Preparation of Quinone Imine Ketals via Intramolecular Condensation of Amino-Substituted Quinone Monoketals. Anodic Oxidation Chemistry of Trifluoroacetamide Derivatives of 1,4-Dimethoxybenzenes and 4-Methoxyphenols

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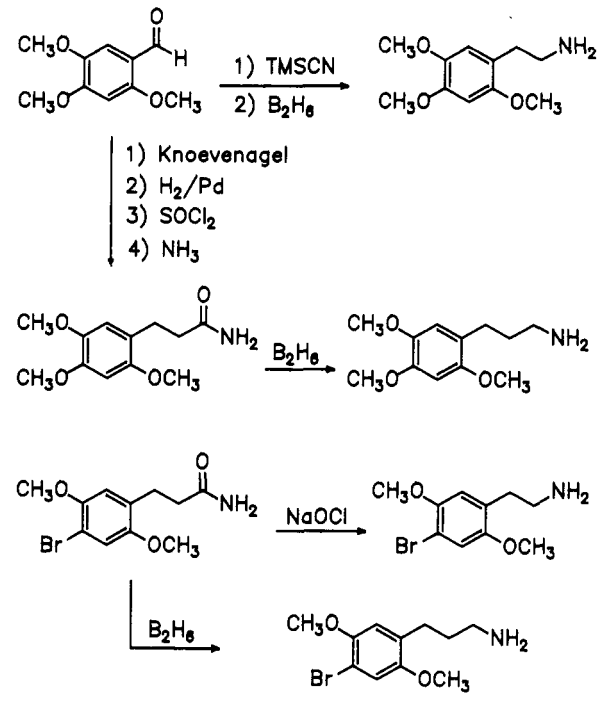
Two routes have been developed to the previously unknown quinone imine ketal moiety. One involves a sequence of anodic oxidation of the *N*-trifluoroacetamide of a 2-(2,5-dimethoxyphenyl)ethylamine or 3-(2,5-dimethoxyphenyl)propylamine derivative to form the respective quinone bisketal followed by basic hydrolysis of the trifluoroacetamide linkage, acidic hydrolysis of the quinone bisketal to a quinone monoketal, and intramolecular condensation to form the quinone imine ketal. This method requires an additional substituent at the 4-position (bromine or methoxy) to direct the regiochemistry of the quinone bisketal hydrolysis. The second method involves similar chemistry except that the anodic oxidation of a 4-methoxyphenol derivative directly affords the quinone monoketal. Hydrolysis of the trifluoroacetamide followed by an intramolecular condensation reaction affords the quinone imine ketal. Selected aspects of the chemistry of these compounds have been studied. Especially interesting is the reaction of a model quinone imine ketal with organolithium reagents. Either 1- or 2-substituted-5-methoxyindole is produced, depending upon the organolithium compound.

Introduction

Quinone imines and diimines have been of long-standing interest in chemistry,[1-3] and the former moieties have been proposed as intermediates in a number of biological processes.[4,5] The preparation of simple quinone imines by chemical oxidation of aniline derivatives is often complicated by the reactivity of the quinone imine under the reaction conditions. Hydrolysis of the quinone imine to the quinone, nucleophile-induced polymerization,[1-3,6] and reactions with starting amines are some of the reactions that lead to rapid destruction of the quinone imine linkage under these conditions. In addition, many of the products from the above reactions are themselves subject to further oxidation. Although subject to many of the same limitations as chemical oxidations, electrochemical oxidation of *o*- and *p*-aminophenols has served as an important method for the in situ generation of quinone imines.[7] Much of the information on the rates of reactions of quinone imines derives from cyclic voltammetry[7,8] and fast flow kinetic studies of compounds generated in this way.

Scheme I. Preparations of Amino-Substituted Methoxylated Aromatics



The *N*-phenylsulfonyl derivatives of quinone imines[9] are much more stable than are the parent systems and have been of some use in synthesis. However, the strongly acidic conditions[9] required for removal of the sulfonylphenylsulfonyl group impose limitations on the use of these quinone imine derivatives in synthesis. Ketals of quinone imines (e.g., **2**, unknown at the inception of this work)[10] have the same oxidation state as does a quinone imine and would serve as masked quinone imines in synthesis. One method for generation of quinone imines would be the

(1) For a review of the older literature, see: Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*; Interscience Publishers: New York, 1970; pp 633–729.

(2) Brown, K. C.; Corbett, J. F. *J. Chem. Soc., Perkin Trans. II* **1981**, 886 and earlier papers in the series.

(3) Nogami, T.; Hishida, T.; Yamada, M.; Mikawa, H.; Shirota, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3709.

(4) For leading references on acylated quinone imine intermediates in the metabolic oxidation of paracetamol, see: (a) Boyd, E. M.; Bereczky, G. M. *Brit. J. Pharmacol.* **1966**, *26*, 606. (b) Potter, W. G.; Davis, D. C.; Mitchell, J. R.; Jollow, D. J.; Gillette, J. R., Brodie, B. B. *J. Pharmacol. Exp. Ther.* **1973**, *187*, 203. (c) Calder, I. C.; Hart, J. S.; Healey, K.; Ham, K. N. *Ibid.* **1981**, *24*, 988. (d) Novak, M.; Bonham, G. A.; Mulero, J. J.; Pelecanou, M.; Zemis, J. N.; Buccigross, J. M.; Wilson, T. C. *J. Am. Chem. Soc.* **1989**, *111*, 4447 and papers cited therein. (e) For leading references to the intermediacy of quinone imines in melanin synthesis, see: d'Ischia, M.; Palumbo, A.; Prota, G. *Tetrahedron Lett.* **1985**, *26*, 2801. Napolitano, A., Corradini, M. G.; Prota, G. *Ibid.* **1985**, *26*, 2805.

(5) For the biological generation of a quinone imine from the horseradish peroxidase reaction of 9-hydroxyellipticene, see: (a) LePeca, J.-B.; Nguyen-Dat-Xuong; Gosse, C.; Paoletti, C. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 5078. (b) Meunier, G.; Meunier, B.; Auclair, C.; Bernadou, J.; Paoletti, C. *Tetrahedron Lett.* **1983**, *24*, 365. (c) Pratviel, G.; Bernadou, J.; Meunier, B. *J. Chem. Soc., Chem. Commun.* **1985**, 60. (d) Kansal, V. K.; Funakoshi, S.; Mangeney, P.; Potier, P.; Gillet, B.; Guittet, E.; Lallemand, J. Y. *Tetrahedron Lett.* **1984**, *25*, 2351. (e) Bernadou, J.; Meunier, B.; Meunier, G.; Auclair, C.; Paoletti, C. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 1297.

(6) Palumbo, P.; d'Ischia, M.; Crescenzi, O.; Prota, G. *Tetrahedron Lett.* **1987**, *28*, 467.

(7) (a) Harmalker, S. P.; Sawyer, D. T. *J. Org. Chem.* **1984**, *49*, 3579. Young, T. E.; Beidler, W. T. *Ibid.* **1984**, *49*, 4833. (b) Young, T. E.; Babbitt, B. W. *Ibid.* **1983**, *48*, 562 and references cited therein.

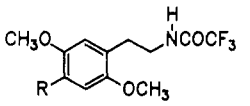
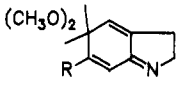
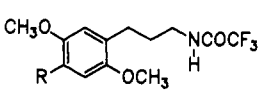
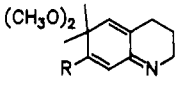
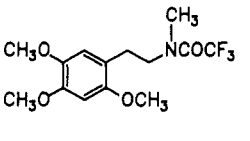
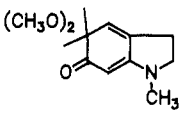
(8) Preddy, C. R.; Miner, D. J.; Meinsam, D. A.; Kissinger, P. T. *Curr. Sep.* **1985**, *6*, 57.

(9) Adams, R.; Looker, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 1145. Adams, R.; Whitaker, L. *Ibid.* **1956**, *78*, 658 and references cited therein.

(10) A preliminary account of some of this work has appeared: Chen, C.-P.; Shih, C.; Swenton, J. S. *Tetrahedron Lett.* **1986**, *27*, 1891.

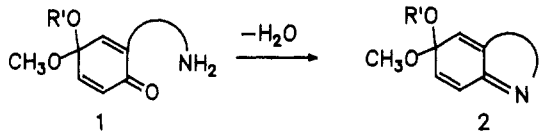
0022-3263/90/1955-2019$02.50/0

Table I. Anodic Oxidation/Hydrolysis/Condensation Route to Quinone Imine Ketals

entry	starting material	product[a]
1	 3a, R=OCH$_3$	 6a (68%)
2	3b, R=Br	6b (40%)
3	 7a, R=OCH$_3$	 8a (45%)
4	7b, R=Br	8b (57%)
5	 9	 10 (39%)

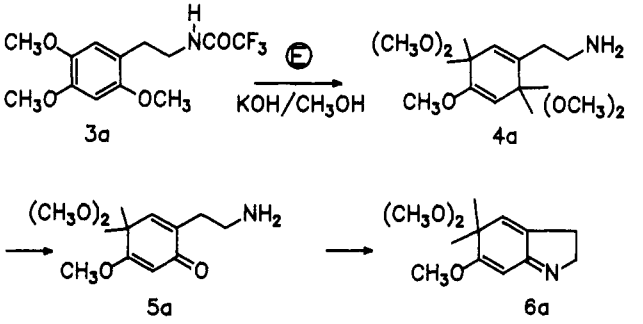
[a] Yields are based on starting trifluoroacetamides. Anodic oxidations were conducted in a divided cell at a potential of 1.0–1.4 V vs a platinum wire reference electrode.

intramolecular condensation between an amino group and the carbonyl group of a quinone monoketal as illustrated by the **1** → **2** reaction. We report the use of this general strategy to quinone imine ketals and some of the chemistry of these compounds.



Quinone Imine Ketals via Hydrolysis of Amino-Substituted Quinone Bisketals. An initial goal was to establish the viability of the **1** → **2** strategy and the stability of the quinone imine unit in a simple system. Since oxidation of a side-chain amino group ($E_{1/2}$ = 0.75–1.0 V vs Ag/Ag$^+$)[11] would complicate the oxidation of a methoxylated aromatic ring ($E_{1/2}$ = 1.09–1.53 V vs Ag/Ag$^+$),[12] anodic oxidation studies were conducted with the amino group converted to its trifluoroacetate derivative. The *N*-trifluoroacetate derivatives are more difficult to oxidize than are the corresponding amines, yet they can be hydrolyzed under mild conditions to regenerate the amines required for the intramolecular condensation. The preparations of the amine(s) employed for these studies are outlined in Scheme I and are detailed in the Experimental Section and supplementary material section.

The anodic oxidation of **3a** in 2% methanolic potassium hydroxide at 10–15 °C in a divided cell using a platinum gauze anode and a platinum sheet cathode under controlled potential conditions[13] ($E_{applied}$ = 1.0–1.3 V vs a platinum wire) was monitored by UV spectroscopy. The UV absorption for the starting material (λ_{max} 290 nm) disappeared as the anodic oxidation progressed, and isosbestic points at 247 and 267 nm resulted. The trifluoroacetate group hydrolyzed during concentration of the basic reaction mixture, and ^{1}H NMR spectroscopy indicated formation of the amino bisketal **4a**. This product decomposed on attempted purification by either alumina or Florisil chromatography and thus was added immediately to water (pH 6.5). Workup of this reaction and chromatography on Florisil furnished the quinone imine **6a** (68%) as a crystalline solid. This product is formed via **5a** or some intermediate in the **4a** → **5a** conversion. The structural assignments for this and other quinone imine ketals are supported by spectroscopic data and chemical transformations (vide infra). Especially informative for **6a** were the imine absorption in the IR spectrum [1622 cm^{-1} (m)] and the imine carbon resonance in the ^{13}C NMR spectrum (δ 164.5).



The results of other anodic oxidation/hydrolysis/condensation chemistry are summarized in Table I. Only one compound having a secondary amide function was studied and yielded the vinylogous amide **10**. The overall yields for these conversions were good, considering that four distinct chemical transformations were involved in the sequence. The above studies established two important points. *First, quinone imine ketals were labile, but isolable, compounds. Second, the intramolecular condensation of the side-chain amino group with the carbonyl group of the monoketal was favored over a possible intramolecular Michael addition to the quinone monoketal.* For the phenethyl derivatives (entries 1, 2, 5), condensation at the carbonyl was expected, based on the poor stereoelectronic situation arising from the intramolecular Michael reaction and by analogy with the cyclization step in the Nenitzescu reaction.[14] However, even for the propyl derivatives (entries 3, 4), condensation of the amino group and the carbonyl group was the favored process.

A key requirement of this route to quinone imine ketals is the regiochemistry of the bisketal hydrolysis. In the compounds studied, the methoxy and bromo substituents were known to direct hydrolysis of the ketal linkage more distant from these substituents,[15] and intramolecular condensation would be favorable. However, when such a directing group is lacking (R = H for compounds in Table I), quinone imine ketals could not be isolated from this four-step sequence.

Quinone Imine Ketals via Anodic Oxidation of Substituted 4-Methoxyphenols. A second method of implementing intramolecular condensation of a side-chain amino group and a quinone monoketal would be the anodic oxidation of an appropriate *p*-methoxyphenol derivative.[16]

(11) (a) Weinberg, N. L. *Technique of Electroorganic Synthesis*, Part I; John Wiley & Sons, Inc.: 1974; Chapter 7, pp 592–620. (b) Mann, C. K.; Barnes, K. K. *Electrochemical Reactions in Nonaqueous Systems*; Decker: New York, 1970; p 279.

(12) Ross, S. D.; Finkelstein, M.; Rudd, E. J. *Anodic Oxidation*; Academic Press: 1975; p 306.

(13) The experiments in this section were performed at constant potential. Subsequent work has indicated that this was probably unnecessary and that the reactions could be performed more conveniently at constant current.

(14) Allen, G. A. *Org. React.* **1973**, *20*, 337.

(15) For studies dealing with the regiochemistry of quinone bisketal hydrolysis, see: Chen, C.-P.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 4569. Henton, D. R.; Anderson, K.; Manning, M. J.; Swenton, J. S. *Ibid.* **1980**, *45*, 3422.

Scheme II. Preparation of Trifluoroacetamido-Substituted *p*-Methoxyphenols

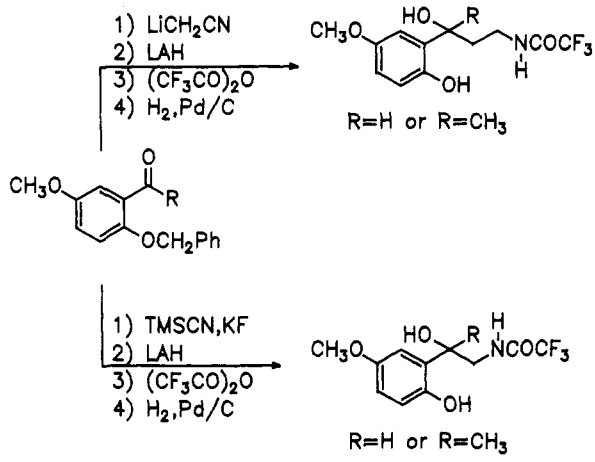


Table II. *p*-Methoxyphenol Route to Quinone Imine Ketals

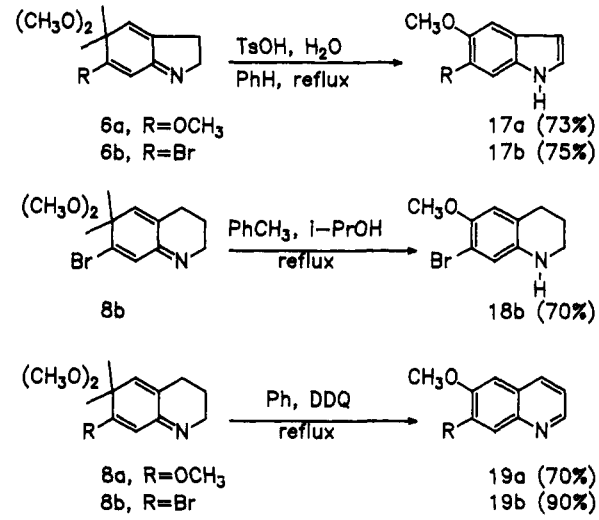
entry	starting material	product
1	11a, $R^1 = R^2 = H$	12a (82%)
2	11b, $R^1 = H$, $R^2 = OH$	12b (91%)
3	11c, $R^1 = CH_3$, $R^2 = OH$	12c (81%)
4	13a, $R^1 = H$, $R^2 = OH$	14a (91%)
5	13b, $R^1 = CH_3$, $R^2 = OH$	14b (89%)
6	15	16 (89%)

Since 2-substituted *p*-methoxyphenol derivatives are available via a number of synthetic routes,[17] this chemistry was investigated to overcome the limitations associated with the regiochemistry of the quinone bisketal hydrolysis. The amines/trifluoroacetamides investigated were prepared via the chemistry outlined in Scheme II. The synthesis of **15** is not shown, but a route similar to that for **13a,b** was followed. (Full experimental details are given in the supplementary material section.)

The anodic oxidation/hydrolysis/condensation chemistry was conducted on the compounds listed in Table II. Several aspects of the anodic oxidation chemistry warrant discussion. The anodic oxidations were conducted in a single-cell apparatus at 0 °C in 2% $LiClO_4$ methanol using a platinum gauze anode and platinum sheet cathode at 0.06 A. Although the effect of current on yield was not extensively studied, currents >0.1 A using these electrodes led to lower yields of product. In each case, the crude anodic oxidation product was dissolved in tetrahydrofuran and the trifluoroacetate group was hydrolyzed with 5% aqueous potassium hydroxide (1–1.5 equiv). This step was followed by in situ intramolecular condensation since workup gave the quinone imine ketals listed in Table II.

The products obtained from this sequence of reactions were of sufficient purity (ca. >90%) for most purposes. These quinone imine ketals can be further purified by chromatography on activity III neutral alumina with some loss of material. The ^1H NMR spectra of the products given in the supplementary section establish purity of >90% for the quinone imines reported herein. The quinone imine ketals listed in Table II decompose on standing at room temperature but can be stored at −20 °C in base-washed glassware. For example, **12a** gave 5-methoxyindole in 70% yield after standing in a glass vial at room temperature for several days—adventitious acid may have catalyzed this reaction. All except one of these compounds gave an acceptable exact mass measurement, but due to the expected instability in transport, no combustion analyses were attempted. All of the compounds showed medium infrared absorptions (ca. 1600 cm^{-1}) characteristic of the imine linkage and ^{13}C NMR peaks due to the imine carbon [δ 163 (imine in five-membered ring) and δ 155 (imine in six-membered ring)]. *This chemistry then establishes a route to quinone imine ketals not limited by the regiochemistry of the bisketal hydrolysis.*

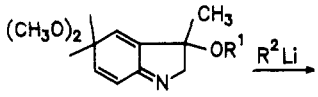
Selected Chemistry of Quinone Imine Ketals. Bicyclic quinone imines such as **6a,b** and **12a** are at the indole oxidation state, and conversion to the respective indole accounts for the instability of these compounds, especially under acidic conditions. The stability of these compounds is markedly improved when they are handled and stored in base-washed apparatus. The bicyclic quinone imines of types **8a,b** and **14a,b** are somewhat more stable but can be converted under either reductive or oxidative condition to the corresponding tetrahydroquinoline or quinoline derivative.



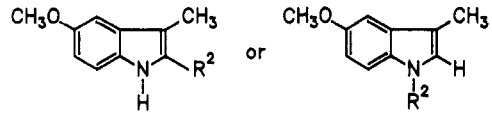
Since organometallic additions to quinone imine derivatives could prove useful in synthesis, the reaction of organolithium reagents with compound **12c** was investigated. This quinone imine ketal was chosen for these exploratory studies since it cannot directly rearrange to the indole ring system. However, reaction of **12c** with methyllithium (2–4 equiv) under a variety of reaction conditions gave either no reaction or complex reaction mixtures. In one attempt, lithium diisopropylamide (LDA) was used to deprotonate the hydroxyl group before addition of the alkyllithium reagent; in this reaction, 2,3-dimethyl-5-methoxyindole (**20a**) was characterized as a product (Table III). Under optimum conditions, the **12c** → **20a** (R = CH_3) conversion was effected in 89% yield.

(16) (a) Nilsson, A.; Ronlán, A. *Tetrahedron Lett.* **1975**, 1107. (b) Chen, C.-P.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1985**, 129.
(17) For leading references, see ref 16b.

Table III. Reactions of Organolithium Compounds with Quinone Imine Ketals



12c, R^1 = H
12d, R^1 = CH_3



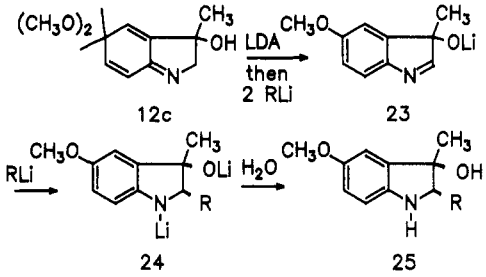
20 21

entry	R^1	conditions	product (% yield)
1	H	LDA (2 equiv)	
		CH_3Li (4 equiv)	**20a** (89)
2	H	LDA (2 equiv)	
		PhLi (4 equiv)	**20b** (68)
3	CH_3	TMEDA	
		CH_3Li (3 equiv)	**20a** (42)
4	H	*n*-BuLi (4 equiv)	**21a** (62)
5	H	LDA (2 equiv)	
		s-BuLi (2 equiv)	**21b** (89)
6	H	*t*-BuLi (2.8 equiv)	**21c** (82)
7	H	allylmagnesium bromide	*a*

[a] Complex mixture of products.

The reasons for the high-yield **12c** → **20a** transformation using these reagents and at their indicated molar ratios are not understood. The beneficial effect of LDA on this chemistry could involve decomplexation of the alkyllithium reagent to give a more reactive organolithium species. Furthermore, this chemistry should be effected with 1 equiv of LDA to deprotonate the hydroxyl group followed by 3 equiv of methyllithium—one to deprotonate the diisopropylamine, one to eliminate the methoxide, and the third to add to the imine linkage as outlined below. However, the optimum conditions for the **12c** → **20a** conversion involved 2 equiv of LDA and 4 equiv of methyllithium. The reaction sequence can be viewed as outlined below. In support of this sequence, **25** (R = CH_3) could be isolated by careful quenching of the reaction. The labile dihydroindole **25** that appeared to be one isomer on the basis of ^1H NMR spectroscopy (see supplementary material section) is assigned as having the methyl group cis to the hydroxyl group based on the known ability of the lithium alkoxide group to complex the entering alkyllithium moiety.[18,19] When **25** was reacted with dilute acid, **20a** was formed.

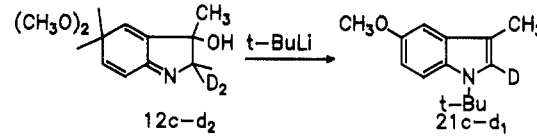
Although the formation of a 2-substituted indole derivative in this reaction was neither expected nor desired,



12c 23 24 25

the reaction of other organolithium reagents with **12c** was examined since this could afford a useful route to 2-substituted-5-methoxyindoles. The reaction of phenyllithium with **12c** followed the same course as did methyllithium and gave the 2-phenyl-substituted indole **20b** in 68% yield. The importance of the hydroxyl group (lithium alkoxide) on the chemistry of the **12c** → **20a** conversion cannot be stated with certainty; however, **12d** can be converted to **20a** under similar conditions (entry 3).

In contrast to the above results, the reaction of *n*, *sec*-, and *tert*-butyllithium with **12c** gave as major products the N-substituted derivatives **21a–c** (Table III). It is possible that an intermediate analogous to **23** was generated in the chemistry and underwent organolithium addition to the nitrogen of the imine.[20] This could be followed by protonation during workup and elimination of water to give the observed N-alkylated product. However, reaction of the dideuterio compound **12c**–d_2 with *tert*-butyllithium gave the monodeuterated derivative **21c**–d_1 with no loss of deuterium, suggesting that an intermediate generated



12c–d_2 **21c**–d_1

from organolithium addition to the nitrogen of imine 23 is not involved in the **12c** → **21** transformation. More likely, the butyllithium reagents transfer an electron to the quinone imine ketal **12c** with subsequent expulsion of lithium methoxide. Combination of the nitrogen-centered radical and the butyl radical followed by loss of water during workup would give the N-alkylated indole.

Summary

The in situ generation of amino-substituted quinone monoketals results in intramolecular condensation to afford bicyclic derivatives of quinone imine ketals. The compounds can be isolated but are easily converted to the respective 5-methoxyindole or 6-methoxyquinoline ring systems under appropriate conditions. Reaction of these quinone imine ketals with organolithium reagents can take two different courses. Reaction of **12c** with methyl- and phenyllithium, which have less tendency than the butyllithium reagents to act as electron-transfer agents, affords 2-substituted-3-methyl-5-methoxyindoles. Since the 3-substituent is determined in the preparation of the quinone imine ketal, this chemistry could serve as a route to 2-methyl and -aryl derivatives of the above indole. For more substituted organolithium reagents, N-substituted-5-methoxyindoles are formed. These products arise via either an electron transfer from the organollithium reagent to the quinone imine ketal or a reaction of the alkyl group of the organolithium reagent with the imine nitrogen

(18) For examples of alkoxide-directed organometallic additions to simple carbon–carbon bonds, see, for example: Eisch, J. J.; Husk, G. R. *J. Am. Chem. Soc.* **1965**, *87*, 4195. Chérest, M.; Felkin, H.; Frajerman, C.; Lion, C.; Roussi, G.; Swierczewski, G. *Tetrahedron Lett.* **1966**, 875. Crandall, J. K.; Clark, A. C. *Tetrahedron Lett.* **1969**, 325; *J. Org. Chem.* **1972**, *37*, 4236. Felkin, H.; Swierczewski, G.; Tambute, A. *Tetrahedron Lett.* **1969**, 707. Newman-Evans, R. H.; Carpenter, B. K. *Tetrahedron Lett.* **1985**, *26*, 1141. Solomon, M., Jamison, W. C. L.; McCormick, M.; Liotta, D.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 3702.

(19) For more recent examples wherein a methoxy group may be exerting a directing effect, see: Stern, A. J.; Rohde, J. R.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 4413. Swenton, J. S.; Jurcak, J. G. *J. Org. Chem.* **1988**, *53*, 1530. Padwa, A.; Wannamaker, M. W. *Tetrahedron Lett.* **1986**, *27*, 2555. Klumpp, G. W.; Kool, M.; Schakel, M.; Schmitz, R. F.; Boutkan, C. *J. Am. Chem. Soc.* **1979**, *101*, 7065. Klumpp, G. W.; Kool, M.; Veefkind, A. H.; Schakel, M.; Schmitz, R. F. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 542.

(20) For a recent study dealing with organolithium additions to fluorenone imine and references to older work in this area, see: Dai, W.; Srinivasan, R.; Katzenellenbogen, J. *J. Org. Chem.* **1989**, *54*, 2204.

(azophilic addition[20]). A reaction sequence initiated by electron transfer seems a more reasonable possibility.

Experimental Section[21]

2,4,5-Trimethoxybenzaldehyde *O*-(Trimethylsilyl)-cyanohydrin.[22] A mixture of the aldehyde (5.0 g, 25.5 mmol) and trimethylsilyl cyanide (2.68 g, 27 mmol) was heated at 160 °C for 1 h. The viscous liquid was then vacuum distilled (151–154 °C/1 mm) to give the title compound as a light yellow liquid (6.6 g, 88%), which then solidified upon freezing to give an off-white solid, mp 100.5–102 °C: IR (neat) 1520, 1465, 1255, 1210, 1125, 1030, 806, 841 cm^{-1}; ^1H NMR (60 MHz) δ 7.08 (s, 1 H), 6.50 (s, 1 H), 5.78 (s, 1 H), 3.38 (3 s, 9 H), 0.19 (s, 9 H); mass spectrum, exact mass calcd for $C_{14}H_{21}NO_4Si$ m/e 295.1240, obsd m/e 295.1246.

(2,4,5-Trimethoxyphenyl)ethylamine Hydrochloride.[22] To a solution of the above compound (4.0 g, 13.56 mmol) in THF (60 mL) at 0 °C was added a 1.0 M borane/THF complex (45 mL) over 10 min. The mixture was then heated at reflux for 3 h, and the reaction was quenched by cautious addition of H_2O (10 mL) and 5% aqueous NaOH (5 mL). After extractive workup (CH_2Cl_2, 3 × 100 mL) and concentration of the solvent to ca. 20 mL, excess HCl gas was bubbled into the solution until a cloudy white suspension formed. The excess solvent was removed in vacuo to give a white solid (2.34 g, 70%) that was recrystallized from Et_2O/CH_3OH to give fine white crystals (1.701 g, 51%), mp 192–194 °C (lit.[22] mp 193–194 °C); IR and ^1H NMR spectra are identical with those reported in the literature.

Preparation of 3a. To a solution of the above hydrochloride (800 mg, 3.23 mmol) in dry pyridine (9 mL) at 0 °C was added dropwise $(CF_3CO)_2O$ (874 mg, 587 μL). The yellow suspension was stirred at room temperature overnight, and the mixture was then poured into a saturated $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (4 × 50 mL). Workup gave a light yellow solid (ca. 920 mg), which was recrystallized from Et_2O/PE to give white crystals (874 mg, 88%): mp 95–97 °C dec; IR 3320, 1700, 1565, 1521, 1470, 1462, 1444, 1402, 1307, 1227 (br), 1205 (br), 1175 (br), 1125, 1042 (shoulder), 1034 cm^{-1}; ^1H NMR (90 MHz) δ 7.03 (br s, 1 H, disappeared with D_2O wash), 6.66 (s, 1 H), 6.52 (s, 1 H), 3.89 (s, 3 H), 3.86 (s, 6 H), 3.53 (q, J = 6 Hz, 2 H, collapsed into a triplet after D_2O wash, J = 6 Hz), 2.83 (t, J = 6 Hz, 2 H); mass spectrum, exact mass calcd for $C_{13}H_{16}NO_4F_3$ m/e 307.1031, obsd m/e 307.1037.

Anodic Oxidation/Hydrolysis/Condensation Reaction of *N*-Trifluoroacetates of Alkylamino-Substituted 1,4-Dimethoxybenzenes. The constant-current electrolyses were performed in a jacketed single-cell apparatus using a platinum gauze anode (25 mm diameter × 50 mm high) and a platinum sheet cathode (8 × 8 mm) and a Kepco Model JQE36-3M power supply. Controlled potential electrolyses were performed by using the above electrodes in a standard H-cell in which the anode and cathode were separated by a medium-porosity frit. The potential was measured versus a platinum wire with a Kepco Model BOP72-5M bipolar operational amplifier as potentiostat. This electrolysis equipment is described in more detail in ref 23.

Electrolysis of 3a. A solution of **3a** (400 mg, 1.30 mmol) in 2% KOH/CH_3OH (150 mL) was anodically oxidized at room temperature in a single cell under constant current (0.4 A). The reaction was monitored by UV at the absorption of ca. 290 nm, and the reaction was quenched after 646 C had passed (39% current efficiency). The light yellow solution was concentrated in vacuo (without heating) to ca. 20 mL, diluted with H_2O (10 mL) and brine (10 mL), and stirred at room temperature for 1.5 h. Extractive workup (CH_2Cl_2, 2 × 100 mL) gave a viscous oil (500 mg). The ^1H NMR spectrum of the oil showed it to be mostly amino bisketal. Further purification was not attempted due to the instability of the compound. The crude amino bisketal was then dissolved in distilled H_2O (50 mL, pH ~ 6.5) and stirred at room temperature for 16 h. Extractive workup (CH_2Cl_2, 2 × 100 mL) and chromatography of the residue on Florisil (2% $CH_3OH/CHCl_3$ as eluant) gave **6a** as a waxy solid. This material was recrystallized from Et_2O/PE to give a white solid: mp 73–75 °C; IR (KBr) 1622, 1240, 1207, 1160, 1075 (br), 975, 960 cm^{-1}; ^1H NMR (90 MHz) δ 6.11 (s, 1 H), 5.94 (t, J = 2.5 Hz, 1 H), 4.3–4.1 (m, 2 H), 3.90 (s, 3 H), 3.38 (s, 6 H), 2.8–2.6 (m, 2 H); ^{13}C NMR (20 MHz) δ 165.4, 162.6, 144.2, 128.8, 119.9, 98.0, 60.0, 55.6, 51.3, 27.3; mass spectrum, exact mass calcd for $C_{11}H_{15}NO_3$ m/e 209.1052, obsd m/e 209.1058.

Electrolysis of 3b. A solution of **3b** (1.19 g, 3.34 mmol) in 2% KOH/CH_3OH (150 mL) was anodically oxidized in a single cell under constant current (0.2 A, 6 V). The reaction was quenched after 100 min, and the mixture was concentrated in vacuo (without heating) to ca. 20 mL. This solution was diluted with H_2O (10 mL) and brine (10 mL), stirred at room temperature for 6 h, and then extracted (CH_2Cl_2, 2 × 100 mL). Workup and concentration without heating gave a yellow oil (ca. 1.0 g), which was immediately treated with a cold mixture of 0.5 N HCl (15 mL) in $(CH_3)_2CO$ (40 mL). The solution was stirred at 0 °C for 4 h, and then the reaction was quenched by the addition of a saturated $NaHCO_3$ solution. Extractive workup (Et_2O, 2 × 100 mL) and chromatography of the dark brown viscous oil on Florisil (1% $CH_3OH/CHCl_3$ as eluant) gave **6b** (325 mg, 40%) as a viscous oil: IR (CCl_4) 1612 (m), 1084, 1069 (shoulder) cm^{-1}; ^1H NMR (90 MHz) δ 7.29 (s, 1 H), 5.94 (t, J = 2 Hz, 1 H), 4.3–4.4 (m, 2 H), 3.23 (s, 6 H), 2.8–2.6 (m, 2 H); mass spectrum, exact mass calcd for $C_{10}H_{12}NO_2{}^{79}Br$ m/e 257.0204, obsd m/e 257.0209.

Electrolysis of 7a. A solution of **7a** (500 mg, 1.558 mmol) in 2% KOH/CH_3OH (60 mL) was anodically oxidized in an H-type divided cell under controlled potential conditions. The applied potential was increased gradually from 1.0 to 1.2 V, and the total current passed was 600 C (50% current efficiency). The anolyte was then concentrated in vacuo (without heating) to ca. 20 mL, and this concentrated solution was diluted with H_2O (10 mL) and brine (10 mL) and stirred at room temperature for 2 h. Extractive workup (CH_2Cl_2, 2 × 100 mL) gave a viscous oil (ca. 350 mg), which was dissolved in distilled H_2O (50 mL, pH ~6.5) and stirred at room temperature for 20 h. Extractive workup (CH_2Cl_2, 3 × 50 mL) and chromatography of the residue on Florisil (3% $CH_3OH/CHCl_3$ as eluant) gave **8a** as an off-white solid, which was recrystallized from Et_2O/PE to give an analytically pure material (155 mg, 45%): mp 95–97 °C; IR (KBr) 1625, 1579, 1212, 1166, 1093, 1057 cm^{-1}; ^1H NMR (90 MHz) δ 5.69 (br s, 2 H), 3.88–3.65 (m, with s at 3.73, 5 H), 3.27 (s, 6 H), 2.6–2.4 (m, 2 H), 1.9–1.7 (m, 2 H); ^{13}C NMR (20 MHz) δ 159.0, 158.1, 131.4, 127.7 (d), 105.1 (d), 96.1, 55.4 (q), 51.3 (2 C, q), 50.5 (t), 27.5 (t), 23.0 (t); mass spectrum, exact mass calcd for $C_{12}H_{17}NO_3$ m/e 223.1208, obsd m/e 223.1213.

Electrolysis of 7b. A solution of **7b** (600 mg, 1.613 mmol) in 2% KOH/CH_3OH (60 mL) was anodically oxidized in an H-type divided cell under controlled potential. The electrolysis was performed at ca. 15 °C at the applied potential (1.1 to 1.4

(21) Melting points were determined in capillaries in a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 283B spectrometer on KBr disks, and strong peaks are reported unless otherwise noted. Routine ^1H NMR spectra were determined at 80 MHz on either an IBM NR 80 spectrometer or a Varian EM-390 using deuteriochloroform as solvent and residual chloroform or tetramethylsilane as internal standard unless noted otherwise. Mass spectral and exact mass measurements were obtained by Mr. Richard Weisenberger on a Kratos MS-30 spectrometer. Alumina and silica gel (Kieselgel 60, 230–400 mesh) were obtained from E. Merck Co. Tetrahydrofuran was purified by distillation from benzophenone ketyl. Thin-layer chromatography (TLC) was done on Merck silica gel 60 F_{254} pre-coated aluminum-backed plates, 0.2-mm thickness. Visualization was by UV or by spraying with 5% ethanolic phosphomolybdic acid and then heating. Unless otherwise noted purified material showed one concentric spot in the R_f range 0.3–0.6. All organometallic reactions were done under nitrogen or argon. Extractive workup refers to the following sequence of operations: concentration of the reaction mixture in vacuo, extraction of the organic product with diethyl ether or methylene chloride, washing the organic layer with brine (diethyl ether only), drying the organic layer over calcium sulfate (Drierite), removal of the solvent in vacuo, and drying to constant weight under <0.3 Torr vacuum. Throughout the Experimental Section, the following abbreviations are used: petroleum ether, bp 35–60 °C (PE), diethyl ether (Et_2O), tetrahydrofuran (THF), *tert*-butyldimethylsilyl (TBDMS).

(22) This one-step preparation of 2-(2,4,5-trimethoxyphenyl)ethylamine via diborane reduction of the (trimethylsilyl)cyanohydrin is operationally much easier and proceeds in much higher yield than the best literature procedure (Short, J. H.; Dunnigan, D. A.; Ours, C. W. *Tetrahedron* **1973**, *29*, 1931).

(23) Henton, D. R.; McCreery, R. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 369.

V relative to a platinum wire reference electrode) with a total current passed of 635 C (49% current efficiency). The anode chamber solution was then concentrated in vacuo (without heating) to ca. 20 mL, diluted with H_2O (10 mL) and brine (10 mL), and stirred at room temperature for 4.5 h before being extracted (CH_2Cl_2, 3 × 75 mL). After workup, the residue was dissolved in $(CH_3)_2CO$ (40 mL) and 0.5 N HCl (10 mL). This light orange mixture was stirred at room temperature for 0.5 h and then neutralized (saturated $NaHCO_3$). Extraction with Et_2O (50 mL) and the usual workup gave a brownish viscous oil, which was chromatographed on Florisil (2% $CH_3OH/CHCl_3$ as eluant) to give **8b** (0.25 g, 57%) as a light brown waxy solid, mp 42–48 °C. The analytical sample was recrystallized from Et_2O/PE to give a white solid: mp 54–54.5 °C; IR (KBr) 2930, 1618, 1588, 1355, 1245, 1088 (br), 997 cm^{-1}; ^1H (90 MHz) δ 6.97 (s, 1 H), 5.87 (br s, 1 H), 3.83 (t, J = 5.5 Hz, 2 H), 3.24 (s, 6 H), 2.6–2.3 (m, 2 H), 1.77 (quintet, J = 5.5 Hz, 2 H); ^{13}C NMR (20 MHz) δ 156.9, 137.6 (d), 132.9, 132.4, 128.7 (d), 96.8, 51.1 (two OCH_3 overlapping a CH_2 group, t and q), 27.2 (t), 22.6 (t); mass spectrum, exact mass calcd for $C_{11}H_{14}NO_2{}^{79}Br$ m/e 271.0209, obsd m/e 271.0218.

Electrolysis of 9. A solution of **9** (600 mg, 1.87 mmol) in 2% KOH/CH_3OH (100 mL) was anodically oxidized in a single cell under constant current (0.4 A, 8 V). The reaction was monitored by UV spectroscopy (isosbestic points at 248 and 267 nm were observed) and was quenched after 600 C of current had passed (60% current efficiency). The mixture was concentrated in vacuo (without heating) to ca. 20 mL, diluted with H_2O (10 mL) and brine (10 mL), and stirred at room temperature for 2 h. Extractive workup (CH_2Cl_2, 3 × 100 mL) and concentration (without heating) gave a brown viscous oil (the ^1H NMR spectrum of this oil showed it to be mostly the amino quinone bisketal). This oil was then dissolved in distilled H_2O (50 mL, pH ~6.5) and stirred at room temperature for 46 h. Extractive workup (CH_2Cl_2, 3 × 50 mL) gave a yellow viscous oil, which was chromatographed on base-washed silica gel (2% $CH_3OH/CHCl_3$ as eluant) to give indoline **10** as an off-white solid, which was recrystallized from Et_2O/PE to give a light yellow solid: mp 90–92 °C dec; IR (KBr) 1620 (shoulder), 1594 (vs, br), 1416, 1269, 1155, 1077, 1032, 952, 783 cm^{-1}; ^1H NMR (60 MHz) δ 6.17 (t, J = 2 Hz, 1 H), 5.03 (s, 1 H), 3.63 (t, J = 7 Hz, 2 H), 3.37 (s, 6 H), 2.93 (s, 3 H, overlapped with a multiplet centered at 2.83, 2 H); mass spectrum, exact mass calcd for $C_{11}H_{15}NO_3$ m/e 209.1052, obsd m/e 209.1058.

Anodic Oxidation/Hydrolysis/Condensation Reaction of *N*-Trifluoroacetates of Alkylamino-Substituted 2-Hydroxy-4-methoxybenzenes. All preparative anodic oxidations were performed at constant current in a single-cell jacketed apparatus in CH_3OH using a circular platinum gauze anode (33 mm diameter × 8 mm high) and platinum sheet cathode (8 × 8 mm) unless otherwise stated. The temperature of the oxidations was not critical but was maintained at 10–20 °C by circulating a cooled liquid through the jacket of the electrolysis beaker. The current listed for the oxidations is important since higher currents often lead to lower yields of product. The voltage on the Kepco Model JQE36-3M power supply is listed for convenience and does not indicate the potential of the anode. For a more extensive discussion of the experimental details of the electrolysis, see ref 23.

12a. A solution of **11a** (0.140 g, 0.531 mmol) in a 2% $LiClO_4$ solution (120 mL) was electrolyzed (3 V, 0.06 A) for 45 min until complete disappearance of starting material as determined by UV spectroscopy. Extractive workup (CH_2Cl_2, 3 × 30 mL) gave a very light oil, which was dissolved in THF (100 mL) and reacted with 5% KOH (5 mL) for 2 h. The mixture was then concentrated in vacuo, and the resulting oil was extracted (CH_2Cl_2, 3 × 30 mL). The aqueous layer was neutralized by addition of saturated NH_4Cl (30 mL) and extracted (CH_2Cl_2, 2 × 30 mL). Workup gave **12a** as a light yellow oil (90.1 mg, 82%): IR (not available); ^1H NMR δ 6.70 (d, J = 10 Hz, 1 H), 6.33 (dd, J = 10, 1.6 Hz, 1 H), 5.90 (m, 1 H), 4.70–4.45 (m, 2 H), 3.24 (s, 6 H), 2.72–2.5 (m, 2 H); ^{13}C NMR δ 164.3, 143.4, 137.5, 125.0, 121.0, 96.7, 60.0, 49.8 (2 C), 27.1; mass spectrum, exact mass calcd for $C_{10}H_{13}NO_2$ m/e 179.0946, obsd m/e 179.0953.

12b. A solution of **11b** (0.51 g, 1.83 mmol) in a 2% $LiClO_4/CH_3OH$ solution (120 mL) was electrolyzed at 0 °C (3.1 V, 0.06 A) for 2 h. Extractive workup (CH_2Cl_2, 4 × 50 mL) gave a light yellow oil, which was dissolved in THF (100 mL) and reacted with 5% KOH (10 mL). After being stirred for 2 h, the resulting solution was concentrated in vacuo, extracted (CH_2Cl_2, 5 × 30 mL), and washed with brine (40 mL). Drying and concentration in vacuo gave **12b** (0.32 g, 91%) as a light yellow oil: IR (film) 3600–3100, 1560, 1370, 1140, 1080, 1050, 1035 (sh), 950 cm^{-1}; ^1H NMR δ 6.6 (d, J = 11 Hz, 1 H), 6.4, 6.3 (two overlapping resonances, 2 H), 4.8–4.7 (m, 1 H), 4.45–3.70 (m, 3 H), 3.26 (s, 6 H); mass spectrum, exact mass calcd for $C_{10}H_{13}NO_3$ m/e 195.0896, obsd m/e 195.0840.

12c. A solution of **11c** (0.51 g, 1.83 mmol) in a 2% $LiClO_4/CH_3OH$ solution (120 mL) was electrolyzed at 0 °C (3.1 V, 0.06 A) for 2 h. Extractive workup (CH_2Cl_2, 5 × 50 mL) gave a light yellow oil, which was dissolved in THF (120 mL) and reacted with 5% KOH (15 mL) for 3 h. The resulting mixture was concentrated in vacuo, extracted (CH_2Cl_2, 5 × 40 mL), and washed with brine (30 mL) to yield crude **12c** (0.375 g, 89%): IR (film) 3600–3000 (br), 2960, 2930, 1580, 1365, 1205, 1120 (sh), 1100, 1060, 1030, 950, 720 cm^{-1}; ^1H NMR δ 6.67 (d, J = 10 Hz, 1 H), 6.38 (dd, J = 10, 2 Hz, 1 H), 6.28 (d, J = 2 Hz, 1 H), 4.06 (s, 2 H), 3.29 (s, 3 H), 3.27 (s, 3 H), 3.15–2.70 (br s, 1 H), 1.43 (s, 3 H); ^{13}C NMR δ 163.3, 148.3, 137.7, 124.7, 123.4, 96.1, 75.7, 74.4, 49.8, 49.7, 26.3; mass spectrum, no parent, M – OCH_3, 50% of base peak), exact mass calcd for $C_{10}H_{12}NO_2$ m/e 178.0868, obsd m/e 178.0847.

14a. A solution of **13a** (0.442 g, 1.51 mmol) in a 1% $LiClO_4/CH_3OH$ solution (120 mL) at 0 °C was electrolyzed (3.3 V, 0.06 A) for 1.6 h. Extractive workup (CH_2Cl_2, 3 × 30 mL) gave a light yellow oil, which was dissolved in THF (100 mL) and reacted with 5% KOH (6 mL) for 3 h. The resulting solution was concentrated in vacuo, extracted (CH_2Cl_2, 4 × 30 mL), and worked up to give **14a** (0.283 g, 91%): IR (film) 3600–3100, 2930, 1580, 1090, 1060, 1030, 950 cm^{-1}; ^1H NMR δ 6.63–6.20 (m, 3 H), 4.5–3.4 (m, 3 H), 3.29 (s, 6 H), 2.5–1.4 (m, 3 H); mass spectrum, exact mass calcd for $C_{11}H_{15}NO_3$ m/e 209.1052, obsd m/e 209.1063.

14b. A solution of **13b** (0.56 g, 1.82 mmol) in a 1% $LiClO_4/CH_3OH$ solution (120 mL) at 0 °C was electrolyzed (3 V, 0.06 A) for 2 h. Extractive workup (CH_2Cl_2, 3 × 40 mL) gave a colorless oil, which was dissolved in THF (100 mL) and reacted with 5% KOH (5 mL) for 2 h. The resulting solution was concentrated in vacuo, extracted (CH_2Cl_2, 4 × 30 mL), and worked up to afford a light yellow oil, **14b** (0.36 g, 89%): IR (film) 3600–3100 (br), 2940, 1695, 1120, 1105, 1060, 1040, 950 cm^{-1}; ^1H NMR δ 6.6–6.15 (m, 3 H), 4.3–3.5 (m, 2 H), 3.27 (s, 6 H), 2.6 (br, 1 H), 1.77 (pseudo t, J = 5 Hz, 2 H), 1.33 (s, 3 H); ^{13}C NMR δ 156.0, 137.7, 132.6, 131.4, 126.5, 94.6, 67.1, 49.5 (2 C), 48.3, 36.7, 27.2; mass spectrum, exact mass calcd for $C_{12}H_{17}NO_3$ m/e 223.1208, obsd m/e 223.1200.

16. A solution of **15** (0.65 g, 2.49 mmol) in a 1% $LiClO_4/CH_3OH$ solution (120 mL) at 0 °C was electrolyzed (3 V, 0.06 A) for 2.8 h. Extractive workup (CH_2Cl_2, 5 × 40 mL) gave a clear oil, which was dissolved in THF (100 mL) and reacted with 5% KOH (10 mL) for 5 h. The mixture was concentrated in vacuo, extracted (CH_2Cl_2, 5 × 40 mL), and worked up to yield a light yellow oil. Recrystallization (CH_2Cl_2/PE) gave **16** (0.53 g, 89%): mp 129–131 °C; IR (KBr) 3600–3100, 2940, 2830, 1540, 1205, 1100, 1060, 930, 910 cm^{-1}; ^1H NMR δ 6.81 (d, J = 10 Hz, 1 H), 6.63 (d, J = 10 Hz, 1 H), 4.23 (d, J = 17 Hz, 1 H), 3.73 (d, J = 17 Hz, 1 H), 3.38 (s, 1 H), 3.20 (s, 3 H), 3.04 (s, 3 H), 2.4–1.2 (m, 6 H); ^{13}C NMR δ 162.9, 143.3, 138.9, 136.7, 126.9, 97.8, 74.8, 71.3, 51.1, 50.6, 31.7, 20.0, 17.6; mass spectrum, exact mass calcd for $C_{13}H_{17}O_3N$ m/e 235.1209, obsd m/e 235.1220.

Conversion of 6a to 5,6-Dimethoxyindole. A solution of **6a** (98 mg, 0.48 mmol) and p-TsOH·H_2O (10 mg) in dry benzene (10 mL) was heated at 60 °C for 0.5 h. The cooled mixture was poured into a saturated $NaHCO_3$ solution and extracted (CH_2Cl_2, 2 × 100 mL). Workup and chromatography on silica gel (10% $CH_3OH/CHCl_3$ as eluant) gave 5,6-dimethoxyindole (62.7 mg, 75%) as a white solid, mp 146–148 °C. This was further recrystallized from Et_2O/PE to give an analytically pure sample: mp 153–154 °C (lit.[24] mp 152–154 °C); IR (KBr) 3364, 1476 (br), 1365, 1218, 1195, 1190, 1129, 845 cm^{-1}; ^1H NMR (90 MHz) δ 8.04 (br s, 1 H), 7.08 (s overlapped with d, 2 H), 6.82 (s, 1 H), 6.41 (t, J = 2.5 Hz, 1 H), 3.92 (s, 3 H), 3.89 (s, 3 H); mass spectrum, exact mass calcd for $C_{10}H_{11}NO_2$ m/e 177.0790, obsd m/e 177.0795.

Conversion of 6b to 5-Methoxy-6-bromoindole. A solution of **6b** (67 mg, 0.26 mmol) and p-TsOH·H_2O (5 mg) in dry benzene

(24) Baxter, I.; Swan, G. A. *J. Chem. Soc. C* **1967**, 2446. Huebner, C. F.; Troxell, H. A.; Schroeder, D. C. *J. Am. Chem. Soc.* **1953**, *75*, 5887.

(10 mL) was heated at 60 °C for 10 min. The cooled mixture was diluted with Et_2O (50 mL) and washed with a saturated $NaHSO_3$ solution (5 mL), H_2O (5 mL), and brine (5 mL). Workup gave a dark brown residue, which was chromatographed on silica gel (15–39% Et_2O/PE as eluant) to give 5-methoxy-6-bromoindole (42.7 mg, 73%) as a white solid: mp 120–120.5 °C; IR (KBr) 3385, 1469, 1308, 1208, 1155, 1037, 815, 756 cm^{-1}; ^1H NMR (90 MHz) δ 8.02 (br s, 1 H), 7.52 (s, 1 H), 7.10 (s overlapping with m, 2 H), 6.43 (m, 1 H), 3.91 (s, 3 H); mass spectrum, exact mass calcd for $C_9H_8NO^{79}Br$ m/e 224.9790, obsd m/e 224.9797.

Conversion of 8b to 6-Methoxy-7-bromo-1,2,3,4-tetrahydroquinoline (18b). A mixture of **8b** (200 mg, 0.735 mmol) in isopropyl alcohol (0.5 mL) and dry toluene (6 mL) was heated at reflux for 0.5 h. The cooled mixture was then diluted with Et_2O (100 mL), washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), and dried over Drierite. Concentration and chromatography on silica gel (20–50% Et_2O/PE as eluant) gave 6-methoxy-7-bromo-1,2,3,4-tetrahydroquinoline (**18b**) (124 mg, 70%) as a white solid: mp 54–55 °C; IR (neat) 1500, 1226, 1048 cm^{-1}; ^1H NMR (60 MHz) δ 6.65 (s, 1 H), 6.53 (s, 1 H), 3.77 (s, 3 H), 3.43 (br s, 1 H) 3.23 (t, J = 6 Hz, 2 H), 2.70 (t, J = 6 Hz, 2 H), 1.90 (quintet, 2 H); mass spectrum, exact mass calcd for $C_{10}H_{12}NO^{79}Br$ m/e 241.0103, obsd m/e 241.0109.

Conversion of 8a to 6,7-Dimethoxyquinoline (19a). A solution of **8a** (8.66 mg, 0.388 mmol) in dry benzene (10 mL) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (88.2 mg, 0.388 mmol), and the resulting dark brown mixture was heated at reflux for 0.5 h. The cooled mixture was diluted with Et_2O (100 mL) and washed successively with saturated $NaHCO_3$ (2 × 15 mL), H_2O (10 mL), and brine (10 mL). Concentration gave a light yellow oil (ca. 100 mg), which was chromatographed on silica gel (1% $CH_3OH/CHCl_3$ as eluant) to give 6,7-dimethoxyquinoline (**19a**) (51 mg, 70%) as light yellow oil: IR (CCl_4) 1495, 1480, 1459, 1430, 1255, 1237, 1196, 1154, 850 cm^{-1}; ^1H NMR (90 MHz) δ 8.63 (m, 1 H), 7.90 (dd, J = 2, 9 Hz, 1 H), 7.33 (s, 1 H), 7.2–7.1 (m, 1 H), 6.93 (s, 1 H), 3.98 (s, 3 H), 3.95 (s, 3 H); mass spectrum, exact mass calcd for $C_{11}H_{11}NO_2$ m/e 189.0790, obsd m/e 189.0795.

Conversion of 8b to 6-Methoxy-7-bromoquinoline. A solution of **8b** (64 mg, 0.264 mmol) in dry benzene (5 mL) was treated with DDQ (120 mg, 0.529 mmol). The dark brown solution was stirred at room temperature for 5 min, diluted with Et_2O (50 mL), and washed with a saturated $NaHCO_3$ solution (3 × 10 mL) and brine (10 mL). Workup gave almost pure **19b**, which was further purified by chromatography on silica gel to give 6-methoxy-7-bromoquinoline (58 mg, 90%) as an off-white solid: mp 105.5–107 °C; IR (KBr) 1479, 1240, 1030, 847 cm^{-1}; ^1H NMR (90 MHz) δ 8.80 (dd, J = 1.5, 4 Hz, 1 H), 8.37 (s, 1 H), 8.06 (dd, J = 1.5, 9 Hz, 1 H), 7.37 (dd, J = 4, 9 Hz, 1 H), 7.09 (s, 1 H), 4.01 (s, 3 H); mass spectrum, exact mass calcd for $C_{10}H_8NO^{79}Br$ m/e 236.9790, obsd m/e 236.9796.

12d. Sodium hydride (60% in mineral oil, 105 mg) was washed free of mineral oil with hexane and added to a solution of **12c** (208.6 mg, 1 mmol) in THF (20 mL). The resulting yellow solution was cooled in an ice bath, and a solution of CH_3I (0.08 mL, 1.29 mmol) in THF (10 mL) was added. After being stirred overnight at room temperature, extractive workup (CH_2Cl_2) and chromatography on neutral alumina (1:1 EtOAc/CH_2Cl_2 as eluant) gave **12d** (112 mg, 50%) as a yellow oil: IR (KBr) 2970, 2940, 1465, 1370, 1210, 1120, 1103, 1069, 1039, 955 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.74 (d, J = 10 Hz, 1 H), 6.42 (dd, J = 10, 2.4 Hz, 1 H), 6.13 (d, J = 2.4 Hz, 1 H), 4.27 (d, J = 8.8 Hz, 1 H), 3.92 (d, J = 8.8 Hz, 1 H), 3.34 (s, 3 H), 3.32 (s, 3 H), 3.07 (s, 3 H), 1.45 (s, 3 H); mass spectrum, exact mass calcd for $C_{12}H_{17}NO_3$ m/e 223.1208, obsd m/e 223.1215.

Organolithium Additions to 12c/12d. 2,3-Dimethyl-5-methoxyindole from 12c. To a solution of i-Pr_2NH (0.15 mL, 1.1 mmol) in THF (20 mL) at 0 °C was added a 1.3 M CH_3Li solution (0.85 mL, 1.1 mmol). After being stirred for 15 min, the solution was cooled at −78 °C for 10 min, after which time **12c** (111.4 mg, 0.5 mmol) in THF (20 mL) was added through a cannula. After being stirred for 30 min, a 1.3 M CH_3Li solution (1.6 mL, 2.1 mmol) was added. The resulting red solution was stirred for 40 min, the dry ice bath was removed, and the reaction was quenched by addition of H_2O (5 mL) to give a light yellow solution. Extractive workup (CH_2Cl_2, 40 mL) gave a yellow solid (151.3 mg), which was dissolved in THF (30 mL), and a 5% HCl solution (2 drops) was added. After being stirred for 10 min at room temperature, the reaction was quenched by addition of an excess of saturated $NaHCO_3$ solution. Extractive workup (CH_2Cl_2, 2 × 30 mL) gave a red solid, which was purified by being passed through a silica gel column (CH_2Cl_2 and EtOAc/CH_2Cl_2 as eluant) to give **20a** (83.2 mg, 89%) as a light yellow solid: mp 106–108 °C (lit.[25] mp 108–112.5 °C); IR (KBr) 3376, 1480, 1452, 1424, 1239, 1214 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H), 2.32 (s, 3 H), 3.86 (s, 3 H), 6.6–7.2 (m, 4 H); mass spectrum, exact mass calcd for $C_{11}H_{13}NO$ m/e 175.0997, obsd m/e 175.0982.

2,3-Dimethyl-5-methoxyindole from 12d. To a solution of **12d** (46.3 mg, 0.21 mmol) in THF (15 mL) was added TMEDA (50 μL). The solution was cooled at −78 °C for 20 min before a 1.2 M CH_3Li solution (0.6 mL) was added, resulting in a red solution. After being stirred at −78 °C for 2 h and at room temperature for 1 h, H_2O was added to quench the reaction. Extractive workup (CH_2Cl_2) gave a red oil, which was dissolved in THF (20 mL), and 5% AcOH (0.1 mL) was added. After being shaken for 10 min, extractive workup (CH_2Cl_2) and chromatography on neutral alumina (CH_2Cl_2 as eluant) gave **20a** (15.6 mg, 43%). The ^1H NMR spectrum of the product was identical with that reported above.

2-Phenyl-3-methyl-5-methoxyindole (20b). To a solution of i-Pr_2NH (0.31 mL, 2.2 mmol) in THF (15 mL) at 0 °C was added a 1.3 M CH_3Li solution (1.7 mL, 2.2 mmol). After being stirred for 10 min, a solution of **12c** (229.6 mg, 1.1 mmol) in THF (20 mL) was added to the LDA solution over 10 min. The resulting brown solution was stirred for 30 min before a 1.5 M PhLi solution (3.0 mL, 4.5 mmol) was added; no color change was observed. After 40 min, the brown solution was warmed to 0 °C, and the reaction was quenched by the addition of H_2O, yielding a light yellow solution. Workup as usual gave a red oil (357 mg), which was dissolved in THF (30 mL), and 5% HCl (0.1 mL) was added. After being stirred for 10 min at room temperature, extractive workup (CH_2Cl_2, 3 × 40 mL) gave a red solid, which was chromatographed on silica gel to give **20b** (177.1 mg, 68%) as a light brown solid: mp 114–116 °C (lit.[26] mp 114–115 °C); IR (KBr) 3460, 1480, 1450, 1120 cm^{-1}; ^1H NMR (250 MHz) δ 8.2–7.8 (br, 1 H), 7.8–6.7 (m, 8 H), 3.91 (s, 3 H), 2.45 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.1, 135.0, 133.4, 131.0, 130.4, 128.7, 127.6, 127.2, 112.4, 111.5, 108.4, 100.8, 55.9, 9.7; mass spectrum, exact mass calcd for $C_{16}H_{15}NO$ m/e 237.1153, obsd m/e 237.1149.

1-Butyl-3-methyl-5-methoxyindole. To a solution of **12c** (86.4 mg, 0.41 mmol) in THF (15 mL) at −78 °C was added a 1.6 M n-BuLi solution (1.1 mL, 1.76 mmol), and the solution immediately turned dark red. After being stirred for 3 h at −78 °C, the brown solution was warmed to 0 °C, and the reaction was quenched by addition of H_2O (5 mL), resulting in a yellow solution. Extractive workup (CH_2Cl_2, 40 mL) gave a brown oil (100 mg). To a solution of the brown oil (67.6 mg) in THF (20 mL) was added a 5% HCl solution (0.1 mL). After being stirred for 10 min, a saturated $NaHCO_3$ solution (5 mL) was added to quench the reaction. Extractive workup (CH_2Cl_2, 40 mL) gave a dark oil (56.1 mg), which was chromatographed on silica gel (CH_2Cl_2 as eluant) to give **21a** as a light yellow oil (55.2 mg, 62%): IR (KBr) 2960, 2935, 1456, 1228 cm^{-1}; ^1H NMR (250 MHz) δ 7.18 (d, J = 8.8 Hz, 1 H), 6.99 (d, J = 2.4 Hz, 1 H), 6.88–6.83 (m, 2 H), 4.01 (t, J = 7 Hz, 2 H), 3.87 (s, 3 H), 2.29 (s, 3 H), 1.82–1.72 (m, 2 H), 1.39–1.20 (m, 2 H), 0.92 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.5, 131.7, 128.8, 126.1, 111.5, 109.9, 109.4, 100.8, 56.0, 46.0, 32.5, 20.2, 13.7, 9.6; mass spectrum, exact mass calcd for $C_{14}H_{19}NO$ m/e 217.1466, obsd m/e 217.1440.

1-*sec*-Butyl-3-methyl-5-methoxyindole. To a solution of i-Pr_2NH (0.3 mL, 2.1 mmol) in THF (30 mL) at 0 °C was added a 1.3 M CH_3Li solution (0.85 mL, 1.1 mmol). After being stirred for 30 min at 0 °C, the pale yellow solution was cooled to −78 °C for 30 min, and a solution of **12c** (185 mg, 0.9 mmol) in THF (20 mL) was added over 10 min. After being stirred at −78 °C for 40 min, a 1.3 M s-BuLi solution (1.75 mL, 2.28 mmol) was added dropwise. The brown reaction mixture was stirred for 1.5 h and

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warmed to 0 °C, and H_2O (5 mL) was added, resulting in a pale yellow solution. Extractive workup (CH_2Cl_2, 70 mL) gave a red oil (170 mg), which was dissolved in THF (30 mL), and a 5% HCl solution (0.1 mL) was added. After being stirred for 10 min at room temperature, the reaction was quenched by addition of a saturated $NaHCO_3$ solution. Workup followed by chromatography on silica gel (CH_2Cl_2 as eluant) gave **21b** (157.7 mg, 82%) as a light yellow oil, which solidified on standing: mp 36–38 °C; IR (NaCl) 2970, 2930, 1490, 1455, 1240, 1220, 1040 cm^{-1}; ^1H NMR (80 MHz) δ 7.3–6.8 (m, 4 H), 4.25 (m, 1 H), 3.85 (s, 3 H), 2.29 (d, J = 0.9 Hz, 3 H), 1.9–1.6 (m, 2 H), 1.42 (d, J = 7.3 Hz, 3 H), 0.79 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.6, 131.9, 128.9, 122.5, 111.4, 110.1, 101.1, 56.1, 53.1, 30.2, 21.0, 11.0, 9.8, one carbon not observed; mass spectrum, exact mass calcd for $C_{14}H_{19}NO$ m/e 217.1466, obsd m/e 217.1454.

1-*tert*-Butyl-3-methyl-5-methoxyindole (21c). To a 1.6 M t-BuLi solution (1.6 mL, 1.96 mmol) in THF (30 mL) at −78 °C was added a solution of **12c** (153.6 mg, 0.7 mmol) in THF (15 mL). The resulting light brown solution was stirred for 1.5 h before quenching the reaction by addition of H_2O (5 mL). Extractive workup (CH_2Cl_2, 50 mL) gave a red oil (97.4 mg), which was dissolved in THF (30 mL), cooled to −78 °C, and treated with a 5% HCl solution (0.1 mL). After reacting for 10 min at −78 °C, the solution was warmed to room temperature and stirred for another 10 min. Workup as usual followed by chromatography on alumina (5% EtOAc/CH_2Cl_2 as eluant) gave **21c** (83 mg, 52%) as a light yellow oil, which solidified on standing: mp 49–51 °C; IR (NaCl) 2980, 2930, 1485, 1455, 1440, 1290, 1260, 1235, 1080, 1040 cm^{-1}; ^1H NMR (250 MHz) δ 7.50 (d, J = 9 Hz, 1 H), 7.01 (m, 2 H), 6.81 (dd, J = 9, 2 Hz, 1 H), 3.89 (s, 3 H), 2.3 (s, 3 H), 1.69 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 153.1, 130.6, 130.4, 123.7, 113.7, 110.8, 108.3, 100.8, 55.8, 55.2, 29.8 (3 C), 9.5, one carbon not observed; mass spectrum, exact mass calcd for $C_{14}H_{19}NO$ m/e 217.1466, m/e obsd 217.1461.

Preparation of Deuterium Isotope Compounds. The procedures for the preparation of deuterium isotope compounds were similar to those described in the supplementary material section except lithium aluminum deuteride was used instead of lithium aluminum hydride.

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Registry No. **3a**, 106103-12-2; **3b**, 106103-14-4; **4a**, 125438-27-9; **6a**, 106103-20-2; **6b**, 106103-22-4; **7a**, 106103-13-3; **7b**, 106103-15-5; **8a**, 106103-21-3; **8b**, 106103-23-5; **9**, 125438-25-7; **9** amino quinone bisketal, 125438-28-0; **10**, 125438-26-8; **11a**, 106103-24-6; **11b**, 106103-25-7; **11c**, 106103-26-8; **11c**-*1,1*-d_2, 125438-51-9; **12a**, 106103-30-4; **12b**, 106103-31-5; **12c**, 106103-32-6; **12c**-d_2, 125438-40-6; **12d**, 125438-36-0; **13a**, 106103-27-9; **13b**, 106103-28-0; **14a**, 106103-33-7; **14b**, 106103-34-8; **15**, 106103-29-1; **16**, 106103-35-9; **17a**, 14430-23-0; **17b**, 106103-36-0; **18b**, 106103-37-1; **19a**, 67278-27-7; **19b**, 103028-33-7; **20a**, 828-94-4; **20b**, 64648-65-3; **21a**, 125438-37-1; **21b**, 125438-38-2; **21c**, 125438-39-3; **21c**-d_1, 125438-41-7; **25** (R = Me), 125438-60-0; 2,4,5-trimethoxybenzaldehyde, 4460-86-0; 2,4,5-trimethoxybenzaldehyde *O*-(trimethylsilyl)cyanohydrin, 125438-24-6; 2-(2,4,5-trimethoxyphenyl)ethylamine hydrochloride, 3166-78-7; malonic acid, 141-82-2; 2,4,5-trimethoxycinnamic acid, 24160-53-0; 2,4,5-trimethoxydihydrocinnamic acid, 125438-30-4; 2,4,5-trimethoxydihydrocinnamamide, 125438-29-1; 3-(2,4,5-trimethoxyphenyl)-propylamine hydrochloride, 125438-31-5; methyl 2,4,5-trimethoxybenzeneacetate, 2638-15-5; *N*-methyl-2-(2,4,5-trimethoxyphenyl)acetamide, 125438-32-6; *N*-methyl-2-(2,4,5-trimethoxyphenyl)ethylamine hydrochloride, 125438-33-7; 2,5-dimethoxydihydrocinnamic acid, 10538-49-5; 4-bromo-2,5-dimethoxydihydrocinnamic acid, 52428-11-2; 4-bromo-2,5-dimethoxydihydrocinnamide, 125438-34-8; 3-(4-bromo-2,5-dimethoxyphenyl)propylamine hydrochloride, 125438-35-9; 2-(4-bromo-2,5-dimethoxyphenyl)ethylamine hydrochloride, 56281-37-9; 2-(2-hydroxy-4-methoxyphenyl)ethylamine, 125438-42-8; 2-benzoxy-5-methoxybenzaldehyde, 56979-57-8; 2-benzoxy-3-methoxybenzaldehyde *O*-(trimethylsilyl)cyanohydrin, 125438-43-9; 2-(2-benzoxy-5-methoxyphenyl)-2-hydroxyethylamine, 125438-44-0; *N*-(trifluoroacetyl)-2-(2-benzoxy-5-methoxyphenyl)-2-hydroxyethylamine, 125438-45-1; 2-benzoxy-5-methoxyacetophenone, 65547-82-2; 2-benzoxy-5-methoxyacetophenone *O*-(trimethylsilyl)cyanohydrin, 125438-46-2; 2-(2-benzoxy-5-methoxyphenyl)-2-hydroxypropylamine, 125438-47-3; 2-(2-benzoxy-5-methoxyphenyl)-2-hydroxy-1,1-dideuteriopropylamine, 125438-48-4; *N*-(trifluoroacetyl)-2-(2-benzoxy-5-methoxyphenyl)-2-hydroxypropylamine, 125438-49-5; *N*-(trifluoroacetyl)-2-(2-benzoxy-5-methoxyphenyl)-2-hydroxy-1,1-dideuteriopropylamine, 125438-50-8; 3-(2-benzoxy-5-methoxyphenyl)-3-hydroxypropionitrile, 125438-52-0; 3-(2-benzoxy-5-methoxyphenyl)-3-hydroxypropylamine, 125438-53-1; *N*-(trifluoroacetyl)-3-(2-benzoxy-5-methoxyphenyl)-3-hydroxypropylamine, 125451-68-5; 3-(2-benzoxy-5-methoxyphenyl)-3-hydroxybutyronitrile, 125438-54-2; 3-(2-benzoxy-5-methoxyphenyl)-3-hydroxybutylamine, 125438-55-3; *N*-(trifluoroacetyl)-3-(2-benzoxy-5-methoxyphenyl)-3-hydroxybutylamine, 125438-56-4; 5-methoxy-8-benzoxy-α-tetralone, 81504-89-4; 5-methoxy-8-benzoxy-α-tetralone *O*-(trimethylsilyl)cyanohydrin, 125438-57-5; 8-benzoxy-1-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-methanamine, 125438-58-6; *N*-(trifluoroacetyl)-8-benzoxy-1-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-methanamine, 125438-59-7.

Supplementary Material Available: Preparation of compounds **3b**, **7a,b**, **9**, **11a–c**, **13a,b**, and **15**, ^1H NMR spectra of **12a,c,d** **14a,b**, and the intermediate from methyllithium addition to **12c**, and UV spectra of the progress on the anodic oxidation of **6a** and **6b** (26 pages). Ordering information is given on any current masthead page.