

Short Note

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

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Abstract: A bis(chloroethyl)amine containing side chain is attached to an oxonaphthalene-annelated pyrrol in expectation of DNA alkylating properties. The cytotoxicity is evaluated against two cell lines, KB-31 and KB-8511, respectively.

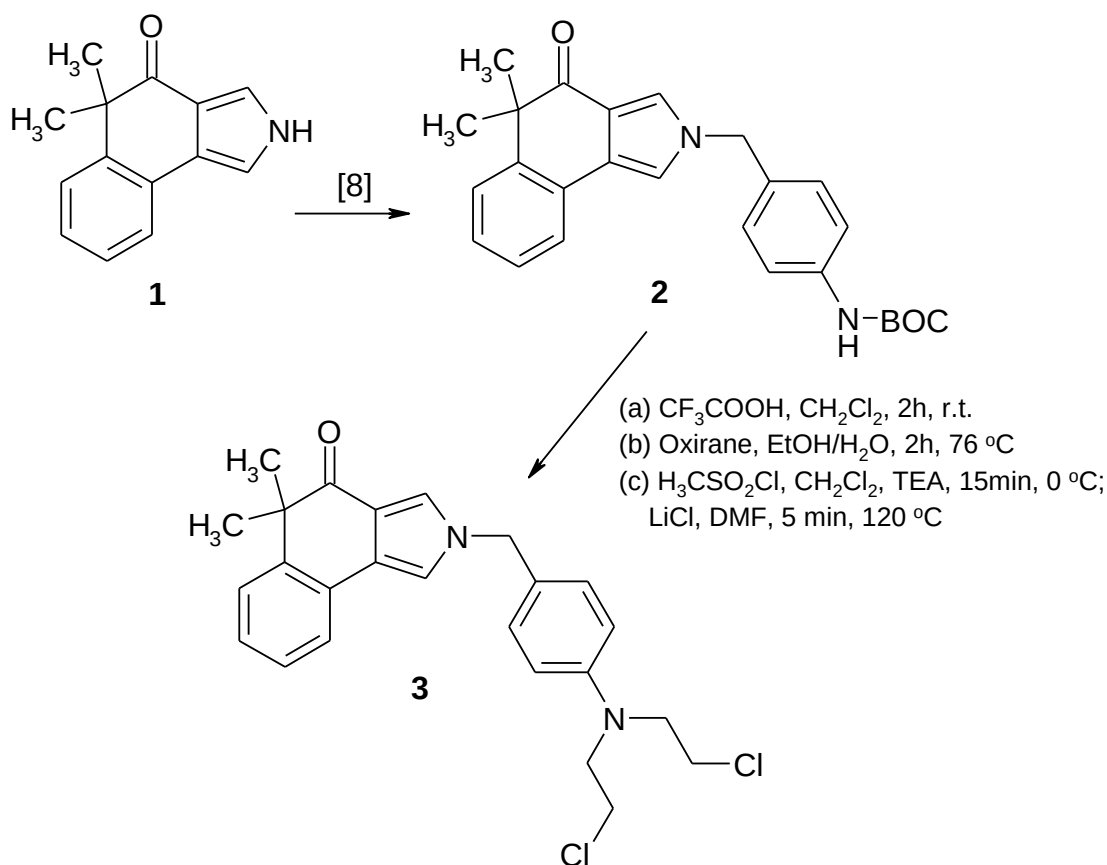
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1. Introduction

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 a clinical agent for many years and remains 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 [2–8] 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.

2. Results and Discussion

As previously published the N-alkylation of **1** [9,10] with BOC-protected 4-aminobenzyl bromide with NaH in DMF afforded selectively **2** [8], following deprotection with trifluoroacetic acid [11] furnished the amine which was treated with ethylene oxide [4]. The resulting diol was converted via its mesylate and subsequent reaction with LiCl [12] to 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 overexpressing P-glycoprotein. The $IC_{50}[\mu M]$ values of **3** are >10.00 (KB-31) and 7.138 (KB-8511), respectively [for experimental details see[13,14)].



3. Experimental

3.1. 2-[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] (1.07 g, 2.56 mmol) in 11.7 mL of dry CH_2Cl_2 were added dropwise under argon 2.3 mL (30.25 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 $NaHCO_3$ -solution and brine, dried (Na_2SO_4) 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/ H_2O (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 (Na_2SO_4) 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 5.5 mL of dry CH_2Cl_2 and 0.5 mL of triethylamine were added dropwise under argon 0.23 mL (2.90 mmol) of methanesulfonic acid 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 5.0 mL DMF and after addition of 0.9 g LiCl (21.5 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 112 mg (11%) of **3**. M.p. 50–52 °C (light petroleum/ethyl acetate). IR (KBr): 1654, 1615, 1523, 1353, 1148. MS (EI, 70 eV) m/z : 442 ($\text{M}^+ + 2$, 2), 440 (M^+ , 3), 234 (11), 232 (66), 231 (14), 230 (100), 118 (58), 63 (9). ^1H NMR (CDCl_3 , 200 MHz) = 7.53 (m, 1H, 9-H), 7.43 (m, 1H, 6-H), 7.38 (d, $J = 2.0$ Hz, 1H, 3-H), 7.21 (m, 2H, 7-H, 8-H), 7.14 (d, $J = 8.8$ Hz, 2H, $2_{\text{phenyl-H}}$, $6_{\text{phenyl-H}}$), 7.0 (d, $J = 2.0$ Hz, 1H, 1-H), 6.65 (d, $J = 8.8$ Hz, 2H, $3_{\text{phenyl-H}}$, $5_{\text{phenyl-H}}$), 5.0 (s, 2H, NCH_2), 3.71 (m, 4H, $2 \times \text{CH}_2\text{CH}_2\text{Cl}$), 3.64 (m, 4H, $2 \times \text{CH}_2\text{CH}_2\text{Cl}$), 1.51 (s, 6H, $(\text{CH}_3)_2$). ^{13}C NMR (CDCl_3 , 50 MHz) = 198.4 (C-4), 146.1 ($\text{C}_{\text{phenyl-4}}$), 144.1 (C-5a), 129.5 ($\text{C}_{\text{phenyl-2}}$, $\text{C}_{\text{phenyl-6}}$), 127.0 (C-6), 126.9 (C-9a), 126.6 (C-7), 126.1 (C-8), 125.3/124.5 ($\text{C}_{\text{phenyl-1}}$, C-9b), 123.3 (C-3), 122.6 (C-9), 118.3 (C-3a), 115.0 (C-1), 112.1 ($\text{C}_{\text{phenyl-3}}$, $\text{C}_{\text{phenyl-5}}$), 53.7/53.3 (NCH_2 , $2 \times \text{CH}_2\text{CH}_2\text{Cl}$), 47.6 (C-5), 40.2 ($2 \times \text{CH}_2\text{Cl}$), 28.1 ($(\text{CH}_3)_2$). HRMS calc. for $\text{C}_{25}\text{H}_{26}\text{N}_2\text{OCl}_2$: 440.1422. Found: 440.1425.

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