

Short Note

4-Hydroxy-1-methyl-7-(propan-2-yl)-4-azatricyclo [5.2.2.0^{2,6}]undec-8-ene-3,5-dione

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Abstract: 1-Methyl-7-(propan-2-yl)-4-oxatricyclo[$5.2.2.0^{2.6}$]undec-8-ene-3,5-dione (1) as starting material and hydroxylamine were used for the preparation of the title compound 4-hydroxy-1-methyl-7-(propan-2-yl)-4-azatricyclo[$5.2.2.0^{2.6}$]undec-8-ene-3,5-dione (2). This product was characterized by ¹H-NMR, ¹³C-NMR, MS and elemental analysis.

Keywords: 4-oxatricyclo[5.2.2.0^{2,6}]undec-8-ene; 4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene; maleimides

1. Introduction

The extensively studied class of cyclic imides is known for a wide spectrum of biological activities. Less examined, but also valuable for their activities are *N*-hydroxy analogues. They were synthesized as potential β -adrenolytic [1], anxiolytic [2], anti-inflammatory and analgesic agents [3]. Some of the reported derivatives possess metal-chelating abilities, and a number of these compounds inhibits the growth of microorganisms [4]. Additionally, cyclic imides were tested *in vitro* against various bacteria including Gram-positive *cocci*, Gram-negtive rods and fungi species (e.g., *Candida*) [5,6]. The large group of 4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene was tested for their affinity to 5-HT_{1A} and 5-HT_{2A} receptors [7]. The most popular method to produce cyclic imides and *N*-hydroxy analogues is the well-known Diels-Alder reaction [8], but this work describes another conventional method for the synthesis of 4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene derivatives [9–11]. This one is reserved for *N*-hydroxy derivatives. The aim of our present work was to prepare 4-hydroxy-1-methyl-7-(propan-2-yl)-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (**2**), starting from the corresponding anhydride

1-methyl-7-(propan-2-yl)-4-oxatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (**1**) using an aqueous solution of hydroxylamine (Scheme 1).

Scheme 1. Synthesis of 4-hydroxy-1-methyl-7-(propan-2-yl)-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione.



2. Experimental

2.1. General

The melting point was determined in an open capillary and is uncorrected. The NMR spectra were recorded on a Bruker AVANCE DMX400 spectrometer, operating at 400 MHz (¹H-NMR) and 100 MHz (¹³C-NMR). The chemical shift values are expressed in ppm relative to TMS as an internal standard. Mass spectra (ESI) measurements were carried out on a Waters ZQ Micro-mass instrument with a quadrupol mass analyzer. The spectra were recorded in positive ion mode at a declustering potential of 40–60 V. The sample was previously separated on a UPLC column (C18) using a Waters UPLC ACQUITYTM system connected with a DPA detector. Flash chromatography was performed on Merck silica gel 60 (200–400 mesh) using a chloroform/methanol (19:1 vol) mixture as eluent. Analytical TLC was carried out on silica gel F_{254} (Merck) plates (0.25 mm thickness).

2.2. Synthesis of 4-Hydroxy-1-methyl-7-(propan-2-yl)-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (2)

A mixture of the anhydride **1** (0.234 g, 1 mmol), K_2CO_3 (0.20 g, 1.4 mmol), $NH_2OH \cdot HCl$ (0.20 g, 2.9 mmol) and H_2O (5 mL) was refluxed for 5 h. The precipitate was filtered, washed with water, dried and purified by column chromatography (silica gel) to obtain a white solid.

Yield: 90%.

m.p.: 139–140 °C.

¹H-NMR (400 MHz, CDCl₃) δ (ppm): 5.97 (d, 1H, CH=, J = 8.4 Hz); 5.89 (d, 1H, CH=, J = 8.4 Hz); 4.18 (br s, 1H, OH); 2.93 (d, 1H, CH-C=O, J = 7.6 Hz); 2.58–2.51 (m, 2H, CH-C=O, CH=); 1.50–1.40 (m, 2H, CH₂); 1.46 (s, 3H, CH₃); 1.36–1.24 (m, 2H, CH₂); 1.08 (d, 3H, CH₃, J = 6.8 Hz); 0.98 (d, 3H, CH₃, J = 6.8 Hz).

¹³C-NMR (100 MHz, CDCl₃) δ (ppm):174.3, 172.5, 136.3, 48.9, 47.7, 45.1, 43.7, 36.9, 34.2, 29.7, 22.6, 18.4, 16.9.

ESI MS: $m/z = 272.4 [M+Na]^+ (100\%)$.

Elemental analysis: Calculated for C₁₄H₁₉NO₃ (249.306): C, 67.45%, H, 7.68%, N, 5.62%. Found: C, 67.48%, H, 7.50%, N, 5.72%.

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