Chinese Journal of Chemistry, **2004**, *22*, 1196—1199 **Article**

Chemoselective Dehydrogenation of 3-[2-(3,4-Dihydro-1-naphthalenyl)ethyl]imidazolidine-2,4-diones: a New and Convenient Synthesis of 13,16-Diazaequilenin analogs

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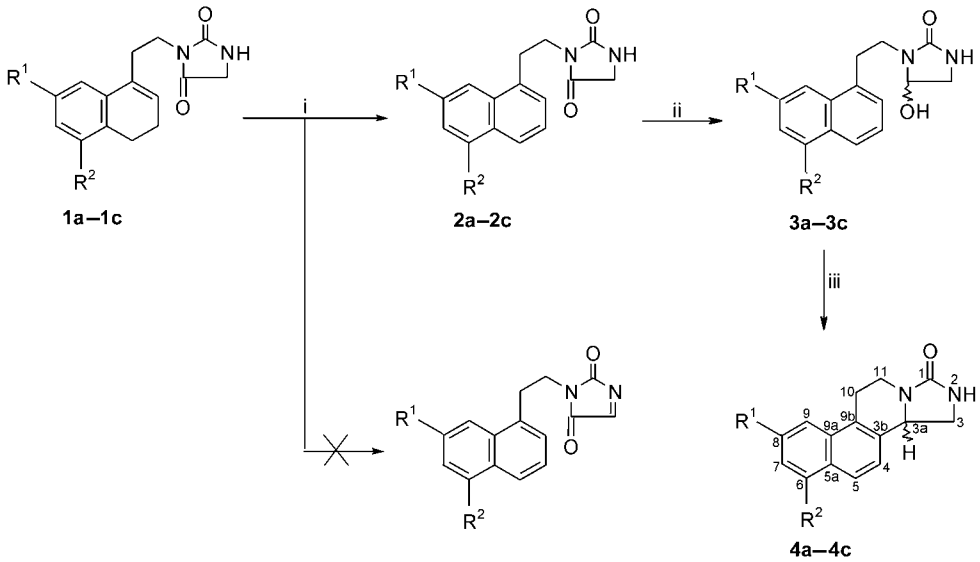
The synthesis of the title compounds starting with the chemoselective dehydrogenation of 3-[2-(3,4-dihydro-1-naphthalenyl)ethyl]imidazolidine-2,4-diones has been described.

Keywords chemoselective dehydrogenation, imide reduction, intramolecular cyclization, 13,16-diazasteroid

Azasteroids are known to exhibit varied biological properties which include analgesic,[1] antiandrogenic,[2] antiphlogistic,[3] antimicrobial,[4] antileukemia,[5] antifungal,[6] bactericidal,[7] antiestrogenic,[8] antifertility,[9] and cardiotonic and hypotensive activity.[10] Moreover some of the azasteroids act as neuromuscular blockers[11] such as 5-α reductase inhibitors or androgen receptors.[12] Though several syntheses of azasteroids[13-18] have been reported, the title compounds have not yet been synthesized. Recently we have reported the first synthesis of 13,16-diazaestrone analogs.[19] In this article we wish to report the first synthesis of 13,16-diazaequilenin analogs.

Towards this end, chemoselective dehydrogenation of 3-[2-(3,4-dihydro-1-naphthalenyl)ethyl]imidazolidine-2,4-diones **1a—1c** which was the key step was explored for the synthesis of **2a—2c**. We heated **1a—1c** with 5% Pd-C at 250 ℃ for 15 min and to our delight the corresponding dehydrogenated products **2a—2c** were obtained in 67%—70% yield. It is noteworthy that only carbocyclic ring was chemoselectively dehydrogenated to afford **2a—2c**. Prolonging the reaction time decreased considerably the yield as well as the purity of the product. The structures of **2a—2c** were ascertained by their elemental analysis and spectroscopic data. The ^{1}H NMR spectrum of **2a** displayed 2H singlet at δ 3.93 for H-5 of the imidazolidine ring and 1H broad singlet at δ 5.39 for N—H apart from two triplets in the

Scheme 1 Synthesis of 13,16-diazaequilenin analogs



Reagents and conditions: i) 5% Pd-C, 250 ℃, 15 min. ii) Method-A: $NaBH_4$, dry MeOH, reflux, 6 h; Method-B: $LiAlH_4$, dry THF, r.t., 30 h; Method-C: DIBAL-H (20% toluene solution), dry THF, −78 ℃, 2 h. iii) PPA, steam bath, 6 h.

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Table 1 Synthesis of 13,16-diazaequilenin analogs

Compound	R^1	R^2	Physical appearance, m.p.[a]/℃	Yield[b]/%
2a	H	H	colourless solid, 127—129	69
2b	CH_3	H	colourless solid, 98	70
2c	H	Cl	colourless oil	67
3a	H	H	pale yellow oil	49[c](25),[d] 71,[e] 69[f]
3b	CH_3	H	colourless solid, 128—129	43[c](27),[d] 64,[e] 72[f]
3c	H	Cl	pale yellow oil	41[c](26),[d] 70,[e] 77[f]
4a	H	H	colourless solid, 221	70
4b	CH_3	H	colourless solid, 210—211	69
4c	H	Cl	colourless solid, 184—186	41

[a] Melting points are un-corrected. [b] Yield refers to purified product. [c] Yield obtained from method-A. [d] % of starting material recovered in method-A. [e] Yield obtained from method-B. [f] Yield obtained from method-C.

aliphatic region, thus confirming the chemoselective dehydrogenation at only carbocyclic ring.

Chemoselective reduction of $NCOCH_2$ group of **2a—2c** was carried out with $NaBH_4$ in MeOH under reflux for 6 h to give the corresponding hydroxy lactam **3a—3c** in 41%—49% yield along with the recovery of the starting material (25%—27%). Prolonging the reaction time (up to 12 h) and using more equivalents of $NaBH_4$ (3 equiv.) did not improve the yield of the hydroxy lactam **3a—3c**. The structures of **3a—3c** were ascertained by their elemental analysis and spectroscopic data. The ^{1}H NMR spectrum of **3a** displayed 1H multiplet at δ 6.10—6.13 for H-4 of the imidazolidine ring, 1H broad singlet at δ 6.24 for O—H and 2H multiplet at δ 2.20—2.33 for H-5 of the imidazolidine ring, confirming the chemoselective reduction at $NCOCH_2$ group. Replacing $NaBH_4$ in MeOH with $LiAlH_4$ in THF for 30 h at r.t. and DIBAL-H (20% toluene solution) in THF at −78 ℃ for 2 h improved the yield of **3a—3c** to 64%—71% and 69%—77% respectively. Intramolecular cyclization of **3a—3c** was carried out in polyphosphoric acid (PPA) on a steam bath for 6 h to afford the corresponding 13,16-diazaequilenin analogs **4a—4c** in 41%—70% yield (Scheme 1, Table 1). The ^{1}H NMR spectrum of **4a** displayed 1H multiplet at δ 4.00—4.03 for H-3a, 1H multiplet at δ 4.30—4.34 for H-3a, 1H broad singlet at δ 5.66 for NH and 5H multiplet at δ 3.01—3.52, which confirms the intramolecular cyclization of **3a** to give **4a**.

In conclusion, the methods described for the synthesis of 13,16-diazasteroids **4a—4c** is short, general and utilizes easily accessible materials.

Experimental

General procedure for the synthesis of dehydrogenated products 2a—2c

Seco-azasteroid **1** (100 mg) was heated with 5% Pd-C (50 mg) at 250 ℃ for 15 min. It was extracted with hot EtOAc (4×50 mL). The combined EtOAc extract was filtered to remove trace of catalyst. The evaporation of solvent gave a brown residue which was purified by column chromatography [alumina (neutral), $CHCl_3$: MeOH (97 : 3, *V* : *V*)] to afford the corresponding dehydrogenated product **2a—2c**.

3-[2-(1-Naphthalenyl)ethyl]imidazolidine-2,4-dione (2a): UV ($CHCl_3$) λ_{max} (log ε): 272 (3.83), 283 (3.92), 292 (3.79) nm; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.39 (t, *J*=7.9 Hz, 2H, ArCH), 3.88 (t, *J*=7.9 Hz, 2H, NCH), 3.93 (s, 2H, H-5 of naphthalene ring), 5.39 (br, s, 1H, NH), 7.77—7.87 (m, 5H, H-3—7 of naphthalene ring), 7.86 (d, *J*=8.0 Hz, 1H, H-2 of naphthalene ring), 8.23 (d, *J*=8.3, 1H, H-8 of naphthalene ring); IR (KBr) *v*: 1720 & 1781 (C=O), 3250 (N—H) cm^{-1}. Anal. calcd for $C_{15}H_{14}N_2O_2$: C 70.85, H 5.55, N 11.02; found C 70.78, H 5.60, N 10.97.

3-[2-(7-Methyl-1-naphthalenyl)ethyl]imidazolidine-2,4-dione (2b): UV ($CHCl_3$) λ_{max} (log ε): 271 (3.84), 282 (3.90), 292 (3.74) nm; ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 2.50 (s, 3H, CH_3), 3.33 (t, *J*=8 Hz, 2H, $ArCH_2$), 3.80—4.00 (m, 4H, NCH), 6.33 (br, s, 1H, NH), 7.10—8.40 (m, 6H, ArH); IR (KBr) *v*: 1705 & 1782 (C=O), 3250 (N—H) cm^{-1}. Anal. calcd for $C_{16}H_{16}N_2O_2$: C 71.62, H 6.01, N 10.44; Found C 71.69, H 5.98, N 10.41.

3-[2-(5-Chloro-1-naphthalenyl)ethyl]imidazolidine-2,4-dione (2c): UV ($CHCl_3$) λ_{max} (log ε): 271 (3.73), 281 (3.76), 292 (3.62) nm; ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 3.25 (t, *J*=8 Hz, 2H, $ArCH_2$), 3.75—4.10 (m, 4H, NCH), 6.15 (br, s, 1H, NH), 7.25—8.40 (m, 6H, ArH); IR (oil film) *v*: 1713 & 1780 (C=O), 3300 (N—H) cm^{-1}. Anal. calcd for $C_{15}H_{13}ClN_2O_2$: C 62.40, H 4.54, Cl 12.28, N 9.70; found C 62.38, H 4.59, Cl 12.33, N 9.64.

General procedure for the synthesis of hydroxy lactams 3a—3c

Method-A: Reduction with $NaBH_4$ in methanol.

To a well-stirred solution of dehydrogenated compound **2** (1 mmol) in dry MeOH (50 mL) was added gradually $NaBH_4$ (76 mg, 2 mmol) in dry MeOH (20 mL) at r.t. and the mixture was refluxed with stirring for

6 h. After MeOH was removed the residue was quenched with 5% NH_4Cl solution (100 mL). It was extracted with $CHCl_3$ (3 × 25 mL). The combined $CHCl_3$ extracts were washed with water (2×25 mL) and then dried (anhydr. Na_2SO_4). The evaporation of solvent gave a brown residue which was purified by column chromatography [alumina (basic), chloroform : MeOH (98 : 2)] to furnish starting material **2a—2c**. Further elution with chloroform : MeOH (96 : 4) followed by recovery of solvents gave hydroxy lactam **3a—3c**.

1-[2-(1-Naphthalenyl)ethyl]-5-hydroxyimidazolidin-2-one (3a): UV ($CHCl_3$) λ_{max} (log ε): 271 (3.67), 283 (3.90), 291 (3.65) nm; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.20—2.33 (m, 2H, NHC**H**$_2$), 3.36 (t, J=7.9 Hz, 2H, $ArCH_2$), 3.78 (t, J=7.9 Hz, 2H, NCH_2), 6.10—6.13 (m, 1H, HOC**H**N), 6.24 (br, s, 1H, OH), 7.05—8.00 (m, 7H, ArH), 8.76 (br s, 1H, NH); IR (oil film) v: 1675 (C=O), 3200—3500 (N—H and O—H) cm^{-1}. Anal. calcd for $C_{15}H_{16}N_2O_2$: C 70.29, H 6.29, N 10.93; found C 70.41, H 6.23, N 10.97.

1-[2-(7-Methyl-1-naphthalenyl)ethyl]-5-hydroxyimidazolidin-2-one (3b): UV ($CHCl_3$) λ_{max} (log ε): 271 (3.79), 282 (3.87), 291 (3.71) nm; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.18—2.30 (m, 2H, NHC**H**$_2$), 2.51 (s, 3H, CH_3), 3.40 (t, J=7.8 Hz, 2H, $ArCH_2$), 3.80 (t, J=7.8 Hz, 2H, NCH_2), 6.04—6.07 (m, 1H, HOC**H**N), 6.19 (br, s, 1H, OH), 7.20—7.89 (6H, m, ArH), 8.90 (br, s, 1H, N—H); IR (KBr) v: 1677 (C=O), 3200—3500 (N—H and O—H) cm^{-1}. Anal. calcd for $C_{16}H_{18}N_2O_2$: C 71.09, H 6.71, N 10.36; found C 70.98, H 6.74, N 10.30.

1-[2-(5-Chloro-1-naphthalenyl)ethyl]-5-hydroxyimidazolidin-2-one (3c): UV ($CHCl_3$) λ_{max} (log ε): 271 (3.73), 282 (3.84), 292 (3.61) nm; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.20—2.32 (m, 2H, NHC**H**$_2$), 3.38 (t, J=7.8 Hz, 2H, $ArCH_2$), 3.80 (t, J=7.8 Hz, 2H, NCH_2), 6.00—6.03 (m, 1H, HOC**H**N), 6.24 (br, s, 1H, OH), 7.28—8.04 (m, 6H, ArH), 8.84 (br, s, 1H, N—H); IR (oil film) v: 1680 (C=O); 3200—3500 (N—H and O—H) cm^{-1}. Anal. calcd for $C_{15}H_{15}Cl\ N_2O_2$: C 61.97, H 5.20, Cl 12.19, N 9.63; found C 61.89, H 5.24, Cl 12.24, N 9.59.

Method-B: Reduction with $LiAlH_4$ in THF.

To a well-stirred suspension of $LiAlH_4$ (38 mg, 1 mmol) in dry THF (50 mL) at r.t. was added gradually dehydrogenated compound **2** (1 mmol) in dry THF (20 mL) and the mixture was stirred at the same temperature for 30 h. THF was removed by distillation at r.t. on rota-vapour and the residue was quenched with 5% NH_4Cl solution (100 mL). For isolation and purification the same procedure as given in method-A was followed. The ^{1}H NMR spectral data of **3a—3c** were consistent with its authentic data obtained in method-A.

Method-C: Reduction with DIBAL-H (20% toluene solution) in THF.

To a well-stirred solution of dehydrogenated compound **2** (1 mmol) in dry THF (50 mL) was added DIBAL-H (2 mL of 20% toluene solution, 2 mmol) at −78 ℃ and the mixture was stirred for 2 h at the same temperature. The reaction mixture was quenched with 5% NH_4Cl solution (100 mL). For isolation and purification the same procedure as given in method-A was followed. The ^{1}H NMR spectral data of **3a—3c** were consistent with its authentic data obtained in method-A.

General procedure for the synthesis of 13,16-diazasteroids 4a—4c

A mixture of hydroxy lactam **3** (50 mg) and PPA (10 g) was heated on steam bath for 6 h. The reaction mixture was poured onto ice and allowed to stand overnight. It was extracted with EtOAc (3×25 mL). The combined EtOAc layer was washed with 10% Na_2CO_3 (2×25 mL), water (2 × 25 mL) and then dried (anhydr. Na_2SO_4). The evaporation of solvent gave a brown residue which was purified by column chromatography [alumina (basic), chloroform : MeOH (98 : 2)] to furnish the title compounds **4a—4c**.

3,3a,10,11-Tetrahydrobenzo[*f*]imidazo[5,1-*a*]isoquinolin-1[2*H*]-one (4a): UV ($CHCl_3$) λ_{max} (log ε): 272 (3.83), 281 (3.86), 293 (3.70) nm; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.01—3.52 (m, 5H, H-3, H-10 & H-11 axial), 4.00—4.03 (m, 1H, H-3a), 4.30—4.34 (m, 1H, H-11 equatorial), 5.66 (br, s, 1H, N—H), 7.18—8.10 (m, 6H, ArH); IR (KBr) v: 1695 (C=O), 3200 (N—H) cm^{-1}. Anal. calcd for $C_{15}H_{14}N_2O$: C 75.61, H 5.92, N 11.76; found C 75.72, H 5.88, N 11.82.

3,3a,10,11-Tetrahydro-8-methylbenzo[*f*]imidazo[5,1-*a*]isoquinolin-1[2*H*]-one (4b): UV ($CHCl_3$) λ_{max} (log ε): 271 (3.77), 283 (3.92), 291 (3.68) nm; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.51 (s, 3H, CH_3), 3.00—3.50 (m, 5H, H-3, H-10 & H-11 axial), 4.01—4.04 (m, 1H, H-3a), 4.33—4.37 (m, 1H, H-11 equatorial), 5.07 (br, s, 1H, N—H), 7.11—8.00 (m, 5H, ArH); IR (KBr) v: 1695 (C=O str.), 3300 (N—H str.) cm^{-1}. Anal. calcd for $C_{16}H_{16}N_2O$: C 76.16, H 6.39, N 11.10; found C 76.07, H 6.43, N 11.06.

6-Chloro-3,3a,10,11-Tetrahydrobenzo[*f*]imidazo[5,1-*a*]isoquinolin-1[2*H*]-one (4c): UV ($CHCl_3$) λ_{max} (log ε): 271 (3.68), 283 (3.77), 291 (3.60) nm; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.06—3.54 (m, 5H, H-3, H-10 & H-11 axial), 4.04—4.07 (m, 1H, H-3a), 4.38—4.42 (m, 1H, H-11 equatorial), 5.51 (br, s, 1H, N—H), 7.20—8.08 (m, 5H, ArH); IR (KBr) v: 1700 (C=O), 3350 (N—H) cm^{-1}. Anal. calcd for $C_{15}H_{13}ClN_2O$: C 66.06, H 4.80, Cl 13.00, N 10.27; found C 65.98, H 4.82, Cl 13.04, N 10.25.

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