Formation of 4,5,6,7-Tetrahydroisoindoles by Palladium-Catalyzed Hydride Reduction

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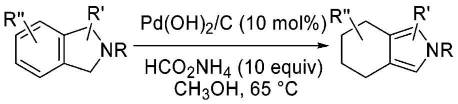
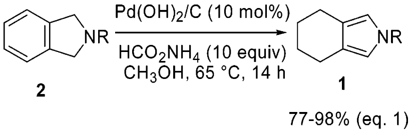


Substituted 1,3-dihydro-*2H*-isoindoles (**2**, isoindolines) were prepared and subjected to palladium-catalyzed formate reduction. Alkyl isoindolines were reduced to 4,5,6,7-tetrahydro-*2H*-isoindoles (**1**). Only partial reduction was observed for 5-methoxyisoindoline, and 4-methoxy-, 5-carbomethoxy-, amino-, and amidoisoindolines were inert to the reaction. Halogen-substituted isoindolines were dehalogenated and reduced to 4,5,6,7-tetrahydro-*2H*-isoindoles. Isoindole **24** was also reduced to a mixture of an isoindoline and a 4,5,6,7-tetrahydro-*2H*-isoindole. In contrast, 2,3-dihydro-1*H*-indoles **21** underwent dehydrogenation to give thermodynamically stable indoles. Theoretical calculations show the significant difference in aromaticity between isoindoles and indoles, corresponding to the observed differences in reactivities. Tetrahydro-2*H*-isoindoles **1** were oxidized to 4,5,6,7-tetrahydroisoindole-1,3-diones in the presence of NBS and air.

Introduction

Pyrroles and indoles are important groups of *N*-heterocyclic compounds, occur widely in living matter, and have significant biological roles.[1] Isoindoles and their derivatives are less known, but they have been found as inhibitors of cyclooxygenase isoenzyme (COX-2) and thrombin.[2] These factors and the versatile chemistry of these heterocycles have attracted the attention of organic chemists.[3] Recently we reported a new approach for forming 4,5,6,7-tetrahydro-2*H*-isoindoles, **1**, from 1,3-dihydro-2*H*-isoindoles (isoindolines), **2**, under palladium-catalyzed hydrogenation conditions (eq 1).[4] In this transformation, formation of the pyrrole is accompanied by partial reduction of the benzene moiety. We also found that this process is quite general for many functional groups attached to the nitrogen atom, such as alcohol, ether, ester, and amide. Extensive C−H/C−D exchange in the products was also observed. However, the effects of the substituents on the isoindoline ring and the mechanistic rationale for this process remain unknown. Here, we report our further studies on this process, including effects of substituents, comparison with indolines to show their remarkable differences in reactivity, and application of theoretical calculations to facilitate understanding of the experimental observations.



Results and Discussion

Studied first were the effects of substituents at the carbon atoms of **2** on the course of the reaction. Thus, substituted isoindolines **5** were prepared using two strategies: alkylation of glycine methyl ester with various α,α′-dibromo-*o*-xylene

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(1) (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, p 313. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; Blackwell Publishing: Oxford, U.K., 2000; p 237 and p 324. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.

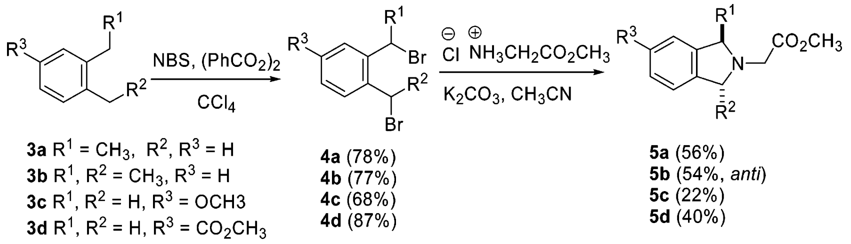
(2) (a) Portevin, B.; Tordjman, C.; Pastoureau, P.; Bonnet, J.; De Nanteuil, G. *J. Med. Chem.* **2000**, *43*, 4582. (b) Peterlin-Mašič, L.; Mlinšek, G.; Šolmajer, T.; Trampuš-Bakija, A.; Stegnard, M.; Kikelja, D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 789.

(3) Selected synthesis to indoles and isoindoles: (a) Shen, L.; Hsung, R. P. *Org. Lett.* **2005**, *7*, 775. (b) Clayden, J.; Kenworthy, M. N. *Synthesis* **2004**, 1721. (c) Thomson, D. W.; Commeureuc, A. G. J.; Berlin, S.; Murphy, J. A. *Syn. Commun.* **2003**, *33*, 3631. (d) Basaric, N.; Marinic, Z.; Sindler-Kulyk, M. *Tetrahedron Lett.* **2003**, *44*, 7337. (e) Uchiyama, K.; Hayashi, Y.; Narasaka, K. *Tetrahedron* **1999**, *55*, 8915. (f) Erian, A. W. *Chem. Rev.* **1993**, *93*, 1991.

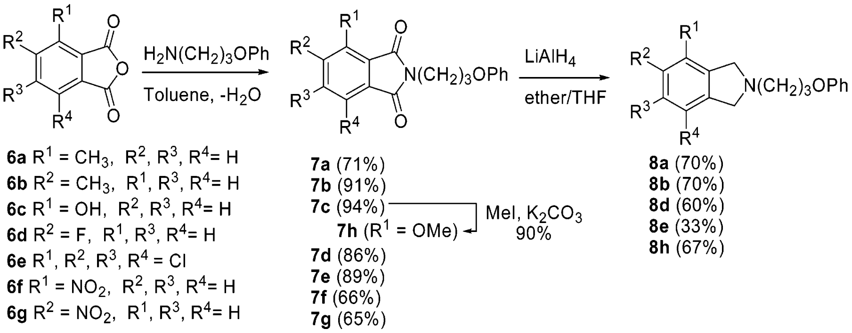
(4) Hou, D.-R.; Hsieh, Y.-D.; Hsieh, Y. W. *Tetrahedron Lett.* **2005**, *46*, 5927.

10.1021/jo7016845 CCC: $37.00

SCHEME 1. Synthesis of Isoindolines 5



SCHEME 2. Synthesis of Isoindolines 8



derivatives **4** (Scheme 1) and the reduction of substituted phthalimides (Scheme 2). Radical bromination at the two benzylic positions of arenes **3** gave a series of dibromides **4**,[5] the precursors to isoindolines **5a**−**d**. The stereochemistry of compounds **4b** and **5b** needed further clarification. Although Utley and Wyatt reported that the bromination reaction produced 1,2-bis-(bromoethyl)benzene (**4b**) as a mixture of two diastereomers and that one of them dominated after recrystallization by a factor of 15:1, they did not assign their stereochemistry.[5a] Thus, we performed the dialkylation of glycine methyl ester with the recrystallized, dibromide **4b** and harvested the diastereomerically pure isoindoline **5b** after flash column chromatography. The stereochemistry of the isoindoline **5b** produced was assigned as *anti* (*d*,*l*) because of two ^{1}H NMR spectroscopic facts: the two hydrogens of α-methylene are diastereotopic ($^2J_{H-H} = 17.0$ Hz) and protonated **5b** showed two distinct methyl and two methine absorptions, both of equal intensity. The *syn* (*meso*) isomer of **5b** contains an enantiotopic α-methylene, and its *N*-protonated form still possesses a plane of symmetry, leading to single methyl and methine groups.[6] The formation of *anti*-**5b** also indicates that the main diastereomer harvested in recrystallization of dibromide **4b** is a *d*,*l*-isomer, since the alkylation process is stereochemically conservative.[7]

The second route to isoindolines **8** started from condensation of phthalic anhydrides **6** and 3-phenoxypropanamine[8] to form phthalimide derivatives **7**,[9] followed by reduction with lithium aluminum hydride. We found that the nitro- and hydroxy-substituted phthalimides (**7c**, **7f**, and **7g**) gave complicated mixtures after reduction. To circumvent this, hydroxyphthalimide **7c** was first converted into its methoxy derivative, **7h**, which was then smoothly reduced to isoindoline **8h**; the reduction of nitrophthalimides (**7f** and **7g**) was achieved by the sequence of hydrogenation, acetylation, and reduction to provide the isoindolines bearing secondary amine, tertiary amine, or amide groups (**11f**,**g**, **13f**,**g**, and **12f**,**g**, respectively, Scheme 3).

With these substituted isoindolines in hand, we studied the effect of substituents on the formation of tetrahydroisoindoles under palladium-catalyzed hydride reduction. The results are summarized in Table 1. Previous results using *N*-substituted isoindolines **14** and **15** are also included for purposes of reference (entries 1, 2).[4] All methyl-substituted isoindolines (**5a**,**b** and **8a**,**b**, entries 3−6) were successfully transformed into the corresponding 4,5,6,7-tetrahydroisoindoles. However, isoindolines with a methyl group on the benzene moiety (**8a**,**b**), only gave modest yields (53−71%, entries 5, 6). Isoindoline **18**, which bears a sterically bulky *N*-*tert*-butyl group, is also a good substrate for this reaction (entry 15). Our results indicate that this reaction is compatible with alkyl groups. However, the results from other substituted isoindolines are variable. 5-Methoxyisoindole **5c** was converted to tetrahydroisoindole **16c** in poor yield with an extended reaction time (43 h) and 20 equiv of ammonium formate, but its 4-methoxy analogue **8h** was inert to these reaction conditions (entries 7, 8). The 5-methylcarboxylateisoindoline **5d** also failed to undergo the transformation. Fluorinated and chlorinated isoindolines **8d**,**e** were first dehalogenated to isoindoline **15** and then reduced to **1a** in good yields (entries 10−13). The cleavage of the carbon−fluorine bond in **8d** shows that this reaction is highly reductive. Unfortunately, all nitrogen substituents, including secondary and tertiary amines and amides at the 4- or 5-positions of isoindolines, prohibited the formation of tetrahydroisoindole **1** (entry 14).

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(5) (a) Eru, E.; Hawkes, G. E.; Utley, J. H. P.; Wyatt, P. B. *Tetrahedron* **1995**, *51*, 3033. (b) Liu, X.; Barrett, S. A.; Kilner, C. A.; Thornton-Pett, M.; Halcrow, M. *Tetrahedron* **2002**, *58*, 603. (c) Bourdonnec, B. L.; Ajello, C. W.; Seida, P. R.; Susnow, R. G.; Cassel, J. A.; Belanger, S.; Stabley, G. J.; DeHaven, R. N.; DeHaven-Hudkins, D. L.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2647.

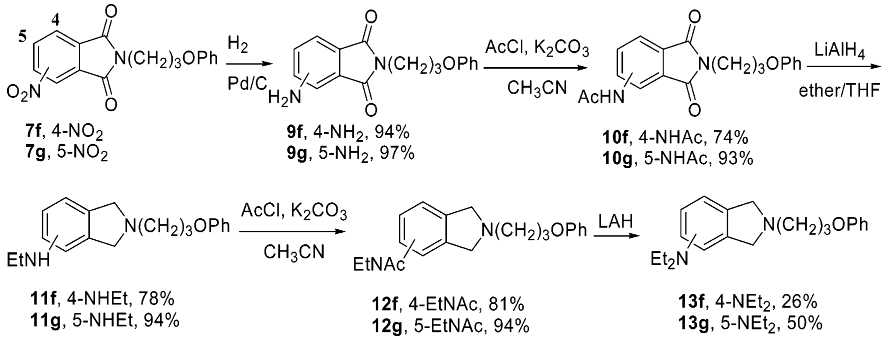
(6) Theoretically, protonation of *syn* **5b** gives two isomers: the methyl and the α-methylene groups either on the same side of the isoindoline plane or not. However, the two protonated forms, if they do exist, should be energetically different and recorded as a mixture of major/minor isomers in NMR. For a related example in assigning the stereochemistry of *N*-substituted-2,5-dimethyl-2,5-dihydropyrrole by protonation, see: Beattie, D. E.; Dover, G. M.; Ward, T. J. *J. Med. Chem.* **1985**, *28*, 1617.

(7) Murai, S.; Sugise, R.; Sonoda, N. *Angew. Chem., Int. Ed.* **1981**, *20*, 475.

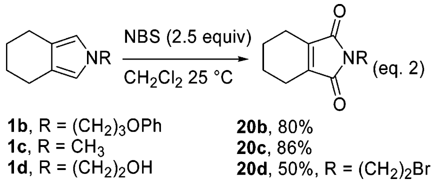
(8) Lever, O. W., Jr.; Bell, L. N.; McGuire, H. M.; Ferone, R. *J. Med. Chem.* **1985**, *28*, 1870.

(9) Raasch, A.; Scharfenstein, O.; Trankle, C.; Holzgrabe, U.; Mohr, K. *J. Med. Chem.* **2002**, *45*, 3809.

SCHEME 3. Synthesis of Isoindolines 12 and 13



There are few reports describing the chemical reactions of 4,5,6,7-tetrahydroisoindoles.[10−12] Our previous studies had shown that compound **1b** is the donor component in a Michael addition with dimethyl maleate.[4] In the present study, however, when 4,5,6,7-tetrahydroisoindoles **1b−d** were treated with another electrophile, namely, *N*-bromosuccinimide (NBS), the pyrrole moiety was oxidized to form 4,5,6,7-tetrahydroisoindole-1,3-diones **20b−d** (eq 2) instead of the expected 2-bromopyrroles. *N*-Substituted 2-bromo- and 2-chloropyrroles are known to be unstable,[13] and multiple halogenations at 5- or 3-positions were often observed in their reaction with NBS.[13b,14] In this case, we speculate that the diimides **20** come from oxidation of labile, brominated intermediates, generated from tetrahydroisoindoles **1** and NBS, in the presence of air.



The unique formation of pyrroles from 4,5,6,7-tetrahydroisoindoles prompted us to apply this reaction to related indoles. Therefore, 2,3-dihydroindoles **21a**,**b** were prepared and subjected to palladium-catalyzed hydride reduction. We were amazed to find that oxidized products, indoles **22a**,**b**, were generated rather than reduced, hydrogenated products (Scheme 4). Although the reaction conditions are reductive, the catalytic palladium promotes the dehydrogenation process to form indoles with 10 π-electrons. This result was further confirmed when we found that methyl 3-indolecarboxylates **23a**,**b**[15] were stable under the reduction conditions.

We further explored the reduction of isoindole **24**, prepared from partial reduction of phthalimide **25**.[16] In contrast to indoles **23**, **24** was reduced to isoindoline **15** and 4,5,6,7-tetrahydroisoindole **1b** in a ratio of 9:1 (Scheme 5). In spite of their structural resemblance, indoles and indolines have a reaction pathway opposite to that of isoindole and isoindoline. For compounds with the indole skeleton, the reaction leads to aromatic compounds having 10 π-electrons; however, molecules with the isoindole skeleton can be further reduced to 4,5,6,7-tetrahydroisoindoles, an aromatic system with six π-electrons.

Density functional theory calculations at the B3LYP/6-31G(d,p) level were employed to define the relative aromaticities of these compounds and to provide further insights into the experimental results. For computational convenience, the substituent at the nitrogen atom was modeled as a methyl group. The aromaticity of a target molecule was evaluated by the enthalpy of its hydrogenation. For example, the addition of one hydrogen molecule to 4,5,6,7-tetrahydroisoindole **1c** is accompanied by the loss of aromaticity; on the other hand, hydrogenation of hexahydroisoindole **26** (Scheme 6) involves no change in aromaticity. The resonance energy of compound **1c**, then, is the enthalpy difference between these two quasi-reactions (15.83 kcal/mol at 25 °C). The resonance energy of **1c** is lower than that of pyrrole. The accuracy of this strategy is confirmed by calculating the aromaticity of benzene and pyrrole to give 35.9 kcal/mol and 21.7 kcal/mol, respectively. Both values are in good agreement with the experimental data (36 kcal/mol and 21 kcal/mol).[17]

Similar calculations were applied to obtain the resonance energies of other related indoles and isoindoles (see Supporting Information). However, the aromaticity of *N*-methylindole could not be calculated directly by the above approach because of the coexistence of the benzene and pyrrole moieties. Therefore, the aromaticity of this 10 π-electron system is considered to be the sum of the resonance energy (33.7 kcal/mol) of *N*-methylindoline and extra stabilization (10.2 kcal/mol) gained in conjunction of pyrrole, as shown in Scheme 7. The resulting resonance energy (43.8 kcal/mol) of *N*-methylindole is in agreement with calculated and thermodynamic data reported previously.[17,18] The calculated resonance energies of related isoindole and indole derivatives obtained by this approach are summarized in Table 2.

The resonance energies of the three indole derivatives follow the order of increasing stabilization of pyrrole < benzene < indole, and the difference between each two is at least 10 kcal/mol. On the other hand, this trend disappears among isoindole derivatives. This is mainly because isoindole has a much lower

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[10] Diels-Alder reactions: (a) Ando, K.; Kankake, M.; Suzuki, T.; Takayama, H. *Synlett* **1994**, *9*, 741. (b) Stephan, D.; Gorgues, A.; Le Coq, A. *Tetrahedron Lett.* **1988**, *29*, 1025.

[11] Aldol condensation: Fuhrhop, J. H.; Hosseinpour, D. *Liebigs Ann. Chem.* **1985**, *4*, 689.

[12] Electrophilic substitution: Kobayashi, T.; Tsuzuki, T.; Tayama, Y.; Uchiyama, Y. *Tetrahedron* **2001**, *57*, 9073.

[13] (a) Cordell, G. A. *J. Org. Chem.* **1975**, *40*, 3161. (b) Gilow, H. M.; Burton, D. E. *J. Org. Chem.* **1981**, *46*, 2221.

[14] Martina, S.; Enkelmann, V.; Wegner, G.; Schluter, A.-D. *Synthesis* **1991**, 613.

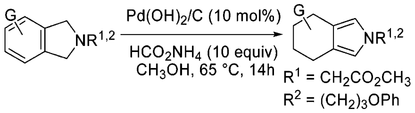
[15] Hopkins, C. R.; Czekaj, M.; Kaye, S. S.; Gao, Z.; Pribish, J.; Pauls, H.; Liang, G.; Sides, K.; Cramer, D.; Cairns, J.; Luo, Y.; Lim, H.-K.; Vaz, R.; Rebello, S.; Maignan, S.; Dupuy, A.; Mathieu, M.; Levell, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2734.

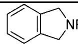
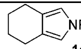
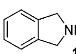
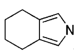
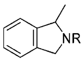
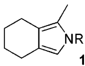
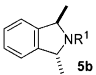
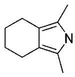
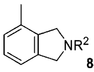
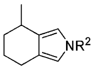
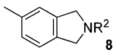
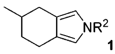
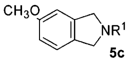
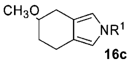
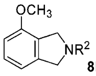
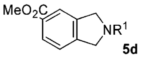
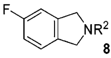
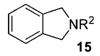
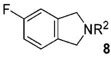
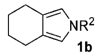
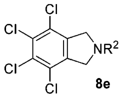
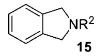
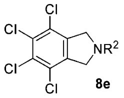
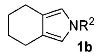
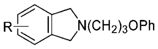
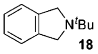
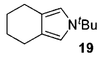
[16] Carpino, L. A.; Padykula, R. E.; Barr, D. E.; Hall, F. H.; Krause, J. G.; Dufresne, R. F.; Thoman, C. J. *J. Org. Chem.* **1988**, *53*, 2565.

[17] Katritzky, A. R.; Jug, K.; Oniciu, D. C. *Chem. Rev.* **2001**, *101*, 1421 and references cited therein.

[18] Lloyd, D.; Marshall, D. R. *Chem. Ind.* **1972**, 335.

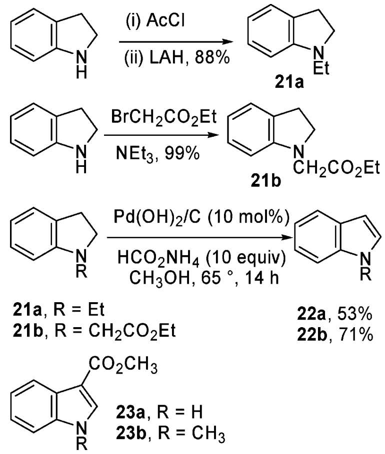
TABLE 1. Formation of 4,5,6,7-Tetrahydroisoindoles



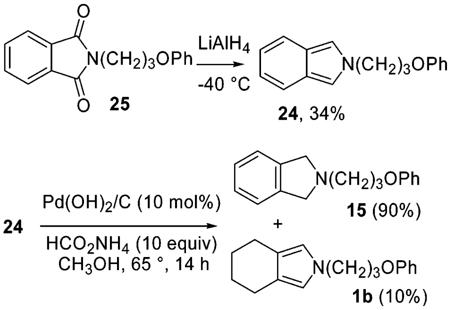
Entry	Reactants	Products	Yield (%)
1	 **14**	 **1a**	80
2	 **15**	 **1b**	97
3	 **5a**	 **16a**	93
4	 **5b**	 **16b**	90
5	 **8a**	 **17a**	71
6	 **8b**	 **17b**	53
7	 **5c**	 **16c**	$24^{a,b}$
8	 **8h**	-	$0^{a,c}$
9	 **5d**	-	$0^{a,c}$
10	 **8d**	 **15**	86
11	 **8d**	 **1b**	88^{a}
12	 **8e**	 **15**	86
13	 **8e**	 **1b**	$50^{a,d}$
14	 **11g**, R = 4-NHEt **11h**, R = 5-NHEt **12g**, R = 4-NAcEt **12h**, R = 5-NAcEt **13g**, R = 4-NEt$_2$ **13h**, R = 5-NEt$_2$	-	$0^{a,c}$
15	 **18**	 **19**	95

[a] Ammonium formate: 20 equiv, 43 h. [b] A total of 32% of **5c** recovered. [c] Starting material recovered. [d] Yield of **15**: 24%.

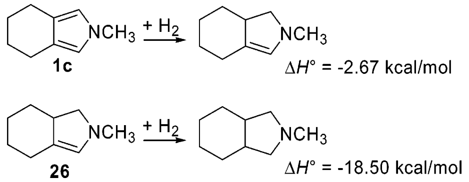
SCHEME 4. Synthesis and Dehydrogenation of Indolines 21



SCHEME 5. Synthesis of Isoindole and Its Reduction

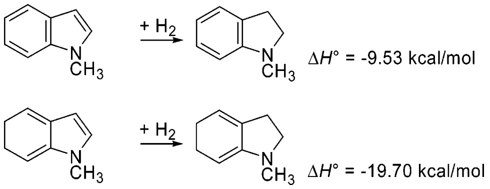


SCHEME 6. Calculated Aromaticity of 1c by the B3LYP/6-31G(d,p) Method[a]



[a] Resonance energy of **1c** = $-2.67 - (-18.50) = 15.83$ kcal/mol.

SCHEME 7. Calculated Aromaticity of Indole by the B3LYP/6-31G(d,p) Method[a]



[a] Indole gains extra resonance energy (10.17 kcal/mol).

resonance energy, ~13 kcal/mol less than its indole counterpart[19] and ~4 kcal/mol less than isoindoline. The lower aromaticity of *N*-methylisoindole is also revealed in its structural characteristics of alternating single and double bonds. On the basis of the optimized structures at the B3LYP/6-31G(d,p) level, the root-mean-square deviation of these bond lengths of the benzene moiety in *N*-methylisoindole is 0.031 Å, which is significantly larger than the corresponding value for 2-methylindole (0.014 Å). A similar result is also observed in the X-ray crystal structure of isoindoles.[20] This is in agreement with previous studies, which indicated that isoindole has a large decrease in the aromaticity of the benzene ring based on the *n-center* delocalization indices.[19a] The *diene* character of isoindoles is also shown by

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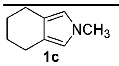
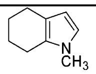
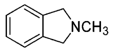
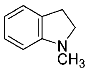
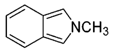
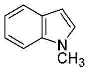
(19) Similar computational results: (a) Mandado, M.; Otero, N.; Mosquera, R. A. *Tetrahedron* **2006**, *62*, 12204. (b) Jursic, B. S. *J. Mol. Struct.* **1999**, *468*, 171. (c) Mandado, M.; Gonzalez-Moa, M. J.; Mosquera, R. A. *J. Comput. Chem.* **2007**, *28*, 127.

(20) X-ray structures of isoindoles also show the large deviation in the bond lengths: (a) Bonnett, R.; Hursthouse, M. B.; North, S. A.; Trotter, J. *J. Chem. Soc., Perkin Trans. 2*, **1985**, *2*, 293. (b) Simons, S. S.; Ammon, H. L.; Doherty, R.; Johnson, D. F. *J. Org. Chem.* **1981**, *46*, 4739.

TABLE 2. Resonance Energies of Isoindole, Indole, and Their Derivatives

Isoindoles	Resonance energy (kcal/mol)	Indoles	Resonance energy (kcal/mol)
 NCH₃ **1c**	15.83		20.36
	34.75		33.66
	30.76		43.83

their reactivity in Diels−Alder reactions.[21] Moreover, other studies have also demonstrated that indoles are much more stable than isoindoles based on indices such as the HOMO−LUMO energy gap and NICS values.[22]

The aromaticity difference between the two series rationalizes the observed differences in reactivities. Under palladium-catalyzed formate reduction, isoindole **24** was first reduced to isoindoline **15**. However, the formation of 4,5,6,7-tetrahydroisoindole is a stepwise, endothermic process requiring multiple hydrides. The unusually low aromaticity of isoindole prevents a thermodynamic sink, e.g., a stable indole, to dictate the reaction. On the other hand, the excess of hydride and the presence of catalyst provide a subtle reaction channel to form 4,5,6,7-tetrahydroisoindole in a stepwise manner as a kinetic product, produced and trapped in the highly reductive environment. If so, it is natural that the reduction of an isoindoline to a tetrahydroisoindole is more sensitive to the substituents on the benzene moiety, since they have a direct influence on the resonance energy of the isoindoline.

Conclusion

The formation of a 4,5,6,7-tetrahydroisoindole by palladium-catalyzed formate reduction is selective to the substituents on their isoindole ring. Oxidation rather than bromination occurs in the reaction of tetrahydroisoindoles with NBS. Isoindole and its derivatives have a chemical behavior distinct from that of the corresponding indoles, i.e., hydrogenation vs dehydrogenation, under the reaction conditions. This difference can be rationalized in terms of the difference in resonance energies between the indole and isoindole systems.

Experimental Section

Computational Methods. All calculations were performed with gradient-corrected hybrid density functional theory (DFT) using the Gaussian 03 suite of programs[23] on a PC cluster at the National Center for High-Performance Computing (Taiwan). The B3LYP density functional (Becke's three-parameter exchange functional[24] and the Lee−Yang−Parr gradient-corrected correlation functional[25]) was employed. All calculations used the moderate-sized 6-31G-(d,p) basis set.[26]

(1-Methyl-1,3-dihydroisoindol-2-yl)acetic Acid Methyl Ester (5a). Potassium carbonate (0.93 g, 10.2 mmol) was added to the solution of **4a** (0.373 g, 1.34 mmol) and glycine methyl ester hydrochloride (0.215 g, 1.61 mmol)in acetonitrile (3 mL). The reaction mixture was heated at reflux for 16 h, filtered, and concentrated to give the crude product. Pure **5a** (0.15 g, 0.75 mmol, 56%) was isolated after column chromatography (SiO_2; hexane/ethyl acetate, 1:1; R_f 0.60). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.37 (d, $J = 6.3$ Hz, 3H), 3.47 (d, $J = 16.8$ Hz, 1H), 3.70 (s, 3H), 3.72 (d, $J = 16.8$ Hz, 1H), 3.87 (dd, $J = 12.6$ Hz, $J = 2.5$ Hz, 1H), 4.02−4.08 (m, 1H), 4.38 (dd, $J = 12.6$ Hz, $J = 1.7$ Hz, 1H), 7.02−7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.4, 143.8, 138.8, 126.7, 126.6, 122.0, 121.6, 62.8, 57.9, 53.1, 51.4, 18.6; HRMS (FAB) calcd for $[M + H]^+$ ($C_{12}H_{16}NO_2$) 206.1181, found 206.1180.

***trans*-(1,3-Dimethyl-1,3-dihydroisoindol-2-yl)acetic Acid Methyl Ester (5b).** The procedure to prepare **5a** was followed. Starting with **4b** (39 mg, 0.134 mmol) and glycine methyl ester hydrochloride (21 mg, 0.167 mmol), **5b** (15.8 mg, 0.072 mmol, 54%) was isolated after column chromatography (SiO_2; hexane/ethyl acetate, 3:1; R_f 0.40). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.26 (d, $J = 6.5$ Hz, 3H), 3.60 (d, $J = 17.0$ Hz, 1H), 3.65 (d, $J = 17.0$ Hz, 1H), 3.74 (s, 3H), 4.40 (q, $J = 6.0$ Hz, 2H), 7.12−7.13 (m, 2H), 7.18−7.20 (m, 2H); ^1H NMR ($CDCl_3$ + one drop of triflouroacetic acid, 300 MHz) δ 1.56 (d, $J = 6.9$ Hz, 3H), 1.78 (d, $J = 6.6$ Hz, 3H), 3.83 (s, 3H), 4.06 (d, $J = 17.0$ Hz, 1H), 4.16 (d, $J = 17.0$ Hz, 1H), 4.74 (q, $J = 6.6$ Hz, 1H), 5.54 (q, $J = 6.9$ Hz, 1H), 7.20−7.30 (m, 2H), 7.40−7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.2, 143.8, 126.9, 121.8, 60.5, 51.8, 48.8, 17.3; HRMS (FAB) calcd for $[M + H]^+$ ($C_{13}H_{18}$ NO_2) 220.1338, found 220.1339.

(5-Methoxy-1,3-dihydroisoindol-2-yl)acetic Acid Methyl Ester (5c). The procedure to prepare **5a** was followed. Starting with **4c** (0.6 g, 2.04 mmol) and glycine methyl ester hydrochloride (0.26 g, 2.04 mmol), **5c** (0.10 g, 0.47 mmol, 22%) was isolated after column chromatography (SiO_2; hexane/ethyl acetate, 1:1; R_f 0.53). ^1H NMR ($CDCl_3$, 200 MHz) δ 3.56 (s, 2H), 3.70 (s, 3H), 3.73 (s, 3H), 4.00 (s, 2H), 4.03 (s, 2H), 6.58−6.75 (m, 2H), 7.03 (d, $J = 8.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.1, 158.9, 141.0, 131.6, 122.7, 112.6, 107.7, 58.8, 58.1, 55.9, 55.3, 51.5; HRMS (FAB) calcd for $[M + H]^+$ ($C_{12}H_{16}O_3N$) 222.1130, found 222.1127.

2-Methoxycarbonylmethyl-2,3-dihydro-1*H*-isoindole-5-carboxylic Acid Methyl Ester (5d). The procedure to prepare **5a** was followed. Starting with **4d** (1.20 g, 3.71 mmol) and glycine methyl ester hydrochloride (0.512 g, 4.08 mmol), **5d** (0.368 g, 1.48 mmol, 40%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 1:1; R_f 0.40). ^1H NMR ($CDCl_3$, 500 MHz) δ 3.60 (s, 2H), 3.72 (s, 3H), 3.86 (s, 3H), 4.12 (s, 4H), 7.21 (d, $J = 7.7$ Hz, 1H), 7.83 (s, 1H), 7.87 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 167.0, 145.1, 140.1, 129.0, 128.6, 123.5, 122.2, 58.5, 58.2, 55.6, 52.0, 51.8; HRMS (FAB) calcd for $[M + H]^+$ ($C_{13}H_{16}O_4$ N) 250.1079, found 250.1085.

5-Methyl-2-(3-phenoxypropyl)isoindole-1,3-dione (7b). 4-Methylphthalic anhydride (**6b**) (1.73 g, 10.68 mmol) was dissolved in

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[21] (a) Kreher, R. P.; Seubert, J.; Schmitt, D.; Use, G.; Koh, N.; Muleta, T. *Chem. Ber.* **1990**, *123*, 381. (b) Kreher, R. P.; Sewarte-Ross, G.; Vogt, G. *Chem. Ber.* **1992**, *125*, 183. (c) Malpass, J. R.; Sun, G.; Fawcett, J.; Warrener, R. N. *Tetrahedron Lett.* **1998**, *39*, 3083.

[22] Martínez, A.; Vázquez, M. V.; Carreón-Macedo, J. L.; Sansores, L. E.; Salcedo, R. *Tetrahedron* **2003**, *59*, 6415.

[23] Frisch, M. J.; Trucks, G. W..; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03* (Revision B02); Gaussian, Inc.: Pittsburgh, PA, 2003.

[24] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

[25] Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

[26] Petersson, G. A.; Al-Laham, M. A. *J. Chem. Phys.* **1991**, *94*, 6081.

toluene (12 mL) at 80 °C, 3-phenoxypropanamine[8] (1.78 g, 11.8 mmol) was added dropwise, and the resulting solution was heated at reflux in an apparatus fitted with a Dean−Stark trap. After about 16 h, the reaction mixture was concentrated to give the crude phthalimide. This was further purified by column chromatography (SiO_2; ethyl acetate/hexanes, 1:1; R_f 0.63) to give pure **7b** as a colorless solid (2.9 g, 9.8 mmol, 91%). Mp 102−104 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.15 (m, 2H), 2.49 (s, 3H), 3.87 (t, $J = 6.9$ Hz, 2H), 4.00 (t, $J = 6.1$ Hz, 2H), 6.79−6.95 (m, 3H), 7.19−7.28 (m, 2H), 7.48 (d, $J = 7.6$ Hz, 1H), 7.62 (s, 1H), 7.69 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6, 168.4, 158.7, 145.1, 134.4, 132.5, 129.5, 129.3, 123.8, 123.1, 120.7, 114.4, 65.5, 35.4, 28.4, 22.0; HRMS (FAB) calcd for $[M + H]^+$ ($C_{18}H_{18}NO_3$) 296.1287, found 296.1291; IR (neat) 2942, 2930, 1695, 1610, 1500, 1450, 1250, 1050, 840, 750, 700 cm^{-1}.

4-Methyl-2-(3-phenoxypropyl)isoindole-1,3-dione (7a). The procedure to prepare **7b** was followed. Starting with **6a** (0.05 g, 0.34 mmol) and 3-phenoxypropanamine (0.06 g, 0.37 mmol), **7a** (0.07 g, 0.24 mmol, 71%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 3:1; R_f 0.50). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.16 (m, 2H), 2.65 (s, 3H), 3.87 (t, $J = 7.0$ Hz, 2H), 4.01 (t, $J = 6.0$ Hz, 2H), 6.72−6.98 (m, 3H), 7.11−7.29 (m, 2H), 7.40−7.73 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.2, 168.5, 158.7, 137.9, 136.3, 133.4, 132.5, 129.4, 128.8, 120.9, 120.7, 114.5, 65.6, 35.3, 28.4, 17.6; HRMS (FAB) calcd for $[M + H]^+$ ($C_{18}H_{18}NO_3$) 296.1287, found 296.1292.

4-Hydroxy-2-(3-phenoxypropyl)isoindole-1,3-dione (7c). The procedure to prepare **7b** was followed. Starting with **6c** (0.11 g, 0.70 mmol) and 3-phenoxypropanamine (0.12 g, 0.77 mmol), **7c** (0.20 g, 0.66 mmol, 94%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 3:1; R_f 0.23). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.15 (m, 2H), 3.84 (t, $J = 6.8$ Hz, 2H), 4.00 (t, $J = 6.0$ Hz, 2H), 6.77−6.94 (m, 3H), 7.11−7.37 (m, 4H), 7.52−7.70 (m, 1H), 7.60 (br, 1H, OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.4, 167.9, 158.6, 154.6, 136.3, 132.1, 129.4, 122.6, 120.8, 115.9, 114.6, 114.4, 65.4, 35.3, 28.2; HRMS (FAB) calcd for $[M + H]^+$ ($C_{17}H_{16}NO_4$) 298.1079, found 298.1085.

5-Fluoro-2-(3-phenoxypropyl)isoindole-1,3-dione (7d). The procedure to prepare **7b** was followed. Starting with **6d** (0.73 g, 4.4 mmol) and 3-phenoxypropanamine (0.80 g, 5.3 mmol), **7d** (1.13 g, 3.78 mmol, 86%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 3:1; R_f 0.60). Mp 106−108 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.15 (m, 2H), 3.89 (t, $J = 6.9$ Hz, 2H), 4.00 (t, $J = 6.0$ Hz, 2H), 6.70−6.90 (m, 3H), 7.10−7.25 (m, 2H), 7.30−7.40 (m, 1H), 7.49 (dd, $J = 7.0$ Hz, $J = 2.2$ Hz, 1H), 7.82 (dd, $J = 8.2$ Hz, $J = 4.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4, 167.3, 166.1 ($J_{C-F} = 204$ Hz), 158.6, 135.0 ($J_{C-F} = 9.5$ Hz), 129.4, 127.9, 125.6 ($J_{C-F} = 9.1$ Hz), 121.0, 120.8, 114.4, 111.1 ($J_{C-F} = 24.8$ Hz), 65.5, 35.8, 28.2; HRMS (FAB) calcd for $[M + H]^+$ ($C_{17}H_{15}FNO_3$) 300.1036, found 300.1031; IR (neat) 2930, 1700, 1610, 1500, 1450, 1250, 1050, 850, 750, 700 cm^{-1}

4,5,6,7-Tetrachloro-2-(3-phenoxypropyl)isoindole-1,3-dione (7e). The procedure to prepare **7b** was followed. Starting with **6e** (1.04 g, 3.65 mmol) and 3-phenoxypropanamine (0.66 g, 4.4 mmol), **7e** (1.36 g, 3.24 mmol, 89%) was isolated after solvent evaporation. Mp 182−187 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.17 (m, 2H), 3.91 (t, $J = 6.9$ Hz, 2H), 4.02 (t, $J = 5.9$ Hz, 2H), 6.77 (d, $J = 7.9$ Hz, 2H), 6.90 (t, $J = 7.3$ Hz, 1H), 7.17−7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.6, 158.5, 140.0, 129.6, 129.4, 127.7, 120.9, 114.4, 65.4, 36.5, 27.9; HRMS (FAB) calcd for $[M]^+$ ($C_{17}H_{11}Cl_4NO_3$) 416.9493, found 416.9502; IR (neat) 1717, 1250, 1110, 1060, 1050, 750, 700 cm^{-1}.

4-Nitro-2-(3-phenoxypropyl)isoindole-1,3-dione (7f). The procedure to prepare **7b** was followed. Starting with **6f** (0.77 g, 4.0 mmol) and 3-phenoxypropanamine (0.67 g, 4.4 mmol), **7f** (0.87 g, 2.7 mmol, 66%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 1:1; R_f 0.57). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.18 (m, 2H), 3.92 (t, $J = 6.9$ Hz, 2H), 4.01 (t, $J = 5.9$ Hz, 2H), 6.72−6.92 (m, 3H), 7.15−7.24 (m, 2H), 7.83−8.10 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.8, 162.9, 158.5, 145.0, 135.2, 134.1, 129.3, 128.4, 126.9, 123.8, 120.8, 114.3, 65.4, 36.3, 27.9; HRMS (FAB) calcd for $[M + H]^+$ ($C_{17}H_{15}N_2O_5$) 327.0981, found 327.0984.

5-Nitro-2-(3-phenoxypropyl)isoindole-1,3-dione (7g). The procedure to prepare **7b** was followed. Starting with **6g** (0.50 g, 2.6 mmol) and 3-phenoxypropanamine (0.43 g, 2.7 mmol), **7g** (0.56 g, 1.7 mmol, 65%) was isolated after column chromatography (SiO_2; CH_2Cl_2; R_f 0.67). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.19 (m, 2H), 3.95 (t, $J = 6.9$ Hz, 2H), 4.02 (t, $J = 5.9$ Hz, 2H), 6.71−7.00 (m, 3H), 7.05−7.30 (m, 2H), 8.00 (d, $J = 8.0$ Hz, 1H), 8.45−8.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.2, 165.9, 158.5, 151.7, 136.5, 133.5, 129.4, 129.2, 124.4, 120.9, 118.6, 114.3, 65.4, 36.3, 28.0; HRMS (FAB) calcd for $[M + H]^+$ ($C_{17}H_{15}N_2O_5$) 327.0981, found 327.0972.

4-Methoxy-2-(3-phenoxypropyl)isoindole-1,3-dione (7h). To a solution of phthalimide **7c** (0.20 g, 0.66 mmol) and potassium carbonate (0.45 g, 3.3 mmol) in acetone (3 mL) was added methyl iodide (0.19 g, 1.3 mmol). The reaction mixture was refluxed for 16 h, then cooled to rt, filtered, and concentrated to give the crude product. This was further purified by column chromatography (SiO_2; ethyl acetate/ hexanes, 1:1; R_f 0.67) to give pure **7h** as a colorless solid (0.18 g, 0.59 mmol, 90%). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.13 (m, 2H), 3.83 (t, $J = 6.9$ Hz, 2H), 3.90−4.05 (m, 5H), 6.70−6.95 (m, 3H), 7.05−7.25 (m, 3H), 7.37 (d, $J = 7.3$ Hz, 1H), 7.55−7.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.9, 166.9, 158.6, 156.4, 135.9, 134.1, 129.2, 120.6, 117.3, 115.3, 114.4, 65.4, 56.2, 35.1, 28.2; HRMS (FAB) calcd for $[M + H]^+$ ($C_{18}H_{18}NO_4$) 312.1236, found 312.1240.

5-Methyl-2-(3-phenoxypropyl)-2,3-dihydro-1*H*-isoindole (8b). A solution of phthalimide **7b** (1.0 g, 3.4 mmol) in anhydrous ether (8 mL) was added dropwise to a suspension of lithium aluminum hydride (0.39 g, 12 mmol) and ether (2 mL) in a flame-dried flask at 0 °C. After the addition, the reaction mixture was heated at reflux for 3 h, then quenched with water (1 mL) and sat. K_2CO_3(aq) (4 mL) to form a gray-white precipitate. The liquid was decanted, and the solid was further washed with ethyl acetate (9 mL). The organic solution was combined, concentrated, and purified with column chromatography (SiO_2; ethyl acetate/hexanes, 1:3; R_f 0.23) to give pure **8b** as a light brown solid (0.65 g, 2.4 mmol, 70%). Mp 46−48 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.08 (m, 2H), 2.32 (s, 3H), 2.91 (t, $J = 7.3$ Hz, 2H), 3.92 (s, 4H), 4.08 (t, $J = 6.4$ Hz, 2H), 6.85−6.94 (m, 3H), 6.95−7.05 (m, 2H), 7.07 (d, $J = 7.5$ Hz, 1H), 7.24−7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.0, 140.0, 136.8, 136.4, 129.4, 127.5, 122.9, 122.0, 120.5, 114.5, 65.9, 59.1, 58.9, 52.8, 28.7, 21.3; HRMS (FAB) calcd for $[M + H]^+$ ($C_{18}H_{22}NO$) 268.1701, found 268.1703; IR (neat) 3017, 2947, 2930, 2876, 2791, 1600, 1497, 1468, 1450, 1250, 1050, 860, 750, 700 cm^{-1}.

4-Methyl-2-(3-phenoxypropyl)-2,3-dihydro-1*H*-isoindole (**8a**). The procedure to prepare **8b** was followed. Starting with **7a** (0.07 g, 0.24 mmol) and LAH (0.03 g, 0.73 mmol), **8a** (0.05 g, 0.17 mmol, 70%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 1:1; R_f 0.42). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.09 (m, 2H), 2.25 (s, 3H), 2.93 (t, $J = 7.0$ Hz, 2H), 3.93 (s, 2H), 3.98 (s, 2H), 4.10 (t, $J = 6.4$ Hz, 2H), 6.80−7.18 (m, 6H), 7.20−7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.0, 140.0, 138.9, 132.0, 129.4, 127.6, 126.9, 120.5, 119.5, 114.5, 65.9, 59.4, 58.1, 52.8, 28.8, 18.7; HRMS (FAB) calcd for $[M + H]^+$ ($C_{18}H_{22}NO$) 268.1701, found 268.1705.

5-Fluoro-2-(3-phenoxypropyl)-2,3-dihydro-1*H*-isoindole (8d). The procedure to prepare **8b** was followed. Starting with **7d** (0.68 g, 2.3 mmol) and LAH (0.30 g, 8.0 mmol), **8d** (0.37 g, 1.36 mmol, 60%) was isolated after column chromatography (SiO_2; hexanes/ ethyl acetate, 3:1; R_f 0.23). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.06 (m, 2H), 2.91 (t, $J = 7.0$ Hz, 2H), 3.85−3.98 (br, 4H), 4.08 (t, $J = 6.3$ Hz, 2H), 6.80−7.00 (m, 5H), 7.05−7.18 (m, 1H), 7.20−7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.2 ($J_{C-F} = 241.6$ Hz), 159.0, 142.2 ($J_{C-F} = 8.5$ Hz), 135.5 ($J_{C-F} = 2.5$ Hz), 129.5, 123.3 ($J_{C-F} = 8.7$ Hz), 120.6, 114.5, 113.6 ($J_{C-F} = 22.5$ Hz), 109.6

(J_{C-F} = 23.0 Hz), 65.9, 59.1 (J_{C-F} = 2.4 Hz), 58.5, 52.7, 28.8; HRMS (FAB) calcd for $[M + H]^+$ ($C_{17}H_{19}FNO$) 272.1451, found 272.1452.

4,5,6,7-Tetrachloro-2-(3-phenoxypropyl)-2,3-dihydro-1*H*-isoindole (**8e**). The procedure to prepare **8b** was followed. Starting with **7e** (0.50 g, 1.2 mmol) and LAH (0.14 g, 3.6 mmol), **8e** (0.15 g, 0.39 mmol, 33%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 3:1; R_f 0.67). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.04 (m, 2H), 2.91 (t, J = 7.1 Hz, 2H), 3.95−4.15 (m, 6H), 6.80−7.00 (m, 3H), 7.20−7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.9, 139.2, 130.9, 129.4, 126.6, 120.7, 114.5, 65.4, 59.7, 52.2, 28.6; HRMS (FAB) calcd for $[M + H]^+$ ($C_{17}H_{16}Cl_4NO$) 389.9986, found 389.9978.

4-Methoxy-2-(3-phenoxypropyl)-2,3-dihydro-1*H*-isoindole (**8h**). The procedure to prepare **8b** was followed. Starting with **7h** (0.18 g, 0.59 mmol) and LAH (0.07 g, 1.8 mmol), **8h** (0.11 g, 0.40 mmol, 67%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 3:1; R_f 0.50). ^1H NMR ($CDCl_3$, 500 MHz) δ 2.05 (m, 2H), 2.90 (t, J = 7.0 Hz, 2H), 3.80 (s, 3H), 3.94 (s, 2H), 3.96 (s, 2H), 4.08 (t, J = 6.4 Hz, 2H), 6.69 (d, J = 8.2 Hz, 1H), 6.80 (d, J = 3.8 Hz, 1H), 6.88−6.95 (m, 3H), 7.14−7.20 (m, 1H), 7.22−7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 154.6, 142.0, 129.4, 128.3, 127.7, 120.6, 114.7, 114.6, 108.6, 66.0, 59.6, 56.4, 55.3, 52.8, 28.8; HRMS (FAB) calcd for $[M + H]^+$ ($C_{18}H_{22}NO_2$) 284.1651, found 284.1649.

4-Amino-2-(3-phenoxypropyl)-isoindole-1,3-dione (9f). Palladium on carbon (5%, 85 mg) was added to the solution of **7f** (0.13 g, 0.39 mmol) in methanol (4 mL) and DMF (1 mL). Hydrogen gas was bubbled through the reaction mixture at rt for 14 h. The solution was filtered and concentrated. The crude product was further purified by column chromatography (SiO_2; ethyl acetate/hexanes, 1:1; R_f 0.75) to give pure **9f** as a light yellow solid (0.11 g, 0.37 mmol, 94%). Mp 77−79 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.13 (m, 2H), 3.82 (t, J = 6.8 Hz, 2H), 3.99 (t, J = 6.1 Hz, 2H), 5.23 (br, 2H), 6.68−6.98 (m, 4H), 7.05−7.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.1, 168.6, 158.6, 145.2, 135.0, 132.7, 129.3, 120.9, 120.6, 114.4, 112.5, 111.2, 65.4, 34.9, 28.4; HRMS (FAB) calcd for $[M + H]^+$ ($C_{17}H_{17}N_2O_3$) 297.1239, found 297.1240.1

5-Amino-2-(3-phenoxypropyl)isoindole-1,3-dione (9g). The procedure to prepare **9f** was followed. Starting with **7g** (0.38 g, 1.2 mmol), **9g** (0.34 g, 1.13 mmol, 97%) was isolated after column chromatography (SiO_2; ethyl acetate; R_f 0.77). Mp 107−110 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.15 (m, 2H), 3.84 (t, J = 7.0 Hz, 2H), 4.01 (t, J = 6.2 Hz, 2H), 4.36 (br, 2H), 6.67−7.07 (m, 5H), 7.12−7.32 (m, 2H), 7.58 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.6, 168.5, 158.7, 152.2, 134.9, 129.3, 125.0, 120.7, 120.6, 117.8, 114.5, 108.5, 65.5, 35.1, 28.5; HRMS (FAB) calcd for $[M + H]^+$ ($C_{17}H_{17}N_2O_3$) 297.1239, found 297.1242.

***N*-[1,3-Dioxo-2-(3-phenoxypropyl)-2,3-dihydro-1*H*-isoindol-4-yl]acetamide (10f)**. Acetyl chloride (0.16 g, 2.1 mmol) in acetonitrile (5 mL) was added to the mixture of **9f** (0.51 g, 1.7 mmol) and potassium carbonate (0.60 g, 4.3 mmol) in acetonitrile (7 mL). The reaction mixture was stirred at rt for 16 h, filtered, concentrated, and purified by flash column chromatography (SiO_2; hexanes/ethyl acetate, 1:1; R_f 0.50) to give pure **10f** (0.43 g, 1.3 mmol, 74%) as a light yellow solid. Mp 115−118 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.15 (m, 2H), 2.22 (s, 3H), 3.86 (t, J = 6.8 Hz, 2H), 4.01 (t, J = 5.8 Hz, 2H), 6.63−6.97 (m, 3H), 7.10−7.30 (m, 2H), 7.40−7.70 (m, 2H), 8.73 (d, J = 8.4 Hz, 1H), 9.45 (br, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.2, 169.2, 167.8, 158.6, 137.3, 135.8, 131.6, 129.4, 124.6, 120.8, 117.9, 115.7, 114.4, 65.5, 35.6, 28.2, 24.9; HRMS (FAB) calcd for $[M + H]^+$ ($C_{19}H_{19}N_2O_4$) 339.1345, found 339.1349.

***N*-[1,3-Dioxo-2-(3-phenoxypropyl)-2,3-dihydro-1*H*-isoindol-5-yl]acetamide (10g).** The procedure to prepare **10f** was followed. Starting with **9g** (0.19 g, 0.65 mmol), **10g** (0.21 g, 0.61 mmol, 93%) was produced as a light yellow solid. ^1H NMR ($CDCl_3$, 200 MHz) δ 2.12 (m, 2H), 2.24 (s, 3H), 3.87 (t, J = 7.0 Hz, 2H), 4.00 (t, J = 6.0 Hz, 2H), 6.72−6.95 (m, 3H), 7.15−7.30 (m, 2H), 7.63 (br, 1H), 7.76 (d, J = 8.6 Hz, 1H), 7.90−8.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.8, 168.2, 167.9, 158.6, 143.6, 133.6, 129.4, 126.7, 124.5, 123.7, 120.8, 114.4, 113.9, 65.5, 35.6, 28.3, 24.7; HRMS (FAB) calcd for $[M + H]^+$ ($C_{19}H_{19}N_2O_4$) 339.1345, found 339.1343.

Ethyl-[2-(3-phenoxypropyl)-2,3-dihydro-1*H*-isoindol-4-yl]-amine (11f). The procedure to prepare **8b** was followed. Starting with **10f** (0.43 g, 1.26 mmol) and LAH (0.14 g, 3.79 mmol), **11f** (0.29 g, 0.99 mmol, 78%) was produced after column chromatography (SiO_2; ethyl acetate; R_f 0.47). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.21 (t, J = 6.9 Hz, 3H), 2.02 (m, 2H), 2.86 (t, J = 7.0 Hz, 2H), 3.13 (q, J = 7.1 Hz, 2H), 3.15 (br, 1H, NH), 3.75 (s, 2H), 3.91 (s, 2H), 4.04 (t, J = 6.4 Hz, 2H), 6.43 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 7.3 Hz, 1H), 6.80−6.97 (m, 3H), 7.00−7.13 (m, 1H), 7.18−7.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.0, 143.1, 140.6, 129.4, 128.3, 124.2, 120.5, 114.5, 111.2, 108.5, 65.9, 59.8, 56.6, 52.8, 38.4, 28.8, 15.0; HRMS (FAB) calcd for $[M + H]^+$ ($C_{19}H_{25}N_2O$) 297.1967, found 297.1968.

***N*-Ethyl,*N*-[2-(3-phenoxypropyl)-2,3-dihydro-1*H*-isoindol-5-yl]amine (11g)**. The procedure to prepare **8b** was followed. Starting with **10g** (0.05 g, 0.13 mmol) and LAH (0.02 g, 0.40 mmol), **11g** (0.04 g, 0.12 mmol, 94%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 1:1; R_f 0.27). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.23 (t, J = 7.0 Hz, 3H), 2.04 (m, 2H), 2.89 (t, J = 7.2 Hz, 2H), 3.13 (q, J = 7.2 Hz, 2H), 3.14 (br, NH), 3.86 (s, 2H), 3.88 (s, 2H), 4.08 (t, J = 6.4 Hz, 2H), 6.46 (m, 2H), 6.85−7.03 (m, 4H), 7.20−7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.0, 147.8, 141.2, 129.4, 128.7, 122.7, 120.5, 114.5, 111.8, 106.7, 66.0, 59.4, 58.7, 52.9, 38.8, 28.8, 14.9; HRMS (FAB) calcd for $[M + H]^+$ ($C_{19}H_{25}N_2O$) 297.1967, found 297.1967.

***N*-Ethyl,*N*-[2-(3-phenoxypropyl)-2,3-dihydro-1*H*-isoindol-4-yl]acetamide (12f)**. The procedure to prepare **10f** was followed. Starting with **11f** (0.23 g, 0.78 mmol) and acetyl chloride (0.12 g, 1.6 mmol), **12f** (0.21 g, 0.63 mmol, 81%) was produced. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 (t, J = 7.1 Hz, 3H), 1.80 (s, 3H), 2.05 (m, 2H), 2.92 (m, 2H), 3.29−3.50 (m, 1H), 3.80−4.15 (m, 7H), 6.75−7.00 (m, 4H), 7.08−7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.8, 158.8, 142.5, 138.1, 137.2, 129.3, 128.3, 126.8, 122.1, 120.6, 114.4, 65.6, 59.3, 57.3, 52.6, 42.7, 28.6, 22.4, 13.1; HRMS (FAB) calcd for $[M + H]^+$ ($C_{21}H_{27}N_2O_2$) 339.2073, found 339.2079.

***N*-Ethyl,*N*-[2-(3-phenoxypropyl)-2,3-dihydro-1*H*-isoindol-5-yl]acetamide (12g).** The procedure to prepare **10f** was followed. Starting with **11g** (0.19 g, 0.65 mmol) and acetyl chloride (0.10 g, 1.3 mmol), **12f** (0.21 g, 0.61 mmol, 94%) was produced. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.07 (t, J = 7.1 Hz, 3H), 1.79 (s, 3H), 2.06 (m, 2H), 2.93 (m, 2H), 3.70 (q, J = 7.1 Hz, 2H), 3.96 (s, 4H), 4.08 (t, J = 6.3 Hz, 2H), 6.75−7.05 (m, 5H), 7.15−7.36 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.0, 158.9, 141.8, 141.7, 139.8, 129.4, 126.8, 123.3, 122.1, 120.6, 114.5, 65.8, 58.9, 58.7, 52.6, 43.8, 28.7, 22.8, 13.0; HRMS (FAB) calcd for $[M + H]^+$ ($C_{21}H_{27}N_2O_2$) 339.2073, found 339.2079.

***N*,*N*-Diethyl,*N*-[2-(3-phenoxypropyl)-2,3-dihydro-1*H*-isoindol-4-yl]amine (13f)**. The procedure to prepare **8b** was followed. Starting with **12f** (0.15 g, 0.42 mmol) and LAH (0.02 g, 0.42 mmol), **13f** (0.68 g, 0.21 mmol, 50%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 1:1 and Et_3N, 2%; R_f 0.62). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.04 (t, J = 7.0 Hz, 3H), 2.09 (m, 2H), 2.92 (m, 2H), 3.11 (q, J = 7.0 Hz, 4H), 3.94 (s, 4H), 4.10 (t, J = 6.4 Hz, 2H), 6.75−7.00 (m, 5H), 7.09−7.36 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.0, 145.8, 141.6, 132.7, 129.3, 127.3, 120.5, 117.4, 115.1, 114.5, 66.0, 59.5, 58.8, 52.8, 45.9, 28.8, 12.6; HRMS (FAB) calcd for $[M + H]^+$ ($C_{21}H_{29}N_2O$) 325.2280, found 325.2274.1

***N*,*N*-Diethyl,*N*-[2-(3-phenoxypropyl)-2,3-dihydro-1*H*-isoindol-5-yl]amine (13g)**. The procedure to prepare **8b** was followed. Starting with **12g** (0.11 g, 0.34 mmol) and LAH (0.01 g, 0.34 mmol), **13g** (0.03 g, 0.09 mmol, 26%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 1:1 and Et_3N, 2%; R_f 0.43). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.13 (t, J = 7.0 Hz, 3H), 2.06 (m, 2H), 2.89 (m, 2H), 3.31 (q, $J = 7.0$ Hz, 4H), 3.86 (s, 2H), 3.90 (s, 2H), 4.09 (t, $J = 6.4$ Hz, 2H), 6.50−6.63 (m, 2H), 6.90−7.09 (m, 4H), 7.17−7.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.0, 147.3, 141.2, 129.4, 127.2, 122.7, 120.5, 114.5, 111.2, 106.4, 66.0, 59.7, 58.6, 52.9, 44.7, 28.8, 12.5; HRMS (FAB) calcd for $[M + H]^+$ ($C_{21}H_{29}N_2O$) 325.2280, found 325.2272.

2-*tert*-Butyl-2,3-dihydro-1*H*-isoindole (18). The procedure to prepare **5a** was followed. Starting with α,α′-dibromo-*o*-xylene (0.51 g, 1.9 mmol) and *tert*-butylamine (0.17 g, 2.3 mmol), compound **18** (0.31 g, 1.8 mmol, 92%) was isolated after column chromatography (SiO_2; hexane/ethyl acetate, 1:1; R_f 0.20). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.18 (s, 9H), 4.04 (s, 4H), 7.18 (s, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.9, 126.5, 122.4, 52.6, 52.0, 26.0; HRMS (FAB) calcd for $[M + H]^+$ ($C_{12}H_{18}N$) 176.1439, found 176.1440.

(1-Methyl-4,5,6,7-tetrahydro-isoindol-2-yl)acetic Acid Methyl Ester (16a). A solution of **5a** (80 mg, 0.39 mmol), palladium hydroxide on carbon (20%, 28 mg, 0.04 mmol), and ammonium formate (0.25 g, 3.90 mmol) in methanol (1 mL) was heated at reflux for 14 h. After being cooled to rt, the reaction mixture was diluted with ethyl acetate (5 mL), filtered, and concentrated. The crude product was further purified by column chromatography (SiO_2; hexane/ethyl acetate, 3:1; R_f 0.50) to give **16a** (75 mg, 0.36 mmol, 93%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.64−1.75 (m, 5H), 2.01 (s, 3H), 2.40−2.58 (m, 4H), 3.73 (s, 3H), 4.47 (s, 2H), 6.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.7, 119.5, 116.7, 115.4, 52.4, 48.0, 24.0, 23.9, 21.9, 21.7, 9.2; HRMS (FAB) calcd for $[M + H]^+$ ($C_{12}H_{18}NO_2$) 208.1338, found 208.1335.

(1,3-Dimethyl-4,5,6,7-tetrahydro-isoindol-2-yl)acetic Acid Methyl Ester (16b). The procedure to prepare **16a** was followed. Starting with **5b** (51 mg, 0.23 mmol), **16b** (46 mg, 0.21 mmol, 90%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 9:1; R_f 0.33). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.65−1.74 (m, 4H), 2.03 (s, 3H), 2.37−2.48 (m, 4H), 3.74 (s, 3H), 4.46 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.8, 121.2, 115.4, 52.3, 44.8, 24.1, 21.6, 9.5; HRMS (FAB) calcd for $[M]^+$ ($C_{12}H_{19}NO_2$) 221.1416, found 221.1407.

(5-Methoxy-4,5,6,7-tetrahydroisoindol-2-yl)acetic Acid Methyl Ester (16c). The procedure to prepare **16a** was followed. Starting with **5c** (66 mg, 0.30 mmol) and ammonium formate (380 mg, 6.0 mmol), **16c** (16 mg, 0.07 mmol, 24%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 3:1; R_f 0.30) and **5c** (22 mg, 0.09 mmol) was recovered. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.70−1.80 (m, 1H), 2.00−2.10 (m, 1H), 2.50−2.60 (m, 2H), 2.70−2.79 (m, 1H), 2.90−3.00 (m, 1H), 3.41 (s, 3H), 3.75 (s, 3H), 6.33 (s, 1H), 6.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 119.8, 118.8, 118.0, 117.4, 77.7, 56.3, 55.6, 52.8, 51.0, 29.0, 28.5, 19.9; HRMS (FAB) calcd for $[M]^+$ ($C_{12}H_{17}NO_3$) 223.1208, found 223.1203.

4-Methyl-2-(3-phenoxypropyl)-4,5,6,7-tetrahydro-2*H*-isoindole (17a). The procedure to prepare **16a** was followed. Starting with **8a** (30 mg, 0.11 mmol), **17a** (22 mg, 0.08 mmol, 71%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 9:1; R_f 0.50). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.15 (d, $J = 6.8$ Hz, 3H), 1.20−1.30 (m, 1H), 1.53−1.65 (m, 1H), 1.82−1.90 (m, 2H), 2.18 (m, 2H), 2.43−2.74 (m, 3H), 3.93 (t, $J = 5.95$ Hz, 2H), 4.00 (t, $J = 6.8$ Hz, 2H), 6.31 (s, 1H), 6.38 (s, 1H), 6.88−6.996 (m, 3H), 7.24−7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.5, 129.5, 126.1, 120.8, 119.3, 116.0, 115.8, 114.5, 64.5, 46.0, 33.4, 31.4, 28.5, 23.4, 22.2, 22.0; HRMS (FAB) calcd for $[M + H]^+$ ($C_{18}H_{24}NO$) 270.1858, found 270.1859.

5-Methyl-2-(3-phenoxypropyl)-4,5,6,7-tetrahydro-2*H*-isoindole (17b). The procedure to prepare **16a** was followed. Starting with **8b** (44 mg, 0.16 mmol), **17b** (23 mg, 0.09 mmol, 53%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 9:1; R_f 0.57) along with starting material (8.3 mg, 0.03 mmol, 20%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (d, $J = 6.5$ Hz, 3H), 1.29−1.39 (m, 1H), 1.71−1.85 (m, 2H), 2.07−2.21 (m, 3H), 2.47−2.70 (m, 3H), 3.93 (t, $J = 5.9$ Hz, 2H), 3.99 (t, $J = 6.8$ Hz, 2H), 6.32 (s, 1H), 6.33 (s, 1H), 6.88−7.00 (m, 3H), 7.27−7.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.7, 129.4, 120.8, 119.9, 119.2, 116.0, 115.9, 114.5, 64.4, 45.9, 32.6, 31.4, 30.7, 30.4, 22.2, 21.7; HRMS (FAB) calcd for $[M + H]^+$ ($C_{18}H_{24}NO$) 270.1858, found 270.1852; IR (neat) 3038, 2909, 1680, 1244, 1601, 1497, 1394, 1045, 810, 754, 692, cm^{-1}.

2-*tert*-Butyl-4,5,6,7-tetrahydro-2*H*-isoindole (19). The procedure to prepare **16a** was followed. Starting with **18** (34 mg, 0.20 mmol), **19** (33 mg, 0.19 mmol, 95%) was isolated. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.49−1.55 (s, 9H), 1.66−1.80 (m, 4H), 2.48−2.69 (m, 4H), 6.51 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 118.7, 113.0, 54.2, 30.8, 24.2, 22.0; HRMS (FAB) calcd for $[M]^+$ ($C_{12}H_{19}N$) 177.1517, found 177.1521.

2-(3-Phenoxypropyl)-4,5,6,7-tetrahydro-isoindole-1,3-dione (20b). *N*-Bromosuccinimide (91 mg, 0.51 mmol) was added to a solution of **1b** (52 mg, 0.20 mmol) in CH_2Cl_2 (10 mL) at rt. The reaction mixture was stirred at rt for 2 h, washed with sat. Na_2SO_3(aq) (5 mL), water (10 mL × 2), dried over Na_2SO_4(s), filtered, and concentrated. The crude product was further purified by column chromatography (SiO_2; hexanes/ethyl acetate, 3:1; R_f 0.65) to give **20b** (42 mg, 0.16 mmol, 80%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.67−1.76 (br, 4H), 2.01−2.08 (m, 2H), 2.26−2.32 (m, 4H), 3.62−3.70 (m, 2H), 3.88−3.98 (m, 2H), 6.69−6.73 (d, 1H), 6.81−6.94 (m, 2H), 7.20−7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.2, 158.7, 141.5, 132.2, 129.4, 120.7, 116.2, 114.5, 65.6, 34.9, 28.5, 21.3, 19.9; HRMS (FAB) calcd for $[M + H]^+$ ($C_{17}H_{20}NO_3$) 286.1443, found 286.1435.

2-Methyl-4,5,6,7-tetrahydroisoindole-1,3-dione (20c). The procedure to prepare **20b** was followed. Starting with **1c** (46 mg, 0.34 mmol) and NBS (150 mg, 0.84 mmol), compound **20c** (42 mg, 0.16 mmol, 85%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 3:1; R_f 0.66) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.71−1.75 (br, 4H), 2.27−2.32 (br, 4H), 2.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.3, 141.6, 23.4, 21.3, 19.9 HRMS (FAB) calcd for $[M + H]^+$ ($C_9H_{12}NO_2$) 166.0868, found 166.0870.

2-(2-Bromoethyl)-4,5,6,7-tetrahydroisoindole-1,3-dione (20d). The procedure to prepare **20b** was followed. Starting with **1d** (79 mg, 0.48 mmol) and NBS (213 mg, 1.20 mmol), **20d** (65.3 mg, 0.24 mmol, 50%) was isolated after column chromatography (SiO_2; hexanes/ethyl acetate, 1:1; R_f 0.83) as a light yellow oil. ^{1}H NMR (CDCl3, 200 MHz) δ 1.72 (br, 4H), 2.29 (br, 4H), 3.44 (t, $J = 6.7$ Hz, 2H), 3.83 (t, $J = 6.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.4, 141.6, 38.8, 28.5, 21.1, 19.9; HRMS (FAB) calcd for $[M + H]^+$ ($C_{10}H_{13}BrNO_2$) 258.0130, found 258.0120.

1-Ethyl-2,3-dihydro-1*H*-indole (21a). Acetyl chloride (3.95 g, 50.4 mmol) was added to a solution of indoline (1.0 g, 8.4 mmol) in acetic acid (14 mL), and the reaction mixture was refluxed for 3 h. After removing the solvent, *N*-acetyl indoline (1.34 g, 8.32 mmol, 99%) was produced. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.22 (s, 3H), 3.18 (t, $J = 8.5$ Hz, 2H), 4.03 (t, $J = 8.5$ Hz, 2H), 6.97−7.01 (m, 1H), 7.19−7.27 (m, 2H), 8.16−8.22 (d, $J = 7.8$, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.5, 142.8, 131.0, 127.4, 124.4, 123.5, 116.9, 48.7, 27.9, 24.1; HRMS (FAB) calcd for $[M + H]^+$ ($C_{10}H_{12}NO$) 162.0919, found 162.1917. *N*-Acetylindoline (500 mg, 3.1 mmol) was added to a suspension of LAH (176 mg, 4.65 mmol) in THF (10 mL) and ether (20 mL) at 0 °C. After the addition, the reaction mixture was refluxed for 2 h, then quenched with water (1 mL) and sat. K_2CO_3(aq) (4 mL). The organic solution was decanted, and the precipitate was washed with ethyl acetate (15 mL). The combined organic solution was concentrated to give **21a** (402 mg, 2.72 mmol, 88%) as a light purple oil.[27] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.18 (t, $J = 7.2$ Hz, 3H)), 2.95 (t, $J = 8.2$ Hz, 2H), 3.14 (q, $J = 7.2$ Hz, 2H), 3.32 (t, $J = 8.2$ Hz, 2H), 6.48 (d, $J = 7.9$ Hz, 1H), 6.60−6.68 (m, 1H), 7.02−7.09 (m, 2H), ^{13}C NMR ($CDCl_3$,

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(27) Selvakumar, K.; Rangareddy, K.; Harrod, J. F. *Can. J. Chem.* **2004**, *82*, 1244.

50 MHz) δ 152.3, 130.3, 127.2, 124.3, 117.4, 107.2, 52.3, 43.1, 28.5, 11.9; HRMS (FAB) calcd for $[M]^+$ ($C_{10}H_{13}N$) 147.1048, found 147.1039.

(2,3-Dihydro-indol-1-yl)acetic Acid Ethyl Ester (21b).[28] Ethyl bromoacetate (0.7 mL, 6.3 mmol) was added to a solution of indoline (0.50 g, 4.2 mmol) and triethylamine (1.17 mL, 8.38 mmol) in THF (15 mL). The reaction mixture was refluxed for 6 h, filtered, and concentrated to give **21b** (0.85 g, 4.2 mmol, 99%) as a light purple oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.46 (t, $J = 7.1$ Hz, 3H), 3.02 (t, $J = 8.3$ Hz, 2H), 3.52 (t, $J = 8.4$ Hz, 2H), 3.87 (s, 2H), 4.20 (q, $J = 7.1$ Hz, 2H), 6.40 (d, $J = 7.8$ Hz, 1H), 6.63−6.71 (m, 1H), 7.00−7.09 (m, 2H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.3, 151.3, 129.6, 127.2, 124.5, 118.1, 106.6, 60.8, 53.8, 50.6, 28.6, 14.2; HRMS (FAB) calcd for $[M + H]^+$ ($C_{16}H_{12}NO_2$) 206.1181, found 206.1180.

***N*-Ethyl-1*H*-indole (22a).**[29] A solution of **21a** (53 mg, 0.36 mmol), palladium hydroxide on carbon (20%, 25 mg), and ammonium formate (225 mg, 3.6 mmol) in methanol (5 mL) was heated at reflux for 14 h. After cooling to rt, the reaction mixture was filtered and concentrated. The crude product was further purified by column chromatography (SiO_2; hexane/ethyl acetate, 3:1; R_f 0.70) to give **22b** (28 mg, 0.19 mmol, 53%) as a light green oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.46 (t, $J = 7.3$ Hz, 3H), 4.18 (q, $J = 7.3$ Hz, 2H), 6.48 (d, $J = 0.7$ Hz, 1H), 7.09−7.33 (m, 4H), 7.65 (d, $J = 1.2$ Hz, 1H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 135.6, 128.6, 126.9, 121.3, 120.9, 119.1, 109.2, 101.0, 40.9, 15.4; HRMS (FAB) calcd for $[M + H]^+$ ($C_{10}H_{11}N$) 145.0891, found 145.0883.

Indol-1-yl-acetic Acid Ethyl Ester (22b).[30] A solution of **21b** (53 mg, 0.26 mmol), palladium hydroxide on carbon (20%, 18 mg), and ammonium formate (164 mg, 2.6 mmol) in methanol (5 mL) was heated at reflux for 14 h. After cooling to rt, the reaction mixture was filtered and concentrated. The crude product was further purified by column chromatography (SiO_2; hexane/ethyl acetate, 9:1; R_f 0.50) to give **22b** (37.5 mg, 0.18 mmol, 71%) as a light brown oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.17 (t, $J = 7.2$ Hz, 3H), 4.13 (q, $J = 7.2$ Hz, 2H), 4.76 (s, 2H), 6.48−6.50 (d, 1H), 7.01−7.54 (m, 4H), 7.58 (d, $J = 1.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.5, 136.4, 128.6, 128.4, 122.0, 121.1, 119.8, 108.9, 102.4, 61.6, 47.8, 14.1; HRMS (FAB) calcd for $[M]^+$ ($C_{12}H_{13}NO_2$) 203.0946, found 203.0942.

2-(3-Phenoxypropyl)-2*H*-isoindole (24). Methanol (2.6 mL) was added dropwise to a solution of LAH (1.40 g, 37.9 mmol) in THF (25 mL) at 0 °C. The resulting solution was cooled to −40 °C, and then **25** (3.0 g, 10.7 mol) in THF (15 mL) was added to the reaction mixture. After 30 min at −40 °C, the reaction mixture was stirred at 0 °C for 30 min, quenched with Na_2SO_4(aq) (1.0 g in 9 mL of water), and filtered. The undissolved material was washed with acetone (30 mL), and the combined filtrate was concentrated to give a dark yellow solid. The crude product was recrystallized in 95% ethanol (40 mL) to give pure **24** (0.92 g, 3.66 mmol, 34.5%). Mp 89−91 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.32 (m, 2H), 3.88 (t, $J = 5.7$ Hz, 2H), 4.41 (t, $J = 6.7$ Hz, 2H), 6.82−6.97 (m, 5H), 7.08 (s, 2H), 7.24−7.30 (m, 2H), 7.47−7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.6, 129.5, 124.4, 121.0, 120.6, 119.5, 114.5, 110.8, 63.9, 47.5, 31.5; HRMS (FAB) calcd for $[M]^+$ ($C_{17}H_{17}NO$) 251.1310, found 251.1315; IR (neat) 3019, 2850, 1684, 1600, 1497, 1495, 1470, 1398, 1242, 1039, 810, 750, 690, cm^{-1}.

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Supporting Information Available: Calculations of the aromaticity of indoles and isoindoles, and spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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