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Short Report

Short Synthesis of New 13,16-Diazaestrone and 13,16-Diazaequilenin Analogs

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Diferentes 3-[2-(3,4-diidro-1-naftil)etil]imidazolidina-2,4-dionas e 3-[2-(1-naftil)etil]-imidazolidina-2,4-dionas, quando aquecidas em ácido polifosfórico a 150 °C, sofrem ciclização quimioseletiva intramolecular resultado nos respectivos esteróides 13,16-diazaestrona e 13,16-diazaequilenina.

Different 3-[2-(3,4-dihydro-1-naphthyl)ethyl]imidazolidine-2,4-diones and 3-[2-(1-naphthyl)ethyl]imidazolidine-2,4-diones, when heated in polyphosphoric acid at 150 °C, underwent chemoselective intramolecular cyclization to afford the 13,16-diazaestrone steroids and 13,16-diazaequilenin steroids respectively.

Keywords: polyphosphoric acid, chemoselective cyclization, 13,16-diazaestrone steroids, 13,16-diazaequilenin steroids

Introduction

Azasteroids are known to exhibit various biological properties which include analgesic,[1] antiandrogenic,[2] antiphlogistic,[3] antimicrobial,[4] antileukemic,[5] antifungal,[6] bactericide,[7] antiestrogenic,[8] antifertility,[9] and cardiotonic and hypotensive activities.[10] Moreover, some azasteroids act as neuromuscular blockers[11] and inhibitors of 5-α reductase and androgen receptor binding.[12] Recently we have reported[13,14] the syntheses of 13,16-diazaestrone and 13,16-diazaequilenin analogs from the intramolecular cyclization of the corresponding 5-hydroxyimidazolidin-2-ones. We now wish to report a new synthesis of the title compounds from intramolecular cyclization of the corresponding imidazolidine-2,4-diones.

Results and Discussion

Towards this end, the intramolecular cyclization of 3-[2-(3,4-dihydro-1-naphthyl)ethyl]imidazolidine-2,4-dione[13] **1a** was undertaken. All our attempts to cyclize **1a** employing $POCl_3$ and P_2O_5 in different solvents such as benzene, dichloroethane, toluene and xylene were unsatisfactory and gave the starting material back. Heating **1a** with $POCl_3$ in refluxing tetralin gave a brown solid, which was insoluble in all organic solvents and hence could not be characterized. Attempts to cyclize **1a** in polyphosphoric acid (PPA) at 100 °C gave starting material back. When the temperature increased to 120 °C the TLC ($CHCl_3$-MeOH, 96:4) showed the formation of a new spot but the bulk of starting material remained intact even after 12h. The reaction was then carried out at 150 °C, which led to consumption of the starting material in 6h to give a yellow solid in 44% yield after aqueous work-up (Scheme 1). IR spectrum of the yellow solid showed the N-H band at 3250 cm^{-1} and the ^1H NMR spectrum displayed a 1H broad singlet due to N-H at δ 8.91 and ^1H singlet due to vinylic proton at δ 6.70 thus confirming the chemoselective formation of 13,16-diazaestrone **2a** and not the corresponding 13,15-diazasteroids. This may be explained on the basis of more electrophilic nature of carbonyl carbon of amide than urea.[15,16] Proposed mechanism for intramolecular cyclization of **1a** to give **2a** is shown in Scheme 2. Following the above standardized protocol, intramolecular cyclization of other imidazolidine-2,4-diones[13,14] **1b-h** were carried out to afford the corresponding 13,16-diazasteroids **2b-h** in 42-59 % yields (Scheme 1). It is important to notice that the earlier attempts by Schleigh *et al*.[17] to synthesize 13-azaestrone and 13-azaequilenin analogs by such one-step intramolecular cyclization of the corresponding pyrrolidine-2,5-diones under various acidic conditions were unsuccessful and gave either starting material back

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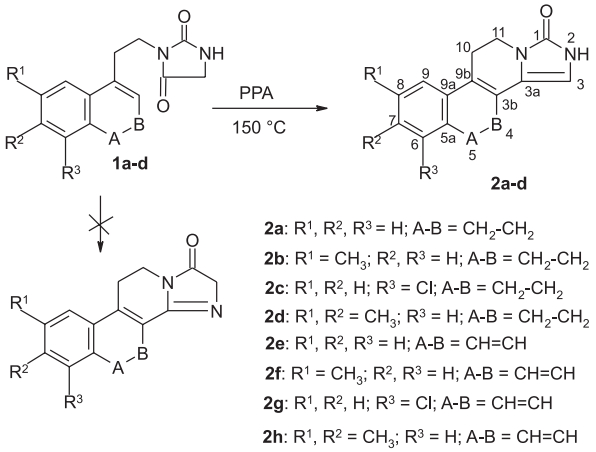


Scheme 1. Syntheses of 13,16-diazaestrone and 13,16-diazaequilenin analogs.

or a trace amount of uncharacterized solid material melting over a wide range.

In conclusion, the present work describes a new synthesis of 13,16-diazasteroids **2a-h** by chemoselective cyclization of **1a-h** in PPA. The method is short, general and utilizes easily accessible materials for the synthesis of the new 13,16-diazasteroids.

Experimental

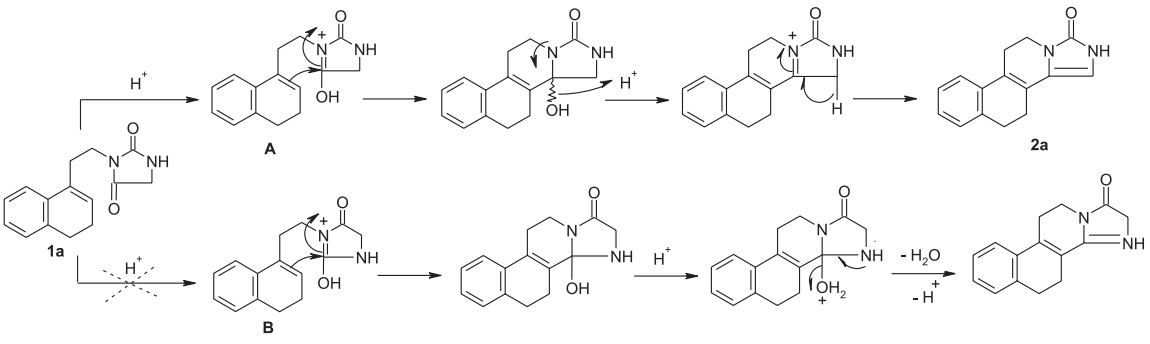
Reagents were of LR grade and were used without further purification. Column chromatography was carried out using silica gel (S. D. Fine Chemicals, India) 60-120 mesh. Boiling point of Petroleum ether used was in the range of 60-80 °C. The melting points (uncorrected) were determined on a Gallenkamp melting apparatus. The IR spectra (wavenumbers in cm^{-1}) were recorded on a Shimadzu FTIR-4200 spectrometer either as oil film or KBr discs. UV spectra were recorded on a Shimadzu UV-Visible spectrophotometer UV-2100. ^1H NMR spectra were recorded on Varian EM-360L (60 MHz), Varian 200 (200 MHz), Bruker 300 (300 MHz) and Varian VR (500 MHz) instruments in $CDCl_3$ with tetramethylsilane as internal standard. Chemical shifts are given in ppm and coupling constants (*J*) in Hz. Elemental analyses were carried out on a Carlo Erba EA-1108 elemental analyser. The electron impact spectrum was recorded on a Katros MS-80.

General procedure for the synthesis of 13,16-diazasteroids ***2a-h***

A mixture of compound **1a-h** (50 mg) and PPA (2 g) was heated at 150 °C for 6h. The reaction mixture was poured onto ice. It was extracted with EtOAc (3 × 25 mL). The combined EtOAc extracts were washed with 10% Na_2CO_3 (2 × 25 mL), water (2 × 25 mL) and then dried (anhydrous Na_2SO_4). Evaporation of solvent gave a brown residue, which was purified by column chromatography (basic alumina, $CHCl_3$-MeOH, 95:5) to afford the corresponding compound **2a-h**.

*4,5,10,11-Tetrahydro-2H-benzo[f]imidazo-[5,1-a]isoquinolin-1-one (**2a**).* Yield 44%, mp 242-245 °C (decomp.). IR (KBr) ν_{max}/ cm^{-1}: 1680 (C=C), 1715 (C=O), 3250 (N-H). ^1H NMR ($CDCl_3$, 300 MHz): d 2.43 (t, 2H, *J* 6.5, H-4), 2.86 (t, 2H, *J* 6.5, H-5), 3.44 (t, 2H, *J* 7.8, H-10), 4.01 (t, 2H, *J* 7.8, H-11), 6.70 (s, 1H, C=C-H), 7.45-7.80 (m, 4H, Ar-H), 8.91 (s, 1H, N-H). UV ($CHCl_3$) λ_{max}/ nm (log ε): 288 (3.97), 307 (3.89), 322 (3.81). Analysis calc. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76; Found: C, 75.53; H, 5.97; N, 11.72.

*8-Methyl-4,5,10,11-tetrahydro-2H-benzo[f]imidazo[5,1-a]isoquinolin-1-one (**2b**).* Yield 52%, mp 220-222 °C (decomp.). IR (KBr) ν_{max}/ cm^{-1}: 1680 (C=C), 1716 (C=O), 3270 (N-H). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.33 (s, 3H, CH_3), 2.39 (t, 2H, *J* 6.5, H-4), 2.84 (t, 2H, *J* 6.5, H-5), 3.41 (t, 2H, *J* 7.6, H-10), 3.87 (t, 2H, *J* 7.6, H-11), 6.30 (s, 1H, C=C-H), 7.50-7.72 (m, 3H, Ar-H), 8.54 (s, 1H, N-H). MS (EI, *m/z* (rel.%)): 252 (M^+, 80%), 251 (20), 250 (35), 223 (20), 184 (17), 168 (40), 155 (16), 141 (42), 128 (33), 115



Scheme 2. Proposed mechanism for intramolecular cyclization of imidazolidine-2,4-diones.

(58), 77 (100). UV ($CHCl_3$) λ_{max}/ nm (log e): 288 (3.79), 307 (3.85), 322 (3.98). Analysis calc. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10; Found: C, 76.19; H, 6.34; N, 11.14.

*6-Chloro-4,5,10,11-tetrahydro-2H-benzo[f]imidazo[5,1-a]isoquinolin-1-one (**2c**).* Yield 42%, mp 202-205°C (decomp.). IR (KBr) ν_{max}/ cm^{-1}: 1670 (C=C), 1713 (C=O), 3304 (N-H). ^1H NMR ($CDCl_3$, 200 MHz): δ 2.40 (t, 2H, *J* 6.6, H-4), 2.83 (t, 2H, J 6.6, H-5), 3.41 (t, 2H, *J* 7.8, H-10), 4.02 (t, 2H, *J* 7.8, H-11), 6.62 (s, 1H, C=C-H), 7.50-7.80 (m, 3H, Ar-H), 8.60 (s, 1H, N-H). UV ($CHCl_3$) λ_{max}/ nm (log ε): 287 (3.91), 304 (3.86), 321 (3.82). Analysis calc. for $C_{15}H_{13}N_2OCl$: C, 66.06; H, 4.80; N, 10.27; Cl, 13.00; Found: C, 65.97; H, 4.82; N, 10.32; Cl, 12.94.

*7,8-Dimethyl-4,5,10,11-tetrahydro-2H-benzo[f]imidazo[5,1-a]isoquinolin-1-one (**2d**).* Yield 59%, mp 238-241 °C (decomp.). IR (KBr) ν_{max}/ cm^{-1}: 1670 (C=C), 1715 (C=O), 3315 (N-H). ^1H NMR ($CDCl_3$, 60 MHz): δ 2.25-4.00 (m, 14H, aliphatic H), 6.43 (s, 1H, C=C-H), 7.35 (s, 1H, Ar-H), 7.60 (s, 1H, Ar-H), 8.72 (s, 1H, NH). UV ($CHCl_3$) λ_{max}/nm (log ε): 292 (3.93), 305 (3.87). Analysis calc. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52; Found: C, 76.75; H, 6.78; N, 10.50.

*10,11-Dihydro-2H-benzo[f]imidazo-[5,1-a]isoquinolin-1-one (**2e**).* Yield 47%, mp 252-255 °C (decomp.). IR (KBr) ν_{max}/ cm^{-1}: 1680 (C=C), 1715 (C=O), 3270 (N-H). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.44 (t, 2H, *J* 6.4, H-10), 4.01 (t, 2H, *J* 6.4, H-11), 6.70 (s, 1H, C=C-H), 7.46- 7.83 (m, 5H, Ar-H), 8.00 (d, 1H, *J* 8.41, H-9), 8.91 (br s, 1H, N-H). UV ($CHCl_3$) λ_{max}/ nm (log ε): 288 (3.83), 307 (3.81), 321 (3.75). Analysis calc. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86; Found: C, 76.15; H, 5.16; N, 11.80.

*8-Methyl-10,11-dihydro-2H-benzo[f]imidazo-[5,1-a]isoquinolin-1-one (**2f**).* Yield 55%, mp 229-231 °C (decomp.). IR (KBr) ν_{max}/ cm^{-1}: 1680 (C=C), 1715 (C=O), 3250 (N-H). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.51 (s, 3H, CH_3), 3.41 (t, 2H, *J* 6.3, H-10), 4.00 (t, 2H, *J* 6.3, H-11), 6.66 (s, 1H, C=C-H), 7.38-7.98 (m, 5H, Ar-H), 8.90 (br s, 1H, N-H). UV ($CHCl_3$) λ_{max}/ nm (log ε): 288 (3.89), 307 (3.84), 322 (3.79). Analysis calc. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19; Found: C, 76.88; H, 5.66; N, 11.24.

*6-Chloro-10,11-dihydro-2H-benzo[f]imidazo-[5,1-a]isoquinolin-1-one (**2g**).* Yield 45%, mp 208-211 °C (decomp.). IR (KBr) ν_{max}/ cm^{-1}: 1680 (C=C), 1710 (C=O), 3200 (N-H). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.43 (t, 2H, *J* 6.5, H-10), 4.03 (t, 2H, *J* 6.5, H-11), 6.68 (s, 1H, C=C-H), 7.60-7.92 (m, 4H, Ar-H), 8.00 (d, 1H, *J* 8.41, H-9), 8.97 (br s, 1H, N-H). UV ($CHCl_3$) λ_{max}/ nm (log ε): 288 (3.92), 305 (3.90), 321 (3.85). Analysis calc. for $C_{15}H_{11}N_2OCl$: C, 66.55; H, 4.10; N, 10.35; Cl, 13.10; Found: C, 66.48; H, 4.14; N, 10.31; Cl, 13.07.

*7,8-Dimethyl-10,11-dihydro-2H-benzo[f]imidazo-[5,1-a]isoquinolin-1-one (**2h**).* Yield 60%, mp 245-247 °C (decomp.). IR (KBr) ν_{max}/ cm^{-1}: 1680 (C=C), 1715 (C=O), 3260 (N-H). ^1H NMR ($CDCl_3$, 60 MHz): δ 2.51 (s, 6H, 2 × CH_3), 3.33-4.08 (m, 4H, H-10 and H-11), 6.70-7.64 (m, 5H, 4 Ar-H and C=C-H), 8.82 (br s, 1H, NH). UV ($CHCl_3$) λ_{max}/ nm (log ε): 288 (3.98), 307 (3.92), 322 (3.84). Analysis calc. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60; Found: C, 77.15; H, 6.14; N, 10.62.

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References

1. Taylor, E. C.; Lenard, K.; *J. Chem. Soc., Chem. Commun.* **1967**, 97.
2. Shibata, K.; Takeguwa, S.; Koizumi, N.; Yamakoshi, N.; Shimazawa, E.; *Chem. Pharm. Bull.* **1992**, *40*, 935.
3. Akherm, A. A.; Lakhvich, F. A.; Pshenichnyi, V. N.; Lis, L. G.; Kuzmitskii, B. B.; Mizulo, N. A.; *USSR 636236* **1978**. (*CA 90:104210t*)
4. Norman, F. P.; Doorenbos, N. J.; *J. Miss. Acad. Sci.* **1976**, *21*, 23. *(CA 86:165794a)*
5. Anastasiou, A.; Catsoulacus, P.; Epitheor, K.; *Farmakol. Farmakokinet. Intl. Ed.* **1992**, *6*, 130. *(CA 119:72911w)*
6. Patrick, G. L.; Kinsman, O. S.; *Eur. J. Med. Chem.* **1996**, *31*, 615.
7. William, R. H.; Hoehn, M. M.; Michel, K. H.; *US 147808* **1994**. *(CA 123:75620u)*
8. Greenbalatt, R. B.; Bornstan, R.; Bohler, C. S. S.; *J. Reprod. Med.* **1974**, *13*, 201.
9. Kierstead, R. W.; Faraone, A.; Boris, A.; *J. Med. Chem.* **1969**, *12*, 629.
10. Akherm, A. A.; Lakhvich, F. A.; Pshenichnyi, V. N.; Lakhvich, O. F.; Kuzmitskii, B. B.; Gorbatenko, S. F.; *USSR 636235* **1978.** *(CA 90:104211u)*
11. Li, X.; Singh, S. M.; Lourdusamy, M.; Merand, Y.; Veitleux, R.; Labrie, F.; *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1061.
12. Bakshi, R. K.; Patel, G. F.; Rasmussan, G. H.; *US 373341*, **1995**. *(CA 123:212693c)*
13. Parihar, J. A.; Ramana, M. M. V.; *Tetrahedron Lett.* **2003,** *44*, 1843.
14. Parihar, J. A.; Ramana, M. M. V.; *Chin. J. Chem.* **2004**, *22*, 1196.
15. Kallies, B.; Mitzner, R.; *J. Mol. Struct. (THEOCHEM).* **1998**, *428*, 267.
16. Kallies, B; Mitzner, R.; *J. Mol. Modeling*. **1998**, *4*, 183.
17. Schleigh, W. R.; Catala, A.; Popp, F. D.; *J. Heterocycl. Chem.* **1965**, *2*, 379.

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