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Synthesis, Anticancer and Anti-HIV Activities of Some Nitrogen Mustard Type Nucleoazasteroids

D.P. JINDAL and DEVENDER PATHAK*
University Institute of Pharmaceutical Sciences
Panjab University, Chandigarh-160 014, India

17a-(2-Hydroxyethyl)-17a-aza-D-homo-4-androsten-3-one (1) have been synthesised by the reaction of 17a-aza-D-homo-4-androsten-3-one with ethylene chlorohydrin and 4-(2-hydroxyethyl)-4-aza-5α-androstan-17β-ol (3) have been prepared by the reaction of 4-aza-5α-androsten-17β-ol with ethylene chlorohydrin. The compound 1 on treatment with mesyl chloride and then treatment with 10% sodium carbonate gave 17a-(2-chloroethyl)-17a-aza-D-homo-4-androsten-3-one (2). The compound 3 on treatment with thionyl chloride gave 4-(2-chloroethyl)-4-aza-5α-androsten-17β-ol (4).

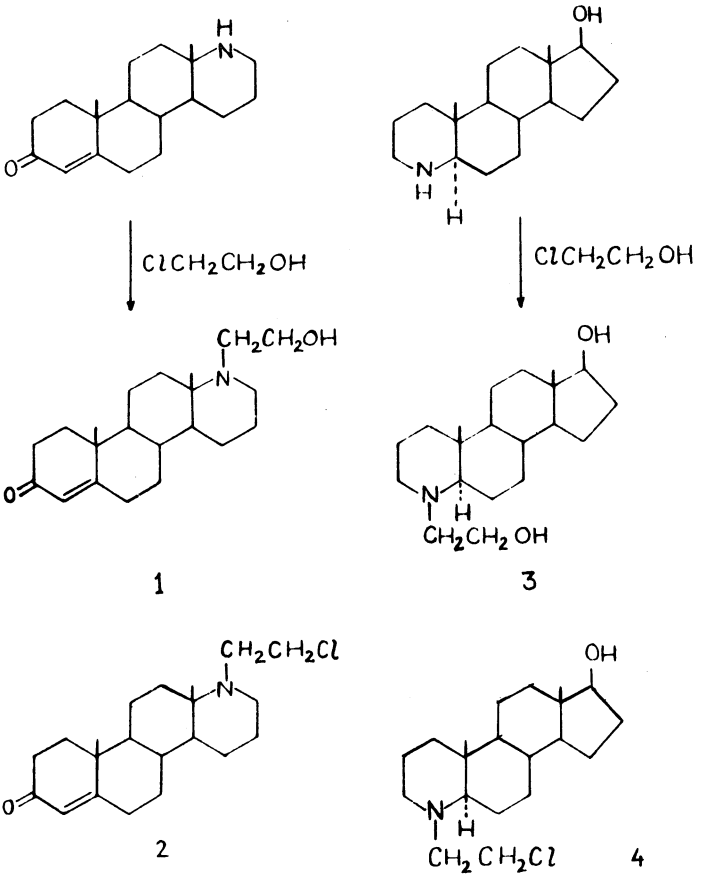
INTRODUCTION

On heteromodification the altered chemical and physical properties are envisaged to lead to the discovery of new substances having potential of proving some useful drugs. Heterosteroids of medicinal interest have been reported from our research laboratory.[1–5] It had been reported in the literature that nitrogen mustard exhibit anticancer activity.[6] Mechlorethamine, chlorambucil and cyclophosphamide are some of the nitrogen mustard used clinically as anticancer agents. Mechlorethamine is useful in Hodgkin's disease[7] whereas chlorambucil is approved for and is the agent of choice in the treatment of chronic lymphocytic leukemia, multiple myeloma, lymphosarcoma and to a lesser extent in chorio carcinoma, Hodgkin's disease and ovarian and testicular tumours.[8, 9] The steroid nucleus can be used as a supporting moiety for carrying nitrogen mustard group directly attached to the nucleus, but such products have not shown promising antineoplastic activity.[10–12] However, *p*-[N,N-bis(2-chloroethyl)amino] phenyl acetic acid esters of estradiol, cholesterol and 3β-hydroxy-17a-aza-D-homo-5α-androsten-17-one have shown good anticancer activity.[13–15] Therefore, we thought it worthwhile to synthesise nitrogen mustard like azasteroids which possess 2-chloroethyl group attached to the nitrogen forming part of the steroid nucleus. The synthesised compounds were screened for anticancer and anti-HIV activity.

Department of Pharmaceutical Chemistry, Dr. K.N. Modi Institute of Pharmaceutical Education and Research, Modi-Nagar, India.

EXPERIMENTAL

The melting points reported are uncorrected. The structures of the compounds were established on the basis of their elemental analysis and spectral data. The NMR spectra (60/90 MHz) were recorded for solutions in deuteriochloroform containing tetramethyl silane as internal reference. IR spectra (KBr) were recorded on a Perkin Elmer spectrophotometer.



17a-(2-Hydroxyethyl)-17a-aza-D-homo-4-androsten-3-one (1)

Ethylene chlorohydrin (3.0 mL) was added to a refluxing solution of 17a-aza-D-homo-4-androsten-3-one (3.0 g) in absolute ethanol (80 mL) containing anhydrous potassium carbonate (4.0 g). The refluxing was continued for 16 h. The reaction mixture was cooled, filtered and the filtrate was evaporated to dryness. The residue so obtained was crystallised from acetone. m.p. 188°C; yield 66.5%. Analysis: found (%) C 76.06, H 10.10, N 4.20; required C 76.13, H 10.07, N 4.23; UV_{max} (MeOH): 241 nm (log ε 4.18). IR: ν(O—H) 3390 cm^{-1}, ν(C—H) 2880 cm^{-1}, ν(C=O) 1660 cm^{-1}, ν(C=C) 1625 cm^{-1}. NMR ($CDCl_3$) δ : 0.96

(s, 3H), 1.17 (s, 3H), 2.30–2.60 (m, 3H collapsing to 2H on deuterium exchange), 3.30–3.65 (m, 2H) and 5.76 ppm (s, 1H).

17a-(2-Chloroethyl)-17a-aza-D-homo-4-androsten-3-one (2) hydrochloride

Mesyl chloride (0.1 mL) was added to a stirred solution of 1 (0.25 g) in dry pyridine (2.0 mL) for 2 min. The temperature of the reaction mixture was maintained below 90°C. The resulting brown solution was heated at 100°C for 20 min. The organic solvent was evaporated under vacuum and was crystallised from acetone. m.p. 264°C; yield 72.6% Analysis: found (%) C 65.05, H 8.55, N 3.48; required C 65.27, H 8.61, N 3.62; UV_{max} (MeOH): 241 nm (log E 4.34). IR: ν(C=O) 1675 cm^{-1}, ν(C=C) 1610 cm^{-1}, ν(C—Cl) 750 cm^{-1}, EIMS: m/z 385 (M^+).

17a-(2-Chloroethyl)-17a-aza-D-homo-4-androsten-3-one (2)

A mixture containing (2) HCl (0.5 g), distilled water (100 mL) and 10% aqueous sodium carbonate (10 mL) was shaken for 10 min. The precipitated compound was extracted with chloroform (3 × 50 mL). The chloroform extract was washed with water, dried and solvent was removed to obtain a yellow oily residue which was crystallised from methanol-acetone. m.p. 105°C; yield: 54.0%. Analysis: found (%) C 72.00, H 9.26, N 4.08; required C 72.10, H 9.16, N 4.00. UV_{max} (MeOH): 241 nm. IR: ν(C=O) 1670 cm^{-1}, ν(C=C) 1615 cm^{-1}, ν(C—Cl) 750 cm^{-1}. NMR ($CDCl_3$) δ: 0.93 (s, 3H), 1.20 (s, 3H), 2.30–2.60 (t, 2H), 3.40–3.60 (t, 2H) and 5.87 ppm (s, 1H).

4-(2-Hydroxyethyl)-4-aza-5α-androsten-17β-ol (3)

A mixture of 4-aza-5α-androsten-17β-ol (2.0 g), ethylene chlorohydrin (2.0 mL), and absolute ethanol (50 mL) was heated for 30 min. Potassium carbonate (3.0 g) was added to the above solution, which was refluxed for 20 h and worked up in the usual manner. The residue was crystallised in acetone. m.p. 172°C; yield 84.0%. Analysis: found (%) C 75.10, H 11.24, N 4.36; required C 74.70, H 11.00, N 4.40. IR (KBr): ν(O—H) 3350 cm^{-1}, ν(C—H) 2960 cm^{-1}. NMR ($CDCl_3$) δ: 0.74 (s, 3H), 0.96 (m, 3H), 2.90 (s, 2H), 3.20 (m, 1H) and 3.50 (m, 3H).

4-(2-Chloroethyl)-4-aza-5α-androsten-17β-ol (4) hydrochloride

Thionyl chloride (2.0 mL) was added to the refluxing solution of 3 (2 g) in dry benzene (60 mL) and refluxing continued for 1 h. After usual work up, the residue was taken up in methanol, filtered and crystallised in methanol-acetone to give hydrochloride of (4). m.p. 264°C; yield: 76.8%.

4-(2-Chloroethyl)-4-aza-5α-androstan-17β-ol (4)

A mixture containing 4 HCl (0.5 g), distilled water (100 mL) and 10% aqueous sodium carbonate (10 mL) was shaken for 5 min. Precipitated compound was extracted with chloroform and processed as usual. The oily residue was crystallised from n-hexane. m.p. 97°C; yield: 82%. Analysis: found C 70.60,

H 10.20, N 3.80 required C 70.70, H 10.10, N 4.10. IR (KBr): ν(O—H) 3410 cm^{-1}, ν(C—H) 3000 cm^{-1}, ν(C—Cl) 740 cm^{-1}. NMR ($CDCl_3$) δ: 0.73 (s, 3H), 0.93 (s, 3H), 2.71–3.16 (m, 3H; $>NCH_2CH_2Cl$ and 5α-H) and 3.20–3.80 (m, 3H; $>NCH_2CH_2Cl$ and 17α-H).

Biological activity

Anticancer activity: The newly synthesised compounds (1–4) were tested for their anticancer activity. The compounds did not show significant anticancer activity.

Anti-HIV activity: The newly synthesised compounds (1–4) have been tested for anti-HIV activity. The compounds did not show significant activity.

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