Synthesis of *N*-Alkoxycarbonyl and *N*-Carboxamide Derivatives of Anti-Inflammatory Oxindoles

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The synthesis of *N*-alkoxycarbonyl and *N*-carboxamide derivatives of anti-inflammatory oxindoles is described. These compounds, sought as potential prodrugs of the parent anti-inflammatory agents, were obtained by ring opening of the oxadiazine dione intermediates formed by the treatment of 1-unsubstituted 3-acyloxindoles with chlorocarbonyl isocyanate.

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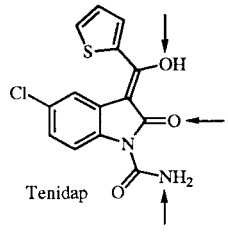
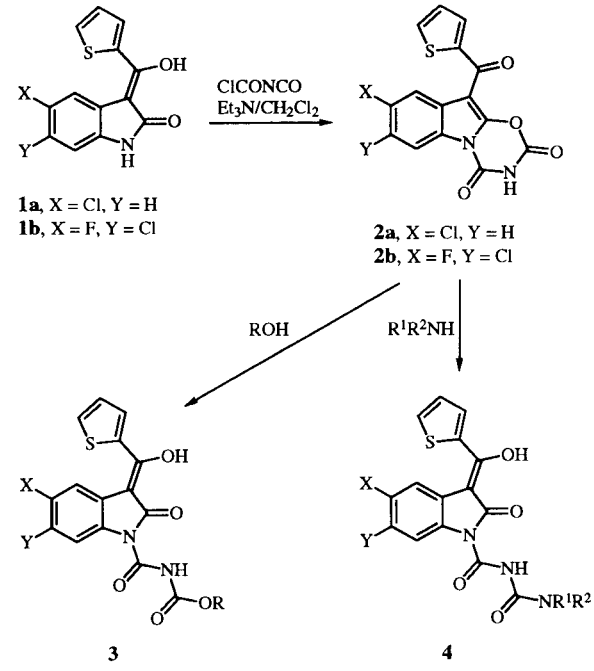
Oxindole-1-carboxamides are an important new class of anti-inflammatory agents [1-4]. One member of this group, tenidap (CP-66,248), is currently in advanced clinical trials for rheumatoid and osteoarthritis [1]. We recently sought to discover prodrugs of these compounds, derivatives which are cleaved *in vivo* to yield the parent drug by the action of site-specific hydrolytic processes. Tenidap itself offers three positions, indicated on the structure below, where a potential prodrug residue might be introduced. This paper describes the synthesis of two series of potential oxindole-1-carboxamide prodrugs (general structures **3** and **4**) in which the carboxamide nitrogen atom is substituted. In both cases, linkage to the carboxamide nitrogen *via* carbonyl group functionality was employed to enable the possibility for hydrolytic regeneration of the parent oxindole-1-carboxamide.



Tenidap

Tenidap analogs of structure **3** where OR = aryl or alkyl are known in the patent literature and can be prepared by the reaction of an *N*-unsubstituted oxindole (*e.g.* **1a**) with acyl isocyanates [4]. Early in our program we were able to prepare the *N*-ethoxycarbonyl derivative **3a** by the analogous reaction of **1a** with commercially available ethoxycarbonyl isocyanate. Unfortunately, few other alkoxycarbonyl isocyanates are commercially available. While the preparation of these reactive intermediates from the corresponding alkyl carbamates is straightforward in simple cases [5], potential complications arising from intramolecular reactions were foreseen in preparing alkoxycarbonyl isocyanates with functionalized alkyl groups. Thus, we sought an alternative route to the desired *N*-alkoxycarbonyl compounds and considered the



ring-opening of an oxadiazine dione intermediate (*e.g.* **2a** or **2b**) by alcohols as an attractive possibility. In addition to the potential of this approach for preparing various functionalized and non-functionalized *N*-alkoxycarbonyl derivatives, we realized that the use of amines as nucleophiles for ring-opening of **2a** or **2b** would allow the preparation of the previously unknown *N*-carboxamide derivatives **4**.

The intermediates **2a** and **2b** were readily synthesized by addition of chlorocarbonyl isocyanate (1 equivalent) to a cold solution of the *N*-unsubstituted oxindole **1a** or **1b** (1 equivalent) and triethylamine (1 equivalent) in methylene chloride [6]. The insoluble product **2a** or **2b** was obtained directly from the reaction mixture by filtration, a typical yield being about 75%. For the preparation of alkoxycarbonyl derivatives (*e.g.*, **3a-c**, Table 1), the intermediate **2a** or **2b** was usually dissolved in a large excess of the alcohol containing 1.1 equivalents of triethylamine [7] and stirred at 50° overnight. The products were typi-

Table 1

Structures, Melting Points, Yields and Analytical Data for Compounds **3a-e**

Compound	R X,Y	Mp°C	Yield (%) [a]	Formula	Analysis (Calcd./Found) C	 H	 N
3a	Et Cl, H	203-205	73	$C_{17}H_{13}ClN_2O_5S$	51.98 52.13	3.34 3.25	7.13 7.29
3b	CH_2Ph F, Cl	195-197	57 [b]	$C_{22}H_{14}ClFN_2O_5S$	55.88 55.90	2.98 2.76	5.92 5.84
3c	$(CH_2)_7CH_3$ Cl, H	129-131	52	$C_{23}H_{25}ClN_2O_5S$	57.92 57.84	5.28 5.04	5.87 5.89
3d [c]	(S)-$CH_2CH(CO_2H)NHBOC$ F, Cl	147-150	56	$C_{23}H_{21}ClFN_3O_9S$	48.47 48.00	3.71 3.41	7.37 7.32
3e	Ph F, Cl	205-210	63	$C_{21}H_{12}ClFN_2O_5S$	54.97 54.61	2.64 2.40	6.10 6.21

[a] Except where indicated yields are of material recrystallized from acetonitrile. [b] Crystallized from diethyl ether. [c] $[\alpha]_D^{24}$ -2.6° (c 1.0, *N,N*-dimethylformamide).

Table 2

Structures, Melting Points, Yields and Analytical Data for Compounds **4a-e**

Compound	R^1, R^2 X,Y	Mp°C	Yield (%)	Formula	Analysis (Calcd./Found) C	 H	 N
4a	$(CH_2)_3CH_3$, H Cl, H	162-164	43 [a]	$C_{19}H_{18}ClN_3O_4S$	54.35 54.27	4.32 4.04	10.00 9.95
4b	CH_2Ph, H Cl, H	171-175	63 [a]	$C_{22}H_{16}ClN_3O_4S$	58.22 58.14	3.55 3.38	9.26 9.29
4c	Et, Et F, Cl	192-194	64 [b]	$C_{19}H_{17}ClFN_3O_4S$	52.10 51.64	3.91 3.72	9.60 9.41
4d [c]	(S)-$CH(CO_2H)CH_2Ph$, H Cl, H	228-231	58 [d]	$C_{24}H_{18}ClN_3O_6S$	56.31 56.01	3.54 3.34	8.21 8.26
4e [e]	(S)-$CH(CO_2H)CH_2OH$, H Cl, H	204-206	48 [f]	$C_{18}H_{14}ClN_3O_7S$	47.85 47.63	3.12 2.84	9.30 9.18

[a] Recrystallized from acetonitrile. [b] Purified by trituration with acetone. [c] $[\alpha]_D^{24}$ +3.0° (c 1.0, *N,N*-dimethylformamide). [d] Purified by trituration with hot acetonitrile. [e] $[\alpha]_D^{24}$ +16.1° (c 1.0, *N,N*-dimethylformamide). [f] Purified by trituration with methylene chloride.

Table 3

^{1}H NMR, Mass and IR Spectroscopic Data for Compounds **3a-e**

Compound	^{1}H NMR (δ, ppm) [8]	FAB MS m/z (MH^+)	IR (cm^{-1}) C=O (KBr)
3a	(deuteriochloroform): 1.37 (t, 3 H, J = 7.2 Hz), 4.34 (q, 2 H, J = 7.2 Hz), 7.25 (dd, 1 H, J = 2.1, 8.8 Hz), 7.31 (dd, 1 H, J = 3.9, 5.0 Hz), 7.65 (d, 1 H, J = 2.1 Hz), 7.81 (dd, 1 H, J = 1.1, 5.0 Hz), 7.95 (dd, 1 H, J = 1.1, 3.9 Hz), 8.34 (d, 1 H, J = 8.8 Hz), 11.00 (br s, 1 H), 13.40 (br s, 1 H).	393	1800, 1725, 1656
3b	(deuteriochloroform): 5.30 (s, 2 H), 7.30 (dd, 1 H, J = 3.8, 5.0 Hz), 7.36-7.47 (m, 6 H), 7.82 (dd, 1 H, J = 1.1, 5.0 Hz), 7.90 (dd, 1 H, J = 1.1, 3.8 Hz), 8.51 (d, 1 H, J = 6.9 Hz), 11.00 (br s 1 H), 13.30 (br s, 1 H).	473	1802, 1728, 1645
3c	(deuteriochloroform): 0.89 (t, 3 H, J = 6.9 Hz), 1.25-1.40 (m, 10 H), 1.68-1.78 (m, 2 H), 4.26 (t, 2 H, J = 6.8 Hz), 7.25 (dd, 1 H, J = 2.1, 8.8 Hz), 7.31 (dd, 1 H, J = 4.0, 5.0 Hz), 7.65 (d, 1 H, J = 2.1 Hz), 7.80 (dd, 1 H, J = 1.0, 5.0 Hz), 7.94 (dd, 1 H, J = 1.0, 4.0 Hz), 8.34 (d, 1 H, J = 8.8 Hz), 11.00 (br s, 1 H), 13.35 (br s, 1 H).	477	1795, 1722, 1648
3d	(DMSO-d_6): 1.39 (s, 9 H), 4.22 (dd, 1 H, J = 7.2, 10.3 Hz), 4.30-4.40 (m, 1 H), 4.45 (dd, 1 H, J = 3.5, 10.3 Hz), 7.13 (dd, 1 H, J = 3.9, 4.9 Hz), 7.37 (br d, 1 H, J = 8.0 Hz), 7.69 (dd, 1 H, J = 0.9, 4.9 Hz), 8.02 (d, 1 H, J = 11.4 Hz), 8.10 (d, 1 H, J = 7.2 Hz), 8.46 (dd, 1 H, J = 0.9, 3.9 Hz), 12.82 (br s, 1 H).	570	1798, 1725, 1653
3e	(deuteriochloroform): 7.23-7.34 (m, 4 H), 7.40-7.52 (m, 3 H), 7.83 (dd, 1 H, J = 1.1, 5.0 Hz), 7.97 (dd, 1 H, J = 1.1, 3.8 Hz), 8.57 (d, 1 H, J = 6.9 Hz), 11.30 (br s, 1 H), 13.30 (br s, 1 H).	459	1810, 1730, 1753

cally isolated by acidification of the reaction mixture with 1*N* hydrochloric acid, extraction, evaporation of solvent and excess alcohol, trituration with ether and recrystallization. In instances where the alcohol was precious or could not be used as solvent (*e.g.*, the reaction with *N*-BOC-L-serine with **2b** to give **3d**), an inert solvent such as

Table 4
^{1}H NMR, Mass and IR Spectroscopic Data for Compounds **4a-e**

Compound	^{1}H NMR (δ, ppm) [8]	FAB MS m/z (MH+)	IR (cm^{-1}) C=O (KBr)
4a	(deuteriochloroform): 0.97 (t, 3 H, J = 7.0 Hz), 1.36-1.48 (m, 2 H), 1.56-1.65 (m, 2 H), 3.35-3.41 (m, 2 H), 7.24 (dd, 1 H, J = 2.1, 8.8 Hz), 7.30 (dd, 1 H, J = 3.8, 5.0 Hz), 7.67 (d, 1 H, J - 2.1 Hz), 7.81 (dd, 1H, J = 1.1, 5.0 Hz), 7.94 (dd, 1 H, J = 1.1, 3.8 Hz), 8.02 (br t, 1 H), 8.23 (d, 1 H, J = 8.8 Hz), 10.60 (br s, 1 H), 13.40 (br s, 1 H).	420	1715, 1700, 1650
4b	(deuteriochloroform): 4.59 (d, 2 H, J = 5.8 Hz), 7.22 (dd, 1 H, J = 2.2, 8.8 Hz), 7.30 (dd, 1 H, J = 3.9, 5.0 Hz), 7.34-7.38 (m, 5 H), 7.67 (d, 1 H, J = 2.2 Hz), 7.81 (dd, 1 H, J = 1.1, 5.0 Hz), 7.94 (dd, 1 H, J = 1.1, 3.9 Hz), 8.20 (d, 1 H, J = 8.8 Hz), 8.40 (br t, 1 H), 10.74 (br s, 1 H), 13.30 (br s, 1 H).	454	1722, 1693, 1658, 1610
4c	(DMSO-d_6): 1.13 (t, 6 H, J = 7.0 Hz), 3.32 (q, 4 H, J = 7.0 Hz), 7.11 (dd, 1 H, J = 3.8, 5.0 Hz), 7.68 (dd, 1 H, J = 1.1, 5.0 Hz), 8.00 (d, 1 H, J = 11.2 Hz), 8.12 (d, 1 H, J = 7.3 Hz), 8.49 (dd, 1 H, J = 1.1, 3.7 Hz), 12.60 (br s, 1 H).	438	1769, 1693, 1638
4d	(DMSO-d_6): 3.06 (dd, 1 H, J = 6.9, 13.8 Hz), 3.17 (dd, 1 H, J = 5.1, 13.8 Hz), 4.55-4.63 (m, 1 H), 6.94 (dd, 1 H, J = 2.3, 8.6 Hz), 7.12 (dd, 1 H, J = 3.8, 4.8 Hz), 7.19-7.32 (m, 5 H), 7.69 (d, 1 H, J = 4.8 Hz), 7.94 (d, 1 H, J = 8.6 Hz), 8.12 (d, 1 H, J = 2.3 Hz), 8.38 (d, 1 H, J = 3.8 Hz), 8.47 (d, 1 H, J = 7.6 Hz), 12.28 (br s, 1 H).	512	1741, 1727, 1695, 1647
4e	(DMSO-d_6): 3.72 (dd, 1 H, J = 3.5, 10.9 Hz), 3.83 (dd, 1 H, J = 3.3, 10.9 Hz), 4.30-4.34 (m, 1 H), 5.80 (br s, 1 H), 6.95 (dd, 1 H, J = 2.3, 8.6 Hz), 7.12 (dd, 1 H, J = 3.8, 5.0 Hz), 7.69 (dd, 1 H, J = 1.1, 5.0 Hz), 8.00 (d, 1 H, J = 8.6 Hz), 8.12 (d, 1 H, J = 2.3 Hz), 8.39 (dd, 1 H, J = 1.1, 3.8 Hz), 8.68 (d, 1 H, J = 7.7 Hz), 12.27 (br s, 1 H).	452	1733 (br), 1658 (br)

1,4-dioxane was used. The reaction of **2b** with phenol to afford **3e** was carried out by prior *in situ* formation of sodium phenoxide in 1,2-dimethoxyethane followed by addition of **2b**. As anticipated, the reaction of **2a** or **2b** with simple primary and secondary amines took place smoothly in methylene chloride to give substituted *N*-carboxamides (*e.g.* **4a-c**). Couplings with amino acids (*e.g.*, the reactions providing **4d** and **4e**) were carried out in the presence of triethylamine in *N,N*-dimethylformamide.

As exemplified here by compounds **3a-e** and **4a-e**, the use of intermediates such as **2a** and **2b** has allowed the preparation of a large number of new oxindole-1-carboxamide derivatives, including derivatives of tenidap, for evaluation as prodrugs of the parent anti-inflammatory agents.

EXPERIMENTAL

All reactions were carried out in dry glassware under an atmosphere of nitrogen. The ^{1}H nmr spectra were recorded at 300 MHz on a Bruker AC300 spectrometer [8]. The ir spectra were recorded on a Nicolet 510 (FT IR) spectrophotometer using potassium bromide pellets. The FAB mass spectra were obtained on a Kratos Concept 1S spectrometer using a DTT/DTE matrix and a CsI gun at 16 kV. All melting points are uncorrected.

8-Chloro-10-(2-thienylcarbonyl)-2*H*-1,3,5-oxadiazino[3,2-*a*]-indole-2,4(3*H*)dione (**2a**).

A solution of compound **1a** [4] (11.8 g, 0.042 mole) and triethylamine (5.8 ml, 0.042 mole) in anhydrous methylene chloride (780 ml) was cooled in an ice bath. A solution of chlorocarbonyl isocyanate (3.4 ml, 0.042 mole) in anhydrous methylene chloride (20 ml) was then added dropwise with stirring. When addition of the chlorocarbonyl isocyanate solution was complete, stirring was continued at 20° for 18 hours. The mixture was filtered and washed well with methylene chloride, to collect the off-white, finely crystalline product **2a**, 11.0 g (76%), mp >250°; ir (potassium bromide): υ CO 1815, 1805, 1780 cm^{-1}; ^{1}H nmr (perdeuterioacetone): δ 7.27 (dd, 1 H, J = 4.0, 5.0 Hz), 7.45 (dd, 1 H, J = 2.2, 8.8 Hz), 7.99 (dd, 1 H, J = 1.1, 5.0 Hz), 8.04 (d, 1 H, J = 2.2 Hz), 8.11 (dd, 1 H, J = 1.1, 4.0 Hz), 8.22 (d, 1 H, J = 8.7 Hz); ms: (fast atom bombardment) m/z 349 [M + H$^+$ (^{37}Cl)], 347 [M + H$^+$ (^{35}Cl)].

Anal. Calcd. for $C_{15}H_7ClN_2O_4S$: C, 51.96; H, 2.03; N, 8.08. Found: C, 51.38; H, 1.88; N, 8.27.

7-Chloro-8-fluoro-10-(2-thienylcarbonyl)-2*H*-1,3,5-oxadiazino-[3,2-*a*]indole-2,4(3*H*)-dione (**2b**).

A solution of compound **1b** [4] (18.6 g, 0.063 mole) and triethylamine (8.7 ml, 0.063 mole) in anhydrous methylene chloride (1500 ml) was cooled in an ice bath. A solution of chlorocarbonyl isocyanate (5.0 ml, 0.062 mole) in anhydrous methylene chloride (20 ml) was then added dropwise with mechanical stirring. When addition of the chlorocarbonyl isocyanate solution was complete, stirring was continued at 0° for 1 hour and then at 20° for 18 hours. The mixture was filtered and washed well with methylene chloride to collect the off-white, finely crystalline product **2b** which was recrystallized from acetonitrile, 16.6 g (73%), mp >260°; ir (potassium bromide): υ CO 1805, 1780 cm^{-1}; ^{1}H nmr (perdeuterioacetone): δ 7.28 (dd, 1 H, J = 4.0, 5.0 Hz), 7.90 (d, 1 H, J = 11.2 Hz), 8.00 (dd, 1 H, J = 1.1, 5.0 Hz), 8.12 (dd, 1 H, J = 1.1, 4.0 Hz), 8.31 (d, 1 H, J = 7.3 Hz); ms: (fast atom bombardment) m/z 367 [M + H$^+$ (^{37}Cl)], 365 [M + H$^+$ (^{35}Cl)].

Anal. Calcd. for $C_{15}H_6ClFN_2O_4S$: C, 49.40; H, 1.66; N, 7.68. Found: C, 49.21; H, 1.64; N, 7.84.

General Reaction of Compounds **2a** and **2b** with Alcohols.

A slurry of **2b** (1.0 mg, 2.74 mmoles) and triethylamine (0.42 ml, 3.03 mmoles) in benzyl alcohol (16 ml) was warmed at 50° for 18 hours to give a homogeneous yellow solution. After pouring into 1*N* hydrochloric acid, the mixture was extracted with

methylene chloride. The methylene chloride extract was washed with water, dried over magnesium sulfate and concentrated to leave an oil. Addition of ether resulted in crystallization of **3b** as a yellow, finely crystalline solid, 745 mg (57%). Compounds **3a** and **3c** were similarly obtained by the reaction of **2a** with ethanol and *n*-octanol respectively. Both compounds were recrystallized from acetonitrile.

N-[(1,1-Dimethylethoxy)carbonyl]-L-serine, [[6-Chloro-5-fluoro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1*H*-indol-1-yl]carbonyl]carbamate (Ester), **3d**.

A solution of **2b** (570 mg, 1.56 mmoles), diisopropylethylamine (0.78 ml, 4.5 mmoles), and *N*-BOC-L-serine (923 mg, 4.50 mmoles) in anhydrous 1,4-dioxane (3 ml) was heated at 50° for 18 hours. After pouring into 1*N* hydrochloric acid, the mixture was extracted with methylene chloride. The methylene chloride extract was washed with water, dried over magnesium sulfate and concentrated to leave a yellow foam. This was taken up in hot acetonitrile. On cooling, the product **3d** precipitated as a yellow crystalline solid, 500 mg (56%).

[[6-Chloro-5-fluoro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1*H*-indol-1-yl]carbonyl]carbamic Acid, Phenyl Ester (**3e**).

Phenol (141 mg, 1.49 mmoles) was added to a slurry of sodium hydride (36 mg, 1.5 mmoles) in anhydrous 1,2-dimethoxyethane (15 ml). After stirring for 15 minutes, **2b** (570 mg, 1.56 mmoles) was added and the mixture was warmed at 40° for 6 hours. After pouring into 1*N* hydrochloric acid, the mixture was extracted with methylene chloride. The methylene chloride extract was washed with water, dried over magnesium sulfate and concentrated to leave a yellow solid. This was recrystallized from acetonitrile to provide **3e** as a yellow crystalline solid, 450 mg (63%).

General Reaction of **2a** and **2b** with Amines.

n-Butylamine (0.16 ml, 1.62 mmoles) was added to a slurry of **2a** (520 mg, 1.50 mmoles) in methylene chloride (25 ml). The mixture was stirred at 20° for 18 hours. After pouring into 1*N* hydrochloric acid, the mixture was extracted with methylene chloride. The methylene chloride extract was washed with water, dried over magnesium sulfate and concentrated to leave a yellow solid. This was recrystallized from acetonitrile to give **4a** as a yellow crystalline solid, 270 mg (43%). Compounds **4b** and **4c** were similarly obtained by the reactions of **2a** with benzylamine and **2b** with diethylamine respectively. Both compounds were recrystallized from acetonitrile.

General Reaction of **2a** with Amino Acids.

To a solution of **2a** (520 mg, 1.50 mmoles) and triethylamine (0.22 ml, 1.58 mmoles) in *N,N*-dimethylformamide (20 ml) was added L-phenylalanine (264 mg, 1.60 mmoles). The mixture was stirred at 20° for 18 hours. After pouring into 1*N* hydrochloric acid, the mixture was extracted with methylene chloride. The methylene chloride extract was washed with water, dried over magnesium sulfate and concentrated to leave an oil containing residual *N,N*-dimethylformamide. Most of this was removed by evaporation under high vacuum. The residue was triturated with hot acetonitrile to leave **4d** as a fine yellow powder, 450 mg (58%). The reaction of **2a** with L-serine was carried out using the same procedure except that the crude product was triturated with methylene chloride.

REFERENCES AND NOTES

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[7] Diisopropylethylamine was used as the base in some instances.

[8] The NH proton in **2a** and **2b**, the OH proton(s) in compounds **3d**, **4c-e** and the CO_2H proton in compounds **3d**, **4d** and **4e** were not distinctly observed in the ^1H nmr spectra presumably due to rapid exchange with traces of water in the solvent (deuterioacetone or DMSO-d_6).