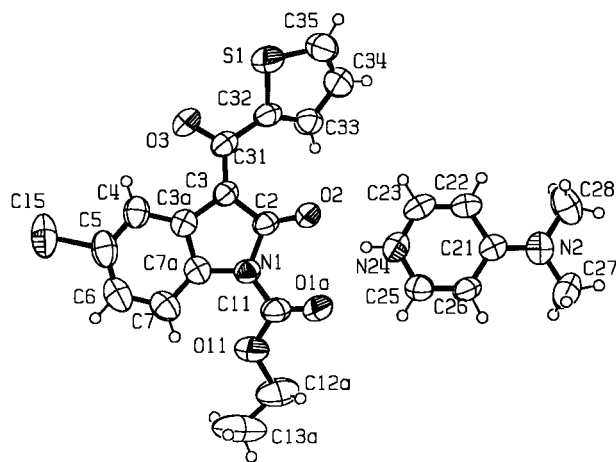
is driven by enolisation to the right as demonstrated by the isolation of enolates **11a** and **11c**, which were converted to the corresponding enols **12** by acidification.

The structure of **11a** was investigated by single-crystal X-ray analysis and  $^1\text{H}$  NMR studies in detail. The X-ray structure analysis revealed that **11a** adopts an *E* configuration in the crystalline state (Figure 2). The protonated DMAP (HDMAP<sup>+</sup>) cation is linked with hydrogen bonds to the oxygens of the ring and the carbamate carbonyls (i.e., it is not connected with the oxygen of the thenoyl carbonyl).

However, the *E* isomer which is stable in the crystalline state interconverts to the *Z* isomer in solution, as suggested by the  $^1\text{H}$  NMR spectra. The temperature dependence of the chemical shifts of oxindole C4 and thiophene C3 hydrogens and the NOE observed between them indicates the presence of the *Z* isomer in solution that is, practically free rotation about the bond between oxindole C3 and the carbon attached to the ring. The *E* isomer is expected to be the more stable one due to the unfavourable interaction (electrostatic repulsion) between the oxygens in the *Z* isomer.<sup>11</sup>

Attempts to convert ethylcarbamate **12a** to tenidap **1**, under different conditions, failed. The reaction of **12a** with

(11) Sun, L.; Tran, N.; Tang, F.; App, H.; Hirth, P.; McMahon, G.; Tang, C. *J. Med. Chem.* **1998**, *41*, 2588.



**Figure 2.** ORTEP drawing of **11a**. Thermal ellipsoids have been drawn at the 50% probability level.

ammonium carbonate in DMF at room temperature for 2 h resulted in the formation of ammonium salt **13a**. After treatment of **12a** with ammonium carbonate in DMF at 80 °C for 6 h, the starting material was recovered after acidic work-up. The application of other ammonia sources and more vigorous reaction conditions resulted in the formation of substantial amounts of deethoxycarbonylated product **3**, and experiments with methylcarbamate **12b** gave similar results (Scheme 5).

However, phenylcarbamate **12c** could be converted to tenidap **1** under straightforward conditions. Thus, treatment of **12c** with 2 equiv of ammonium carbonate in DMF at 75–80 °C for 5 h, followed by an acidic work-up gave tenidap **1** in excellent yield. The reaction may also be accomplished at a lower temperature by stirring at 25 °C for 24 h. An important requirement for a smooth reaction is an adequate solubility of the rather insoluble initially formed ammonium salt **13c**. Therefore, the use of DMF in the reaction is crucial. The ammonium salt crystallises out in less polar solvents and does not react further. For instance treatment of **12c** with ammonium carbonate in refluxing dichloromethane gave **13c** in high yield.

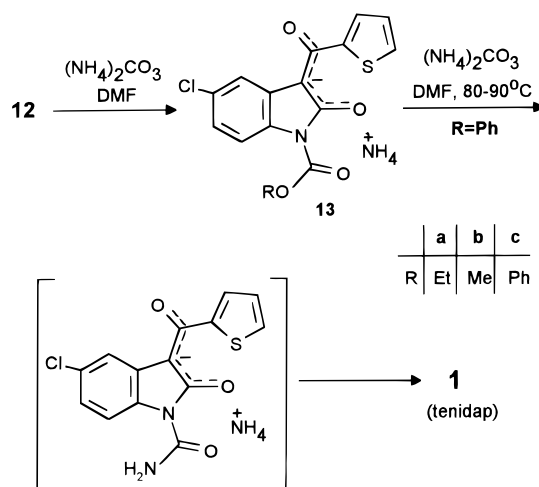
It is interesting to note that oxindoles **6c** and **12c** show different reactivity of the *N*-phenyloxycarbonyl group when treated with ammonium carbonate in DMF at elevated temperatures; whereas removal of phenyloxycarbonyl group (formation of **2**) was observed with the former, the latter gave a clean carbamoylation reaction to the corresponding *N*-carboxamide.

The studies described above allowed the development of a patent-free simple one-pot process for the preparation of tenidap (**1**) starting from *N,O*-diphenoxycarbonyl derivative **8c** by successive treatments with ammonium carbonate, thiophen-2-carbonyl chloride in the presence of DMAP and ammonium carbonate, in an optimized overall yield of 75%.

## Experimental Section

Melting points are uncorrected. Infrared spectra were recorded as KBr pellets. <sup>1</sup>H NMR spectra were recorded at 200 or 400 MHz and <sup>13</sup>C NMR spectra at 50.3 or 101 MHz as indicated. All unspecified reagents were from commercial resources.

## Scheme 5



**Structure Determination of 11a and 12a by X-ray Crystallography.** The X-ray measurements were carried out by Professor A. Kálmán and Mr. Gy. Argay (Institute of Chemistry, Chemical Research Center of the Hungarian Academy of Sciences). Intensity data were collected on an Enraf Nonius CAD4 diffractometer. The structures were solved by direct methods.

**11a:** C<sub>23</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>4</sub>S; *M<sub>r</sub>* = 471.95, crystallized from acetonitrile as orange crystals. The monoclinic cell parameters and calculated cell volume are *a* = 10.949(1) Å, *b* = 11.013(2) Å, *c* = 19.142(2) Å, β = 100.56(1)°, *V* = 2269.1(5) Å<sup>3</sup>. Space group: *P*12<sub>1</sub>/*n* 1. Refinement on *F*<sup>2</sup> values for all non-hydrogen atoms yielded *R*1 = 0.0506 and *wR*2 = 0.1756 for 3867 [*I* > 2σ(*I*)] observations.

**12a:** C<sub>16</sub>H<sub>12</sub>ClNO<sub>4</sub>S; *M<sub>r</sub>* = 349.78, crystallized from aqueous ethanol as yellow crystals. The monoclinic cell parameters and calculated cell volume are *a* = 6.972(1) Å, *b* = 17.572(2) Å, *c* = 12.809(1) Å, β = 96.93(2)°, *V* = 1558.1(3) Å<sup>3</sup>. Space group: *P**c*. Refinement on *F*<sup>2</sup> values for all non-hydrogen atoms yielded *R*1 = 0.0382 and *wR*2 = 0.0803 for 3635 [*I* > 2σ(*I*)] observations.<sup>12</sup>

**5-Chloro-1-ethoxycarbonyl-2-oxo-2,3-dihydroindole (6a).** To a solution of **8a** (31.2 g, 0.1 mol) in DMF (200 mL) was added finely powdered ammonium carbonate (7.80 g, NH<sub>3</sub> content 22%, 0.1 mol) at 0–5 °C. The mixture was stirred for 6 h at room temperature. It was poured into ice–water (400 g). The crude product (21.3 g, 89%) was filtered, washed with ethanol, and recrystallized from ethyl acetate to give **6a** (17.3 g, 72%) as colorless crystals: mp 101–102 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.81 (1H, d, *J* = 8.8 Hz), 7.31 (1H, dd, *J* = 8.8 Hz, *J* = 2.2 Hz), 7.26 (1H, d, *J* = 2.2 Hz), 4.48 (2H, q, *J* = 7.4 Hz), 3.67 (2H, s), 1.49 (3H, t, *J* = 7.4 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ 171.7, 150.5, 139.1, 129.7, 128.0, 124.9, 124.3, 116.2, 63.4, 36.1, 14.1; IR (KBr, cm<sup>−1</sup>) 3111, 2947, 1786, 1730. Anal. Calcd for C<sub>11</sub>H<sub>10</sub>ClNO<sub>3</sub>: C, 55.13; H, 4.21; Cl, 14.79; N, 5.84. Found: C, 55.52; H, 4.20; Cl, 14.68; N, 5.82.

(12) The authors have deposited atomic coordinates for **11a** and **12a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.



**5-Chloro-1-methoxycarbonyl-2-oxo-2,3-dihydroindole (6b).** This compound was prepared analogously to **6a**, starting from **8b** (28.4 g, 0.1 mol). The resulting crystalline product (19.7 g, 88%) was recrystallized from ethyl acetate to give **6b** (15.8 g, 70%) as white crystals: mp 129–130 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.81 (1H, d, *J* = 8.7 Hz), 7.27 (1H, dd, *J* = 8.7 Hz, *J* = 2.2 Hz), 7.24 (1H, d, *J* = 2.2 Hz), 4.01 (3H, s), 3.67 (2H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ 171.6, 151.1, 138.9, 129.8, 128.0, 124.8, 124.2, 116.1, 53.9, 36.0; IR (KBr, cm<sup>-1</sup>) 1782, 1767. Anal. Calcd for C<sub>10</sub>H<sub>8</sub>ClNO<sub>3</sub>: C, 53.23; H, 3.57; Cl, 15.72; N, 6.21. Found: C, 53.01; H, 3.59; Cl, 15.64; N, 6.24.

**5-Chloro-2-oxo-1-phenoxyacarbonyl-2,3-dihydroindole (6c).** This compound was prepared analogously to **6a**, starting from **8c** (40.8 g, 0.10 mol). The resulting crystalline product (27.1 g, 94%) was recrystallized from ethanol to give **6c** (25.2 g, 85%) as colorless crystals: mp 175–176 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.90 (1H, d, *J* = 8.6 Hz), 7.45 (2H, m), 7.30 (5H, m), 3.75 (2H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ 171.5, 149.9, 149.3, 138.8, 130.4, 129.6, 128.4, 126.5, 124.9, 124.6, 121.4, 116.6, 36.2; IR (KBr, cm<sup>-1</sup>) 3455, 1785, 1740. Anal. Calcd for C<sub>15</sub>H<sub>10</sub>ClNO<sub>3</sub>: C, 62.62; H, 3.50; Cl, 12.32; N, 4.87. Found: C, 62.79; H, 3.57; Cl, 12.35; N, 4.79.

**5-Chloro-1-ethoxycarbonyl-2-(ethoxycarbonyloxy)indole (8a).** To a solution of 5-chloro-2-oxindole<sup>3,4</sup> **2** (16.8 g, 0.10 mol) and triethylamine (30.7 mL, 22.3 g, 0.22 mol) in THF (360 mL) was added ethyl chloroformate (21.0 mL, 23.9 g, 0.22 mol) dropwise, maintaining the temperature below 30 °C. After the mixture stirred for 30 min at room temperature, the solvent was evaporated. The residue was diluted with cold water (100 mL) and stirred for 2 h at 0–5 °C. The crude crystalline product (29.2 g, 94%) was filtered and recrystallized from hexane to give **8a** (24.3 g, 78%) as colorless crystals: mp 76–77 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.0 (1H, d, *J* = 8.8 Hz), 7.47 (1H, d, *J* = 2.1 Hz), 7.25 (1H, dd, *J* = 8.8 Hz, *J* = 2.1 Hz), 6.26 (1H, s), 4.86 (2H, q, *J* = 6.9 Hz), 4.37 (2H, q, *J* = 7.1 Hz), 1.43 (6H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ 152.2, 149.8, 142.3, 130.9, 129.0, 127.6, 124.6, 120.3, 116.6, 96.6, 65.9, 63.7; IR (KBr, cm<sup>-1</sup>) 2987, 1780, 1738. Anal. Calcd for C<sub>14</sub>H<sub>14</sub>ClNO<sub>5</sub>: C, 53.94; H, 4.53; Cl, 11.37; N, 4.49. Found: C, 53.72; H, 4.54; Cl, 11.12; N, 4.38.

**5-Chloro-1-methoxycarbonyl-2-(methoxycarbonyloxy)indole (8b).** This compound was prepared analogously to **8a** using methyl chloroformate (18.2 mL, 20.8 g, 0.22 mole) instead of ethyl chloroformate. The crude crystalline product (24.7 g, 87%) was recrystallized from a mixture of ethyl acetate and hexane to give **8b** (20.0 g, 71%) as colorless crystals: mp 97–98 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.97 (1H, d, *J* = 8.9 Hz), 7.48 (1H, d, *J* = 2.1 Hz), 7.26 (1H, dd, *J* = 8.9 Hz, *J* = 2.1 Hz), 6.28 (1H, s), 4.03 (3H, s), 3.98 (3H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ 152.9, 150.4, 142.3, 130.7, 129.2, 127.7, 124.7, 120.4, 116.6, 96.8, 56.4, 54.2; IR (KBr, cm<sup>-1</sup>) 1788, 1751. Anal. Calcd for C<sub>12</sub>H<sub>10</sub>ClNO<sub>5</sub>: C, 50.80; H, 3.55; Cl, 12.50; N, 4.94. Found: C, 50.47; H, 3.52; Cl, 12.31; N, 4.89.

**5-Chloro-1-phenoxyacarbonyl-2-(phenoxyacarbonyloxy)indole (8c).** This compound was prepared analogously to **8a** using phenyl chloroformate (27.6 mL, 34.4 g, 0.22 mol) instead of ethyl chloroformate. The crude crystalline product (40.0 g, 98%) was recrystallized from a mixture of ethyl acetate and hexane to give **8c** (34.3 g, 84%) as colorless crystals: mp 130–132 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.10 (1H, d, *J* = 8.9 Hz), 7.55 (1H, d, *J* = 2.1 Hz), 7.38–7.25 (9H, m), 7.10 (2H, m), 6.46 (1H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ 150.7, 149.7, 141.9, 131.1, 129.8, 129.6, 127.8, 126.9, 126.7, 125.2, 121.5, 120.7, 116.8, 97.9; IR (KBr, cm<sup>-1</sup>) 1788, 1753. Anal. Calcd for C<sub>22</sub>H<sub>14</sub>ClNO<sub>5</sub>: C, 64.79; H, 3.46; Cl, 8.68; N, 3.43. Found: C, 65.08; H, 3.47; Cl, 8.53; N, 3.49.

#### **5-Chloro-2-(ethoxycarbonylamino)phenylacetamide (9).**

*Method A:* To a solution of **8a** (3.11 g, 0.01 mol) in DMF (20 mL) was added finely powdered ammonium acetate (1.54 g, 0.02 mol) at 0–5 °C. The mixture was stirred for 5 h at room temperature. It was poured into ice–water (40 g). The crude product (2.37 g, 92%) was filtered, washed with water and recrystallized from ethanol to give **9** (0.8 g, 32%) as colorless crystals: mp 182–184 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.43 (1H, s, exchangeable), 7.78 (1H, m), 7.26 (1H, m), 7.15 (1H, d, *J* = 2.6 Hz), 5.78 (1H, s, exchangeable), 5.4 (1H, s, exchangeable), 4.22 (2H, q, *J* = 7.1 Hz), 3.51 (2H, s), 1.18 (3H, t, *J* = 7.1 Hz); IR (KBr, cm<sup>-1</sup>) 3392, 3186, 1713, 1680. Anal. Calcd for C<sub>11</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>3</sub>: C, 51.47; H, 5.10; Cl, 13.81; N, 10.92. Found: C, 51.83; H, 5.22; Cl, 13.78; N, 10.89.

*Method B:* To a solution of **8a** (3.11 g, 0.01 mol) in DMF (20 mL) was added finely powdered ammonium carbonate (1.56 g, NH<sub>3</sub> content 22%, 0.02 mol) at room temperature. The mixture was stirred for 6 h at 80–90 °C. It was poured into ice–water (40 g). The crude product (2.04 g, 79%) was filtered, washed with water and recrystallized from ethyl acetate to give **9** (1.53 g, 59.6%) as colorless crystals: mp 184–186 °C, having identical IR and <sup>1</sup>H NMR spectrum with the sample obtained in *Method A*.

#### **5-Chloro-1-phenoxyacarbonyl-2-(thenoyloxy)indole (10c).**

To a suspension of **6c** (1.44 g, 0.005 mol) and triethylamine (0.76 mL, 0.55 g, 0.055 mol) in DMF (10 mL) was added a solution of thiophen-2-carbonyl chloride (0.6 mL, 0.81 g, 0.0055 mol) in DMF (2.8 mL) at 4–8 °C over a period of 30 min. The mixture was stirred at this temperature for further 30 min. A mixture of water (20 mL) and concentrated HCl (0.85 mL) was added and it was stirred for an additional 2 h at 5 °C. The solid precipitate was filtered, the crude product (1.87 g, 94%) was recrystallized from ethanol to give **10c** (1.06 g, 53%) as yellow crystals: mp 108–110 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) δ 8.10 (1H, d, *J* = 8.8 Hz), 8.00 (1H, dd, *J* = 1.1 Hz, *J* = 3.7 Hz), 7.65 (1H, dd, *J* = 1.1 Hz, *J* = 5.1 Hz), 7.54 (1H, d, *J* = 1.8 Hz), 7.40–7.15 (7H, m), 7.12 (1H, dd, *J* = 3.7 Hz, *J* = 5.1 Hz), 6.46 (1H, s); IR (KBr, cm<sup>-1</sup>) 3102, 1754, 1610. Anal. Calcd for C<sub>20</sub>H<sub>12</sub>ClNO<sub>4</sub>S: C 60.38; H, 3.04; Cl, 8.91; N, 3.52; S, 8.06. Found: C, 59.97; H, 3.08; Cl, 8.79; N, 3.43; S, 7.77.

#### **4-Dimethylaminopyridinium Salt of 5-Chloro-1-ethoxycarbonyl-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-**

**dihydroindole (11a).** To a suspension of **6a** (2.40 g, 0.01 mol) and 4-(dimethylamino)pyridine (2.69 g, 0.022 mole) in DMF (20 mL) was added a solution of thiophen-2-carbonyl chloride (1.17 mL, 1.61 g, 0.011 mol) in DMF (5 mL) at 4–8 °C over a period of 30 min. The mixture was stirred at this temperature for further 30 min. Water (40 mL) was added, and the mixture was stirred for an additional 2 h at 5 °C. The solid precipitate was filtered, and the crude product (4.37 g, 93%) was recrystallized from acetonitrile to give **11a** (2.86 g, 60%) as orange crystals: mp 183–184 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.12 (1H, dd, *J* = 3.3 Hz, *J* = 1.3 Hz), 8.00 (2H, d, *J* = 7.4 Hz), 7.93 (1H, d, *J* = 2.0 Hz), 7.72 (1H, d, *J* = 8.8 Hz), 7.51 (1H, dd, *J* = 4.8 Hz, *J* = 1.3 Hz), 7.11 (1H, dd, *J* = 3.7 Hz, *J* = 5.1 Hz), 6.99 (1H, dd, *J* = 2.2 Hz, *J* = 8.8 Hz), 6.5 (2H, d, *J* = 7.3 Hz), 4.45 (2H, q, *J* = 7.1 Hz), 3.01 (6H, s), 1.45 (3H, t, *J* = 7.1 Hz); IR (KBr, cm<sup>-1</sup>) 2929, 1735, 1635. Anal. Calcd for C<sub>23</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>4</sub>S: C, 58.53; H, 4.70; Cl, 7.51; N, 8.90; S, 6.79. Found: C, 58.30; H, 4.58; Cl, 7.37; N, 8.76; S, 6.69.

**4-Dimethylaminopyridinium Salt of 5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-1-phenoxycarbonyl-2,3-dihydroindole (11c).** This compound was prepared analogously to **11a**, starting from **6c** (2.88 g, 0.01 mol). The resulting crystalline product (5.10 g, 98%) was recrystallized from acetonitrile to give **11c** (3.06 g, 58.8%) as yellow crystals: mp 195–195.5 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.06 (3H, m), 7.86 (1H, d, *J* = 8.6 Hz), 7.82 (1H, bs), 7.58 (1H, bd, *J* = 4.8 Hz), 7.42 (2H, m), 7.30 (3H, m), 7.18 (1H, m), 7.06 (1H, bd, *J* = 8.6 Hz), 6.60 (2H, d, *J* = 7.3 Hz), 3.16 (6 H, s); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 200 MHz) δ 8.62 (1H, dd, *J* = 3.6 Hz, *J* = 1.1 Hz), 8.22 (1H, d, *J* = 2.5 Hz), 8.20 (2H, d, *J* = 7.7 Hz), 7.65 (1H, d, *J* = 8.6 Hz), 7.58 (1H, dd, *J* = 1.1 Hz, *J* = 5.0 Hz), 7.48 (2H, m), 7.32 (3H, m), 7.07 (1H, dd, *J* = 3.6 Hz, *J* = 5.0 Hz), 6.97 (2H, d, *J* = 7.7 Hz), 6.84 (1H, dd, *J* = 2.4 Hz, *J* = 8.6 Hz), 3.17 (6H, s); IR (KBr, cm<sup>-1</sup>) 3219, 3062, 2930, 1754, 1715, 1688, 1645. Anal. Calcd for C<sub>27</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>4</sub>S: C, 62.36; H, 4.26; Cl, 6.82; N, 8.08; S, 6.17. Found: C, 62.01; H, 4.23; Cl, 6.67; N, 8.17; S, 5.92.

**5-Chloro-1-ethoxycarbonyl-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-dihydroindole (12a).** To a suspension of **6a** (24.0 g, 0.1 mol) and 4-(dimethylamino)pyridine (26.9 g, 0.22 mole) in DMF (200 mL) was added a solution of thiophen-2-carbonyl chloride (11.7 mL, 16.1 g, 0.11 mol) in DMF (50 mL) at 4–8 °C over a period of 30 min. The mixture was stirred at this temperature for further 30 min. A mixture of water (400 mL) and concentrated HCl (17 mL) was added, and the mixture was stirred for an additional 2 h at 5 °C. The solid precipitate was filtered, and the crude product (33.1 g, 95%) was recrystallized from aqueous ethanol to give **12a** (31.4 g, 90%) as yellow crystals: mp 118–120 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.95 (1H, d, *J* = 8.6 Hz), 7.88 (1H, dd, *J* = 3.8 Hz, *J* = 1.2 Hz), 7.75 (1H, dd, *J* = 1.2 Hz, *J* = 5.0 Hz), 7.62 (1H, d, *J* = 2.2 Hz), 7.27 (1H, dd, *J* = 5.0 Hz, *J* = 3.8 Hz), 7.22 (1H, dd, *J* = 8.6 Hz, *J* = 2.2 Hz), 4.54 (2H, q, *J* = 7.4 Hz), 1.49 (3H, t, *J* = 7.4 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ 171.1, 167.0, 150.2, 135.1, 132.9, 132.3, 131.6, 129.5, 127.8, 126.1, 123.2, 118.8,

116.0, 99.6, 63.8, 14.2; IR (KBr, cm<sup>-1</sup>) 3433, 3092, 1743, 1669. Anal. Calcd for C<sub>16</sub>H<sub>12</sub>ClNO<sub>4</sub>S: C, 54.94; H, 3.46; Cl, 10.14; N, 4.00; S, 9.17. Found: C, 55.13; H, 3.33; Cl, 10.02; N, 3.90; S, 9.07.

**5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-1-methoxycarbonyl-2-oxo-2,3-dihydroindole (12b).** This compound was prepared analogously to **12a**, starting from **6b** (22.5 g, 0.10 mol). The resulting crystalline product (32.9 g, 98%) was recrystallized from acetonitrile to give **12b** (24.0 g, 72%) as white crystals: mp 156–158 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) δ 7.95 (1H, d, *J* = 8.8 Hz), 7.88 (1H, dd, *J* = 1.1 Hz, *J* = 3.7 Hz), 7.75 (1H, dd, *J* = 1.1 Hz, *J* = 4.8 Hz), 7.61 (1H, d, *J* = 2.2 Hz), 7.27 (1H, dd, *J* = 4.8 Hz, *J* = 3.7 Hz), 7.21 (1H, dd, *J* = 2.2 Hz, *J* = 8.8 Hz), 4.08 (3H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50.3 MHz) δ 171.2, 167.3, 150.9, 135.1, 133.0, 132.4, 131.7, 129.8, 127.9, 126.3, 123.4, 119.0, 116.2, 99.8, 54.3; IR (KBr, cm<sup>-1</sup>) 3429, 1767, 1612. Anal. Calcd for C<sub>15</sub>H<sub>10</sub>ClNO<sub>4</sub>S: C, 53.66; H, 3.00; Cl, 10.56; N, 4.17; S, 9.55. Found: C, 53.80; H, 2.97; Cl, 10.45; N, 4.10; S, 9.64.

**5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-1-phenoxycarbonyl-2,3-dihydroindole (12c).** *Method A.* This compound was prepared analogously to **12a**, starting from **6c** (28.8 g, 0.1 mol). The resulting crystalline product (39.7 g, 99.8%) was recrystallized from acetonitrile to give **12c** (33.0 g, 83%) as yellow crystals: mp 140–142 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) δ 7.95 (1H, d, *J* = 8.8 Hz), 7.87 (1H, dd, *J* = 3.8 Hz, *J* = 1.0 Hz), 7.78 (1H, dd, *J* = 5.0 Hz, *J* = 1.0 Hz), 7.63 (1H, d, *J* = 2.1 Hz), 7.45 (2H, m), 7.33 (3H, m), 7.28 (1H, dd, *J* = 5.0 Hz, *J* = 3.8 Hz), 7.18 (1H, dd, *J* = 8.8 Hz, *J* = 2.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50.3 MHz) δ 171.1, 167.4, 150.0, 149.0, 135.0, 132.9, 132.5, 131.8, 130.1, 129.7, 127.9, 126.6, 126.5, 123.7, 121.4, 119.1, 116.4, 99.8; IR (KBr, cm<sup>-1</sup>) 3097, 1750, 1691, 1634. Anal. Calcd for C<sub>20</sub>H<sub>12</sub>ClNO<sub>4</sub>S: C, 60.38; H, 3.04; Cl, 8.91; N, 3.52; S, 8.06. Found: C, 60.59; H, 3.10; Cl, 8.81; N, 3.50; S, 7.85.

*Method B.* A mixture of **10c** (1.0 g, 0.0025 mol) and DMAP (0.33 g, 0.00275 mol) was dissolved in DMF (5 mL) at 0 °C. After 1–2 min stirring a yellow precipitate formed. A mixture of water (12.5 mL) and concentrated HCl (0.7 mL) was added, and the mixture was stirred for an additional 30 min at 5 °C. The solid precipitate was filtered, and the crude product (1.0 g, 100%) was recrystallized from acetonitrile to give **12c** (0.62 g, 62%) as yellow crystals: mp 136–137 °C, having IR and <sup>1</sup>H NMR spectra identical to those of the sample obtained in *Method A*.

**Ammonium Salt of 5-Chloro-1-ethoxycarbonyl-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-dihydroindole (13a).** To a solution of **12a** (0.7 g, 0.002 mol) in DMF (4 mL) was added ammonium carbonate (0.16 g, NH<sub>3</sub> content 22%, 0.002 mol), and the mixture was stirred for 2 h at 25 °C. Water (10 mL) was added. The solid precipitate was filtered to give **13a** (0.61 g, 83%) as yellow crystals: mp 193–197 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 200 MHz) δ 8.61 (1H, bd, *J* = 3.5 Hz), 8.18 (1H, d, *J* = 2.1 Hz), 7.58 (1H, d, *J* = 8.5 Hz), 7.55 (1H, m), 7.1 (5H, m), 6.78 (1H, dd, *J* = 8.4 Hz, *J* = 2.2 Hz), 4.35 (2H, q, *J* = 7.1 Hz), 1.32 (3H, t, *J* = 7.1 Hz); IR (KBr, cm<sup>-1</sup>) 2982, 1737, 1621. Anal. Calcd for

C<sub>16</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>4</sub>S: C, 52.39; H, 4.12; Cl, 9.67; N, 7.64; S, 8.74. Found: C, 52.63; H, 4.18; Cl, 9.65; N, 7.49; S, 8.34.

**Ammonium Salt of 5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-1-methoxycarbonyl-2-oxo-2,3-dihydroindole (13b).** To a suspension of **12b** (1.67 g, 0.005 mol) in DMF (12.5 mL) was added ammonium carbonate (0.78 g, NH<sub>3</sub> content 22%, 0.01 mol). The solution resulted was stirred for 2 h at room temperature. Water (25 mL) was added. The solid precipitate was filtered to give **13b** (1.20 g, 68%) as yellow crystals: mp 190–190.5 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 8.60 (1H, bd, *J* = 3.9 Hz), 8.17 (1H, d, *J* = 2.2 Hz), 7.60 (1H, d, *J* = 8.4 Hz), 7.55 (1H, bd, *J* = 4.4 Hz), 7.08 (4H, bs), 7.04 (1H, dd, *J* = 4.5 Hz, *J* = 3.9 Hz), 6.79 (1H, dd, *J* = 2.2 Hz, *J* = 8.4 Hz), 3.84 (3H, s); IR (KBr, cm<sup>-1</sup>) 2958, 1721. Anal. Calcd for C<sub>15</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>4</sub>S: C, 51.07; H, 3.71; Cl, 10.05; N, 7.94; S, 9.09. Found: C, 50.60; H, 3.65; Cl, 9.88; N, 8.12; S, 9.01.

**Ammonium Salt of 5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-1-phenoxycarbonyl-2,3-dihydroindole (13c).** To a solution of **12c** (1.00 g, 0.0025 mol) in dichloromethane (7 mL) was added ammonium carbonate (0.39 g, NH<sub>3</sub> content 22%, 0.005 mol). A crystalline mass formed instantaneously. It was refluxed for 4 h. After the mixture cooled, the suspension was filtered off to give 0.94 g (91%) **13c** as yellow crystals: mp 188–190 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 8.61 (1H, dd, *J* = 3.8 Hz, *J* = 0.9 Hz), 8.2 (1H, d, *J* = 2.2 Hz), 7.66 (1H, d, *J* = 8.2 Hz), 7.58 (1H, dd, *J* = 5.1 Hz, *J* = 0.9 Hz), 7.48 (2H, m), 7.3 (3H, m), 7.14 (4H, s), 7.06 (1H, dd, *J* = 3.8 Hz, *J* = 5.1 Hz), 6.84 (1H, dd, *J* = 8.2 Hz, *J* = 2.2 Hz); IR (KBr, cm<sup>-1</sup>) 3005, 1747. Anal. Calcd for C<sub>20</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>4</sub>S: C, 57.90; H, 3.64; Cl, 8.55; N, 6.75; S, 7.73. Found: C, 57.73; H, 3.52; Cl, 8.61; N, 6.69; S, 7.97.

**5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-dihydroindole-1-carboxamide (1, tenidap).** *Method A.* To a solution of **12c** (39.8 g, 0.10 mol) in DMF (250 mL) was added finely powdered ammonium carbonate (15.60 g, NH<sub>3</sub> content 22%, 0.20 mol). The reaction was completed by stirring at 75–80 °C for 5 h. The solution was poured with stirring into a mixture of ice–water (500 g) and concentrated HCl (25 mL). After the mixture stirred for an additional 2 h at 0–5 °C, the crystalline product was filtered to give the crude tenidap (**1**, 32.3 g, ~100%) as yellow crystals: mp 221–224 °C. The crude product (32.3 g) was purified as follows: it was dissolved in a refluxing mixture of methanol (635 mL) and 2-amino-ethanol (6.3 mL, 6.4 g, 0.11 mol), treated with charcoal. After filtration concentrated HCl (18.8 mL) was added dropwise at 40–45 °C. The suspension obtained was stirred for 2 h at 20–30 °C and filtered to give the title compound (25.8 g, 81%) as yellow crystals: mp 229–230 °C. [lit<sup>5,6</sup> 232–234 °C; lit<sup>6</sup> 229–231.5 °C]. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.48 (1H, bs), 8.32 (1H, d, *J* = 8.8 Hz), 7.92 (1H, dd, *J* = 1.1 Hz, *J* = 3.8 Hz), 7.78 (1H, dd, *J* = 1.1 Hz, *J* = 5.0 Hz), 7.64 (1H, d, *J* = 2.2 Hz), 7.28 (1H, dd, *J* = 3.8 Hz, *J* = 5.0 Hz), 7.23 (1H, dd, *J* = 2.2 Hz, *J* = 8.8 Hz), 5.35 (1H, bs); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50.3 MHz) δ 169.0, 165.5, 152.4, 135.4, 134.1, 132.1, 131.6, 127.9, 127.4, 125.0, 120.3, 116.1, 101.1; IR (KBr, cm<sup>-1</sup>)

3395, 3233, 1744, 1661, 1620, 1589. Anal. Calcd for C<sub>14</sub>H<sub>9</sub>ClN<sub>2</sub>O<sub>3</sub>S: C, 52.42; H, 2.83; Cl, 11.05; N, 8.73; S, 10.00. Found: C, 52.80; H, 2.90; Cl, 10.99; N, 8.59; S, 9.90.

*Method B.* To a solution of **13c** (1.04 g, 0.0025 mol) in DMF (6.25 mL) was added finely powdered ammonium carbonate (0.20 g, NH<sub>3</sub> content 22%, 0.0025 mol). The reaction was completed by stirring at 75–80 °C for 5 h. The solution was poured with stirring into a mixture of ice–water (12.5 g) and concentrated HCl (0.62 mL). After the mixture stirred, for an additional 2 h at 0–5 °C, the crystalline product was filtered to give the crude tenidap (**1**, 0.80 g, ~100%) as yellow crystals: mp 221–224 °C. The crude product was purified as described in method A, resulting in the title compound (0.64 g, 80%): mp 229–230 °C.

*Method C.* To a solution of **8c** (40.7 g, 0.1 mol) in DMF (200 mL) was added finely powdered ammonium carbonate (7.8 g, NH<sub>3</sub> content 22%, 0.1 mol) at 0–5 °C. The mixture was stirred for 5 h at room temperature. After addition of 4-(dimethylamino)pyridine (26.9 g, 0.22 mol) the reaction mixture was cooled to 4–8 °C, and a solution of thiophen-2-carbonyl chloride (11.7 mL, 16.1 g, 0.11 mole) in DMF (50 mL) was added during 30 min. The mixture was stirred at this temperature for further 30 min, and ammonium carbonate (15.6 g, NH<sub>3</sub> content 22%, 0.20 mol) was added. The mixture was stirred for 5 h at 75–80 °C. The solution was poured with stirring into a mixture of ice–water (500 g) and concentrated HCl (25 mL). After the mixture stirred for an additional 2 h at 0–5 °C, the crystalline product was filtered to give crude tenidap (**1**, 25.4 g, 79%) as yellow crystals: mp 212–221 °C. The crude product was purified as described in method A, resulting in the title compound (19.2 g, 75%): mp 229–230 °C.

*Method D.* To a suspension of **6c** (28.7 g, 0.1 mol) and 4-(dimethylamino)pyridine (26.9 g, 0.22 mol) in DMF (200 mL) was added a solution of thiophen-2-carbonyl chloride (11.7 mL, 16.1 g, 0.11 mole) in DMF (50 mL) at 4–8 °C during 30 min. The mixture was stirred at this temperature for further 30 min, and ammonium carbonate (15.6 g, NH<sub>3</sub> content 22%, 0.20 mol) was added. The reaction was completed by stirring at 75–80 °C for 5 h. The solution was poured with stirring into a mixture of ice–water (500 g) and concentrated HCl (25 mL). After the mixture stirred for an additional 2 h at 0–5 °C, the crystalline product was filtered to give the crude tenidap (**1**, 31.0 g, 97%) as yellow crystals: mp 215–220 °C. The crude product was purified as described in method A, resulting in the title compound (24.3 g, 79%): mp 229–230 °C.

## Supporting Information Available

<sup>1</sup>H NMR, <sup>13</sup>C NMR, and IR spectra for compounds **1**, **6a–c**, **8a–c**, **12a–c**, <sup>1</sup>H NMR and IR spectra for compounds **9**, **10c**, **11a**, **11c**, **13a–c** respectively. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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