

Short Note

2-[3-(Aziridin-1-yl)-2-hydroxypropyl]-5,5-dimethyl-2,5-dihydro-4H-benzo[e]isoindol-4-one (Cytotoxic Oxonaphthalene-Pyrroles, Part III)

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Abstract: An hydroxypropyl-aziridine-containing side chain is attached to an oxonaphthalene-annelated pyrrole in expectation of DNA alkylating properties. The cytotoxicity is evaluated against two cell lines, KB-31 and KB-8511, respectively.

Keywords: pyrrole; DNA-alkylation; anticancer

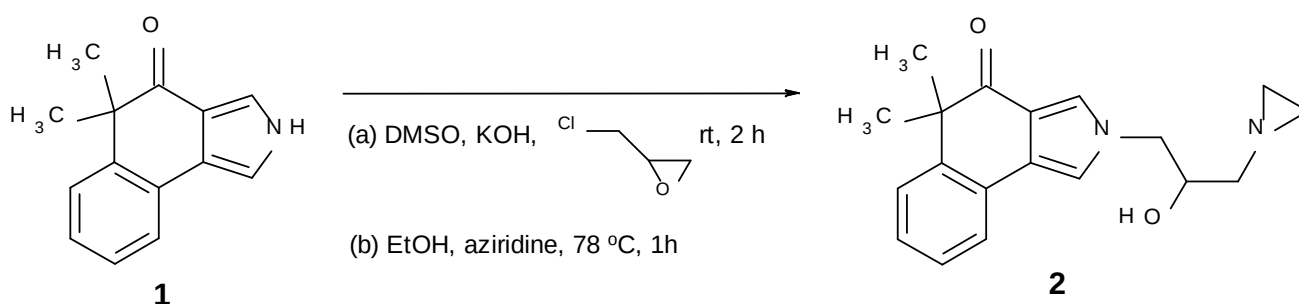
Introduction

Chlorambucil and melphalan are chemotherapy drugs belonging to the class of nitrogen mustard alkylating agents. Both compounds are believed to exert their antitumor effects by cross-linking DNA via aziridinium cation intermediates arising from the bis(2-chloroethyl)amine moiety [1]. Besides that there are anticancer agents with the aziridine moiety, such as TEPA, thio-TEPA and triethylenemelamine with a 1,3,5-triazine nucleus. In continuation of our department's previous studies in the field of antitumor agents [2–10], we are reporting in this paper the synthesis of the oxonaphthalene-annelated pyrrole **2** with an attached side chain containing an aziridine group. The rationale is that the three-membered aziridine ring is structurally analogous to the immonium-intermediate formed from the nitrogen mustards. The aziridine moiety is not charged and the reactivity results from the strain on the three-member ring structure [11]. Recent studies with aziridine substituted quinones showed promising results against breast cancer tumor cells [12,13]. The cytotoxic activity of **2** was evaluated.

Results and Discussion

Reaction of **1** [14] with 2-(chloromethyl)oxirane with KOH in DMSO [15] afforded the *N*-alkylated product. The following reaction with aziridine [16] gave the target compound **2** (Scheme 1). The biological activity of **2** was tested against two cancer cell lines, KB-31 and KB-8511, respectively. KB-31 is a drug sensitive human epidermoid cell line, whereas KB-8511 is a multi-drug resistant subline, typically overexpressing P-glycoprotein. The $IC_{50}[\mu M]$ values of **2** are 9.362 (KB-31) and 6.452 (KB-8511), respectively (3 days incubation time; staining with 0.05% methylene blue; optical density measured at 665 nm; for further experimental details, see [17,18]).

Scheme 1. Synthesis of target compound **2**.



Experimental

2-[3-(Aziridin-1-yl)-2-hydroxypropyl]-5,5-dimethyl-2,5-dihydro-4H-benzo[e]isoindol-4-one (**2**)

(a) To a solution of **1** [12] (0.5 g, 2.37 mmol) in 4.7 mL of dry DMSO were added at room temperature dropwise under argon 1.5 mL (18.96 mmol) of 2-(chloromethyl)oxirane. Subsequently 0.265 g (4.74 mmol) of KOH were added and stirring was continued for 2 h at room temperature. The reaction mixture was diluted with 9.5 mL of H₂O, extracted with CH₂Cl₂, dried (Na₂SO₄), concentrated *in vacuo* and isolated after column chromatography (silica gel, ethyl acetate/light petroleum 70/30). Yield 284 mg (45%) of a colorless oil.

(b) The resulting product (284 mg) was dissolved in 4.6 mL EtOH (1% TEA) and after the addition of 0.37 mL (7.2 mmol) of aziridine under argon the reaction mixture was refluxed for 1 h. After concentration *in vacuo* the resulting crude product was purified by column chromatography (silica gel, ethyl acetate/ethanol 95/5) to afford 104 mg (32%) of colorless crystals of **2**. m.p.: 118–119 °C (ethyl acetate/ethanol). IR (KBr): 3397, 1650, 1526, 1208, 1159 cm⁻¹. MS (EI, 70 eV) m/z : 310 (M^+ , 5%), 268 ($M^+ - 42$, 0.5), 101 (20), 59 (100), 58 (42), 57 (33), 56 (28), 55 (26), 45 (26). ¹H-NMR (CDCl₃, 200 MHz) δ = 7.56 (m, 1H, 9-H), 7.43 (m, 1H, 6-H), 7.40 (d, J = 2.2 Hz, 1H, 3-H), 7.22 (m, 2H, 7-H, 8-H), 7.10 (d, J = 2.2 Hz, 1H, 1-H), 4.14–3.99 (m, 3H, 1'-H, 2'-H), 3.8 (s_{br}, 1H, OH), 2.41 (dd, J = 7.5 and 12 Hz, 1H, 3'-H), 2.12 (dd, J = 3.8 and 12 Hz, 1H, 3'-H), 1.82–1.73 (m, 2H, aziridine-CH₂), 1.50 (s, 6H, (CH₃)₂), 1.29–1.16 (m, 2H, aziridine-CH₂). ¹³C-NMR (CDCl₃, 50 MHz) δ = 198.6 (C-4), 144.1 (C-5a), 127.1 (C-6), 126.8 (C-9a), 126.6 (C-7), 126.2 (C-8), 125.0 (C-9b), 124.1 (C-3), 122.7 (C-9), 118.3 (C-3a), 116.1 (C-1), 70.3 (C-2'), 64.0 (C-3'), 54.3 (C-1'), 47.6 (C-5), 28.2/28.1 ((CH₃)₂), 27.6/27.2 (2× aziridine-CH₂). HRMS calc. for C₁₉H₂₂N₂O₂: 310.94 Calc.: 310.1680. Found: 310.1680.

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