Preparation and Alkylation of Regioisomeric Tetrahydrophthalimide-substituted Indolin-2(3*H*)-ones

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A series of novel regioisomeric tetrahydrophthalimide-substituted indolin-2-ones has been prepared *via* the Sommelet-Hauser type cyclization of appropriately substituted anilines as potential herbicides. The resultant indolin-2-ones were then regioselectively alkylated at N-1 and C-3 to give 1,3,3-trisubstituted indolin-2-ones. The most active series was also prepared by the *bis*-nitration of *m*-fluorophenylacetic acid followed by reduction and cyclization to give 6-amino-5-fluoroindolin-2-one. Elaboration to the tetrahydrophthalimide-substituted indolin-2-one was followed by *C*- and *N*-alkylation to give the desired compounds.

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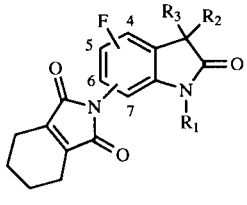
A number of herbicides act by interfering with chlorophyll biosynthesis. Diphenyl ethers have been found to inhibit a key enzyme, protoporphyrinogen oxidase [1,2]. Recently, the herbicidal activity of diphenyl ethers containing the indolin-2(3*H*)-one (oxindole) moiety has been reported [3-5]. Another class of herbicides that interfere with chlorophyll biosynthesis is the *N*-aryl cyclic imides. Recent studies have confirmed that the *N*-aryl cyclic imides share the same mechanism of action as the diphenyl ethers [6,7].

As an extension of our work directed towards the synthesis of novel herbicides containing the indolin-2-one moiety [8], we desired an efficient route to a variety of functionalized cyclic imide-substituted indolin-2-ones, **1**, in an effort to explore their herbicidal activity. While many methods exist for the preparation of indolin-2-ones [9], we found that the Sommelet-Hauser type rearrangement reported by Gassman [10-12] allows for the rapid entry to a variety of substituted indolin-2-ones.

The 1,2,3,4-tetrahydrophthalimide moiety was chosen for study as this is a highly active structural component of many cyclic imide herbicides. The introduction of a fluorine atom *ortho* to the cyclic imide group usually enhances herbicidal activity further. There are six possible regioisomers consisting of two substituents in an *ortho* orientation about the four benzenoid positions of the indolin-2-one ring system (C-4 to C-7). Our goal was to prepare the four regioisomers comprising substitution at C-4 through C-6.



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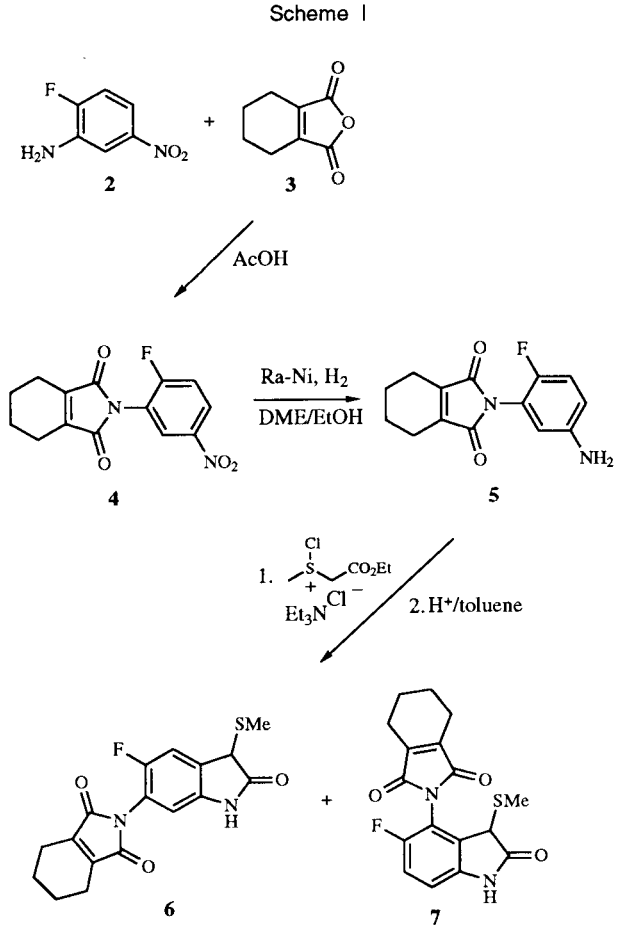
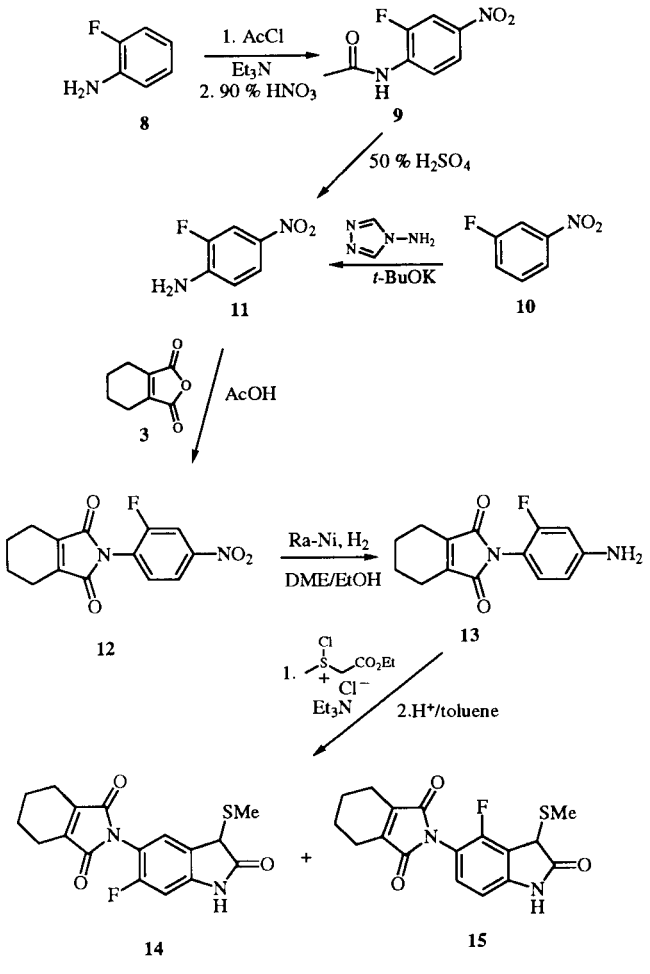
Scheme I

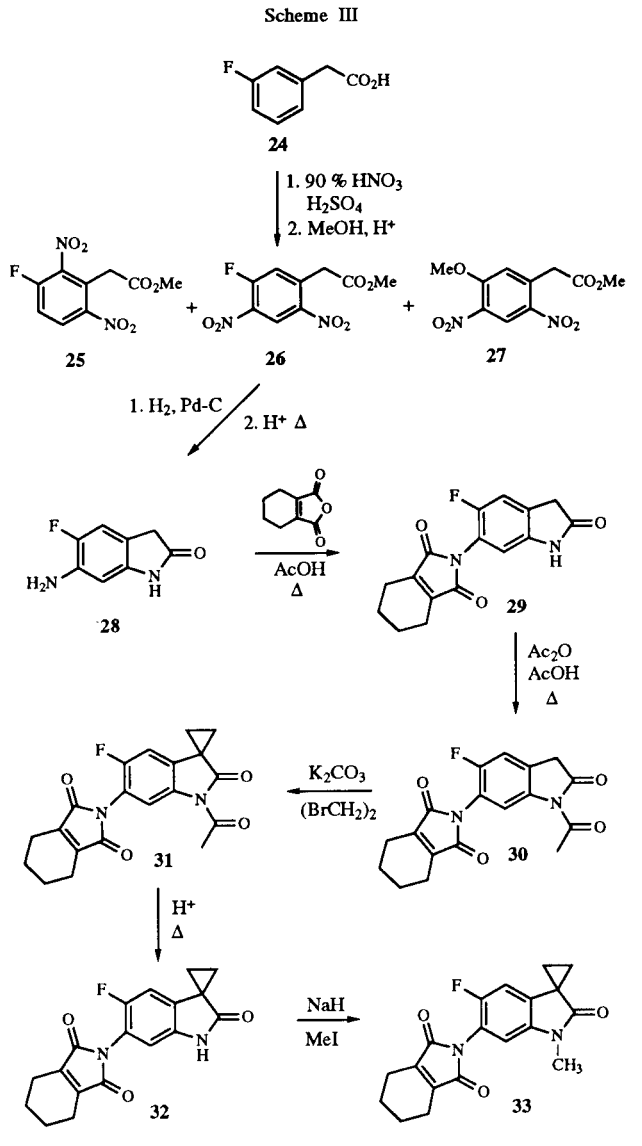


Strategically, the most direct route entails incorporation of the tetrahydrophthalimide moiety prior to indolin-2-one ring formation as this would obviate the need for *N*-protection. To this end, the desired tetrahydrophthalimide-

Scheme II



Scheme III

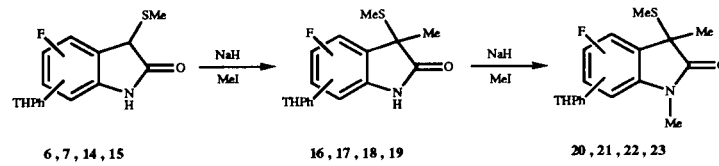


substituted indolin-2-ones were prepared as shown (Scheme I). Acylation of 2-fluoro-5-nitroaniline, **2**, with 1,2,3,4-tetrahydrophthalic anhydride gave the tetrahydrophthalimide **4** in 66% yield [13]. Reduction of the nitro group was effected with Raney-nickel, affording the aniline **5** in 87% yield. The Sommelet-Hauser type cyclization was carried out by treatment of the unsymmetrical aniline **5** with the chlorosulfonium salt of ethyl (methylthio)acetate and triethylamine at low temperature. The resultant amino esters were cyclized under acidic conditions (*p*-toluenesulfonic acid/toluene) to give a mixture of the 6- and 4-tetrahydrophthalimide-substituted 3-(methylthio)indolin-2-ones **6** and **7** as expected [8,14]. Compounds **6** and **7** were obtained as a chromatographically inseparable mixture. It was fortuitous that the minor isomer **7** crystallized from the crude reaction mixture. The major isomer **6** could then be isolated from the filtrate. In this manner **6** and **7** were obtained in 39% and 22% yield, respectively.

Preparation of the two regioisomeric 5-tetrahydrophthalimide-substituted series was sought next. To carry out a sequence similar to that described above necessitated the use of 2-fluoro-4-nitroaniline **11**. The desired aniline **11** could be prepared by two different methods (Scheme II). The more direct route, ring amination of 3-fluoronitrobenzene **10** was carried out using 4-amino-1,2,4-triazole [15], affording only 29% yield of desired product. The alternative approach consisted of acetylation, nitration and deacetylation of 2-fluoroaniline **8**. Acetylation of compound **8** which was carried out in nearly quantitative yield was followed by nitration [16] to give the nitroacetanilide **9** in 54% yield for the two steps. Heating compound **9** in aqueous acid then gave the desired aniline **11**. The crude aniline was converted to the tetrahydrophthalimide **12** upon reaction with tetrahydrophthalic anhydride **3** in 50% yield from compound **9** (two steps). Reduction to the cyclization precursor **13** was carried out in the pres-

Table

C- and *N*-alkylation of Substituted 3-(Methylthio)indolin-2-ones



6, 7, 14, 15 16, 17, 18, 19 20, 21, 22, 23

Compound	Flouro Position	THPh [a] Position	Product	Yield % [b]
6	5-	6-	**16**	66
7	5-	4-	**17**	74
14	6-	5-	**18**	44
15	4-	5-	**19**	44
16	5-	6-	**20**	0 [c]
17	5-	4-	**21**	40
18	6-	5-	**22**	41
19	4-	5-	**23**	48

[a] THPh refers to the 1,2,3,4-tetrahydrophthalimide group. [b] Yields refer to isolated yields by flash chromatography. [c] Upon attempted alkylation of **16** only polar, baseline material was noted. Compound **20** was not isolated.

ence of Raney-nickel in quantitative yield. The Sommelet-Hauser type cyclization of aniline **13** gave two chromatographically separable 5-tetrahydrophthalimide-substituted indolin-2-ones; the 6-fluoro isomer **14** (31% yield) and the 4-fluoro isomer **15** (23% yield).

During an earlier study we observed that herbicidal activity increased upon increasing substitution at the indolin-2-one N-1 and C-3 [3-5]. The demonstration that the resultant 3-(methylthio)indolin-2-ones, obtained *via* the Sommelet-Hauser cyclization, could be alkylated regioselectively lead to the preparation of a large number of analogs [8]. In the present study, the four regioisomeric tetrahydrophthalimide-substituted indolin-2-ones **6**, **7**, **14** and **15** were subjected to stepwise *C*- and *N*-alkylation in similar fashion. The products obtained are shown in the Table. The first alkylation takes place at the kinetically favored 3-position due to the influence of the 3-methylthio group. The second alkylation takes place at the indolin-2-one N-1. The products were obtained in moderate to good yields (not optimized), with the exception of compound **20**. Attempted alkylation of compound **16** failed to give any of the desired indolin-2-one **20**, instead resulting in only polar, baseline material being detected.

The indolin-2-ones **6**, **7** and **14-23** were screened for their herbicidal activity. The most active series was the 5-fluoro-6-tetrahydrophthalimide-substituted indolin-2-ones, comprised of indolin-2-ones **6** and **16** [17]. The difficulties encountered in the separation of indolin-2-one **6** from the less active regioisomeric **7** and the inability to *N*-alkylate **16** warranted further study. A more regioselective route to this herbicidally active series was sought. The known preparation of 6-aminoindolin-2-one from ethyl 2,4-dinitrophenylacetate [18] prompted us to consider an analogous strategy which is shown in Scheme III. *m*-Fluorophenylacetic acid **24** was *bis*-nitrated [19] resulting in a difficult to separate mixture of acids. Fischer esterification of the crude reaction mixture gave three chromatographically separable components. The desired 2,4-dinitro isomer **26** (49% yield) was obtained along with the 2,6-dinitro isomer **25** (10% yield). In addition compound **27**, arising from methanolysis of **26** during the esterification reaction, was also obtained (7% yield).

Elaboration of **26** to the 6-tetrahydrophthalimide-substituted indolin-2-one series was then carried out. Reduction of **26** over palladium on carbon gave the crude diamino compound which was induced to cyclize upon treatment with aqueous acid, giving indolin-2-one **28**. Reaction with tetrahydrophthalic anhydride then gave the tetrahydrophthalimide-substituted indolin-2-one **29**.

The alkylation of 1,3,3-unsubstituted indolin-2-ones generally proceeds with poor selectivity, resulting in varying amounts of *C*- and *N*-substituted indolin-2-ones [9]. This makes the alkylation of compounds such as **29** considerably more difficult as the directing influence of the 3-methylthio group is no longer present. In order to overcome this difficulty, 1,3,3-unsubstituted indolin-2-ones have been *N*-protected prior to *C*-alkylation [3-5, 20]. The elaboration of compound **29** to the spirocyclopropyl-sub-

stituted indolin-2-one **32** demonstrates the utility of this approach. Treatment of **29** with acetic anhydride at reflux gave the N-acetyl indolin-2-one **30** in 91% yield. *Bis*-alkylation of **30** (potassium carbonate, 1,2-dibromoethane, dimethyl sulfoxide) gave the spirocyclopropylindolin-2-one **31**, which was isolated in only 21% yield [21]. Heating **31** in aqueous acid furnished the deprotected indolin-2-one **32** in 71% yield. Finally, *N*-methylation (sodium hydride, methyl iodide, dimethylformamide) gave the 1,3,3-trisubstituted indolin-2-one **33** in 34% yield. A manuscript detailing the comparative herbicidal activities of these and related compounds will be published at a later date.

EXPERIMENTAL

All reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Dimethylformamide, dimethyl sulfoxide, dimethoxyethane, methylene chloride and tetrahydrofuran were stored over 4A sieves. Acetonitrile was stored over 3A sieves. Organic layers from aqueous extractions were dried over magnesium sulfate and concentrated *in vacuo*. Melting points are uncorrected. The ^{1}H nmr spectra were determined at 300 MHz (Varian Unity 300 or XL 300 series NMR) and are reported in ppm downfield from internal tetramethylsilane in deuteriochloroform or DMSO-d_6. Significant ^{1}H nmr data are tabulated in the following order: multiplicity (s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) in hertz, number of protons. The ir spectra were recorded on a Perkin-Elmer 1600 Series FTIR as Nujol mulls. Chemical ionization mass spectra (ms) were recorded on a Finnegan-MAT TSQ4500 mass spectrometer using isobutane as carrier gas and recorded in units of m/z. Elemental analyses were performed by Microlit Laboratories, Caldwell, NJ. Flash chromatography was performed with 230-400 mesh silica gel 206 (ICN Biochemicals). Analytical thin-layer chromatography was done with glass-backed silica plates, 250 microns (Analtech).

N-(2-Fluoro-5-nitrophenyl)-1-cyclohexene-1,2-dicarboximide (**4**).

A mixture of 2-fluoro-5-nitroaniline (**2**) (23.4 g, 150 mmoles) and 1,2,3,4-tetrahydrophthalic anhydride (**3**) (22.8 g, 150 mmoles) in 75 ml of glacial acetic acid was heated at reflux for 23 hours. After cooling to room temperature, the reaction mixture was partitioned in toluene and water, the aqueous phase was removed, and the organic layer was washed successively with water and saturated sodium bicarbonate. The aqueous layers were combined and back-extracted with toluene and the combined organic layers were dried and concentrated to afford a yellow solid. Recrystallization from ethanol gave 28.9 g (66%) of white plates, mp 154-156° (lit, 155° [13]); ir 1718 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 8.32-8.26 (m, 1H), 8.21 (dd, J = 2.7, 6.0, 1H), 7.37 (t, J = 9, 1H), 2.44 (br s, 4H), 1.83, (br s, 4H); ms: 291 (MH^+).

Anal. Calcd. for $C_{14}H_{11}FN_2O_4$: C, 57.93; H, 3.82; N, 9.65. Found: C, 57.87; H, 3.88; N, 9.62.

N-(5-Amino-2-fluorophenyl)-1-cyclohexene-1,2-dicarboximide (**5**).

A 500 ml Parr bottle was charged with *N*-(2-fluoro-5-nitrophenyl)-1-cyclohexene-1,2-dicarboximide (**4**) (22.0 g, 75.9 mmoles), dimethoxyethane (150 ml) and ethanol (38 ml) and hydrogenated at 50 psi over Raney-nickel (13.5 g of aqueous slurry) [22] until hydrogen uptake ceased. The reaction mixture was then filtered and the catalyst was washed with additional ethanol. The filtrate was concentrated to give 17.5 g (87%) of a yellow solid. A small sample was purified by flash chromatography using ethyl acetate/chloroform (10/90), mp 134-136°; ir 3463, 3376, 1703 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 6.91 (t, J = 9.9, 1H), 6.56 (dt, J = 3.0, 9.0, 1H), 6.44 (dd, J = 2.1, 6.0, 1H), 3.66 (s, 2H), 2.37 (br s, 4H), 1.76 (br s, 4H); ms: 261 (MH^+).

Anal. Calcd. for $C_{14}H_{13}FN_2O_2$: C, 64.61; H, 5.04; N, 10.76. Found: C, 64.65; H, 5.17; N, 10.72.

N-[5-Fluoro-3-(methylthio)-2-oxo-6-indolinyl]-1-cyclohexene-1,2-dicarboximide (**6**) and *N*-[5-fluoro-3-(methylthio)-2-oxo-4-indolinyl]-1-cyclohexene-1,2-dicarboximide (**7**).

A 500 ml 4-neck flask was equipped with an addition funnel, mechanical stirrer, nitrogen inlet and thermometer. The flask was charged with 100 ml of methylene chloride and cooled to less than -70° by means of a dry ice-acetone bath. Chlorine (2.75 ml, 60.5 mmoles) which was precondensed in a 10 ml graduated cylinder was added in one portion to the reaction flask. A solution of ethyl (methylthio)acetate (7.15 ml, 55.4 mmoles) in methylene chloride (20 ml) was added *via* the addition funnel during 15 minutes. After an additional 5 minutes, a solution comprised of *N*-(5-amino-2-fluorophenyl)-1-cyclohexene-1,2-dicarboximide (**5**) (13.1 g, 50.4 mmoles) and triethylamine (7.0 ml, 50.4 mmoles) in methylene chloride (35 ml) was added to the reaction flask *via* the addition funnel during a 20 minute period while maintaining the internal temperature below -60°. After stirring for an additional hour, triethylamine (10.5 ml, 75.6 mmoles) was added. The resultant reddish reaction mixture was stirred for an additional 10 minutes at *ca.* -70° and then allowed to warm up to room temperature. The crude reaction mixture was then poured into water, the phases were separated, and the aqueous phase was back-extracted with methylene chloride. The organic layers were combined, dried, and concentrated to afford a brown oil. The brown oil (which contained the crude amino esters) was diluted with 100 ml of toluene and heated to reflux in the presence of *p*-toluenesulfonic acid (0.48 g, 2.5 mmoles) for 2 hours and then cooled to room temperature overnight. The minor isomer, compound **7**, which precipitated from the filtrate as a white solid, was recrystallized from methylene chloride/hexanes to give 3.9 g (22%) of pure **7**. The major isomer **6** was obtained by concentrating the toluene-containing filtrate to a semi-solid and re-suspending in toluene. Filtration gave 6.8 g of **6** (39%) as a tan solid.

N-[5-Fluoro-3-(methylthio)-2-oxo-6-indolinyl]-1-cyclohexene-1,2-dicarboximide (6).

A small sample was recrystallized from ethanol/water to give an analytically pure sample as a tan solid, mp 252-255° dec; ir 1711 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 10.3 (br s, 1H), 7.34 (d, J =

9.3, 1H), 6.86 (d, J = 6.0, 1H), 4.63 (s, 1H), 2.34 (br s, 4H), 2.04 (s, 3H), 1.74 (br s, 4H); ms: 347 (MH^+).

Anal. Calcd. for $C_{17}H_{15}FN_2O_3S$: C, 58.95; H, 4.37; N, 8.09. Found: C, 58.77; H, 4.25; N, 7.93.

N-[5-Fluoro-3-(methylthio)-2-oxo-4-indolinyl]-1-cyclohexene-1,2-dicarboximide (**7**).

A small sample was recrystallized from ethanol/water to give an analytically pure sample as a white solid, mp 225-226°; ir 1710 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 10.4 (br s, 1H), 7.31 (dd, J = 8.7, 10.5, 1H), 6.94 (dd, J = 4.2, 8.7, 1H), 4.20 (s, 1H), 2.38 (br s, 4H), 1.75 (br s, 4H), 1.73 (s, 3H); ms: 347 (MH^+).

Anal. Calcd. for $C_{17}H_{15}FN_2O_3S$: C, 58.95; H, 4.37; N, 8.09. Found: C, 58.89; H, 4.14; N, 8.06.

2'-Fluoro-4'-nitroacetanilide (**9**).

o-Fluoroaniline (**8**) (111 g, 1.00 mole) and triethylamine (153 ml, 1.10 moles) were dissolved in tetrahydrofuran (700 ml) and cooled to *ca.* -30° by means of a methanol/water/dry ice bath. Acetyl chloride (75 ml, 1.05 moles) was added through an addition funnel at such a rate that the internal temperature remained below 20°. After stirring for an additional 15 minutes, the solution was partitioned in ethyl acetate and water (600 ml each). The aqueous phase was removed and the organic layer was washed with additional water. The aqueous phases were back-extracted with ethyl acetate, and the organic phases were combined, dried and concentrated to afford 153 g (100%) of 2'-fluoroacetanilide as an off white solid which was used directly in the next step.

2'-Fluoroacetanilide obtained above (50.0 g, 327 mmoles) was added portionwise over 30 minutes to 400 ml of 90% nitric acid while maintaining the internal temperature between 0-3° by means of an acetone/ice bath. After stirring for an additional 20 minutes, the solution was slowly poured onto 2 liters of ice. After stirring for 45 minutes, the resultant solid was obtained by filtration. The crude product was then added portionwise to a solution of ethanol (60 ml) and 2.2 M potassium hydroxide (400 ml) while maintaining the internal temperature below 10°. The resultant yellow heterogeneous solution was stirred at 0-5° for an additional hour and then filtered. The yellow solid was washed with water and then recrystallized from 1 liter of ethanol to give 34.8 g (54%) of 2'-fluoro-4'-nitroacetanilide (**9**) as pale yellow needles, mp 199-201°; ir: 1686, 1619 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 10.19 (s, 1H), 8.36 (t, J = 8.7, 1H), 8.13-8.00 (m, 2H), 2.14 (s, 3H); ms: 199 (MH^+).

Anal. Calcd. for $C_8H_7FN_2O_3$: C, 48.49; H, 3.56; N, 14.14. Found: C, 48.69; H, 3.53; N, 14.10.

2-Fluoro-4-nitroaniline (**11**).

Method 1.

Following the method of Katritzky and Laurenzo [15], a solution containing 3-fluoronitrobenzene (**10**) (1.41 g, 10 mmoles) and 4-amino-1,2,4-triazole (0.84 g, 10 mmoles) in 10 ml of dimethyl sulfoxide was added to a solution of potassium *t*-butoxide (1.12 g, 10 mmoles) in dimethyl sulfoxide (20 ml) during 20 minutes. The resultant dark brown reaction mixture was stirred for a total of 17 hours and then diluted with 60 ml of saturated ammonium chloride. The crude reaction mixture was then extracted with ether (3x) and the combined organic phases were washed with saturated sodium chloride and then dried and concentrated to afford a brown solid. Flash chromatography (ethyl acetate/hexanes, 20/80) gave 0.46 g (29%) of a yellow solid, mp 128-130° (lit, 133-133.5° [15]); ir 3502, 3405, 1630 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 7.93 (m, 2H), 6.77 (t, J = 9.0, 1H), 4.47 (br s, 2H); ms: 157 (MH^+).

Method 2.

2'-Fluoro-4'-nitroacetanilide (**9**) (36.5 g, 184 mmoles) was heated at reflux in 400 ml of 50% aqueous sulfuric acid for 45 minutes. The brown solution was cooled and enough 50% sodium hydroxide solution was added dropwise until the solution was neutralized. The yellow solid which was obtained was collected by filtration and dried to give the desired product, containing some inorganic salts. The crude product, identical by tlc and ^1H-nmr to the product obtained by method 1, was used directly in the next step.

N-(2-Fluoro-4-nitrophenyl)-1-cyclohexene-1,2-dicarboximide (**12**).

Using a procedure similar to that used for the preparation of compound **4**, 2-fluoro-4-nitroaniline (**11**) (from method 2, above) and 1,2,3,4-tetrahydrophthalic anhydride (**3**) were reacted to give compound **12** as an orange-yellow solid. Recrystallization from ethanol gave 26.9 g (50% yield from compound **9**) of beige plates, 132-134°; ir 1717, 1527 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.13-8.04 (m, 2H), 7.47 (t, J = 9, 1H), 2.43 (br s, 4H), 1.81 (br s, 4H); ms: 290 (M^+).

Anal. Calcd. for $C_{14}H_{11}FN_2O_4$: C, 57.93; H, 3.82; N, 9.65. Found: C, 58.22; H, 3.62; N, 9.62.

N-(4-Amino-2-fluorophenyl)-1-cyclohexene-1,2-dicarboximide (**13**).

Using a procedure similar to that used for the preparation of compound **5**, *N*-(2-fluoro-4-nitrophenyl)-1-cyclohexene-1,2-dicarboximide (**12**) was hydrogenated in the presence of Raney-nickel to give compound **13** in 22.7 g (100%) as an amber glass, mp 56-60°; ^1H-nmr (deuteriochloroform): δ 6.93 (t, J = 8.4, 1H), 6.45-6.40 (m, 2H), 3.92 (br s, 2H), 2.40 (br s, 4H), 1.80 (br s, 4H); ms: 260 (M^+).

Anal. Calcd. for $C_{14}H_{13}FN_2O_2$: C, 64.61; H, 5.03. Found: C, 64.89; H, 5.20.

N-[6-Fluoro-3-(methylthio)-2-oxo-5-indolinyl]-1-cyclohexene-1,2-dicarboximide (**14**) and *N*-[4-Fluoro-3-(methylthio)-2-oxo-5-indolinyl]-1-cyclohexene-1,2-dicarboximide (**15**).

Using a procedure similar to that used for the preparation of compounds **6** and **7**, *N*-(4-amino-2-fluorophenyl)-1-cyclohexene-1,2-dicarboximide (**13**) was treated with the chlorosulfonium salt of ethyl (methylthio)acetate and triethylamine to give a mixture of amino esters which were cyclized to the indolin-2-ones **14** and **15** by heating in toluene in the presence of *p*-toluenesulfonic acid. Upon cooling, no precipitate was noted. The crude reaction mixture was concentrated and purified by flash chromatography using ethyl acetate/hexanes (35-45%) to give compound **14** (less polar) and compound **15** (more polar).

N-[6-Fluoro-3-(methylthio)-2-oxo-5-indolinyl]-1-cyclohexene-1,2-dicarboximide (**14**).

This compound was obtained as a yellow solid in 8.93 g (31% yield), mp 165-168°; ir: 1714, 1633 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 9.46 (s, 1H), 7.21 (d, J = 6.9, 1H), 6.78 (d, J = 9.9, 1H), 4.27 (s, 1H), 2.41 (br s 4H), 2.01 (s, 3H), 1.81 (br s, 4H);

ms: 347 (MH^+).

Anal. Calcd. for $C_{17}H_{15}FN_2O_3S$: C, 58.95; H, 4.37; N, 8.09. Found: C, 58.64; H, 4.43; N, 7.80.

N-[4-fluoro-3-(methylthio)-2-oxo-5-indolinyl]-1-cyclohexene-1,2-dicarboximide (**15**).

This compound was obtained as an amber solid in 6.80 g (23% yield). An analytically pure sample was recrystallized from ethanol/water to give an orange-yellow solid, mp 228-229°; ir: 1729, 1636 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 10.89 (s, 1H), 7.24 (t, J = 7.8, 1H), 6.77 (d, J = 8.4, 1H), 4.78 (s, 1H), 2.32 (br s, 4H), 2.01 (s, 3H), 1.72 (br s, 4H); ms: 347 (MH^+).

Anal. Calcd. for $C_{17}H_{15}FN_2O_3S$: C, 58.95; H, 4.37; N, 8.09. Found: C, 58.80; H, 4.21; N, 8.12.

General Procedure for the *C*-Alkylation of Indolin-2-ones **6**, **7**, **14** and **15**.

The Preparation of *N*-[5-Fluoro-3-methyl-3-(methylthio)-2-oxo-6-indolinyl]-1-cyclohexene-1,2-dicarboximide (**16**) is representative.

Sodium hydride (0.73 g, 18.2 mmoles, 60% oil dispersion) was added in one portion to a solution of *N*-[5-fluoro-3-(methylthio)-2-oxo-6-indolinyl]-1-cyclohexene-1,2-dicarboximide (**6**) (6.00 g, 17.3 mmoles) in 80 ml of dimethyl sulfoxide. After hydrogen evolution was complete (30 minutes), a solution of methyl iodide (2.59 g, 18.2 mmoles) in 5 ml of dimethyl sulfoxide was added dropwise during 5 minutes. After stirring at room temperature for an additional 2 hours, the crude reaction mixture was partitioned in ethyl acetate and water. The aqueous phase was removed and the organic layer was washed with three additional portions of water. The combined aqueous phases were back-extracted with ethyl acetate and the organic layers were combined, washed with saturated sodium chloride, and then dried and concentrated to give the crude product. Trituration in ethyl acetate/hexanes gave 4.1 g (66% yield) of compound **16** as a tan solid, mp 268-272° dec; ir: 1715, 1686 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 9.60 (s, 1H), 7.16 (d, J = 8.7, 1H), 6.85 (d, J = 5.7, 1H), 2.41 (br s, 4H), 1.91 (s, 3H), 1.80 (br s, 4H), 1.62 (s, 3H); ms: 361 (MH^+).

Anal. Calcd. for $C_{18}H_{17}FN_2O_3S$: C, 59.99; H, 4.75; N, 7.77. Found: C, 59.83; H, 4.95; N, 7.52.

N-[5-Fluoro-3-methyl-3-(methylthio)-2-oxo-4-indolinyl]-1-cyclohexene-1,2-dicarboximide (**17**).

This compound was obtained from the alkylation of *N*-[5-fluoro-3-(methylthio)-2-oxo-4-indolinyl]-1-cyclohexene-1,2-dicarboximide (**7**) with methyl iodide as a yellow solid in 2.30 g (74% yield) after trituration (ethyl acetate/hexanes). A small sample was recrystallized from ethanol/water to give an analytically pure sample, mp 267-271°; ir: 1703, 1623 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 9.77 (br s, 1H), 7.09 (t, J = 9, 1H), 7.00 (dd, J = 3.9, 8.4, 1H), 2.44 (br s, 4H), 1.84 (br s, 4H), 1.78 (s, 3H), 1.55 (s, 3H); ms: 361 (MH^+).

Anal. Calcd. for $C_{18}H_{17}FN_2O_3S$: C, 59.99; H, 4.75; N, 7.77. Found: C, 59.97; H, 4.47; N, 7.85.

N-[6-Fluoro-3-methyl-3-(methylthio)-2-oxo-5-indolinyl]-1-cyclohexene-1,2-dicarboximide (**18**).

This compound was obtained from the alkylation of *N*-[6-fluoro-3-(methylthio)-2-oxo-5-indolinyl]-1-cyclohexene-1,2-dicarboximide (**14**) with methyl iodide as a light yellow solid in 2.95 g (44% yield) after flash chromatography (ethyl acetate/hexanes, 20-30%), mp 216-218°; ir: 1716, 1630, 1615 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 9.21 (br s, 1H), 7.17 (d, J = 6.9, 1H), 6.83 (d, J = 9.0, 1H), 2.43 (br s, 4H), 1.93 (s, 3H), 1.83 (br s, 4H), 1.66 (s, 3H); ms: 361 (MH^+).

Anal. Calcd. for $C_{18}H_{17}FN_2O_3S$: C, 59.99; H, 4.75; N, 7.77. Found: C, 59.81; H, 4.48; N, 7.78.

N-[4-fluoro-3-methyl-3-(methylthio)-2-oxo-5-indolinyl]-1-cyclohexene-1,2-dicarboximide (**19**).

This compound was obtained from the alkylation of *N*-[4-fluoro-3-(methylthio)-2-oxo-5-indolinyl]-1-cyclohexene-1,2-dicarboximide (**15**) with methyl iodide as a light orange solid in 1.87 g (44% yield) after flash chromatography (ethyl acetate/hexanes, 40/60). A small sample was recrystallized from ethanol/water to give an analytically pure sample as a beige solid, mp 231-233°; ir: 1714, 1632, cm^{-1}; ^1H-nmr (deuteriochloroform): δ 9.52 (br s, 1H), 7.12 (t, J = 7.5, 1H), 6.82 (d, J = 8.4, 1H), 2.41 (br s, 4H), 1.96 (s, 3H), 1.81 (br s, 4H), 1.77 (s, 3H); ms: 361 (MH^+).

Anal. Calcd. for $C_{18}H_{17}FN_2O_3S$: C, 59.99; H, 4.75; N, 7.77. Found: C, 59.91; H, 4.57; N, 7.63.

General Procedure for the *N*-alkylation of Indolin-2-ones **17**, **18** and **19**.

Compounds **21**, **22** and **23** were prepared using a procedure similar to that used for the *C*-alkylation of compounds **16-19**.

N-[5-Fluoro-1,3-dimethyl-3-(methylthio)-2-oxo-4-indolinyl]-1-cyclohexene-1,2-dicarboximide (**21**).

This compound was obtained from the alkylation of *N*-[5-fluoro-3-methyl-3-(methylthio)-2-oxo-4-indolinyl]-1-cyclohexene-1,2-dicarboximide (**17**) with methyl iodide as a white solid in 0.75 g (40% yield) after flash chromatography (ethyl acetate/hexanes, 33-50%), mp 226-229°; ir 1715, 1614 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 7.14 (t, J = 9.0, 1H), 6.87 (dd, J = 3.9, 8.7, 1H), 3.22 (s, 3H), 2.42 (br s, 4H), 1.83 (br s, 4H), 1.73 (s, 3H), 1.51 (s, 3H); ms: 375 (MH^+).

Anal. Calcd. for $C_{19}H_{19}FN_2O_3S$: C, 60.95; H, 5.11; N, 7.48. Found: C, 60.78; H, 4.92; N, 7.34.

N-[6-Fluoro-1,3-dimethyl-3-(methylthio)-2-oxo-5-indolinyl]-1-cyclohexene-1,2-dicarboximide (**22**).

This compound was prepared from the alkylation of *N*-[6-fluoro-3-methyl-3-(methylthio)-2-oxo-5-indolinyl]-1-cyclohexene-1,2-dicarboximide (**18**) with methyl iodide as a white solid in 0.98 g (41% yield) after flash chromatography (ethyl acetate/hexanes, 40/60), mp 140-142°; ir 1716, 1624 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 7.10 (d, J = 6.9, 1H), 6.67 (d, J = 9.3, 1H), 3.15 (s, 3H), 2.34 (br s, 4H), 1.86 (s, 3H), 1.74 (br s, 4H), 1.57 (s, 3H); ms: 375 (MH^+).

Anal. Calcd. for $C_{19}H_{19}FN_2O_3S$: C, 60.95; H, 5.11; N, 7.48. Found: C, 60.95; H, 5.16; N, 7.33.

N-[4-Fluoro-1,3-dimethyl-3-(methylthio)-2-oxo-5-indolinyl]-1-cyclohexene-1,2-dicarboximide (**23**).

This compound was prepared from the alkylation of *N*-[4-fluoro-3-methyl-3-(methylthio)-2-oxo-5-indolinyl]-1-cyclohexene-1,2-dicarboximide (**19**) with methyl iodide as a yellow solid in 0.65 g (48% yield) after flash chromatography (ethyl acetate/hexanes, 40/60). A small sample was recrystallized from ethanol/water to give an analytically pure sample as yellow nee-

dles, mp 218.5-220°; ir: 1714, 1632 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 7.20 (dd, J = 6.9, 8.4, 1H), 6.73 (d, J = 8.4, 1H), 3.25 (s, 3H), 2.44 (br s, 4H), 1.98 (s, 3H), 1.83 (br s, 4H), 1.77 (s, 3H); ms: 375 (MH^+).

Anal. Calcd. for $C_{19}H_{19}FN_2O_3S$: C, 60.95; H, 5.11; N, 7.48. Found: C, 60.85; H, 5.06; N, 7.37.

Nitration of *m*-Fluorophenylacetic Acid (**24**).

m-Fluorophenylacetic acid (**24**) (20.0 g, 130 mmoles) was dissolved in 40 ml of concentrated sulfuric acid. A solution consisting of 90% nitric acid (24 ml) and concentrated sulfuric acid (30 ml) was added dropwise during 1 hour while maintaining the internal temperature between 20-35°. After the addition, the solution was stirred for an additional 20 hours at 35° and the resultant yellow slurry was poured onto ice and filtered to give 29.5 g of an off-white solid.

The solid obtained (a mixture of nitro acids) was dissolved in 300 ml of methanol. Sulfuric acid (1 ml) was added and the solution was heated at reflux for 5 hours and then cooled in an ice bath. The *p*H was brought to *ca.* 5 by the dropwise addition of 3*N* sodium hydroxide. Most of the methanol was removed by rotary evaporation and the remainder of the solution was partitioned in ethyl acetate and water. After removing the aqueous phase, the organic layer was washed with water and saturated sodium chloride, dried and then concentrated to give a light brown oil comprised of the following three compounds (listed in order of increasing polarity by tlc): methyl (3-fluoro-2,6-dinitrophenyl)acetate (**25**), methyl (5-fluoro-2,4-dinitrophenyl)acetate (**26**) and methyl (5-methoxy-2,4-dinitrophenyl)acetate (**27**). The compounds were separated by flash chromatography (ethyl acetate/hexanes, 15-50%).

Methyl (3-Fluoro-2,6-dinitrophenyl)acetate (**25**).

This compound was obtained as a yellow oil in 3.5 g (10% yield); ir: 1744, 1622, 1598, 1544 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.29 (dd, J = 4.8, 9.3, 1H), 7.45 (t, J = 8.7, 1H), 4.01 (s, 2H), 3.72 (s, 3H); ms: 259 (MH^+).

Anal. Calcd. for $C_9H_7FN_2O_6$: C, 41.87; H, 2.73; N, 10.85. Found: C, 42.05; H, 2.81; N, 10.90.

Methyl (5-Fluoro-2,4-dinitrophenyl)acetate (**26**).

This compound was obtained as an amber oil in 16.3 g (49% yield), ir: 1741, 1606, 1542 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.87 (d, J = 7.0, 1H), 7.39 (d, J = 10.8, 1H), 4.11 (s, 2H), 3.71 (s, 3H); ms: 259 (MH^+).

Anal. Calcd. for $C_9H_7FN_2O_6$: C, 41.87; H, 2.73; N, 10.85. Found: C, 41.80; H, 2.48; N, 10.80.

Methyl (5-Methoxy-2,4-dinitrophenyl)acetate (**27**).

This compound was obtained as a white solid in 2.4 g (7% yield), mp 90-93°; ir: 1728, 1618, 1590, 1515 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.75 (s, 1H), 7.05 (s, 1H), 4.11 (s, 2H), 4.08 (s, 3H), 3.72 (s, 3H); ms 271 (MH^+).

Anal. Calcd. for $C_{10}H_{10}N_2O_7$: C, 44.45; H, 3.73; N, 10.37. Found: C, 44.08; H, 3.62; N, 10.30.

6-Amino-5-fluoroindolin-2-one (**28**).

A 500 ml Parr hydrogenation bottle was charged with methyl (5-fluoro-2,4-dinitrophenyl)acetate (**26**) (12.35 g, 47.86 mmoles), 10% Palladium on charcoal (1.23 g, 10 wt %) and 100 ml of ethanol/dimethoxyethane (1/1). The reaction was hydrogenated at 50 psi until hydrogen uptake ceased and the crude reaction mixture was filtered to remove the catalyst. The solvents were concentrated leaving the crude diamino ester as an oil.

The oil was taken up in 100 ml of 1*M* hydrochloric acid and heated at reflux for 20 minutes. After cooling, the solution was neutralized with 1*M* sodium hydroxide and extracted with three portions of ethyl acetate. The organic layers were combined, dried and concentrated to afford 6.65 g (85% yield) of a greenish-brown solid which was used without further purification, mp 185-187°; ir: 1691, 1644 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 10.09 (br s, 1H), 6.81 (d, J = 10.8, 1H), 6.28 (d, J = 7.8, 1H), 5.01 (s, 2H), 3.25 (s, 2H); ms: 167 (MH^+).

N-(5-Fluoro-2-oxo-6-indolinyl)-1-cyclohexene-1,2-dicarboximide (**29**).

Using a procedure similar to that used for the preparation of compound **4**, 6-amino-5-fluoroindolin-2-one (**28**) (5.00 g, 3.01 mmoles) and 1,2,3,4-tetrahydrophthalic anhydride (**3**) (4.58 g, 3.01 mmoles) were reacted to give, after purification by flash chromatography (ethyl acetate/hexanes, 2/1), compound **29** in 6.0 g (66% yield) as a violet solid, mp 234-236°; ir: 1717, 1676 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 9.00 (br s, 1H), 7.02 (d, J = 9.0, 1H), 6.67 (d, J = 6.0, 1H), 3.46 (s, 2H), 2.36 (br s, 4H), 1.76 (br s, 4H); ms: 301 (MH^+).

Anal. Calcd. for $C_{16}H_{13}FN_2O_3$: C, 63.99; H, 4.36; N, 9.33. Found: C, 63.65; H, 4.29; N, 9.03.

N-(1-Acetyl-5-fluoro-2-oxo-6-indolinyl)-1-cyclohexene-1,2-dicarboximide (**30**).

A mixture comprised of *N*-(5-fluoro-2-oxo-6-indolinyl)-1-cyclohexene-1,2-dicarboximide (**29**) (14.7 g, 49.0 mmoles), acetic anhydride (7.0 ml, 74 mmoles) and acetic acid (12 ml) were heated at reflux. Two additional portions of acetic anhydride (2.4 ml each) were added during the course of 25 hours. The reaction mixture was cooled and then concentrated to give a brown semi-solid which, after trituration (ethyl acetate/hexanes, 20/80), gave 15.3 g (91% yield) of a light brown solid. A small sample was recrystallized from ethanol/water to give an analytically pure sample as a light brown solid, mp 191-193.5°; ^1H-nmr (deuteriochloroform): δ 8.15 (d, J = 4.8, 1H), 7.13 (d, J = 8.1, 1H), 3.73 (s, 2H), 2.63 (s, 3H), 2.42 (br s, 4H), 1.82 (br s, 4H); ms: 343 (MH^+).

Anal. Calcd. for $C_{18}H_{15}FN_2O_4$: C, 63.16; H, 4.42; N, 8.18. Found: C, 62.99; H, 4.45; N, 8.05.

N-(1'-Acetyl-5'-fluoro-2'-oxospiro[cyclopropane-1,3'-indolin]-6'-yl)-1-cyclohexene-1,2-dicarboximide (**31**).

A mixture comprised of *N*-(1-acetyl-5-fluoro-2-oxo-6-indolinyl)-1-cyclohexene-1,2-dicarboximide (**30**) (4.65 g, 13.6 mmoles), potassium carbonate (3.76 g, 27.2 mmoles) and 1,2-dibromoethane (2.81 g, 15.0 mmoles) in 50 ml of dimethyl sulfoxide was stirred at room temperature for 23 hours. The crude reaction mixture was then partitioned in ether and water, and after removing the aqueous phase, the organic layer was washed with three additional portions of water followed by saturated sodium chloride. The aqueous phases were combined and back-extracted with ethyl acetate. The combined organic layers were dried and concentrated to a semi-solid. Flash chromatography (ethyl acetate/hexane, 15-20%) gave 1.04 g (21% yield) of a tan solid, mp 199-201°; ir: 1759, 1712 cm-1; ^1H-nmr (deuteriochloroform): δ 8.16 (d, J = 6.3, 1H), 6.64 (d, J = 8.1, 1H), 2.60 (s, 3H), 2.37 (br s, 4H), 1.84-1.77 (m, 2H), 1.76 (br s, 4H), 1.60-

1.55 (m, 2H); ms: 369 (MH^+).

Anal. Calcd. for $C_{20}H_{17}FN_2O_4$: C, 65.21; H, 4.65; N, 7.60. Found: C, 64.90; H, 4.57; N, 7.53.

N-(5'-Fluoro-2'-oxospiro[cyclopropane-1,3'-indolin]-6'-yl)-1-cyclohexene-1,2-dicarboximide (**32**).

A mixture of *N*-(1'-acetyl-5'-fluoro-2'-oxospiro[cyclopropane-1,3'-indolin]-6'-yl)-1-cyclohexene-1,2-dicarboximide (**31**) (1.03 g, 2.69 mmoles) in tetrahydrofuran (15 ml) and 3*N* sulfuric acid (15 ml) was heated at reflux for 2 hours. The reaction mixture was then cooled and partitioned in ethyl acetate and water. The aqueous phase was removed and the organic layer was washed successively with water and saturated sodium bicarbonate. The aqueous phases were combined and then back-extracted with ethyl acetate. The combined organic layers were then dried and concentrated to give 0.66 g (72% yield) of a beige solid. A small sample was recrystallized from ethanol/water to give an analytically pure sample as beige needles, mp: 284-285°; ir: 1716 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 9.07 (br s, 1H), 6.76 (d, J = 5.7, 1H), 6.61 (d, J = 9.3, 1H), 2.36 (br s, 4H), 1.76 (m, 4H), 1.76-1.70 (m, 2H), 1.51-1.46 (m, 2H); ms: 327 (MH^+).

Anal. Calcd. for $C_{18}H_{15}FN_2O_3$: C, 66.25; H, 4.63; N, 8.58. Found: C, 65.96; H, 4.53; N, 8.45.

N-(5'-Fluoro-1'-methyl-2'-oxospiro[cyclopropane-1,3'-indolin]-6'-yl)-1-cyclohexene-1,2-dicarboximide (**33**).

A solution of *N*-(5'-fluoro-2'-oxospiro[cyclopropane-1,3'-indolin]-6'-yl)-1-cyclohexene-1,2-dicarboximide (**32**) (0.65 g, 2.00 mmoles) in 5 ml of dimethylformamide was added dropwise over 5 minutes to a flask containing sodium hydride (0.11 g, 2.80 mmoles, 60% oil dispersion) in dimethylformamide (5 ml), precooled to -10°. After stirring for 20 minutes, a solution of methyl iodide (0.34 g, 2.40 mmoles) in dimethylformamide (5 ml) was added over 2 minutes. The reaction mixture was allowed to warm to ambient temperature and after 4 hours was warmed to 30° and stirring was continued for a total of 20 hours. At this time tlc analysis (ethyl acetate/hexanes, 25/75) showed there to be a significant amount of starting material still present. The reaction mixture was then cooled to -25° and additional portions of sodium hydride (0.05 g) and methyl iodide (0.50 g) were added. The reaction mixture was warmed to 0° during 5 hours and then poured into water. Ether was added and the aqueous phase was removed. The organic layer was washed with saturated sodium chloride and the combined aqueous phases were back-extracted with ethyl acetate. The organic layers were combined, dried, and concentrated in vacuo to give a residue which was chromatographed (ethyl acetate/hexane, 30/70) to give 0.23 g (34% yield) of a white solid. A small sample was recrystallized from ethanol/water to give an analytically pure sample as a white solid, mp 251-252°; ir: 1709 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 6.75-6.70 (m, 2H), 3.27 (s, 3H), 2.45 (br s, 4H), 1.85 (br s, 4H), 1.84-1.78 (m, 2H), 1.57-1.52 (m, 2H); ms: 341 (MH^+).

Anal. Calcd. for $C_{19}H_{17}FN_2O_3$: C, 67.05; H, 5.03; N, 8.23. Found: C, 66.85; H, 4.96; N, 8.15.

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[22] Raney-nickel was purchased from Aldrich Chemical Co., Inc., as an aqueous suspension (*p*H 9-10) and was used without further treatment.