Acid-Promoted Competing Pathways in the Oxidative Polymerization of 5,6-Dihydroxyindoles and Related Compounds: Straightforward Cyclotrimerization Routes to Diindolocarbazole Derivatives

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Oxidation of 5,6-dihydroxyindole (**1a**) in acidic aqueous media led to isomeric hexahydroxydiindolocarbazoles, isolated as the acetyl derivatives **5a** (29%) and **6a** (19%). When the reaction is stopped in the very early stages, small amounts of the indolylindoline **17** and the open trimer **18** can be isolated. Similar oxidation of the *N*-methyl (**1b**) and *O*,*O*-dimethyl (**1c**) derivatives of **1a**, as well as of 5-methoxyindole (**9b**), 6-hydroxyindole (**14a**), and 6-benzyloxyindole (**14b**), afforded the corresponding diindolocarbazoles **5b** and **6b**, **5c** and **6c**, **10**, **16**, and the related tetramer **15** in up to 70% overall yield, whereas 5,6-diacetoxyindole (**1d**), 5-hydroxyindole (**9a**), and indole failed to give cyclotrimerization products. Formation of diindolocarbazoles could be explained by a mechanism in which the electron-donating substituents propitiate an array of acid-induced couplings and subsequent dehydrogenation steps driven by the energetically favorable closure of the fused aromatic framework.

Introduction

Because of the technological and commercial importance of indigo dyes,[1] whose history stretches back into antiquity, studies of the oxidation chemistry of hydroxyindoles have traditionally been concentrated on the 3-hydroxylated members of the series, the indoxyls, leaving behind the scenes their congeners with one or more hydroxyl groups on the benzene moiety. The latter compounds, nevertheless, are currently attracting increasing interest in view of their occurrence as the core structural moiety in a number of compounds of outstanding biomedical and industrial relevance, including neurotransmitters and hormones,[2] antitumor agents,[3] alkaloids, antibiotics, and enzyme cofactors.[4]

A prominent position, in this scenario, is occupied by 5,6-dihydroxyindole (**1a**) and its 2-carboxylic acid, which represent the key monomer intermediates in the biosynthesis of melanins, the primary pigments of skin, hair, and eyes in man and nonhuman mammals.[5] Despite pressing motivations for studies of the oxidation of 5,6-dihydroxyindoles, knowledge in this area until a decade ago was very scanty and fragmentary because of the discouraging chemistry of these compounds, which yield on oxidation intractable mixtures of polymers via bewildering arrays of oligomer intermediates.

A major breakthrough came in the 1980s, when the first isolation and structural characterization of a dimer of **1a** by an improved methodology[6] set the stage for a series of studies which opened up unprecedented vistas into the oxidation chemistry of 5,6-dihydroxyindoles[7] as well as of 4-, 5-, 6-, and 7-hydroxyindoles.[8]

The structural anatomy of the isolated oligomers disclosed different patterns of reactivity dictated by the position of the hydroxyl group on the indole ring. In particular, the mode of coupling of **1a** and related 5,6-dihydroxyindoles reflected an unanticipated propensity to couple through 2,2′-, 2,4′-, and 2,7′-linkages, as highlighted by the structures of the main dimers **2**−**4** isolated from oxidation of **1a** and **1b**. Such a mode of coupling stems from the peculiar dioxygenation pattern pertaining to the 5,6-dihydroxyindole system, which directs significant electron density on the 2-position of the indole ring,[7] favoring attack to the 4- and 7-positions of transient 5,6-indolequinone intermediates generated in the process.

In a reexamination of the oxidation chemistry of **1a**, we have now found that the typical mode of polymerization is inhibited at acidic pH, under which conditions a complex and entirely different pattern of products is

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(8) (a) Napolitano, A.; d'Ischia, M.; Prota, G. *Tetrahedron* **1988**, *44*, 7265−7270. (b) Napolitano, A.; d'Ischia, M.; Prota, G.; Schultz, T. M.; Wolfram, L. J. *Tetrahedron* **1989**, *45*, 6749−6760.

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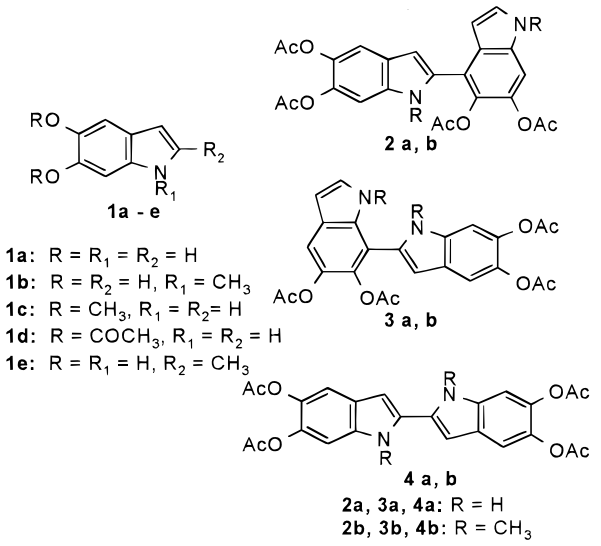


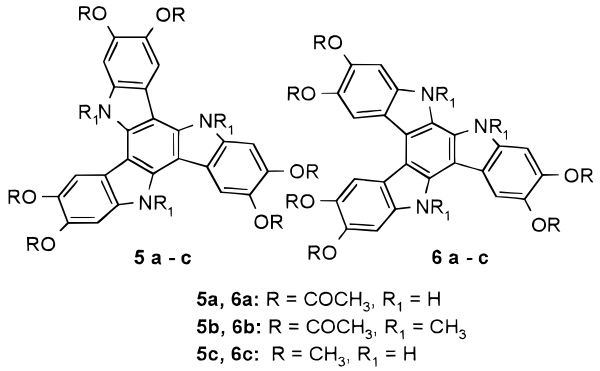
formed. This observation has prompted us to investigate in detail the oxidation chemistry of **1a** at acidic pH and to extend the study to a series of structurally related compounds, including 5- and 6-hydroxyindole and their *O*-alkyl derivatives.

Results and Discussion

Structural Characterization of the Products Formed by Acid-Promoted Oxidation of 1a. The ability of persulfate to bring about oxidation of various phenolic substrates in acidic media[9] inspired choice of this reagent to investigate oxidation of **1a** and related compounds. Careful analysis (TLC, HPLC) of reaction mixtures obtained by oxidation of **1a** at acidic pH, e.g., 1.4 or 3, followed by acetylation of the ethyl acetate-extractable fractions, revealed the formation of two main species whose chromatographic and spectrophotometric properties did not match with those of any known oligomer of **1a**. The more abundant of the two products gave a distinct pseudomolecular ion peak $(M + H)^+$ in the mass spectrum (FAB) at *m*/*z* 694, indicating a trimer of **1a**. The ^{1}H NMR and the ^{13}C NMR spectra displayed a relatively low number of resonances, denoting a highly symmetric structure. Only two singlets were present in the aromatic region of the proton spectrum, one of which shifted unusually downfield at δ 8.59.

Though structurally related (pseudomolecular ion peak at *m*/*z* 694), the companion product exhibited more complex ^{1}H and ^{13}C NMR spectra, including a characteristic set of three relatively downfield singlets (1H each) at δ 8.36, 8.43, and 8.67 compatible with an isomer in which the symmetrical structural architecture was disrupted. On the basis of these data, the products could be formulated as the symmetrical 2,3,7,8,12,13-hexaacetoxydiindolo[3,2-*a*:3′,2′-*c*]carbazole (**5a**) and its unsymmetrical isomer, 2,3,6,7,11,12-hexaacetoxydiindolo[2,3-*a*:2′,3′-*c*]carbazole[10] (**6a**).

Apparently, the low yields of **5a** and **6a** were partly due to the instability of their nonacetylated precursors in the oxidative reaction medium. This was checked in separate experiments in which removal of the acetyl groups by mild alkaline hydrolysis caused the deprotected



hexahydroxydiindolocarbazoles to suffer degradation to intractable materials in air or in the presence of oxidants.

The yields of **5a** and **6a** vs **2a** and **3a** obtained by oxidation of **1a** with various oxidizing systems and at different pH values are reported in Table 1. The formation of **5a** and **6a** increased with decreasing pH, whereas formation of **2a** and **3a** was virtually suppressed at pHs lower than 6. At pH 6, overall formation of **5a** and **6a** plus **2a** and **3a** was very poor after 20 min of oxidation, on account of a slow polymerization of **1a** affording dark melanin-like pigments without significant accumulation of intermediate oligomers. At pH 1.4 the material balance was one of the best ever obtained by oxidation of **1a**. In all cases examined, the remainder of the oxidation mixtures was accounted for by polar, chromatographically ill-defined species difficult to separate.

With ammonium persulfate, **5a** was prevailing over the whole acidic pH range, with the ratio of **5a**:**6a** being maximum at the lowest pH examined, i.e., 1.4. A similar product distribution was found with Fe^{2+}/H_2O_2 (Fenton reagent), whereas with cerium(IV) ammonium nitrate **6a** was obtained in a slight excess over that of **5a**. It is of interest that at pH 1.4 as weak an oxidant as molecular oxygen was able to bring about conversion of **1a** to **5a** and **6a**, albeit at slow rate, with a product distribution similar to that obtained with persulfate and Fenton reagent. In air-equilibrated solution at pH 1.4, decay of **1a** was negligible in the absence of oxidant over at least 30 min. No detectable formation of **5a** or **6a** was observed rigorously under oxygen-free conditions.

Oxidation of Substituted 5,6-Dihydroxyindoles and Derivatives in Acidic Medium. With these results available, another series of experiments was aimed at investigating the generality of the cyclotrimerization pathway and the effects of substituents on the course of the reaction. In the first instance, the possible involvement of the NH center in the acid-promoted oxidation of 5,6-dihydroxyindoles was probed using as substrate 5,6-dihydroxy-1-methylindole (**1b**). Oxidation of this compound under the usual conditions afforded, after acetylation, the corresponding trimers **5b** and **6b** in comparable yields.

Since the typical oxidation behavior of 5,6-dihydroxyindoles is governed by the peculiar position of the *o*-dihydroxy functionality, causing generation of highly unstable indolequinones,[11] it seemed of interest to investigate whether the *o*-dihydroxy group is directly involved

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(11) Napolitano, A.; Pezzella, A.; d'Ischia, M.; Prota, G. *Tetrahedron Lett.* **1996**, *37*, 4241−4242.

Table 1. Yields of Formation[a] of Diindolocarbazoles 5a−6a and of Dimers 2a−3a by Oxidation of 1a with Various Oxidants in Acidic Media

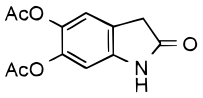
oxidant	pH	5a	6a	2a	3a	1d[b]
$(NH_4)_2S_2O_8$	1.4	33	21			5
$(NH_4)_2S_2O_8$	3.0	12	8			12
$(NH_4)_2S_2O_8$	5.0	7	5			17
$(NH_4)_2S_2O_8/Cu^{2+}$	5.0	4	5			25
$(NH_4)_2S_2O_8$	6.0	1	1	trace	trace	37
$(NH_4)_2S_2O_8/Cu^{2+}$	6.0	trace	1			35
$(NH_4)_2S_2O_8$	7.4			2	3	55
$(NH_4)_2S_2O_8/Cu^{2+}$	7.4			3	4	8
$Ce(NH_4)_2(NO_3)_6$	1.4	7	10			10
$Ce(NH_4)_2(NO_3)_6$	3.0	8	9			20
O_2	1.4	17[c]	8[c]			22[c]
Fe^{2+}/H_2O_2	3.0	14	9			16

[a] Percent yields determined at 30 min (HPLC). Data are means of two or three experiments. Normally, S.D. did not exceed ±10%. [b] Unreacted **1a**, recovered as the acetyl derivative. [c] Determined after 24 h.

in the acid-promoted cyclotrimerization route. To this aim, the oxidation reaction was carried out on suitable derivatives of **1a** protected on the hydroxyl groups, namely, 5,6-dimethoxyindole (**1c**) and 5,6-diacetoxyindole (**1d**), to which access to the corresponding semiquinones and quinones was clearly precluded.

Persulfate oxidation of **1c** at pH 1.4 afforded the corresponding trimers **5c** and **6c** in good overall yield (70%). Separation of the individual components proved, however, difficult despite considerable efforts. By close scrutiny of the ^{1}H NMR spectrum of the mixture, a prevalent formation of the unsymmetrical trimer **6c** could be observed.

Quite surprisingly, oxidation of **1d** at acidic pH failed to afford any diindolocarbazole derivative. Whatever the oxidant concentration and reaction times, substrate consumption was largely incomplete, and complex mixtures of products were invariably obtained, of which 5,6-diacetoxyoxindole (**7**) was the only isolable component (26%).



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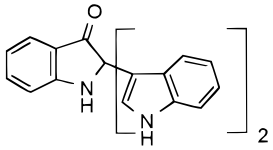

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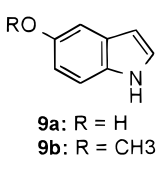
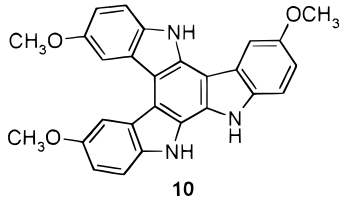
The observed suppression of the acid-driven cyclotrimerization pathway in the oxidation of **1d** was conceivably a consequence of the lower electron donating properties of the acetoxyl groups with respect to hydroxyl and alkoxyl groups, entailing that the latter groups were critical for viability of the cyclotrimerization route. To further probe this issue, recourse was made to the oxidation of the parent heterocycle, indole. This underwent slow conversion under the same reaction conditions adopted for oxidation of **1a** and derivatives, affording as main products oxindole and the trimer **8**,[12] with no detectable formation of diindolocarbazoles.

Since at low pH the catechol functionality of **1a** is virtually undissociated ($pK_a = 8.9$[13]) and is thus anticipated to be relatively more resistant to oxidation, it was considered important at this stage to assess whether such a group is still susceptible to oxidation with persulfate at acidic pH 3. For this purpose, preclusion of the cyclotrimerization route was deemed necessary and this was anticipated in the presence of a methyl group on the pyrrole moiety of the indole ring. Accordingly, 5,6-dihydroxy-2-methylindole (**1e**) was subjected to oxidation and was found to give, after acetylation, a complex pattern of products virtually identical to those formed at neutral pH, reflecting oxidation at the catechol functionality.[14]

Oxidation of 5- and 6-Hydroxyindoles and Derivatives in Acidic Medium. In another set of experiments we examined the oxidation behavior of 5- and 6-hydroxy- and -alkoxyindoles, to specifically evaluate and discriminate the relative effects of electron donating groups present on either the 5- or 6-position of the indole ring.

When 5-hydroxyindole (**9a**) and 5-methoxyindole (**9b**) were subjected to persulfate oxidation at pH 1.4, only the latter gave a cyclotrimerization product, identified as the unsymmetrical diindolocarbazole **10**, along with the indoxyl red dimer **11** and the trimers **12** and **13**, whereas the former afforded a pattern of products virtually superimposable to those obtained by oxidation at neutral pH,[8] with no detectable formation of cyclic trimers.





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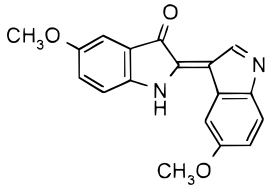

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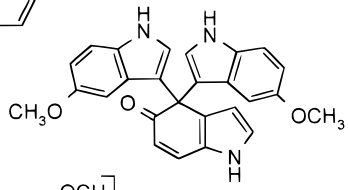

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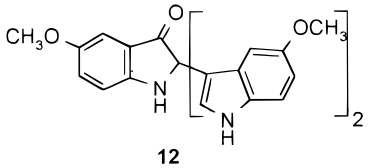

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Such a different behavior might be taken to indicate that, because of hindered resonance delocalization of the lone pair into the pyrrole moiety, the hydroxyl group on the 5-position is unable to activate the indole ring toward the acid-induced polymerization route, whereby viability of the phenolic oxidation route still constitutes the most accessible option. Alkylation of the hydroxyl group, however, partially hinders this oxidative route in **9b**, allowing the cyclotrimerization pathway to become competitive.

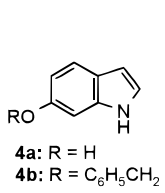
Both 6-hydroxyindole (**14a**) and 6-benzyloxyindole (**14b**) proved susceptible to acid-promoted oxidation to

(12) Remers, W. A.; Brown, R. K. In *Indoles*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Part I, pp 145−152.

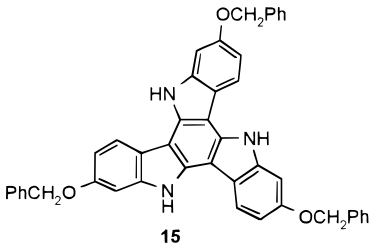
(13) Murphy, B. P.; Schultz, T. M. *J. Org. Chem.* **1985**, *50*, 2790−2791.

(14) Napolitano, A.; Crescenzi, O.; Tsiakas, K.; Prota, G. *Tetrahedron* **1993**, *49*, 9143−9150.

give complex patterns of products comprising diindolocarbazole derivatives. While **14b** was oxidized to the corresponding symmetrical diindolocarbazole **16**, **14a** gave as the main isolable product a tetramer in which a 6-acetoxyindol-3-yl unit was apparently linked to an unsymmetrical diindolocarbazole skeleton at one of the 7-positions of the fused 6-hydroxyindole rings. Unfortunately, attempts to establish the exact position of attachment of the indole unit by NMR techniques gave inconclusive results, so the product was only tentatively formulated as **15**.



4a: R = H
4b: R = $C_6H_5CH_2$



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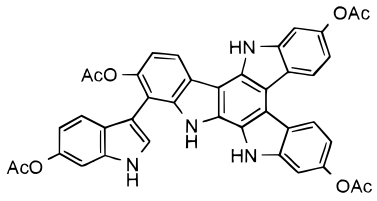

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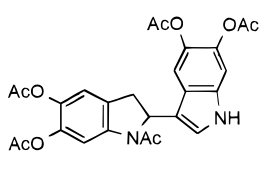
Mechanistic Issues. Having investigated the main structural factors inducing formation of cyclic trimers from 5,6-dihydroxyindole derivatives, we returned to the oxidation of **1a** at acidic pH to glean some information on the nature of possible intermediates in the construction of the isomeric diindolocarbazole rings.

By stopping the persulfate oxidation of **1a** after 1 or 2 s with sodium dithionite, it was possible to isolate small amounts of two species as the acetyl derivatives. The faster migrating of these species on TLC (silica gel) was identified as the indolylindoline **17** by straightforward spectral analysis. That the compound was not produced by reduction of a 2,3′-biindolyl precursor during workup was confirmed in separate experiments in which **17** could be obtained by usual workup of a reaction mixture but omitting treatment with sodium dithionite.

The other compound proved to be a trimer (pseudomolecular ion peak at *m*/*z* 742 by FAB-MS) and was readily identified as **18** by NMR analysis. TLC and HPLC analysis showed that **17** was present during the very first minutes, whereas **18** survived for a longer time, though only traces could be detected after 30 min. No detectable amount of the 2,2′-dimer **4a** or of other isolable dimers of **1a** was found by careful analysis of the reaction mixture, most of the remaining material being difficult to isolate and characterize.



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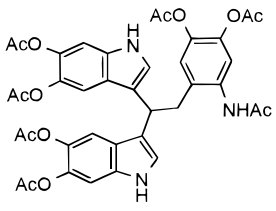

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The isolation of **17** and **18** furnished circumstantial, yet convincing evidence to suggest that formation of diindolocarbazoles is triggered by the reversible, acid-induced dimerization of **1a** via an indolylindoline intermediate.[15] This intermediate, isolated as the acetyl derivative **17**, represents a branching point from which two divergent routes depart, one driven by oxidants and leading to diindolocarbazoles and the other involving acid-induced ring opening,[15] to afford a trimer, obtained as **18** after acetylation (Scheme 1).

In the former route, the crucial steps would be dehydrogenation of the indolylindoline to a 2,3′-biindolyl and its subsequent reaction with protonated **1a** to give isomeric terindolyls which would readily cyclize to diindolocarbazoles in an acidic medium.[16] By delocalizing a higher electron density into the pyrrole moiety of the indole ring,[8b] the electron donating hydroxyl and alkoxyl groups would expectedly facilitate the initial protonation and dimerization equilibria and would accentuate the oxidizability of the intermediate indolylindoline, which is critical to tip the balance of competing routes in favor of the cyclotrimerization process. The factors governing the regiochemical outcome are intriguing and difficult to rationalize on the basis of available evidence. It is possible that the problem is somewhat compounded by the lack of complete product inventories, due to the complexity of the mixtures, and by differences in the inherent stability of the two isomers.

The one-pot formation of symmetrical diindolocarbazoles by oxidation of an indole substrate is, to the best of our knowledge, unprecedented. Unsymmetrical diindolocarbazole has however been reported to form in up to 19% yield by reaction of indole with Ti(III)− or Fe(II)−hydrogen peroxide systems in acidic media.[10]

Concluding Remarks

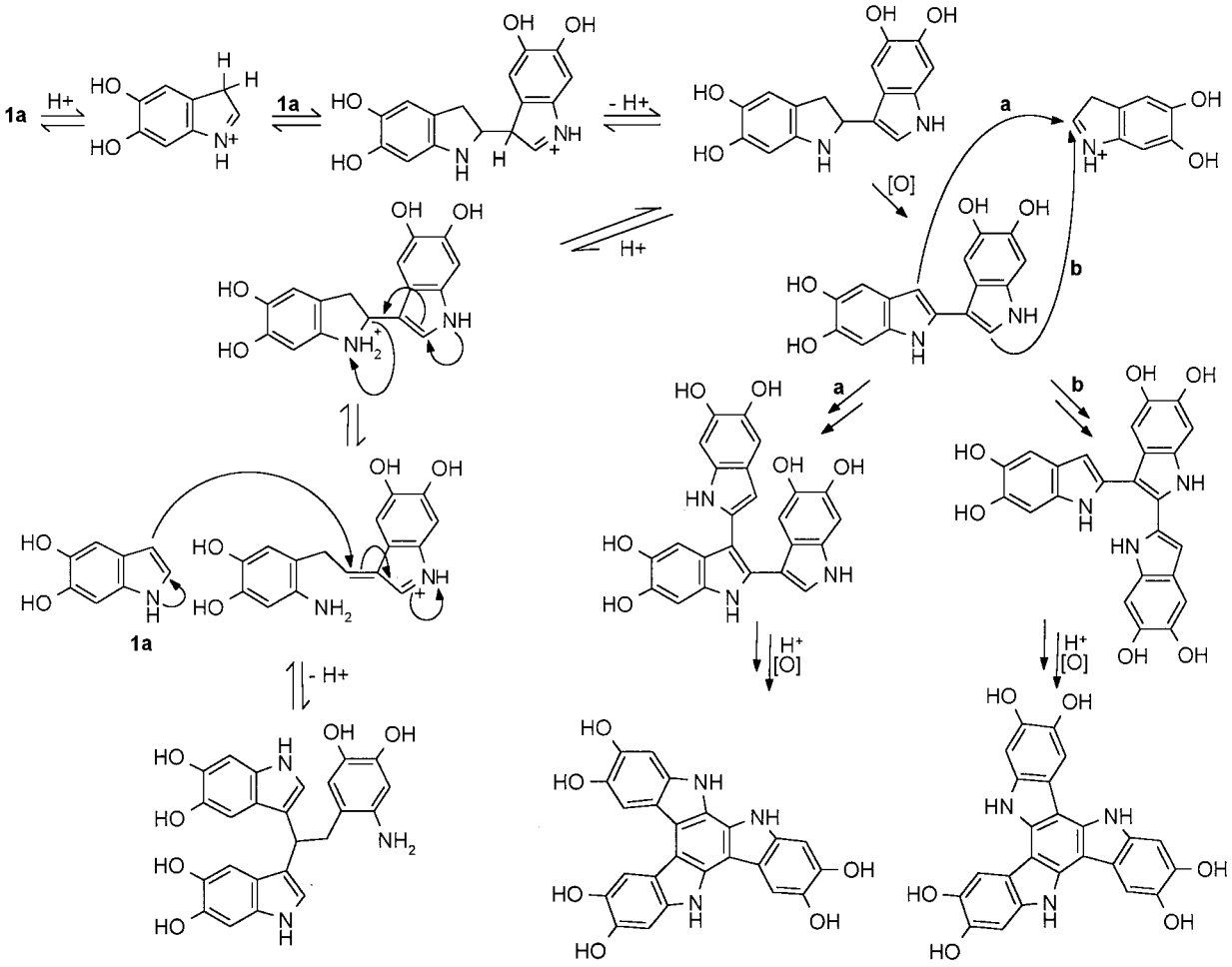
In this paper we have described novel oxidation pathways of 5,6-dihydroxyindoles and related compounds in acidic media leading to unusual symmetrical and/or unsymmetrical diindolocarbazoles as the most typical products. The cyclotrimerization reactions can be brought about by various oxidizing systems and occur only with electron-rich indoles carrying hydroxyl or alkoxyl groups, but not acetoxyl groups.

Besides expanding current knowledge of the oxidation chemistry of 5,6-dihydroxyindoles and related systems, the results of this study shed light on new reactions of potential synthetic value for preparation of hitherto little investigated diindolocarbazoles. Reported routes to this heterocyclic system generally involve multistep approaches and lead to complex mixtures of products with variable overall yields.[16] For synthetic purposes, control over formation of symmetrical versus unsymmetrical trimers appears a desirable goal. The pursuit of this objective as a means for expanding the synthetic scope

(15) Remers, W. A.; Brown, R. K. In *Indoles*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Part I, pp 66−70.

(16) (a) Bergman, J.; Eklund, N. *Tetrahedron* **1980**, *36*, 1445−1450. (b) Bergman, J.; Eklund, N. *Tetrahedron* **1980**, *36*, 1439−1443. (c) Bocchi, V.; Palla, G. *Tetrahedron* **1986**, *42*, 5019−5024. (d) Eissenstat, M. A.; Bell, M. R.; D'Ambra, T. E.; Alexander, E. J.; Daum, S. J.; Ackerman, J. H.; Gruett, M. D.; Kumar, V.; Estep, K. G.; Olefirowicz, E. M.; Wetzel, J. R.; Alexander, M. D.; Weaver, J. D.; Haycock, D. A.; Luttinger, D. A.; Casiano, F. M.; Chippari, S. M.; Kuster, J. E.; Stevenson, J. I.; Ward, S. J. *J. Med. Chem.* **1995**, *16*, 3094−3105.

Scheme 1. Main Reaction Pathways in the Acid-Promoted Oxidation of 1a



of these reactions holds mechanistic interest as well and may disclose new facets of theoretical and practical relevance.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on apparatuses operating at 400, 250, or 200 MHz with tetramethylsilane as internal reference. Wherever necessary, ^{1}H NMR and ^{13}C NMR assignments were supported by appropriate 2D heteronuclear correlation and DEPT experiments. Mass spectra were recorded using the electron ionization (EI) at 70 eV or the fast atom bombardment (FAB) techniques. For FAB-MS spectra, glycerol was preferably used as the matrix. Thin-layer chromatography (TLC) was performed on glass plates coated with a 0.25 or 0.5 mm layer of silica gel 60 F254. Analytical and preparative HPLC were carried out on reverse phase C18 columns (4.6 × 250 mm and 22 × 250 mm, respectively). The flow rate was 1 mL/min for analytical runs and 10 mL/min for preparative chromatography.

5,6-Dihydroxyindole (**1a**),[17] 5,6-dihydroxy-2-methylindole (**1e**),[14] and 5,6-dihydroxy-1-methylindole (**1b**)[17] were prepared by literature methods. 5,6-Diacetoxyindole (**1d**) and 6-benzyloxyindole (**14b**) were kindly provided by Clairol Research Laboratories (Stamford, CT). 6-Hydroxyindole (**14a**) was obtained by catalytic hydrogenolysis[18] of **14b**. All other indoles were commercially available. Ammonium persulfate was crystallized twice from hot water before use.

Oxidation of Indolic Compounds in Acidic Media. General Procedure. To a solution of the indole at indicated concentration in 0.1 M phosphoric acid, pH 1.4, unless otherwise stated, was added a freshly prepared aqueous solution of ammonium persulfate to the desired concentration. The progress of the reaction was monitored by TLC. When required, cupric acetate was added at equimolar concentration with respect to the indole substrate. Sodium dithionite was then added, and the mixture was rapidly extracted three times with ethyl acetate. The combined organic extracts were washed with small quantities of brine and water, carefully dried over anhydrous sodium sulfate, and concentrated by rotary evaporation at ambient temperature. When appropriate, the residue was acetylated overnight with acetic anhydride/pyridine. Adherence to this protocol was imposed by the need to destroy excess oxidant and prevent undesired oxidative degradation of the labile products after the reaction had gone to completion or during workup.

Oxidations with ceric ammonium nitrate were carried out as above by adding equimolar amounts of the oxidant to the substrate in 0.1 M phosphate buffer, pH 1.4 or 3.0. When most of the substrate was consumed (TLC evidence), sodium dithionite was added and the mixture rapidly extracted with ethyl acetate and subjected to workup as above.

Oxidations with the Fenton reagent were carried out in 0.1 M perchloric acid, pH 3.0, essentially as described by Kaneko et al.[10] under a nitrogen atmosphere.

Oxidations with molecular oxygen were carried out by bubbling oxygen gas through a solution of the substrate in 0.1 M phosphoric acid, pH 1.4. Product analysis and workup were as above.

Oxidation of 1a. From 500 mg of **1a** (10 mM) oxidized with ammonium persulfate (755 mg, 10 mM) was obtained 2,3,7,8,12,13-hexaacetoxydiindolo[3,2-*a*:3′,2′-*c*]carbazole (**5a**) as

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(18) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91−95.

a pale green solid (225 mg, 29%) which separated from the acetylated mixture taken up in ethyl acetate: mp 282 °C dec; UV (DMSO) λ_{max} (log ϵ) 317 (4.58), 338 (4.40, sh), 346 (4.03) nm; ^{1}H NMR (DMSO-d_6) δ 12.20 (s, 1H × 3), 8.56 (s, 1H × 3), 7.58 (s, 1H × 3), 2.46 (s, 3H × 3), 2.41 (s, 3H × 3); ^{13}C NMR (DMSO-d_6) δ 169.1, 168.7, 138.3, 135.9, 135.9, 134.56, 119.4, 113.5, 105.4, 100.5, 20.6, 20.3; MS (FAB) *m*/*z* 694; HRMS calcd for $C_{36}H_{28}N_3O_{12}$ ($M^+ + 1$) 694.1673, found 694.1669. Anal. Calcd for $C_{36}H_{27}N_3O_{12}$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.26; H, 3.90; N, 6.09.

Preparative TLC of the residue (silica gel, 0.5 mm, eluent benzene−acetone 65:35 v/v) gave a little more **5a** ($R_f = 0.33$) and 2,3,6,7,11,12-hexaacetoxydiindolo[2,3-*a*:2′,3′-*c*]carbazole (**6a**) ($R_f = 0.24$) as a brown solid which was crystallized from methanol (147 mg, 19%): mp 251 °C dec; UV (EtOH) λ_{max} (log ϵ) 247 (3.98), 315 (3.96), 331 (3.78, sh), 359 (3.48, sh), 377 (3.27, sh), 400 (3.06); ^{1}H NMR (DMSO-d_6) δ 12.11 (s, 1H), 11.72 (s, 1H), 11.63 (s, 1H), 8.67 (s, 1H), 8.43 (s, 1H), 8.36 (s, 1H), 7.79 (s, 1H), 7.79 (s, 1H), 7.63 (s, 1H), 2.59 (s, 3H), 2.46 (s, 3H), 2.45 (s, 3H × 2), 2.42 (s, 3H × 2); ^{13}C NMR (DMSO-d_6) δ 169.3 (3C), 168.8 (3C), 139.5 (2C), 138.3, 136.3, 136.0 (2C), 135.3, 135.2, 130.2, 126.7, 122.7, 120.1, 120.0, 119.6, 115.2, 114.5, 114.3, 113.5, 110.1, 107.9, 106.3, 106.2, 105.6, 105.4, 20.7 (3C), 20.6 (3C); MS (FAB) *m*/*z* 694; HRMS calcd for $C_{36}H_{28}N_3O_{12}$ ($M^+ + 1$) 694.1673, found 694.1675. Anal. Calcd for $C_{36}H_{27}N_3O_{12}$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.43; H, 3.92; N, 6.10.

For isolation of intermediate products, **1a** (200 mg) was oxidized as above, except that the reaction was stopped after about 1 s by treatment with sodium dithionite. After acetylation of the ethyl acetate-extractable fraction, the residue was chromatographed on silica gel plates (0.5 mm layer, eluent benzene−acetone 65:35 v/v) to give, besides much unreacted starting material as the acetyl derivative **1d**, *N*,5,6-triacetoxy-2-(5′,6′-diacetoxyindol-3′-yl)indoline (**17**) ($R_f = 0.36$) and impure **18** ($R_f = 0.18$).

17: 31 mg (9%); mp 136−137 °C; UV (EtOH) λ_{max} (log ϵ) 262 (4.10), 286 (3.96) nm; ^{1}H NMR (acetone-d_6) δ 10.34 (s, 1H), 8.05 (s, 1H), 7.27 (s, 1H), 7.23 (d, $J = 1.8$ Hz, 1H), 7.06 (s, 1H), 7.05 (s, 1H), 5.97 (dd, $J = 9.8, 1.9$ Hz, 1H), 3.81 (ddd, $J = 16.1, 9.8, 1.1$ Hz, 1H), 3.04 (dd, $J = 16.3, 2.1$ Hz, 1H), 2.28 (s, 3H), 2.23 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (acetone-d_6) 169.7, 169.4, 169.2, 168.9, 168.9, 142.1, 142.0, 139.6, 139.1, 137.5, 135.3, 129.5, 124.4, 122.7, 120.4, 118.6, 113.1, 112.4, 107.0, 58.8, 37.8, 23.6, 20.5 (4C); MS (EI) *m*/*z* 508; HRMS calcd for $C_{26}H_{24}N_2O_9$ (M^+) 508.1482, found 508.1477. Anal. Calcd for $C_{26}H_{24}N_2O_9$: C, 61.42; H, 4.76; N, 5.51. Found: C, 61.33; H, 4.70; N, 5.45.

The band containing **18** was rechromatographed on HPLC, mobile phase 0.1 M acetic acid−acetonitrile 60:40 v/v, to give pure **18**: 16 mg (5%); mp 158−160 °C; UV (EtOH) λ_{max} (log ϵ) 227 (3.98), 275 (3.29, sh), 288 (3.37), 294 (3.35, sh) nm; ^{1}H NMR (acetone-d_6) δ 10.08 (s, 1H × 2), 7.80 (s, 1H), 7.55 (s, 1H), 7.29 (s, 1H × 2), 7.22 (s, 1H × 2), 7.17 (d, $J = 1.8$ Hz, 1H × 2), 7.06 (s, 1H), 4.75 (t, $J = 7.3$ Hz, 1H), 3.51 (d, $J = 7.3$ Hz, 2H), 2.21 (s, 3H × 3), 2.19 (s, 3H × 2), 2.15 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (acetone-d_6) 169.4 (2C), 169.2 (3C), 168.7, 168.6, 141.1, 139.7, 139.1 (2C), 136.9 (2C), 135.5, 135.0 (2C), 132.3, 125.2 (2C), 125.1 (2C), 125.0, 119.4, 118.8 (2C), 113.2 (2C), 106.6 (2C), 37.0, 35.7, 23.6, 20.5 (3C), 20.5 (3C); MS (FAB) *m*/*z* 742; HRMS calcd for $C_{38}H_{36}N_3O_{13}$ ($M^+ + 1$) 742.2249, found 742.2244. Anal. Calcd for $C_{38}H_{35}N_3O_{13}$: C, 61.54; H, 4.76; N, 5.67. Found: C, 61.68; H, 4.71; N, 5.61.

Oxidation of 1b. From 500 mg of **1b** (10 mM), oxidized with ammonium persulfate (700 mg, 10 mM) was obtained a mixture of 2,3,7,8,12,13-hexaacetoxy-5,10,15-trimethyldiindolo[3,2-*a*:3′,2′-*c*]carbazole (**5b**) and 2,3,6,7,11,12-hexaacetoxy-9,14,15-trimethyldiindolo[2,3-*a*:2′,3′-*c*]carbazole (**6b**) as a solid which separated from the acetylated mixture taken up in ethyl acetate. Extensive washing of the solid with boiling acetone gave a white solid[19] consisting of virtually pure **5b** (195 mg, 26%): mp 293 °C dec; UV (DMSO) λ_{max} (log ϵ) 324 (4.85), 341 (4.57, sh), 356 (4.23) nm; ^{1}H NMR (DMSO-d_6) δ 8.02 (s, 1H × 3), 7.48 (s, 1H × 3), 3.97 (s, 3H × 3), 2.48 (s, 3H × 3), 2.38 (s, 3H × 3); MS (FAB) *m*/*z* 736; HRMS calcd for $C_{39}H_{34}N_3O_{12}$ ($M^+ + 1$) 736.2143, found 736.2150. Anal. Calcd for $C_{39}H_{33}N_3O_{12}$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.74; H, 4.54; N, 5.63.

Evaporation of the acetone washings to dryness afforded pure **6b** ($R_f = 0.70$, chloroform−acetone 8:2 v/v) as a greenish solid (180 mg, 24%): mp 237 °C dec; UV (DMSO) λ_{max} (log ϵ) 303 (3.22), 356 (2.78) nm; ^{1}H NMR (DMSO-d_6) δ 8.40 (s, 1H), 8.39 (s, 1H), 8.33 (s, 1H), 7.72 (s, 1H × 2), 7.68 (s, 1H), 4.35 (s, 3H), 4.15 (s, 3H), 4.10 (s, 3H), 2.40 (s, 3H × 6); ^{13}C NMR[19] (DMSO-d_6) δ 168.9 (3C), 168.5 (3C), 141.7, 141.2, 140.0, 139.7, 138.7, 138.6, 136.0, 135.7, 135.4, 131.2, 126.5, 120.5, 119.8, 119.0, 116.5, 115.7 (2C), 114.8, 109.4, 107.6, 106.0, 105.7, 104.6 (2C), 37.1, 36.7, 35.7, 20.7 (3C), 20.4 (3C); MS (FAB) *m*/*z* 736; HRMS calcd for $C_{39}H_{34}N_3O_{12}$ ($M^+ + 1$) 736.2143, found 736.2148. Anal. Calcd for $C_{39}H_{33}N_3O_{12}$: C, 63.67; H, 4.52; N, 5.71. Found: 63.61; H, 4.49; N, 5.61.

Oxidation of 1c. From 500 mg of **1c** (5 mM), oxidized with ammonium persulfate (645 mg, 20 mM) was obtained a green solid (345 mg, 70%) containing 2,3,7,8,12,13-hexamethoxydiindolo[3,2-*a*:3′,2′-*c*]carbazole (**5c**) and 2,3,6,7,11,12-hexamethoxydiindolo[2,3-*a*:2′,3′-*c*]carbazole (**6c**) as an intimate mixture which could not be separated:[20] ^{1}H NMR (DMSO-d_6) (mixture, integrated areas refer to each set of resonances) δ 11.45 (s, 1H × 3), 11.40 (s, 1H), 10.95 (s, 1H), 10.85 (s, 1H), 8.17 (s, 1H × 2), 8.16 (s, 1H), 8.14 (s, 1H × 3), 7.33 (s, 1H × 3), 7.29 (s, 1H), 7.25 (s, 1H × 2), 4.03 (s, 3H), 4.00 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H × 3); MS (FAB) *m*/*z* 526; HRMS calcd for $C_{30}H_{28}N_3O_6$ ($M^+ + 1$) 526.1979, found 526.1971.

Oxidation of 1d. From 500 mg of **1d** (10 mM), oxidized with ammonium persulfate (704 mg, 15 mM) in 0.1 M phosphate buffer, pH 3, 5,6-diacetoxyoxindole (**7**) ($R_f = 0.28$) could be isolated by preparative TLC (benzene−acetone 65:35 v/v), as a yellow solid (139 mg, 26%): mp 185−186 °C; UV (EtOH) λ_{max} (log ϵ) 251 (3.00), 286 (2.25) nm; ^{1}H NMR (acetone-d_6) δ 9.49 (s, 1H), 7.09 (s, 1H), 6.76 (s, 1H), 3.48 (s, 2H), 2.25 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (acetone-d_6) 176.8, 169.1, 168.7, 142.8, 142.4, 137.8, 124.4, 120.7, 105.4, 36.2, 20.5 (2C); MS (EI) *m*/*z* 249; HRMS calcd for $C_{12}H_{11}NO_5$ (M^+) 249.0637, found 249.0630. Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.90; H, 4.39; N, 5.70.

Oxidation of 1e. Oxidation of **1e** with ammonium persulfate, as reported in the general procedure, afforded a complex pattern of products identical to that obtained by oxidation at neutral pH.[14] By preparative TLC (chloroform−methanol 8:2 containing 1% acetic acid) three main oligomers could be isolated (see Supporting Information), which proved identical (^{1}H and ^{13}C NMR, TLC, EI-MS) with authentic samples.

Oxidation of 9a. Oxidation of **9a** as reported in the general procedure afforded a complex pattern of products identical to that obtained by oxidation at neutral pH.[8] By preparative TLC (benzene−acetone 65:35 v/v), four main oligomers could be isolated (see Supporting Information) which proved identical (^{1}H and ^{13}C NMR, TLC, EI-MS) with authentic samples.[8]

Oxidation of 9b. From 500 mg of **9b** (10 mM), oxidized with ammonium persulfate (7.26 g, 50 mM), 3,6,11-trimethoxydiindolo[2,3-*a*:2′,3′-*c*]carbazole (**10**), the indoxyl red derivative **11**, 2,2-bis(5-methoxyindol-3-yl)-5-methoxyindol-3-one (**12**), and 4,4-bis(5-methoxyindol-3-yl)indol-5(4*H*)-one (**13**) were obtained by preparative TLC (benzene−acetone 8:2 v/v).

10: green solid (133 mg, 26%); $R_f = 0.53$; mp 217 °C dec; UV (EtOH) λ_{max} (log ϵ) 252 (4.73), 311 (4.61), 359 (4.48), 403 (4.09) nm; ^{1}H NMR (DMSO-d_6) δ 11.61 (s, 1H), 11.30 (s, 1H), 11.19 (s, 1H), 8.27 (d, $J = 2.4$ Hz, 1H), 8.23 (d, $J = 2.4$ Hz, 1H), 8.19 (d, $J = 2.4$ Hz, 1H), 7.68 (d, $J = 8.7$ Hz, 1H), 7.67 (d, $J = 8.7$ Hz, 1H), 7.66 (d, $J = 8.7$ Hz, 1H), 7.10 (dd, $J = 8.2, 2.3$ Hz, 1H), 7.08 (dd, $J = 8.8, 2.6$ Hz, 1H), 7.05 (dd, $J = 7.3, 2.6$ Hz, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 4.00 (s, 3H); ^{13}C NMR (DMSO-d_6) 153.8, 152.9, 152.8, 133.7, 133.6, 133.2, 130.1, 126.9, 123.4, 123.3, 122.7, 122.5, 113.8, 113.2, 112.9, 112.4, 112.0, 111.8, 111.3, 107.9, 105.9, 104.1, 104.0, 103.5, 56.1, 55.3

(19) Compounds **5b** and **6b** were only sparingly soluble in DMSO and acetone and insoluble in all other solvents examined. The exceedingly low solubility of **5b** prevented acquisition of its ^{13}C NMR spectrum, whereas a poor spectrum was obtained in the case of **6b** even after a high number of scans.

(2C); MS (EI) *m/z* 435; HRMS calcd for $C_{27}H_{21}N_3O_3$ (M^+) 435.1584, found 435.1590. Anal. Calcd for $C_{27}H_{21}N_3O_3$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.56; H, 4.82; N, 9.52.

11: purple solid (104 mg, 20%); mp 205−207 °C; $R_f = 0.75$; UV (EtOH) λ_{max} (log ϵ) 278 (2.95), 305 (2.62), 368 (2.15), 561 (2.09) nm; ^{1}H NMR (acetone-d_6) δ 11.06 (s, 1H), 8.46 (s, 1H), 8.05 (d, $J = 2.6$ Hz, 1H), 7.44 (d, $J = 8.8$ Hz, 1H), 7.23 (dd, $J = 6.5$, 2.4 Hz, 1H), 7.05 (dd, $J = 7.1$, 2.7 Hz, 1H), 7.04 (d, $J = 2.2$ Hz, 1H), 6.90 (dd, $J = 8.8$, 2.6 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (acetone-d_6) 196.4, 159.7, 158.4, 157.2, 156.9, 133.1, 132.7, 128.1, 124.6, 122.1, 121.5, 114.0, 113.6, 111.3, 108.2, 106.0, 56.3, 55.9; MS (EI) *m/z* 306; HRMS calcd for $C_{18}H_{14}N_2O_3$ (M^+) 306.1005, found 306.0998. Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.71; H, 4.72; N, 9.10.

12: yellow-green solid (67 mg, 14%); mp 201−203 °C; $R_f = 0.49$; UV (EtOH) λ_{max} (log ϵ) 275 (4.41), 298 (4.38), 343 (3.88), 360 (3.94), 382 (3.75), 404 (3.78), 430 (3.64) nm; ^{1}H NMR (acetone-d_6) δ 9.97 (s, 1H × 2), 7.26 (d, $J = 8.8$ Hz, 1H × 2), 7.21 (dd, $J = 9.0$, 2.7 Hz, 1H), 7.20 (d, $J = 2.4$ Hz, 1H × 2), 7.06 (d, $J = 2.7$ Hz, 1H), 7.03 (d, $J = 9.0$ Hz, 1H), 6.96 (d, $J = 2.5$ Hz, 1H × 2), 6.77 (s, 1H), 6.71 (dd, $J = 8.8$, 2.5 Hz, 1H × 2), 3.77 (s, 3H), 3.55 (s, 3H × 2); ^{13}C NMR (acetone-d_6) 202.0, 157.7, 154.3 (2C), 153.8, 133.5 (2C), 128.2, 127.5 (2C), 125.6 (2C), 120.6, 115.7 (2C), 114.8, 112.8 (2C), 112.0 (2C), 105.5, 103.9 (2C), 69.9, 56.0, 55.5 (2C); MS (EI) *m/z* 453; HRMS calcd for $C_{27}H_{23}N_3O_4$ (M^+) 453.1690, found 453.1681. Anal. Calcd for $C_{27}H_{23}N_3O_4$: C, 71.51; H, 5.11; N, 9.27. Found: C, 71.42; H, 5.13; N, 9.34.

13: orange solid (72 mg, 14%); mp 227−228 °C; $R_f = 0.25$; UV (EtOH) λ_{max} (log ϵ) 289 (3.76), 350 (3.62), 446 (3.10) nm; ^{1}H NMR (acetone-d_6) δ 10.56 (s, 1H), 9.89 (s, 1H × 2), 7.47 (d, $J = 9.7$ Hz, 1H), 7.24 (d, $J = 8.8$ Hz, 1H × 2), 6.94 (t, $J = 2.7$ Hz, 1H), 6.86 (d, $J = 2.5$ Hz, 1H × 2), 6.79 (d, $J = 2.6$ Hz, 1H × 2), 6.69 (dd, $J = 8.8$, 2.5 Hz, 1H × 2), 5.84 (t, $J = 2.2$ Hz, 1H), 5.68 (d, $J = 9.7$ Hz, 1H), 3.57 (s, 3H × 2); ^{13}C NMR (acetone-d_6) 201.2, 154.7 (2C), 133.5, 133.4, 128.0 (2C), 126.5 (2C), 126.4, 125.2, 122.5 (2C), 122.3, 119.5, 117.4 (2C), 112.3 (2C), 111.6 (2C), 111.4, 105.0 (2C), 55.3 (2C), 55.0; MS (EI) *m/z* 423; HRMS calcd for $C_{26}H_{21}N_3O_3$ (M^+) 423.1584, found 423.1593. Anal. Calcd for $C_{26}H_{21}N_3O_3$: C, 73.74; H, 5.00; N, 9.92. Found: C, 73.81; H, 5.10; N, 9.80.

Oxidation of 14a. From 100 mg of **14a** (20 mM), oxidized with ammonium persulfate (172 mg, 20 mM), tetramer **15** could be obtained by preparative TLC (benzene−acetone 7:3 v/v) as a brown solid (7 mg, 5%): $R_f = 0.43$; mp 163−165 °C; UV (EtOH) λ_{max} (log ϵ) 255 (3.83), 310 (3.72), 351 (3.51), 369 (3.12), 391 (3.03) nm; ^{1}H NMR (acetone-d_6) δ 10.87 (s, 1H), 10.78 (s, 1H), 10.69 (s, 1H), 10.38 (s, 1H), 8.87 (d, $J = 9.4$ Hz, 1H), 8.76 (d, $J = 9$ Hz, 1H), 8.32 (d, $J = 9$ Hz, 1H), 7.79 (m, 1H), 7.53 (d, $J = 9$ Hz, 1H), 7.47 (d, $J = 2$ Hz, 1H), 7.43 (d, $J = 2$ Hz, 1H), 7.38 (d, $J = 2$ Hz, 1H), 7.26 (d, $J = 9$ Hz, 1H), 7.14 (dd, $J = 9$, 2 Hz, 1H), 6.93 (dd, $J = 9$, 2 Hz, 1H), 6.89 (dd, $J = 9$, 2 Hz, 1H), 2.34 (s, 3H × 2), 2.31 (s, 3H), 2.30 (s, 3H); MS (FAB) *m/z* 693; HRMS calcd for $C_{40}H_{29}N_4O_8$ ($M^+ + 1$) 693.1987, found 693.1992.

Oxidation of 14b. From 200 mg of **14b** (10 mM), oxidized with ammonium persulfate (307 mg, 15 mM), 2,7,12-tribenzyloxydiindolo[3,2-*a*:3′,2′-*c*]carbazole (**16**) could be obtained by preparative TLC (benzene−acetone 9:1 v/v) as a gray solid (46 mg, 24%): $R_f = 0.37$; mp 229−230 °C; UV (EtOH) λ_{max} (log ϵ) 246 (3.39), 272 (3.30), 315 (3.40), 341 (2.89), 382 (2.20) nm; ^{1}H NMR (acetone-d_6) δ 10.90 (s, 1H × 3), 8.37 (d, $J = 9.1$ Hz, 1H × 3), 7.55 (dd, $J = 7.2$, 1.7 Hz, 1H × 2 × 3), 7.41 (dd, $J = 7.2$, 1.7 Hz, 1H × 2 × 3), 7.37 (dd, $J = 7.2$, 1.7 Hz, 1H × 3), 7.30 (d, $J = 2.4$ Hz, 1H × 3), 7.02 (dd, $J = 9.1$, 2.4 Hz, 1H × 3), 5.24 (s, 2H × 3); ^{13}C NMR (acetone-d_6) 157.2, 141.1, 139.1, 129.5, 129.2, 128.7, 128.6, 121.2, 118.2, 109.8, 102.1, 97.6, 71.1; MS (FAB) *m/z* 664; HRMS calcd for $C_{45}H_{34}N_3O_3$ ($M^+ + 1$) 664.2602, found 664.2614. Anal. Calcd for $C_{45}H_{33}N_3O_3$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.57; H, 5.08; N, 6.28.

Oxidation of Indole. From 500 mg of indole (10 mM), oxidized with ammonium persulfate (950 mg), oxindole and **8** could be obtained by preparative TLC (benzene−acetone 8:2 v/v).

Oxindole: 195 mg (26%); $R_f = 0.34$; mp 124−126 °C (lit.[21] mp 126−127 °C). **8**: 162 mg (32%); $R_f = 0.45$; mp 240−242 °C (lit.[22] mp 243−245.5 °C). All other properties (^{1}H and ^{13}C NMR, TLC, EI-MS) were identical with those of authentic samples.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **5a**, **6a**, **10**, **16**, **17** and **18**. ^{1}H NMR spectra of **5b**, **6b**, **5c**+**6c** (mixture), and **15**. Spectral data of **8**. Structures of oligomers obtained by oxidation of **1e** and **9a** in acidic medium (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(20) Attempts to separate **5c** and **6c** by crystallization, TLC, or HPLC were frustrated by their extreme insolubility and the similar chromatographic behavior under a variety of conditions. Removal of impurities could only be achieved by repeated washings with acetone. In three different reactions, **5c**:**6c** ratios were found to be in the range of 0.33−0.5, as apparent from integrated signal areas in the ^{1}H NMR spectra of the mixtures. The solubility problem and the tendency of the compounds to exhibit signal broadening prevented acquisition of a meaningful ^{13}C NMR spectrum. In spite of our efforts, a satisfactory result of elemental analysis could not be obtained. To show the purity of the sample, a copy of the ^{1}H NMR spectrum (400 MHz) is provided as Supporting Information.

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