Novel Ring Contraction of 3-Hydroxy-2,4(1*H*,3*H*)-quinolinediones in Aqueous Alkali. The First Convenient Route to 2-Hydroxyindoxyls

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Ring contraction of 3-hydroxy-2,4(1*H*,3*H*)-quinolinediones (**1**) in aqueous potassium hydroxide resulted in the formation of 2-hydroxyindoxyls and/or dioxindoles. The choice of N-substituent and the reaction conditions govern the chemoselectivity of the reaction. *N*-Phenyl-substituted derivatives **1** give 2-hydroxyindoxyls, while *N*-alkyl- and *N*-benzyl-substituted derivatives afford the corresponding dioxindols. On the basis of byproduct analysis, as well as independent experiments, the most plausible reaction mechanism is proposed.

Introduction

Indoxyls play a role in chemistry and biochemistry. They have proved to be useful synthetic intermediates for the synthesis of various natural products and biologically active compounds[1] such as the naturally occurring antitumor antibiotic FR900482,[2] mitomycin C,[3] dragmacidin A,[4] and others.[5] 2-Hydroxyindoxyl alkaloid melochicorin was found in the plant *Melochia corchorifolia*,[6] while other indoxyl alkaloids are documented as well.[7] Similarly, dioxindole derivatives are encountered in nature. Dioxindole derivatives were isolated from the culture of a marine *Streptomyces* species.[8,9] A rare example of sulfur-containing phytoalexins, exemplified by dioxindole dioxibrassinin,[10] was isolated from cabbage inoculated with *Pseudomonas cichorii*.[11] Very recently, four proteasome inhibitors of dioxindole structure were isolated from the fermentation broth of *Apiospora montagnei* Sacc. TC 1093.[12]

While dioxindoles are relatively easily obtained by Grignard reaction on isatins[13] and by oxidation of 1,3-disubstituted 2-indolinones,[14] the preparation of 2-hydroxyindoxyls still remains a synthetic challenge. Most of the reported methods involve the oxidation of indolic compounds whereby using *m*-CPBA,[5a,15] monoperphthalic acid,[16] and dimethyldioxirane,[17] 2-hydroxyindoxyls are often formed only as byproducts. Better results were obtained with Davis' reagent.[3] Sakamoto et al.[18] carried out extensive work on oxidation of 2-substituted *N*-acylindoles by MoO_5·HMPA, which directly afforded 1-acetyl-2-hydroxyindoxyls. However, relatively long reaction times and rather low yields render such an approach less attractive. Other approaches to *N*-acyl-2-hydroxyindoxyls involve oxidation of 2,3,6-trimethyl-4-(1*H*)-quinolinone by NaOCl[19] and 2-methyl-3-phenylquinolinone by acidic potassium permanganate,[20] in 30% and 12% yields, respectively. To our knowledge, there is only one example in the literature for the synthesis of *N*-aryl (or alkyl)-substituted 2-hydroxyindoxyls, where 3-(1-adamantyl)-3-hydroxy-1-methylindolin-2-one was formed by the oxidation of the corresponding indole derivative with dimethyldioxirane at −78 °C, in 10% yield.[17]

Recently, we reported the unique reactivity of 3-hydroxy-2,4(1*H*,3*H*)-quinolinediones (**1**) in the presence of a base under nonaqueous conditions, where 3-acyloxy-1,3-dihydro-2*H*-indol-2-ones were formed via an α-ketol

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(1) Kawasaki, T.; Masuda, K.; Baba, Y.; Terashima, R.; Takada, K.; Sakamoto, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 729−733 and references cited therein.
(2) Zhang, W.; Wang. C.; Jimenez, L. S. *Synth. Commun.* **2000**, *30*, 351−366.
(3) Wang, Z.; Jimenez, L. S. *J. Am. Chem. Soc.* **1994**, *116*, 4977−4978.
(4) Kawasaki, T.; Enoki, H.; Matsumura, K.; Ohyama, M.; Inagawa, M.; Sakamoto, M. *Org. Lett.* **2000**, *2*, 3027−3029.
(5) For example, see: (a) Desarbre, E.; Savelon, L.; Cornec, O.; Mérour, J. Y. *Tetrahedron* **1996**, *52*, 2983−2994. (b) Kawasaki, T.; Tang, C.-Y.; Koizumi, E.; Nakanishi, H.; Sakamoto, M. *Heterocycles*, **1998**, *48*, 975−980. (c) Nonaka, Y.; Kawasaki, T.; Sakamoto, M. *Heterocycles* **2000**, *53*, 1681−1684. (d) Mérour, J.-Y.; Gadonneix, P.; Malapel-Andrieu, B.; Desarbre, E. *Tetrahedron*, **2001**, *57*, 1995−2002 and references cited therein.
(6) Bhakuni, R. S.; Shukla, Y. N.; Thakur, R. S. *Phytochemistry* **1991**, *30*, 3159−3160.
(7) Seigler, D. S. *Plant Secondary Metabolism;* Kluwer Academic Publishers: Norwell, MA, 1998.
(8) Tang, Y.-Q.; Sattler, I.; Thiericke, R.; Grabley, S.; Feng, X.-Z. *Eur. J. Org. Chem.* **2001**, 261−267.
(9) Balk-Bindseil, W.; Helmke, E.; Weyland, H.; Laatsch, H. *Liebigs Ann. Chem.* **1995**, 1291−1294.
(10) Soledade, M.; Pedras, C.; Okanga, F. I. *Chem. Commun.* **1998**, 67−68.
(11) Monde, K.; Sasaki, K.; Shirata, A.; Takasugi, M. *Phytochemistry* **1991**, *30*, 2915−2917.
(12) Kohno, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Kuroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990−995.
(13) (a) Ogata, M.; Matsumoto, H.; Tawara, K. *Eur. J. Med. Chem. Chim. Ther.* **1981**, *16*, 373−379. (b) Wierenga, W.; Griffin, J.; Warpehoski, M. A. *Tetrahedron Lett.* **1983**, *24*, 2437−2440.
(14) Nishio, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1717−1720.
(15) Bourlot, A. S.; Desarbre, E.; Mérour, J. Y. *Synthesis* **1994**, 411−416.
(16) Braudeau, E.; David, S.; Fischer, J.-C. *Tetrahedron* **1974**, *30*, 1445−1455.
(17) Zhang, X.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867−8868.
(18) Chien, C.-S.; Takanami, T.; Kawasaki, T.; Sakamoto, M. *Chem. Pharm. Bull.* **1985**, *33*, 1843−1848.
(19) Staskun, B. *J. Org. Chem.* **1988**, *53*, 5287−5291 and ref 3 cited therein.
(20) Rees, C. W.; Sabet, C. R. *J. Chem. Soc.* **1965**, 870−875.

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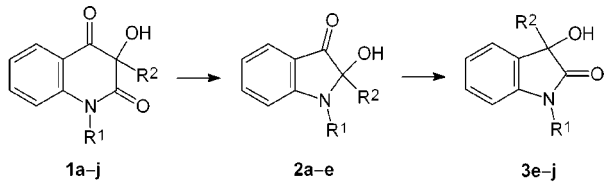
Scheme 1



rearrangement.[21] Since these types of rearrangements are of great importance in metabolism,[22−24] we were prompted to investigate the reactivity of **1** under aqueous, basic conditions in the presence of air.[25,26] Although our primary goal was aimed at better understanding the metabolism of **1**, the high product yields in these reactions led us to explore their synthetic utility as well. Herein, we wish to demonstrate that 3-hydroxy-2,4-(1*H*,3*H*)-quinolinediones (**1**) react with aqueous potassium hydroxide to produce 2-hydroxy-1,2-dihydroindol-3-ones (2-hydroxyindoxyls, **2**) and/or isomeric 3-hydroxy-1,3-dihydroindol-2-ones (dioxindoles, **3**) in good yields.

Results and Discussion

Starting compounds **1a**−**j** were readily obtained according to the literature procedure by condensation of N-substituted anilines with diethyl malonates to the corresponding 4-hydroxy-2(1*H*)-quinolones, followed by oxidation with peroxyacetic acid.[27−29] In a typical ring-contraction experiment, the reaction of **1a** (Scheme 1, Table 1) was conducted in a vigorously stirred mixture of 1.3 M aqueous KOH and benzene at room temperature and in the presence of air. The reaction mixture turned yellow, and after 0.5 h the reaction was complete. According to TLC analysis, one major product was formed, accompanied by small amounts of a few byproducts. Layers were separated, and the aqueous phase was extracted with benzene. The combined organic layers were concentrated, and the crude product was subjected to column chromatography to yield **2a**. Similarly, four other *N*-phenyl-substituted quinolinediones **1b**−**e** (Table 1, entries 2−5) were reacted to yield 2-hydroxyindoxyls **2b**−**e**. In the case of **1e**, benzoin **4** was also formed and was isolated in low yield (Figure 1, Table 1).

In contrast to *N*-phenyl-3-hydroxy-2,4(1*H*,3*H*)-quinolinediones **1a**−**e**, a significant decrease in the reactivity was observed for *N*-alkyl-substituted analogues **1f**−**j** (Table 1, entries 7−11). In reactions with these compounds, two products were initially formed (as indicated by TLC analysis), and according to the characteristic yellow color, one was tentatively identified as 2-hydroxyindoxyl. However, along with the consumption of the starting material, the yellow product disappeared from the reaction mixture as well. Isolation as described above yielded colorless dioxindoles **3f**−**j**. In some cases, we succeeded in isolating some byproducts as indicated in Table 1.

Table 1. Reaction of 1a−j with Aqueous KOH

entry	substrate **1**	R^1	R^2	reaction time (h)	products (yield)[a] **2**	**3**	others
1	**1a**	Ph	Me	0.5	**2a** (52)		
2	**1b**	Ph	Et	6	**2b** (71)		
3	**1c**	Ph	Pr	3	**2c** (73)		
4	**1d**	Ph	Bu	4.5	**2d** (51)		
5	**1e**	Ph	Ph	2.5	**2e** (57)		**4** (21)
6	**1e**	Ph	Ph	4	**2e** (25)	**3e** (11)	**4** (21)
7	**1f**	Me	Bu	7[b]		**3f** (64)	
8	**1g**	Et	Bn	39[b]		**3g** (45)	**6g** (29), **8g** (38)
9	**1h**	Bn	Bn	43[b]		**3h** (42)	
10	**1i**	Me	Ph	12		**3i** (57)	**6i** (10), **8i** (5)
11	**1j**	Bn	Ph	160		**3j** (33)	**5** (16), **6j** (5), **7j** (9), **8i** (10)

[a] Refers to isolated percent yield. [b] Reaction conducted at reflux.

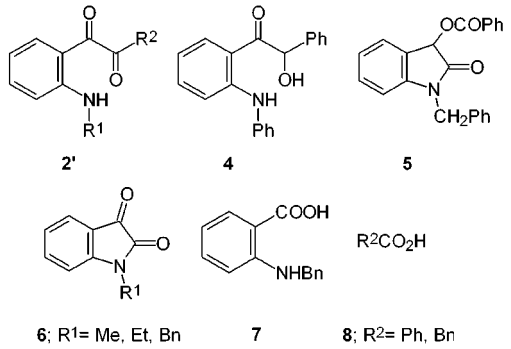
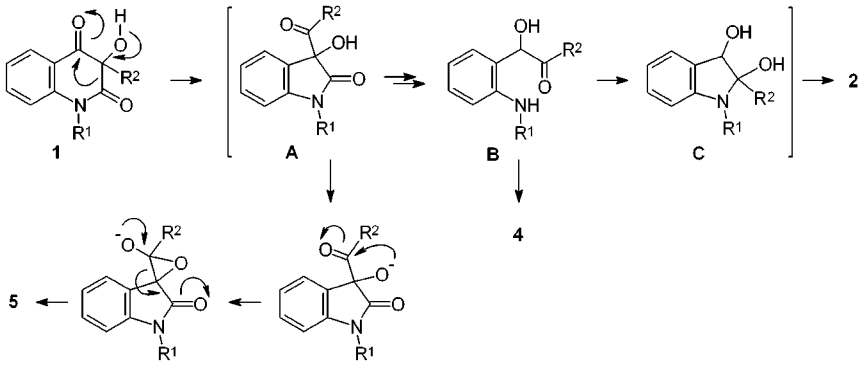


Figure 1. Structures of byproducts.

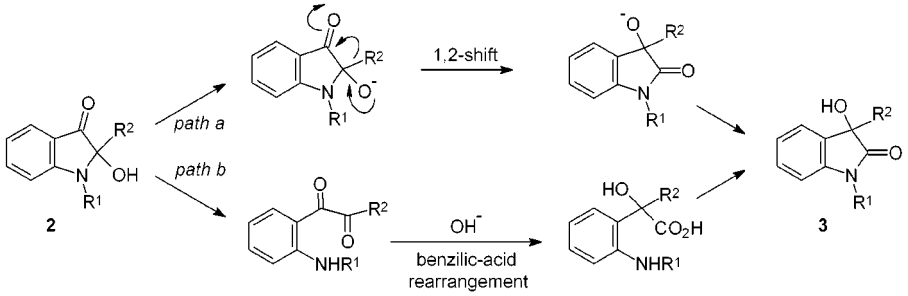
A plausible reaction path leading to the formation of **2** is presented in Scheme 2. First, the quinolinedione **1** may undergo base-catalyzed ketol rearrangement to intermediate **A**. This is in accord with our previous findings on the reaction of quinolinediones **1** with different organic bases in the absence of water.[21] The formation of intermediate **A** in the proposed mechanism is supported by the isolation of the ester **5** (Figure 1 and Table 1, entry 11), a result of an "α-hydroxy-β-diketone to α-acyloxy amide" rearrangement of **A**. However, from this point on the course of the reaction differs substantially from the one under nonaqueous conditions. In the presence of water, hydrolysis of the lactam ring in **A** can take place, followed by decarboxylation leading to the intermediate **B**. Alternatively, **A** can first undergo a molecular rearrangement to the 3,1-benzoxazin-2-one intermediate,[21] which is then hydrolyzed and decarboxylated to **B**. Ring closure and subsequent oxidation of a glycol intermediate **C** with air finally results in **2**. Attempts to isolate intermediates **A**, **B**, or **C** were unsuccessful, which, considering their instability, is not surprising. The intermediate **B** can be, under the basic conditions employed, transformed via enediol to the isomeric benzoin **4** (Table 1, entries 5 and 6). The fact that **4** was obtained from **1e** thus additionally supports the mechanism

(21) Klásek, A.; Kořistek, K.; Polis, J.; Košmrlj, J. *Tetrahedron* **2000**, *56*, 1551−1560.
(22) Crout, D. H. G.; Lee, E. R.; Rearson, D. P. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 381−385 and references cited therein.
(23) Brunner, H.; Stöhr, F. *Eur. J. Org. Chem.* **2000**, 2777−2786 and references cited therein.
(24) Sprecher, M. *Chemtracts: Org. Chem.* **1991**, *4*, 307−311 and references cited therein.
(25) Quinolines and their derivatives are often involved as intermediates in biochemical processes. For reviews, see: Fetzner, S.; Tshisuaka, B.; Lingens, F.; Kappl, R.; Hüttermann, J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 576−597. For example, see: Boyd, D. R.; Sharma, N. D.; Carroll, J. G.; Malone, J. F.; Mackerracher, D. G.; Allen, C. C. R. *Chem. Commun.* **1998**, 683−684 and references cited therein.
(26) Compounds **1** were found as metabolites produced by *Pseudomonas* species: (a) Neuenhaus, W.; Budzikiewicz, H. *Z. Naturforsch. B* **1979**, *34*, 313−315. (b) Budzikiewicz, H.; Schaller, U.; Korth, H.; Pulverer, G. *Monatsh. Chem.* **1979**, *110*, 947−953. (c) Kitamura, S.; Hashizume, K.; Iida, T.; Miyashita, E.; Shirahata, K.; Kase, H. *J. Antibiot.* **1986**, *39*, 1160−1166.
(27) Klásek, A.; Kořistek, K.; Polis, J.; Košmrlj, J. *Heterocycles* **1998**, *48*, 2309−2326.
(28) Kafka, S.; Kovář, M.; Klásek, A.; Kappe, T. *J. Heterocycl. Chem.* **1996**, *33*, 1977−1982.
(29) Stadlbauer, W.; Lutschounig, H.; Schindler, G.; Witoszynskyj, T.; Kappe, T. *J. Heterocycl. Chem.* **1992**, *29*, 1535−1540.

Scheme 2



Scheme 3



proposed in Scheme 2. For the benzoin **B** it is known to exist in the equilibrium with the dihydrodiol **C**.[30−32] A rapid oxidation of the latter removes it from the equilibrium, giving **2**. Such a facile oxidation of indole-2,3-dihydrodiols has been reported by several authors.[2,5a,30,33]

From the observations discussed above, it can be concluded that the primary products of the base-mediated ring contraction of **1a**−**j** are the 2-hydroxyindoxyls **2a**−**j**. They are stable under the relatively mild reaction conditions required for the transformation of *N*-phenyl-substituted **1a**−**e** and can be isolated from the reaction mixture. This, however, does not account for the more vigorous conditions necessary to achieve the reaction of the *N*-alkyl (or benzyl) analogues **1f**−**j** where 2-hydroxyindoxyls, only detected during the progress of the reaction, rearrange further to dioxindoles (Table 1, entries 7−11). The resistance of **2** to the rearrangement also depends on the basic conditions used. For example, compound **2e**, initially obtained in the reaction of **1e** with 1.3 M KOH/benzene as described above, was in an independent experiment easily transformed to **3e** using a mixture of solid KOH in benzene. With a view to achieving the highest yield of **2**, careful optimization of the reaction time is important, which is illustrated by the following example. Compound **1e** reacted completely within a period of 2.5 h to the mixture of **2e** (57%) and **4** (21%), with **3e** being undetected (Table 1, entry 5). However, when **1e** was subjected to the same reaction conditions for 4 h, the mixture of **2e** (25%), **3e** (11%), and **4** (21%) was isolated (Table 1, entry 6). Additionally, the consistent yield of **4** in these two experiments indicates that **4** must be formed in an early stage in the reaction path, such as proposed in Scheme 2.

Observations of a similar rearrangement, leading to dioxindoles, have been reported.[20,34] Kalb showed that ethyl 2-hydroxyindoxyl-2-carboxylate with aqueous sodium hydroxide yielded ethyl 3-hydroxyoxindole-3-carboxylate (Scheme 3; R^1 = H, R^2 = CO_2Et).[35] Two mechanistic possibilities have been discussed for the migration of the ester group.[36] One (path a) involves removal of a proton from 2-hydroxy group with the subsequent 1,2-shift of carbethoxy group (base-catalyzed α-ketol rearrangement).[37] The other route (path b) requires the opening of the carbinolamine function, followed by the benzilic acid rearrangement[38] and recyclization to lactam.

For the formation of **3** in our example (Scheme 3; R^1, R^2 = alkyl, Bn, Ph), both scenarios could be plausible.[39] Though in the case of Kalb's rearrangement, ingenious ^{18}O isotope labeling experiments revealed the α-ketol rearrangement as the most plausible, we sought another, simpler experiment that would provide us with an adequate answer to this issue. Thus, we subjected compound **2e** to acetylation with a mixture of pyridine

(30) Harrison, D. M. *Tetrahedron Lett.* **1984**, *25*, 6063−6064.
(31) Kawasaki, T.; Ohtsuka, H.; Chien, C.-S.; Omata, M.; Sakamoto, M. *Chem. Pharm. Bull.* **1987**, *35*, 1339−1346.
(32) It is noteworthy that related indole-2,3-dihydrodiol has been postulated as an intermediate in the metabolism of indole by *Pseudomonas putida*; see: (a) Ensley, B. D.; Ratzkin, B. J.; Osslund, T. D.; Simon, M. J.; Wackett, L. P.; Gibson D. T. *Science* **1983**, *222*, 167−169. (b) Boyd, D. R.; Sharma, N. D.; Boyle, R.; McMurray, B. T.; Evans, T. A.; Malone, J. F.; Dalton, H.; Chima, J.; Sheldrake, G. N. *J. Chem. Soc., Chem. Commun.* **1993**, 49−51.
(33) Carpentier, J.-F.; Mortreux, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1083−1099.
(34) For recent example, see: Malapel-Andrieu, B.; Mérour, J.-Y. *Tetrahedron Lett.* **1998**, *39*, 39−42.
(35) Kalb, L. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 1455−1464.
(36) Acheson, R. M.; Booth, S. R. G. *J. Chem. Soc. C* **1968**, 30−32.
(37) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience: New York, 2001; p 1402.
(38) For review, see: Selman, S.; Eastham, J. F. *Quart. Rev.* **1960**, *14*, 221−235.
(39) Precedent for such aryl and alkyl migration in indolic compounds is documented in the literature. For examples, see: (a) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 2188−2195. (b) Giovannini, E.; Rosales, J. *Helv. Chim. Acta* **1963**, *46*, 1332−1338. (c) Giovannini, E.; Karrer, F. *Chimia*, **1967**, *21*, 517−556. (d) Sukari, M. A.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2219−2223.

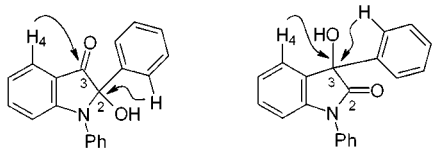
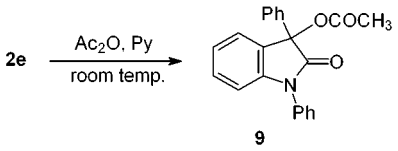


Figure 2. Selected correlations for **2e** and **3e** obtained from HMBC data analysis.

Scheme 4



and acetic anhydride, resulting in 3-*O*-acetate **9** (Scheme 4). Since it is unlikely that the acetate of **2e** transforms to **9**, the rearrangement to **3e** should take place first, accompanied by a slower acetylation process of the tertiary alcohol **3e**. The presumption that these reaction conditions are hydroxyl anion-free makes the alternative of the benzilic acid rearrangement path (path b) unlikely in our case. The identity of **9** was confirmed by an independent acetylation of **3e**.

As expected, the quantity of byproducts formed in the reactions of **1a**−**j** is influenced by the experimental conditions, being higher for the transformation of **1f**−**j** (Table 1, entries 7−11), and in a few cases we were successful in isolating and identifying them. From a mechanistic viewpoint, they additionally support the proposed pathway via intermediate **A** (Scheme 2). For instance, the alkaline hydrolysis of **5** leads to benzoic acid (**8i**) and 1-benzyl-3-hydroxy-1,3-dihydro-2*H*-indol-2-one, which is further oxidized to *N*-benzylisatin (**6j**). The origin of *N*-benzylanthranilic acid (**7j**) can be explained by hydrolysis of **6j** with subsequent oxidation and decarboxylation.[40] It is noteworthy that anthranilic acid was found as a metabolite of quinoline by *Pseudomonas putida*.[41]

Structure Elucidation. The infrared spectra without supporting data cannot clearly identify the structure of **2** and **3**, since the ν(C=O) vibrations for lactams **3e**−**j** appear in the same range (1698−1710 cm^{-1}) as those of **2a**−**e** (1678−1705 cm^{-1}). Analysis of ^{1}H, ^{13}C, and 2D NMR spectra suggested the molecular structure of **2** and **3**. As a representative example, the carbonyl of **2e** resonates at δ 199.4 while that of **3e** appears at δ 177.0 (typical for an amide group). In the HMBC spectrum of **2e**, H-4 shows a correlation to the carbonyl at δ 199.4, while in the case of **3e** such a correlation is not observed (Figure 2). Instead, both H-4 and the *o*-phenyl protons show a correlation to the carbon resonating at δ 78.1 (C-3, carbinol C). In general, two carbon resonances are strongly diagnostic of the structure of each isomeric compound. In the isomer **2**, carbons C-2 and C-3 resonate in the range of δ 89−92 and 199−201, while in **3** the lactam carbonyl (C-2) and carbon C-3 resonate at δ 177−179 and 76−78, respectively (Table 2).

Table 2. Selected Characteristic Spectral Data for 2-hydroxyindoxyls 2a−e and Dioxindoles 3e−j

compd	UV/vis (MeOH) λ_{max}, nm (log ϵ)	δ C-2, C-3[a] (ppm)
2a	207 (4.19), 228 (4.34), 254 (4.11), 281 (3.98), 418 (3.54)	89.1, 200.6
2b	206 (4.19), 228 (4.31), 255 (4.14), 285 (4.05), 422 (3.54)	91.5, 200.9
2c	206 (4.21), 229 (4.32), 255 (4.14), 285 (4.04), 424 (3.53)	91.0, 201.0
2d	206 (4.22), 228 (4.34), 255 (4.16), 285 (4.06), 422 (3.54)	91.0, 200.9
2e	207 (4.34), 230 (4.31), 253 (4.22), 286 (4.01), 424 (3.47)	91.6, 199.4
2e	(235, 255, 287, 420)[b]	
3e	214 (4.44), 246 (4.07)	177.0, 78.1
3f	213 (4.30), 258 (3.78)	178.5, 76.7
3g	214 (4.35), 260 (3.75)	177.4, 77.5
3h	213 (4.47), 259 (3.75)	177.8, 77.6
3i	214 (4.44), 259 (3.81)	177.5, 78.0
3j	212 (4.50), 259 (3.76)	177.6, 78.0

[a] In $CDCl_3$. [b] Crystalline state, see text.

It has been reported that *N*-acyl-2-hydroxyindoxyls exist in equilibrium with their open-chain tautomers, *o*-acylaminobenzils, especially in less polar solvents, such as deuteriochloroform.[20,31] The presence of the open-chain isomer **2′** (Figure 1), at least in deuteriochloroform solution, was in our case easily ruled out by the appearance of signals due to C-2 and C-3 (see above) and the lack of the additional signal due to the keto carbonyl (δ near 200) of **2′** (Figure 1).

UV−visible spectra of 2-hydroxyindoxyls **2a**−**e** (Table 2) show four distinct bands in the ultraviolet region and one in the visible region (λ_{max} (MeOH) 418−424 nm, log ϵ 3.47−3.54). This is in a fairly good agreement with λ_{max} (MeOH) literature reports for some structurally related N-unsubstituted 2-hydroxyindoxyls (λ_{max} 400−406 nm, log ϵ 3.39−3.46).[16] For comparison, the spectra of *N*-methylisatin[42] (λ_{max} (EtOH) 420 nm, log ϵ 2.70) and spiro-[cyclopentane-1,2′-indoxyl][39a] (λ_{max} (EtOH) 400 nm, log ϵ 3.57) that contain similar chromophors are notable. However, any conclusion based only on the comparison with the sparse examples of the UV−vis spectra of 2-hydroxyindoxyls reported in the literature is not unambiguous. As pointed out by Rees and Sabet, the yellow color of *N*-acetyl-2-phenyl-2-hydroxyindoxyl in various solvents is probably due to the presence of the open-chain tautomer (benzil derivative).[20] Unfortunately, these authors did not provide any UV−vis evidence. The yellow color of benzils is well-known. Although their absorption maxima in neutral solutions are typically at 370 nm, bathochromic shifts of up to 90 nm have also been reported.[43,44] Moreover, in favor of Rees and Sabet's discussion is also the fact that some 2-O-protected 2-hydroxyindoxyls do not show maxima in the visible region of the spectra.[45] Therefore, to avoid any speculation on the origin of the visible absorption for **2**, we decided to compare the UV−vis spectrum of the methanolic solution of **2e** (λ_{max} 228, 255, 285, 422 nm) to that in crystalline state (λ_{max} 235, 255, 287, 420 nm). Nearly

(40) Casey, L. A.; Galt, R.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1993**, 23−28.

(41) (a) Boyd, D. R.; McMordie, R. A. S.; Porter, H. P.; Dalton, H.; Jenkins, R. O.; Howarth, O. W. *J. Chem. Soc., Chem. Commun.* **1987**, 1722−1724. (b) Boyd, D. R.; Sharma, N. D.; Dorrity, M. R. J.; Hand, M. V.; McMordie, R. A. S.; Malone, J. F.; Porter, H. P.; Dalton, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1065−1071.

(42) Ault, R. G.; Hirst, E. L.; Morton, R. A. *J. Chem. Soc.* **1935**, 1653−1657.

(43) Kwart, H.; Baevsky, M. M. *J. Am. Chem. Soc.* **1958**, *80*, 580−588.

(44) Leonard, N. J.; Rapala, R. T.; Herzog, H. L.; Blout, E. R. *J. Am. Chem. Soc.* **1949**, *71*, 2997−3002.

(45) (a) Szmuszkovicz, J. *J. Org. Chem.* **1964**, *29*, 178−184. (b) Letcher, R. M.; Kwok, N.-C. Lo, W.-H.; Ng, K.-W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1715−1719.

identical absorption maxima in both cases confirm that the wavelengths above 418 nm are indeed attributable to 2-hydroxyindoxyl structure of **2** and not to its open-chain tautomer form (**2′**, Figure 1).

Conclusions

In summary, the novel base-mediated ring transformation of 3-hydroxy-2,4(1*H*,3*H*)-quinolinediones described above provides a direct access to *N*-aryl-2-hydroxyindoxyls or *N*-alkyldioxindoles. The chemoselectivity of the reaction is governed by the choice of the *N*-substituent. *N*-Phenyl substituted 3-hydroxy-2,4(1*H*,3*H*)-quinolinediones give 2-hydroxyindoxyls while the *N*-alkyl derivatives afford the corresponding dioxindols. With respect to the choice of the substrates discussed, the selectivity seems to be general. The simple experimental procedure and the good yields of the products render this protocol superior to the existing strategies and attractive for additional applications, especially for the synthesis of 2-hydroxyindoxyls.

Experimental Section

General Methods. UV−visible (UV−vis) spectra were obtained either from methanol solutions or as Nujol mulls. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded at 302 K. Chemical shifts are in ppm (δ) and are referenced to internal TMS. Coupling constants (J) are given in Hz. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broadened). High-resolution mass spectra were obtained using EI ionization at 70 eV. Data are reported as *m*/*z* (relative intensity). Analytical TLC was performed on Kavalier silica plates with UV 254 nm indicator. Column chromatography was carried out on Kavalier silica gel L 100/160 μm. Benzene and subsequently benzene−ethyl acetate (19:1) (solvent system S_1), benzene and subsequently benzene−ethyl acetate (9:1) (solvent system S_2), or chloroform were used as eluants.

Isatins **6g**,[46] **6i**,[47] and **6j**,[47] phenylacetic acid (**8g**), and benzoic acid (**8i**), were identified by comparison of their spectral data to literature reports and to those of the authentic samples.

General Procedure for the Reaction of 3-Hydroxy-2,4-(1*H*,3*H*)-quinolinediones (1a−j) with Potassium Hydroxide. A mixture of **1** (5 mmol) in 1.3 M aqueous potassium hydroxide in the presence of air (30 mL) and benzene (60 mL for **1d**,**f**−**i**, and 120 mL for **1a**−**c**,**e**,**j**) was vigorously stirred at the temperature and the duration indicated in Table 1. Layers were separated, and the aqueous phase was extracted with benzene (5 × 20 mL). The combined organic layer was shortly dried over K_2CO_3. The solvent was evaporated to dryness, and the residue was crystallized from the solvent indicated in Table 2 to give the corresponding products **2a**−**d** and **3f**−**i**. In the case of the reaction of **1j** (Table 1, entry 11), the residue was purified by column chromatography using solvent system S_1, to give **3j** and **5**. The residue from the reaction of **1e** was subjected to column chromatography using S_1 to give **2e** and **4** (Table 1, entry 5) or **2e**, **3e**, and **4** (Table 1, entry 6).

In the case of **1g**, **1i**, and **1j** (Table 1, entries 6, 9−11), we were successful in isolating the byproducts from the alkaline aqueous phase remaining after the benzene extraction described above, as follows:

(a) The alkaline aqueous phase remaining after the benzene extraction from the reaction of **1g** was acidified with concentrated hydrochloric acid and extracted with chloroform. The combined organic layer was concentrated in vacuo and the crude product was subjected to column chromatography using chloroform to give *N*-ethylisatin (**6g**, mp 92−93 °C from hexane (lit.[46] mp 94 °C), and phenylacetic acid (**8g**, mp 75−77 °C from hexane).

(b) The alkaline aqueous phase remaining after the benzene extraction from the reaction of **1i** was acidified with concentrated hydrochloric acid and extracted with benzene. The combined organic layer was concentrated in vacuo and the crude product was subjected to column chromatography using solvent system S_1 to yield bezoic acid (**8i**) and *N*-methylisatin (**6i**, mp 131−133 °C from benzene (lit.[48] mp 132−134 °C)).

(c) The alkaline aqueous phase remaining after the benzene extraction from the reaction of **1j** was acidified with concentrated hydrochloric acid and extracted with chloroform. The combined organic layers were concentrated in vacuo and subjected to column chromatography using solvent system S_2. Two fractions were collected. The more polar fraction ($R_f \approx$ 0.25; benzene/ethyl acetate 4:1) was after evaporation suspended in benzene and filtered, and the filtrate was concentrated in vacuo to give benzoic acid (**8i**). The less polar fraction ($R_f \approx$ 0.65, benzene/ethyl acetate 4:1) was concentrated in vacuo and subjected to column chromatography using chloroform as eluant, to give *N*-benzylisatin (**6j**, mp 128−131 °C from benzene (lit.[48] mp 129−131 °C)) and *N*-benzylanthranilic acid (**7j**, mp 174.5−175.5 °C from cyclohexane/benzene (lit.[49] mp 175−176 °C)).

2-Hydroxy-2-methyl-1-phenyl-1,2-dihydro-3*H*-indol-3-one (2a): yellow crystals; mp 124−126 °C (benzene/cyclohexane); ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3H, CH_3), 2.76 (s, 1H, OH), 6.84 (dd, J = 7.0, 7.0 Hz, 1H, H-5), 6.90 (m, 1H, H-7), 7.28−7.36 (m, 1H, *o*-Ph), 7.41−7.50 (m, 5H, Ph, H-6), 7.67 (m, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_3), 89.0 (C-2), 111.0 (C-7), 117.9 (C-3), 119.5 (C-5), 125.6 (C-4), 126.2, 126.7, 129.6, 138.2 (C-6), 138.4, 158.3 (C-7a), 200.6 (C-3).

2-Ethyl-2-hydroxy-1-phenyl-1,2-dihydro-3*H*-indol-3-one (2b): yellow crystals; mp 120−123 °C (cyclohexane); ^{1}H NMR ($CDCl_3$) δ 0.70 (t, J = 7.4 Hz, 3H), 1.75−2.01 (m, 2H), 2.74 (br s, 1H), 6.84 (dd, J = 7.7, 7.2 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 7.28−7.32 (m, 1H), 7.40−7.47 (m, 3H), 7.51−7.55 (m, 2H), 7.65 (d, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 7.2, 28.0, 91.5, 110.5, 118.8, 119.3, 125.3, 125.6, 126.3, 129.5, 138.1, 138.2, 159.1, 200.9.

2-Hydroxy-1-phenyl-2-propyl-1,2-dihydro-3*H*-indol-3-one (2c): yellow crystals; mp 106−108 °C (cyclohexane); ^{1}H NMR ($CDCl_3$) δ 0.72 (t, J = 7.3 Hz, 3H), 0.97−1.30 (m, 2H), 1.68−1.92 (m, 2H), 2.70 (br s, 1H), 6.82 (dd, J = 7.5, 7.1 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 7.25−7.33 (m, 1H), 7.39−7.48 (m, 3H), 7.49−7.54 (m, 2H), 7.62 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 16.2, 37.2, 91.0, 110.5, 118.7, 119.3, 125.3, 125.6, 126.4, 129.5, 138.1, 138.1, 159.0, 201.0.

2-Butyl-2-hydroxy-1-phenyl-1,2-dihydro-3*H*-indol-3-one (2d): yellow crystals; mp 81−83 °C (cyclohexane); ^{1}H NMR ($CDCl_3$) δ 0.70 (t, J = 6.8 Hz, 3H, CH_3), 0.88−1.20 (m, 4H, 2 × CH_2), 1.71−1.95 (m, 2H, CH_2), 2.96 (s, 1H, OH), 6.83 (dd, J = 7.7, 7.2 Hz, 1H, H-5), 6.95 (d, J = 8.4 Hz, 1H, H-7), 7.28−7.32 (m, 1H, *p*-Ph), 7.40−7.48 (m, 3H, *m*-Ph, H-6), 7.49−7.54 (m, 2H, *o*-Ph), 7.63 (dd, J = 7.7, 1.3 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 13.6, 22.5, 24.7, 34.7, 91.0 (C-2), 110.5 (C-7), 118.7 (C-3a), 119.3 (C-5), 125.3 (C-4), 125.6 (C-2 and C-6 of Ph), 126.3 (C-4 of Ph), 129.5 (C-3 and C-5 of Ph), 138.1, 138.1, 159.0 (C-7a), 200.9 (C-3).

1,2-Diphenyl-2-hydroxy-1,2-dihydro-3*H*-indol-3-one (2e): yellow crystals; mp 107−109 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 3.34 (s, 1H, OH), 6.90 (dd, J = 7.8, 7.8 Hz, 1H, H-5), 7.08 (d, J = 8.4 Hz, 1H, H-7), 7.10−7.46 (m, 10H, 2 × Ph), 7.47−7.54 (m, 1H, H-6), 7.64−7.69 (m, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 91.6 (C-2), 110.9 (C-7), 118.2 (C-3a), 120.0 (C-5), 124.9, 125.9, 126.1, 126.2, 128.6, 128.8, 129.3, 136.9, 138.2, 138.4 (C-6), 159.3 (C-7a), 199.4 (C-3).

(46) Kaupp, G.; Matthies, D. *Chem. Ber.* **1987**, *120*, 1897−1903.
(47) Morales-Rios, M. S.; Joseph-Nathan, P. *Magn. Reson. Chem.* **1991**, *29*, 893−896.
(48) Katritzky, A. R.; Fan, W.-Q.; Liang, D.-S.; Li, Q.-L. *J. Heterocycl. Chem.* **1989**, *26*, 1541−1545.
(49) Nonnenmacher, E.; Hever, A.; Mahamound, A.; Aubert, C.; Molnar, J.; Barbe, J. *Org. Prep. Proced. Int.* **1997**, *29*, 711−715.

1,3-Diphenyl-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (3e): colorless crystals; mp 169−171 °C (methanol); ^{1}H NMR ($CDCl_3$) δ 3.55 (br s, 1H, OH), 6.89 (d, J = 7.9 Hz, 1H, H-7), 7.10 (ddd, J = 7.5, 7.5, 0.9 Hz, 1H, H-5), 7.29 (dd, J = 6.8, 1.3 Hz, 1H, H-6), 7.28−7.60 (m, 11H, H-4, 2 × Ph); ^{13}C NMR ($CDCl_3$) δ 78.1 (C-3), 110.0 (C-7), 124.0 (C-5), 125.3 (C-4), 125.3 (C-2 and C-6 of C_3-*Ph*), 126.5, 128.3, 128.4, 128.7, 129.7, 129.7 (C-6), 131.4 (C-3a), 134.0, 140.4, 143.5 (C-7a), 177.0 (C-2).

3-Butyl-3-hydroxy-1-methyl-1,3-dihydro-2*H*-indol-2-one (3f): colorless crystals; mp 98 °C (cyclohexane); ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J = 7.2 Hz, 3H), 0.95−1.32 (m, 4H), 1.84−2.02 (m, 2H), 3.14 (s, 1H), 3.18 (s, 3H), 6.83 (d, J = 7.8 Hz, 1H), 7.10 (ddd, J = 7.7, 7.2, 0.7 Hz, 1H), 7.32 (ddd, J = 7.8, 7.7, 1.2 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.7, 25.3, 26.2, 38.4, 76.7, 108.4, 123.1, 123.9, 129.5, 130.3, 143.5, 178.5.

3-Benzyl-1-ethyl-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (3g): colorless crystals; mp 144−145 °C (cyclohexane); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 3H), 3.22 and 3.33 (2 × d, J = 12.6 Hz, 2H), 3.33−3.43 and 3.59−3.73 (2 × m, 2H), 6.63 (d, J = 7.8 Hz, 1H), 6.87−6.90 (m, 2H), 7.03−7.13 (m, 4H), 7.24 (ddd, J = 7.8, 7.7, 1.2 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.1, 34.4, 45.2, 77.5, 108.3, 122.7, 124.5, 126.8, 127.7, 129.6, 130.3, 134.0, 142.4, 177.4.

1,3-Dibenzyl-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (3h): colorless crystals; mp 188−190 °C (benzene/cyclohexane); ^{1}H NMR ($CDCl_3$) δ 3.32 and 3.43 (2 × d, J = 12.7 Hz, 2H), 3.60 (s, 1H), 4.44 and 4.98 (2 × d, J = 16.0 Hz, 2H), 6.43 (d, J = 7.4 Hz, 1H), 6.70−6.73 (m, 2H), 6.91−6.95 (m, 2H), 7.04−7.21 (m, 8H), 7.35−7.39 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 43.7, 44.8, 77.6, 109.6, 123.0, 124.4, 126.7, 126.9, 127.3, 128.1, 128.7, 129.3, 129.7, 130.4, 133.9, 134.9, 142.7, 177.8.

3-Hydroxy-1-methyl-3-phenyl-1,3-dihydro-2*H*-indol-2-one (3i): colorless crystals; mp 141−143 °C (benzene) (lit.[50] mp 142−143 °C (diethyl ether), lit.[51] mp 139−141 °C (methanol)); ^{1}H NMR ($CDCl_3$) δ 3.24 (s, 3H), 3.47 (s, 1H), 6.90 (d, J = 7.8 Hz, 1H), 7.08 (ddd, J = 7.6, 7.6, 0.9 Hz, 1H), 7.25−7.40 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 26.5, 78.0, 108.7, 123.5, 125.0, 125.4, 128.3, 128.6, 129.9, 131.6, 140.1, 143.6, 177.5.

1-Benzyl-3-hydroxy-3-phenyl-1,3-dihydro-2*H*-indol-2-one (3j): colorless crystals; mp 144−145 °C (benzene/cyclohexane); ^{1}H NMR ($CDCl_3$) δ 3.44 (s, 1H), 4.81 and 5.04 (2 × d, J = 15.6 Hz, 2H), 6.78 (d, J = 7.8 Hz, 1H), 7.03 (dd, J = 7.3, 8.0 Hz, 1H), 7.19−7.45 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 44.1, 78.0, 109.7, 123.5, 125.0, 125.3, 127.3, 127.8, 128.3, 128.6, 128.9, 129.8, 131.6, 135.4, 140.2, 142.7, 177.6.

1-(2-Anilinophenyl)-2-hydroxy-2-phenyl-1-ethanone (4): yellow glass; ^{1}H NMR ($CDCl_3$) δ 4.66 (d, J = 6.6 Hz, 1H, OH), 5.99 (d, J = 6.6 Hz, 1H, CH), 6.60 (dt, J = 6.5, 1.6 Hz, 1H, H-5), 7.10−7.40 (m, 12H, H-3, H-4, and two Ph), 7.70 (dd, J = 8.0, 1.0 Hz, 1H, H-6), 10.38 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 75.4 (C-OH), 114.5 (C-3), 115.2 (C-1), 116.6 (C-5), 123.6 (C-2 and C-6 of *N*-Ph), 124.6 (C-4 of *N*-Ph), 127.6 (C-2 and C-6 of C-Ph), 128.4 (C-4 of C-Ph), 129.1 (C-3 and C-5 of *N*-Ph), 129.5 (C-3 and C-5 of C-Ph), 131.9 (C-6), 135.4 (C-4), 139.8 (C-1 of *N*-Ph), 140.3 (C-1 of C-Ph), 149.2 (C-2), 199.8 (C=O).

1-Benzyl-2-oxo-1,3-dihydro-2*H*-indol-3-yl benzoate (5): colorless crystals; mp 124−125 °C (cyclohexane); ^{1}H NMR ($CDCl_3$) δ 4.91 and 5.00 (2 × d, J = 15.7 Hz, 2H, CH_2), 6.27 (s, 1H, H-3), 6.74 (d, J = 7.7 Hz, 1H, H-7), 7.01 (ddd, J = 7.7, 7.7, 0.5 Hz, 1H, H-5), 7.22 (d, J = 7.8 Hz, 1H, H-6), 7.23−7.60 (m, 9H), 8.12 (d, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 44.1 (CH_2), 70.4 (C-3), 109.6 (C-7), 123.1 (C-5), 124.5 (C-3a), 125.6 (C-4), 127.4, 127.8, 128.4, 128.9, 129.1, 130.2 (C-2 and C-6 of CO*Ph*), 130.2 (C-6), 133.6, 135.3, 143.7 (C-7a), 165.9 (COO), 172.3 (C-2).

Isomerization of 1,2-Diphenyl-2-hydroxy-1,2-dihydro-3*H*-indol-3-one (2e) to 3e. Powdered KOH (50 mg, 0.9 mmol) was added to the solution of **2e** (175 mg, 0.58 mmol) in benzene (5 mL), and the reation mixture was vigorously stirred at room temperature for 1 h. The precipitate was filtered, and the filtrate was evaporated to dryness. The residue was crystallized from methanol to give **3e** (53 mg, 30%), mp 168−171 °C.

Reaction of 1,2-Diphenyl-2-hydroxy-1,2-dihydro-3*H*-indol-3-one (2e) with Pyridine and Acetic Anhydride. Acetic anhydride (1 mL) was added to the solution of **2e** (290 mg, 0.96 mmol) in pyridine (3 mL). After 12 h at room temperature, the solution was evaporated to dryness. The residue was crystallized from benzene to give 1,3-diphenyl-2-oxo-1,3-dihydro-2*H*-indol-3-yl acetate (**9**, 89 mg, 27%).

9: colorless crystals; mp 202−204 °C (benzene); ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H, CH_3), 6.83 (dd, J = 7.7, 1.1 Hz, 1H), 7.12 (dt, J = 7.9, 0.9 Hz, 1H), 7.25−7.54 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 20.9, 81.3, 109.9, 123.4, 124.4, 126.4, 126.9, 128.0, 128.3, 128.7, 129.0, 129.6, 130.0, 134.6, 136.4, 145.0, 169.3, 173.5.

Acetylation of 1,3-Diphenyl-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (3e). Acetic anhydride (0.5 mL) was added to the solution of **3e** (55 mg, 0.18 mmol) in pyridine (1 mL), and the reaction mixture was left at room temperature for 12 h. The volatile compounds were evaporated in vacuo, and the resulting solid was crystallized from benzene to yield **9** (38 mg, 61%).

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Supporting Information Available: Synthesis and spectroscopic data (IR, NMR, and MS) for 4-hydroxy-2(1*H*)-quinolones and compounds **1**; IR and MS data for compounds **2**−**5** and **9**; results of combustion analysis for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(50) Walker, G. N.; Alkalay, D.; Smith, R. T. *J. Org. Chem.* **1965**, *30*, 2973−2983.

(51) Aeberli, P.; Houlihan, W. J. *J. Org. Chem.* **1968**, *33*, 1640−1643.