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Conversion of Pregabalin to 4-Isobutylpyrrolidone-2

Amanda M. Drachnik, [a] Harshita Kumari,* [b] Collin M. Mayhan,[a] Drew A. Fowler,[a] Wei G. Wycoff,[a] Charles L. Barnes, [a] John E. Adams,[a] Carol A. Deakyne,* [a] and Jerry L. Atwood*[a]

Dedication ((optional))

Abstract: Solid state studies of *C*-butyl-resorcin[4]arene with pregabalin (Lyrica, Nervalin) in nitrobenzene yielded a cocrystal of *C*-butyl-resorcin[4]arene with 4-isobutylpyrrolidone-2. A combined experimental and quantum chemical investigation was implemented to further our understanding of the factors affecting the conversion process.

1. Introduction

The inhibitory neurotransmitter γ-aminobutyrate (GABA) has received increased recognition as a potential pharmacophore among pharmaceutical researchers.[1-5] GABA, composed of an amino and a carboxylic acid moiety, has a framework analogous to that of an amino acid. Too low a concentration of GABA within the human body is known to have adverse effects related to epileptic seizures. Within the past twenty-five years, two pharmaceuticals with the GABA functionality, gabapentin (1993) and pregabalin (2004), have been marketed successfully as anticonvulsants, among other usages.[2,4-12]

In their patented work on the synthesis of various 2-pyrrolidones, Meyer and Geurts may have inadvertently achieved the first synthesis of pregabalin.[13] Previous work had shown that an amino acid product is a byproduct of 2-pyrrolidone synthesis.[14] In the conversion of 1,2-dicyano-4-methylpentane to 4-isobutylpyrrolidone-2 carried out by Meyer and Geurts, the amino acid byproduct may have been pregabalin.[13]

The effectiveness of an active pharmaceutical ingredient (API) may be dependent on the characteristics of the polymorphic crystalline form(s) isolated. One approach to modification of the pharmaceutical properties of an API is through cocrystallization. We have previously reported formation of pharmaceutical cocrystals of gabapentin with both pyrogallol[4]arenes, PgCn, and resorcin[4]arenes, RsCn.[15,16] In this notation, Cn refers to the length of the alkyl chain off the bridging carbon. Herein, we describe a follow-up investigation of cocrystallization of pregabalin with C-butyl-resorcin[4]arene, RsC_4, in which an unexpected conversion of pregabalin to 4-isobutylpyrrolidone-2 occurred.

In the 1970s the interest was in closing the ring to make 2-pyrrolidones;[13,14,17] in the 1990s the spectacular pharmaceutical properties of the linear molecule pregabalin were discovered.[18-21] We have now closed the loop by showing conditions under which the amino acid product is converted to the 2-pyrrolidone.

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2. Experimental Section

All experiments were carried out using commercially available reagents and solvents with no further purification. RsC_4 was synthesized through acid catalysis of resorcinol and valeraldehyde, as described in the literature.[22]

2.1. X-ray Diffraction Analysis

Equimolar solutions of pregabalin and RsC4 in nitrobenzene (NB) were mixed to give a total solute concentration of 0.3 M. The solution was then heated to 150○C for three hours and allowed to slowly cool to RT. Crystals suitable for single-crystal X-ray diffraction were obtained overnight. Data was collected on a Bruker Apex II CCD diffractometer using a CuK□ radiation source (1.5418 Å) at 100 K. CCDC No: 1500198

2.2. NMR Analysis

All solutions were prepared at 0.2 M using deuterated NB, H2O, MeOH, or DMSO. Pregabalin dissolved readily in H2O and MeOH; however, in DMSO and NB additional measures were needed. To dissolve the pharmaceutical in DMSO, even at low concentration, the solution must be sonicated with gentle heating. Complete dissolution in DMSO or NB was achieved when the solution was heated to 150○C, as in the procedural steps taken for the crystallization. The solutions were studied via the 1H, 13C, COSY, NOSEY, HMQC, and HMBC NMR techniques.The spectra were obtained on Bruker 300, 500, and 600 MHz instruments.

2.3. Quantum Chemical Analysis

Electronic structure calculations were performed with the Gaussian 09 suite of programs,23 and the results were viewed with GaussView5.24 Geometries were fully optimized with the keywords int = ultrafine and opt = tight. Minimization and