A SHORT TOTAL SYNTHESIS OF PALONOSETRON USING CATALYTIC HYDROGENATION†

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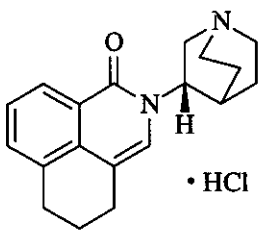
Abstract- The 5-HT_3 receptor antagonists (**1**) and (**2**) (palonosetron) were synthesized by an efficient new route. The critical hydrogenation of imide (**4**) was carried out with either Pd/C catalyst or PtO_2 catalyst.

A highly successful strategy to block emesis during chemotherapeutic treatment of cancer patients has been the use of 5-HT_3 receptor antagonists.[1] In an effort to improve on the current 5-HT_3 based anti-emetics available to oncologists, the highly potent 5-HT_3 receptor antagonists RS-42358-197 (**1**) and palonosetron (**2**) were introduced into clinical trials.[2] Palonosetron is currently in clinical development, while **1** has been dropped for this indication.



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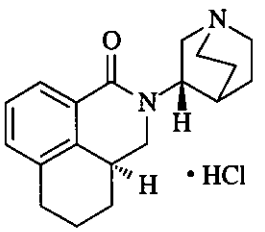
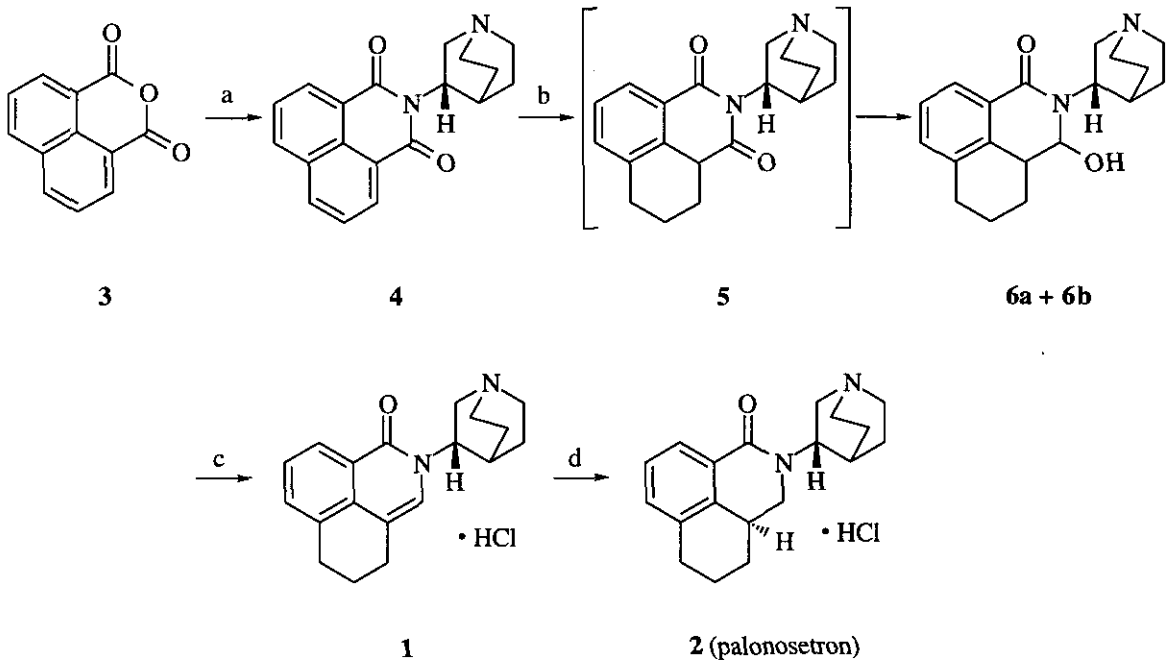


2 (palonosetron)

The initial synthetic route to make both **1** and palonosetron was used to make necessary drug supplies for initiating the clinical program, however, this was not suitable as a production process due to several drawbacks.[2] A different second generation synthesis was used to supply the clinical and development needs for drug substance. In this paper, an efficient and shorter third generation synthetic route to **1** and palonosetron is reported.

The new third generation synthetic route to **1** and palonosetron is outlined in the Scheme. The first step was the condensation of 1,8-naphthalic anhydride (**3**) with *S*-3-aminoquinuclidine to give imide (**4**) isolated as the free base. The carbon framework was intact at this point but the oxidation state of various centers needed adjustment.

Scheme[a]

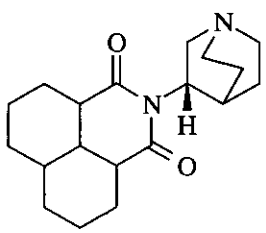


3 **4** **5** **6a + 6b**

1 **2** (palonosetron)

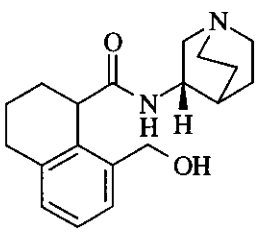
[a](a) *S*-3-aminoquinuclidine, 86 %; (b) H_2, 10 % Pd/C or PtO_2;
(c) H^+, from **4** to **1** 43 % (Pd/C) or 61 % (PtO_2); (d) H_2, 10 % Pd/C, 57 %.

The second step was the hydrogenation of imide (**4**) using either 10 % Pd/C or PtO_2 as the catalyst. While there have been many imides of 1,8-naphthalic anhydride made no study of their catalytic hydrogenation has been done.[3] The hydrogenation of imide (**4**) using 10 % Pd/C produced a mixture of hydroxy compound (**6b**) (67.5 %), hydroxy compound (**6a**) (7.5 %), and imide (**7**) (25 %). Hydroxy compounds (**6a**) and (**6b**) were two of the four possible diastereomers. The 9 to 1 selectivity between the hydroxy compounds was somewhat surprising and may have resulted from the tertiary nitrogen atom coordinating with the Pd catalyst surface providing a bias to one side of the molecule during hydrogenation.



(one major diastereomer)

7



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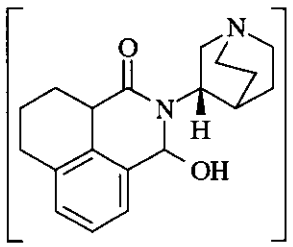

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Imide (**7**) was formed as an undesired side product during the Pd/C catalyzed hydrogenation of imide (**4**). Presumably, imide (**7**), and hydroxy compounds (**6a**) and (**6b**) were formed by further hydrogenation of imide (**5**). The hydrogenation of imide (**5**) proceeded by two competitive pathways, either hydrogenation of the aliphatic carbonyl to give hydroxy compounds (**6a**) and (**6b**), or hydrogenation of the aromatic ring to give imide (**7**). The selectivity was 3 to 1 for the desired hydrogenation of the aliphatic carbonyl versus the aromatic ring for imide (**5**). Imide (**7**) could be isolated from the hydrogenation mixture by chromatography. For preparative purposes, the mixture of **6a**, **6b**, and **7** was treated directly with HCl to effect dehydration giving **1** and unaffected **7**. Conveniently, **1** was isolated as the crystalline HCl salt.

When the second step hydrogenation was done with PtO_2 caltalyst, the products were hydroxy compound (**6b**) (51 %), hydroxy compound (**6a**) (29 %), and primary alcohol (**8**) (20 %). The selectivity between hydroxy compounds (**6b**) and (**6a**) was only 1.8 to 1 which was much less than with palladium catalyst. The lower selectivity may have been due to less coordination of the quinuclidine portion of the molecule with the Pt suface, versus the Pd surface.

Primary alcohol (**8**) was an undesired byproduct formed during the PtO_2 catalyzed hydrogenation of imide (**4**). Presumably, primary alcohol (**8**), and hydroxy compounds (**6a**) and (**6b**) were all formed by further hydrogenation of imide (**5**). The hydrogenation of imide (**5**) proceeded by two competitive pathways; either hydrogenation of the aliphatic carbonyl to desired hydroxy compounds (**6a**) and (**6b**), or hydrogenation of the aromatic carbonyl to undesired primary alcohol (**8**). The formation of primary alcohol (**8**) was almost certainly a two step process with the first step being hydrogenation of the aromatic carbonyl of imide (**5**) to secondary alcohol (**9**). The second step to primary alcohol (**8**) proceeds either by hydrogenolysis of the carbon-nitrogen bond of **9** or by equilibration of **9** to the amide-aldehyde followed by

hydrogenation of the aldehyde to form primary alcohol (**8**). The selectivity was 4 to 1 for the desired hydrogenation of the aliphatic carbonyl to the undesired hydrogenation of the aromatic carbonyl. It was surprising that the PtO_2 catalyzed hydrogenation of imide (**4**) led to primary alcohol (**8**) as a byproduct and the Pd/C catalyzed hydrogenation led to imide (**7**) as a byproduct, since Pt catalysts usually hydrogenate aromatic rings more efficiently than Pd catalysts, and aromatic carbonyls are more easily reduced by Pd rather than Pt catalysts.[4] For preparative purposes, HCl was added to the mixture of **6a**, **6b**, and **8** which effected dehydration to give **1** and unaffected **8**. As before, (**1**) was isolated as the crystalline HCl salt.

The isolated yield from imide (**4**) to **1** was better using PtO_2 catalyst (61 %) compared to using Pd/C catalyst (43 %) despite the similarity in contained yields (80 % vs. 75 %). The higher yield using PtO_2 catalysis was primarily a result of imide (**7**) interferring with the crystallization of **1** as the HCl salt more than primary alcohol (**8**).

The overall yield from 1,8-naphthalic anhydride (**3**) to **1** in three efficient steps was 52 % and in four steps to palonosetron was 30 %. Palonosetron was made from **1** by a catalytic hydrogenation process which has already been reported.[2]

In summary, a new efficient third generation synthetic route to **1** and the anti-emetic palonosetron was developed. The hydrogenation with both Pd/C and PtO_2 catalysts were studied on the key 1,8-naphthalic imide (**4**) intermediate. The selectivity for desired aliphatic carbonyl hydrogenation versus aromatic ring hydrogenation was 3 to 1 for imide (**5**) using Pd/C catalyst. The selectivity for desired aliphatic carbonyl hydrogenation versus aromatic carbonyl hydrogenation for imide (**5**) was 4 to 1 using PtO_2 catalyst.

EXPERIMENTAL

(*S*)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,3-dihydro-1,3-dioxo-1*H*-benz[*de*]isoquinoline (4). A mixture containing *S*-3-aminoquinuclidine (6.7 g, 53 mmol), 1,8-naphthalic anhydride (10.0 g, 50.5 mmol), and *i*-PrOH (150 ml) was refluxed for 3 h. Distilled out solvent (50 ml) and cooled the solution slowly to rt. The solution was filtered to give a first crop of **4** (10.9 g) as light yellow crystals. A second crop was obtained by concentration of the filtrate by distillation (volume of 20 ml), cooling the

solution, and filtration of the mixture to give a second crop of **4** (2.4 g, total yield 86%) as light yellow crystals: mp 202.9-203.4 °C; $[\alpha]^{25}_{D}$ -69.4 ° (c=0.74, MeOH); ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.39-1.49 (m, 1), 1.67-1.77 (m, 1), 1.89-2.06 (m, 2), 2.13-2.25 (m, 1), 2.87-2.98 (m, 3), 3.08-3.16 (m, 1), 3.52-3.61 (m, 1), 4.11 (dd(br), 1, *J* = 7.2, 13.3), 5.24-5.30 (m, 1), 7.75 (dd, 2, *J* = 7.4, 8.2), 8.20 (dd, 2, *J* = 1.1, 8.3), 8.58 (dd, 2, *J* = 1.1, 7.3); ^{13}C nmr (75 MHz, $CDCl_3$) δ 23.32 (2), 28.55 (1), 30.46 (2), 47.49 (2), 47.54 (2), 48.59 (2), 52.32 (1), 123.27 (0), 126.99 (1), 128.00 (0), 131.19 (1), 131.35 (0), 133.58 (1), 165.43 (0); ir (KBr) 1699, 1659, 1628, 1590 cm^{-1}; Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.13; H, 5.80; N, 8.93.

(*S*)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1-oxo-1*H*-benz[*de*]isoquinoline hydrochloride (1) by hydrogenation using 10 % Pd/C catalyst. A mixture containing imide (**4**) (9.5 g, 31 mmol), wet 10 % Pd/C (39 g, 60 % H_2O), and EtOH (140 ml) was stirred under 120 psig of hydrogen at room temperature for 6 d 18 h. The mixture was warmed to 50 °C and filtered through a pad of celite which was washed with EtOH (3 X 150 ml, 50 °C). The filtrates were combined and concentrated *in vacuo* to a light yellow foam. From analysis of the ^{1}H nmr spectrum, the foam was composed of hydroxy compound (**6b**) (67.5 %), hydroxy compound (**6a**) (7.5 %), and imide (**7**) (25 %). The foam was dissolved in *i*-PrOH (100 ml) and 4 M HCl/*i*-PrOH (10 ml, 40 mmol) was added. The solution was heated to reflux and solvent (81 ml) was distilled out. The solution was cooled to room temperature overnight and further cooled for 3h in an ice/water bath. The solution was filtered to give **1** (4.37 g, 43 %) as white crystals: identical to material made previously.[2]

(*S*)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1-oxo-1*H*-benz[*de*]isoquinoline hydrochloride (1) by hydrogenation using PtO_2 catalyst. A mixture containing imide (**4**) (5.33 g, 17.4 mmol), PtO_2 (0.80 g), and EtOH (80 ml) was stirred under 120 psig of hydrogen at room temperature for 6 d 17 h. The reaction mixture was filtered through a pad of celite which was washed with EtOH (50 ml). The filtrates were combined and concentrated *in vacuo* to a yellow foam. From analysis of the ^{1}H nmr spectrum, the foam was composed of hydroxy compound (**6b**) (51 %), hydroxy compound (**6a**) (29 %), and amide-alcohol (**8**) (20 %). The foam was dissolved in i-PrOH (80 ml) and added 4 M HCl/*i*-PrOH (7.2 ml, 28.8 mmol). The solution was heated to reflux and solvent (66 ml) was distilled out.

The solution was cooled to room temperature overnight and further cooled for 4 h in an ice/water bath. The solution was filtered to give **1** (3.53 g, 61 %) as off-white crystals: identical to material made previously.[2]

2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-3-hydroxy-1-oxo-1*H*-benz[*de*]isoquinoline (6a) and (6b). The foam from another PtO_2 catalyzed hydrogenation was purified by flash chromatography using 1 % NH_4OH/10 % MeOH/89 % CH_2Cl_2 as the eluent to give **6a** and **6b**. Hydroxy compound (**6a**) was recrystallized from *i*-PrOH to give an analytical sample as white crystals: mp 188.1-188.8 °C; $[\alpha]^{25}_D$ 70.8 ° (c=0.42, MeOH); ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.47-2.16 (m, 9), 2.75-3.26 (m, 9), 4.77 (m, 1), 5.19 (d, 1, *J* = 3.3), 7.27 (m, 2), 7.87 (m, 1); ^{13}C nmr (75 MHz, $CDCl_3/C_6D_6$) δ 20.77, 21.91, 25.04, 26.45, 26.82, 28.21, 40.38, 46.83, 47.25, 49.96, 50.60, 78.46, 125.67, 126.58, 128.89, 132.31, 133.04, 136.59, 164.18; ir (KBr) 1644, 1593 cm^{-1}; Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 72.70; H, 7.69; N, 9.02. Further elution gave **6b**: oil or foam, free base: $[\alpha]^{25}_D$ -110.8 (c=0.48, MeOH); ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.56 (m, 1), 1.74-1.87 (m, 4), 2.00-2.16 (m, 3), 2.20 (m, 1), 2.79-2.92 (m, 6), 3.03-3.11 (m, 1), 3.23 (m, 1), 3.46-3.56 (m, 1), 4.42 (m, 1), 5.07 (d, 1, *J* = 3.2), 7.28 (m, 2), 7.88 (m, 1); ^{13}C nmr (75 MHz, $CDCl_3$) δ 20.88, 21.99, 25.06, 25.20, 27.40, 28.30, 40.84, 46.06, 46.88, 52.39, 53.31, 80.59, 125.81, 126.88, 128.21, 132.89, 132.96, 137.05, 165.38; ir (KBr) 1651, 1593 cm^{-1}; ms *m/z* (M^+) 312.

Isolation of 6b as HCl salt. The foam from another hydrogenation using 10 % Pd/C was dissolved in i-PrOH and then cooled in an ice/water bath. The HCl presumably came from the catalyst. The solution was filtered to give **6b** (HCl salt) as white crystals: mp >280 °C; $[\alpha]^{25}_D$ -91.3 ° (c=0.63, MeOH); ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.61-2.16 (m, 8), 2.47 (m, 1), 2.75-2.87 (m, 2), 3.12-3.37 (m, 6), 3.74-3.80 (m, 1), 4.24-4.29 (m, 1), 5.05 (d, 1, *J* = 3.1), 5.97 (s(br), 1), 7.20-7.28 (m, 2), 7.73 (dd, 1, *J* = 1.6, 7.3); ^{13}C nmr (75 MHz, $CDCl_3$) δ 20.08 (2), 23.26 (2), 24.55 (2), 25.00 (1), 25.95 (2), 29.41 (2), 41.80 (1), 47.29 (2), 47.64 (2), 53.45 (1), 53.54 (2), 82.33 (1), 126.38 (1), 127.70 (1), 128.99 (0), 134.47 (1), 135.43 (0), 138.34 (0), 168.60 (0); ir (KBr) 1647, 1593 cm^{-1}; ms *m/z* (M^+) 312; Anal. Calcd for $C_{19}H_{25}N_2O_3Cl$: C, 65.41; H, 7.22; N, 8.03; Cl, 10.16. Found: C, 65.38; H, 7.41; N, 8.13; Cl, 10.29.

2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6,6a,7,8,9,9a,9b-dodecahydro-1,3-dioxo-1*H*-benz[*de*]isoquinoline (7). From flash chromatography of the foam from the hydrogenation using 10 % Pd/C as the catalyst could be isolated **7** as an oil: $[\alpha]^{25}_{D}$ -37.9 ° (c=2.9, MeOH). All the nmr data is for the major diastereomer only. ^{1}H nmr (300 MHz, $CDCl_3$) δ 0.91-2.07 (m, 16), 2.12-2.21 (m, 2), 2.32-2.41 (m, 2), 2.55-2.97 (m, 5), 3.31-3.40 (m, 1), 3.67-3.77 (m, 1), 4.73-4.79 (m, 1); ^{13}C nmr (75 MHz, $CDCl_3$) δ 23.03, 25.02, 25.19, 27.30, 27.49, 28.21, 30.26, 32.19, 32.27, 42.31, 43.84, 46.61, 46.91, 47.27, 47.32, 48.61, 51.61, 175.51, 175.61; HRms Calcd for $C_{19}H_{28}N_2O_2$: 316.2151. Found: 316.2146. Anal. Calcd for $C_{19}H_{28}O_2N_2 \cdot 0.2H_2O$: C, 71.31; H, 8.94; N, 8.75. Found: C, 71.36; H, 8.74; N, 8.90.

***N*-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-1,2,3,4-tetrahydro-8-hydroxymethylnaphthalene-1-carboxamide (8).** From flash chromatography of the foam from the hydrogenation using PtO_2 as the catalyst could be isolated **8** as an oil: ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.32-1.37 (m, 2), 1.56-1.62 (m, 2), 1.70-1.92 (m, 4), 2.20-2.26 (m, 1), 2.34-2.42 (m, 1), 2.55-2.91 (m, 6), 3.10 (ddd, 1, J = 2.0, 9.6, 14.1), 3.80-3.88 (m, 1), 3.91-3.93 (m, 1), 4.28 (s (br), 1, exchanged with D_2O), 4.54 (s, 2), 6.34 (d (br), 1, J = 7.3, exchanged with D_2O), 7.08-7.11 (m, 1), 7.17-7.23 (m, 2); ^{13}C nmr (75 MHz, $CDCl_3$) δ 19.36, 19.76, 25.19, 25.26, 26.08, 29.10, 42.58, 46.32, 46.44, 47.04, 55.20, 62.44, 126.49, 127.28, 129.08, 133.31, 138.74, 139.45, 174.38; HRms Calcd for $C_{19}H_{26}N_2O_2$: 314.1994. Found: 314.1992. Anal. Calcd for $C_{19}H_{26}N_2O_2 \cdot 0.2H_2O$: C, 71.76; H, 8.37; N, 8.81. Found: C, 71.75; H, 8.32; N, 8.92.

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† Contribution # 936 from the Institute of Organic Chemistry, Syntex Research.

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Received, 26th February, 1996