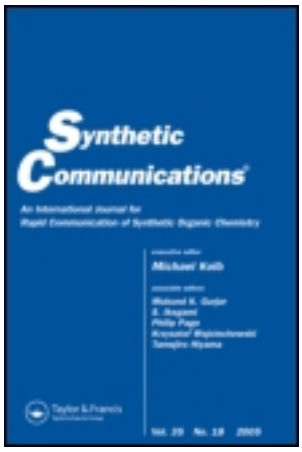

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Alkylation of Pyrrolidine-2,5-dione with 2-(3,4-Dihydro-1-napthalenyl)ethyl-4-methylphenylsulph A New and General Approach to 13-Azaequilenin Analogs

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Alkylation of Pyrrolidine-2,5-dione with 2-(3,4-Dihydro-1-napthalenyl)ethyl-4-methylphenylsulphonates: A New and General Approach to 13-Azaequilenin Analogs

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ABSTRACT

Pyrrolidine-2,5-dione was *N*-alkylated with three different 2-(3,4-dihydro-1-napthalenyl)ethyl-4-methylphenylsulphonates to give the corresponding seco-azasteroids which on chemoselective dehydrogenation, reduction with $NaBH_4$ in MeOH at 0°C gave the corresponding 5-hydroxy-2-pyrrolidones. Intramolecular cyclization of these 5-hydroxy-2-pyrrolidones afforded the corresponding title compounds.

Key Words: *N*-Alkylation; Chemoselective dehydrogenation; Imide reduction; Intramolecular cyclization; 13-Azasteroids.

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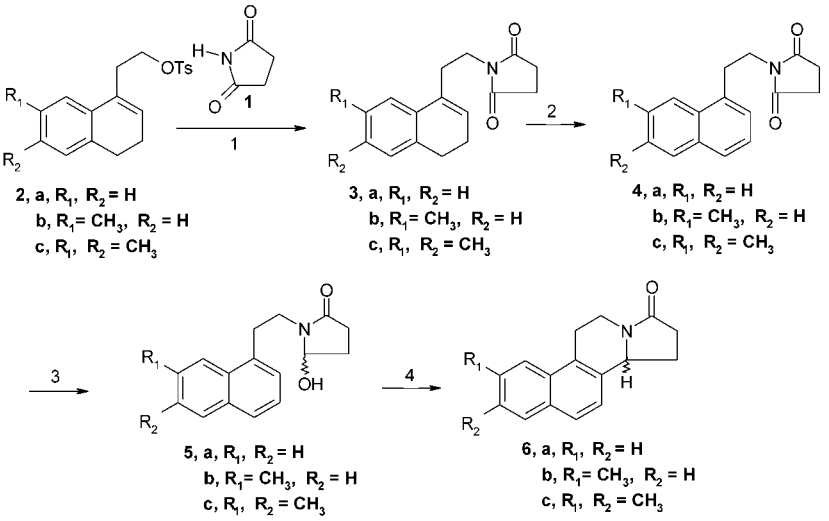
Several azasteroids[1–7] have been synthesized due to their potential biological properties such as analgesic,[2] antiandrogenic,[8] antiphlogistic,[9,10] antimicrobial,[11,12] antileukemia,[13,14] antifungal,[15,16] bactericides,[17,18] antiestrogenic,[19] antifertility,[20] and cardiotonic and hypotensive activity.[21,22] These observations and our interest in the synthesis of azasteroids led us to investigate a new synthesis of the title compounds.

More recently, we have reported a fruitful preparation of 2-(3,4-dihydro-1-napthalenyl)ethyl-4-methylphenylsulphonates[23] from the corresponding alcohols and 4-methylphenylsulphonyl chloride in presence of pyridine in $CHCl_3$. In our investigation of a new synthesis of the title compounds, we *N*-alkylated pyrrolidine-2,5-dione **1** with **2a–c** using K_2CO_3 in dry DMF under reflux for 45 min to afford the corresponding seco-azasteroids **3a–c**. It is noteworthy that earlier **3a** has been synthesized by Schleigh et al.[1] using K salt of **1** in MeOH in 42 h. **3a–c** were then heated with 5% Pd-C at 250°C to give the corresponding dehydrogenated seco-azasteroids **4a–c** for the first time. It is noteworthy that only carbocyclic ring was dehydrogenated chemoselectively to afford **4a–c**. The structures of **4a–c** were ascertained from their elemental and spectroscopic data. The MS spectrum of **4a** showed its molecular ion peak and PMR spectrum displayed 4H singlet at 2.66 δ, one 2H triplet at 3.33 δ and one 2H triplet at 3.87 δ in the aliphatic region. **4a–c** were then reduced selectively at one of the carbonyl group with $NaBH_4$ in dry



Scheme 1. Reagents and conditions: 1) K_3CO_3, dry DMF, reflux, 45 min. 2) 5% Pd-C, 250°C, 15 min, 3) $NaBH_4$, dry MeOH, 0°C, N_2, 4) $POCl_3$, 50°C, 8 h.

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Table 1. Synthesis of 13-azaequilenin analogs.

Compound	R_1	R_2	mp[a] (°C)	Yield[b] (%)
3a	H	H	88 (lit[1] mp : 88–89)	78
3b	CH_3	H	104	76
3c	CH_3	CH_3	180	78
4a	H	H	89 (Lit[1] mp : 88–90)	72
4b	CH_3	H	108	70
4c	CH_3	CH_3	159	69
5a	H	H	113 (Lit[25] mp : 113–115)	60
5b	CH_3	H	72	60
5c	CH_3	CH_3	80	52
6a	H	H	126 (Lit[7] mp : 126–128)	65
6b	CH_3	H	102	59
6c	CH_3	CH_3	128	67

[a]Melting points are uncorrected.
[b]Yield refers to purified product.

MeOH[24] at 0°C under N_2 to give the corresponding 5-hydroxy-2-pyrrolidones **5a–c** which were then subjected to intramolecular cyclization in $POCl_3$ at 50°C under N_2 for 8 h to afford the corresponding title compounds **6a–c** (Sch. 1, Table 1). The structures of **6a–c** were ascertained from their elemental and spectroscopic data. The MS spectrum of **6a** showed its molecular ion peak at $m/z = 237$ and base peak at $m/z = 236$ ($M^+ - 1$) for the loss of H radical and PMR spectral data was consistent with the reported data.[7]

In conclusion, the present work describes a new synthesis of the title compounds **6a–c** starting from 4-methylphenylsulphonates **2a–c** which involves *N*-alkylation of **1** with **2a–c**, chemoselective dehydrogenation of **3a–c**, selective reduction of **4a–c** and then finally intramolecular cyclization of **5a–c** in $POCl_3$. Thus the method is short, general and utilizes easily accessible materials.

EXPERIMENTAL

1. General Procedure for the Synthesis of Seco-azasteroids (3)

A mixture of 4-methylphenylsulphonate **2a–c** (2 mmole), pyrrolidine-2,5-dione **1** (294 mg, 3 mmole), anhyd. K_2CO_3 (1 g, 7.25 mmole) and dry

DMF (20 cm^3) was refluxed with stirring for 45 min. The reaction mixture was diluted with water and extracted with EtOAc (4 × 50 cm^3). The combined EtOAc extracts were washed with water (3 × 50 cm^3) and then dried (anhydrous Na_2SO_4). Evaporation of the solvent gave a brown residue which was purified by column chromatography [alumina (neutral), $CHCl_3$: MeOH (99.50 : 0.50)] to afford the corresponding seco-azasteroid **3a–c**.

1-[2-(3,4-Dihydro-1-naphthalenyl)ethyl]pyrrolidine-2,5-dione (3a). IR (KBr): 1700, 1780 (C═O str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz): $\delta = 2.0–3.0$ (10H, m), 3.66 (2H, t, $J = 7$ Hz, CH_2–N), 5.83 (1H, t, $J = 5$ Hz, C═C–H), 7.0–7.5 (4H, m, Ar–H); MS: $m/z = 255$ (M^+, 34%), 156 (100), 155 (95), 141 (95), 127 (95), 126 (73), 128 (69), 115 (52); UV ($CHCl_3$): λ_{max}, nm ($\log \varepsilon$) = 261 (3.92); Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.38; H, 6.67; N, 5.54.

1-[2-(3,4-Dihydro-7-methyl-1-naphthalenyl)ethyl]pyrrolidine-2,5-dione (3b). IR (KBr): 1700, 1775 (C═O str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz): $\delta = 2.0–2.93$ (13H, m); 3.66 (2H, t, $J = 7$ Hz, CH_2–N); 5.79 (1H, t, $J = 5$ Hz, C═C–H); 6.8–7.36 (3H, m, Ar–H); MS: $m/z = 269$ (M^+, 41%), 170 (76), 155 (88), 143 (100), 142 (44), 141 (44), 127 (44), 115 (23); UV ($CHCl_3$): λ_{max}, nm ($\log \varepsilon$) = 262 (3.93); Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.73; H, 7.08; N, 5.24.

1-[2-(3,4-Dihydro-6,7-dimethyl-1-naphthalenyl)ethyl]pyrrolidine-2,5-dione (3c). IR (KBr): 1705, 1775 (C═O str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz): $\delta = 2.0–3.0$ (16H, m); 3.66 (2H, t, $J = 7$ Hz, CH_2–N); 5.76 (1H, t, $J = 5$ Hz, C═C–H); 6.93 (1H, s, Ar–H); 7.16 (1H, s, Ar–H); MS: $m/z = 283$ (M^+, 54%), 184 (54), 182 (41), 169 (78), 157 (100), 141 (34), 127 (20), 115 (14); UV ($CHCl_3$): λ_{max}, nm ($\log \varepsilon$) = 266 (3.94); Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.42; H, 7.41; N, 4.80.

2. General Procedure for the Synthesis of Dehydrogenated Seco-azasteroids (4a–c)

Seco-azasteroid **3a–c** (200 mg) was heated with 5% Pd–C (100 mg) at 250°C for 15 min. It was extracted with hot EtOAc (4 × 50 cm^3). The combined EtOAc extracts were filtered to remove the traces of catalyst. Evaporation of the solvent gave a brown residue which was purified by column chromatography [silica gel, $CHCl_3$: MeOH (99.5 : 0.5)] to furnish the corresponding dehydrogenated compound **4a–c**.

1-[2-(1-Naphthalenyl)ethyl]pyrrolidine-2,5-dione (4a). ^{1}H-NMR ($CDCl_3$, 500 MHz): $\delta = 2.66$ (4H, s, CO–CH_2CH_2–CO), 3.33 (2H, t, $J = 7.8$ Hz, Ar–CH), 3.87 (2H, t, $J = 7.8$ Hz, N–CH), 7.38–7.76 (5H, m, H3-7 of naphthalene ring), 7.86 (1H, d, $J = 8.0$ Hz, H_2 of naphthalene ring), 8.22

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(1H, d, $J = 8.3$ Hz, H8 of naphthalene ring); MS: $m/z = 253$ (M^+, 24%), 155 (15), 154 (100), 153 (45), 152 (12), 141 (47), 139 (10), 115 (33); UV ($CHCl_3$): λ_{max}, nm ($\log \varepsilon$) = 271 (3.68); 283 (3.78); 291 (3.60); Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.77; H, 6.01; N, 5.51.

1-[2-(7-Methyl-1-naphthalenyl)ethyl]pyrrolidine-2,5-dione (4b). IR (KBr): 1700,1770 (C═O str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz): $\delta = 2.0$–2.8 (7H, m), 3.25 (2H, t, $J = 8$ Hz, Ar–CH_2), 3.9 (2H, t, $J = 8$ Hz, N–CH_2), 7.0–8.25 (6H, m, Ar–H); UV ($CHCl_3$): λ_{max}, nm ($\log \varepsilon$) = 271 (3.79), 283 (3.87), 291 (3.70); Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.48; H, 6.44; N, 5.30.

1-[2-(6,7-Dimethyl-1-naphthalenyl)ethyl]pyrrolidine-2,5-dione (4c). IR (KBr): 1700, 1770 (C═O str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz): $\delta = 2.0$–2.8 (10H, m), 3.33 (2H, t, $J = 8$ Hz, Ar–CH_2), 3.9 (2H, t, $J = 8$ Hz, N–CH_2), 7.0-8.1 (5H, m, Ar–H); MS: $m/z = 281$ (M^+, 34%), 183 (14), 182 (100), 170 (10), 169 (73), 168 (15), 167 (97), 165 (17), 154 (13), 153 (27), 152 (26), 128 (8); UV ($CHCl_3$): λ_{max}, nm ($\log \varepsilon$) = 272 (3.84), 280 (3.92), 292 (3.68); Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.79; H, 6.78; N, 4.95.

3. General Procedure for the Synthesis of Hydroxy Lactams (5a–c)

To a well-stirred mixture of dehydrogenated product **4a–c** (1 mmole) in dry MeOH (50 cm^3) under N_2 was added $NaBH_4$ (76 mg, 2 mmole) in dry MeOH (20 cm^3) at 0°C during a period of 15 min. The mixture was stirred at the same temperature for additional 2 h. MeOH was removed under vacuum at R.T. and the residue was quenched with 5% NH_4Cl solution (100 cm^3). It was extracted with $CHCl_3$ (3 × 25 cm^3). The combined $CHCl_3$ extracts were washed with water (2 × 25 cm^3) and then dried (anhyd. Na_2SO_4). Evaporation of solvent gave a brown residue which was purified by column chromatography [alumina (basic), $CHCl_3$: MeOH (98 : 2)] to furnish the corresponding hydroxy lactam **5a–c**.

1-[2-(1-Naphthalenyl)ethyl]-5-hydroxy-2-pyrrolidone (5a). IR (oil film): 1680 (C═O str.), 3350 (O–H str.); ^{1}H-NMR ($CDCl_3$, 200 MHz): $\delta = 2.23$–2.81 (7H, m, $H_{aliphatic}$ and 1 OH), 3.33 (1H, m, N–CH), 3.65 (1H, m, N-CH), 5.14 (1H, t, $J = 5.2$ Hz, N–CH–O), 7.00–7.28 (7H, m, Ar–H); UV ($CHCl_3$): λ_{max}, nm ($\log \varepsilon$) = 269 (3.67); 284 (3.89); 295 (3.61); Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.27; H, 6.71; N, 5.40. Found: C, 75.19; H, 6.77; N, 5.45.

1-[2-(7-Methyl-1-naphthalenyl)ethyl]-5-hydroxy-2-pyrrolidone (5b). IR (oil film): 1685 (C═O str.), 3400 (O–H str.); ^{1}H-NMR ($CDCl_3$, 200 MHz):

$\delta = 2.23-2.77$ (10H, m, $H_{aliphatic}$ and 1 OH), 3.38 (1H, m, N–CH), 3.63 (1H, m, N–CH), 5.11 (1H, t, $J = 5.2$ Hz, N–CH–O), 6.97–7.22 (6H, m, Ar–H); UV ($CHCl_3$): λ_{max}, nm ($\log \varepsilon$) = 271 (3.73); 282 (3.84); 290 (3.66); Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.69; H, 7.14; N, 5.15.

1-[2-(6,7-Dimethyl-1-naphthalenyl)ethyl]-5-hydroxy-2-pyrrolidone (5c). IR (oil film): 1685 (C═O str.), 3350 (O–H str.) cm^{-1}; ^{1}H–NMR ($CDCl_3$, 200 MHz): $\delta = 2.23-2.93$ (13H, m, $H_{aliphatic}$ and 1 OH), 3.36 (1H, m, N–CH), 3.66 (1H, m, N–CH), 5.26 (1H, t, $J = 5.2$ Hz, N–CH–O), 6.84–7.25 (5H, m, Ar–H); UV ($CHCl_3$): λ_{max}, nm ($\log \varepsilon$) = 272 (3.84), 281 (3.90), 291 (3.72); Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.42; H, 7.42; N, 4.99.

4. General Procedure for the Synthesis of Title Compounds (6)

A mixture of hydroxy lactam **5a–c** (50 mg) and $POCl_3$ (8 g) was allowed to stand under N_2 at 50°C for 8 h. The reaction mixture was poured onto ice and allowed to stand overnight. It was extracted with $CHCl_3$ ($3 \times 25\,cm^3$). The combined $CHCl_3$ extracts were washed with 10% Na_2CO_3 ($2 \times 25\,cm^3$), water ($2 \times 25\,cm^3$) and then dried (anhyd. Na_2SO_4). Evaporation of solvent gave a brown residue which was purified by column chromatography [alumina (basic), $CHCl_3$: MeOH (99.5 : 0.5)] to afford the corresponding title compound **6a–c**.

5,6,10,10a-Tetrahydrobenzo[*f*]pyrrolo[*2,1-a*]isoquinolin-8[9*H*]-one (6a). IR (KBr): 1680 (C═O str.) cm^{-1}; MS: $m/z = 237$ (M^+, 63%), 236 ($M^+ - 1$, 100), 181 (10), 180 (24), 165 (11), 153 (73), 152 (15); UV ($CHCl_3$): λ_{max}, nm ($\log \varepsilon$) = 272 (3.83), 281 (3.86), 293 (3.71); Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.36; H, 6.80; N, 5.61.

5,6,10,10a-Tetrahydro-3-methylbenzo[*f*]pyrrolo[*2,1-a*]isoquinolin-8[9*H*]-one (6b). IR (KBr): 1685 (C═O str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): $\delta = 2.51$ (3H, s, CH_3), 3.01–3.52 (7H, m), 4.01 (1H, m, H10*a*), 4.31 (1H, m, H6), 7.21–7.81 (5H, m, Ar–H); UV ($CHCl_3$): λ_{max}, nm ($\log \varepsilon$) = 271 (3.78), 281 (3.89), 291 (3.69); Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.36; H, 6.80; N, 5.61.

5,6,10,10a-Tetrahydro-2,3-dimethylbenzo[*f*]pyrrolo[*2,1-a*]isoquinolin-8[9*H*]-one (6c). IR (KBr): 1680 (C═O str.) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): $\delta = 2.50$ (3H, s, CH_3), 2.52 (3H, s, CH_3), 3.09–3.65 (7H, m), 4.03 (1H, m, H10*a*), 4.38 (1H, m, H6), 7.08–7.60 (4H, m, Ar–H); UV ($CHCl_3$): λ_{max}, nm ($\log \varepsilon$) = 272 (3.84), 281 (3.90), 293 (3.71); Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.39; H, 7.28; N, 5.24.

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