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Synthesis of 1,4-Benzodiazepine-3,5-diones

Per Wiklund,[†] Mark Rogers-Evans,[‡] and Jan Bergman*[,†]

Unit for Organic Chemistry, Department of Biosciences, Karolinska Institute and Södertörn University College, Novum Research Park, SE-141 57 Huddinge, Sweden, and F. Hoffmann-La Roche Ltd, Pharmaceuticals Division, Lead Generation, PRBC-CI, Bldg 65/416, CH-4070 Basel, Switzerland

jabe@biosci.ki.se

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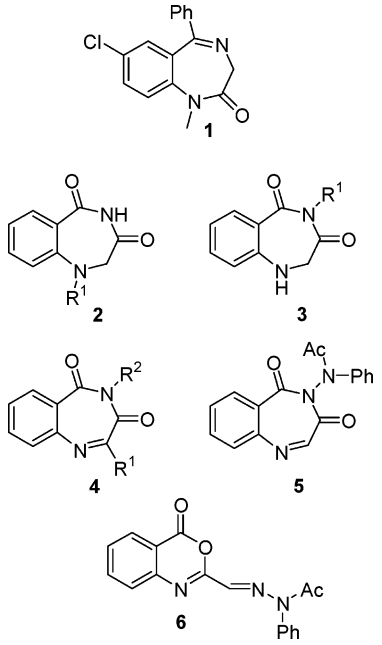
Even though benzodiazepines have a strong position in medicinal chemistry, very few synthetic routes to 1*H*-1,4-benzodiazepine-3,5(2*H*,4*H*)-diones have ever been published and the claimed products have often been poorly characterized. Through the present work several 1*H*-1,4-benzodiazepine-3,5(2*H*,4*H*)-diones have become available from *N*-carbamoylmethylanthranilic acids. The required ring closures were achieved only when the amino groups of the starting materials were substituted with electron withdrawing groups such as acetyl, alkyloxycarbonyl, or nitroso. During the synthetic work a novel ring contraction rearrangement from a 1-nitroso-1*H*-1,4-benzodiazepine-3,5(2*H*,4*H*)-dione to a 3*H*-quinazoline-4-one was observed. The proposed mechanism involves elimination of HNO followed by a proton-mediated loss of CO. The 1-nitrosated 1,4-benzodiazepinediones could be separately denitrosated to the corresponding amino compounds.

Introduction

Despite the fact that thousands of 1,4-benzodiazepinones have been synthesized, analyzed, and tested for bioactivity since the initial discovery of the sedative and tranquilizing effects of chlordiazepoxide in 1958, followed by the patent for diazepam (**1**) in 1963,[1] only a few examples of the isomeric 1*H*-1,4-benzodiazepine-3,5-(2*H*,4*H*)-diones (**2** and **3)** are to be found in the literature. The dehydrogenated parent compounds **4** are still unknown.[2] The first benzodiazepine ever reported, compound **5**,[3] was of this type, but the assigned structure was subsequently disproved in favor of the benzoxazinone **6**.[4] In this paper we present syntheses of, and structural evidence for, compounds of the types **2** and **3**, and describe reactions of molecules of these types.

The most general synthetic approach to 1,4-benzodiazepine-3,5-diones yet reported involves DCC mediated ring closure of *N*-carboxymethylanthranilamides. This procedure has been purported to yield compounds **3a**[5] and **3b**−**d**.[6] However, in our hands this method failed to yield any products which would be consistent with seven-membered rings. The products appeared to be polymeric. The reported data on these products are sketchy at best, and serious doubt arose about the claimed syntheses of **3a**−**d**. There are also a couple of brilliant approaches to these systems, which are alas limited to very specific targets, i.e., compounds **7**[7] and **8**.[8] There are also two patents which include claims on 1,4-benzodiazepin-2,5-diones.[9,10] They both involve substances with large substituents on N4 as exemplified by compound **9**. This



[†] Karolinska Institute and Södertörn University College.
[‡] F. Hoffmann-La Roche Ltd.

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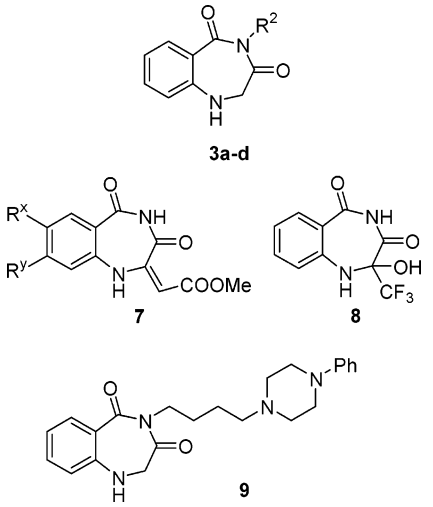
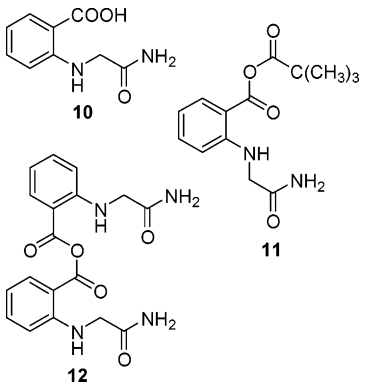


FIGURE 1. Compounds **3a** (R^2 = Et)[5] and **3b**−**d** (**b**, R^2 = Ph; **c**, R^2 = Bn; **d**, R^2 = *p*-toluyl),[6] **7** (R^x and R^y combinations of H, Me, OMe, F, Cl, Br, and I),[7] **8**,[8] and compounds similar to **9**[9,10] appear in the literature.

buspirone like molecule, and analogues with other atoms in the 1-position (C, O, S), have been reported to have high affinities for the 5-HT_{1A} receptor[9,11] and the opioid σ-receptor.[10]

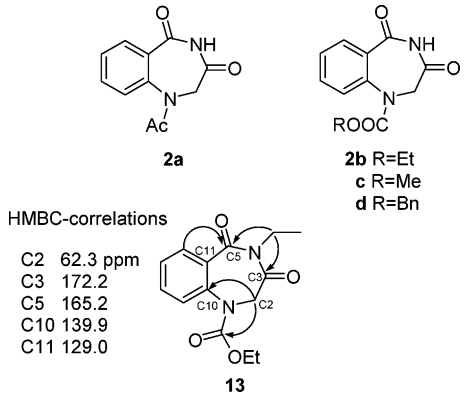
Results and Discussion

In the initial investigations it was examined how 2-(carbamoylmethylamino)benzoic acid (**10**) could be converted into 1,4-benzodiazepinediones. The acid **10** readily formed anhydrides, i.e., activated forms of the carboxy functionality, proven by the transformation into the mixed anhydride **11** and the symmetric anhydride **12**, both of which are previously unknown.



The nucleophilicity of the carboxylate ion of the starting material is increased by the electron donating amine functionality in the ortho position, which explains the ready formation of the anhydride **12**. As soon as one molecule is activated by the coupling reagent (Mukaiyama's reagent), it is attacked by another (unactivated) molecule. The reaction is driven by the formation of the rather insoluble product that is presumably stabilized by internal hydrogen bonds. The product could be purified by boiling in acetonitrile followed by filtration, and it was very resistant to hydrolysis (water in warm DMSO).

The anhydrides **11** and **12** could not be forced to cyclize, which is not surprising as this would require attack from a poorly nucleophilic amide onto a deactivated (and hindered) anhydride. However, after treatment of **10** with acetic anhydride and base, a low yield of the ring closed and N1-acetylated product **2a** could be isolated. Thus it was clear that an electron withdrawing substituent on N1, as would be expected, will enable ring closure. The ^{1}H NMR spectrum of **2a** showed an imide N−H signal at 11.15 ppm and an AB-type doublet of a doublet from the methylene protons (in DMSO-d_6).



When the precursor **10** was treated with chloroformates and triethylamine in refluxing acetonitrile, the ring closed products **2b**−**d** were formed. The reaction with ethyl chloroformate produced compound **2b** in a 66% yield. Similarly, reactions with methyl and benzyl chloroformate yielded **2c** and **2d**, respectively, albeit in lower yields. The methylene protons of these compounds displayed themselves as broad humps in the ^{1}H NMR spectra, and the imide NH gave sharp singlets at around 11.2 ppm (in DMSO-d_6).

All attempts to remove the *N*-ethyloxycarbonyl function of compound **2b** failed even under conditions as harsh as HBr in hot acetic acid, conditions which have been reported to work for deprotection of an *N*-ethyloxycarbonyl-substituted tetrahydroquinoline.[12] Compound **2b** could easily be alkylated to form the N4-ethylated compound **13**, of which an HMBC spectrum was obtained proving the cyclic structure. Compound **13** could also be prepared by ring synthesis from the amide **14** (Scheme 1), which in turn was prepared from the ester **15** by aminolysis. The required ester was easily prepared by a selective Fischer esterification of *N*-carboxymethylanthranilic acid.[13,14]

The mixed anhydride approach was further pursued and a novel scheme for preparation of 1,4-benzodiazepine-3,5-diones was devised in which the system is activated for ring closure by a nitroso group attached to N1 (Scheme 1). Introduction of nitroso groups was found to be possible even on strongly deactivated secondary

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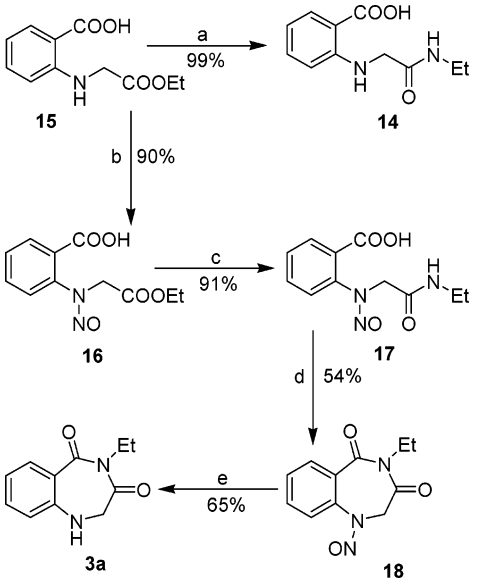
SCHEME 1. Synthesis of the Benzodiazepinedione 3a by Nitrosation, Ring Closure, and Denitrosation[a]



[a] Reagents and conditions: (a) $EtNH_2$, rt, (b) isoamyl nitrite, cat. TFA in PhMe at rt, (c) $EtNH_2$, rt, (d) Et_3N in MeCN followed by ClCOOEt, heating, (e) TFA/urea, heating in EtOAc.

amines. Deprotection of the nitrosamine to the free amine (denitrosation) could be preformed with acidic conditions,[15] or reductively removed with $SnCl_2$. The *N*-nitroso group can thus function as a protective group with an *Umpolung* effect due to its strongly electron withdrawing character. *N*-Nitroso chemistry has been utilized throughout the history of organic chemistry, but the discovery of the biochemical importance of NO[16] combined with the well-known carcinogenic effects of *N*-nitroso compounds[17] has led to a renewed interest in the field. A recent example is a study on nitrosation of amidines.[18]

The ester **16** was prepared from **15** by nitrosation with isoamyl nitrite, a very fast reaction catalyzed by a very small quantity of TFA. Aminolysis with aqueous ethylamine at room temperature then converted **16** into the ethylamide **17**. The nitrosation followed by aminolysis gave an 82% overall yield with a very simple work up procedure. Ring closure to the benzodiazepinedione **18** was performed with ethyl chloroformate and Et_3N in MeCN. In standard peptide coupling by the mixed anhydride method only 1 equiv of base is normally used.[19] In this case the reaction stopped at the anhydride stage if additional base was not added. The structure of **18** was determined by X-ray crystallography (Figure 2). Although there is a published work on conformational analysis of *N*-nitrosohexahydro-1,4-diazepine-5-ones,[20] *N*-nitroso de-

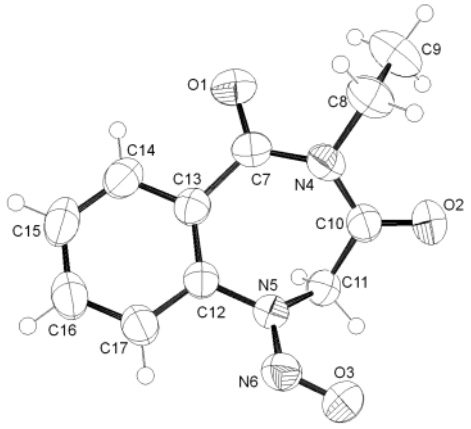
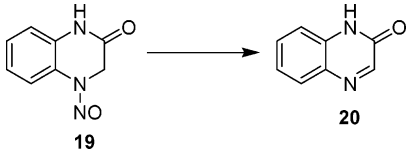


FIGURE 2. ORTEP drawing of the X-ray structure of **18**.

SCHEME 2



rivatives have not previously been used in the ring synthesis of seven-membered rings.

Denitrosation of **18** to **3a** was achieved by heating in EtOAc with TFA, using urea as a scavenger. Alternatively it could also be performed by heating with tin chloride dihydrate. The physical characteristics of **3a** do not match the previously reported data,[5] and it therefore seems clear that this is in fact a novel compound.

Perkin and Riley found that the nitrosamine **19** gives 1*H*-quinoxaline-2-one (**20**) when heated in alcohols, benzene, or acetic acid (Scheme 2).[21] No mechanistic explanation was given, but the transformation could be brought about by denitrosation followed by oxidation (dehydrogenation), or more likely a direct elimination of HNO (variously known as nitrosyl, nitroxyl, nitrosylhydride, etc.).[22] There are a few known nitrosyl donating compounds, one of which is Angeli's salt ($Na_2N_2O_3$).[23] Recent results have suggested that HNO has biological effects, and this has prompted investigations into the mechanism of decay of Angeli's salt into HNO and NO.[24] The structural similarities between **18** and **19** are obvious, and therefore **18** was heated in acetic acid in the hope of achieving elimination. However, in this case the reaction did not yield the expected seven-membered ring **4a** (Scheme 3), but rather a compound lacking one carbonyl signal in the ^{13}C NMR spectrum. It was determined that a ring contraction with loss of CO had occurred and that the product was in fact the known quinazolinone **21**.[25] Scheme 3 shows a plausible mechanism for this rearrangement.

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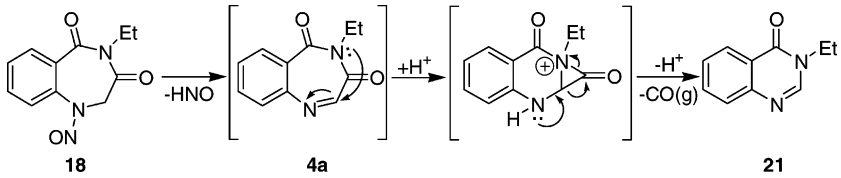
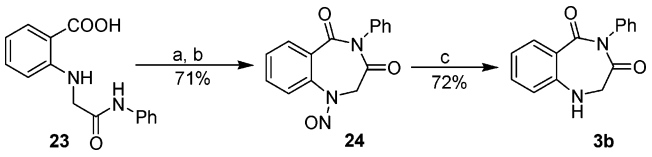
SCHEME 3. Proposed Mechanism for Ring Contraction Rearrangement



SCHEME 4. Synthesis of the Benzodiazepindione 3b[a]



[a] Reagents and conditions: (a) isoamyl nitrite at rt, (b) Et_3N/ClCOOEt at rt, (c) heating with $SnCl_2$ in EtOAc.

As would be expected, ester aminolysis according to Scheme 1 did not work well when a less basic/nucleophilic amine, such as aniline, was utilized. Hence there was a need for a procedure where an acetamide derivative could be introduced on a derivative of an anthranilic acid. To this end methyl anthranilate was reacted with chloroacetanilide (2-chloro-*N*-phenylacetamide). The latter was prepared in situ in MeCN/$NaHCO_3$ which was also the medium for the following substitution reaction. Although requiring a long reaction time this procedure has the definite advantage that the highly lachrymatory and skin irritating chloroacetanilide does not need to be handled at all outside the reaction vessel. The resulting ester (**22**) was hydrolyzed to the starting material **23** in quantitative yield. The direct approach of reacting anthranilic acid with chloroacetanilide under the same conditions also gave this product, but of inferior purity and after a cumbersome workup. A one-pot nitrosation/ring closure of **23** afforded the benzodiazepinedione **24** in good yield (71%). Also in this case it was necessary to add 2 equiv or more of base to achieve cyclization of the mixed anhydride, but the reaction proceeded at room temperature. The spectral properties of the product bear very close similarities with those of the ethyl-substituted compound **18** (e.g., IR 1705/1702, 1659/1641, 1463/1466 cm^{-1}). In this case prolonged heating in acetic acid did not yield a ring-contracted product, but a complex mixture of degraded material. Reductive denitrosation with $SnCl_2$ afforded **3b**, the spectral properties of which are very similar to those of its ethyl-substituted homologue **3a**. The characteristics of **3b** do not match the previously reported data.[6] As mentioned above the previously prepared material is likely to be polymeric.

Conclusions

Through this work we have shown that synthesis of 1*H*-1,4-benzodiazepine-3,5(2*H*,4*H*)-diones from *N*-carbamoylmethylanthranilic acids is feasible if the electron distribution of the starting materials is reversed by electron withdrawing substituents on the secondary amino groups. This could be achieved by N-acylation, or by N-nitrosation. The latter method of *Umpolung* gave the 1-nitroso-1*H*-1,4-benzodiazepine-3,5(2*H*,4*H*)-diones **18** and **24**. Denitrosation under acidic conditions, exemplified on **18**, or under reductive conditions, exemplified on **24**, gave access to the 1*H*-1,4-benzodiazepine-3,5-(2*H*,4*H*)-diones **3a** and **3b**, respectively. Preparations of these compounds have previously appeared in the literature, but the current data indicate these results to be in error. Furthermore, it was discovered that compound **18** rearranged to a six-membered system on heating in acetic acid. The proposed mechanism for this novel rearrangement involves the 1,4-benzodiazepine-3,5(2*H*,4*H*)-dione intermediate **4a**. If correct, this suggests that such seven-membered structures are not stable.

Experimental Section

^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz. respectively, in DMSO-d_6 or $CDCl_3$ with the solvent signals as reference.[26] Coupling constants (*J*) are given in Hz. All column flash chromatography was performed with HPFC (High Performance Flash Chromatography) on 60 Å prepacked silica columns.

1-Acetyl-1*H*-1,4-benzodiazepine-3,5(2*H*,4*H*)-dione (2a). 2-(Carbamoylmethylamino)benzoic acid[27] (0.99 g, 5.0 mmol) was refluxed in THF (20 mL) with diisopropylethylamine (2.8 mL, 16 mmol) and acetic anhydride (1.5 mL, 16 mmol) for 5 h. The reaction mixture was filtered while hot, and the filtrate was thoroughly evaporated in vacuo (25 mmHg, 70 °C) until a semisolid material remained. This material was crystallized from MeCN to yield a yellow tinted white crystalline material (0.20 g, 18%); mp 201−202 °C (from MeCN); IR ν_{max} 3213, 1729, 1655, 1601 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.93 (3H, s), 4.10 (1H, d, J = 16.9), 4.91 (1H, d, J = 16.9), 7.54−7.59 (2H, m), 7.73 (1H, m), 8.00 (1H, dd, J = 1.1, 7.2), 11.15 (1H, s); ^{13}C NMR (DMSO-d_6) δ 21.8 (CH_3), 51.8 (CH_2), 127.4 (CH), 128.5 (CH), 129.1 (C), 132.6 (CH), 134.2 (CH), 140.8 (C), 164.8 (C), 169.2 (C), 172.3 (C). Anal. Calcd for $C_{11}H_{10}N_2O_3$ (218.21): C, 60.55; H, 4.62; N, 12.84. Found: C, 60.43; H, 4.45; N, 12.91.

1-Ethyloxycarbonyl-1*H*-1,4-benzodiazepine-3,5(2*H*,4*H*)-dione (2b). 2-(Carbamoylmethylamino)benzoic acid[27] (2.0 g, 10.2 mmol) was refluxed in MeCN (20 mL) with Et_3N (5.0 mL, 36 mmol) for 15 min. Ethyl chloroformate (2.0 mL, 21 mmol) was added dropwise and the reflux then continued for 75 min. The reaction mixture was poured on 5% citric acid (aq, 50 mL) and diluted with crushed ice (to a total volume of 100 mL). After 1 h the solid product was filtered off, washed with water, and dried to yield an off-white solid (1.63 g, 66%); mp 180 °C (from PhMe); IR ν_{max} several peaks at 3187−2893, 1725, 1655 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.14 (3H, br s), 4.12 (2H, apparent br d), 4.45 (2H, very br s), 7.44−7.51 (2H, m), 7.67 (1H, m), 7.98 (1H, d, J = 7.2), 11.18 (1H, s); ^{13}C NMR (DMSO-d_6) δ 14.2 (CH_3), 53.2 (CH_2), 62.3 (CH_2), 127.5 (CH), 127.6 (C), 132.1 (CH), 133.5 (CH), 140.0 (C), 153.6 (C), 164.8 (C), 172.1 (C). Anal. Calcd for $C_{12}H_{12}N_2O_4$ (248.23): C, 58.06; H, 4.87; N, 11.29. Found: C, 58.54; H, 4.80; N, 11.12.

1-Methyloxycarbonyl-1*H*-1,4-benzodiazepine-3,5-(2*H*,4*H*)-dione (2c). The same procedure as for **2b**, but with

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MeOCOCl (2.0 mL, 26 mmol) and 2 h reaction time yielded a beige crystalline material (0.69 g, 30%); mp 108−110 °C; IR ν_{max} 3519, 3473, 3045, 2897, 1707, 1662 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.66 (3H, br s), 4.45 (2H, very br s), 7.45−7.52 (2H, m), 7.67 (1H, m), 7.98 (1H, dd, J = 1.1, 7.5), 11.18 (1H, s); ^{13}C NMR (DMSO-d_6) δ 53.3 (CH_2), 53.5 (CH_3), 127.59 (CH), 127.65 (CH), 128.4 (C), 132.2 (CH), 133.6 (CH), 139.8 (C), 154.1 (C), 164.8 (C), 172.1 (C). Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.42; H, 4.61; N, 11.54.

1-Benzyloxycarbonyl-1*H*-1,4-benzodiazepine-3,5-(2*H*,4*H*)-dione (2d). 2-(Carbamoylmethylamino)benzoic acid[27] (2.0 g, 10.2 mmol) was refluxed in MeCN (40 mL) with Et_3N (3.0 mL, 22 mmol) for 15 min. Benzyl chloroformate (3.0 mL, 21 mmol) was added dropwise and the reflux then continued for 16 h. The reaction mixture was poured on 10% citric acid (aq, 100 mL) and extracted with Et_2O (2 × 100 mL). The combined extracts were washed with sat. $NaHCO_3$ (50 mL), water (50 mL), and brine (50 mL). The solution was dried (Na_2SO_4), filtered through a plug of silica, and evaporated to form a solid material that could be triturated with diisopropyl ether (0.96 g, 31%); mp 122−122.5 °C; IR ν_{max} 3368, 3193, 1663, 1576, 1251, 1221 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.50 (2H, very br s), 2.10 (2H, br s), 7.20−7.38 (5H, m), 7.46−7.51 (2H, m), 7.67 (1H, m), 7.98 (1H, d, J = 7.9), 11.20 (1H, s); ^{13}C NMR (DMSO-d_6) δ 53.4 (CH_2), 67.5 (CH_2), 127.4 (CH), 127.6 (CH), 127.8 (CH), 128.0 (CH), 128.4 (C), 128.5 (CH), 132.2 (CH), 133.6 (CH), 136.0 (C), 153.5 (C), 164.8 (C), 172.1 (C). Anal. Calcd for $C_{17}H_{14}N_2O_4$ (310.30): C, 65.80; H, 4.55; N, 9.03. Found: C, 65.69; H, 4.57; N, 8.83.

4-Ethyl-1*H*-1,4-benzodiazepine-3,5(2*H*,4*H*)-dione (3a). Compound **18** (0.35 g, 1.5 mmol) was dissolved in EtOAc (50 mL) and heated at reflux with urea (0.36 g, 6.0 mmol) and TFA (1.5 mL) for 16 h. The solution was then washed with 2 M NaOH (50 mL), followed by water (50 mL). The two combined aqueous layers were extracted with EtOAc (2 × 25 mL). The three combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (0−50% EtOAc in hexane) to yield a white crystalline solid (0.20 g, 65%); mp 95.5−96 °C (from heptane); IR ν_{max} 3352, 1703, 1594, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t, J = 7.2), 3.91 (2H, s), 3.94 (2H, q, J = 7.2), 4.63 (1H, br s), 6.80 (1H, dd, J = 1.1, 7.9), 6.96 (1H, m), 7.34 (1H, m), 8.26 (1H, dd, J = 1.9, 8.3); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3), 40.7 (CH_2), 52.4 (CH_2), 117.6 (CH), 117.8 (C), 120.2 (CH), 134.0, (CH), 134.7 (CH), 149.3 (C), 168.0 (C), 169.4 (C). Anal. Calcd for $C_{11}H_{12}N_2O_2$ (204.23): C, 64.69; H, 5.92; N, 13.72. Found: C, 64.30; H, 5.76; N, 13.61. MS (ESI) m/z 205 $[M + H]^+$, 177 $[M + H - C_2H_5]^+$.

4-Phenyl-1*H*-1,4-benzodiazepine-3,5(2*H*,4*H*)-dione (3b). Compound **24** (1.41 g, 5.00 mmol) was dissolved in EtOAc (20 mL). $SnCl_2{\cdot}2H_2O$ (2.26 g, 10.0 mmol) was added and the mixture heated to reflux for 1 h. The mixture was filtered by suction through a plug of aluminum oxide (basic, activity 1). The plug was thoroughly rinsed with EtOAc. The filtrate was evaporated in vacuo to give the solid product (0.91 g, 72%); mp 159 °C (from diisopropyl ether); IR ν_{max} 3325, 1700, 1639, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.03 (2H, s), 4.95 (1H, very br s), 6.79 (1H, dd, J = 0.8, 8.3), 6.95 (1H, m), 7.17−7.20 (2H, m), 7.34−7.48 (4H, m), 8.20 (1H, dd, J = 1.5, 8.3); ^{13}C NMR ($CDCl_3$) δ 52.0 (CH_2), 117.1 (C), 117.8 (CH), 120.0 (CH), 128.4 (CH), 128.6 (CH), 129.4 (CH), 134.4 (CH, 134.8 (CH), 138.8 (C), 149.7 (C), 168.2 (C), 169.6 (C). Anal. Calcd for $C_{15}H_{12}N_2O_2$ (252.09): C, 71.42; H, 4.79; N, 11.10. Found: C, 71.20; H, 4.82; N, 11.15.

2-(Carbamoylmethylamino)benzoyl Pivaloyl Anhydride (11). 2-(Carbamoylmethylamino)benzoic acid[27] (0.99 g, 5.0 mmol) in DMF (10 mL) was treated with NaH (0.20 g 60% in mineral oil, 5.0 mmol), the solution was cooled to 0 °C, and pivaloyl chloride (0.61 mL, 5.0 mmol) was added. The mixture was stirred for 15 min at 0−25 °C, and then poured on water (50 mL). The solid formed was collected and washed with water followed by Et_2O. After drying, this gave a light yellow fine powder (0.82 g, 60%); mp 151 °C; IR ν_{max} 3395, 3184, 1791, 1700, 1653, 1576 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.28 (9H, s), 3.87 (2H, d, J = 4.9), 6.61−6.70 (2H, m), 7.25 (1H, br s), 7.51 (1H, m), 7.57 (1H, br s), 7.71 (1H, dd, J = 1.5, 8.3), 8.09 (1H, t, J = 4.9); ^{13}C NMR (DMSO-d_6) δ 26.2 (C), 45.0 (CH_2), 107.9 (C), 112.2 (CH), 115.1 (CH), 132.0 (CH), 136.8 (CH), 151.2 (C), 164.1 (C), 170.3 (C), 174.1 (C). Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.43; H, 6.42; N, 10.16.

2-(Carbamoylmethylamino)benzoic Acid Anhydride (12). 2-(Carbamoylmethylamino)benzoic acid[27] (2.0 g, 10.2 mmol) and 2-chloro-1-methylpyridinium iodide (3.04 g, 12.0 mmol) were heated at refluxed in dry THF (40 mL) with Et_3N (2.0 mL) for 1 h. After the mixture was cooled to room temperature, water (20 mL) was added and the solid product was filtered off. After washing with MeCN (2 × 10 mL) a pale yellow fine powder was obtained (1.70 g, 92%); mp 169−170 °C; IR ν_{max} 3382, 3180, 1756, 1742, 1674, 1649, 1611, 1574 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.88 (4H, d, J = 4.9), 6.64−6.71 (4H, m), 7.25 (2H, br s), 7.53 (2H, m), 7.55 (2H, br s), 7.87 (2H, dd, J = 1.5, 8.1), 8.09 (2H, t, J = 4.9); ^{13}C NMR (DMSO-d_6) δ 45.1 (CH_2), 108.0 (C), 112.2 (CH), 115.2 (CH), 132.1 (CH), 136.6 (CH), 151.1 (C), 164.2 (C), 170.4 (C). Anal. Calcd for $C_{18}H_{18}N_4O_5$ (370.36): C, 58.37; H, 4.90; N, 15.13. Found: C, 58.01; H, 4.95; N, 15.30. MS (ESI) m/z 369 $[M - H]^-$.

4-Ethyl-1-ethyloxycarbonyl-1*H*-1,4-benzodiazepine-3,5(2*H*,4*H*)-dione (13). Method 1: Compound **2b** (2.0 g, 8.0 mmol) was dissolved in DMF (10 mL) and NaH (0.35 g, 60% in mineral oil, 8.8 mmol) was added. The reaction flask was cooled by immersion in an ice bath and EtBr (1.5 mL, 20 mmol) was added. The mixture was stirred at 0−25 °C for 4 h and then poured on water (50 mL). The material gained by extraction with Et_2O was purified by silica column flash chromatography, eluting with diisopropyl ether, to give a white solid (1.56 g, 71%). **Method 2:** Et_3N (0.70 mL, 5.0 mmol) was added to compound **14** (1.11 g, 5.00 mmol) in MeCN (10 mL) and the mixture was heated at reflux for 5 min. Ethyl chloroformate (1.5 mL, 16 mmol) was added, followed by another portion of Et_3N (1.5 mL, 11 mmol). Gas evolved (CO_2). The mixture was heated at reflux for 75 min, followed by the same workup as in the first method to give the product in 74% yield; mp 74 °C; IR ν_{max} several peaks at 3187−2893, 1722, 1657, 1600, 1218, 765 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.05−1.21 (6H, m), 3.86 (2H, q, J = 6.8), 4.13 (2H, q, J = 7.2), 4.58 (2H, br s), 7.44−7.49 (2H, m), 7.66 (1H, m), 8.01 (1H, d, J = 8.3); ^{13}C NMR (DMSO-d_6) δ 13.0 (CH_3), 14.2 (CH_3), 54.7 (CH_2), 62.3 (CH_2), 126.6 (CH), 127.2 (CH), 129.0 (C), 132.9 (CH), 133.3 (CH), 139.9 (C), 153.3 (C), 165.2 (C), 172.2 (C). Anal. Calcd for $C_{14}H_{16}N_2O_4$ (276.29): C, 60.86; H, 5.84; N, 10.14. Found: C, 61.05; H, 5.83; N, 10.38.

2-(Ethoxycarbonylmethylamino)benzoic Acid (14). *N*-Ethoxycarbonylmethylanthranilic acid[13,14] (4.48 g, 20.0 mmol) was dissolved in $EtNH_2$ (20 mL 70% aq), and the solution was kept at 25 °C for 24 h. The mixture was poured on crushed ice and acidified with concd HCl (25 mL) leading to precipitation of the product. The solid formed was filtered off and dried (4.42 g, 99%); mp 203 °C; IR ν_{max} 3396, 3283, 1647, 1580, 1516, 1244, 739 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.02 (3H, t, J = 7.2), 3.12 (2H, m), 3.78 (2H, s), 6.50 (1H, d, J = 8.2), 6.59 (1H, t, J = 8.2), 7.36 (1H, m), 7.80 (1H, dd, J = 1.5, 7.9), 8.02 (1H, t, J = 5.3), 12.60 (1H, br s); ^{13}C NMR (DMSO-d_6) δ 14.7 (CH_3), 33.4 (CH_2), 45.8 (CH_2), 110.7 (C), 111.3 (CH), 114.6 (CH), 131.7 (CH), 134.4 (CH), 150.2 (C), 168.6 (C), 169.6 (C). Anal. Calcd for $C_{11}H_{14}N_2O_3$ (222.24): C, 59.45; H, 6.35; N, 12.61. Found: C, 59.07; H, 6.32; N, 12.29.

2-(Ethoxycarbonylmethylnitrosoamino)benzoic Acid (16). *N*-Ethoxycarbonylmethylanthranilic acid[13,14] (4.48 g, 20.0 mmol) was suspended in toluene (40 mL). Isoamyl nitrite (3.0 mL, 22 mmol) was added followed by a small drop of TFA. The mixture was stirred for 1 h and the solution was passed through a plug of silica to which the product bound. The toluene was rinsed out of the silica with hexane after which the product could be eluted with Et_2O. The Et_2O−filtrate was

thoroughly evaporated in vacuo to form an oil (used without further purification in the following transformation). Addition of toluene and evaporation again gave a yellowish white crystalline solid (4.55 g, 90%); mp 101−102 °C (from toluene/hexane); IR ν_{max} 1750, 1698, 1599, 1422 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, t, J = 7.2), 4.26 (2H, q, J = 7.2), 4.59 (2H, s), 7.62 (1H, m), 7.69 (1H, dd, J = 1.5, 7.9), 7.76 (1H, m), 8.20 (1H, dd, J = 1.5, 7.9); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 50.3 (CH_2), 62.0 (CH_2), 125.8 (C), 128.9 (CH), 129.9 (CH), 132.6 (CH), 134.6 (CH), 141.5 (C), 166.3 (C), 170.0 (C). Anal. Calcd for $C_{11}H_{12}N_2O_5$ (252.22): C, 52.38; H, 4.80; N, 11.11. Found: C, 52.38; H, 4.72; N, 10.96. MS (ESI) m/z: 251 [M − H]$^-$, 221 [M − H − NO]$^-$.

2-(Ethylcarbamoylmethylnitrosoamino)benzoic Acid (17). The oil of compound **16** was dissolved in $EtNH_2$ (20 mL 70% aq), and the solution was kept at 25 °C for 24 h. The mixture was poured on crushed ice and acidified with concd HCl (20 mL). On standing, and oil formed which solidified after several hours. The beige solid was collected and dried (4.12 g, 82% from *N*-ethoxycarbonylmethylanthranilic acid); mp 120−122 °C; IR ν_{max} 1677, 1623, 1600, 1570, 1461, 1441 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.99 (3H, t, J = 7.2), 3.06 (2H, m), 4.52 (2H, s), 7.59−7.81 (3H, m), 7.95 (1H, dd, J = 1.2, 7.7), 8.18 (1H, t, J = 5.1), 13.3 (1H, br s); ^{13}C NMR (DMSO-d_6) δ 14.5 (CH_3), 33.6 (CH_2), 51.2 (CH_2), 126.9 (CH), 128.0 (C), 129.1 (CH), 130.7 (CH), 132.8 (CH), 140.5 (C), 164.6 (C), 167.0 (C). Anal. Calcd for $C_{11}H_{13}N_3O_4$ (251.24): C, 52.59; H, 5.22; N, 16.73. Found: C, 52.57; H, 5.17; N, 16.56. MS (ESI) m/z 250 [M − H]$^-$, 220 [M − H − NO]$^-$.

4-Ethyl-1-nitroso-1*H*-1,4-benzodiazepine-3,5(2*H*,4*H*)-dione (18). Compound **17** (2.52 g, 10.00 mmol) was dissolved in MeCN (20 mL). Et_3N (1.5 mL, 11 mmol) was added and the mixture was stirred 15 min. Ethyl chloroformate (1.5 mL, 16 mmol) was added and the stirring continued at room temperature for 15 min. The mixture was then heated at reflux for 2 h. The mixture was cooled to room temperature and poured into citric acid (10%, 100 mL). After addition of crushed ice an oil separated out. Eventually the oil solidified and could be collected and dried. The brown solid was heated in diisopropyl ether, upon which the product dissolved, leaving the dark material unsolved. Evaporation of the liquid phase gave an oil that slowly crystallized to yield a light yellow solid (1.32 g, 54%); mp 118−119 °C ($CHCl_3$/hexane 1:1); IR ν_{max} 1702, 1641, 1598, 1466, 1447; ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t, J = 7.1), 3.96 (2H, q, J = 7.1), 7.57−7.62 (1H, m), 7.72−7.74 (2H, m), 8.43 (1H, d, J = 7.9); ^{13}C NMR ($CDCl_3$) δ 13.4 (CH_3), 41.1 (CH_2), 48.7 (CH_2), 121.8 (CH), 125.0 (C), 128.9 (CH), 134.6 (CH), 134.7 (CH), 139.8 (C), 164.6 (C), 166.0 (C). Anal. Calcd for $C_{11}H_{11}N_3O_3$ (233.22): C, 56.65; H, 4.75; N, 18.02; O, 20.58. Found: C, 56.48; H, 4.72; N, 17.95. MS (ESI) m/z 251 [M + NH_4]$^+$, 234 [M + H]$^+$, 204 [M + H − NO]$^+$, 176 [M + H − NO − C_2H_5]$^+$. The structure was confirmed by single-crystal X-ray crystallography.

3-Ethyl-3*H*-quinazoline-4-one (21). Compound **18** (0.70 g, 3.0 mmol) was heated at reflux in AcOH (20 mL) for 15 h. The solvent was evaporated in vacuo and the residual material was purified on a silica flash column, eluting first with 10−35% EtOAc in hexane then with 60−80% EtOAc in hexane. The product (0.33 g, 63%) was isolated from the latter elution portion; mp 99−100 °C (from diisopropyl ether) (lit.[25] mp 99−101 °C); IR ν_{max} 1668, 1608, 1471, 1371, 1248 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.28 (3H, t, J = 7.2), 4.01 (2H, q, J = 7.2), 7.54 (1H, m), 7.67 (1H, d, J = 7.9), 7.81 (1H, m), 8.15 (1H, dd, J = 1.2, 7.9), 8.41 (1H, s); ^{13}C NMR (DMSO-d_6) δ 14.5 (CH_3), 41.2 (CH_2), 121.6 (C), 126.0 (CH), 126.9 (CH), 127.1 (CH), 134.2 (CH), 147.8 (CH), 148.0 (C), 160.0 (C).

2-[[2-Oxo-2-(phenylamino)ethyl]amino]benzoic Acid Methyl Ester (22). Aniline (20 mL, 0.22 mol) was dissolved in MeCN (100 mL) containing $NaHCO_3$ (50 g, 0.60 mol). Chloroacetyl chloride (16 mL, 0.22 mol) was added in portions during 15 min, after which methyl anthranilate (20 mL, 0.15 mol) was added. The mixture was then heated to reflux for 70 h. The flask was cooled to room temperature and the contents was poured into ice−water (400 mL). The solid that eventually formed was collected and recrystallized from MeOH to yield a white powder (15.06 g, 24%); mp 137−139 °C (lit.[13] mp 140−142 °C); IR ν_{max} 3385, 3278, 1672, 1597 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.83 (3H, s), 4.08 (2H, d, J = 5.3), 6.61−6.66 (2H, m), 7.06 (1H, m), 7.30−7.35 (2H, m), 7.42 (1H, m), 7.60−7.63 (2H, m), 7.83 (1H, dd, J = 1.5, 8.3), 8.15 (1H, t, J = 5.3), 10.17 (1H, s); ^{13}C NMR (DMSO-d_6) δ 46.2 (CH_2), 51.5 (CH_3), 109.8 (C), 111.7 (CH), 114.9 (CH), 119.2 (CH), 123.3 (CH), 128.8 (CH), 131.1 (CH), 134.8 (CH), 138.8 (C), 149.8 (C), 167.8 (C), 167.9 (C).

2-[[2-Oxo-2-(phenylamino)ethyl]amino]benzoic Acid (23). Compound **22** (8.53 g, 30.0 mmol) in water (50 mL) and MeOH (50 mL) was heated to a boil with NaOH (1.3 g, 33 mmol). After letting the mixture cool to room temperature, it was filtered and acidified with concd HCl. The white product formed was collected and dried (8.07 g, 100%); mp 226 °C (lit.[13] 235 dec); IR ν_{max} 3381, 3265, 1662, 1599 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.09 (2H, s), 6.58−6.62 (2H, m), 7.05 (1H, m), 7.28−7.40 (3H, m), 7.62−7.65 (2H, m), 7.82 (1H, dd, J = 1.5, 7.9), 10.35 (1H, s), 12.63 (1H, br s); ^{13}C NMR (DMSO-d_6 $CDCl_3$) δ 46.3 (CH_2), 110.7 (C), 111.4 (CH), 114.7 (CH), 119.2 (CH), 123.3 (CH), 128.8 (CH), 131.7 (CH), 134.5 (CH), 138.9 (CH), 150.1 (CH), 168.0 (C), 169.7 (C).

1-Nitroso-4-phenyl-1*H*-1,4-benzodiazepine-3,5(2*H*,4*H*)-dione (24). Compound **23** (2.70 g, 10.00 mmol) was stirred in toluene (40 mL) and MeCN (20 mL) with isoamyl nitrite (1.5 mL, 11 mmol) for 1 h (on which the starting material had fully dissolved). Et_3N (1.5 mL, 11 mmol) was added and after 5 min ethyl chloroformate (1.5 mL, 16 mmol) was added and the stirring continued at room temperature for 15 min. Another portion of Et_3N was added and the mixture was stirred for 1 h at room temperature. The mixture was poured into citric acid (10%, 50 mL) in a separatory funnel. After shaking, the aqueous phase was discarded and the organic phase washed with sat. $NaHCO_3$. The product precipitated from the solution on standing (1.99 g, 71%); mp 189−190 °C (from 95% EtOH); IR ν_{max} 1704, 1659, 1599, 1463, 1248, 1133, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.02 (2H, s), 7.07−7.10 (2H, m), 7.38−7.49 (3H, m), 7.62 (1H, m), 7.79−7.82 (2H, m), 8.40 (1H, dd, J = 0.8, 8.4); ^{13}C NMR ($CDCl_3$) δ 48.7 (CH_2), 122.2 (CH), 124.7 (C), 128.4 (CH), 128.8 (CH), 129.2 (CH), 129.5 (CH), 134.9 (CH), 135.0 (CH), 137.9 (C), 140.0 (C), 165.0 (C), 166.1 (C). Anal. Calcd for $C_{15}H_{11}N_3O_3$ (281.27): C, 64.05; H, 3.94; N, 14.94. Found: C, 63.87; H, 3.90; N, 15.0.

Supporting Information Available: X-ray crystallographic data for compound **18** in CIF format and ^{1}H and ^{13}C NMR data for compounds **3a**, **3b**, **21**, **22**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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