A General Synthesis of Tris-Indole Derivatives as Potential Iron Chelators

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Abstract: The development of a novel route for the synthesis of a new class of compounds is described. The first tripodal, tris-indole amines are prepared by straightforward routes.

Keywords: Indole, TRENSOX, iron chelation.

Introduction

Recent research in the area of oral iron-chelation therapy centers on the TRENSOX drugs. Both N-TRENSOX (1) [1] and O-TRENSOX (2) [2] have shown promising results in iron binding and water solubility studies [3]. These novel compounds contain three quinoline units which each contain two oxygen functional groups. The oxygen atoms are located in such a way to provide the six electron-donating ligands required to chelate an iron ion in an octahedral configuration.
Due to their wide range of biological activities, indole and its derivatives continue to serve as important synthetic targets [4]. 3-Substituted indoles [5], particularly 3-acylindoles [6], are commonly found in pharmaceutical agents and are important synthetic intermediates.

Results and Discussion

Here, we describe the preliminary results toward the synthesis of two new TRENSOX derivatives, containing indole units in place of the quinolines. We have previously shown that indole-3-glyoxalyl chloride (3) will react with tris(2-aminoethyl)amine (TREN) to produce a 3-armed, claw-like structure (4) (Scheme 1) [7]. The tripodal amine appears to be fluxional in solution, as seen by NMR, and tightly closed as a solid, as seen by x-ray diffraction. To prepare the derivative, indole was first reacted with oxalyl chloride, and the resulting glyoxalyl chloride was added to TREN and triethylamine (TEA) in THF. After 24 hours, the resulting slurry was filtered, crystallized from methanol and filtered again to provide 4 as a beige powder.

Scheme 1.

Having established the success in the preparation of the first member in this new class of compounds, a related tripodal amine (5) with one carbonyl unit per arm was also been prepared by a modification of the above procedure. As seen in Scheme 2, indole-3-carboxylic acid was reacted with thionyl chloride to produce the acyl chloride 6, which was then reacted with TREN and TEA in THF.

Scheme 2.
The temperature of the reactions at the point when TREN is added seems to have a significant impact on the success of the reactions. Several attempts to add TREN at room temperature resulted in dark-colored gums, while additions in an ice bath gave relatively clean products. The rapidity of the addition of TREN is also critical, as the acyl chloride derivatives initially prepared are moisture sensitive.

**Conclusions**

We have developed a facile method for the synthesis of two novel tris-indolyl amines. These tripodal compounds are important intermediates in the development of new drugs with potential iron-chelating abilities. As efforts to improve the water-solubility of these compounds are underway, the success in their preparation should provide a general route to a new class of compounds.

**Experimental**

**General**

Melting points are uncorrected. 1H-NMR spectra were obtained using a Bruker 250 MHz multinuclear spectrometer. MS were measured using a Shimadzu QP 5050A instrument.

*Tris(2-[indole-3-glyoxylamido]ethyl)amine (4).* To indole (10.07 g, 86.1 mmol) in ether (200 mL) was added dropwise oxalyl chloride (14.6 g, 114.6 mmol) over 15 mins. After stirring for 30 min, the solution was filtered to yield 3 as a yellow solid, which was rapidly dissolved in THF (50 mL). To 3 in THF at 0°C was added a solution of TREN (6.14 g, 42.0 mmol) and TEA (42.3 mmol) in THF (10 mL). After stirring at 0°C for 1 h, the solution was filtered and the filtrate was evaporated to yield 4 as a beige solid which crystallized from MeOH. Yield 5.93 g (31.4%); mp > 250°C. 1H-NMR (250 MHz, DMSO-$d_6$) 8.75 (s, 3H, H2), 8.65 (t, J=5.29 Hz, 3H, H1), 8.14 (d, J=6.9 Hz, 3H, H4), 7.47 (d, J=7.1 Hz, 3H, H7), 7.22 (t, J=7.0 Hz, 3H, H5 or H6), 7.16 (t, J=7.0 Hz, 3H, H6 or H5), 3.31 (m, 6H, Ha), 2.71 (bt, 6H, Hb); MS (M+1)$^+ = 660$ for C$_{36}$H$_{33}$N$_7$O$_6$

*Tris(2-[indole-3-amido]ethyl)amine (5).* Indole-3-carboxylic acid (0.56 g, 3.4 mmol) dissolved in SOCl$_2$ (6 mL) was stirred at 0°C. After 1.5 h, the solution was rotary evaporated, and to the resulting oil was added TREN (0.62 g, 4.2 mmol) and TEA (0.46 g, 4.6 mmol) in THF (25 mL). After stirring at 0°C for 30 min, the solution was vacuum filtered to yield 5 as a beige solid which was recrystallized from MeOH. Yield 0.28 g (43.0%); mp > 250°C. 1H-NMR (250 MHz, DMSO-$d_6$) 7.98 (s, 3H, H2), 7.44 (m, 3H, H1), 7.17 (m, 3H, H4), 7.15 (d, 3H, H7), 7.14 (m, 3H, H5 or H6), 7.12 (m, 3H, H6 or H5), 3.40 (m, 12H, Ha and Hb); MS (M+1)$^+ = 576$ for C$_{33}$H$_{33}$N$_7$O$_3$.

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*Sample availability:* Not available.

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