Synthesis of Novel 1,3-Oxazino[6,5-*b*]indole-2,4-(3*H*,9*H*)-dione and 2*H*-1,3,5-Oxadiazino[3,2-*a*]indole-2,4-(3*H*)-dione from Oxindoles

Randall J. Gallaschun* and Rodney C. Schnur

Medicinal Chemistry, Central Research, Pfizer, Inc.,
Groton, CT 06340

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Two novel tricyclic ring systems were designed as serine protease inhibitors and synthesized from oxindoles; the first series, 1,3-oxazino[6,5-*b*]indole-2,4-(3*H*,9*H*)-diones, were prepared from 2,3-dihydro-2-oxo-(1*H*)-indole-3-carboxamides and phosgene in tetrahydrofuran with triethylamine. The second, a 2*H*-1,3,5-oxadiazino[3,2-*a*]indole-2,4-(3*H*)-dione was made using a similar cyclization on 2,3-dihydro-2-oxo-*N*-phenyl-(1*H*)-indole-1-carboxamide.

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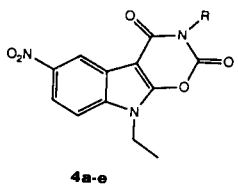
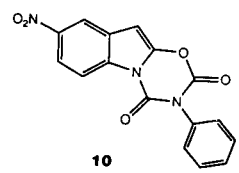
Plasminogen activator is one of the serine proteases that has been implicated in tumor metastatic progression and outgrowth [1]. While there are a wide variety of structures known to inhibit these proteases, nevertheless, there have been few examples of antiprotease drugs that have shown *in vivo* antitumor activity, a notable exception being the guanidinobenzoate protease inhibitor, FOY-305 [2]. In our empirical search for plasminogen activator inhibitors, the lead, **11** [3], was found to possess *in vitro* activity when tested in a screen designed to uncover selectivity among serine proteases. The structure of **11** bore striking resemblence to benzoxazinone protease inhibitors discovered by Powers [4] and also shares certain structural similarities with the saccharin derived 6,5-bicyclic protease inhibitors discovered by Zimmerman [5].

The potential to produce a related but novel series of tricyclic heterocycles derivatives of type **4a-e** or **10** was suggested both by the structure of lead **11** and by our earlier observation of the facile and selective *O*-acylation of 1-ethyl-5-nitrooxindole when treated with furoyl chloride and triethylamine in tetrahydrofuran. *O*-Acylation is not the usual mode of reactivity reported for oxindoles. Indeed, under slightly different conditions *C*-acylation exclusively occurs, *e.g.* with isocyanates and triethylamine in dimethylformamide. The 3-carboxamido analogs **3a-e**, resulting from this latter procedure, appeared attractive as starting materials for preparation of new tricyclics employing *O*-acylation procedures and a bifunctional acylating agent. Thus oxindoles **3a-e** were reacted with phosgene under *O*-acylation conditions to afford new 6,5,6-tricyclic heterocyclic ring systems, **4a-e**, 1,3-oxazino[6,5-*b*]indole-2,4(3*H*,9*H*)-diones. In a similar fashion **10**, 2*H*-1,3,5-oxadiazino[3,2-*a*]indole-2,4-(3*H*)-dione, was prepared under *O*-acylation conditions from the oxindole 1-carboxamide, **9**.

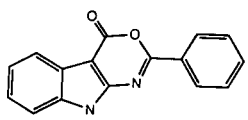
The approach of using a bifunctional acylating agent has been previously reported in the synthesis of novel benzazepine tricyclic heterocycles of 6,7,5-ring systems, the 1*H*-imidazo[5,1-*b*]benzazepine-1,3(2*H*)-diones and the 6,7,6-ring system pyrimido[6,1-*b*][3]benzazepine-1,3,4(2*H*)-trione [6]. Heterocycles **4a-e** and **10** have now been prepared using this strategy and represent the first examples



4a-e



10



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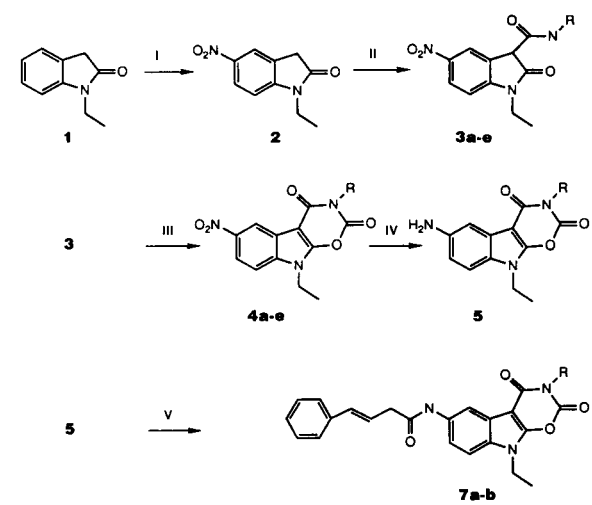
Scheme 1
Synthesis of 1,3-Oxazino[6,5-b]indole-2,4(3*H*,9*H*)-diones



I. 10 eq. H_2SO_4, 1.1 eq. fuming HNO_3, 15-20°C
II. 1.2 eq. R-N=C=O, 2.4 eq. TEA, DMF, 4 hours
III. excess $COCl_2$, 2 eq. TEA, THF, 0°C
IV. 5% Pd/C, H_2, THF
V. 0.85 eq. styryl acetic acid hydroxysuccinimide ester, 1.67 eq. $NaHCO_3$, THF/H_2O

of these 6,5,6-tricyclic ring systems to be reported in the literature.

The synthesis of 1,3-oxazino[6,5-*b*]indole-2,4-(3*H*,9*H*)-diones, **4a-e**, is shown in Scheme 1. It begins with nitration of *N*-ethyloxindole followed by the *C*-acylation of that product 1-ethyl-1,3-dihydro-5-nitro-(2*H*)-indol-2-one, **2**, according to the procedure of McManus [7]. Compound **2** reacts with a variety of isocyanates to yield 1-ethyl-2,3-dihydro-2-oxo-(1*H*)-indole-3-carboxamides, **3a-e**, Table 1. The novel tricyclics were prepared in moderate yield by cyclization of **3a-e** with phosgene and triethylamine in tetrahydrofuran at 0°. These products were isolated by quenching the reaction mixture with ice water, extraction into organic solvents and purification by the method indicated in Table 2. The oxaziniediones **4a-e** were stable to water and hot alcohols during the purification process. An X-ray structure determination of **4b** has indicated a completely planar tricyclic ring system as expected from a Huckel 14 π-electron configuration. The fractional atom coordinates are given in Table 3.

Table 1

Substituted 2,3-dihydro-2-oxo(1*H*)indole-3-carboxamides

Cmpd #	R	mp°	solvent
3a	CH_3	202-204	ethanol
3b	phenyl	164-166	ethanol
3c	4-CN-phenyl	219-221	methanol
3d	4-F-phenyl	189-191	ethanol
3e	4-OCH_3-phenyl	154-156	ethanol

Table 2

Substituted 1,3-oxazino[6,5-b]indole-2,3(3*H*,9*H*)-diones

Cmpd #	R	R'	mp°	solvent [a]	yield
4a	CH_3	NO_2	234-236	ethanol	65
4b	phenyl	NO_2	217-219	ethanol trit.	45
4c	4-CN-phenyl	NO_2	220-222	[a]	6
4d	4-F-phenyl	NO_2	172-174	ethanol	16
4e	4-OCH_3-phenyl	NO_2	216-218	[b]	56
5	phenyl	NH_2	192-194	[b]	34
7a	CH_3	styryl-N	209-211	ethanol	44 [c]
7b	phenyl	styryl-N	142-144	ethanol	74

[a] recrystallization solvent except for compound 4c which was purified by flash column chromatography using 10% $CHCl_3$-hexanes on silica gel. [b] crystallized from chloroform-hexanes. [c] overall yield from 4a including reduction and acylation.

1,3,5-Oxadiazino[3,2-*a*]indole-2,4(3*H*)-dione, **10**, was prepared according to Scheme 2 using a similar ring forming strategy. 5-Nitrooxindole was acylated at the 1-position with phenyl isocyanate in xylene to yield 2,3-dihydro-2-oxo-(1*H*)-indole-1-carboxamide, **9**. Perfusion of a solution of **9** in tetrahydrofuran and triethylamine with phosgene at 0° afforded **10** in high yield. Compounds **4a-e** and **10** were found to possess time dependent protease inhibition of plasminogen activator, trypsin, plasmin and α-thrombin but were not useful as tumor inhibitors.

Table 3

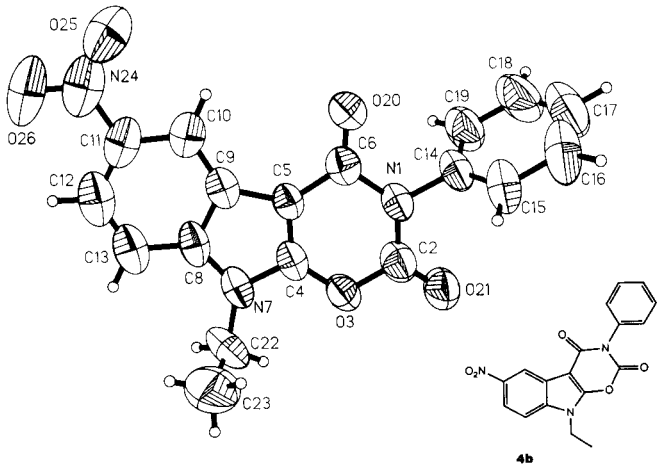
Fractional Coordinates (x 10^4) for 4b

Estimated Standard Deviations are in Parentheses

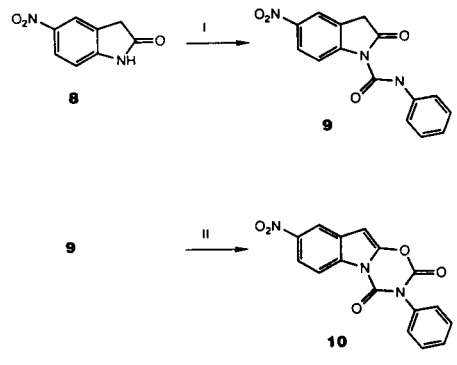
	X	Y	Z
N (1)	4406 (7)	1427 (2)	6778 (3)
C (2)	4510 (10)	1940 (3)	6243 (4)
O (3)	4153 (6)	1819 (2)	5370 (2)
C (4)	3572 (8)	1216 (3)	5125 (4)
C (5)	3383 (7)	706 (3)	5627 (3)
C (6)	3845 (8)	771 (3)	6537 (4)
N (7)	3080 (7)	1092 (3)	4279 (3)
C (8)	2530 (8)	452 (3)	4233 (4)
C (9)	2698 (8)	186 (3)	5063 (4)
C (10)	2158 (8)	-444 (3)	5170 (4)
C (11)	1525 (8)	-792 (3)	4427 (4)
C (12)	1370 (9)	-520 (4)	3618 (5)
C (13)	1848 (10)	98 (4)	3502 (4)
C (14)	4827 (10)	1563 (3)	7684 (4)
C (15)	6699 (11)	1716 (4)	8031 (4)
C (16)	7041 (13)	1838 (4)	8905 (5)
C (17)	5542 (15)	1792 (4)	9374 (5)
C (18)	3713 (15)	1647 (5)	9023 (5)
C (19)	3384 (11)	1525 (4)	8170 (4)
O (20)	3779 (6)	356 (2)	7063 (3)
O (21)	4907 (8)	2480 (2)	6445 (3)
C (22)	3032 (12)	1548 (4)	3575 (4)
C (23)	4752 (16)	1477 (5)	3184 (6)
N (24)	921 (8)	-1451 (3)	4523 (5)
O (25)	962 (9)	-1680 (3)	5234 (4)
O (26)	304 (10)	-1761 (3)	3873 (5)
X (1)	1580 (15)	1140 (7)	1092 (5)
X (2)	13	1477	1336
X (3)	-1583	1140	1549
X (4)	-1614	465	1520
X (5)	-47	127	1277
X (6)	1550	465	1063
X (7)	3224 (19)	92 (8)	794 (11)

Elemental Analysis of Novel Compounds

Compound No. and Formula	Calculated C	H	N	Found C	H	N
3a $C_{12}H_{13}N_3O_4 \cdot ½\ H_2O$	52.94	5.18	15.43	53.45	5.24	15.34
3b $C_{17}H_{15}N_3O_4$	62.76	4.65	12.92	62.66	4.69	12.94
3c $C_{18}H_{14}N_4O_4$	61.71	4.03	15.99	61.48	3.97	15.97
3d $C_{17}H_{14}FN_3O_4 \cdot ¼\ H_2O$	58.70	4.20	12.08	58.95	3.99	12.04
3e $C_{18}H_{17}N_3O_5$	60.84	4.82	11.82	60.74	4.48	11.74
4a $C_{13}H_{11}N_3O_5$	53.98	3.83	14.53	53.89	3.81	14.82
4b $C_{18}H_{13}N_3O_5$	61.54	3.73	11.96	61.90	3.79	11.91
4c $C_{18}H_{12}N_4O_5 \cdot ¼\ H_2O$	59.92	3.31	14.71	60.02	3.43	15.08
4d $C_{18}H_{12}FN_3O_5 \cdot 1\ H_2O$	55.82	3.64	10.85	55.99	3.12	10.46
4e $C_{19}H_{15}N_3O_6 \cdot ¼\ H_2O$	59.14	4.04	10.89	59.22	4.07	10.86
5 $C_{18}H_{15}N_3O_3 \cdot ½\ H_2O$	65.44	4.88	12.71	65.80	4.49	12.66
7a $C_{23}H_{21}N_3O_4 \cdot ¾\ H_2O$	66.26	5.44	10.07	66.45	5.40	10.27
7b $C_{28}H_{23}N_3O_4 \cdot ½\ H_2O$	70.87	4.89	8.86	71.16	4.96	8.85
10 $C_{10}H_5N_3O_5 \cdot ½\ H_2O$	57.83	3.03	12.65	57.90	2.85	12.67
11 $C_{16}H_{16}N_2O_2 \cdot CF_3CO_2H \cdot ¼\ H_2O$	56.77	3.04	7.36	57.03	2.98	7.80



Scheme 2
Synthesis of 1,3,5-oxadiazino[3,2-a]indole-2,4(3*H*,4*H*)-dione



I. 1.0 eq. phenyl isocyanate, xylene, reflux
II. excess $COCl_2$, 2 eq. TEA, THF

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by the Pfizer Central Research "Microanalysis" Laboratory and results obtained for specified elements are within ±0.40% of the theoretical values (hydrates incorporated as indicated). The ir spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer with the stipulated solvents and are reported in reciprocal centimeters. The ^{1}H nmr spectra of deuteriochloroform of DMSO-d_6 (TMS as internal standard) were recorded on a Varian A-60, a Perkin-Elmer T-60, a Bruker 250 or a Bruker 300 spectrometer. High resolution mass spectral data were recorded on an Kratos Concept 1S EB Sector. Low resolution mass spectral data were recorded on a Hitachi RMU6-E spectrometer. Silica gel used was EM Science particle size 0.040-0.063 mm.

1-Ethyl-1,3-dihydro-5-nitro-2*H*-indol-2-one (**2**).

1-Ethyl-1,3-dihydro-2*H*-indol-2-one, **1**, [8] (40.0 g, 248.1 mmoles) was added to 132 ml of sulfuric acid at 0°. Fuming nitric acid (90%, 11.7 ml, 276.2 mmoles) was added dropwise to the dark brown solution so as to maintain the temperature between 15-20°. The reaction mixture was then stirred at room temperture for 3 hours, poured into 1500 ml of water/ice chips and a tan solid formed. The solid was filtered and dried *in vacuo* at 110° overnight to yield **2**, (49.4 g, 97%), mp 159-161°; ^{1}H nmr (deuteriochloroform): δ 1.30 (t, 3H, CH_3, J = 7 Hz), 3.59 (s, 2H, CH_2), 3.79 (q, 2H, CH_2, J = 7 Hz), 6.85 (d, 1 phenyl proton, J = 8 Hz), 8.15-8.28 (m, 2 phenyl protons); ir (dichloromethane): 2936 (CH_2), 1727 (C=O), 1617 (O=C-N), 1520 (C-NO_2), cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.26; H, 4.87; N, 13.57.

1-Ethyl-2,3-dihydro-5-nitro-2-oxo-*N*-phenyl-1*H*-indole-3-carboxamide (**3b**).

1-Ethyl-1,3-dihydro-5-nitro-2*H*-indol-2-one, **2**, (5.0 g, 24.25 mmoles) and triethylamine (8.11 ml, 58.20 mmoles) were dissolved in 30 ml of anhydrous dimethylformamide. The resultant red-brown mix was stirred at room temperature for 10 minutes then cooled to between −20 and −40° using an acetonitrile/dry ice bath. To the cold mixture was added phenyl isocyanate (3.16 ml, 29.09 mmoles) slowly dropwise *via* a syringe and then the reaction was allowed to gradually warm to room temperature (achieved by removing dry ice bath). After 1 hour at room temperature the mix was poured into 200 ml of water/ice chips containing 100 ml of 1*N* hydrochloric acid and extracted with 2 x 250 ml of ethyl acetate. Pooled organic layers were washed with 3 x 300 ml of water and brine, dried with magnesium sulfate, filtered and evaporated *in vacuo* to a light orange solid (8.21 g). The solid was recrystallized with 100 ml of ethanol which yielded **3b** as light tan crystals (3.11 g, 40%), mp 164-166°; ^{1}H nmr (deuteriochloroform): δ 1.35 (t, 3H, CH_3, J = 8 Hz), 3.90 (q, 2H, CH_2, J = 8 Hz), 4.48 (s, 1H, CH), 7.01 (d, 2 phenyl protons, J = 10 Hz), 7.14 (t, 1 phenyl proton, J = 10 Hz), 7.35 (t, 2 phenyl protons, J = 10 Hz), 7.59 (d, 1 phenyl proton, J = 10 Hz), 8.33 (dd, 1 phenyl proton, J = 9 and 2 Hz), 8.70 (d, 1 phenyl proton, J = 2 Hz), 9.37 (br s, 1H, NH); ir (dichloromethane): 3330 (O=C-N), 1720 (C=O), 1606 (O=C-N), 1528 (C-NO_2), cm^{-1}.

In a similar manner **3a** and **3c-e** were prepared.

9-Ethyl-6-nitro-3-phenyl-1,3-oxazino[6,5-*b*]indole-2,4-(3*H*,9*H*)-dione (**4b**).

1-Ethyl-2,3-dihydro-5-nitro-2-oxo-*N*-phenyl-1*H*-indole-3-carboxamide, **3b**, (2.5 g, 7.69 mmoles) was dissolved in 350 ml of anhydrous tetrahydrofuran and cooled to 0°. Next triethylamine (2.14 ml, 15.38 mmoles) was added followed by a slow perfusion of phosgene for 45 minutes (**caution: toxic gas!**, must be trapped using a 1:1 aniline/ethanol followed by a 6*N* potassium hydroxide trap). After this time nitrogen was bubbled through the reaction for 1 hour then the mixture was carefully poured into 1000 ml of ice chips. The solution was extracted with 3 x 250 ml of ethyl acetate. The pooled organics were washed with 2 x 200 ml of water, dried with magnesium sulfate, filtered and evaporated *in vacuo* to a yellow solid (2.61 g). This solid was triturated with 100 ml of hot ethanol which yielded **4b** as a light yellow solid (1.21 g, 45%), mp 217-219°; ^{1}H nmr (deuteriochloroform); δ 1.58 (t, 3H, CH_3, J = 8 Hz), 4.38 (q, 2H, CH_2, J = 8 Hz), 7.35 (dd, 1 phenyl proton, J = 8 and 2 Hz), 7.48-7.59 (m, 5 phenyl protons), 8.29 (dd, 1 phenyl proton, J = 9 and 2 Hz), 8.90 (d, 1 phenyl proton, J = 2 Hz); ir (dichloromethane): 1784 (O=C-O-C=C), 1726 (C=O), 1620 (O=C-N), 1511 (C-NO_2) cm^{-1}.

In a similar manner **4a** and **4c-e** were prepared.

6-Amino-9-ethyl-3-phenyl-1,3-oxazino[6,5-*b*]indole-2,4(3*H*,9*H*)-dione (**5b**).

9-Ethyl-6-nitro-3-phenyl-1,3-oxazino[6,5-*b*]indole-2,4-(3*H*,9*H*)-dione, **4b**, (0.5 g, 1.42 mmoles) was dissolved in 125 ml of anhydrous tetrahydrofuran and 5% palladium on carbon (0.1 g) was added. The reaction mixture was hydrogenated on a Parr shaker at 50 psi. After 18 hours the mix was filtered through Celite and the filtrate was evaporated *in vacuo* to yield **5b** as a light yellow crystalline solid (0.43 g). Analytically pure sample was obtained by recrystallization from 30 ml of 1:1 chloroform/hexanes and recieved a white crystalline solid (0.17 g, 35%), mp 192-194°; ^{1}H nmr (DMSO-d_6): δ 1.39 (t, 3H, CH_3, J = 8 Hz), 4.24 (q, 2H, CH_2, J = 8 Hz), 5.07 (br s, 2H, NH_2), 6.66 (dd, 1 phenyl proton, J = 9 and 2 Hz), 7.06 (d, 1 phenyl proton, J = 2 Hz), 7.33-7.58 (m, 6 phenyl protons); ir (dichloromethane): 3460 (Ar-NH_2), 1774 (O=C-O-C=C), 1714 (C=O), 1636 (O=C-N) cm^{-1}.

4-Phenyl-3-butenoic Acid Succinimide Ester (**6**).

4-Phenyl-3-butenoic acid (styrylacetic acid) (Aldrich 15.0 g, 92.48 mmoles) was dissolved in 45 ml of anhydrous tetrahydrofuran and hydroxysuccinimide (15.97 g, 138.72 mmoles) was added followed by an additional 45 ml of tetrahydrofuran. After stirring for 15 minutes at room temperature, the mixture was cooled to 0° and 1,3-dicyclohexylcarbodiimide (28.61 g, 138.72 mmoles) in 90 ml of anhydrous tetrahydrofuran was added dropwise. The reaction was allowed to warm to room temperature, stirred overnight then filtered to remove dicyclohexylurea. The filtrate was evaporated *in vacuo* to a light yellow solid. The solid was dissolved in 500 ml of chloroform and washed with 2 x 200 ml of 5% sodium bicarbonate, 3 x 200 ml of 10% citric acid, 2 x 100 ml of water and brine, dried with magnesium sulfate, filtered and evaporated *in vacuo* to an off-white solid. The solid was dissolved in 300 ml of ethyl acetate and precipitated with the addition of 900 ml of hexanes yielding **6** as a white solid (20.45 g, 85%), mp 130-132°; ^{1}H nmr (deuteriochloroform): δ 2.82 (s, 4H, $2CH_2$), 3.59 (d, 2H, CH_2, J = 6 Hz), 6.05 (t, 1H, CH, J = 16 and 6 Hz), 6.60 (t, 1H, CH, J = 16 and 6 Hz), 7.30 (m, 5 phenyl protons).

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.66; H, 4.98; N, 5.23.

N-(9-Ethyl-2,3,4,9-tetrahydro-3-phenyl-2,4-dioxo-1,3-oxazino-[6,5-*b*]indol-6-yl)-4-phenyl-3-butenamide (**7b**).

6-Amino-9-ethyl-3-phenyl-1,3-oxazino[6,5-*b*]indole-2,4(3*H*,9*H*)-dione, **5b**, (2.55 g, 0.792 mmole) and sodium bicarbonate (0.171 g, 0.660 mmole) were slurried in 8 ml of tetrahydrofuran and 1 ml of water. Next 4-phenyl-3-butenoic acid succinimide ester, **6**, (0.11 g, 1.32 mmoles) was added in 3 portions over 5 minutes followed by the addition of 5 ml of tetrahydrofuran and 1 ml of water. The mix was stirred at room temperature overnight then diluted with 50 ml of water and extracted with 3 x 100 ml of ethyl acetate. The pooled organics were washed with 2 x 100 ml of 1*N* hydrochloric acid, 100 ml of water, dried with magnesium sulfate, filtered and evaporated *in vacuo* to a light yellow solid. The solid was recrystallized with 20 ml of ethanol which yielded **7b** as white needles (0.226 g, 73%), mp 142-144°; ^{1}H nmr (deuteriochloroform): δ 1.51 (t, 3H, CH_3, J = 8 Hz), 3.35 (d, 2H, CH_2, J = 8 Hz), 4.27 (q, 2H, CH_2, J = 8 Hz), 6.32-6.45 (m, 1H, CH), 6.64 (d, 1H, CH, J = 16 Hz), 7.25-7.45 (m, 7 phenyl protons), 7.48-7.6 (m, 4 phenyl protons), 7.74 (d, 1 phenyl proton, J = 2 Hz), 7.93 (dd, 1 phenyl proton, J = 9 and 2 Hz); ir (dichloromethane): 3423 (O=C-N), 1775 (O=C-O-C=C), 1715 (C=O), 1633 (O=C-N) cm^{-1}.

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

2,3-Dihydro-5-nitro-2-oxo-*N*-phenyl-1*H*-indole-1-carboxamide, **9**, [9], (0.5 g, 1.68 mmoles) was slurried in 80 ml of anhydrous tetrahydrofuran and then cooled to 0°. Next triethylamine (0.47 ml, 3.36 mmoles) was added followed by a slow perfusion of phosgene for 45 minutes (**caution: toxic gas!**, must be trapped by using a 1:1 aniline/ethanol followed by a 6*N* potassium hydroxide trap). After this time nitrogen was bubbled through the reaction for 1 hour then the mixture was carefully poured into 200 ml of ice chips. The solution was extracted with 3 x 100 ml of ethyl acetate. The pooled organics were washed with 3 x 100 ml of water and brine, dried with magnesium sulfate, filtered and evaporated *in vacuo* to yield **10** as a light orange tan solid (0.50 g, 95%). Analytically pure sample was obtained by recrystallization from 50 ml of xylene and received a tan solid (0.265 g, 62%), mp 273-276°; ^{1}H nmr (DMSO-d_6): δ 6.65 (s, 1H, CH), 7.75-7.65 (m, 6 phenyl protons), 8.21-8.30 (m, 2 phenyl protons), 8.63 (d, 1 phenyl protons, J = 2 Hz); ^{13}C nmr (DMSO-d_6): 85.4, 114.3, 116.5, 118.5, 128.1, 128.6, 129.0, 129.2, 129.3, 131.9, 133.9, 143.3, 144.5, 144.6 ppm.

2-Phenyl[1,2]oxazino[4,5-*b*]indol-4(9*H*)-one, **11**.

This compound was synthesized by cyclization of the 1,1-dimethylethyl 2-benzoylamino-1*H*-indole-3-carboxylate, itself prepared from 1,1-dimethyl ethyl ester analog, 2-amino-3-carbo-*t*-butoxyindole. This ester was synthesized by a procedure directly analogous to that of Grob *et al.* [3b] and Munshi *et al.* [3c] used to prepare the ethyl ester except that the intermediate oils obtained in the preparation were used in their crude state.

Sodium hydride (4.8 g, 100 mmoles, 50% oil dispersion) was washed free of its oil with 3 x 50 ml of pentane and slurried in 120 ml of dimethyl sulfoxide. Next *t*-butyl cyanoacetate (Aldrich, 14.24 ml, 100 mmoles) was slowly added dropwise over 20 minutes. After an additional 20 minutes, 1-chloro-2-nitrobenzene (15.7 g, 100 mmoles), dissolved in 50 ml of dimethyl sulfoxide, was added. The reaction was heated at 100° for 4 hours, cooled to room temperature, poured into 200 ml of saturated ammonium chloride, acidified to *p*H 3.0 with 6*N* hydrochloric acid and extracted with 2 x 250 ml of 1:1 ethyl acetate/hexanes. The pooled organics were washed with 2 x 250 ml of 0.6*N* sodium hydroxide. The aqueous layer was washed with 2 x 200 ml of diethyl ether, acidified with 6*N* hydrochloric acid to *p*H 3.0 and extracted with 2 x 250 ml of diethyl ether. The ether layer was washed with 2 x 100 ml of brine, dried with magnesium sulfate, filtered and evaporated *in vacuo* to an oily *t*-butyl 2-nitrophenylcyanoacetate (16.14 g, 62%) which was used without further purification. The crude oil (8.0 g, 30.5 mmoles) was dissolved in 150 ml of acetic acid and heated to 100° while zinc dust (32 g, 489 mmoles) was added portionwise over 5 minutes. The reaction, after heating for an additional 15 minutes, was cooled and filtered. The filtrate was poured into 500 ml of water/ice chips, filtered and evaporated *in vacuo* to an oil. The oil was flash chromatographed on 200 g of silica gel eluted with 5% ethyl acetate/chloroform and collected in 20 ml fractions. Fractions 34-70 were combined and evaporated *in vacuo* to an oily 2-amino-3-carbo-*t*-butoxyindole (2.2 g, 32%) which was used directly in the next step. The ^{1}H nmr and ir spectral data were consistent with structures assigned to the oily intermediates obtained above. This latter oil (0.34 g, 1.46 mmoles) was dissolved in 3.5 ml of pyridine and treated dropwise with benzoyl chloride (.34 ml, 2.93 mmoles). After 24 hours at

room temperature the mix was poured into 100 ml of water, acidified with 6*N* hydrochloric acid and extracted with 3 x 100 ml of ethyl acetate. The combined organics were washed with 2 x 50 ml of 0.5*N* hydrochloric acid, 2 x 50 ml of brine, dried with magnesium sulfate, filtered and evaporated *in vacuo* to a off-white solid. The solid was flash chromatographed using 100 g of silica gel eluted with 10% hexanes/ethyl acetate and collected in 20 ml fractions. Fractions 14-24 were combined and evaporated *in vacuo* to an off-white solid which was recrystallized with 50 ml of hexanes to afford pure 1,1-dimethylethyl 2-benzoylamino-1*H*-indole-3-carboxylate as a white solid (0.23 g, 47%), mp 183-185°; ^{1}H nmr (deuteriochloroform): δ 1.73 (s, 9H, $[CH_3]_3$), 7.25 (m, 2 phenyl protons), 7.40 (m, 1 phenyl protons), 7.60 (m, 3 phenyl protons), 7.95 (d, 2 phenyl protons, J = 8 Hz), 8.08 (d, 2 phenyl protons, J = 8 Hz), 11.5 (br s, amide), 11.62 (br s, indole NH); ir (potassium bromide): 1680 (COO-1,1-dimethylethyl), 1650 (N-C=O) cm^{-1}.

Anal. Calcd. for $C_{20}H_{20}NO_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.47; H, 5.96; N, 8.29.

Compound **11** was prepared by cyclization of this ester using the procedure as follows: 1,1-dimethylethyl 2-benzoylamino-1*H*-indole-3-carboxylate (0.49 g, 1.46 mmoles) was dissolved in 5 ml of methylene chloride and cooled to 0°. To this solution was added trifluoroacetic acid (2.24 ml, 29.2 mmoles) and the reaction was stirred for 2 hours at room temperature. After this time trifluoroacetic anhydride (2.06 ml, 14.6 mmoles) was added and the reaction was stirred for 18 hours. The heterogeneous reaction was diluted with 50 ml of carbon tetrachloride and filtered the off white solid (0.23 g, 42%), mp 268-269°; silica gel (CH_2Cl_2) rf = 0.2 and (5% ethyl acetate/methylene chloride) rf = 0.7; ^{1}H nmr (DMSO-d_6): δ 7.35 (t, 1 phenyl proton, J = 8 Hz), 7.41 (t, 1 phenyl proton, J = 8 Hz), 7.55-7.60 (m, 1 phenyl proton), 7.62-7.68 (m, 2 phenyl protons), 7.70 (d, 1 phenyl proton, J = 8 Hz), 7.92 (d, 1 phenyl proton, J = 8 Hz), 8.25 (d, 2 phenyl protons, J = 9 Hz), 12.89 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): 92.46, 112.55, 120.11, 122.09, 122.61, 124.92, 128.00, 129.21, 130.10, 133.09, 135.66, 152.41, 155.52, 162.06 ppm; ms: (70 eV, electron impact) m/z 262.0739 (calcd. for 262.2672).

X-ray Crystallographic Analysis of **4b**.

A large plate crystal of **4b** was obtained by recrystallization from toluene: $C_{18}H_{13}N_3O_5 \cdot C_7H_8$; MW = 443.5, 4 molecules per unit cell, cell constants: a = 6.974(2) Å, b = 20.653(7) Å, c = 15.802(7) Å, δ = 90.00°, β = 98.09(3)°, ν = 2253(1) $Å^3$, density calculated = 1.31 g/cm^3. Lattice constants and intensity data were measured by using graphite-monochromated CuKα on a Nicolet R3m/μ diffractometer. Atomic scattering factors were taken from the International Tables for X-Ray crystallography [10]. All crystallographic calculations were facilitated by the SHELXTL system [11]. A difference map revealed a toluene molecule of crystallization. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R-index was 0.087. A total of 2289 reflections and 1626 non zero reflections were observed. The final difference Fourier revealed no missing or misplaced election density except in the region of the toluene of crystallization. This molecule was slightly disordered as demonstrated by its large thermal parameters. No attempt was made to better fit the disorder.

Supplementary Materials.

Tables of hydrogen atom coordinates, bond angles and lengths and anisotrobic thermal parameters are available upon request from the authors.

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