Synthesis of 7-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine

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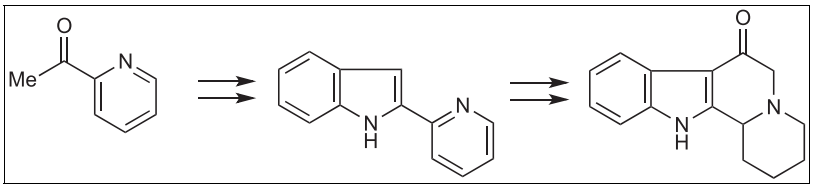

A short synthesis of 7-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine from 2-acetylpyridine and phenylhydrazine is described. Ring C is forged using 2-chloro-*N*,*N*-dimethylacetamide. This derivative of the natural alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine is an inhibitor of the ZipA–FtsZ protein–protein complex, which is a novel antibacterial target.

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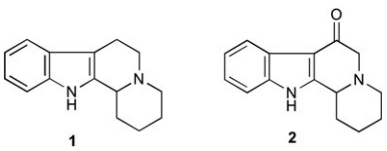
INTRODUCTION

In connection with our interest in the synthesis, spectroscopy, and chemistry of the alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**) [1–11] (more recently named as desbromoarborescidine A [12]) and of its keto derivatives [13–15], we now describe a convenient synthesis of 7-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**2**).



During our early work on this project, we became aware of the first synthesis of ketone **2** by Rosemund [16], and subsequently, we learned of the discovery by Sutherland [17–19] that **2** is a novel inhibitor of the ZipA–FtsZ protein–protein complex. This discovery has led ketone **2** to become a potential target for a new antibiotic strategy. Thus, the ZipA–FtsZ interaction is crucial for cell division in *Escherichia coli*, and ketone **2** and *N*-substituted analogues are pronounced inhibitors of this interaction [19]. We desired our synthesis of ketone **2** to be scalable and efficient and, in particular, to mimic our reported synthesis of 6-oxo-1,2,3,4,6,7,12,12b-octahydroindolo [2,3-*a*]quinolizine [14] in terms of starting materials and with the intent of forging ring C at the end.

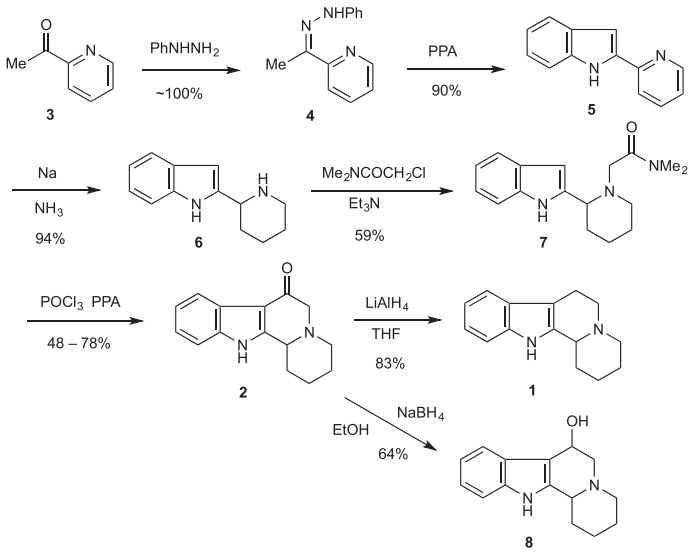
Our synthesis of ketone **2** is shown in Scheme 1. It differs from that of Rosemund [16] and Sutherland [18] in that we avoid using the toxic, lachrymatory, and carcinogenic [20] bromoacetates and bromoacetic acid that were used by the previous workers in the key step of their syntheses. The known 2-(2-piperidyl)indole (**6**) was prepared in three steps (85% yield) from commercially available 2-acetylpyridine (**3**) via 2-(2-pyridyl)indole (**5**) obtained by a Fischer indolization followed by Na metal selective reduction of the pyridine ring [2]. Treatment of **6** with 2-chloro-*N*,*N*-dimethylacetamide in a solution of acetone and triethylamine afforded amide **7** in 59% yield. Cyclization of **7** was achieved by heating it with a mixture of polyphosphoric acid and phosphorus oxychloride to afford ketone **2** in yields ranging from 48 to 78%. Phosphorus oxychloride alone gave no **2**. The structure of ketone **2** was supported by elemental analysis, spectral data, and comparison with the literature [16]. Notably, the carbonyl stretching frequency at 1620 cm^{-1} is consistent with that of 3-acetylindole [21]. Likewise, the ultraviolet spectrum is that of a 3-acetylindole [21]. Reduction of **2** with $LiAlH_4$ gave the (racemic) alkaloid **1**, identical with a sample prepared in our laboratory. Similarly, reduction of **2** with $NaBH_4$ gave indole alcohol **8**.

In summary, we have synthesized 7-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**2**) in five steps from commercial 2-acetylpyridine (**3**) in 24% overall yield.

EXPERIMENTAL

General. Melting points were determined in open capillaries with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Infrared spectra were recorded on a PerkinElmer 257 spectrophotometer (PerkinElmer, Inc., Waltham, MA). NMR spectra were determined on a Jeol JNM-FX60 Q Fourier transform spectrometer (JEOL, Tokyo, Japan). Ultraviolet spectra

Scheme 1



were recorded on a Unicam SP-800A spectrophotometer. Microanalyses were performed by Micro-Tech Laboratories, Skokie, IL. The adsorbent for thin-layer chromatography (TLC) was silica gel PF 254 + 366 (Merck, Kenilworth, NJ). TLC spots were visualized either under 254-nm UV light or by spraying with a solution of 3% $(NH_4)_4Ce(SO_4)_4$-$2H_2O$ in 10% aqueous H_2SO_4. Organic solutions were concentrated *in vacuo* with a Büchi Rotavaporator. Dry solvents were obtained by distillation from the following drying agents: $LiAlH_4$ (THF), CaH_2 (DMSO and DMF), P_4O_{10} (EtOAc), Na (*t*-BuOH, benzene, and Et_2O), and BaO (amines).

2-Acetylpyridine phenylhydrazone (4). A solution of 39.9 g (0.33 mol) of 2-acetylpyridine (**3**), 35.6 g (0.33 mol) of phenylhydrazine, and 24 mL of EtOH was heated to approximately 50°C for 90 min. At the end of this time, a solid mass of yellow crystals that formed was collected and dried to give 70.4 g (quant.) of **4**: mp 149–154°C (lit [22], mp 155°C).

2-(2-Pyridyl)indole (5). A mixture of 25.5 g (0.121 mol) of **4** and approximately 85 g of PPA acid was heated to 130°C with efficient stirring. After a few minutes, a vigorous, exothermic reaction ensued that rapidly increased the temperature of the mixture to >200°C. The reaction mixture was cooled to 70–80°C and basified to pH >10 by dilution with H_2O and addition of NaOH pellets. Much NH_3 gas was evolved during the basification. Exhaustive extraction with CH_2Cl_2, followed by washing of the organic phase with H_2O (3×) and brine (1×), drying (K_2CO_3), and concentration *in vacuo* afforded 21.5 g (91%) of **5**. TLC (5% Et_3N in EtOAc) showed a single, high R_f spot. Column chromatography (activity III basic alumina, elution with benzene) gave material having mp 151–152.5°C (lit [22], mp 154°C); UV λ_{max} (95% EtOH) 325 nm; IR ($CHCl_3$) 3550 cm^{-1}; NMR ($CDCl_3$) δ 6.96–7.43 (m, 6H), 7.53–7.81 (m, 2H), 8.58 (d, 1H), and 10.10 ppm (broad s, 1H).

2-(2-Piperidyl)indole (6) using Na/EtOH. To a solution of 10.00 g (0.052 mol) of **5** in 500 mL of absolute EtOH, freshly cut Na (~50 g) in portions was added so as to keep the solution at reflux. After the final addition, the solution was refluxed for 90 min. After cooling, the solid mass of NaOEt was dissolved in H_2O and extracted with benzene. The organic phase was washed with brine, dried over K_2CO_3, and concentrated *in vacuo* to yield 9.35 g (90%) of **6** as white crystals. Recrystallization from Et_2O–petroleum ether gave material with mp 134–135°C; (lit [2], mp 128–129°C); UV λ_{max} (95% EtOH) 271, 278, 281, and 289 nm; NMR ($CDCl_3$) δ 1.16–2.21, 2.56–3.38, 3.73–4.04 (m, 10H), 6.30 (broad s, 1H), 6.95–7.67 (m, 4H), and 8.88 ppm (broad s, 1H).

2-(2-Piperidyl)indole (6) using Na/NH₃. Sodium spheres (1.03 g, 56.5 mmol) were added to a flask equipped with a dry ice–acetone condenser and containing liquid NH_3 (125 mL), 2-(2-pyridyl)indole (**5**) (1.18 g, 6.03 mmol), and dry *t*-BuOH (20 mL). After the blue color had disappeared, EtOH (50 mL) was added, and the NH_3 was allowed to evaporate. The mixture was poured into H_2O and extracted with $CHCl_3$. The combined extracts were dried (K_2CO_3), and the solvent was removed to give **6** (1.15 g, 94%) as a fluffy white solid. This material was identical to that prepared using Na and EtOH (*vide supra*) and was sufficiently pure to be used in the next reaction.

N,N-[2-(2-Indolyl)-1-piperidineacetyl]dimethylamine (7). A mixture of (**6**) (9.50 g, 0.0474 mol), Et_3N (20 mL), and 2-chloro-*N*,*N*-dimethylacetamide (10.5 g, 0.0864 mol) in acetone (500 mL) was stirred at room

temperature for 12 h. The solvent was removed *in vacuo*, and the residue was distributed between 10% K_2CO_3 and $CHCl_3$. The combined $CHCl_3$ extracts were washed with 10% K_2CO_3 and dried (K_2CO_3), and the solvent was removed *in vacuo* to give a brown oil (20 g), which was chromatographed over 294 g of Woelm activity III neutral alumina. Elution with benzene (300 mL) and 25% $CHCl_3$-benzene (600 mL) gave an oil (16.1 g), which was dissolved in Et_2O and hexane and stored at 0°C. The resulting crystalline **7** (6.4 g) was collected. Elution with 50% $CHCl_3$-benzene (600 mL), $CHCl_3$ (300 mL), and 0.3% MeOH–$CHCl_3$ (300 mL) afforded additional **7** (1.6 g). Further elution with 0.3% MeOH–$CHCl_3$ (600 mL) gave a mixture (441 mg) of **7** and starting material **6**, which was not further separated. The total yield of **7** was 8.0 g (59%). Recrystallization from EtOAc give mp 156–157°C; IR 1645 (C=O), and 3500 cm^{-1} (NH); NMR δ 9.22 (m, 1H), 7.6–6.9 (m, 4H), 6.35 (s, 1H), 3.22 (s, 1H, CH_2C=O), 3.00 (s, 1H, CH_2C=O), 2.83 (s, 3H, N(CH_3)$_2$), 2.78 (s, 3H, N(CH_3)$_2$), and 3.5–1.5 (m, 9H).

Anal. Calcd for $C_{17}H_{23}N_3O$: C, 71.55; H, 8.12; N, 14.72. Found: C, 71.65; H, 8.14; N, 14.99.

7-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (2). A mixture of amide **7** (3.25 g, 0.0114 mol), PPA (50 g), and freshly distilled $POCl_3$ (100 mL) was heated at reflux under nitrogen for 0.5 h. The reaction was cooled, and the excess $POCl_3$ was decanted and discarded. The remaining purple sludge was decomposed with H_2O and ice. The resulting mixture was made alkaline with NaOH (70 g in 400 mL of H_2O), and the precipitate was isolated by filtration, washed with $CHCl_3$ (3×), and dried (K_2CO_3), and evaporated *in vacuo* to give 775 mg of ketone **2**. The aqueous filtrate was extracted with $CHCl_3$. The combined $CHCl_3$ extracts and filter cake washings (about 500 mL) were dried (K_2CO_3) and chromatographed (without reducing the volume of solvent) over 70 g of Woelm activity III basic alumina. Elution with $CHCl_3$ (920 mL) gave 539 mg of ketone (**2**). The total yield of **2** that was homogeneous by TLC was 1.314 g (48%). Material crystallized from *n*-BuOH had mp 251°C (lit [16], mp 260°C); UV λ_{max} (95% MeOH) (log ε) 241 (4.21), 263 (4.09), and 295 (4.02) nm (lit [16]; λ_{max} (MeOH) (log ε) 243 (4.22), 262 (4.07), and 297 (4.00) nm); IR (KBr) 1580 (C=C), 1620 cm^{-1} (C=O). A smaller scale reaction (0.005 mol of amide **7**) afforded **2** in 78% yield.

Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.82; H, 6.64; N, 11.75.

Reduction of ketone 2 with lithium aluminum hydride to afford alcohol 1. A mixture of ketone **2** (108 mg, 0.449 mmol) and $LiAlH_4$ (107 mg) in dry THF (70 mL) was heated at reflux for 4 h. The reaction mixture was cooled, and the lithium compounds were decomposed by successively adding H_2O, 40% NaOH, and then H_2O. After filtering and washing the filter cake with acetone, the solvent was evaporated to afford a residue that was partitioned between $CHCl_3$ and 10% K_2CO_3. The $CHCl_3$ extracts were dried (K_2CO_3), and the solvent was removed to give 84 mg (83%) of off-white crystals identical with that of authentic tetracyclic base (**1**) prepared in our laboratory [4].

7-Hydroxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (8). Sodium borohydride (180 mg) was added to a solution of ketone (**2**) (94 mg, 0.39 mmol) in EtOH (100 mL). After stirring at room temperature for 21 h, the EtOH was removed, and the residue was suspended in water. The insoluble material was filtered and washed with H_2O (2×) and with $CHCl_3$ (3×). After drying the white powder (61 mg, 64%), it had mp 215–216°C dec. Material crystallized from hot DMF had mp 210–211°C dec; UV λ_{max} (95% EtOH) (log ε) 282 (3.88) and 289 (3.30) nm. This material was too insoluble to obtain satisfactory NMR spectra.

Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.25; H, 7.55; N, 11.73.

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