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Short Note

2-[2-(Aziridin-1-yl)ethyl]-5,5-dimethyl-2,5-dihydro-4*H*-benzo [*e*]isoindol-4-one (Cytotoxic Oxonaphthalene-Pyrroles, Part IV)

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Abstract: An 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

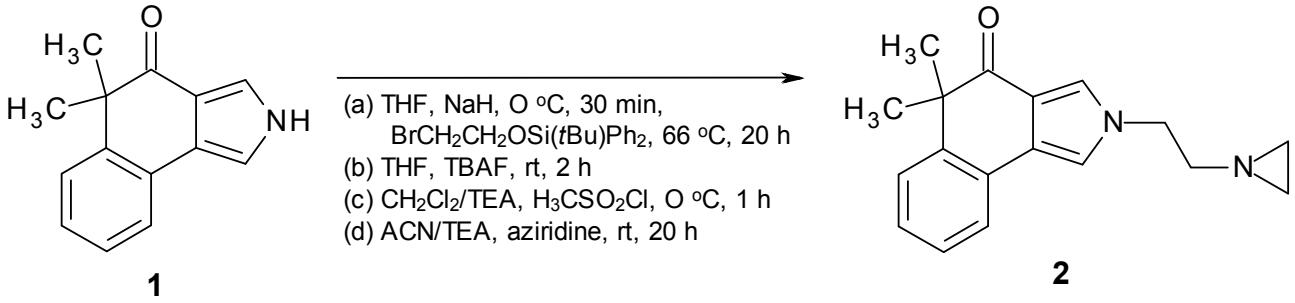
Chlorambucil and melphalan are chemotherapy drugs belonging to the class of nitrogen mustard alkylating agents. Both compounds are believed to exert their antitumor effects by cross-linking DNA via aziridinium cation intermediates arising from the bis(2-chloroethyl)amine moiety [1]. In continuation of 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 ammonium-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 [12–16]. The cytotoxic activity of 2 was evaluated.

Results and Discussion

Reaction of 1 [17] with *t*-BuPh$_2$Si-protected hydroxyethyl bromide [18] with NaH in THF afforded the *N*-alkylated product. The following deprotection with tetrabutylammonium fluoride [19] furnished the alcohol which was treated with methansulfonic chloride [20]. The resulting mesylate was

converted via reaction with aziridine into 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}[μM] values of **2** are >10.000 (KB-31) and 8.680 (KB-8511), respectively (3 days incubation time; staining with 0.05% methylene blue; optical density measured at 665 nm; for further experimental details, see [21,22]).

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



Experimental

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

(a) To a solution of 0.3 g (12.38 mmol) NaH (60% in mineral oil, washed twice with hexane) in 20 mL of dry THF was added dropwise under argon a solution of **1** [8] (2.61 g, 12.38 mmol) in 20 mL of dry THF. After stirring for 0.5 h at 0 °C at room temperature, a solution of 6.74 g (18.58 mmol) of 2-(bromoethoxy)(*tert*-butyl)diphenylsilane in 30 mL of dry THF was added. After stirring for 20 h under reflux the reaction mixture was treated with a saturated aqueous solution of ammonium chloride and extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated. Yield 3.34 g (55%) of colorless crystals (m.p. 117–118 °C, TLC, silica gel, light petroleum/ethyl acetate 70/30).

(b) The resulting product from (a) (3.34 g, 6.78 mmol) was dissolved under argon in a mixture of 40 mL of dry THF and 13.5 mL of a 1M solution of TBAF in THF and stirred for 2 h at room temperature. Subsequently after addition of H_2O the resulting mixture was extracted with ether. The ether extract was dried (Na_2SO_4) and concentrated. Yield 1.23 g (71%) of colorless crystals (m.p. 112–113 °C, TLC, silica gel, ethyl acetate/light petroleum 80/20).

(c) The obtained product from (b) (1.23 g, 4.88 mmol) was dissolved under argon in a mixture of 1.0 mL (7.39 mmol) of dry TEA and 16 mL of dry CH_2Cl_2. Afterwards 0.46 mL (5.89 mmol) of freshly distilled methanesulfonic chloride under argon was added dropwise and the resulting reaction mixture was stirred for 1 h at 0 °C. Subsequently the reaction mixture was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated. Yield: 1.56 g (96%) of colorless crystals (m.p. 122–123 °C, TLC, silica gel, ethyl acetate/light petroleum 80/20).

(d) The resulting crude product from (c) (1.56 g, 4.67 mmol) was dissolved under argon in a dry mixture of acetonitrile/triethyl amine (18 mL, 1:1) and treated with 9.69 mL (18.7 mmol) of aziridine. After stirring for 20 h at room temperature the reaction mixture was diluted with a mixture of CH_2Cl_2/EtOH (9/1) and subsequently filtered by use of 125 g of silica gel. Evaporation furnished 1.27 g

of crude product which was purified by column chromatography (silica gel, ethyl acetate/triethylamine 95/5) to afford 0.29 g (22%) of colorless crystals of **2**. M.p. 96–98 °C (ethyl acetate). IR (KBr): 3350, 2950, 1643, 1523, 1207, 1160 cm^{-1}. MS (EI, 70 eV) *m/z*: 280 (M^+, 10%), 224 (M^+-56, 1), 88 (17), 73 (20), 70 (67), 61 (81), 56 (59), 45 (100). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ = 7.56 (m, 1H, 9-H), 7.46 (m, 1H, 6-H), 7.41 (d, *J* = 2.0 Hz, 1H, 3-H), 7.21 (m, 2H, 7-H, 8-H), 7.07 (d, *J* = 2.0 Hz, 1H, 1-H), 4.15 (t, *J* = 5.9 Hz, 2H, 1'-H), 2.60 (t, *J* = 5.9 Hz, 2H, 2'-H) 1.72 (m, 2H, aziridine-H), 1.51 (s, 6H, $(CH_3)_2$), 1.03 (m, 2H, aziridine-H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ = 198.4 (C-4), 144.1 (C-5a), 127.0 (C-6), 126.9 (C-9a), 126.6 (C-7), 126.2 (C-8), 125.1 (C-9b), 123.5 (C-3), 122.6 (C-9), 118.5 (C-3a), 115.5 (C-1), 61.6 (C-2'), 50.8 (C-1'), 47.6 (C-5), 28.1 ($(CH_3)_2$), 27.0 (aziridine-CH_2). HRMS calc. for $C_{18}H_{20}N_2O$: 280.1576. Found: 280.1569.

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