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A Serendipitous Synthesis of 11a-Hydroxy-11,11a-dihydrobenzo[*e*]indeno[2,1-*b*][1,4]diazepine-10,12-dione Derivatives by Condensation of 2-Aminobenzamides with Ninhydrin in Water

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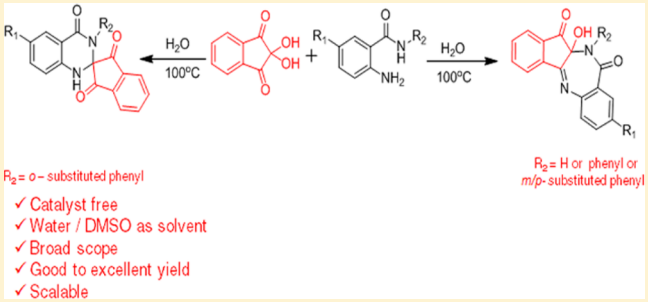
Supporting Information

ABSTRACT: Ninhydrin undergoes an unprecedented condensation reaction with various 2-aminobenzamide derivatives in boiling water to afford 11a-hydroxy-11,11a-dihydrobenzo[*e*]indeno[2,1-*b*][1,4]diazepine-10,12-dione derivatives. These hitherto unreported products are easily isolated in high yield by a simple filtration step. An interesting "ortho effect" was observed in the condensation reaction of ninhydrin with 2-amino-*N*-phenylbenzamide derivatives having an ortho-substituent in the *N*-phenyl moiety wherein the corresponding expected 3′-phenyl-1′*H*-spiro[indene-2,2′-quinazoline]-1,3,4′(3′*H*)-triones were obtained.

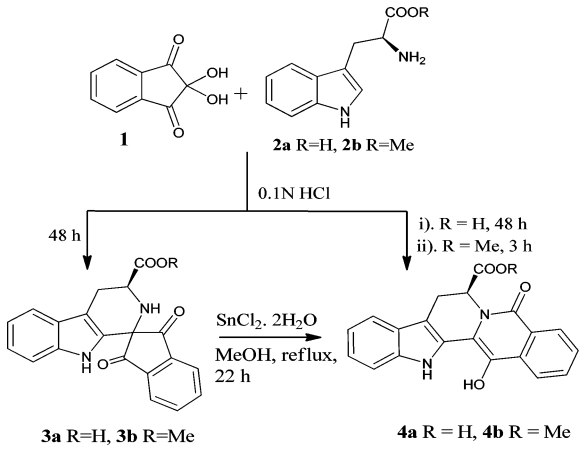


Ninhydrin has been used in the synthesis of a wide variety of heterocyclic compounds.[1−10] While the central carbon, C-2, flanked by two carbonyl groups is generally more electron-deficient compared to the other two carbonyl centers, in the case of condensation with *ortho*-aminophenols and *N*-benzylsulfonyl-*o*-phenylenediamine, the amino group reacts at C-1 of ninhydrin to afford tetracyclic products.[11]

The condensation reaction of ninhydrin with tryptophan derivatives has been studied extensively by various groups. On the basis of elemental analysis, Heesing et al. reported[12] the formation of a spirocyclic derivative of 1,2,3,4-tetrahydro-*β*-carboline (**3a**) (Scheme 1) as a yellow solid from the reaction of L-tryptophan (**2a**) with ninhydrin (**1**) in aqueous acid at room temperature. However, 20 years later, Neuzil et al. with the help of single crystal X-ray analysis confirmed[13] the structure to be **4a**, a yohimbanone derivative. Joullie et al. subjected L-tryptophan methyl ester (**2b**) to the same reaction conditions and isolated[14] the Pictet − Spengler condensation product (**3b**) as an intermediate, which upon subsequent acid mediated rearrangement provided yohimbanone (**4b**). The conversion of **3b** to **4b** was proposed to proceed via the attack of the *β*-carboline nitrogen on the adjacent carbonyl of the indanedione moiety. The resulting hydroxyaziridine intermediate then opened up to produce yohimbanone (**4b**).

To the best of our knowledge, the condensation of ninhydrin with 2-aminobenzamide derivatives has not been explored. We anticipated this reaction to afford the spiroquinazolinone derivative (**6**) (Scheme 2). Product **6** is hitherto unknown and could possibly serve as a potential bioactive molecule. Since

Scheme 1. Reaction of Ninhydrin with L-Tryptophan and Its Methyl Ester



ninhydrin and 2-aminobenzamide are soluble in water at room temperature and at boil respectively, we decided to conduct the reaction in boiling water. Water has emerged as a sustainable alternative to conventional solvents, and several reactions[15−23] have been carried out in water.

We report here a serendipitous synthesis of the hitherto unknown 11a-hydroxy-11,11a-dihydrobenzo[*e*]indeno[2,1-*b*]-

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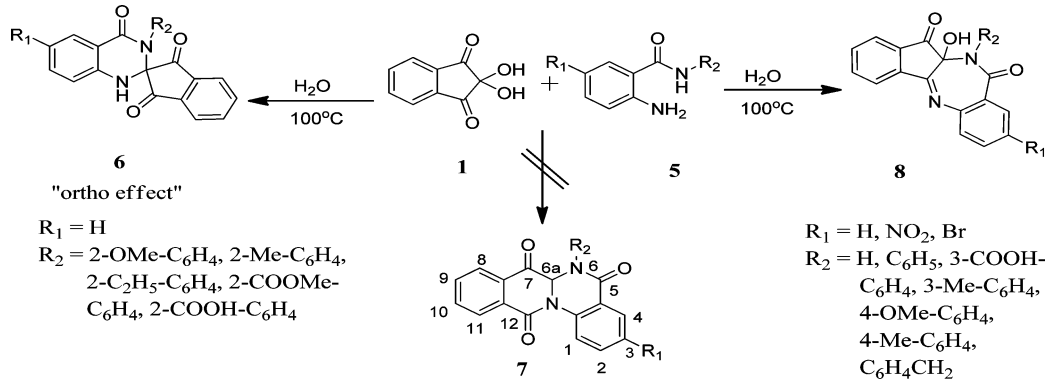
Scheme 2. Reaction of Ninhydrin with 2-Aminobenzamide Derivatives



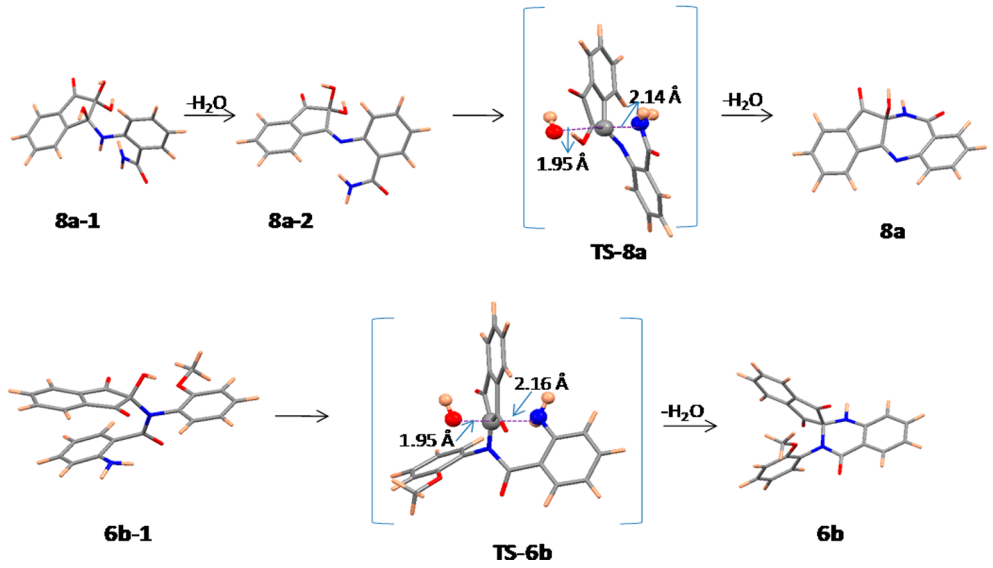


Figure 1. Calculated structures of intermediate, TS, and products applying B3LYP/6-31+G(d,p) method.

[1,4]diazepine-10,12-dione system (**8**) by the condensation of 2-aminobenzamides with ninhydrin in water.

We initially boiled a mixture of aqueous ninhydrin and 2-aminobenzamide under reflux. To our delight, the reaction proceeded smoothly within 30 min furnishing a solid product that was easily filtered. It exhibited a sharp melting point and a clean ^{1}H NMR spectrum indicating its purity. However, its ^{13}C NMR spectrum exhibited only one peak at δ_c = 195.80 ppm confirming the presence of one carbonyl group thereby ruling out the spirocyclic structure (**6**). Two peaks at δ_c = 168.15 ppm and δ_c = 166.02 ppm indicating the presence of two amide carbonyl groups suggested the formation of a rearranged product (**7**) as observed by Joullie and co-workers. The presence of a singlet at δ_H = 9.29 ppm in the ^{1}H NMR spectrum could be assigned to the amide proton. The other singlet at δ_H = 7.20 ppm may be assigned to the proton attached to C-6a. However, we needed more data to confirm the structure of the isolated product.

Fortunately, we were able to grow crystals and carry out a single crystal X-ray analysis which unambiguously established the structure of the product as **8** (see Figure 1 in the Supporting Information (SI) for an ORTEP diagram). This result is interesting as it is contrary to the generally accepted view that the central carbonyl group (C-2) of ninhydrin is more reactive in addition−elimination reactions. We next conducted this reaction in water at different temperatures and found that the reaction at room temperature took a longer time and led to a reduced yield. Reactions conducted in organic solvents such as MeOH, EtOH, THF, CH_3CN, $CHCl_3$, DCM, etc. under reflux also resulted in poor yields. Good to excellent yields were obtained only when the reaction was performed in DMF and DMSO at 80−100 °C. Thus, the use of polar solvents and high temperature favor the reaction. The optimum conditions for this reaction turned out to be boiling water under reflux. With the optimized protocol in hand, we carried out the reaction with several 2-aminobenzamide derivatives. Results are presented in Table 1 (see Experimental Section). The reaction tolerated electron-withdrawing and -donating groups in 2-aminobenzamide although a nitro group at the 5 position in the aromatic ring (Table 1, entries 8−12; see Experimental Section) retarded the reaction rate. While 2-aminobenzamide derivatives having a bromo substituent at the 5 position failed to react in water, the reaction took place in DMSO at 100 °C (Table 1, entries 13−15; see Experimental Section). This can be attributed to the lower solubility of the anthranilamide derivatives in water, even at boiling. This observation limits the scope of this protocol to water-soluble starting material.

Interestingly, in the case of 2-amino-*N*-phenylbenzamide derivatives having a substituent (−CH_3, −OCH_3, −C_2H_5, −COOH, −$COOCH_3$) at the *ortho* position in the *N*-phenyl moiety (Table 1, entries 16−20; see Experimental Section), 3′-phenyl-1′*H*-spiro[indene-2,2′-quinazoline]-1,3,4′(3′*H*)-trione

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derivatives (**6a**−**e**) were obtained exclusively. ^{13}C NMR spectra of these compounds display two carbonyl peaks. The structure of **6b** was unambiguously established with the help of single crystal X-ray analysis (see Figure 2 in SI for an ORTEP diagram). 2-Amino-*N*-phenylbenzamide derivatives having a *m*- and a *p*- substituent in the *N*-phenyl moiety (Table 1, entries 2, 3, 6, 7, 9, 10, 14; see Experimental Section) exclusively furnished product (**8**). Thus, there exists an "ortho effect" that favors formation of the spiro system.

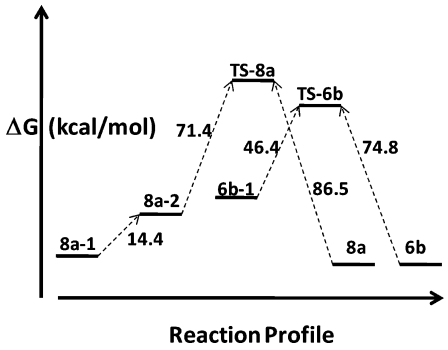

Figure 2. Energy profile diagram of reactions yielding products **8a** and **6b**. Values shown are calculated free energy change (zero point energy corrected) at 100 °C for various reaction steps.

The scale up potential of this protocol was investigated through a gram scale synthesis of **8a**. Thus, a mixture of ninhydrin (4.52 g, 25 mmol), 2-aminobenzamide (3.45 g, 25 mmol), and 110 mL of water was boiled under reflux to furnish 11a-hydroxy-11,11a-dihydrobenzo[*e*]indeno[2,1-*b*][1,4]-diazepine-10,12-dione (**8a**) (6.63g, 94%) as a white solid.

Benzodiazepinones have widespread biological and pharmacological importance. The seven membered 1,4-diazepine ring occurs as the main structural core in a variety of biologically active synthetic and natural products.[24−28] The 1,4-benzodiazepine scaffold has been synthesized[29,30] through the postcondensation transformations of four-component Ugi reaction products. A multigram synthesis of 1,4-benzodiazepines has been reported[31] wherein 2-aminobenzophenone is treated with bromoacetyl bromide in diethyl ether followed by amination and cyclization under acidic conditions. The most extensively used methods for the synthesis of benzodiazepines involve the condensation of *o*-phenylenediamines with *α*,*β*-unsaturated carbonyl compounds;[32] with ketones in the presence of $NaBH_4$,[33] polyphosphoric acid, or SiO_2;[34] Al_2O_3/P_2O_5 or AcOH under microwave conditions;[35] amberlyst-15 in the ionic liquid 1-butyl-3-methylimidazolium bromide;[36] $CeCl_3 \cdot 7H_2O$/NaI supported on silica gel;[37] and InBr,[38] $Sc(OTf)_3$,[39] and sulfated zirconia.[40] Other methods include cyclocondensation of 1,2-diamines with ketones, enones, and *β*-haloketones in ionic liquids;[41] under microwave irradiation;[35] and by using ytterbium triflate,[42] $MgO/POCl_3$,[43] and a zinc montmorillonite heterogeneous catalyst.[44]

In contrast, our one-pot protocol provides an efficient and environmentally benign entry into this important class of heterocyclic compounds from easily accessible starting materials such as ninhydrin and 2-aminobenzamide.

COMPUTATIONAL RESULTS

To provide mechanistic insights on the condensation reactions of ninhydrin (**1**) and two different 2-aminobenzamides (**5**, R_1 = H, R_2 = H and R_1 = H, R_2 = 2-OMe-C_6H_4) leading to two different types of products (**8** and **6**), density functional theory (DFT) based quantum chemical methods have been applied.[45] Full geometry optimizations of the reactants, products and possible transition state structures have been carried out at B3LYP/6-31+G(d,p) level of theory including macroscopic solvent effect in water to find out the minimum energy structures. For macroscopic solvent effect, SMD model has been adopted in which continuum solvation is based on the quantum mechanical charge density of the solute molecule interacting with continuum solvent.

There are two C-1 type and one C-2 type electrophilic centers in ninhydrin (**1**). Thus, nucleophilic attack at C-1 is intrinsically favored. Also, calculated atomic charge (Mulliken) of ninhydrin suggests C-1 (+0.41 au) is a better electrophile than C-2 (+0.34 au). Similar calculations suggest amine N (−0.10 au) is more nucleophilic than amide N (0.0 au) in 2-aminobenzamide (**5a**). However, in case of aminobenzamides having an *ortho*-substitution in the *N*-phenyl group (**5q**), amine N (−0.10 a.u) is less nucleophilic than amide N (−0.33 au). Calculated atomic charge suggests that amine N of 2-aminobenzamide should attack one of the two C-1 centers of ninhydrin to initiate the reaction leading to the intermediate, **8a-1** (see Figure 1) followed by elimination of H_2O (OH^- and H^+) to form another intermediate, **8a-2**. This intermediate undergoes S_N2 reaction to eliminate OH^- from C-2 of the ninhydrin moiety and form product **8a** after proton elimination from the amide group. Optimized structures of all the intermediates and the TS are provided in Figure 1. For the other aminobenzamide system (**5q**), amide N should also undergo nucleophilic addition reaction at one of the two C-1 centers. However, modeling studies suggest that because of steric repulsion owing to the *ortho*-substitution in the *N*-phenyl group the addition reaction at the C-1 center cannot proceed. Due to the same reason the reaction cannot initiate at the C-2 center either. However, ninhydrin is known to have an equilibrium with Indane-1,2,3 trione in water.[46,47]

Scheme 3. Plausible Reaction Mechanism

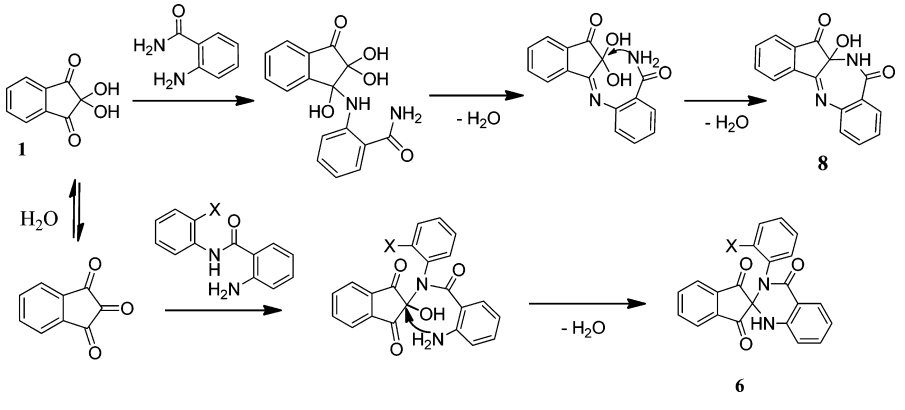

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Table 1. Substrate Scope of 2-Aminobenzamide Derivatives 5 (Scheme 2)[a]

entry	2-amino benzamide derivative	R_1	R_2	product	time (h)	yield[b] (%)	melting point (°C)
1	**5a**	H	H	**8a**	1	94	220−222
2	**5b**	H	4-OCH_3-C_6H_4	**8b**	2	80	204−206
3	**5c**	H	4-CH_3-C_6H_4	**8c**	2	70	198−200
4	**5d**	H	C_6H_5	**8d**	2.5	89	218−220
5	**5e**	H	$C_6H_4CH_2$	**8e**	4	86	168−170
6	**5f**	H	3-CH_3-C_6H_4	**8f**	5	85	222−224
7	**5g**	H	3-COOH-C_6H_4	**8g**	6.5	81	180−182
8	**5h**	NO_2	H	**8h**	12	80	218−220
9	**5i**	NO_2	4-OCH_3-C_6H_4	**8i**	12	60	228−230
10	**5j**	NO_2	4-Me-C_6H_4	**8j**	12	40	218−220
11	**5k**	NO_2	C_6H_5	**8k**	12	30	228−230
12	**5l**	NO_2	$C_6H_4CH_2$	**8l**	12	65	225−227
13	**5m**	Br	H	**8m**[c]	12	77	208−210
14	**5n**	Br	4-CH_3-C_6H_4	**8n**[c]	12	80	212−214
15	**5o**	Br	$C_6H_4CH_2$	**8o**[c]	12	70	172−174
16	**5p**	H	2-CH_3-C_6H_4	**6a**	1	77	226−228
17	**5q**	H	2-OCH_3-C_6H_4	**6b**	1	80	212−214
18	**5r**	H	2-C_2H_5-C_6H_4	**6c**	2.5	81	204−206
19	**5s**	H	2-COOH-C_6H_4	**6d**	1	72	207−209
20	**5t**	H	2-$COOCH_3$-C_6H_4	**6e**	2	88	155−157

[a]Reaction conditions: Ninhydrin (0.7 mmol), 2-aminobenzamides (0.7 mmol) and water (3 mL) at 100 °C. [b]Isolated yield. [c]These compounds were prepared by using DMSO (3 mL) as solvent at 100 °C.

Moreover, calculated atomic charges suggest that the C-2 (+0.35 au) center of Indane-1,2,3 trione is a better electrophile than C-1 (+0.34 au) center. When amide N of reactant **5q** attacks C-2, intermediate **6b-1** (see Figure 1) is formed after rearrangement. This intermediate undergoes an S_N2 reaction to eliminate OH^- from C-2 forming product **6b** after proton elimination from the amine group. Optimized structures of the intermediates, TS, and the product are given in Figure 1. Transition state structures are confirmed by Hessian calculations producing only one imaginary frequency (~453 cm^{-1}) for product **8a** and ~421 cm^{-1} for product **6b**. The corresponding normal mode connects to the respective reactants and products. An energy profile diagram of the reactions leading to the formation of products **8a** and **6b** is depicted in Figure 2.

Based on the computational results, a plausible reaction mechanism is depicted in Scheme 3 to rationalize product formation.

In summary, we have developed an efficient synthesis of 11a-hydroxy-11,11a-dihydrobenzo[*e*]indeno[2,1-*b*][1,4]diazepine-10,12-dione derivatives. Our protocol is environmentally benign, simple, and catalyst-free and provides easy isolation of the product. Since the 1,4-benzodiazepine scaffold is encountered in several biologically and pharmacologically active products, this protocol may serve as a platform for the synthesis of a diverse array of potentially active molecules from simple starting materials. The reaction proceeds by a nucleophilic attack on C-1 of ninhydrin rather than on C-2. The reaction follows the normal route of nucleophilic attack on C-2 when a 2-amino-*N*-phenylbenzamide derivative having an *ortho*-substituent in the *N*-phenyl group is used.

EXPERIMENTAL SECTION

Instrumentation and Chemicals. All reactions were monitored utilizing TLC on silica gel 60 F_{254}. Column chromatographic purification of compounds was performed by using silica gel (mesh 100−200) and a hexane−ethyl acetate mixture as eluent. NMR spectra were recorded on a 400, 600, or 800 MHz instrument for ^1H NMR and a 100 or 150 MHz instrument for ^{13}C NMR. Chemical shift values are reported in parts per million (δ ppm) using DMSO-d_6 as solvent and trimethylsilane (TMS) as the internal standard. High-resolution mass spectra (HRMS) were recorded by ESI on an iFunnel Q-TOF (time-of-flight) mass spectrometer. Melting points of the compounds were determined by using a digital melting point apparatus and are uncorrected. 2-Aminobenzamide derivatives were prepared according to reported procedures.[48−53]

Typical Experimental Procedure for the Synthesis of 11a-Hydroxy-11,11a-dihydrobenzo[*e*]indeno[2,1-*b*][1,4]diazepine-10,12-dione Derivatives. A mixture of ninhydrin (**1**, 0.7 mmol) and 2-aminobenzamide (**5a−5t**, 0.7 mmol) in 3 mL of water or 3 mL of DMSO was boiled under reflux for 1−12 h. The reaction completion was checked using TLC. The reaction mixture was allowed to cool, and the solid product obtained was diluted with water in the case of DMSO as solvent, filtered, and dried. The crude product was purified by column chromatography over silica gel by using an appropriate mixture of *n*-hexane−ethyl acetate to yield products **8a−8o** and **6a−6e** (Table 1).

*11a-Hydroxy-11,11a-dihydrobenzo[e]indeno[2,1-b][1,4]-diazepine-10,12-dione (**8a**).* Isolated yield: 181 mg (94%), white solid, mp 220−222 °C. ^1H NMR (600 MHz, DMSO-*d6*): δ 9.294 (s, 1H, NH), 8.194 (d, J = 5.4 Hz, 1H), 8.024−7.892 (m, 4H), 7.617−7.356 (m, 3H), 7.203 (s, 1H); ^{13}C NMR (150 MHz, DMSO-*d6*): δ 195.8, 168.1, 166.0, 145.6, 142.9, 138.1, 135.7, 135.1, 132.4, 131.3, 128.1, 127.8, 126.8, 124.8, 124.0, 76.1. HRMS (ESI-TOF) (m/z): calcd for $C_{16}H_{10}N_2O_3$ $[M + H]^+$ 279.0769; found 279.0738.

*11a-Hydroxy-11-(4-methoxyphenyl)-11,11a-dihydrobenzo[e]-indeno[2,1-b][1,4]diazepine-10,12-dione (**8b**).* Isolated yield: 213 mg (80%), reddish orange solid, mp 204−206 °C. ^1H NMR (600 MHz, DMSO-*d6*): δ 8.017 (dd, J = 3.0, 5.4 Hz, 2H), 7.961 (dd, J = 3.0, 5.4 Hz, 2H), 7.828 (s, 1H), 7.693 (dd, J = 1.2, 7.8 Hz, 1H), 7.328 (dt, J = 1.2, 7.8 Hz, 1H), 6.827 (d, J = 9.0 Hz, 2H), 6.801 (t, J = 7.8 Hz, 1H), 6.754 (d, J = 9.0 Hz, 2H), 6.628 (d, J = 7.8 Hz, 1H), 3.622 (s, 3H); ^{13}C NMR (150 MHz, DMSO-*d6*): δ 195.6, 163.5, 159.1, 146.0, 139.4, 138.4, 134.5, 131.2, 129.7, 128.1, 124.6, 118.9, 114.7, 114.4, 75.8, 55.6. HRMS (ESI-TOF) (m/z): calcd for $C_{23}H_{16}N_2O_4$ $[M + H]^+$ 385.1188; found 385.1159.

*11a-Hydroxy-11-(p-tolyl)-11,11a-dihydrobenzo[e]indeno[2,1-b]-[1,4]diazepine-10,12-dione (**8c**).* Isolated yield: 179 mg (70%), orange solid, mp 198−200 °C. ^1H NMR (400 MHz, DMSO-*d6*): δ 7.897−7.861 (m, 4H), 7.696 (s, 1H), 7.662 (t, J = 7.2 Hz, 1H), 7.226 (t, J = 6.4 Hz, 1H), 6.917 (d, J = 6.8 Hz, 2H), 6.754 (d, J = 7.6 Hz, 2H), 6.734 (d, J = 8.4 Hz, 1H), 6.569 (d, J = 7.6 Hz, 1H), 2.101 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d6*): δ 194.8, 163.0, 145.4, 139.0, 137.6, 137.5, 134.3, 133.8, 129.4, 129.2, 127.6, 123.9, 118.3, 114.2, 114.0, 75.2, 20.5. HRMS (ESI-TOF) (m/z): calcd for $C_{23}H_{16}N_2O_3$ $[M + H]^+$ 369.1239; found 369.1211.

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*11a-Hydroxy-11-phenyl-11,11a-dihydrobenzo[e]indeno[2,1-b]-[1,4]diazepine-10,12-dione (**8d**).* Isolated yield: 220 mg (89%), orange solid, mp 218−220 °C. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.988−7.966 (m, 2H), 7.931−7.909 (m, 2H), 7.790 (s, 1H), 7.743 (d, *J* = 7.6 Hz, 1H), 7.312 (t, *J* = 7.6 Hz, 1H), 7.185 (m, 3H), 6.949 (d, *J* = 6.8 Hz, 2H), 6.805 (t, *J* = 7.6 Hz, 1H), 6.653 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 194.7, 162.9, 145.4, 139.0, 137.5, 137.0, 133.8, 129.5, 128.9, 128.1, 127.6, 123.9, 118.3, 114.1, 114.0, 75.2. HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{22}H_{14}N_2O_3$ [M + H]$^+$ 355.1082; found 355.1059.

*11-Benzyl-11a-hydroxy-11,11a-dihydrobenzo[e]indeno[2,1-b]-[1,4]diazepine-10,12-dione (**8e**).* Isolated yield: 220 mg (86%), orange solid, mp 168−170 °C. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.956−7.933(m, 2H), 7.847−7.825 (m, 2H), 7.785 (dd, *J* = 1.2, 6.4 Hz, 1H), 7.614 (s, 1H), 7.328 (dt, *J* = 1.2, 7.8 Hz, 1H), 6.974−6.938 (m, 5H, Ar), 6.791 (dt, *J* = 0.8, 7.6 Hz, 1H), 6.575 (d, *J* = 7.6 Hz, 1H), 4.562 (s, 2H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 194.0, 163.2, 145.1, 138.9, 137.1, 135.5, 133.4, 128.4, 127.6, 127.1, 123.7, 118.4, 114.7, 114.0, 73.3, 45.5. HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{23}H_{16}N_2O_3$ [M + H]$^+$ 369.1239; found 369.1218.

*11a-Hydroxy-11-(m-tolyl)-11,11a-dihydrobenzo[e]indeno[2,1-b]-[1,4]diazepine-10,12-dione (**8f**).* Isolated yield: 217 mg (85%), orange solid, mp 222−224 °C. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.022−7.991 (m, 2H), 7.975−7.944 (m, 2H), 7.835 (s, 1H), 7.732 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.335 (dt, *J* = 1.6, 7.6 Hz, 1H), 7.084 (t, *J* = 7.6 Hz, 1H), 6.992 (d, *J* = 7.6 Hz, 1H), 6.187 (dt, *J* = 1.2, 8.4 Hz, 1H), 6.774 (s, 1H), 6.703 (d, *J* = 7.6 Hz, 1H), 6.662 (d, *J* = 8.0 Hz, 1H), 2.142 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d6*): δ 194.8, 162.8, 145.5, 139.0, 138.4, 137.7, 130.1, 128.9, 128.7, 127.6, 126.2, 124.0, 118.4, 114.1, 114.0, 75.2, 20.6. HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{23}H_{16}N_2O_3Na$ [M + Na]$^+$ 391.1059; found 391.1030.

*3-(11a-Hydroxy-10,12-dioxo-11a,12-dihydrobenzo[e]indeno[2,1-b][1,4]diazepin-11(10H)-yl)benzoic Acid (**8g**).* Isolated yield: 225 mg (81%), yellow solid, mp 180−182 °C. ^{1}H NMR (800 MHz, DMSO-*d6*): δ 13.121 (bs, 1H), 8.054−8.043 (m, 2H), 8.011−8.000 (m, 2H), 7.970 (s, 1H), 7.782 (d, *J* = 7.2 Hz, 1H), 7.751 (d, *J* = 8 Hz, 1H), 7.488 (s, 1H), 7.420−7.379 (m, 2H), 7.226 (d, *J* = 8.0 Hz, 1H), 6.862 (t, *J* = 7.2 Hz, 1H), 6.697 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-*d6*): δ 194.4, 166.1, 163.1, 145.4, 138.9, 137.5, 137.1, 131.8, 130.4, 129.1, 129.0, 127.6, 124.0, 118.5, 114.2, 114.0, 75.2. HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{23}H_{14}N_2O_5$ [M + H]$^+$ 399.0981; found 399.0950.

*11a-Hydroxy-8-nitro-11,11a-dihydrobenzo[e]indeno[2,1-b][1,4]-diazepine-10,12-dione (**8h**).* Isolated yield: 180 mg (80%), yellow solid, mp 218−220 °C. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.625 (s, 1H), 8.578 (s, 1H), 8.416 (d, *J* = 2.8 Hz, 1H), 8.075−8.046 (m, 5H), 6.682 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 194.2, 161.1, 151.2, 139.0, 138.1, 137.6, 129.2, 124.3, 123.7, 114.0, 112.3, 70.3. HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{16}H_9N_3O_5$ [M + H]$^+$ 324.0620; found 324.0604.

*11a-Hydroxy-11-(4-methoxyphenyl)-8-nitro-11,11a-dihydro-benzo[e]indeno[2,1-b][1,4]diazepine-10,12-dione (**8i**).* Isolated yield: 179 mg (60%), yellow solid, mp 228−230 °C. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.912 (s, 1H), 8.501 (d, *J* = 2.4 Hz, 1H), 8.118 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.969 (dd, *J* = 3.2, 5.6 Hz, 2H), 7.915 (dd, *J* = 3.2, 5.6 Hz, 2H), 6.826 (d, *J* = 8.8 Hz, 2H), 6.747 (d, *J* = 8.8 Hz, 1H), 6.682 (d, *J* = 9.2 Hz, 2H), 3.606 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 193.9, 161.2, 159.0, 150.7, 139.0, 138.6, 137.8, 130.7, 129.2, 128.1, 124.1, 114.2, 112.4, 74.9, 55.0. HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{23}H_{15}N_3O_6$ [M + H]$^+$430.1039; found 430.1027.

*11a-Hydroxy-8-nitro-11-(p-tolyl)-11,11a-dihydrobenzo[e]indeno-[2,1-b][1,4]diazepine-10,12-dione (**8j**).* Isolated yield: 115 mg (40%), yellow solid, mp 218−220 °C. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.928 (s, 1H), 8.599 (d, *J* = 2.4 Hz, 1H), 8.503 (d, *J* = 2.4 Hz, 1H), 8.134−8.095 (m, 1H), 7.976−7.946 (m, 2H), 7.930−7.898 (m, 2H), 6.960 (d, *J* = 8.0 Hz, 2H), 6.784 (d, *J* = 8.8 Hz, 2H), 2.137 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 193.8, 161.1, 155.3, 150.7, 139.0, 138.6, 138.3, 137.8, 135.0, 133.2, 129.6, 129.2, 128.7, 126.2, 124.3, 124.1, 120.9, 114.2, 112.5, 74.8, 20.5. HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{23}H_{15}N_3O_5$ [M + H]$^+$ 414.1090; found 414.1090.

*11a-Hydroxy-8-nitro-11-phenyl-11,11a-dihydrobenzo[e]indeno-[2,1-b][1,4]diazepine-10,12-dione (**8k**).* Isolated yield: 83 mg (30%), yellow solid, mp 228−230 °C. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.976 (s, 1H), 8.561 (d, *J* = 2.8 Hz, 1H), 8.164 (dd, *J* = 2.8, 9.2 Hz, 1H), 8.001−7.979 (m, 2H), 7.957−7.926 (m, 2H), 7.212−7.180 (m, 3H), 6.957 (dd, *J* = 2.4, 8.0 Hz, 2H), 6.801 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 193.7, 161.0, 150.7, 139.0, 138.7, 137.8, 135.9, 129.5, 129.3, 129.0, 128.6, 124.3, 124.1, 114.3, 112.5, 74.8. HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{22}H_{13}N_3O_5$ [M + H]$^+$ 400.0933; found 400.0899.

*11-Benzyl-11a-hydroxy-8-nitro-11,11a-dihydrobenzo[e]indeno-[2,1-b][1,4]diazepine-10,12-dione (**8l**).* Isolated yield: 187 mg (65%), yellow solid, mp 225−227 °C. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.854 (s, 1H), 8.605 (d, *J* = 2.4 Hz, 1H), 8.116 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.990 (dd, *J* = 2.8, 5.6 Hz, 2H), 7.873 (dd, *J* = 2.8, 5.6 Hz, 2H), 7.004−6.904 (m, 5H), 6.719 (d, *J* = 8.8 Hz, 1H), 4.594 (s, 2H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 193.0, 161.5, 150.4, 138.9, 138.7, 137.5, 134.9, 129.0, 128.4, 127.7, 127.4, 124.3, 124.0, 114.1, 113.2, 73.0, 45.8. HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{23}H_{15}N_3O_5$ [M + H]$^+$ 414.1090; found 414.1080.

*8-Bromo-11a-hydroxy-11,11a-dihydrobenzo[e]indeno[2,1-b]-[1,4]diazepine-10,12-dione (**8m**).* Isolated yield: 191 mg (77%), orange solid, mp 208−210 °C. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.307 (s, 1H), 8.083−8.055 (m, 4H), 7.709 (d, *J* = 2.4 Hz, 1H), 7.617 (s, 1H), 7.352 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.553 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 194.9, 161.9, 145.1, 139.0, 137.2, 135.9, 129.1, 124.0, 116.1, 115.5, 108.8, 70.2. HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{16}H_9BrN_2O_3$ [M + H]$^+$ 356.9875; found 356.9866.

*8-Bromo-11a-hydroxy-11-(p-tolyl)-11,11a-dihydrobenzo[e]-indeno[2,1-b][1,4]diazepine-10,12-dione (**8n**).* Isolated yield: 249 mg (80%), orange solid, mp 212−214 °C. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.988−7.957 (m, 3H), 7.943−7.912 (m, 2H), 7.795 (d, *J* = 2.4 Hz, 1H), 7.403 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.987 (d, *J* = 8.4 Hz, 2H), 6.815 (d, *J* = 8.0 Hz, 2H), 6.616 (d, *J* = 8.8 Hz, 1H), 2.173 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 194.4, 170.0, 161.9, 144.6, 138.9, 137.9, 137.5, 133.9, 129.7, 129.5, 129.1, 124.0, 116.3, 115.8, 109.5, 74.9, 20.5. HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{23}H_{15}BrN_2O_3$ [M + H]$^+$ 447.0344; found 447.0313.

*11-Benzyl-8-bromo-11a-hydroxy-11,11a-dihydrobenzo[e]-indeno[2,1-b][1,4]diazepine-10,12-dione (**8o**).* Isolated yield: 217 mg (70%), yellow solid, mp 172−174 °C. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.943 (dd, *J* = 3.2, 5.6 Hz, 2H), 7.855 (d, *J* = 2.0 Hz, 1H), 7.832 (dd, *J* = 3.2, 5.6 Hz, 3H), 7.354 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.965−6.924 (m, 5H), 6.549 (d, *J* = 8.8 Hz, 1H), 4.577 (s, 2H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 193.6, 162.1, 144.2, 138.8, 137.1, 135.8, 135.1, 129.8, 128.5, 127.6, 127.2, 123.7, 116.5, 116.2, 109.6, 73.0, 45.6. HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{23}H_{15}BrN_2O_3$ [M + H]$^+$ 447.0344; found 447.0329.

*3′-(o-Tolyl)-1′H-spiro[indene-2,2′-quinazoline]-1,3,4′(3′H)-trione (**6a**).* Isolated yield: 197 mg (77%), orange solid, mp 226−228 °C. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.105−8.048 (m, 2H), 7.975−7.923 (dt, *J* = 1.6, 7.6 Hz, 1H), 7.831 (d, *J* = 8.8 Hz, 2H), 7.747 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.338 (dt, *J* = 1.6, 7.6 Hz, 1H), 7.224 (d, *J* = 7.2 Hz, 1H), 7.0935 (dt, *J* = 1.2, 7.6 Hz, 1H), 6.860 (dt, *J* = 1.2, 7.6 Hz, 1H), 6.830 (dt, *J* = 1.2, 7.6 Hz, 1H), 6.687 (d, *J* = 8.0 Hz, 1H), 6.546 (dd, *J* = 1.6, 8.0 Hz, 1H), 2.277 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d6*): δ 195.8, 192.7, 161.9, 145.6, 140.0, 138.4, 138.1, 138.0, 137.4, 136.4, 133.9, 130.9, 128.3, 127.7, 126.7, 126.3, 124.5, 123.8, 118.5, 114.8, 114.3, 75.0, 18.0. HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{23}H_{16}N_2O_3Na$ [M + Na]$^+$ 391.1059; found 391.1027.

*3′-(2-Methoxyphenyl)-1′H-spiro[indene-2,2′-quinazoline]-1,3,4′(3′H)-trione (**6b**).* Isolated yield: 214 mg (80%), yellow solid, mp 212−214 °C. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 8.022−7.990 (m, 2H), 7.920 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.791 (d, *J* = 7.8 Hz, 1H), 7.677 (d, *J* = 7.8 Hz, 1H), 7.665 (s, 1H), 7.334 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.151 (dt, *J* = 1.8, 8.4 Hz, 1H), 6.959 (dd, *J* = 1.8, 7.8 Hz, 1H), 6.846−6.800 (m, 2H), 6.725 (d, *J* = 7.8 Hz, 1H), 6.686 (d, *J* = 8.4 Hz, 1H), 3.189 (s, 3H); ^{13}C NMR (150 MHz, DMSO-*d6*): δ 193.7, 193.6, 162.5, 155.5, 146.5, 139.6, 139.1, 137.99, 137.2, 134.3, 131.8, 130.1, 128.1, 125.7, 124.1, 124.0, 120.9, 118.9, 115.7, 114.8, 112.0, 74.6, 54.8.

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J. Org. Chem. 2016, 81, 1689−1695

HRMS (ESI-TOF) (m/z): calcd for $C_{23}H_{16}N_2O_4Na$ $[M + Na]^+$ 407.1008; found 407.0973.

*3′-(2-Ethylphenyl)-1′H-spiro[indene-2,2′-quinazoline]-1,3,4′(3′H)-trione (**6c**).* Isolated yield: 216 mg (81%), orange solid, mp 204−206 °C. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.055−8.001 (m, 2H), 7.927 (dt, J = 2, 7.6 Hz, 1H), 7.783 (d, J = 7.6 Hz, 1H), 7.748 (d, J = 9.0 Hz, 2H), 7.304 (dt, J = 1.2, 7.6 Hz, 1H), 7.249 (d, J = 6.8 Hz, 1H), 7.134 (dt, J = 1.2, 7.6 Hz, 1H), 6.854−6.790 (m, 2H), 6.671 (d, J = 8.0 Hz, 1H), 6.543 (dd, J = 1.2, 7.6 Hz, 1H), 2.801−2.629 (m, 2H), 1.166 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 195.7, 192.4, 162.5, 145.5, 143.2, 139.9, 138.4, 137.6, 137.0, 135.7, 133.6, 128.5, 128.4, 127.6, 126.8, 125.9, 124.2, 123.6, 118.4, 115.0, 114.3, 74.9, 23.2, 13.2. HRMS (ESI-TOF) (m/z): calcd for $C_{24}H_{18}N_2O_3$ $[M + H]^+$ 383.1395; found 383.1370.

*2-(1,3,4′-Trioxo-1,3-dihydro-1′H-spiro[indene-2,2′-quinazolin]-3′(4′H)-yl)benzoic Acid (**6d**).* Isolated yield: 199 mg (72%), yellow solid, mp 207−209 °C. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 12.664 (bs, 1H), 8.053−8.019 (m, 2H), 7.978 (t, J = 7.2 Hz, 1H), 7.846−7.808 (m, 3H), 7.698 (d, J = 7.8 Hz, 1H), 7.336−7.288 (m, 3H), 6.810 (t, J = 7.2 Hz, 1H), 6.723−6.695 (m, 1H), 6.659 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 194.8, 192.3, 165.9, 162.5, 145.5, 139.9, 138.2, 137.4, 137.0, 136.8, 133.4, 132.1, 131.8, 131.2, 129.0, 128.0, 127.7, 124.2, 123.8, 118.3, 115.5, 114.4, 74.9. HRMS (ESI-TOF) (m/z): calcd for $C_{23}H_{14}N_2O_5$ $[M + H]^+$ 399.0981; found 399.0951.

*Methyl 2-(1,3,4′-Trioxo-1,3-dihydro-1′H-spiro[indene-2,2′-quinazolin]-3′(4′H)-yl)benzoate (**6e**).* Isolated yield: 253 mg (88%), yellow solid, mp 155−157 °C. ^{1}H NMR (400 MHz, DMSO-*d6*): 8.068−8.033 (m, 2H), 7.995 (dt, J = 2.0, 6.0 Hz, 1H), 7.867 (td, J = 0.8, 6.8 Hz, 1H), 7.837−7.814 (m, 2H), 7.733 (dd, J = 1.6, 8.0 Hz, 1H), 7.393−7.338 (m, 3H), 6.848 (dt, J = 0.8, 7.6 Hz, 1H), 6.799−6.776 (m, 1H), 6.704 (d, J = 8.0 Hz, 1H), 3.721 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d6*): δ 195.1, 192.8, 164.7, 162.4, 145.6, 138.1, 137.7, 133.0, 131.1, 130.0, 128.6, 127.7, 124.5, 123.9, 118.5, 115.0, 114.4, 75.0, 52.0. HRMS (ESI-TOF) (m/z): calcd for $C_{24}H_{16}N_2O_5Na$ $[M + Na]^+$ 435.0957; found 435.0924.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02327.

Spectral, analytical data (PDF)
Single crystal X-ray analysis of compound **8a** (CIF)
Single crystal X-ray analysis of compound **6b** (CIF)

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Notes

The authors declare no competing financial interest.

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