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Synthesis Of Benzazepine-based Nitrones As Radical Traps

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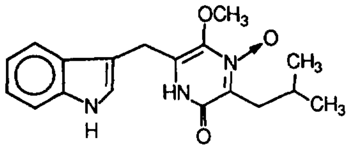
Abstract: Benzazepine-based nitrones have been synthesized utilizing a modified Bischler-Napieralski reaction as the key step. These compounds are cyclic analogs of the radical trap phenyl t-butyl nitrone.

Free radicals are postulated to play a major role in the development of age-related diseases.[1] The proposed deleterious effects of free radicals might be minimized if they could be trapped before significant tissue or cell damage had occurred.[2] To this end, several classes of compounds have been examined as radical trapping agents including nitrogen oxides such as **1**,[3] vitamin E (**2**),[4] and nitrones such as phenyl t-butyl nitrone **3**.[5] Recently, we reported that cyclic nitrone **4** is effective in both trapping radicals *in vitro* and in reducing radical-related damage in rodents *in vivo*.[6] The radical scavenging activity of dihydroisoquinoline **4** led us to prepare nitrones **5a-c** as potential radical traps.



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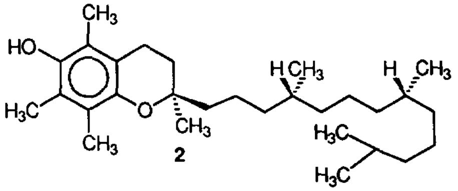

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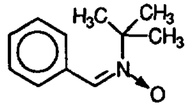

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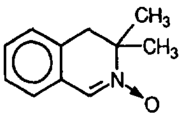

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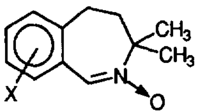
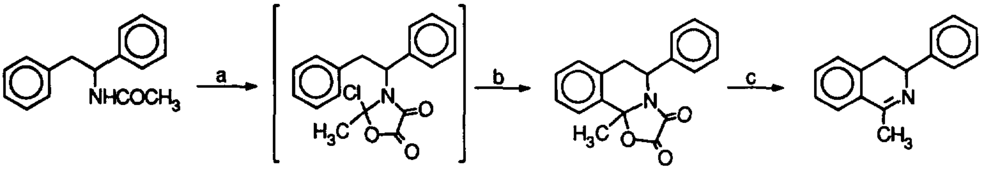


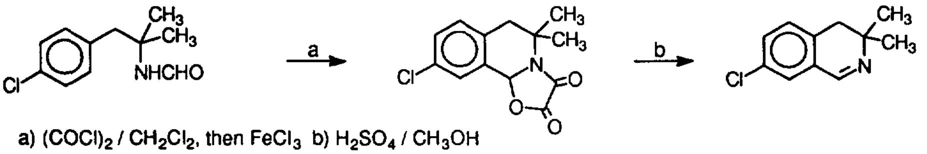
5a X = H
5b X = 8-Cl
5c X = 7,9-Cl2



(1)

a) $ClCOCOCl / CH_2Cl_2$ b) $FeCl_3$ c) H_2SO_4 / CH_3OH

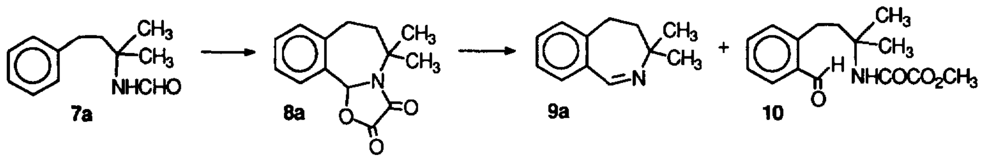
Our initial approach to the synthesis of nitrones **5a-c** followed the work of Larsen and coworkers at Merck[7] which utilized a modified Bischler-Napieralski reaction to form a series of 3-aryl-3,4-dihydroisoquinolines from amides (Equation 1). Proceeding through an oxazolidine-4,5-dione, this sequence avoided the facile elimination of the benzylic amide. Faced with a similar problem in preparing cyclic nitrones related to **4** from a tertiary formamide, we had used this modification to prevent elimination during cyclization to 3,3-dialkyl-3,4-dihydroisoquinolines (Equation 2). Based on these results, we decided to synthesize homologous nitrones **5a-c** employing a parallel procedure.



(2)

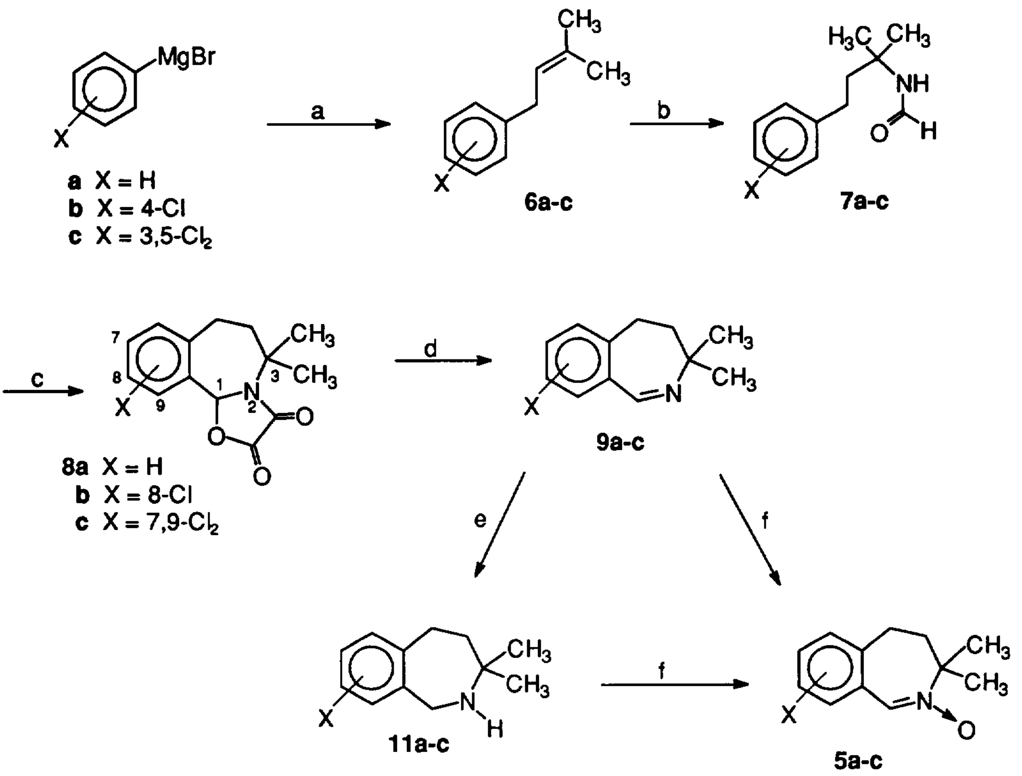
a) $(COCl)_2 / CH_2Cl_2$, then $FeCl_3$ b) H_2SO_4 / CH_3OH

The key starting materials were formamides **7a-c**. (Scheme 1) Utilizing either uncatalyzed or copper-catalyzed alkylations, the appropriate aryl Grignard reagents were converted into alkenes **6a-c**[8] which were subjected to Ritter reactions affording cyclization precursors **7a-c** in good yield.[9] Attempts to form the benzazepine ring by the two-step Merck procedure involving cyclization of **7a** to **8a** followed by conversion of the crude product to imine **9a** in methanolic sulfuric acid gave poor yields of **9a** (~10%). Stepwise examination of the sequence suggested the cyclization of **7a** to **8a** had proceeded cleanly, indicating the problem lay in the conversion of **8a** to **9a**. Purification of crude cyclization product gave **8a** as a crystalline solid; however, attempts to convert this material to the imine using sulfuric acid in methanol gave only modest yields of **9a** (40%) along with **10** (40%) (Equation 3). During characterization of **8a** we had observed vigorous gas evolution at the melting point of **8a**, yet the resulting liquid did not significantly darken nor did it resolidify on cooling.[10] Suspecting a thermal decarboxylation and/or decarbonylation of the oxazolidine-4,5-dione may have occurred, a larger sample of **8a** was warmed with a heat gun under vacuum until the sample had melted and gas evolution had ceased. ^1H and ^{13}C NMR spectra of the liquid product showed a clean conversion of **8a** into **9a**. Under more controlled conditions, a neat sample of **8a** was heated at 130-140°C for 0.5 hour providing **9a** in good yield. The imine rapidly absorbs carbon dioxide from the atmosphere to form a carbamic acid which can be converted back to **9a** by treatment with saturated sodium bicarbonate.



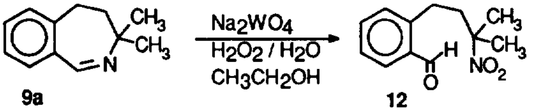
7a **8a** **9a** **10**

(3)



SCHEME 1: a) 1-chloro-3-methyl-2-butene /THF b) NaCN /AcOH/H_2SO_4 c) $(COCl)_2$/ CH_2Cl_2, then $FeCl_3$ d) heat e) $NaBH_4/CH_3OH$ f) $H_2O_2/H_2O/CH_3CH_2OH/Na_2WO_4 \cdot 2H_2O$

With a satisfactory synthesis of **9a** in hand, we turned to its oxidation. Previously, the direct oxidation of 3,3-dimethyl-3,4-dihydroisoquinoline to **4** using hydrogen peroxide and catalytic sodium tungstate in aqueous ethanol[11] had given good results but the reaction was slow (2-7 days) and required several equivalents of hydrogen peroxide to approach completion. Application of this procedure to the homologous benzazepine **9a** afforded only traces of nitrone **5a**; the majority of the product was nitroaldehyde **12** (Equation 4). This product may arise from opening of the hydrolytically less stable seven-membered ring to an amino aldehyde followed by oxidation of the amine.[12] Switching to *m*-chloroperbenzoic acid in dichloromethane[13] to minimize hydrolytic ring opening gave an unimpressive yield of **5a** (~25%). Ultimately, the problem was overcome by a two-step procedure. Crude imine **9a** from thermolysis was reduced with sodium borohydride in methanol giving **11a**[14] which was then oxidized by aqueous hydrogen peroxide and catalytic sodium tungstate to give an excellent yield of nitrone **5a**. This reaction was complete in under two hours and required only a slight molar excess of oxidant.



(4)

Previous work had shown that mono and dichloro substitution in the homologous isoquinoline series increased antioxidant activity 10- to 50-fold[15] so we turned to the synthesis of halogenated analogs of **5a**. Symmetrical substitution patterns were chosen so cyclization would yield a single regioisomer. Both 1-(4-chlorophenyl)-3-methyl-2-butene and its 3,5-dichloro analog were prepared from the appropriate Grignard reagent and converted to the formamide using the Ritter reaction. Cyclization to the dione intermediate and thermal conversion to the imine followed the route of the unsubstituted case. Subsequent reactions as above with each imine produced **5b** and **5c**.

In summary, several one carbon higher analogs (**5a-c**) of radical trapping agent **4** were synthesized. The key step was cyclization of a formamide to an oxazolidine-4,5-dione, extending to benzazepines a modified Bischler-Napieralski reaction developed by chemists at Merck for synthesizing 3,4-dihydroisoquinolines. A novel thermolytic conversion of this intermediate into a 4,5-dihydro-[3*H*]-2-benzazepine was discovered when acidic conversion proved troublesome. The radical scavenging activity of nitrones **5a-c** is reported elsewhere.[15]

Acknowledgements: We thank Dr. John French and Dr. Craig Thomas for biological testing and Dr. Thaddeus Nieduzak for helpful discussions.

EXPERIMENTAL

Caution! *The Ritter reaction involves the use of sodium cyanide in acidic medium. This reaction must be carried out in an efficient hood using all appropriate precautions. The use of gloves and other safety equipment is required when handling sodium cyanide.* Reaction solvents were Aldrich anhydrous grade except for CH_2Cl_2 which was obtained from EM Sciences and used as received. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were obtained on Varian XL300 and Gemini 300 spectrometers. In ^{1}H NMR data for the formamides, "M" refers to peaks assigned to the major isomer and "m" refers to peaks assigned to the minor isomer.

5,5-Dimethyl-4,6,7,11b-tetrahydro-[5H]-oxazolo[2,3-a]-2-benzazepine-2,3-dione (8a)

3-Formamido-3-methyl-1-phenylbutane (13.37 g, 70.0 mmol) was dissolved in CH_2Cl_2 (600 mL) under nitrogen at ~ 20°C. Oxalyl chloride (6.72 mL, 77.0 mmol) was added to the stirred solution over 5 min. Rapid gas evolution ensued. After 1 h, the reaction was cooled in an ice bath and anhydrous ferric chloride (13.6 g, 84.0 mmol) was added. The cold bath was removed 10 min later. After 16 h, 2.0 M aqueous hydrochloric acid (600 mL) was added to the rapidly stirred reaction. The layers were separated after 1.5 h and the organic portion was washed with brine (200 mL), dried with Na_2SO_4, and concentrated *in vacuo*. Chromatography with 50:50 ethyl acetate:hexane gave the title compound as an off-white solid (12.56 g, 73%, $R_f \sim 0.6$). Melting point: 119-121°C (gas evolved). IR ($CHCl_3$): 1817, 1734, 1395, 1321 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.53 (1H, dd, J = 1.2, 7.2 Hz), 7.35-7.19 (3H), 6.85 (1H, s), 3.25-3.15 (2H), 2.31 (1 H, ddd, J = 4.0, 11.9, 15.7 Hz), 1.91 (1H, ddd, J = 4.0, 5.4, 15.6 Hz), 1.87 (3 H, s), 1.59 (3H, s). ^{13}C NMR ($CDCl_3$): δ 158.92, 152.35, 136.89, 133.73, 130.28, 129.52, 126.73, 125.50, 83.83, 59.45, 37.97, 29.80, 26.66, 24.21. EIMS: 245 (42%), 145 (53%), 117 (100%). Anal. calc. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.61; H, 6.21; N, 5.68.

4,5-Dihydro-3,3-dimethyl-[3H]-2-benzazepine (9a)

A flask containing neat **8a** (1.26 g, 5.14 mmol) was immersed in a preheated bath at 140°C. The solid melted and evolved gas. After 0.5 h, **9a** as isolated as a clear, nearly colorless liquid (0.89 g, 100%). IR ($CHCl_3$): 2967, 2922, 1642, 758 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.21 (1H, s), 7.45 (1H, m), 7.27 (3H, m), 3.01 (2H, m), 1.95 (2H, m), 1.34 (6H, s). ^{13}C NMR ($CDCl_3$): δ 156.70, 142.60, 135.05, 132.57, 129.77, 129.34, 126.14, 60.06, 59.65, 38.32, 31.39, 30.50. CIMS (methane): 174 (100%). Anal. calc. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.08. Found: C, 82.91; H, 8.68; N, 8.02. (Compound **9a** decomposed on standing and so was used immediately after synthesis.)

Methanolysis of 8a to 9a and 10

A solution of **8a** (1.225 g, 5.00 mmol) in 1:19 conc. H_2SO_4:methanol (50 mL) was heated at reflux for 24 h. The reaction was cooled and then concentrated *in vacuo* to remove excess methanol. The resulting brown liquid was treated with water (100 mL) and ethyl acetate (100 mL) and the layers were separated. The organic layer was extracted with 1.0 M hydrochloric acid (2 x 50 mL). The combined aqueous extracts were made basic with conc. NH_4OH and extracted with CH_2Cl_2 (2 x 100 mL). The CH_2Cl_2 extracts were dried with Na_2SO_4 and concentrated *in vacuo* to give **9a** as a nearly colorless liquid (0.350 g, 40%). (Spectral data for **9a** is given above.) The ethyl acetate layer was dried with $MgSO_4$ and concentrated *in vacuo*. The resulting oil was chromatographed using 20:80 ethyl acetate:hexane to give **10** as a clear, colorless liquid (0.549 g, 40%). **10**: IR (neat): 1738, 1696, 1238, 1209 cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.12 (1H, s), 7.79 (2H, dd, J = 7.6, 1.5 Hz), 7.50 (1H, td, J = 1.6, 7.5 Hz), 7.41 (1H, td, J = 1.1, 7.5 Hz), 7.28 (1H, bd, J = 7.5 Hz), 3.90 (3H, s), 3.02 (2H, m), 1.89 (2H, m), 1.47 (6H, m). ^{13}C NMR ($CDCl_3$): δ 193.72, 161.75, 155.75, 144.12, 135.23, 133.88, 133.42, 131.35, 126.72, 54.39, 53.48, 42.78, 28.27, 25.84. CIMS (methane): 278 (67%), 175 (100%). HRMS calc. for $C_{15}H_{19}NO_4$: 278.1392. Found: 278.1394.

3,3-Dimethyl-1,2,4,5-tetrahydro-[3H]-2-benzazepine (11a)

A flask containing **8a** (2.45 g, 10.0 mmol) under nitrogen was immersed in a preheated bath at 140-145°C (bath temperature). The solid melted and gas was evolved. After 15 min, gas evolution had nearly ceased. The resulting liquid was cooled in an ice bath and dissolved in methanol (20 mL). To the stirred reaction was added $NaBH_4$ (0.76 g, 20 mmol) over 5 min. Gas and heat were evolved. After 5 min, the ice bath was removed. Two hours later, the reaction was treated with aqueous 1.0 M NaOH (20 mL) and stirred 20 min. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried with Na_2SO_4 and concentrated *in vacuo* to an orange-brown oil. The oil was chromatographed using ethyl acetate as the initial eluant followed by 5:95 $(CH_3CH_2)_2NH$:ethyl acetate to give amine **11a** (R_f ~ 0.1, ethyl acetate) as a slightly orange oil (1.09 g, 62%). IR (neat): 2967, 2957, 756 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.14-7.07 (4H, m), 3.89 (3H, s), 2.86 (2H, m), 1.66 (2H, m), 1.37 (1H, bs), 1.18 (6H, s). ^{13}C NMR ($CDCl_3$): δ 142.59, 142.23, 129.08, 127.96, 126.80, 125.91, 53.20, 47.88, 40.68, 30.82, 28.65 (broad). CIMS (methane): 176 (68%), 175 (100%). HRMS calc. for $C_{12}H_{17}N$: 176.1439. Found: 176.1439.

4,5-Dihydro-3,3-dimethyl-[3H]-2-benzazepine 2-oxide (5a)

Amine **11a** (1.09 g, 6.22 mmol) was dissolved in ethanol (8 mL) at ~ 20°C and treated with a solution of $Na_2WO_4 \cdot 2H_2O$ (0.102 g, 0.31 mmol) in water (4 mL), followed by 30% hydrogen peroxide (1.41 mL). After 6 h, the reaction was diluted with water (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting yellow oil was chromatographed, eluting first with ethyl acetate followed by 80:20 ethyl acetate:ethanol. The oil isolated (R_f ~ 0.2 in ethyl acetate) solidified to a white solid (1.15 g, 98%) after storing at 0°C overnight. Melting point: 62-65°C. IR (KBr): 2980, 2951, 1543, 1159, 1146, 1130, 662 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.91 (1H, s), 7.28-7.15 (4H, m), 3.05-3.01 (2H, m), 2.21-2.17 (2H, m), 1.63 (6H, s). ^{13}C NMR ($CDCl_3$): δ 140.54, 139.52, 131.59, 129.11, 128.83, 128.07, 126.67, 72.66, 37.97, 29.88, 28.17. CIMS (methane): 190 (100%). Anal. calc. for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.85; H, 8.21; N, 7.27.

1-(4-Chlorophenyl)-3-formamido-3-methylbutane (7b)

A mixture of NaCN (2.87 g, 58.6 mmol) in glacial acetic acid (30 mL) was cooled in an ice bath. The stirred suspension was treated with a 1:1 mixture of H_2SO_4:CH_3CO_2H (14 mL). After 10 min, 1-(4-chlorophenyl)-3-methyl-2-butene (5.29 g, 29.3 mmol) was added to the reaction mixture and the cold bath was removed. After stirring for 21 h, nitrogen was bubbled through the reaction for 2 h. Then the reaction mixture was poured slowly onto a stirred mixture of ice (200 g) and Na_2CO_3 (48 g). The resulting mixture was extracted with ether (2 x 200 mL). The combined ether extracts were washed with brine (100 mL), dried with $MgSO_4$, filtered through Na_2SO_4, and concentrated *in vacuo*. The resulting oil was chromatographed eluting first with 50:50 ethyl acetate:hexanes, then with ethyl acetate, to give a viscous oil crystallizing to a waxy solid on standing (5.81

g, 88%). By ^{1}H NMR, this was a 53:47 ratio of formamide isomers. Melting point: 67-70°C. IR (KBr): 3287, 2972, 1674, 1493, 1386, 1093, 810 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 8.28 (m, 1H, d, *J* = 12.3 Hz), 8.08 (M, 1H, d, *J* = 1.9 Hz), 7.28-7.22 (M+m, 2H), 7.13-7.08 (M+m, 2H), 6.39 (m, 1H, bs), 5.38 (M, 1H, bs), 2.64-2.53 (M+m, 2H), 2.07-2.01 (M+m, 1H), 1.83-1.77 (M+m, 1H), 1.39 (M, 6H, s), 1.38 (m, 6H, s). ^{13}C NMR (CDCl$_3$): δ 163.02, 160.41, 140.43, 139.70, 131.79, 131.48, 129.70, 129.54, 128.60, 128.42, 53.92, 52.67, 45.54, 41.77, 30.04, 29.67, 28.62, 27.28. CIMS (CH$_4$): 226 (100%). Anal. calc. for $C_{12}H_{16}ClNO$: C, 63.86; H, 7.14; N, 6.21. Found: C, 63.78; H, 7.27; N, 6.06.

10-Chloro-5,5-dimethyl-4,6,7,11b-tetrahydro-[5H]-oxazolo[2,3-a]-2-benzazepine-2,3-dione (8b)

Formamide **7b** (1.85 g, 8.20 mmol) was dissolved in CH$_2$Cl$_2$ (80 mL) under nitrogen at 20°C. To this stirred solution was added, over 5 min, oxalyl chloride (0.79 mL, 9.02 mmol). Gas evolved. After 1 h, the reaction was cooled in an ice bath and treated with anhydrous ferric chloride (1.59 g, 9.84 mmol). After 10 min, the cold bath was removed. After 16 h, 2.0 M hydrochloric acid (80 mL) was added to the rapidly stirred reaction. After 2 h, the organic and aqueous layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 50 mL). The combined organic layers were dried with Na$_2$SO$_4$ and concentrated *in vacuo*. Chromatography of the resulting oil, eluting with 50:50 ethyl acetate:hexane, then ethyl acetate, gave a solid (R_f ~ 0.3 in 50:50 ethyl acetate:hexane). Recrystallization from a mixture of ether:CH$_2$Cl$_2$:hexanes afforded **8b** as an off-white solid (1.13g, 49%). Melting point: 126-128°C (gas evolved). IR (KBr): 1821, 1724, 1327 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 7.53 (1H, d, *J* = 2.2 Hz), 7.28 (1H, dd, *J* = 2.2, 8.2 Hz), 7.14 (1H, d, *J* = 8.2 Hz), 6.80 (1H, s), 3.28-3.07 (2H), 2.30 (1H, ddd, *J* = 3.9, 11.9, 15.6 Hz), 1.90 (1H, ddd, *J* = 4.0, 5.5, 15.6 Hz) 1.72 (3H, s), 1.59 (3H, s). ^{13}C NMR (CDCl$_3$): δ 158.42, 152.19, 135.39, 135.33, 132.68, 131.73, 129.58, 125.69, 82.97, 59.57, 37.76, 29.28, 26.54, 24.08. CIMS (CH$_4$): 280 (95%), 191 (100%). Anal. calc. for $C_{14}H_{14}ClNO_3$: C, 60.11; H, 5.04; N, 5.01. Found: C, 60.03; H, 5.14; N, 4.94.

8-Chloro-4,5-dihydro-3,3-dimethyl-[3H]-2-benzazepine (11b)

Neat **8b** (4.21 g, 15.0 mmol) was placed in a flask under nitrogen and the flask immersed in a preheated bath (~165-170°C). The solid melted and gas was evolved. After 1 h, the resulting liquid was cooled to ~20°C and dissolved in methanol (30 mL). NaBH$_4$ (1.14 g, 30 mmol) was added over 5 min. Gas and heat were evolved. After 18 h, 1.0 M aqueous NaOH (20 mL) was added. After stirring 1 h, the reaction mixture was diluted with water (50 mL) and extracted with CH$_2$Cl$_2$ (2 x 100 mL). The combined extracts were dried with MgSO$_4$, filtered through Na$_2$SO$_4$, and concentrated *in vacuo*. The product was chromatographed, eluting first with ethyl acetate, then with 5:95 diethylamine:ethyl acetate, to give a slightly yellow oil (1.97g, 63%, R_f ~ 0.1, streaking, in ethyl acetate). ^{1}H NMR (CDCl$_3$): δ 7.10-7.03 (3H, m), 3.85 (2H, s), 2.83 (2H, m), 1.63 (2H, m), 1.47 (1H, bs), 1.19 (6H, s). ^{13}C NMR (CDCl$_3$): δ 144.44, 140.84, 131.39, 130.56, 128.02, 126.66, 53.08, 47.29, 40.25, 29.94, 28.38 (broad peak). This was carried on without further analysis.

8-Chloro-4,5-dihydro-3,3-dimethyl-[3H]-2-benzazepine 2-oxide (5b)

Amine **11b** (1.26 g, 6.00 mmol) was dissolved in ethanol (12 mL) and treated with a solution of $Na_2WO_4 \cdot 2H_2O$ (99 mg, 0.30 mmol) in water (6 mL). The cloudy mixture was cooled in an ice bath and treated with 30% hydrogen peroxide (1.36 mL). After 20 min, the cold bath was removed. After 6 h, the reaction was diluted with water (20 mL) and extracted with CH$_2$Cl$_2$ (2 x 50 mL). The extracts were dried with Na$_2$SO$_4$ and concentrated *in vacuo*. The crude product was chromatographed with ethyl acetate, isolating a white solid (1.13 g, 84%, R_f ~ 0.25). Melting point: 102-103°C. IR (CHCl$_3$): 2980, 1539, 1491, 1250, 1157 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 7.80 (1H, s), 7.20-7.08 (3H), 3.00 (2H, m), 2.18 (2H, m), 1.87 (6H, s). ^{13}C NMR (CDCl$_3$): δ 138.76, 137.90, 132.34, 130.54, 130.48, 129.74, 128.43, 73.24, 37.95, 29.39, 28.21. CIMS (CH$_4$): 226 (33%), 224 (100%). Anal. calc. for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.37; H, 6.42; N, 6.25.

1-(3,5-Dichlorophenyl)-3-formamido-3-methylbutane (7c)

1-Bromo-3,5-dichlorobenzene (7.00 g, 31.0 mmol) was added to a mixture of magnesium turnings (0.83 g, 34.1 mmol) and anhydrous ether (30 mL) under nitrogen. One crystal of iodine was added and the resulting exothermic reaction was controlled with external cooling. After 45 min, the reaction was cooled to 0°C and treated dropwise with 1-chloro-3-methyl-2-butene (4.40 mL, 38.7 mmol). After 55 h at ~20°C, the reaction was quenched by slow addition of 1.0 M hydrochloric acid (75 mL). The reaction mixture was extracted with ether (2 x 100 mL) and the combined extracts were washed with water (50 mL) and brine (50 mL). The combined extracts were dried over $MgSO_4$, filtered through Na_2SO_4, and concentrated *in vacuo*. The resulting tan oil was chromatographed using hexane to give a clear oil, **6b** (5.13 g, $R_f \sim 0.8$). A stirred mixture of acetic acid (27 mL) and NaCN (2.34 g, 47.7 mmol) at 0°C was treated with a 1:1 mixture of acetic acid:concentrated sulfuric acid (11.6 mL). The cold bath was removed. After 15 min, **6b** (5.13 g, 23.8 mmol) was added to the reaction mixture. After stirring 24 h, nitrogen was bubbled through the reaction for 30 min. The reaction mixture was then carefully poured onto a stirred mixture of ice (200 g) and Na_2CO_3 (53 g). The resulting mixture was extracted with ether (2 x 200 mL) The combined extracts were washed with water (100 mL) and brine (100 mL), then dried over $MgSO_4$ and filtered through Na_2SO_4. The dried extracts were concentrated *in vacuo* to a tan oil. Chromatography eluting with 50:50 ethyl acetate:hexane followed by ethyl acetate gave an oil ($R_f \sim 0.5$ in the first eluant). Further purification by distillation in a Kugelrohr apparatus at 170-174°C under vacuum (~0.5 mm) afforded the title compound as a clear oil (4.57 g, 56% for two steps). Proton NMR data indicate a 60:40 ratio of formamide isomers. IR (neat): 1667, 1568, 799 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.28 (1H (m), d, J = 12.3 Hz), 8.09 (1H (M), d, J = 2.0 Hz), 7.20 (1H (m), t, J = 2.0 Hz), 7.17 (1H (M), t, J = 1.8 Hz), 7.07 (2H (M), d, J = 1.8 Hz), 7.06 (2H (m), d, J = 2.0 Hz), 6.38 (1H (m), bd, J = 11.0 Hz), 5.36 (1H (M), s), 2.63-2.51 (2H (M+m), m), 2.09-2.03 (1H (M+m), m), 1.84-1.78 (1H (M+m), m), 1.39 (6H (M), s), 1.38 (6H (m), s). ^{13}C NMR ($CDCl_3$): δ 163.04, 160.45, 145.33, 144.59, 134.87, 134.65, 126.90, 126.79, 126.32, 126.04, 53.80, 52.56, 45.07, 41.19, 30.25, 29.85, 28.54, 27.30. CIMS (CH_4): 260 (100%). Anal. calc. for $C_{12}H_{15}Cl_2NO$: C, 55.40; H, 5.82; N, 5.38. Found: C, 55.21; H, 5.93; N, 5.33.

9,11-Dichloro-5,5-dimethyl-4,6,7,11b-tetrahydro-[5H]-oxazolo[2,3-a]-2-benzazepine-2,3-dione (8c)

To a solution of **7c** (4.34 g, 16.68 mmol) in CH_2Cl_2 (165 mL) under nitrogen was added oxalyl chloride (1.61 mL, 18.3 mmol). Gas evolved. After stirring 1 h, the reaction was cooled in an ice bath and treated with anhydrous $FeCl_3$ (3.25 g, 20.0 mmol). The cold bath was removed after 10 min. After 24 h, the reaction was treated with 2.0 M hydrochloric acid (165 mL) and stirred vigorously for 1 h. The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered through Na_2SO_4, and concentrated *in vacuo*. The crude product was chromatographed using 40:60 ethyl acetate:hexane. The resulting product ($R_f \sim 0.6$) was recrystallized from a mixture of hexane and acetonitrile to give white crystals (2.41 g, 46%). A second crop yielded 0.58 g (11%). Melting point: 182-184°C. IR (KBr): 1815, 1734, 1400, 1333 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.42 (1H, dd, J = 0.6, 2.1 Hz), 7.11 (1H, d, J = 2.1 Hz), 6.89 (1H, s), 2.92-2.81 (1H, m), 2.62 (1H, dq, J = 4.4, 15.1 Hz), 2.45 (1H, dq, J = 5.9, 13.8 Hz), 1.92 (3H, s), 1.76 (1H, dt, J = 4.4, 13.3 Hz), 1.22 (3H, s). ^{13}C NMR ($CDCl_3$): δ 158.65, 152.94, 141.69, 136.97, 135.83, 130.40, 130.34, 129.26, 128.66, 85.04, 57.85, 36.77, 31.71, 29.03, 28.05. CIMS (methane): 314 (100%), 225 (100%). Anal. calc. for $C_{14}H_{13}Cl_2NO_3$: C, 53.52; H, 4.18; N, 4.46. Found: C, 53.43; H, 4.26; N, 4.39.

7,9-Dichloro-4,5-dihydro-3,3-dimethyl-[3H]-2-benzazepine (11c)

Neat **8c** (2.91g, 9.26 mmol) was heated at 185°C under nitrogen for 1 h. Gas evolved. The resulting liquid was dissolved in methanol (19 mL) and carefully treated with $NaBH_4$ (0.70 g, 19.5 mmol). Gas evolved. After 56 h, the reaction was treated with 1.0 M aqueous NaOH (10 mL) and stirred for 6 h. The reaction was diluted with water (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were washed with brine (50 mL), dried with $MgSO_4$, filtered through Na_2SO_4, and concentrated *in vacuo*. The crude product was chromatographed using ethyl acetate to give a tan oil, partially solidifying on standing (1.89 g, 84%, $R_f \sim 0.5$). IR (KBr): 2961, 2932, 1584, 1561, 1175, 854 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.19 (1H, d, J = 2.1 Hz), 7.03 (1H, d, J = 2.1 Hz), 4.09 (2H, s), 2.88-2.84 (2H, m), 1.67 (2H, m), 1.54 (1H, s), 1.19 (6H, s). ^{13}C NMR ($CDCl_3$): δ 145.84, 137.90, 133.42, 131.92, 127.96, 126.68, 52.93, 42.36, 39.90, 30.94, 28.47 (broad). CIMS (CH_4): 244 (100%). Anal. calc. for $C_{12}H_{15}Cl_2N$: C, 59.02; H, 6.21; N, 5.73. Found: C, 57.35; H, 6.36; N, 5.60.

7,9-Dichloro-4,5-dihydro-3,3-dimethyl-[3H]-2-benzazepine 2-oxide (5c)

To a stirred solution of **11c** (1.83 g, 7.49 mmol) in ethanol (19 mL) was added a solution of $Na_2WO_4 \cdot 2H_2O$ (0.12 g, 0.37 mmol) in water (4.5 mL) followed by 30% aqueous hydrogen peroxide (1.7 mL). After 42 h, the reaction was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a solid. Chromatography using ethyl acetate gave **5c** as a white solid (1.79 g, 92%, $R_f \sim 0.5$). Melting point: 95-97°C. IR (KBr): 1523, 1229, 1186, 1157, 856 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.27 (1H, s), 7.31 (1H, d, J = 2.2 Hz), 7.07 (1H, dd, J = 2.2 Hz), 2.93-2.89 (2H, m), 2.23-2.19 (2H, m), 1.59 (6H, s). ^{13}C NMR ($CDCl_3$): δ 144.41, 134.62, 134.59, 134.00, 128.09, 127.07, 125.43, 74.22, 40.70, 30.09, 28.91. EIMS: 257 (100%). Anal. calc. for $C_{12}H_{13}Cl_2NO$: C, 55.93; H, 5.09; N, 5.42. Found: C, 55.97; H, 5.16; N, 5.35.

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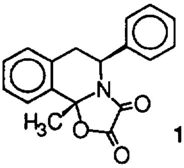

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