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Enamino Derivatives of 1,3-Dioxoindane-2-carboxylic Acid

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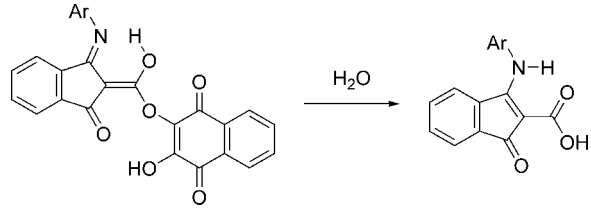
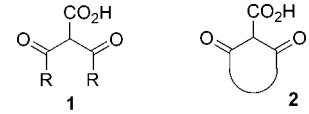


Although 1,3-dioxoindane-2-carboxylic acid is highly unstable, its enamino derivatives can be isolated by careful hydrolysis of their esters with 2,4-dihydroxy-1,4-naphthoquinone. Crystal structure determination reveals the formation of two intramolecular hydrogen bonds, offering thus a possible explanation for the stability of these acids.

Introduction

It is well-known that β-keto acids are easily decarboxylated[1] and that their decarboxylation is an important transformation in organic chemistry[2] as well as in biological systems.[3] It is generally accepted that this decarboxylation proceeds through a cyclic transition state[2] with the participation of the keto group and that both electronic[4] and steric factors[5] influence the rate of decarboxylation. The tendency of β-keto acids to decarboxylate has as a consequence that a considerable number of them cannot be isolated in pure form. Their formation usually is detected by their reaction with alcohols and their transformation to the more stable β-keto esters, although the latter can also be dealkoxycarbonylated.[6]

Despite their instability, certain β-keto acids can be isolated, especially if elevated temperatures are avoided during their preparation and isolation, but that is not the case for α-acyl-β-keto acids. To our knowledge no unambiguous preparation and characterization of compounds of the general types **1** or **2** has been reported.



R = alkyl, aryl

Exploring the chemistry of aryliodonium ylides of hydroxyquinones and using the phenyl iodonium ylide of lawsone **3** as a model compound, we found that its thermal decomposition in moistened acetonitrile afforded indanedione **7** in quantitative yield.[7a] The same type of ring contraction was observed with phenyliodonium ylides of other hydroxyquinones.[7b–d] The reaction pathway involves the formation of 1,3-dioxoindane-2-carboxylic acid (**6**), the product of the reaction of α,α-dioxoketene **4** with water present in the solvent. This ketene is a result of a Wolff-type rearrangement following the thermal degradation of ylide **3**. This rearrangement was initially thought to proceed through carbenes, but it was shown recently that it follows a single-step concerted mechanism, via a four-membered [1,1,0] bicyclic ring transition state for the ketene formation.[8] The ketene is very reactive and it can be trapped with aromatic

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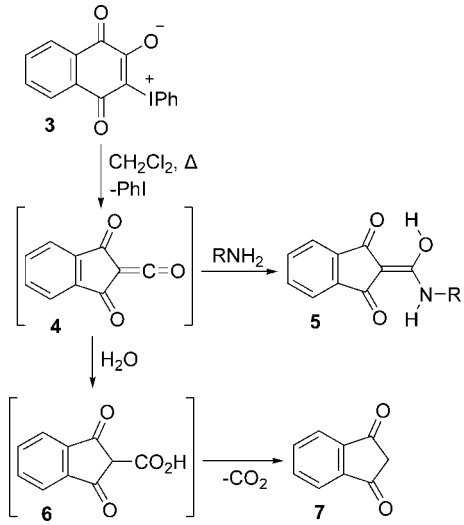

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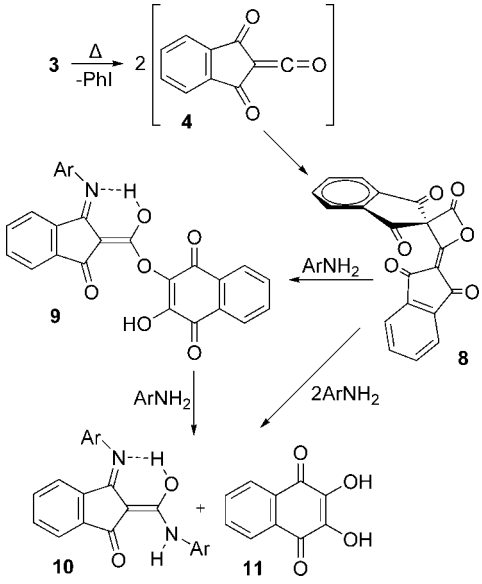
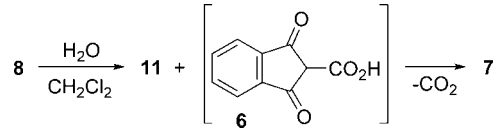


amines to the anilides **5**, existing in solution in the enol form,[9] as illustrated in Scheme 1. Analogous dioxoketenes produced in the same manner from the thermal decomposition of other iodonium ylides can be trapped by methanol affording the methyl esters of the corresponding to **6** acids.[7b,c] Although the amides of acid **6** can be isolated, the acid itself is spontaneously decarboxylated to indanedione **7**, especially under the conditions of the reaction.

Ylide **3** decomposes in refluxing CH_2Cl_2 to dioxoketene **4**, which in the absence of water (or other nucleophiles) dimerizes quantitatively to tetraoxo-oxetanone **8**.[10,11] The latter reacts with 1 and 2 equiv of primary aromatic amines to afford the esters **9** and the amides **10**, respectively (Scheme 2). Besides **10**, 2,3-dihydroxy-1,4-naphthoquinone (**11**) was the other product of the reaction of **8** with 2 equiv of amine, regardless if it was

SCHEME 3



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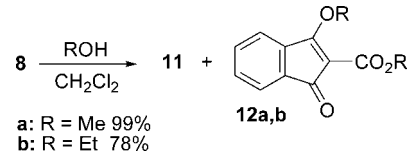

conducted in one or two steps. Aiming to the isolation of acid **6** or at least some of its derivatives from the carbonyl group, we used the tetraoxo-oxetanone **8** and the esters **9** as starting materials and we report the results of our efforts herein.

Results and Discussion

Oxetanone **8** is a labile compound and its yellow color turns slowly into reddish after exposure to air for some time. It was found that the red color belongs to 2,3-dihydroxy-1,4-naphthoquinone (**11**) and that indanedione (**7**) was the other product of the decomposition. The same compounds, **11** and **7**, were also the only products of the decomposition of a dispersion of **8** in CH_2Cl_2 saturated with water (Scheme 3). Presumably indanedione resulted from the decarboxylation of the intermediately formed acid **6**, (Scheme 2). The formation of indanedione is indicative of the instability of acid **6** even at room temperature.

When methanol or ethanol was added to a suspension of **8** in CH_2Cl_2, the corresponding alkoxy alkyl esters of indenone carboxylic acid **12** were obtained along with dihydroxyquinone **11** (Scheme 4). Esters **12** were isolated by column chromatography, although they are labile compounds and have the tendency to decompose to indanedione **7** after exposure to air for some time. Indanedione **7** was the sole product of the attempted hydrolysis of esters **12** with water at room temperature, verifying again the instability of acid **6**.

Regarding the reaction pathway, it is most possible that it is analogous to the one proposed previously for the reaction of **8** with amines.[11] The reaction starts with nucleophilic attack of the alcohol on one of the carbonyls of the spirocyclopentenedione moiety to form **13**, which gives the oxonium intermediate **14**. The latter initiates a skeletal rearrangement, which leads to the esters **15** through ring expansion and attack of the hydroxy anion to the ethylenic carbon of the indanedione moiety, as shown in Scheme 5. These esters through a transesterification reaction with excess alcohol afford **11** and the isolated esters **12**.

After the unsuccessful attempts to isolate dioxo acid **6** we examined the possibility to prepare arylimino derivatives of this acid starting from the available esters **9**, products from the reaction of **8** with 1 equiv of amine (Scheme 2).

Indeed, a transesterification reaction of **9a**−**c** with alcohols afforded the esters **16a**−**c**, but most important, careful hydrolysis of **9a**−**c** led to the isolation of the acids **18a**−**c**, while dihydroxyquinone **11** was the other product of the reaction in both cases (Scheme 6). Esters **16** as well as acids **18** can exist in solution in equilibrium with their enamino forms **17** and **19**, respectively.

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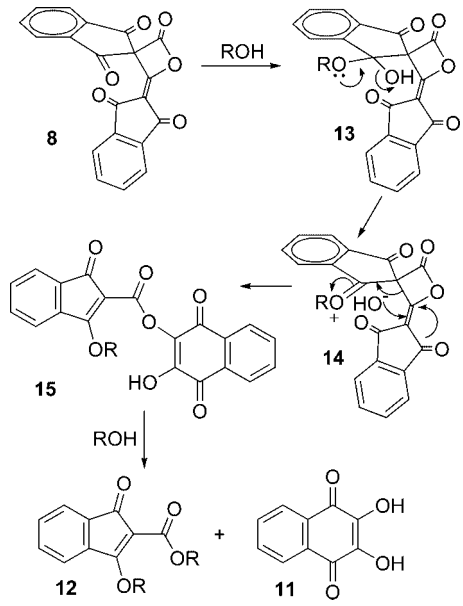
SCHEME 5



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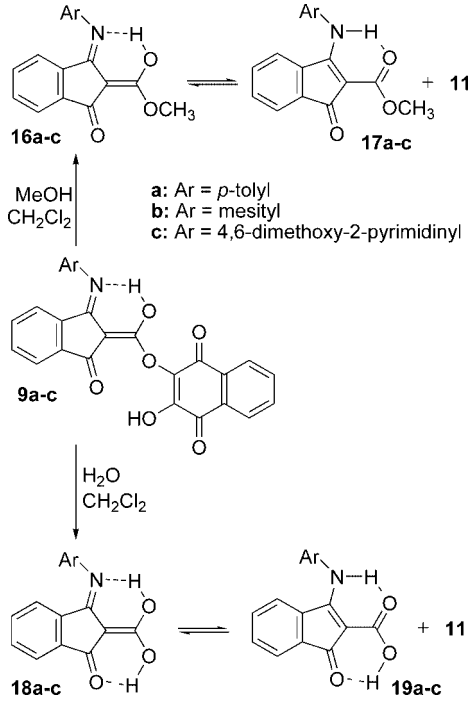
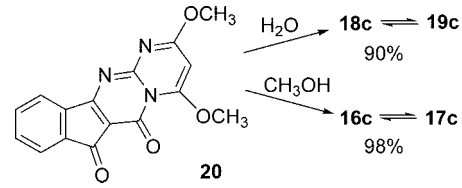


Esters **16/17** are isolated from the reaction mixture by column chromatography, but acids **18/19** are separated from quinone **11** by selective crystallization. This method gave satisfactory results for **18a/19a** and **18b/19b** (yield 74% and 87%, respectively), but the acid **18c/19c** was detected only in traces. Acid **18c/19c** and the corresponding methyl ester **16c/17c** were obtained by another approach, namely, the solvolysis of 2,4-dimethoxyindeno[1,2-*d*]pyrimido[1,2-*a*]pyrimidine (**20**). This compound, as well as analogous derivatives with a similar template and interesting biological activities, was prepared by the reaction of tetraoxo-oxetanone **8** with 4,6-dimethoxy-2-aminopyrimidine.[12] Bearing an amidic group at a position corresponding to that of the ester group in compounds **9**, the polycyclic compound **20** could be susceptible to nucleophilic attack. Indeed, upon heating **20** in a mixture of dichloromethane

SCHEME 7



and methanol a ring opening occurred and the ester **16c/17c** was isolated quantitatively. In an analogous reaction, hydrolysis of **20** under mild conditions this time (suspension of a few drops of H_2O in CH_2Cl_2, 34 °C, 5 days) led to the isolation of the acid **18c/19c** in pure form and excellent yield (Scheme 7).

In the NMR spectra in $CDCl_3$ of esters **16a−c/17a−c** and acids **18a−c/19a−c** signals for only one species are observed. No broadening of peaks was observed when the NMR spectra of ester **17a** were recorded at low temperatures (till −50 °C). ^{13}C NMR spectra display signals at three low field regions, specifically at δ 186.8−188.0 and 191.2−192.9 for C-1 (ketone C═O, Figure 1), at δ 170.6−172.9 and 167.9−168.9 for C-3 and at δ 169.1−172.2 and 167.1−168.0 for the carboxylic carbon, for esters **16a−c/17a−c** and acids **18a−c/19a−c**, respectively. Another quaternary carbon signal, which is attributed to C-2, is observed at δ 95.1−101.5 for the esters and 94.7−99.3 for the acids. In the ^1H NMR spectra, the OH and NH protons resonate at δ 10.50−11.83 (one signal for the esters and two for the acids).

Enols of acids and esters are rare species and only a few cases of stable compounds have been reported in the literature.[13,14] The hydrogen bonded enolic protons of poly(methoxycarbonyl)cyclopentadienes, forming a seven-membered pseudocyclic ring, resonate at 19−20 ppm,[13] whereas the non-hydrogen bonded enolic protons of carboxylic acid enols resonate at 7.65−9.33, depending on the solvent.[14] More examples of stable enols of amides have been reported in contrast to the limited number of enols of carboxylic esters and acids.[9,15,16] In the case of the substituted 2-carbanilido-1,3-indanediones, both isomeric solid enols on amide carbonyl and on ring carbonyl were isolated and their spectra in solid state and in solution ($CDCl_3$) were obtained.[16] The solid state NMR spectra of the two tautomers differ in contrast to the spectra in $CDCl_3$ solution which are identical and resemble those of the amide enol tautomer. Signals for the NH and OH protons are observed at ca. δ 9.9−10.6 in $CDCl_3$ solution, values identical to those reported earlier[9] for 2-carbanilido-1,3-indanediones and analogous to those found for esters **16/17** and acids **18/19**. In the spectrum in $CDCl_3$ solution, two signals at ca. δ 193−190 for the nonequivalent ketone carbonyls, a low field signal at ca. δ 164 for the enol amide carbon and an upfield signal at ca. δ 95 for the other carbon of the enol group are observed. These values strongly resemble of the observed for the esters **16a−c/17a−c** and acids **18a−c/19a−c**.

On the basis of the above it is difficult to distinguish which of the imino **16**, **18** or enamino **17**, **19** structures exists in solution. A strong evidence in favor of the enamino structure was provided by the ^{15}N NMR spectrum of compound **17a/18a**: only one signal is observed at δ −250.9 (reference

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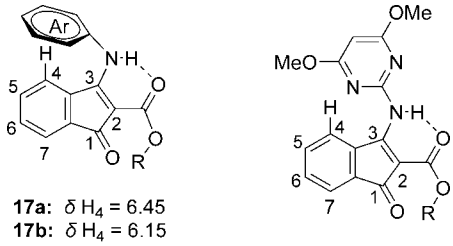

FIGURE 1. Shielding effect in enamino esters **17a,b** and acids **18a,b/19a,b**.

$Me^{15}NO_2$) in $CDCl_3$, which is ascribed to the nitrogen of the enamine group of the tautomer **17a** and certainly not to the imine nitrogen of **18a.**[17] Due to the instability of carboxylic acids **18/19**, especially in solution, it was difficult to record ^{15}N NMR spectra.

Another interesting spectroscopic feature of these compounds is the shift of 4-H in ^1H NMR. In compounds **17a,b** and **18a,b/19a,b** this proton appears as a doublet at low δ values (6.15−6.53) indicated in Figure 1. This shielding effect is attributed to the restricted rotation of the aryl ring, a phenomenon that has been observed also in the spectra of compounds **9** and **10**. Interestingly enough, the same 4-H in the corresponding 2-iminopyrimidyl derivatives **17c** and **18c/19c**, appears at δ 8.09 and 8.35, respectively. 3D models indicate that in these compounds no restriction in the rotation of the aryl ring exists, due to the lack protons at the ortho positions of the ring which are occupied by nitrogen atoms. In this case, all rings lie on a plane and the deshielding effect of the iminopyrimidyl ring explains the spectacular (almost 2 ppm) downfield shift of 4-H.

In acids **18a−c/19a−c** the existence of two intramolecular hydrogen bonds may account for their relative stability despite the instability of β-ketoacids generally. Crystal structure determination for acid **18a/19a** showed the existence of such hydrogen bonds (O1−H2, 189 pm and O3−H1, 216 pm) and that, at least in the solid state, this compound exists in the enamino form **19a**, shown in Figure 2 in Supporting Information. The tilt of the *p*-tolyl ring verifies the observed shielding effect for H on C-4.

Another reason for the stabilization of acid **19a** is possibly the development of intramolecular hydrogen bonds with the symmetry molecule, between O3···H1′ and H1···O3′ with a length of 218 pm, as illustrated in Figure 3 in Supporting Information.

It must be noted that the crystal structure of the only ester analogue to **17** reported in the literature, enamino ester **23**, is in complete analogy with the structure of acid **19a**. This ester was prepared (rather by serendipity) by Padwa et al.,[18] on their way to prepare functionalized azomethine ylides: The cyclopentenone ring is formed by intramolecular insertion of the carbene obtained through catalytic action of Rh(II) on the diazo imino ester **22**, existing as a single *E* isomer. The latter is prepared by the reaction of aniline with the corresponding aldehyde **21**, as illustrated in Scheme 8. Ester **23** exhibits spectroscopic data completely analogous to those of esters **17**, with most characteristic features the shielding of 4-H (doublet at δ 6.41 in ^1H NMR) and C-2 resonating at δ 96.6 in ^{13}C NMR.

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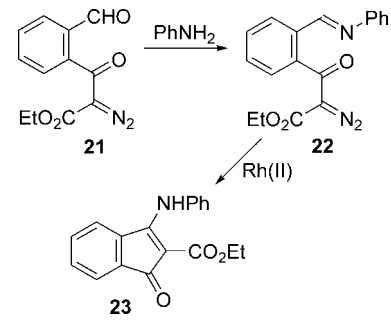
SCHEME 8



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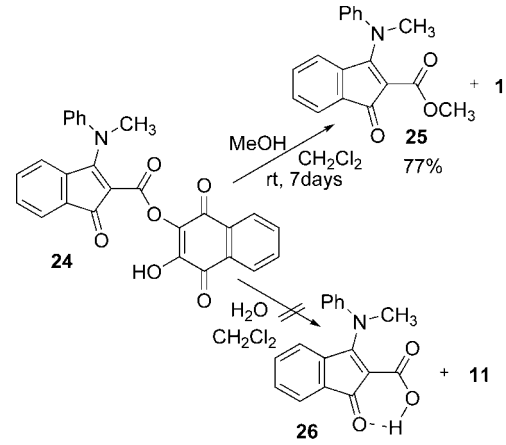
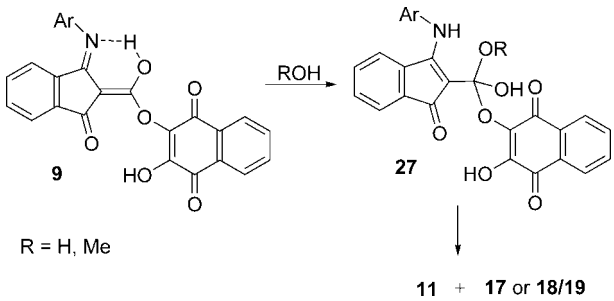


As we reported in a previous publication[11] the reaction of indanedionketene dimer **8** with *N*-methylaniline (as well as with other secondary amines) affords the ester **24**. In spite of our efforts, this ester resisted hydrolysis even in refluxing DME and acid **26,** or even its decarboxylation product, were not formed. On the contrary, transesterification with methanol, a stronger than H_2O nucleophilic agent, afforded good yields of ester **25** and dihydroxyquinone **11** (Scheme 9), albeit after a prolonged reaction time. This ester undoubtedly exists in the enamino form, as there is no hydrogen on the nitrogen atom and hence the imino isomer cannot be formed. In the ^{13}C NMR spectrum, ester **25** lacks the characteristic peak for C-2 at δ 94−96, which is observed for esters **17**, and the most upfield signal for sp^2 carbons is recorded at δ 121.7. This indicates that in this compound the carbon in question is not protected by the lone pair of nitrogen, due probably to the inability of formation of the pseudo six-membered ring, through hydrogen bonding, occurring in esters **17**.

There is a striking difference in the reactivity of esters **9** and ester **24** toward alcohols and water. Whereas it takes only 4 h for the conversion of the former to esters **17** and acids **18/19** respectively, the conversion of the latter to ester **25** is completed after 7 days and the same compound does not react at all with water. We attribute this difference in reactivity of esters **9** and ester **24** to the capability of the former to adopt in solution an imino form analogous to **16**. This imino form is more susceptible to Michael-type addition of the nucleophile (alcohol or water) to the carbon of the ester group and afford easily the intermediate **27**, which decomposes to dihydroxyquinone **11** and esters **17** or acids **18/19** (Scheme 10). Ester **24** lacks the enone moiety that can be found in **9**. As a consequence, Michael-type addition is not possible and hence the observed resistance toward the same nucleophiles.

SCHEME 10



It must be noted that Michael-type addition intermediates analogous to **27**, with amines as nucleophiles, have been isolated and their structure has been elucidated in a previous publication.[11]

In conclusion, by mild hydrolysis of the esters **9** we have isolated the enamino derivatives of 1,3-dioxoindane-2-carboxylic acid **18/19**, belonging to a class of compounds that are considered unstable. In this case the existence of the two intramolecular hydrogen bonds assists their stabilization. Esters of the same acids were also isolated from the transesterification of esters **9**.

Experimental Section

Indanedioneketene dimer, 4′-(1,3-dioxo-1,3-dihydro-2*H*-inden-2-ylidene)spiro[indene-2,3′-oxetane]-1,2′,3-trione (**8**), was prepared as described in previous publications.[9,10] Esters **9a**−**c** and **24** were prepared from the reaction of dimer **8** with 1 equiv of the appropriate amine.[11,12]

Hydrolysis of Oxetanone 8. A suspension of oxetanone **8** (0.5 mmol) in CH_2Cl_2 (4 mL) saturated with water was stirred at room temperature for 4 h. After 1 h, red crystals of dihydroxynaphthoquinone **11** began to deposit. Hexanes (5 mL) was added to facilitate precipitation, and **11** was obtained by filtration in almost quantitative yield. The filtrate was concentrated to a small volume, and the residue was chromatographed on column (silica gel, hexanes−ethyl acetate 3:1) to afford indanedione (**7**) as the only product, again in almost quantitative yield.

Reaction of Oxetanone 8 with Alcohols. Alcohol (2 mL) was added to a stirred suspension of oxetanone **8** (0.5 mmol) in CH_2Cl_2 (4 mL), and stirring was continued until a clear solution resulted (6 h). The solution was concentrated to a small volume, the resulting red crystals of dihydroxynaphthoquinone **11** (yields 80−85%) were filtered off, and the filtrate was chromatographed, as quickly as possible, on column (silica gel, hexanes−ethyl acetate 3:1) to afford the alkoxy esters **12a,b**. The isolated derivatives **12a,b** were pure enough, and no further purification was possible, as they have the tendency to decompose upon attempted recrystallization. It must be noted that compound **12b** is considerably more unstable than the methyl derivative **12a**.

Reaction with Methanol. Methyl 3-methoxy-1-oxo-1*H*-indene-2-carboxylate (12a). Yield 99%; yellow solid, mp 110−112 °C; IR (KBr) cm^{-1} 1720, 1691; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.57−7.52 (m, 1H), 7.48−7.38 (m, 3H), 4.34 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.0, 178.6, 163.9, 138.5, 132.8, 131.9, 131.7, 122.0, 120.5, 103.4, 61.9, 52.1; GC−MS *m*/*z* 218 (M^+, 36), 187 (100), 173 (32), 104 (12). Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.96; H, 4.62.

Reaction with Ethanol. Ethyl 3-Ethoxy-1-oxo-1*H*-indene-2-carboxylate (12b). Yield 78%; oil; IR (KBr) cm^{-1} 1716, 1700; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55−7.49 (m, 1H), 7.46−7.38 (m, 3H), 4.65 (q, J = 7.0 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.3, 176.9, 163.8, 138.8, 132.8, 132.0, 131.7, 121.8, 120.4, 103.8, 70.7, 61.1, 15.0, 14.3; GC−MS *m*/*z* 246 (M^+, 32), 201 (27), 173 (100), 146 (37), 104 (50). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.26; H, 5.48.

Transesterification Reaction of Esters 9a−c with Methanol. A suspension of the proper ester **9a**−**c** (0.5 mmol) in CH_2Cl_2 (4 mL) and MeOH (1 mL) was stirred at room temperature for 4 h, after which time the red crystals of dihydroxyquinone **11** were removed by filtration. In the case of the ester **9c** reflux for 15 h was required for the completion of the reaction. The filtrate was concentrated and chromatographed on column (silica gel, hexanes−ethyl acetate 3:1) to afford the methyl esters **17a**−**c**, as yellow solids, which can be recrystallized from dichloromethane−hexanes.

Reaction of *p*-Tolyl-ester 9a with Methanol. Methyl 3-[(4-Methylphenyl)amino]-1-oxo-1*H*-indene-2-carboxylate (17a). Yield 84%; mp 155−157 °C; IR (KBr) cm^{-1} 1693, 1654; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.19 (brs, 1H), 7.63 (d, J = 7.3 Hz, 1H), 7.42 (t, J = 7.3 Hz, 1H), 7.30 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 7.13 (t, J = 7.3 Hz, 1H), 6.45 (d, J = 7.3 Hz, 1H), 3.91 (s, 3H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.8, 170.6, 167.9, 139.1, 136.9, 134.5, 134.0, 132.8, 131.2, 130.3, 126.6, 124.0, 122.2, 96.2, 51.2, 21.2; ^{15}N NMR ($CDCl_3$, 40 MHz) δ −250.9 (reference $Me^{15}NO_2$); EI-MS *m*/*z* 293 (M^+, 19), 261 (100), 232 (37). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.47; H, 5.12; N, 4.61.

Reaction of Mesityl-ester 9b with Methanol. Methyl 3-(Mesitylamino)-1-oxo-1*H*-indene-2-carboxylate (17b). Yield 86%; mp 172−174 °C; IR (KBr) cm^{-1} 1691, 1650; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.86 (brs, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 7.02 (s, 2H), 6.15 (d, J = 7.4 Hz, 1H), 3.92 (s, 3H), 2.39 (s, 3H), 2.20 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.8, 171.9, 168.0, 139.1, 136.8, 135.4, 134.1, 133.0, 132.6, 131.8, 129.6, 122.3, 122.1, 95.1, 51.1, 21.1, 18.2; EI-MS *m*/*z* 321 (M^+, 49), 289 (100), 274 (12), 260 (27). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.59; H, 6.13; N, 4.66.

Reaction of 4,6-Dimethoxy-2-pyrimidyl-ester 9c with Methanol. Methyl 1-Oxo-3-(pyrimidin-2-ylamino)-1*H*-indene-2-carboxylate (17c). Yield 54%; mp 195−197 °C; IR (KBr) cm^{-1} 1710, 1663; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.54 (s, 1H), 8.09 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 7.1 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.4 Hz, 1H), 5.90 (s, 1H), 3.93 (s, 3H), 3.91 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.0, 172.1, 168.9, 167.3, 155.8, 135.5, 134.8, 132.8, 131.7, 127.4, 122.2, 101.5, 86.7, 54.7, 51.7; ESI-HRMS *m*/*z* calcd for $C_{17}H_{15}N_3O_5$ + Na (MNa^+) 364.09039, found 364.09012.

Hydrolysis of Esters 9a−c. A suspension of the proper ester **9a**−**c** (0.5 mmol) in CH_2Cl_2 (4 mL) and H_2O (3−4 drops) was stirred at room temperature for 4−6 h. The resulting solution was dried with Na_2SO_4, and hexanes (2−3 mL) was added. The precipitated red crystals of dihyhydroxynaphthoquinone **11** were filtered off, the resulting solution was concentrated to dryness (without heating), and ethyl acetate and ethyl ether were added to afford the acids **18a**−**c/19a**−**c**. For simplicity reasons the acids are named after their enamino form **19,** with the acid in its keto form. For example the *p*-tolyl derivative in its imino form (and the carboxyl group in its enol form) **18a** should have been named (3*E*)-2-(dihydroxymethylene)-3-[(4-methylphenyl)imino]indan-1-one.

Hydrolysis of *p*-Tolyl-ester 9a. 3-[(4-Methylphenyl)amino]-1-oxo-1*H*-indene-2-carboxylic Acid (18a/19a). Yield 74%; yellow solid, mp 159−160 °C; IR (KBr) cm^{-1} 1697, 1659; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.14 (brs, 1H), 10.88 (brs, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.20 (t, J = 7.6 Hz, 1H), 6.53 (d, J = 7.6 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.3, 169.1, 167.1, 139.8, 136.7, 134.2, 133.6 133.3, 132.2, 130.5, 126.4, 125.1, 122.6, 95.6, 21.3; EI-MS *m*/*z* 279 (M^+, 10), 261 (100), 232 (41). Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.87; H, 4.56; N, 4.92.

Hydrolysis of Mesityl-ester 9b. 3-(Mesitylamino)-1-oxo-1*H*-indene-2-carboxylic Acid (18b/19b). Yield 87%; yellow solid, mp 222−226 °C; IR (KBr) cm^{-1} 1691, 1665; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.83 (brs, 1H), 10.50 (brs, 1H), 7.64 (d, $J = 7.4$ Hz, 1H), 7.48 (t, $J = 7.4$ Hz, 1H), 7.19 (t, $J = 7.4$ Hz, 1H), 7.05 (s, 2H), 6.23 (d, $J = 7.4$ Hz, 1H), 2.40 (s, 3H), 2.21 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.2, 170.4, 167.1, 139.6, 136.5, 135.0, 134.2, 133.5, 132.7, 131.7, 129.7, 123.5, 122.6, 94.7, 21.1, 18.1; EI-MS *m*/*z* 307 (M^+, 9), 289 (100), 274 (11), 263 (42), 260 (24). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 73.97; H, 5.78; N, 4.84.

Hydrolysis of 4,6-Dimethoxy-2-pyrimidyl-ester (9c). 1-Oxo-3-[(4,6-dimethoxy-pyrimidin-2-ylamino)-1*H*-indene-2-carboxylic Acid (18c/19c). The hydrolysis proceeded as previously but the acid could not be isolated in pure form and the alternative method was followed.

Hydrolysis of 2,4-Dimethoxyindeno[1,2-*d*]pyrimido[1,2-*a*]pyrimidine-6,7-dione (20). Preparation of 1-Oxo-3-[(4,6-dimethoxy-pyrimidin-2-ylamino)-1*H*-indene-2-carboxylic Acid (18c/19c). 2,4-Dimethoxyindeno[1,2-*d*]pyrimido[1,2-*a*]pyrimidine-6,7-dione (**20**)[12] (0.1 mmol) was suspended in CH_2Cl_2 (5 mL), a few drops of H_2O were added, and the suspension was heated at 34 °C under stirring until the complete disappearance of **20** (∼5 days). The resulting solution was dried (Na_2SO_4) and concentrated (without heating). The semi-oily residue was triturated with ether, and the resulting orange solid was collected by filtration. Yield 90%; mp 149−151 °C; IR (KBr) cm^{-1} 1696, 1658; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.45 (brs, 1H), 8.35 (d, $J = 7.7$ Hz, 1H), 7.66 (d, $J = 7.04$ Hz, 1H), 7.58−7.43 (m, 2H), 5.96, (s, 1H), 3.95 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.9, 172.2, 168.0, 166.5, 155.1, 135.5, 135.0, 133.4, 132.8, 129.1, 122.8, 99.3, 87.4, 54.9; ESI-HRMS *m*/*z* calcd for $C_{16}H_{13}N_3O_5 + Na$ (MNa^+) 350.07474, found 350.07478.

It must be noted that at room temperature the reaction was completed in about 20 days, whereas at higher temperatures partial decomposition of the acid occurred.

Reaction of 2,4-Dimethoxyindeno[1,2-*d*]pyrimido[1,2-*a*]pyrimidine-6,7-dione (20) with Methanol. Methyl 1-Oxo-3-(pyrimidin-2-ylamino)-1*H*-indene-2-carboxylate (17c). The previous methodology was followed, but methanol instead of water was added to the initial CH_2Cl_2 suspension of **20**. Ester **17c** was isolated in 98% yield after reflux for 30 min.

Transesterification Reaction of Enamino Ester 24 with Methanol. A suspension of ester **24** (0.5 mmol) in CH_2Cl_2 (4 mL) and MeOH (1 mL) was stirred at room temperature for 7 d, after which time the red crystals of dihydroxyquinone **11** were removed by filtration. The filtrate was concentrated and chromatographed on column (silica gel, hexanes−ethyl acetate 3:1) to afford methyl 3-[methyl(phenyl)amino]-1-oxo-1*H*-indene-2-carboxylate (**25**) as yellow solid, which was recrystallized from dichloromethane-hexanes. Yield 77%; mp 130−132 °C; IR (KBr) cm^{-1} 1695, 1669; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.56 (t, $J = 7.0$ Hz, 1H), 7.53−7.47 (m, 3H), 7.41−7.35 (m, 2H), 7.29 (t, $J = 7.0$ Hz, 1H), 6.99 (t, $J = 7.0$ Hz, 1H), 5.69 (d, $J = 7.0$ Hz, 1H), 3.89 (s, 3H), 3.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.1, 168.8, 164.7, 145.1, 137.7, 137.0, 135.1, 131.4, 131.1, 130.0, 128.7, 126.6, 123.8, 121.7, 51.7, 47.4; EI-MS *m*/*z* 293 (M^+, 60), 262 (71), 261 (100), 260 (83), 234 (33), 158 (35). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.61; H, 5.29; N, 4.44.

X-ray Crystal Structure Determination. Single crystals suitable for X-ray structure determinations were obtained by adding diethyl ether to a solution of **19a** in methylene chloride. All C, N, and O atoms were refined with anisotropic thermal parameters. Hydrogen atoms were located and their positions refined for the amine and hydroxy hydrogen atoms; all other hydrogen positions were calculated for idealized positions.

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Supporting Information Available: X-ray crystallographic file (CIF) for **19a** and copies of ^{1}NMR and ^{13}CNMR spectra of compounds **12a,b**, **17a−c**, **18a−c/19a−c**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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