

Short Note

1-[4-[Bis(2-chloroethyl)amino]benzyl]-5,5-dimethyl-2,5-dihydro-4H-benzo[e]isoindol-4-one (Cytotoxic Oxonaphthalene-pyrroles, Part II)

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Received: 4 December 2009 / Accepted: 26 January 2010 / Published: 29 January 2010

Abstract: A bis(chloroethyl)amine-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.

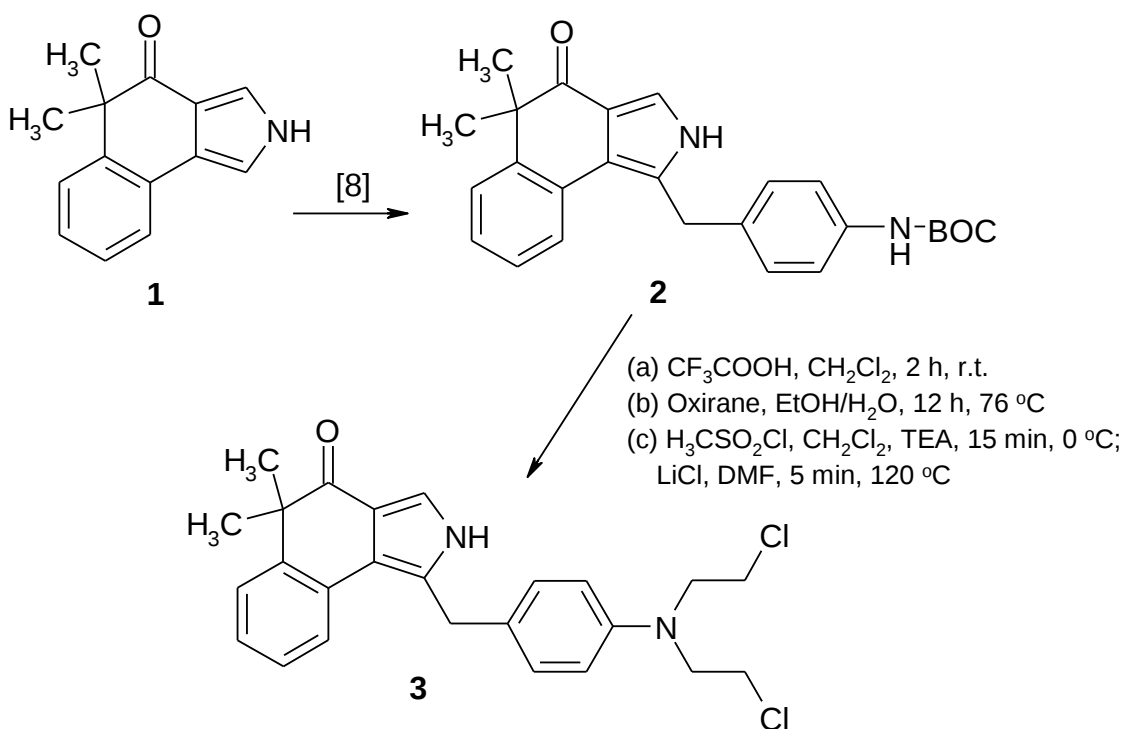
Keywords: pyrrole; DNA-alkylation; anticancer

Introduction

Nitrogen mustards were the first clinically effective cancer therapeutic agents. Chlorambucil and melphalan are two of numerous aromatic derivatives of compounds with a nitrogen mustard moiety that have been synthesized. They have been clinical agents for many years and remain in common use at the present time. The cytotoxic effects are based on the highly active aziridinium cation intermediates arising from the bis(2-chloroethyl)amine moiety [1]. In continuation of our department's previous studies in the field of antitumor agents [2–9], we are reporting in this paper the synthesis of the oxonaphthalene-annelated pyrrole **3** with an attached side chain containing a bis(2-chloroethyl)-amine group. The cytotoxic activity of **3** was evaluated.

Results and Discussion

As previously published, *N*-alkylation of **1** [10,11] with BOC-protected 4-aminobenzyl bromide with NaH in THF selectively afforded **2** [8], the following deprotection with trifluoroacetic acid [12] furnished the amine which was treated with ethylene oxide [4]. The resulting diol was converted *via* its mesylate and subsequent reaction with LiCl [13] into the target compound **3**. The biological activity of **3** 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 over-expressing P-glycoprotein. The IC₅₀[μM] values of **3** are >2.815 (KB-31) and 2.496 (KB-8511), respectively (for experimental details, see [14,15]).



Experimental

1-[4-[Bis(2-chloroethyl)amino]benzyl]-5,5-dimethyl-2,5-dihydro-4H-benzo[e]isoindol-4-one (**3**)

(a) To a solution of **2** [8] (0.7 g, 1.68 mmol) in 7.7 mL of dry CH₂Cl₂ were added dropwise under argon 1.53 mL (19.85 mmol) of trifluoroacetic acid. After stirring for 2 h at room temperature, the reaction mixture was concentrated under vacuum and the residue was dissolved in ethyl acetate. The organic phase was washed with aqueous NaHCO₃-solution and brine, dried (Na₂SO₄) and concentrated.

(b) The resulting crude product was purified by column chromatography (aluminium oxide, light petroleum/ethyl acetate, 60/40) to afford a solid residue which was dissolved in 25 mL of EtOH/H₂O (3/1). 0.55 mL (0.61 g, 1.40 mmol) of oxirane were added to the reaction mixture at 0 °C. After heating for 12 h under reflux, the reaction mixture was concentrated under vacuum and the residue was dissolved in ethyl acetate. The organic phase was dried (Na₂SO₄) and concentrated. The resulting crude product was used for the next reaction step without further purification.

(c) To a solution of the obtained crude product in 4.8 mL of dry CH_2Cl_2 and 0.4 mL of triethylamine were added dropwise under argon 0.20 mL (2.55 mmol) of methanesulfonyl chloride. After stirring for 15 min, the reaction mixture was washed with H_2O , dried (Na_2SO_4) and concentrated under vacuum. The residue was dissolved in 4.5 mL of DMF and, after addition of 0.8 g LiCl (18.90 mmol; dried over P_2O_5 at 100 °C for 12 h), the reaction mixture was heated for 5 min at 120 °C. The cooled reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with H_2O , dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (silica gel, light petroleum/ethyl acetate 60/40 + 0.3% TEA) to afford 298 mg (40%) of **3**. M.p. 67–69 °C (light petroleum/ethyl acetate). IR (KBr): 3236, 1644, 1519, 1353, 1179 cm^{-1} . MS (EI, 70 eV) m/z : 442 ($\text{M}^+ + 2$, 14%), 440 (M^+ , 22), 391 (100), 350 (46), 167 (46), 118 (44), 106 (42). ^1H NMR (CDCl_3 , 200 MHz) δ = 9.12 (s_{br}, 1H, NH), 7.66 (m, 1H, 9-H), 7.47 (m, 1H, 6-H), 7.34 (d, J = 3.0 Hz, 1H, 3-H), 7.22 (m, 2H, 7-H, 8-H), 7.12 (d, J = 8.5 Hz, 2H, 2'-H, 6'-H), 6.62 (d, J = 8.5 Hz, 2H, 3'-H, 5'-H), 4.26 (s, 2H, C-1- CH_2), 3.68 (m, 4H, 2 $\times$ CH_2N), 3.59 (m, 4H, 2 $\times$ CH_2Cl), 1.51 (s, 6H, $(\text{CH}_3)_2$). ^{13}C NMR (CDCl_3 , 50 MHz) δ = 199.8 (C-4), 144.9 (C-4'), 144.1 (C-5a), 130.0 (C-2', C-6'), 128.4/126.7/125.9 (C-1', C-9a, C-9b), 127.1 (C-6), 126.3 (C-7), 125.9 (C-8), 123.5 (C-9), 119.5/118.7 (C-1, C-3a), 118.98 (C-3), 112.4 (C-3', C-5'), 53.4 (2 $\times$ CH_2N), 47.8 (C-5), 40.4 (2 $\times$ CH_2Cl), 33.0 (CH_2 -C-1), 28.2 ($(\text{CH}_3)_2$). HRMS calc. for $\text{C}_{25}\text{H}_{26}\text{N}_2\text{OCl}_2$: 440.1422. Found: 440.1417.

Acknowledgement

We are indepted to Novartis AG (Vienna, Austria) for the evaluation of the cytotoxic activity.

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