Synthesis of *N*-Acyl-2-pyrrolidinones from the Corresponding N-Acyl-GABA Derivatives

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Dedicated to the memory of Professor Nicholas Alexandrou

In this work, the synthesis of 1-(pyridine-3-carbonyl)pyrrolidin-2-one (**1a**) and 1-(2-propyl-1-pentanoyl)pyrrolidin-2-one (**1b**) by cyclization of the corresponding GABA derivatives, is reported. Two different methods are developed. For the synthesis of **1a**, the parent molecule 4-[(pyridine-3-carbonyl)-amino]butanoic acid (**2a**) is treated first with thionyl chloride and then with triethylamine. The second derivative, **1b**, is produced by an intramolecular dehydration of 4-(2-propylpentanoylamino)butanoic acid (**2b**) using an acid catalyst.

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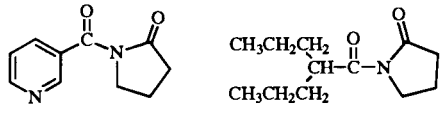
γ-Aminobutyric acid (GABA) has been implicated in several neurologic and psychiatric disorders such as epilepsy, Huntington's disease and Parkinsonism [1]. A number of 1-acyl-2-pyrrolidinone derivatives have been synthesized as possible γ-aminobutyric acid prodrugs and showed to possess anticonvulsant properties [2]. In the present study, two efficient methods for preparing 1-acyl-2-pyrrolidinones are reported. The target compounds were the derivatives **1a-b** (Scheme I). The nicotinoyl moiety of **1a** was chosen because it has been used in candidate prodrugs of γ-aminobutyric acid [3,4] and found to be suitable to confer activity, in some cases [4]. Also, **1b** is a valproic acid derivative. Valproic acid is a well-known anticonvulsant [5]. Therefore, **1b** could act as a mutual prodrug of γ-aminobutyric acid and valproic acid.

Scheme I

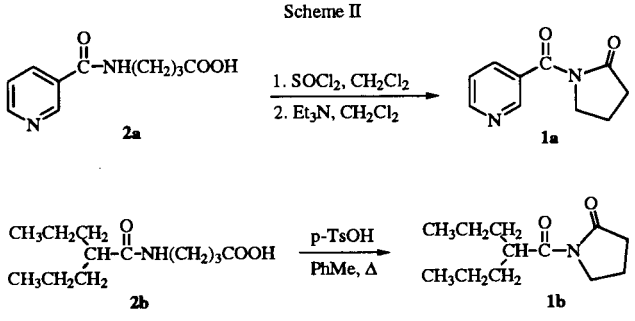


1a **1b**

The initial attempts to synthesize **1a** by reacting 2-pyrrolidinone with nicotinoyl chloride, as reported for the preparation of related compounds [2], led to a complex mixture from which isolating the main product was tedious. Recently, we have reported a high yielding method for the preparation of compounds **2a-b** which involves reaction of γ-aminobutyric acid with the appropriate acyl chloride in the presence of trimethylchlorosilane and triethylamine in dichloromethane [4]. Thus, we sought methodologies for converting these *N*-acyl-γ-aminobutyric acid derivatives to the corresponding *N*-acyl-2-pyrrolidinones (Scheme II).

Compound **1a** was synthesized in good yield by reacting **2a** with thionyl chloride in dichloromethane followed by basification with triethylamine. For the synthesis of **1b**, compound **2b** was cyclized by an intramolecular

Scheme II



2a **1a**

2b **1b**

dehydration in the presence of an acid catalyst (*p*-toluenesulfonic acid), in refluxing toluene using a Dean-Stark apparatus. The same method was also investigated for the synthesis of **1a** but in this case the reaction was very slow, probably because of the low solubility of the formed *p*-toluenesulfonate salt of **2a** in toluene. Finally, we observed that replacing toluene with benzene during the preparation of **1b**, which lowers the reaction temperature, results in a substantial lengthening of the reaction time and a decrease in the yield of the product.

EXPERIMENTAL

Melting points are uncorrected and were determined in open glass capillaries using a Mel-Temp II apparatus. Infrared spectra were recorded with a Schimadzu FTIR-8101 M spectrophotometer, nuclear magnetic resonance spectra with a Bruker AW-80 spectrometer with internal tetramethylsilane reference. Elemental analyses were performed on a Perkin-Elmer 2400 CHN analyzer. Flash chromatography was carried out using Merck 9385 silica gel. Petroleum ether refers to the fraction of bp 40-60°.

1-(Pyridine-3-carbonyl)pyrrolidin-2-one (**1a**).

To a stirred suspension of **2a** [4] (5.00 g, 24 mmoles) in dichloromethane (300 ml) thionyl chloride (2.2 ml, 30 mmoles) was added and the mixture was stirred at room temperature overnight. Then, the volatile material was evaporated under reduced pressure and the white, crystalline residue was dissolved in 200 ml of dichloromethane. After addition of triethylamine

(20 ml, 143 mmoles), a precipitate was formed and the supernatant turned brownish-red. After evaporation of the volatile material, the product was isolated, as white light crystalls, by flash column chromatography using petroleum ether/ethyl acetate (1:2) as the eluent (yield 3.6 g, 79%), mp 104-105° (dichloromethane/petroleum ether); ir (nujol): 1739 cm^{-1} (C=O, pyrrolidinone), 1667 cm^{-1} (pyr-C=O); ^1H nmr (deuteriochloroform): δ 8.6-8.9 (m, 2H, pyridine H-2, H-4), 7.7-8.0 (m, 1H, pyridine H-6), 7.2-7.4 (m, 1H, pyridine H-5), 3.8-4.1 (m, 2H, pyrrolidinone H-5), 2.4-2.7 (m, 2H, pyrrolidinone H-3), 1.9-2.4 (m, 2H, pyrrolidinone H-4).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C 63.15, H 5.30, N 14.73. Found: C 62.91, H 5.33, N 14.49.

1-(2-Propyl-1-pentanoyl)pyrrolidin-2-one (**1b**).

A mixture of *p*-toluenesulfonic acid (0.34 g, 1.8 mmoles) and **2b** [4] (4.59 g, 20 mmoles) in 300 ml of toluene was refluxed, connected to a Dean-Stark apparatus, for 24 hours. The solvent was evaporated under reduced pressure and the residue was dissolved in 150 ml of chloroform. This solution was basified with triethylamine and washed successively with 2 x 50 ml of water, 2 x 30 ml of 10% sodium bicarbonate solution, 30 ml of water and 40 ml of saturated sodium chloride solution. After drying (anhydrous sodium sulphate), it was evaporated under reduced pressure and the product was isolated, as a non-viscous greenish liquid, by flash column chromatography using petroleum ether/ethyl acetate (1:1) as the eluent (yield 3.57 g, 84%); ir (neat): 1739 cm^{-1} (C=O, pyrrolidinone), 1692 cm^{-1} (CHC=O); ^1H nmr (deuteriochloroform): δ 3.6-3.8 (t, 2H, pyrrolidinone H-5), 2.4-2.7 (t, 2H, pyrrolidinone H-3), 0.7-2.2 (m, 17H, pyrrolidinone H-4, CH_2, CH_3, CH).

Anal. Calcd. for $C_{12}H_{21}NO_2$: C 68.21, H 10.02, N 6.63. Found: C 68.50, H 9.67, N 6.50.

REFERENCES AND NOTES

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