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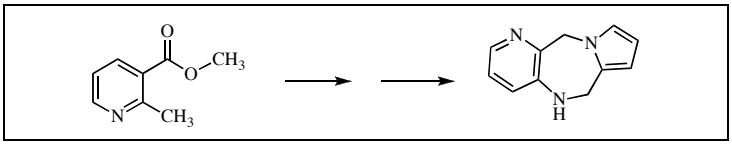

A novel pyrrolopyridodiazepine ring system was synthesized from methyl 2-methyl nicotinate.

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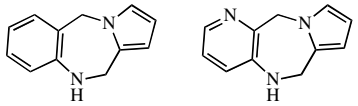
## INTRODUCTION

The pyrrolobenzodiazepine ring system (**1**) is a familiar moiety in pharmacological agents and is well known in the literature [2,3]. In an attempt to produce more water-soluble drug candidates, the first pyridine analog of this ring system was synthesized (**2**) [4].



**1** **2**

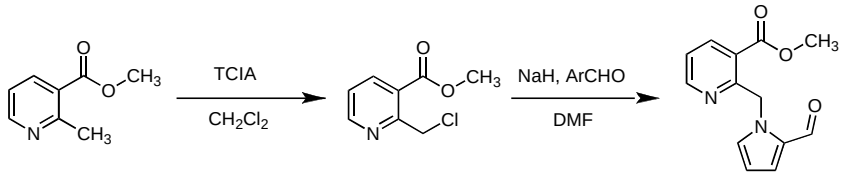
The synthesis begins with commercially available methyl 2-methylnicotinate, which was chlorinated with trichloroisocyanuric acid in dichloromethane in good yield to give methyl 2-(chloromethyl)nicotinate (**3**). Compound **3** was then treated with the sodium salt of pyrrole 2-carboxaldehyde in DMF to give methyl 2-[(2-formyl-1*H*-pyrrol-1-yl)methyl]nicotinate (**4**) [5]. Intermediate **4** was then hydrolyzed to the sodium salt and reacted with diphenylphosphoryl azide in benzene-benzyl alcohol to give benzyl 2-[(2-formyl-1*H*-pyrrol-1-yl)-methyl]pyridin-3-ylcarbamate (**5**) [6].

In the final step **5** was hydrogenated over palladium on carbon in the presence of acetic acid and magnesium sulfate to give the title compound **2**. The acetic acid and magnesium sulfate facilitate the formation of the intermediate imine.

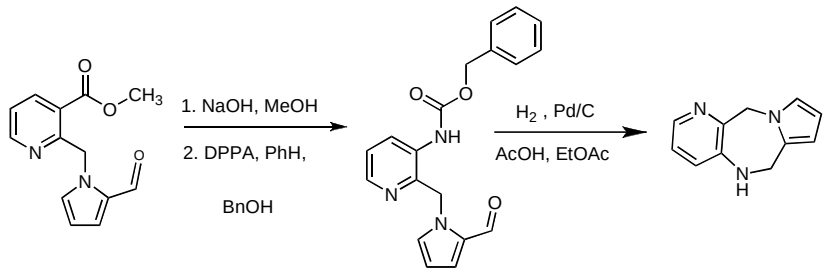
## EXPERIMENTAL

**General Methods**: $^1$H spectra were obtained in $CDCl_3$ using TMS as internal standard. All reagents and solvents were used as obtained commercially. Chromatography was performed using 230-400 mesh silica gel and HPLC grade solvents. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. The TLC eluent for all reactions was 2/1 hexane-ethyl acetate using silica gel plates.

**Preparation of Methyl 2-(chloromethyl)nicotinate (3).** A solution of methyl 2-methylnicotinate (20.0 g, 0.132 mol) and trichloroisocyanuric acid (46.0 g, 0.198 mol) in dichloromethane (100 mL) was stirred at room temperature for 16 hours. The reaction was then washed with 2 X 50 mL of saturated aqueous




**3** **4**




**5**

sodium carbonate, 25 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to provide 3 as a yellow liquid (11.2 g) which was used as such in the next step. $^1$H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 5.10 (s, 2H), 7.35 (dd, 1H), 8.3 (d, 1H), 8.75 (d, 1H).

**Conversion of 3 to Methyl 2-[(2-formyl-1H-pyrrol-1-yl)-methyl]nicotinate (4).** To a suspension of sodium hydride (50 % in oil, 5.8 g, .12 mol) in dry DMF (25 mL) was added slowly under nitrogen a solution of pyrrole 2-carboxaldehyde (10.5 g, 0.11 mol) in 25 mL of DMF and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was then cooled to 5 °C and **3** (11.2 g) was added slowly, the temperature being maintained at or below 20 °C. After the addition was complete, the reaction was stirred at room temperature for 30 minutes, evaporated to dryness, and the residue dissolved in ethyl acetate (250 mL). This solution was washed with water (3 X 25 mL) and dried over anhydrous magnesium sulfate. The solvent was then removed *in vacuo* leaving a crystalline solid (23.4 g) which was purified by chromatography on silica gel eluting with a solvent gradient of 5-50 % ethyl acetate/petroleum ether to provide **4** as a tan crystalline solid (13.75 g), m.p. 91-93 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 4.00 (s, 3H), 6.00 (s, 2H), 6.30 (m, 1H), 7.00 (m, 1H), 7.05 (m, 1H), 7.25 (dd, 1H), 8.25 (d, 1H), 8.60 (d, 1H), 9.45 (s, 1H).

**Conversion of 4 to Benzyl 2-[(2-formyl-1*H*-pyrrol-1-yl)methyl]pyridin-3-ylcarbamate (5).** To a stirred solution of **4** (13.65 g, 55.9 mmol) in methanol (50 mL) was added sodium hydroxide (2.2 g, 55.9 mmol). The reaction mixture was refluxed under nitrogen for 2 hours and the solvent was removed *in vacuo*. The five grams of the sodium salt so obtained were suspended in a mixture of benzyl alcohol (20 mL) and benzene (30 mL). Diphenylphosphoryl azide (6.54 g, 1.2 equiv.) was added and the reaction was slowly heated to reflux. After refluxing for 1 hour, the reaction was cooled and washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to provide **5** as a tan crystalline solid (4.4 g), m.p. 109-111 °C. $^1$H NMR (300 MHz, $CDCl_3$) δ 5.25 (s, 2H), 5.60 (s, 2H), 6.25 (m, 1H), 6.95 (d, 1H), 7.20 (dd, 1H), 7.40 (m, 6H), 8.25 (m, 2H), 9.10 (s, 1H), 9.40 (s, 1H).

**Conversion of 5 to 5,11-Dihydro-6*H*-pyrido[3,2-e]pyrrolo-[1,2-*a*][1,4]diazepine (2).** A stirred mixture of **5** (1.0 g), 10% palladium on carbon (10 mg), anhydrous magnesium sulfate (10 mg) and 5 drops of acetic acid in ethyl acetate (10 mL) was hydrogenated at atmospheric pressure until $H_2$ uptake ceased. The reaction mixture was then filtered through Celite and the solvent removed *in vacuo*. The crude product was a yellow crystalline solid weighing 0.53 g, which was purified by chromatography on silica gel, eluting with a solvent gradient of 5-30 % ethyl acetate/petroleum ether, to provide the title product as a yellow crystalline solid, m.p. 171- 172 °C. Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.59. Found: C, 71.09; H, 6.10; N, 22.95. $^1$H NMR (300 MHz, $CDCl_3$): δ 4.10 (b, 1H), 4.45 (s, 2H), 5.40 (s, 2H), 6.05 (s, 2H), 6.75 (m, 2H), 6.95 (dd, 1H), 7.85 (d, 1H).

## REFERENCES

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