Preparation of 6-, 7-, and 8-Substituted Derivatives of 2-Oxa-1,3,4,10-tetraazacyclopenta[*b*]fluoren-9-one

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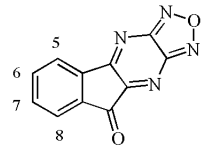
Received November 14, 2000

The preparation of a variety of derivatives of 2-oxa-1,3,4,10-tetraazacyclopenta[*b*]fluoren-9-one **1** is described. A series of substituted indan-1-ones were prepared and oxidized with *N*-bromosuccinimide and dimethyl sulfoxide to the corresponding ninhydrin derivatives. Cyclization of the ninhydrins with furazan-3,4-diamine yielded the target tetracycles. Appropiate choice of substituents in ninhydrins led to a preference for one regioisomer in the target tetracycles. This permitted the synthesis of a variety of 8-substituted heterocycles. In those instances where isomer formation was possible, structural assignments were confirmed by X-ray crystallography.

J. Heterocyclic Chem., **38**, 1103 (2001).

As a part of a screening program to identify new compounds with pharmacological activity, we became interested in 2-oxa-1,3,4,10-tetraazacyclopenta[*b*]fluoren-9-one **1**. The only literature reference to compound **1** [1] describes the preparation by the reaction of ninhydrin and furazan-3,4-diamine [2] under acidic conditions. This reaction is analogous to that of ninhydrin with *o*-phenylenediamine and other heterocyclic diamines [3-5]. We were interested in preparing derivatives of **1** for biological testing by introducing functionality at positions 6-8 of the tetracycle. We found that electrophilic aromatic substitution to **1** (bromination, nitration, or Friedel-Crafts acylation with benzoyl chloride) was unsatisfactory, presumably due to deactivation of the aromatic ring by the ketone and fused pyrazine moieties. Ultimately, our method of choice to synthesize these derivatives was to incorporate a suitable functional group into an indan-1-one for conversion to a substituted ninhydrin derivative [6,7] before cyclization with furazan-3,4-diamine.



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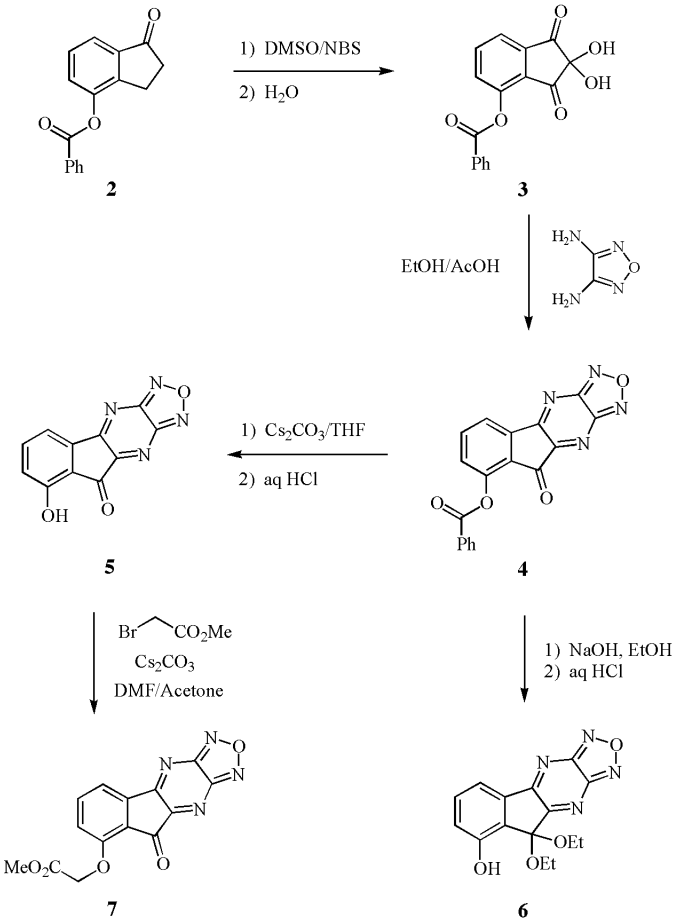
The use of substituted ninhydrins in the cyclization reaction introduces the possibility of regioisomer formation in the teracyclic products. Therefore, our strategy for preparing the 8-substituted analogs of **1** was to incorporate a bulky substituent in the indane-1-one starting material in order to favor formation of one regioisomer after reaction of the corresponding ninhydrin derivative [3]. In those instances where isomer formation was possible, structural assignments were confirmed by X-ray crystallography.

An initial attempt to use a benzyloxy blocking group failed due to problems associated with attempted de-benzylation of the final product. Pyrazine and furazan moieties as found in **1** are known to be susceptible to chemical reduction [8,9] used for removal of the benzyl group. However, a benzoyl ester group was found to be a useful function for isomer control of certain tetracyclic targets (Scheme 1).

The preparation of 8-substituted derivatives of **1** began with indanone ester **2** [10]. Electrophilic bromination of **2** with *N*-bromosuccinimide, followed by oxidation with dimethyl sulfoxide [7,11], gave the substituted ninhydrin **3** in 61% yield. Condensation of **3** with furazan-3,4-diamine

Scheme 1



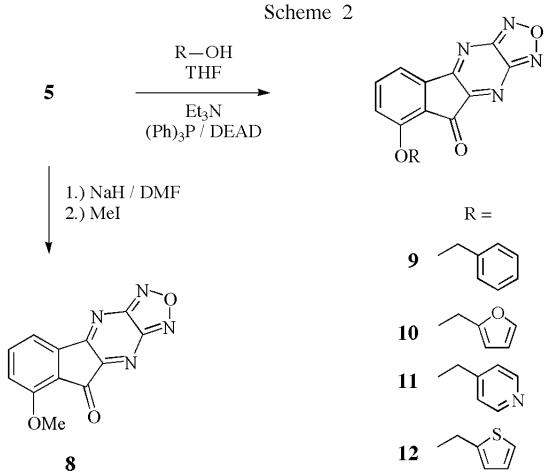
2 **3** **4** **5** **6** **7**

in a mixture of ethanol and acetic acid afforded the 8-substituted tetracycle **4**, the structure of which was confirmed by X-ray analysis. Although, concomitant formation of the 5-substituted regioisomer of **4** was possible, this product was not isolated from the reaction mixture.

Ester cleavage of **4** provided a phenolic derivative that was useful for the introduction of additional functionality. Reaction of **4** with cesium carbonate in tetrahydrofuran [12] provided the phenol **5** in 94% yield. An earlier attempt at preparing **5** by saponification of **4** with sodium hydroxide in ethanol was unsuccessful. Instead, a small amount of the diacetal byproduct **6** was isolated. Similarly, treatment of **4** with lithium hydroxide in aqueous tetrahydrofuran did not produce the desired product. The lack of success, in generating the desired phenol **5** by the reaction of alkali metal hydroxides with **4**, may be attributed to the sensitivity of the pyrazine and furazan parts of the molecule to attack by a strong nucleophile.

Alkylation of **5** was accomplished by treating **5** with cesium carbonate in *N*,*N*-dimethylformamide to form the cesium phenoxide intermediate and then reacting with methyl bromoacetate to give the alkylated product **7**. Likewise, methyl ether **8** was prepared by reaction of **5** with sodium hydride in *N*,*N*-dimethylformamide, followed by alkylation with iodomethane (Scheme 2). Mitsunobu reaction conditions were employed for the introduction of a range of aralkyl groups into the tetracycle. Thus, reactions of phenol **5** with aryl and heteroaryl alcohols in tetrahydrofuran afforded the alkylated products **9-12** in yields of 24-70%.

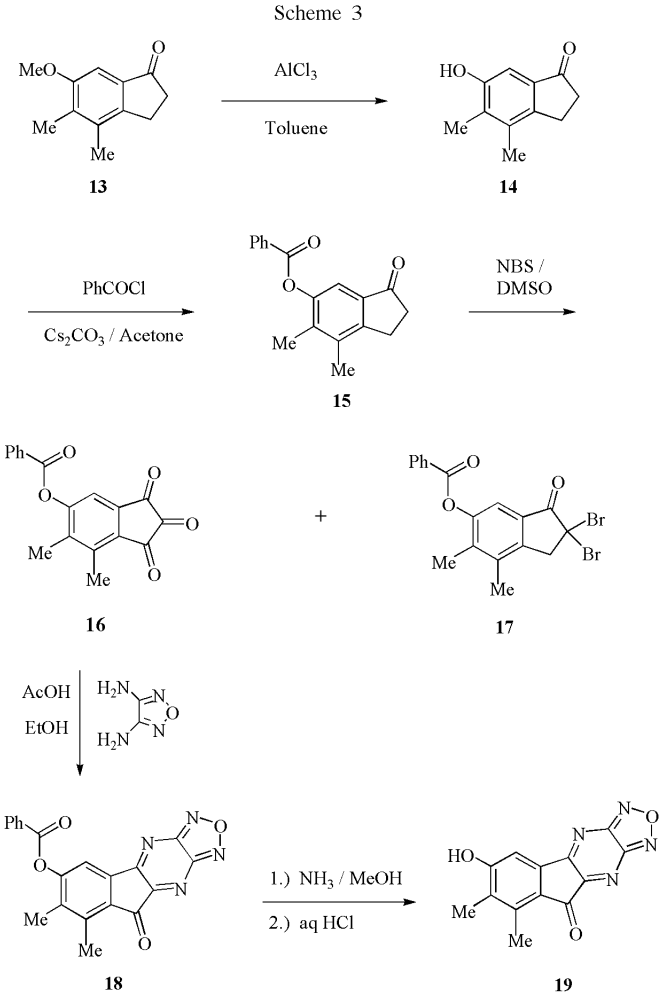
Scheme 2



Several analogs were prepared with functionality attached at the 6-position of the tetracycle (Scheme 3). A 4-methyl substituent in the starting indan-1-one **13** served as a viable blocking group [13] to ensure a single regioisomer in the target tetracycles.

Trisubstituted indanone **13** [14] was demethylated with aluminum chloride in toluene to afford the phenol **14** in

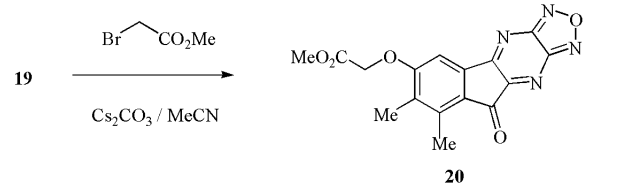
Scheme 3



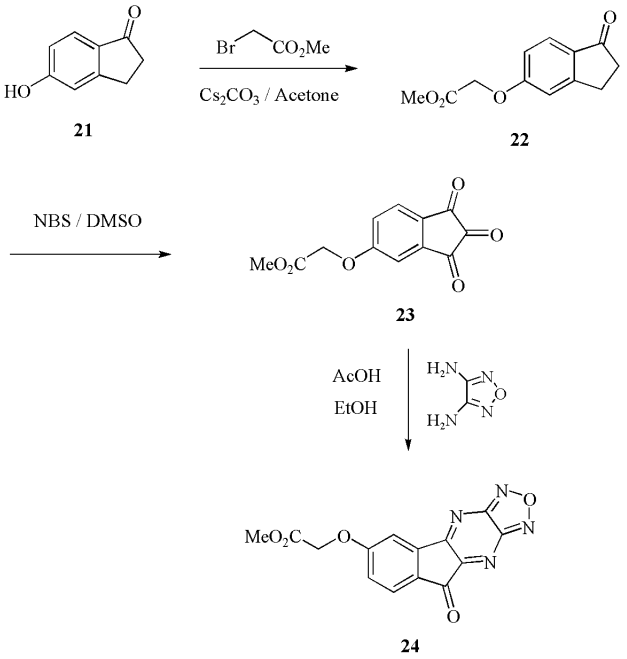
93% yield. Reaction of **14** with benzoyl chloride in acetone under basic conditions gave the benzoyl ester **15**, which was oxidized by the previous method to give ninhydrin **16**. In addition to **16**, the gem-dibromo indanone **17** was isolated as a side product. Condensation of **16** with furazan-3,4-diamine under acidic conditions afforded the tetracycle **18** as a single regioisomer (the structure of **18** was confirmed by X-ray analysis). Ammonia in methanol was used for conversion of **18** to the phenol **19** in 97% yield. Unlike the cleavage of ester **4**, reaction of **18** with cesium carbonate did not result in a complete conversion to the desired phenol product. Alkylation of **19** with methyl bromoacetate and cesium carbonate gave the target ester tetracycle **20** (Scheme 4).

Cyclization reactions of ninhydrin derivatives without a suitable blocking function invariably led to mixtures of tetracyclic isomers. This was realized in the preparation of tetracycle ester **24** (Scheme 5). The indanone **21** [15] was alkylated with methyl bromoacetate, and the ester product **22** was oxidized to yield the ninhydrin derivative **23**. Cyclization of **23** with furazan-3,4-diamine gave a mixture of the 6- and 7-substituted ester tetracycles. However,

Scheme 4



Scheme 5



recrystallization of the isomeric mixture from aqueous acetonitrile afforded the pure 6-substituted isomer **24**, which was structurally confirmed by X-ray analysis.

The observed X-ray structure of **4**, which exists as a stacked dimer, is illustrated as an ORTEP diagram in Figure 1 and confirms the attachment of the benzoyloxy substituent at the 8-position of the tetracycle. Crystal and refinement parameters for compound **4** as well as positional parameters and their estimated standard deviations are shown in Tables 1 and 2. Bond distances and angles for **4** are listed in Tables 3 and 4. Similarly, an X-ray analysis of compound **24** confirmed the attachment of the ester substituent at the 6-position of the tetracycle, and its ORTEP diagram and X-ray data are represented in Figure 2 and Tables 5-8, respectively.

We have described the preparation of a variety of derivatives of 2-oxa-1,3,4,10-tetraazacyclopenta[*b*]fluoren-9-one. A series of substituted indan-1-ones were prepared and oxidized with *N*-bromosuccinimide and dimethyl sulfoxide to ninhydrin derivatives. Cyclization of the ninhydrins with furazan-3,4-diamine yielded the target tetracycles. Isomeric control at the tetracyclic products was made

Table 1

Crystal and Refinement Data for **4**

formula	$C_{18}H_8N_8O_4$
formula weight	344.3
crystal system	triclinic
space group	P-1
a, Å	5.40(5)
b, Å	16.64(5)
c, Å	18.36(5)
V, Å^3	1541.260(1)
Z; density (calc), g/cm^3	4; 1.62
crystal size, mm	0.2 x 0.2 x 0.2
absorption coef., mm^{-1}	10.85
2q (max), deg.	100.28
reflections collected	5357
independent reflections	2346
parameters refined	249
final R indices	R1 = 0.089, wR2 = 0.050
largest diff. Peak, e/Å^3	0.48

Table 2

Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters (Å^2) for **4** [a,b]

Atom	x	y	z	U(eq)
O1	-0.240(4)	0.201(1)	-0.132(1)	0.072(5)
O2	-0.351(4)	0.161(1)	0.201(1)	0.076(5)
C3	-0.729(5)	0.073(2)	-0.108(1)	0.053(6)
N4	-0.561(4)	0.116(2)	0.161(1)	0.077(6)
N6	-0.254(4)	0.191(1)	0.026(1)	0.053(5)
O7	-0.550(4)	0.127(1)	-0.273(1)	0.083(5)
C10	-0.399(7)	0.089(2)	-0.343(2)	0.088(9)
N11	-0.197(4)	0.416(1)	-0.030(1)	0.059(5)
C13	-0.598(5)	0.109(2)	-0.154(1)	0.054(6)
O14	-0.045(3)	0.371(1)	0.276(1)	0.076(5)
N15	0.287(4)	0.304(2)	-0.159(1)	0.070(6)
C16	-0.385(6)	0.163(2)	-0.108(1)	0.060(7)
C17	-0.400(5)	0.158(2)	-0.030(1)	0.052(6)
C18	-0.133(5)	0.396(2)	0.030(1)	0.055(6)
C19	-0.628(5)	0.101(2)	-0.033(1)	0.051(5)
C20	0.100(5)	0.344(2)	0.030(1)	0.052(6)
N21	-0.693(4)	0.083(1)	0.029(1)	0.056(5)
C22	0.112(5)	0.338(2)	0.110(1)	0.059(6)
C23	-0.439(5)	0.483(2)	0.139(1)	0.065(7)
C24	-0.536(5)	0.121(2)	0.092(1)	0.049(6)
C25	-0.652(6)	0.087(2)	-0.232(2)	0.075(7)
N26	0.244(4)	0.309(1)	-0.029(1)	0.061(5)
O27	-0.434(6)	0.003(2)	-0.368(1)	0.123(7)
O28	0.069(5)	0.494(2)	0.367(1)	0.108(7)
C29	0.182(5)	0.332(2)	-0.090(1)	0.059(6)
C30	-0.037(5)	0.384(2)	-0.091(1)	0.057(6)
N31	-0.062(4)	0.386(2)	-0.161(1)	0.072(6)
C32	-0.321(6)	0.172(2)	0.087(1)	0.062(6)
C33	0.094(6)	0.421(2)	0.339(1)	0.064(7)
C34	-0.865(6)	0.035(2)	-0.261(1)	0.072(7)
C36	-0.487(5)	0.504(2)	0.215(1)	0.063(6)
C37	0.235(7)	0.278(2)	0.340(2)	0.083(8)
C38	-0.366(5)	0.470(2)	0.265(1)	0.072(7)
C39	-0.175(5)	0.410(2)	0.231(1)	0.067(7)
C40	-0.984(5)	0.001(2)	-0.214(1)	0.073(7)
C41	-0.097(5)	0.394(2)	0.161(1)	0.061(6)
C48	0.504(6)	0.268(2)	0.437(2)	0.083(8)
C49	0.475(9)	0.345(3)	0.470(2)	0.140(1)
C50	0.342(8)	0.404(3)	0.445(2)	0.130(1)
C63	-0.929(6)	0.017(2)	-0.138(1)	0.076(7)

Table 2 (continued)

Atom	x	y	z	U(eq)
C64	0.203(7)	0.359(2)	0.373(2)	0.081(8)
N65	-0.219(5)	0.195(2)	0.156(1)	0.076(6)
C66	-0.272(9)	0.227(3)	-0.338(2)	0.120(1)
C67	-0.130(1)	0.280(3)	-0.370(3)	0.150(2)
C68	-0.298(7)	0.136(3)	-0.373(2)	0.084(9)
C69	-0.140(1)	0.103(3)	-0.444(3)	0.150(2)
C70	-0.060(1)	0.143(4)	-0.475(3)	0.150(2)
C71	0.014(9)	0.241(4)	-0.433(3)	0.160(1)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits; [b] $U_{eq} = (1/3)\sum_i\sum_j U_{ij}a^*_i a^*_j \mathbf{a}_i.\mathbf{a}_j$.

Table 3

Bond Distances (Å) for **4** [a]

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
O1	C16	1.18(4)	O2	N4	1.42(4)
O2	N65	1.35(4)	C3	C13	1.39(4)
C3	C19	1.40(4)	C3	C63	1.40(5)
N4	C24	1.32(4)	N6	C17	1.26(4)
N6	C32	1.31(4)	O7	C25	1.30(4)
O8	N15	1.40(3)	O8	N31	1.39(3)
O9	C22	1.21(4)	C10	O27	1.35(5)
C10	C68	1.24(6)	N11	C18	1.30(3)
N11	C30	1.37(4)	C13	C25	1.38(4)
O14	C33	1.39(4)	O14	C39	1.40(4)
N15	C29	1.31(4)	C16	C17	1.46(4)
C18	C47	1.43(4)	C19	N21	1.31(3)
C20	N26	1.29(3)	N21	C24	1.39(4)
C23	C36	1.33(4)	C23	C47	1.44(5)
C24	C32	1.45(5)	C25	C34	1.42(5)
N26	C29	1.35(4)	O28	C33	1.14(5)
C32	N65	1.32(4)	C34	C40	1.35(5)
C36	C38	1.39(4)	C37	C42	1.37(6)
C37	C64	1.26(6)	C38	C39	1.42(5)
C39	C41	1.29(4)	C40	C63	1.36(4)
C41	C47	1.47(4)	C42	C48	1.39(5)
C48	C49	1.21(7)	C49	C50	1.42(7)
C50	C64	1.47(6)	C67	C66	1.44(7)
C67	C71	1.35(7)	C66	C68	1.43(7)
C68	C69	1.47(6)	C69	C70	1.13(8)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 4

Bond Angles (deg) for **4** [a]

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
N4	O2	N65	111.3(19)	C13	C3	C19	109.5(24)
C13	C3	C63	121.6(23)	C19	C3	C63	129.0(25)
O2	N4	C24	102.3(21)	C17	N6	C32	111.1(24)
N15	O8	N31	113.8(17)	O27	C10	C68	132.6(33)
C18	N11	C30	112.8(22)	C3	C13	C25	120.3(26)
C33	O14	C39	119.4(22)	O8	N15	C29	102.9(21)
O1	C16	C17	128.1(26)	N6	C17	C16	127.7(26)
N11	C18	C47	128.9(25)	C3	C19	N21	130.4(25)
C19	N21	C24	112.2(21)	C36	C23	C47	117.6(25)
N4	C24	N21	124.9(25)	N4	C24	C32	112.5(22)
N21	C24	C32	122.7(21)	O7	C25	C13	120.8(28)
O7	C25	C34	119.5(25)	C13	C25	C34	118.0(27)

Table 4 (continued)

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C20	N26	C29	112.0(22)	N15	C29	N26	126.2(25)
N15	C29	C30	110.4(22)	N26	C29	C30	123.1(22)
N11	C30	C29	124.0(22)	N11	C30	N31	127.3(24)
C29	C30	N31	108.5(22)	O8	N31	C30	104.5(21)
N6	C32	C24	126.2(24)	N6	C32	N65	129.1(28)
C24	C32	N65	104.7(23)	O14	C33	O28	122.5(28)
C25	C34	C40	118.5(25)	C23	C36	C38	125.4(26)
C42	C37	C64	126.4(32)	C36	C38	C39	116.2(23)
O14	C39	C38	120.9(22)	O14	C39	C41	116.7(25)
C38	C39	C41	122.1(27)	C34	C40	C63	125.4(29)
C39	C41	C47	120.5(26)	C37	C42	C48	116.2(34)
C18	C47	C23	130.2(25)	C18	C47	C41	112.6(24)
C23	C47	C41	117.3(22)	C42	C48	C49	118.7(37)
C48	C49	C50	129.2(39)	C49	C50	C64	110.5(37)
C3	C63	C40	115.8(27)	O2	N65	C32	109.1(24)
C37	C64	C50	118.4(35)	C66	C67	C71	118.4(48)
C67	C66	C68	124.9(38)	C10	C68	C66	125.8(34)
C10	C68	C69	122.6(40)	C66	C68	C69	110.5(37)
C68	C69	C70	124.7(53)				

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

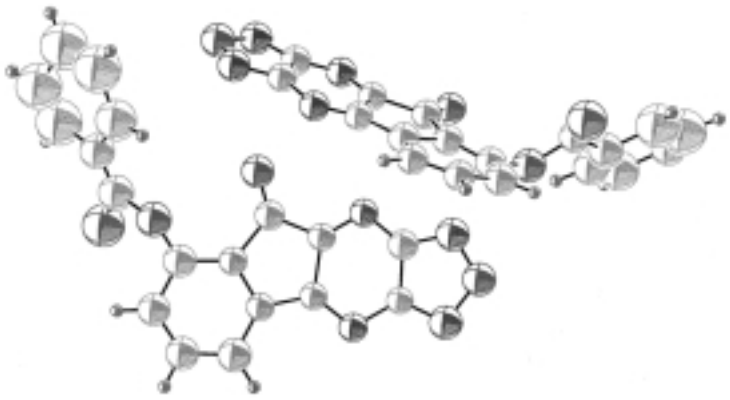


Figure 1. ORTEP Plot of compound **4**.

possible by introduction of a suitable blocking group in the starting indan-1-ones.

EXPERIMENTAL

Melting points were determined on a Mel-Temp or Electrothermal apparatus and are uncorrected. Elemental Analysis was performed by Quantitative Technologies, Inc. (Whitehouse, N. J.). The Proton Nuclear Magnetic Resonance spectra were recorded on a Varian Unity 400 NMR spectrometer with chemical shifts reported in ppm relative to internal tetramethylsilane. Mass spectra were recorded on a Micromass Platform LC Mass spectrometer operating at atmospheric pressure. Infrared spectra were recorded as potassium bromide disks on a Mattson NU 30,000 FT IR or a Biorad FTS 45 IR spectrometer. Reactions were usually run under a nitrogen atmosphere, and solutions were concentrated at reduced

Table 5

Crystal and Refinement Data for **24**

formula	$C_{14}H_8N_4O_5$
formula weight	312.2
crystal system	monoclinic
space group	$P2_1/c$
a, Å	22.26(5)
b, Å	5.28(5)
c, Å	24.87(6)
V, Å^3	1281.190(1)
Z; density (calc), g/cm^3	4; 1.48
crystal size, mm	0.2 x 0.2 x 0.2
absorption coef., mm^{-1}	9.16
2q (max), deg.	100.0
reflections collected	4401
independent reflections	1924
parameters refined	209
final R indices	R1 = 0.058, wR2 = 0.033
largest diff. Peak, e/Å^3	0.23

Table 6

Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters (Å^2) for **24** [a,b]

Atom	x	y	z	*U*(eq)
O1	1.3094(3)	-1.0600(6)	1.3267(3)	0.104(2)
O2	1.1408(3)	-0.7042(6)	1.2172(2)	0.094(2)
O3	0.3456(3)	0.0588(7)	0.4950(3)	0.118(2)
O4	0.7973(3)	0.2299(6)	1.0441(3)	0.137(2)
O5	1.1867(3)	-1.1876(7)	1.1580(3)	0.130(2)
N6	0.5744(3)	0.1823(7)	0.7832(3)	0.106(2)
N9	0.3839(4)	0.2065(8)	0.5696(3)	0.115(3)
C10	0.7152(4)	-0.1790(9)	0.8682(4)	0.093(3)
C11	0.8908(4)	-0.1351(9)	1.0729(4)	0.101(3)
C12	0.6806(4)	0.0384(9)	0.8743(4)	0.097(3)
C13	1.0517(4)	-0.5232(9)	1.1624(4)	0.094(3)
C14	0.5283(4)	-0.1132(9)	0.6714(4)	0.093(3)
C15	0.7919(4)	0.069(1)	1.0056(4)	0.108(3)
C16	1.2070(4)	-1.050(1)	1.2107(4)	0.087(3)
C17	0.9265(4)	-0.4682(9)	1.0359(4)	0.087(3)
C18	1.0141(4)	-0.193(1)	1.1979(4)	0.105(3)
C19	1.1108(4)	-0.8325(9)	1.1443(4)	0.100(3)
C20	0.8481(4)	-0.2755(9)	0.9945(4)	0.082(3)
C21	0.4970(4)	0.1004(9)	0.6780(4)	0.098(3)
C22	1.0933(4)	-0.387(1)	1.2414(4)	0.096(3)
C23	1.4002(4)	-1.276(1)	1.3935(4)	0.112(3)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits; [b] $U_{eq} = (1/3)\sum_i\sum_j U_{ij}a^*_i a^*_j \mathbf{a}_i.\mathbf{a}_j$.

pressure on a rotary evaporator. Flash chromatography was performed with EM Science silica gel 60, 230-400 mesh ASTM.

Benzoic Acid 2,2-Dihydroxy-1,3-dioxo-indan-4-yl Ester (**3**).

To a solution of **2** [10] (2.0 g, 7.9 mmol) in 40 mL of dimethyl sulfoxide was added *N*-bromosuccinimide (2.9 g, 16 mmol). The reaction mixture was stirred at 60° for 3 hours and then at 80° for 4 hours with a vacuum line attached to the top of the reaction flask condenser. The reaction mixture was cooled to room temperature and then poured into 200 mL of water. The product was extracted with three portions of 100 mL of dichloromethane, and then the combined organic extracts were dried (sodium sulfate), filtered and evaporated. The residue was purified by flash chromatography (eluting with 50 and 70% ethyl acetate in hexane, gradient elution) to yield 1.4 g (61%) of **3**. A sample recrystallized from water had mp 133-136°; ir: 3491, 3412, 3353, 1755, 1742, 1719 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 7.55 (s, 2H), 7.63 (t, J = 7.7 Hz, 2H), 7.77 (t, J = 7.5 Hz, 1H), 7.89-7.98 (m, 2H), 8.07-8.19 (m, 3H); ms: *m/z* 280 M$^-$-H$_2$O.

Table 7

Bond Distances (Å) for **24** [a]

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
O1	C16	1.304(5)	O2	C13	1.358(6)
O2	C19	1.420(5)	O3	N7	1.392(6)
O3	N9	1.390(6)	O4	C15	1.201(6)
O5	C16	1.177(6)	N6	C12	1.293(6)
N6	C21	1.376(6)	N7	C14	1.320(6)
N8	C10	1.300(6)	N8	C14	1.386(6)
N9	C21	1.312(6)	C10	C12	1.464(7)
C10	C20	1.474(6)	C11	C15	1.480(7)
C11	C18	1.398(6)	C11	C20	1.388(7)
C13	C17	1.410(6)	C13	C22	1.404(7)
C14	C21	1.411(7)	C17	C20	1.383(7)
C18	C22	1.378(7)			

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

Anal. Calcd. for $C_{16}H_{10}O_6$: C, 64.43; H, 3.38. Found: C, 64.11; H, 3.57.

Benzoic Acid 9-Oxo-9*H*-2-oxa-1,3,4,10-tetraazacyclopenta-[*b*]fluoren-8-yl Ester (**4**).

A mixture of **3** (1.2 g, 4.0 mmoles) and furazan-3,4-diamine (0.40 g, 3.9 mmoles) in 12 mL of ethanol and 12 mL of glacial acetic acid was stirred at room temperature for 18 hours and then heated at reflux for 6 hours. The precipitated solid was filtered and washed with water to yield 0.62 g (46%) of **4**, mp 215-217°; ir: 1741, 1597, 1264, 1229, 1208, 1063 cm^{-1}; ^{1}H nmr (TFA-d): δ 7.67 (t, J = 7.8 Hz, 2H), 7.81-7.88 (m, 2H), 8.22 (t, J = 7.9 Hz, 1H), 8.36 (d, J = 7.9 Hz, 2H), 8.44 (d, J = 7.7 Hz, 1H); ms: *m/z* 344 M$^-$.

Anal. Calcd. for $C_{18}H_8N_4O_4$: C, 62.80; H, 2.34; N, 16.27. Found: C, 62.62; H, 2.19; N, 16.07.

8-Hydroxy-2-oxa-1,3,4,10-tetraazacyclopenta[*b*]fluoren-9-one (**5**).

A mixture of **4** (0.87 g, 2.5 mmoles) and cesium carbonate (1.7 g, 5.3 mmoles) in 50 mL of tetrahydrofuran was stirred at room temperature for 5 days. The precipitated solid was filtered, washed with fresh tetrahydrofuran, and dissolved in 100 mL of water. The aqueous mixture was acidified with 1.0 *M* hydrochloric acid to pH 2-3. The precipitated solid was filtered and rinsed with water to yield 0.57 g (94%) of **5**. A sample recrystallized from methanol had mp 305°; ir: 3431, 1711, 1601, 1443, 1306, 1256 cm^{-1}; ^{1}H nmr (THF-d$_8$): δ 7.22 (d, J = 8.2 Hz, 1H), 7.69-7.85 (m, 2H), 9.94 (bs, 1H); ms: *m/z* 240 M$^-$.

Anal. Calcd. for $C_{11}H_4N_4O_3$: C, 55.01; H, 1.68; N, 23.33. Found: C, 55.09; H, 1.99; N, 23.03.

9,9-Diethoxy-9*H*-2-oxa-1,3,4,10-tetraazacyclopenta[*b*]fluoren-8-ol (**6**).

To a mixture of **4** (0.21 g, 0.60 mmoles) in 10 mL of ethanol was added 0.60 mL of an aqueous solution of 1.0 *M* sodium hydroxide

Table 8

Bond Angles (deg) for **24** [a]

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom3	Angle
C13	O2	C19	117.8(4)	N7	O3	N9	112.3(3)
C12	N6	C21	110.4	O3	N7	C14	103.5(4)
C10	N8	C14	109.0(4)	O3	N9	C21	104.3(4)
N8	C10	C12	126.1(4)	N8	C10	C20	127.4(5)
C12	C10	C20	106.5(4)	C15	C11	C18	128.8(5)
C15	C11	C20	110.8(4)	C18	C11	C20	120.4(5)
N6	C12	C10	125.5(4)	O2	C13	C17	124.0(4)
O2	C13	C22	115.2(4)	C17	C13	C22	120.8(5)
N7	C14	N8	124.9(5)	N7	C14	C21	110.3(4)
N8	C14	C21	124.8(4)	O4	C15	C11	129.1(5)
O1	C16	O5	126.7(5)	C13	C17	C20	117.0(4)
C11	C18	C22	118.5(4)	C10	C20	C11	109.8(4)
C10	C20	C17	127.8(4)	C11	C20	C17	122.3(4)
N6	C21	N9	125.8(5)	N6	C21	C14	124.5(4)
N9	C21	C14	109.7(4)	C13	C22	C18	120.9(4)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

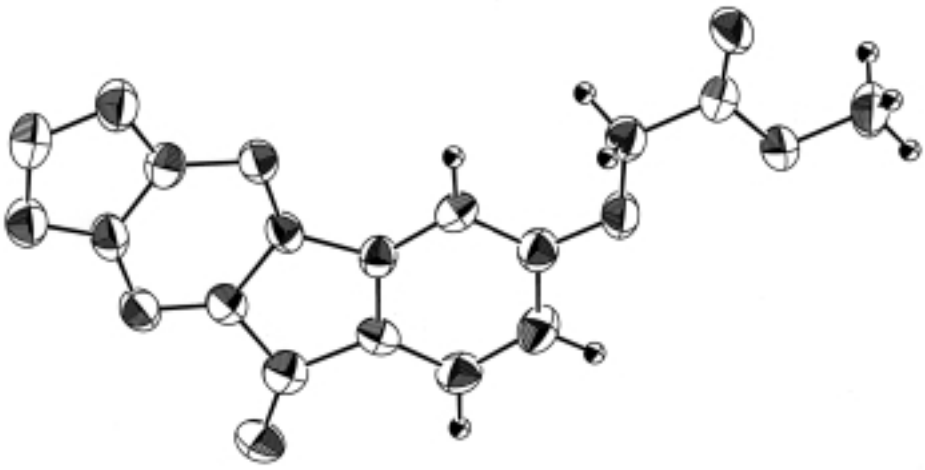


Figure 2. ORTEP Plot of compound **24**.

(0.60 mmoles). The reaction mixture was heated at reflux for 18 hours. The reaction was monitored by thin layer chromatography, and additional aqueous sodium hydroxide was added as needed until all of the starting material **4** was consumed. The reaction mixture was evaporated to give a residue, which was diluted with 10 mL of water and then acidified with aqueous 1.0 *M* hydrochloric acid to pH 2-3. The resulting precipitate was isolated by filtration and purified by flash chromatography (eluting with 30% ethyl acetate in hexane) to give 0.12 g (6%) of **6**; ir: 3285, 1598, 1441, 1309, 1095, 1025 cm^{-1}; ^1H nmr (THF-d_8): δ 1.08 (t, J = 7.0 Hz, 6H), 3.69-3.81 (m, 2H), 3.82-3.95 (m, 2H), 7.03 (d, J = 7.6 Hz, 1H), 7.37-7.46 (m, 1H), 7.57 (d, J = 7.6 Hz, 1H), 8.60 (s, 1H); ms: *m/z* 314 M^-.

Anal. Calcd. for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.39; H, 4.52; N, 17.64.

(9-Oxo-9*H*-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluoren-8-yloxy) Acetic Acid Methyl Ester (**7**).

A mixture of **5** (0.25 g, 1.0 mmol), cesium carbonate (0.37 g, 1.1 mmol) and 0.10 mL of methyl bromoacetate (0.17 g, 1.1 mmol) in 10 mL of acetone was heated at reflux for 18 hours. The precipitated solid was filtered to give 0.48 g of the cesium salt of the starting phenol. The salt was combined with an additional 0.13 mL (0.21 g, 1.4 mmol) of methyl bromoacetate in 10 mL of *N*,*N*-dimethylformamide. The reaction mixture was heated at 60° for 4 hours, stirred at room temperature for 18 hours, and added to a mixture of ice and water. The precipitated solid was filtered and purified by flash chromatography (eluting with 30% ethyl acetate in hexane) to yield 0.11 g (27%) of **7**. A sample recrystallized from aqueous acetonitrile had mp 205-206°; ir: 1753, 1727, 1592, 1486, 1313, 1213 cm^{-1}; ^1H nmr (TFA-d): δ 4.05 (s, 3H), 5.18 (s, 2H), 7.34-7.46 (m, 1H), 8.03-8.16 (m, 2H); ms: *m/z* 312 M^-.

Anal. Calcd. for $C_{14}H_8N_4O_5$: C, 53.85; H, 2.58; N, 17.94. Found: C, 53.80; H, 2.56; N, 17.83.

8-Methoxy-2-oxa-1,3,4,10-tetraazacyclopenta[*b*]fluoren-9-one (**8**).

To a solution of **5** (0.50 g, 2.1 mmol) in 50 mL of *N*,*N*-dimethylformamide was added sodium hydride (0.09 g, 2.3 mmol of 60% dispersion in mineral oil), followed by 0.21 mL of iodomethane (2.3 mmol). The reaction mixture was stirred at 60° for 2 hours, and the solvent was evaporated to give a residue, which was dissolved in

ethyl acetate and washed with three 100 mL portions of water. The organic layer was dried (magnesium sulfate), filtered and evaporated. The residue was purified by flash chromatography (eluting with 20% ethyl acetate in dichloromethane) and recrystallized from acetonitrile/hexane to yield 0.12 g (22%) of **8**, mp 291-293°; ir: 1716, 1588, 1485, 1434, 1308, 1284 cm^{-1}; ^1H nmr (TFA-d): δ 4.49 (s, 3H), 7.83 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 7.5 Hz, 1H), 8.41 (t, J = 8.4 Hz, 1H); ms: *m/z* 254 M^-.

Anal. Calcd. for $C_{12}H_6N_4O_3$: C, 56.34; H, 2.48; N, 21.68. Found: C, 56.70; H, 2.38; N, 22.04.

8-Benzyloxy-2-oxa-1,3,4,10-tetraazacyclopenta[*b*]fluoren-9-one (**9**).

A mixture of **5** (1.0 g, 4.2 mmol), 0.47 mL of phenyl methanol (0.50 g, 4.6 mmol), triphenylphosphine (1.3 g, 5.0 mmol), 0.58 mL of triethylamine (0.42 g, 4.2 mmol) and 0.79 mL of diethyl azodicarboxylate (0.87 g, 5.0 mmol) in 30 mL of tetrahydrofuran was stirred at room temperature for 18 hours. The precipitated solid was filtered and washed with tetrahydrofuran. The crude product was purified by flash chromatography (eluting with chloroform) to yield 0.38 g (27%) of **9**. A sample recrystallized from acetonitrile had mp 236-237°; ir: 1723, 1588, 1487, 1438, 1307, 1029 cm^{-1}; ^1H nmr (THF-d_8): δ 5.42 (s, 2H), 7.29 (t, J = 7.3 Hz, 1H), 7.38 (t, J = 7.3 Hz, 2H), 7.50-7.60 (m, 3H), 7.83 (d, J = 7.3 Hz, 2H); ms: *m/z* 330 M^-.

Anal. Calcd. for $C_{18}H_{10}N_4O_3$: C, 65.45; H, 3.05; N, 16.96. Found: C, 65.22; H, 2.84; N, 17.01.

8-(Furan-2-ylmethoxy)-2-oxa-1,3,4,10-tetraazacyclopenta[*b*]fluoren-9-one (**10**).

A mixture of **5** (2.0 g, 8.3 mmol), 0.79 mL of furan-2-yl-methanol (0.90 g, 9.2 mmol), triphenylphosphine (2.6 g, 10 mmol), 1.2 mL of triethylamine (0.84 g, 8.3 mmol) and diethyl azodicarboxylate (1.7 g, 10 mmol) in 60 mL of tetrahydrofuran was stirred at room temperature for 18 hours. The solvent was evaporated, and the residue was purified by flash chromatography (eluting with 30-50% ethyl acetate in hexane, gradient elution). The chromatographed material was triturated in water to give 0.64 g (24%) of **10**, 184-185°; ir: 1719, 1588, 1484, 1429, 1299, 1276 cm^{-1}; ^1H nmr (THF-d_8): δ 5.36 (s, 2H), 6.38-6.42 (m, 1H), 6.59 (d, J = 3.2 Hz, 1H), 7.52-7.55 (m, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.80-7.95 (m, 2H); ms: *m/z* 320 M^-.

Anal. Calcd. for $C_{16}H_8N_4O_4$: C, 60.01; H, 2.52; N, 17.49. Found: C, 59.71; H, 2.67; N, 17.27.

8-(Pyridin-4-ylmethoxy)-2-oxa-1,3,4,10-tetraazacyclopenta-[*b*]fluoren-9-one (**11**).

A mixture of **5** (2.0 g, 8.3 mmol), pyridin-4-yl-methanol (1.0 g, 9.2 mmol), triphenylphosphine (2.6 g, 10 mmol), 1.2 mL of triethylamine (0.84 g, 8.3 mmol) and diethyl azodicarboxylate (1.7 g, 10 mmol) in 60 mL of tetrahydrofuran was stirred at room temperature for 18 hours. The precipitated solid was filtered and washed with tetrahydrofuran to yield 1.9 g (70%) of **11**, mp 200-201°; ir: 1731, 1589, 1439, 1304, 1279, 1027 cm^{-1}; ^1H nmr (TFA-d): δ 6.07 (s, 2H), 7.89 (d, J = 7.4 Hz, 1H), 8.39-8.47 (m, 2H), 8.89 (d, J = 6.4 Hz, 2H), 9.24 (d, J = 6.5 Hz, 2H); ms: *m/z* 331 M^-.

Anal. Calcd. for $C_{17}H_9N_5O_3$: C, 61.63; H, 2.74; N, 21.14. Found: C, 61.49; H, 3.05; N, 21.34.

8-(Thiophen-2-ylmethoxy)-2-oxa-1,3,4,10-tetraazacyclopenta-[*b*]fluoren-9-one (**12**).

Prepared from **5** (1.0 g, 4.2 mmoles) and 0.43 mL of thiophen-2-yl-methanol (0.52 g, 4.6 mmoles) by the procedure described for the preparation of **10** to yield 0.38 g (27%) of **12**. The crude product was purified by flash chromatography (eluting with chloroform). A sample recrystallized from acetonitrile had mp 198-200°; ir: 1723, 1588, 1483, 1438, 1300, 1275 cm^{-1}; ^1H nmr (THF-d_8): δ 5.59 (s, 2H), 6.97-7.01 (m, 1H), 7.22-7.27 (m, 1H), 7.40-7.45 (m, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.79-8.00 (m, 2H); ms: *m/z* 336 M^-.

Anal. Calcd. for $C_{16}H_8N_4O_3S$: C, 57.14; H, 2.40; N, 16.66. Found: C, 56.94; H, 2.32; N, 16.78.

6-Hydroxy-4,5-dimethylindan-1-one (**14**).

A suspension of aluminum chloride (33.2 g, 249 mmol) in 300 mL of toluene was treated with **13** [14] (22.7 g, 119 mmol). The mixture was stirred at reflux for 1 hour, then added to 2.75 kg of ice and water. The solid was filtered, stirred in 1.5 L of 20% methanol in water, and filtered again to give 19.6 g (93%) of **14**. A sample recrystallized from aqueous 2-propanol had mp 245° (dec); ir: 3309, 1674, 1600, 1437, 1324, 1298 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.10 (s, 3H), 2.15 (s, 3H), 2.49-2.52 (m, 2H), 2.82-2.85 (m, 2H), 6.82 (s, 1H), 9.60 (s, 1H); ms: *m/z* 177 M^++1.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.85; H, 6.78.

Benzoic Acid 6,7-Dimethyl-3-oxo-indan-5-yl Ester (**15**).

A suspension of **14** (21.0 g, 119 mmol) and cesium carbonate (42.9 g, 132 mmol) in 600 mL of acetone was treated dropwise with 14.9 mL of benzoyl chloride (18.0 g, 128 mmol). The mixture was stirred for 24 hours and added to 3.0 kg of ice and water. The solid was filtered, stirred in 1.0 L of 20% methanol in water, and filtered again to give 31.5 g (94%) of **15**. A sample recrystallized from aqueous acetonitrile had mp 125-127°; ir: 1736, 1703, 1601, 1442, 1249, 1088 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.13 (s, 3H), 2.26 (s, 3H), 2.62-2.65 (m, 2H), 2.99-3.02 (m, 2H), 7.29 (s, 1H), 7.57-7.61 (m, 2H), 7.71-7.76 (m, 1H), 8.12-8.14 (m, 2H); ms: *m/z* 279 M^-.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.02; H, 5.76.

Benzoic Acid 7,8-Dimethyl-9-oxo-9*H*-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]-fluoren-6-yl Ester (**18**).

A mixture of **15** (16.3 g, 58.1 mmol) and *N*-bromosuccinimide (20.9 g, 117 mmol) in 150 mL of dimethyl sulfoxide was heated at 40° for 3 hours. A vacuum line was attached to the top of the reaction flask condenser, and the mixture was heated at 80° for 4 hours. The cooled reaction mixture was added to 1.5 L of brine and extracted with four 350 mL portions of dichloromethane. The combined extracts were washed with three 500 mL portions of 5% aqueous sodium bicarbonate solution and two 500 mL portions of brine. The organic layer was dried (sodium sulfate) and evaporated. The residue was purified by flash chromatography (eluting with 50% ethyl acetate in hexane) to yield 11.4 g (64%) of benzoic acid 6,7-dimethyl-1,2,3-trioxoindan-5-yl ester **16** as an oil; ^1H nmr (DMSO-d_6): δ 2.24 (s, 3H), 2.69 (s, 3H), 7.46 (s, 1H), 7.57-7.64 (m, 2H), 7.73-7.81 (m, 1H), 8.12-8.19 (m, 2H); ms: *m/z* 308 M^-.

An additional chromatography product (0.60 g, 8%) was identified as benzoic acid 2,2-dibromo-6,7-dimethyl-3-oxo-indan-5-yl ester **17**. A sample recrystallized from ethyl acetate/hexane had mp 180-182°; ir: 1723, 1598, 1253, 1243, 1221, 1120 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.18 (s, 3H), 2.23 (s, 3H), 4.31 (s, 2H), 7.55-7.66 (m, 3H), 7.70-7.78 (m, 1H), 8.11-8.17 (m, 2H); ms: *m/z* 439 M^++1.

Anal. Calcd. for $C_{18}H_{14}Br_2O_3$: C, 49.35; H, 3.22. Found: C, 49.47; H, 3.22.

A mixture of intermediate **16** (11.4 g, 37 mmol) and furazan-3,4-diamine (3.8 g, 38 mmol) in 25 mL of ethanol and 25 mL of glacial acetic acid was stirred at reflux for 4 hours. The precipitated solid was filtered, stirred in 150 mL of 50% methanol in water, and filtered again. Recrystallization of the final solid from aqueous acetonitrile gave 4.5 g (33%) of **18**, mp 245° (dec); ir: 1719, 1584, 1241, 1199, 1086, 1020 cm^{-1}; ^1H nmr (TFA-d): δ 2.56 (s, 3H), 3.00 (s, 3H), 7.71 (t, J = 7.7 Hz, 2H), 7.88 (t, J = 7.5 Hz, 1H), 8.23 (s, 1H), 8.41 (d, J = 7.5 Hz, 2H); ms: *m/z* 372 M^-.

Anal. Calcd. for $C_{20}H_{12}N_4O_4$: C, 64.52; H, 3.25; N, 15.05. Found: C, 64.38; H, 3.42; N, 14.94.

6-Hydroxy-7,8-dimethyl-2-oxa-1,3,4,10-tetraazacyclopenta-[*b*]fluoren-9-one (**19**).

A suspension **18** (5.0 g, 13.4 mmol) in 100 mL of methanol was treated with a solution of 50 mL of 2.0 *M* ammonia in methanol. The mixture was stirred at room temperature for 18 hours, then added to 500 mL of water. The mixture was filtered, and the filtrate was adjusted to pH 2 by the addition of 4.0 *M* hydrochloric acid. The precipitated solid was filtered, stirred in 100 mL of 20% methanol in water, and filtered again to yield 3.5 g (97%) of **19**. A sample recrystallized from aqueous acetonitrile had mp 280° (dec.); ir: 3237, 1716, 1591, 1548, 1318, 1291 cm^{-1}; ^1H nmr (THF-d_8): δ 2.26 (s, 3H), 2.72 (s, 3H), 7.35 (s, 1H), 10.82 (bs, 1H); ms: *m/z* 267 M^--1.

Anal. Calcd. for $C_{13}H_8N_4O_3$: C, 58.21; H, 3.01; N, 20.89. Found: C, 58.28; H, 3.13; N, 20.63.

(7,8-Dimethyl-9-oxo-9*H*-2-oxa-1,3,4,10-tetraazacyclopenta-[*b*]fluoren-6-yloxy) Acetic Acid Methyl Ester (**20**).

A mixture of **19** (1.0 g, 3.7 mmol), cesium carbonate (2.4 g, 7.4 mmol), and 1.0 mL of methyl bromoacetate (1.6 g, 10.5 mmol) in 25 mL of acetonitrile was stirred at reflux for 3 hours. The precipitated solid was filtered, stirred in 100 mL of 25% methanol in water, and filtered again. Recrystallization from acetonitrile gave 0.55 g (42%) of **20**, mp 230° (dec.); ir: 1723, 1585, 1288, 1224, 1146, 1112 cm^{-1}; ^1H nmr (TFA-d): δ 2.51 (s, 3H), 2.89 (s, 3H), 4.08 (s, 3H), 5.20 (s, 2H), 7.76 (s, 1H); ms: *m/z* 340 M^-.

Anal. Calcd. for $C_{16}H_{12}N_4O_5$: C, 56.47; H, 3.55; N, 16.46. Found: C, 56.55; H, 3.55; N, 16.50.

(1-Oxo-indan-5-yloxy) Acetic Acid Methyl Ester (**22**).

A suspension of **21** [15] (16.0 g, 108 mmol), cesium carbonate (38.7 g, 119 mmol) and 10.8 mL of methyl bromoacetate (17.5 g, 114 mmol) in 700 mL of acetone was stirred at room temperature for 24 hours. The mixture was filtered, and the filter cake was washed several times with fresh acetone. The combined filtrates were evaporated, and the residue was recrystallized from ethyl acetate/hexane to yield 18.2 g (76%) of **22**, mp 116-118°; ir: 1763, 1692, 1614, 1587, 1270, 1220 cm^{-1}; ^1H nmr (deuterochloroform): δ 2.61 (t, J = 5.9 Hz, 2H), 3.03 (t, J = 5.9 Hz, 2H), 3.76 (s, 3H), 4.66 (s, 2H), 6.82 (s, 1H), 6.86 (d, J = 8.6 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H); ms: *m/z* 221 M^++1$^+$.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.44; H, 5.51.

(9-Oxo-9*H*-2-oxa-1,3,4,10-tetraazacyclopenta[*b*]fluoren-6-yloxy) Acetic Acid Methyl Ester (**24**).

Intermediate **23** was prepared from **22** (6.0 g, 27.2 mmol) by the procedure described for the preparation of **16** to yield 0.70 g (10%) of (1,2,3-trioxo-indan-5-yloxy)-acetic acid methyl ester as an oil. The crude product was purified by flash chromatography (eluting with 3% methanol in dichloromethane); ^1H nmr (deuterochloroform): δ 3.78 (s, 3H), 4.75 (s, 2H), 7.22 (s, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H); ms: *m/z* 248 M^-.

A mixture of **23** (0.65 g, 3.0 mmol) and furazan-3,4-diamine (0.31 g, 3.1 mmol) in 4.0 mL of ethanol and 4.0 mL of glacial acetic acid was stirred at reflux for 4 hours. The cooled reaction mixture was added to 100 g of ice and water and extracted with four 50 mL portions of ethyl acetate. The combined extracts were washed with three 150 mL portions of 5% aqueous sodium bicarbonate solution and one 150 mL portion of brine. The organic layer was dried (sodium sulfate) and evaporated. The residue was purified by flash chromatography (eluting with 40% ethyl acetate in hexane) to yield 0.26 g (19%) of **24**. A sample recrystallized from aqueous acetonitrile had mp 203-205°; ir: 1723, 1615, 1591, 1301, 1270, 1251 cm^{-1}; ^1H nmr (TFA-d): δ 4.09 (s, 3H), 5.16 (s, 2H), 7.61 (d, J = 8.6 Hz, 1H), 7.95 (s, 1H), 8.27 (d, J = 8.6 Hz, 1H); ms: *m/z* 312 M^-.

Anal. Calcd. for $C_{14}H_8N_4O_5$: C, 53.85; H, 2.58; N, 17.94. Found: C, 53.65; H, 2.31; N, 17.70.

X-ray Structure Determination of **4**.

Compound **4** crystallized as yellow needles from ethanol solutions. X-ray data were collected on an Enraf-Nonius CAD-4 diffractometer using CuK radiation (λ = 1.54184 Å). The cell constants and the orientation matrix for data collection were determined from centered angles of 25 reflections. X-ray diffraction data were collected at 23° C using the omega scan technique with a variable omega scan rate from 2° to 20° per minute. The data were collected to a maximum 2θ of 100.28°. A total of 5357 reflections were collected, of which 2346 were unique and not systematically absent. Lorentz and polarization corrections were applied to the data as well as an empirical absorption correction based on a series of psi scans. The crystal structure was determined by direct methods using SIR-92. A total of 328 reflections with E > 1.90 were used to produce a phase set with an absolute figure of merit of 0.76. All 52 heavy atoms in the structure were located from the E map calculated using this phase set. Hydrogen atom positions were located in subsequent difference fouriers and added to the structure, but their positions were not refined. The heavy atom parameters including anisotropic temperature factors were refined by full matrix least squares using 893 reflections with intensity greater than three times their standard deviation. The final unweighted R-factor is 0.089. The final difference fourier was essentially featureless. The highest peak in this map had a height of only 0.48 e/Å^3.

X-ray Structure Determination of **24**.

Compound **24** crystallized as amber rods from ethanol solutions. X-ray data were collected on an Enraf-Nonius CAD-4 diffractometer using CuK radiation (λ = 1.54184 Å). The cell constants and an orientation matrix for data collection were deter-

mined from the centered angles of 25 reflections. X-ray diffraction data were collected at 23° C using the omega scan technique with a variable omega scan rate from 2° to 20° per minute. The data were collected to a maximum 2θ of 100.0°. A total of 4401 reflections were collected, of which 1924 were unique and not systematically absent. Lorentz and polarization corrections were applied to the data as well as an empirical absorption correction based on a series of psi scans. The crystal structure was determined by direct methods using SIR-92. Hydrogen atom positions were located in subsequent difference fouriers and added to the structure, and their positions were using isotropic thermal parameters. The heavy atom parameters including anisotropic temperature factors were refined by full matrix least squares using 1147 reflections with intensity greater than three times their standard deviation. The final unweighted R-factor is 0.058. The final difference fourier was essentially featureless. The highest peak in this map had a height of only 0.23 e/Å^3.

Acknowledgements.

We thank Wen-Song Yue for preparing compound **8**.

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[11] Caution: On a single occasion during a large scale preparation of **3**, an exotherm developed, resulting in a run-away reaction during the period of heating at 80°. We believe this resulted from rapid decomposition of the dimethyl sulfoxide solvent due to inadequate removal under vacuum of the liberated hydrogen bromide. Halogenation / oxidation reactions in this solvent should be performed with suitable safety precautions.

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