One Step Synthesis of Dihydropyrrolo[3,2-*e*]indoles from 1,4-Cyclohexanedione

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Condensation of phenylhydrazones **1a-c** with 1,4-cyclohexanedione in the presence of zinc dust, sodium acetate and acetic acid gave the 4,5-dihydropyrrolo[3,2-*e*]indoles **7a-c**. Oxidation of **7a** with DDQ afforded the fully aromatic pyrroloindole **16**.

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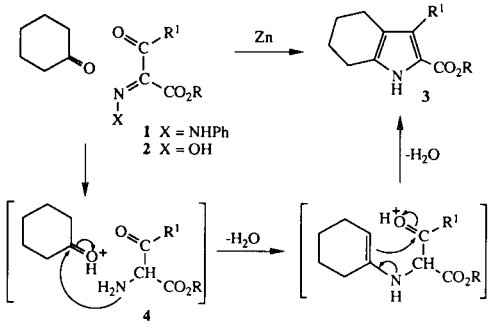
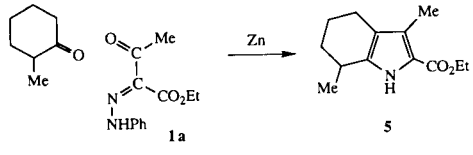
Pyrroles with *b*-annelated carbocyclic rings are valuable intermediates in the synthesis of geochemically significant porphyrins [1-12]. These pyrrolic intermediates are easily prepared from the corresponding cyclic ketones [1-5,7,12-14]. For instance, phenylhydrazones **1** [1,3,14], or oximes **2**, condense with cyclohexanone in the presence of zinc dust and buffered acetic acid to give 4,5,6,7-tetrahydroindoles **3** (Scheme 1) in good yields [1,3,12-14]. Zinc mediated reduction of **1** or **2** leads to the formation of the aminoketones **4** (Scheme 1) and subsequent condensation and cyclization leads to the pyrrolic products. This chemistry is reasonably general and 2-methylcyclohexanone was also found to condense with phenylhydrazone **1a** to afford the 7-methyltetrahydroindole **5** (Scheme 2).

SCHEME 1



SCHEME 2



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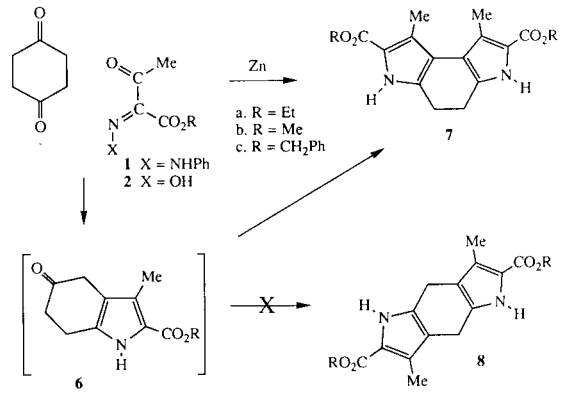
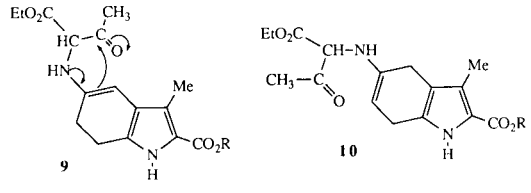
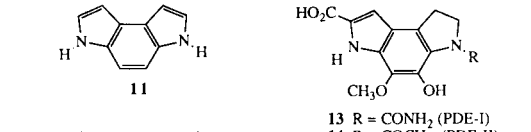
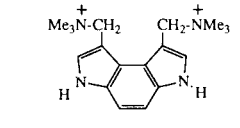
In relation to our studies in the geoporphyrin area, we were interested in adapting this chemistry to the synthesis of 5-oxotetrahydroindole **6** (Scheme 3). However, condensation of 1,4-cyclohexanedione with one equivalent of phenylhydrazone **7a** in the presence of zinc dust, sodium acetate and acetic acid gave none of the required product **6a** under any of the conditions investigated. At higher

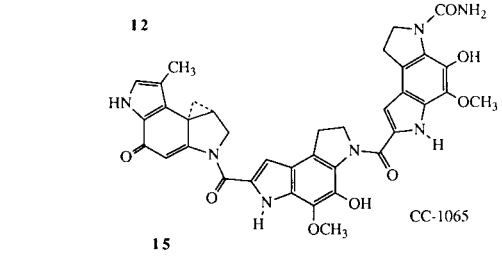
SCHEME 3











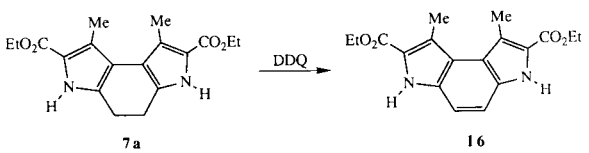
temperatures, a pyrrolic compound was formed, but this proved to not be the anticipated product. The nmr spectroscopy clearly indicated that the dihydropyrrolo[3,2-*e*]-indole **7a** had been formed. The 5-oxotetrahydroindole **6a** may be an intermediate in these reactions but further condensation with a second phenylhydrazone unit presumably take place. It is noteworthy that two dihydropyrroloindole products, **7a** and **8a**, might arise from **6a**. The preference exhibited for **7a** is probably due to the favorability of forming the conjugated enamine **9**, over the non-conjugated isomer **10**, during the later stages of the reaction.

This chemistry provides a remarkably direct route to the pyrrolo[3,2-*e*]indole system. The synthesis and electrophilic substitution reactions of the parent structure **11** has been described by Samsoniya and coworkers [15], and the bis quaternary salt **12** has been reported to have weak curare-like activity [16]. The pyrrolo[3,2-*e*]indole ring system occurs in the phosphodiesterase inhibitors PDE I (**13**) and PDE II (**14**) [17], and three of these units are found in the potent antitumor antibiotic CC-1065 (**15**) [18]. Extensive studies have been reported on the synthesis of ·CC-1065 and its structural analogs [19-24]. Given the intense level of interest on the synthesis of pyrrolo[3,2-*e*]indoles, the chemistry described above (Scheme 3) seemed to justify further study. Hence, the reaction was repeated by condensing two equivalents of phenylhydrazone **1a** with 1,4-cyclohexanedione in the presence of zinc dust, sodium acetate and acetic acid, and dihydropyrrolo[3,2-*e*]indole **7a** was isolated in 29% yield. Under the same conditions, phenylhydrazones **1b** and **1c** [1,3] also condensed with 1,4-cyclohexanedione to give **7b** and **7c**, respectively, in good yields.

It was anticipated that the dihydropyrroloindoles would be easily oxidized to give the correponding fully aromatic structures (Scheme 4). This proved to be the case, since the diethyl ester **7a** was easily dehydrogenated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing chloroform to give pyrrolo[3,2-*e*]indole **16** in excellent yield. The isolation of **16** was aided by the fact that the product was virtually insoluble in chloroform and could be filtered from the reaction mixture.

This study provides a convenient route to pyrrolo[3,2-*e*]-indoles. It may be possible to prepare other tricyclic dipyrroles in a similar fashion using other cyclic ketones, although 1,2-cyclohexanedione gave no useful products under the conditions that we have examined. Nevertheless, this approach could potentially lead to the synthesis of other heterocyclic systems and this possibility is presently under review.

SCHEME 4



EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Ir spectra were run on a Perkin-Elmer 1600 Series FT-IR Spectrometer and nmr spectra were recorded on a Varian Gemini-300 nmr spectrometer. 1,4-Cyclohexanedione and 2-methylcyclohexanone were purchased from Aldrich Chemical Company and were used without further purification. Elemental analyses were obtained from Micro-Analysis, Inc., Wilmington, DE 19808.

Ethyl 4,5,6,7-Tetrahydro-3,7-dimethyl-1*H*-indole-2-carboxylate (**5**).

A mixture of 2-methylcyclohexanone (5.6 g), sodium acetate (5.0 g) and glacial acetic acid (15 ml) was placed in a 250 ml. Erlenmeyer flask and the stirred mixture was heated on an oil bath to 120°. A solution of phenylhydrazone **1a** (11.7 g) in acetic acid (15 ml) was added slowly to the foregoing mixture, whilst simultaneously adding small portions of zinc dust (15.0 g) and maintaining the temperature of the reaction mixture between 120-130°. After the addition was complete, the reaction mixture was stirred for 1 hour, gradually allowing the temperature to drop to approximately 100°. The mixture was cooled to 70° and the solution decanted from the excess zinc into an ice/water slurry (400 ml). The residues were washed several times with hot acetic acid and the resulting solutions decanted into the ice/water mixture. A yellow precipitate formed, which was filtered, washed well with water and recrystallized from ethanol-water to give tetrahydroindole **5** as an off-white solid (2.63 g, 24%), mp 78-80.5°. An analytical sample was obtained as white crystals by a further recrystallization from ethanol-water, mp 82-83°; ir (Nujol mull): ν 3300 (NH str), 1656 (C=O str) cm^{-1}; pmr (deuteriochloroform): δ 1.23 (3H, d, J = 7 Hz, CH-C*H*$_3$), 1.35 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.4 (1H, m), 1.65 (1H, m), 1.92 (2H, m) (5,6-CH_2), 2.22 (3H, s, pyrrole-CH_3), 2.39 (2H, m, 4-CH_2), 2.78 (1H, m, pyrrole-CH), 4.30 (2H, m, OCH_2), 8.6 (1H, br, NH); cmr (deuteriochloroform): δ 10.41, 14.66, 19.94, 21.35, 22.14, 28.61, 32.13, 59.64, 117.39, 119.40, 125.69, 136.97, 162.07.

Anal. Calcd. for $C_{13}H_{19}NO_2$ (221.30): C, 70.56; H, 8.65; N, 6.33. Found: C, 70.56; H, 8.48; N, 6.39.

Dibenzyl 4,5-Dihydro-1,8-dimethyl-3*H*,6*H*-pyrrolo[3,2-*e*]indole-2,7-dicarboxylate (**7c**).

In a 500 ml Erlenmeyer flask, 1,4-cyclohexanedione (1.12 g) and anhydrous sodium acetate (22.00 g) were dissolved in glacial acetic acid (60 ml), and the mixture heated to 115°. Benzyl 2,3-dioxobutanoate-2-phenylhydrazone [3] (5.92 g) was mixed with 20 g of zinc dust, and was added slowly to the stirred mixture keeping the temperature between 120-130°. Once the addition was complete, the solution was stirred at 100° for 30 minutes. The solution was cooled to 80° and poured into 700 ml of ice water with stirring. The residual zinc was washed several times with hot acetic acid and combined with the ice water. The precipitate was filtered and recrystallized from ethanol to give off-white crystals (1.48 g, 35%), mp 218-222°; ir (Nujol mull): 3258 (NH str), 1652 (C=O str) cm^{-1}; pmr (DMSO-d_6): δ 2.51 (6H, s, 2 x pyrrole-CH_3), 2.75 (4H, s, CH_2CH_2), 5.30 (4H, s, 2 x CH_2Ph), 7.30-7.60 (10 H, m, 2 x Ph), 11.58 (2H, s, 2 x NH).

Anal. Calcd. for $C_{28}H_{26}N_2O_4$ (454.52): C, 73.99; H, 5.77; N, 6.16. Found: C, 73.71; H, 5.88; N, 6.06.

Dimethyl 4,5-Dihydro-1,8-dimethyl-3*H*,6*H*-pyrrolo[3,2-*e*]indole-2,7-dicarboxylate (**7b**).

The title compound was prepared from 1,4-cyclohexanedione (1.12 g) and methyl 2,3-dioxobutanoate-2-phenylhydrazone (4.40 g) by the previous procedure. Recrystallization from ethanol gave **7b** as off-white crystals (0.62 g, 20%), mp 278° with decomposition; ir (Nujol mull): 3286 (NH str); 1655 (C=O str) cm^{-1}; pmr (DMSO-d_6): δ 2.47 (6H, s, 2 x pyrrole-CH_3), 2.71 (4H, s, CH_2CH_2), 3.74 (6H, s, 2 x OCH_3), 11.51 (2H, s, 2 x NH).

Anal. Calcd. for $C_{16}H_{18}N_2O_4$ (302.33): C, 63.56; H, 6.00; N, 9.27. Found: C, 63.36; H, 5.85; N, 8.97.

Diethyl 4,5-Dihydro-1,8-dimethyl-3*H*,6*H*-pyrrolo[3,2-*e*]indole-2,7-dicarboxylate (**7a**).

The title compound was prepared from 1,4-cyclohexanedione (2.24 g) and ethyl 2,3-dioxobutanoate-2-phenylhydrazone (9.36 g) by the procedure described above. Recrystallization from ethanol gave the title compound as off-white crystals (1.93 g, 29%), mp 264-266°; ir (Nujol mull): ν 3300 (NH str), 1645 (C=O str) cm^{-1}; pmr (DMSO-d_6): δ 1.30 (6H, t, 2 x -CH_2CH_3), 2.48 (6H, s, 2 x pyrrole-CH_3), 2.72 (4H, s, CH_2CH_2) 4.23 (4H, q, 2 x -OCH_2), 11.44 (2H, s, 2 x NH).

Anal. Calcd. for $C_{18}H_{22}N_2O_4$ (330.38): C, 65.44; H, 6.71; N, 8.48. Found: C, 65.43; H, 6.60; N, 8.25.

Diethyl 1,8-Dimethyl-3*H*,6*H*-pyrrolo[3,2-*e*]indole-2,7-dicarboxylate (**16**).

A stirred mixture of **7a** (0.25 g), DDQ (0.19 g) and chloroform (10 ml) was heated under reflux for 15 minutes. The solution was chilled in ice and the resulting pale yellow precipitate filered off. The product was further purified by heating with ethanol (10 ml), cooling the mixture in an ice bath and refiltering to give a pale pink solid (0.19 g, 76%), mp 269-270°. Recrystallization from acetone gave an analytical sample as a pale pink solid, mp 271.5-272°; ir (Nujol mull): ν 3322 (NH str), 1654 (C=O str) cm^{-1}; pmr (DMSO-d_6-deuteriochloroform): δ 1.35 (6H, t, J = 7 Hz, 2 x -CH_2CH_3), 2.90 (6H, s, 2 x pyrrole-CH_3), 4.32 (4H, q, J = 7 Hz, 2 x -OCH_2), 7.36 (2H, s, CH=CH), 11.64 (2H, s, 2 x NH); cmr (DMSO-d_6-deuteriochloroform): δ 14.03, 14.47, 59.82, 112.30, 118.39, 120.46, 121.41, 132.46, 161.89.

Anal. Calcd. for $C_{18}H_{20}N_2O_4$ (328.37): C, 65.84; H, 6.14; N, 8.53. Found: C, 65.85; H, 6.18; N, 8.53.

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