Synthesis and Reactions of Some Dihydro and Tetrahydro-4*H*-Imidazo[5,4,1-*ij*]quinoline Derivatives

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Reaction of phenyl *N*-(8-quinolinyl)carbamate with sodium borohydride afforded 1,2-dihydro-4*H*-imidazo-[5,4,1-*ij*]quinolin-2-one, **2a**. The 5,6-double bond of **2a** was functionalized by reaction with nitrosyl chloride to give the nitroolefin **4** and by reaction with hypobromous acid to give the *trans*-bromohydrin **5**. Reaction of **5** with sodium azide led to the rearranged *trans*-6-azido-5-ol **7**, the structure of which was determined by ^{1}H nmr studies.

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Although a number of 5,6-dihydro-4H-imidazo[5,4,1-*ij*]-quinoline derivatives have been prepared by cyclization of an 8-amino-1,2,3,4-tetrahydroquinoline (1), relatively few 5,6-unsaturated or substituted compounds have been reported (2,3). For example, 6-keto derivatives have been synthesized (3) by a multi-step sequence terminating in the cyclization of the corresponding 8-amino-1,2,3,4,-tetra-hydroquinolin-4-one. In this report, we described a facile synthesis of the 4*H*-imidazo[5,4,1-*ij*]quinoline ring system and functionalization of the 5- and 6-positions.

Reduction of the phenylcarbamate **1a** with sodium boro-hydride in an ethanol-tetrahydrofuran mixture afforded a 47.6% yield of analytically pure **2a** (Scheme I). In this reaction, hydride adds to the 2-position of the quinoline (4) and initiates cyclization to **2a** with expulsion of phenoxide ion. Attempted reduction of the ethyl carbamate **1b** under the same conditions did not lead to **2a**, but instead gave only recovered carbamate. This result suggests that the conversion of **1a** to **2a** is either a concerted or nearly concerted process with substantial weakening of the phenoxy-carbonyl bond in the transition state. Similarly, the formyl **1c** and acetyl **1d** amides did not undergo cyclization to 4*H*-imidazo[5,4,1-*ij*]quinolines under these conditions. Presence of carbonyl infrared bands at 5.81 μm for **2a** and 5.78 and 5.90 μm for the *N*-acetyl derivative **2b** indicate that the 2-oxo tautomer predominates for **2a** as has been reported for the 5,6-dihydroderivatives (5).

The 2-chloro compound **3** was prepared in 62% yield by reaction of **2a** with phosphorous oxychloride. Initial at-tempts to functionalize the 5,6-double bond of either **2a** or **3** by hydroboration gave only complex mixtures. However, epoxidation of **2a** with m-chloroperbenzoic acid at 60° in the presence of the radical inhibitor bis (3-*t*-butyl-4-hydroxy-5-methylphenyl) sulfide (6) gave a low yield of a mixture of the mono *m*-chlorobenzoate esters of the 5,6-diol.

Nitrosyl cloride has been reported (7) to add to the 5-double bond of cholesteryl acetate to give a chloronitro adduct, evidently arising from oxidation of the initially formed nitrosochloride with excess nitrosyl chloride. Dehydrochlorination with pyridine then led to the cor-responding nitro-olefin. Similarly, reaction of the *N*-acetyl

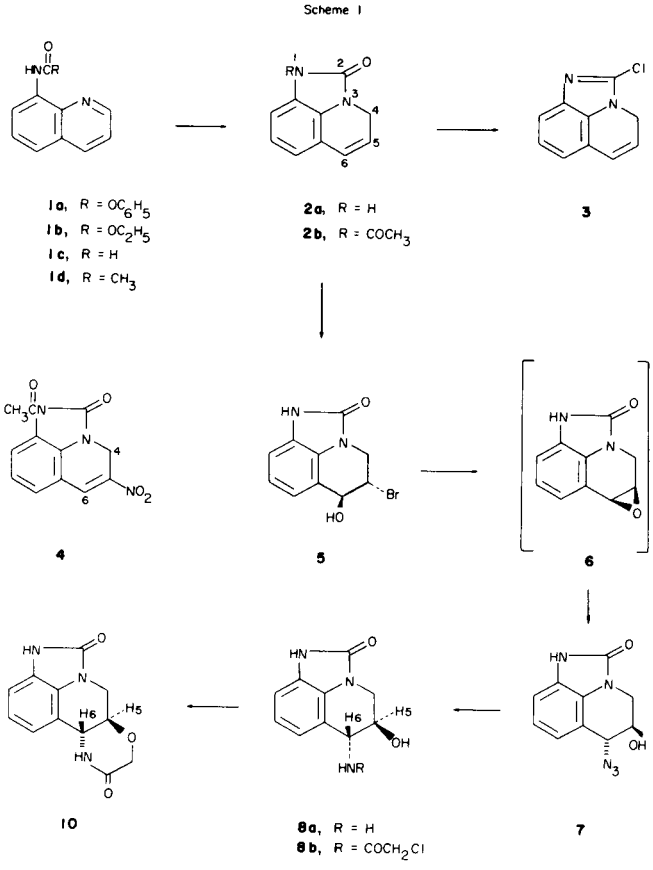
Table I

^{1}H NMR Chemical Shifts (a) (ppm) for **5**, **7**, **8a** and **10**

	5	**7**	**8a**	**10**
NH	10.86 (s)	(b)	10.92 (s)	10.91 (s)
NH_3^+	—	—	8.57 (m)	—
H-9 (c)	7.05 (d, d, J = 8.5, 2.0)	7.08 (d, d, J ~ 8.0, 2.0)	7.16 (d, J = 2.5) (d)	7.03 (d, J ~ 8.0)
H-8	6.98 (t, J = 8.5)	7.02 (t, J ~ 8.0)	7.02 (t, J = 7.5) (d)	6.94 (m)
H-7 (c)	6.95 (d, d, J = 8.5, 2.0)	6.98 (d, d, J ~ 8.0, 2.0)	6.99 (d, J ~ 7.5) (d)	6.94 (m)
OH	6.18 (d, J = 6.1)	5.75 (d, J = 3.9)	5.98 (d, J = 3.7 (4.0) (d)	—
H-6	4.80 (d, d, J = 6.0, 3.5)	4.80 (d, J = 4.7)	4.32 (s) (d, J = 5.0) (d)	4.35 (d, J = 8.6)
H-5	4.68 (d, t, J = 3.5, 3.0, 3.0)	4.14 (q, J ~ 4)	4.32 (s) (q, J ~ 3.5) (d)	3.81 (d, t, J = 5.5, 8.6, 9.5)
H-4	4.12 (d, d, J = 14.5, 3.0) 4.08 (d, d, J = 14.5, 3.0)	3.80 (d, d, J = 12.9, 4.2) 3.63 (d, d, J = 12.9, 3.0	3.78 (s) (d, d, J = 13.0, 3.0) (d) (d, d, J = 13.0, 4.5) (d)	4.22 (d, d, J = 11.5, 5.5) 3.50 (d, d, J = 11.5, 9.5)
$-OCH_2C-$ (O)	—	—	—	3.96 (d, J = 17.0) 3.92 (d, J = 17.0)

(a) Spectra were recorded at 300 MHz with TMS as the internal standard in DMSO-d_6 unless otherwise noted. (b) Not observed. (c) Preferred assignment. (d) Coupling constants determined in DMSO-d_6/perdeuteriobenzene (5:4).

Scheme I



derivative **2b** with nitrosyl chloride followed by treatment with pyridine afforded the nitro-olefin **4** in 32% yield. This product is formulated as the 5-nitro rather than the 6-nitro derivative because of the anticipated regioaddition (7) of nitrosyl chloride to the styrene-like double bond of **2b**. In addition, the fact that $J_{6,4}$ (1.5 Hz) of the nitro-olefin is smaller that either $J_{6,4}$ (2.0 Hz) or $J_{5,4}$ (3.0 Hz) of **2b** strongly suggests that the nitro group is at C-5 rather than C-6.

Conversion of **2a** to the bromohydrin **5** was effected smoothly in high yield with NBS in aqueous dimethylsulfoxide (8). Since this reaction has been shown to result in a net *trans* Markownikoff addition of hypobromous acid, the isolated bromohydrin was assigned the stereochemistry shown in **5**. The position of the alcohol function of **5** was confirmed by ^{1}H nmr spectra in which the signal for the proton α to the alcohol group was observed to be a pair of doublets (H-5 and O-H splitting) in deuterated dimethylsulfoxide which collapsed to a single doublet upon exchange with deuterium oxide. This shows that the alcohol function must reside at C-6 adjacent to only one proton at C-5 and not at C-5 which would then have three adjacent protons at C-4 and C-6.

Reaction of bromohydrin **5** with sodium azide in aqueous dimethylformamide containing acetic acid at 100° resulted in a 70% yield of an azido alcohol which was reduced catalytically to the corresponding amino alcohol. Inspection of coupling patterns of the carbinol protons of these compounds before and after deuterium oxide exchange indicated that the hydroxyl group now resided at C-5 (9). Confirmation that a rearrangement had indeed occurred was obtained upon irradiation of the highly split carbinol resonance in the amino alcohol which resulted in reduced multiplicity of all remaining signals associated with the piperidine protons. This result can only be reconciled with the alcohol function at C-5 as in **7** and **8a**. Also of interest is the observation that in **7**, the signal for the proton α to the azide group, H-6, is downfield from the carbinol proton H-5 (Table I).

Formation of rearranged azido alcohol **7** most likely proceeds through the intermediate oxirane **6**. Opening of the oxirane ring of **6** by azide ion evidently occurs preferentially at C-6 analogous to the regioselective formation of bromohydrin **5** from the intermediate cyclic bromonium ion. *Trans* diaxial ring opening of the presumed oxirane intermediate **6** would generate the *trans* stereochemistry shown for **7**. Unfortunately, the stereochemistry of either **7** or **8a** was not readily defined by ^{1}H nmr as the coupling constants for H-5, H-6 ranged from 3.5-4.7 Hz.

Since Dreiding models of this ring system indicated that C-4, C-5 and C-6 of **7** and **8a** are conformationally flexible, it was thought that elucidation of the stereochemistry of these compounds could be best achieved through conversion to a more rigid derivative. Therefore, the α-chloroacetamide **8b** was cyclized to the oxazinone **10** in 57% yield with potassium hydroxide in ethanol. The observed coupling constant of 8.6 Hz for H-5, H-6 splitting (Table I) in **10** clearly establishes a *trans* diaxial configuration for these protons and confirms the assigned *trans* stereochemistry for **7** and **8**.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus using open capillaries and are uncorrected. ^{1}H nmr spectra were recorded for all intermediates and final products on either a Varian T-60A, a Varian EM-90, or a Varian SC300 instrument using tetramethylsilane as an internal standard and are consistent with assigned structures. Tlc's were performed on Analtech fluorescent silica gel plates and spots detected by uv, exposure to I_2 vapor or spraying with Dragendorff reagent. Infrared spectra were obtained with a Perkin-Elmer 297 grating spectrophotometer. Mass spectral data were acquired with an MS 902 instrument.

Phenyl *N*-(8-Quinolinyl)carbamate (**1a**).

Phenyl chloroformate (17.3 g, 110 mmoles) was added over 15 minutes to a stirred solution of 8-aminoquinoline (14.4 g, 100 mmoles) in 75 ml of

pyridine with ice-bath cooling. After stirring at room temperature for 3 days, the reaction mixture was poured onto ice and the precipitated solid removed by filtration and washed with water. Recrystallization from ethanol gave 22.8 g (86.4%) of phenyl carbamate **1a**, mp 79.0-83.0°. A sample was recrystallized twice more from ethanol to give an analytical sample, mp 81.5-83.0°, homogeneous tlc (50% toluene-chloroform) R_f = 0.3.

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.95; H, 4.83; N, 10.70.

Ethyl *N*-(8-quinolinyl)carbamate (**1b**).

Acylation of 8-aminoquinoline with ethylchloroformate by the same procedure used to prepare the phenyl carbamate afforded **1b**, mp 64-66° (reported (10) mp 66-67°), homogeneous tlc (chloroform) R_f = 0.7, in 91% yield.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60; N, 12.96. Found: C, 66.67; H, 5.63; N, 13.02.

N-(8-Quinolinyl)formamide (**1c**).

A solution of 8-aminoquinoline (7.21 g, 50 mmoles) and 97% formic acid (5.32 g, 112 mmoles) in 75 ml of toluene was heated at reflux under a Dean-Stark water trap for 5 hours. After cooling, the precipitated solid, 7.35 g, was removed by filtration and combined with the solid obtained from concentration of the toluene to give a total of 8.25 g (95.8%) of *N*-formyl derivative **1c**, mp 150-152° (reported (11) mp 152-154°), homogeneous tlc (5% methanol-95% chloroform) R_f = 0.7. Recrystallization from 2-propanol gave an analytical sample, mp 150.5-152.5°.

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.75; H, 4.64; N, 16.30.

N-(8-Quinolinyl)acetamide (**1d**).

A mixture of 8-aminoquinoline (5.0 g 34.7 mmoles) and 25 ml of acetic anhydride was stirred at room temperature for 1 hour and then concentrated under reduced pressure. The residual semi-solid was stirred with 100 ml of water for 1 hour until crystallization was complete. Filtration and drying gave 5.9 g (91%) of the *N*-acetyl derivatives, mp 99-102° (reported (11) mp 100-101°).

1,2-Dihydro-4*H*-imidazo[5,4,1-*ij*]quinolin-2-one (**2a**).

A solution of the phenyl carbamate **1a** (61.57 g, 233 mmoles) in 1 l of ethanol and 300 ml of THF was reduced by the portionwise addition of sodium borohydride (23.64 g, 625 mmoles) over 30 minutes. Reaction temperature was maintained below 35° by means of a cold-water bath. After stirring at room temperature for 20 hours, solvents were removed under reduced pressure. The remaining solid was washed alternately with water, 3*N* hydrochloric acid, water, 5% sodium hydroxide and finally with water to a neutral *p*H and then dried to give 22.6 g of product, mp 233.5-238.5°. Recrystallization from 2-propanol gave 19.1 g (47.6%) of **2a**, mp 237.0-239.5°; homogeneous tlc (5% methanol-95% chloroform) R_f = 0.4. ^{1}H nmr (DMSO-d_6) δ 4.6 (d, d, J = 3.0, 2.0, 2H, CH_2), 5.8 (d, t, J = 10.0, 3.0, 1H, = CH-), 6.5 (d, t, J = 10.0, 2.0, 1H, = CH-), 6.7-6.9 (m, 3H, aromatic), 10.7 (br s, 1H, NH exchangeable); ir (potassium bromide): 5.81 μm, br (C = O); ms: m/e 172.

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.62; H, 4.75; N, 16.45.

1-Acetyl-1,2-dihyro-4*H*-imidazo[5,4,1-*ij*]quinolin-2-one (**2b**).

A solution of **2a** (3.0 g, 17.4 mmoles) and 15 ml of acetic anhydride in 300 ml of toluene was stirred at reflux overnight. After concentrating under reduced pressure, the remaining solid was washed with water and dried to give the *N*-acetyl derivative **2b** (3.64 g, 97.6%), mp 141-143°. Recrystallization from 2-propanol afforded an analytical sample with the same mp; homogeneous tlc (5% methanol-95% chloroform) R_f = 0.8; ^{1}H nmr (DMSO-d_6) δ 2.6 (s, 3H, CH_3), 4.5 (d, d, J = 3.0, 2.0, 2H, CH_2), 5.9 (d, t, J = 10.0, 3.0, 1H, = CH-), 6.5 (d, t, J = 10.0, 2.0, 1H, = CH-), 6.8-7.1 (m, 2H, aromatic), 7.6 (d, d, 1H, aromatic); ir (potassium bromide): 5.78 br, 5.9 μm (C = O).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 67.28; H, 4.71; N, 13.08. Found: C, 66.96; H, 4.63; N, 13.11.

2-Chloro-4*H*-imidazo[5,4,1-*ij*]quinoline (**3**).

A mixture of **2a** (5.0 g, 29 mmoles) and 40 ml of phosphorus oxychloride was heated at 80° for 2.5 hours, cooled and poured onto 500 g of ice. Product was extracted into four 200 ml portions of chloroform which were combined and washed with a saturated solution of sodium chloride. After drying (sodium sulfate), filtering and concentrating under pressure, the residue was recrystallized from hexane to give **3** (3.4 g, 62%) mp 127.5-130.5°. A sample was recrystallized further from hexane to give an analytical sample, mp 129.5-131.5°; homogeneous tlc (5% 2-propanol-95% dichloromethane), R_f = 0.5; ^{1}H nmr (deuteriochloroform): δ 4.9 (d, d, J = 3.0, 2.0, 2H, CH_2), 5.7 (d, t, J = 10.0, 3.0, 1H, = CH-), 6.5 (d, t, J = 10.0, 2.0 1H, = CH-), 6.7-7.5 (m, 3H, aromatic).

Anal. Calcd. for $C_{10}H_7ClN_2$: C, 63.00; H, 3.70; N, 14.70. Found: C, 63.26; H, 3.73; N, 14.67.

1-Acetyl-1,2-dihydro-5-nitro-4*H*-imidazo[5,4,1-*ij*]quinolin-2-one (**4**).

Nitrosyl chloride was bubbled through a solution of **2b** (2.14 g, 10 mmoles) in 25 ml of dichloromethane at 0° for 20 minutes. After stirring at 0° for an additional hour, solvent and excess nitrosyl chloride were removed under reduced pressure. The residual foam was dissolved in 20 ml pyridine, stirred at reflux for 3 hours, cooled and poured into 100 ml of water. The yellow-brown solid that formed was removed by filtration, dried and recrystallized from acetonitrile to give 0.82 g (32%) of **4** as a yellow-orange solid which decomposed slowly from 218°; ^{1}H nmr (DMSO-d_6): δ 2.6 (s, 3H, CH_3), 5.0 (d, J = 1.5, 2H, CH_2), 7.0 (t, J = 8.0, 1H, aromatic), 7.3 (d, d, J = 8.0, 1.5, 1H, aromatic), 7.8 (d, d, J = 8.0, 1.5, 1H, aromatic), 8.2 (t, J = 1.5, 1H, = CH-); ir (potassium bromide) 5.75 μm br (C = O); ms m/e 259.

Anal. Calcd. for $C_{12}H_9N_3O_4$: C, 55.60; H, 3.50; N, 16.21. Found: C, 55.79; H, 3.43; N, 16.32.

Epoxidation of 1,2-Dihydro-4*H*-imidazo[5,4,1-*ij*]quinolin-2-one.

A solution of the olefin **2a** (172 mg, 1 mmole) and 1 mmole of *m*-chloroperbenzoic acid in 10 ml nitrosyl chloride was stirred at room temperature overnight. When tlc indicated that the reaction was not complete, approximately 3 mg of the radical inhibitor bis(3-*t*-butyl-4-hydroxy-5-methylphenyl) sulfide was added and the mixture stirred at 60° for 8 hours. After cooling, the reaction mixture was shaken with saturated sodium bicarbonate solution, the organic layer dried (sodium sulfate), filtered and concentrated under reduced pressure. The residue was chromatographed over 4.5 g, of 40-60 μ mesh silica gel (E. Merck). Elution with a 7% 2-propanol-93% dichloromethane solvent mixture gave an oil which was crystallized from a MeOH-EtOAc-hexane mixture to 90 mg (26%) of a white solid, mp 203-206°; tlc (10% 2-propanol-90% dichloromethane) showed two spots of equal intensity at R_f 0.58 and 0.60. ^{1}H nmr (DMSO-d_6) indicated that this product was a mixture of the mono *m*-chlorobenzoyl esters of 5,6-dihydroxy-1,2,5,6-tetrahydro-4*H*-imidazo-[5,4,1-*ij*]quinolin-2-one.

Anal. Calcd. for $C_{17}H_{13}ClN_2O_4$: C, 59.22; H, 3.80; N, 8.13. Found: C, 59.51; H, 3.83; N, 8.11.

trans-5-Bromo-6-hydroxy-1,2,5,6-tetrahydro-4*H*-imidazo[5,4,1-*ij*]quinolin-2-one (**5**).

N-Bromosuccinimide (5.88 g, 33 mmoles) was added in one portion to a stirred solution of 5.16 g (30 mmoles) of **2a** and 3 ml of water in 100 ml of DMSO at 15°. After stirring for 1.5 hours, the solution was poured into 500 ml of cold water and stirred for 10 minutes. The precipitated white solid was removed by filtration, washed with water and dried to give the bromohydrin **5** (7.95 g, 98.5%) mp 188-191° dec. A sample was recrystallized from ethanol to give an analytical sample, mp 192-194° dec; ms: Calcd: m/e 267.9848; Observed: 267.9835.

Anal. Calcd. for $C_{10}H_9BrN_2O_2$: C, 44.63; H, 3.37; N, 10.41. Found: C, 44.54; H, 3.35; N, 10.17.

trans-6-Azido-5-hydroxy-1,2,5,6-tetrahydro-4*H*-imidazo[5,4,1-*ij*]quinolin-2-one (**7**).

A solution of sodium azide (3.25 g, 50 mmoles) in 10 ml of water was added to a solution of the bromohydrin **5** (5.0 g, 18.6 mmoles) and 3 ml of acetic acid in 150 ml of DMF and the mixture stirred at steam bath temperature for 4 hours. After removing the DMF under reduced pressure, the residue was triturated with 100 ml of water. The solid azidoalcohol was removed by filtration and dried to give 3.0 g (70%) of **7**, mp 205-206° dec. An analytical sample with the same mp was obtained upon recrystallization from ethanol-hexane; ir (potassium bromide): 4.75 μm (-N_3); ms: Calcd: m/e 231.0756; observed: 231.0752.

Anal. Calcd. for $C_{10}H_9N_5O_2$: C, 51.61; H, 3.90; N, 29.86. Found: C, 52.10; H, 4.02; N, 29.82.

trans-6-Amino-5-hydroxy-1,2,5,6-tetrahydro-4*H*-imidazo[5,4,1-*ij*]quinolin-2-one Hydrochloride (**8a**).

A mixture of the azido alcohol (2.0 g, 7.43 mmoles) and 1.5 g of a 10% Pd-C catalyst in 200 ml of ethanol containing 2 ml of concentrated hydrochloric acid was hydrogenated at room temperature and an initial pressure of 30 psig for 5 hours. After rinsing the Paar flask with water and filtering, the filtrate was concentrated under reduced pressure. The residue was washed with 2-propanol and filtered to give 1.8 g of crude product which was recrystallized by dissolving in a mixture of ethanol (100 ml), methanol (400 ml) and water (10 ml), concentrating to 125 ml, adding 100 ml of hot 2-propanol and reconcentrating to 150 ml. In this way 1.1 g (61%) of analytically pure **8a** was obtained, mp >300°; ms: m/e 205.

Anal. Calcd. for $C_{10}H_{11}N_3O_2 \cdot HCl$: C, 49.69; H, 5.01; N, 17.39. Found: C, 49.85; H, 5.27; N, 17.28.

trans-6-(2-Chloroacetylamino)-5-hydroxy-1,2,5,6-tetrahydo-4*H*-imidazo-[5,4,1-*ij*]quinolin-2-one (**8b**).

Chloroacetylchloride (1.02 g, 9 mmoles) was added to a well stirred two phase mixture of the aminoalcohol **8a** (1.23 g, 6 mmoles) and sodium hydroxide (0.72 g, 18 mmole) in 10 ml of water and 30 ml of dichloromethane at room temperature. After 1.5 hours, the precipitated solid was removed, washed with water and dried to give 1.25 g (74%) of chloroacetamide **8b**, mp 260-263.5° dec. An analytical sample, mp 266-270° dec, was obtained upon recrystallization from a mixture of ethanol and methanol; homogeneous tlc (15% methanol-85% chloroform saturated with ammonia) R_f = 0.5; ^{1}H nmr (DMSO-d_6): δ 3.7 (t, J = 3.0, 2H, CH_2), 4.0-4.2 (m, 3H, -CH_2CO and -CHO), 4.9 (d, d, J = 9.0, 3.0, 1H, -CHN), 5.5 (d, J = 3.0, 1H exchangeable, OH), 6.8-7.1 (m, 3H, aromatic), 8.5 (d, J = 9.0 1H, NH), 10.9 (br s, 1H, NH).

Anal. Calcd. for $C_{12}H_{12}ClN_3O$: C, 51.16; H, 4.30; N, 14.92. Found: C, 51.31; H, 4.46; N, 14.59.

Cyclization of **8b** to **10**.

A mixture of chloroamide **8b** (3.20 g, 11.4 mmoles) and 85% potassium hydroxide (1.60 g, 24.2 mmoles) in 400 ml of ethanol was stirred at room temperature for 24 hours and then filtered to remove potassium chloride. After concentrating the filtrate under reduced pressure, the residue was dissolved in 30 ml of water, cooled in an ice bath and neutralized with glacial acetic acid. The precipitated solid was washed with water and dried to give **10** (1.6 g 57%), mp >360°, ms: m/e 245. An analytical sample was obtained by dissolving **10** in dilute sodium hydroxide, filtering, acidifying with 6*N* hydrochloric acid and adjusting the *p*H to 7-8 with dilute sodium bicarbonate.

Anal. Calcd. for $C_{12}H_{11}N_3O_3 \cdot H_2O$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.35; H, 5.35; N, 15.76.

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