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Hydrogenation of a Chiral 1*H*-Benz[*de*]isoquinolin-1-one and an Equilibration Using Palladium Catalyst

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Abstract:

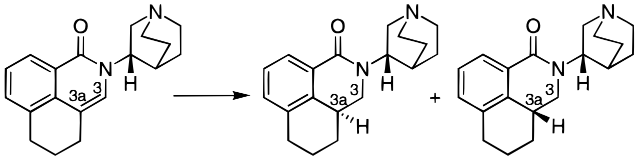
The catalytic hydrogenation of a chiral 1*H*-benz[*de*]isoquinolin-1-one to palonosetron and the undesired diastereomer was optimized using a variety of conditions and catalysts. The most selective catalyst for the production of palonosetron was an unreduced palladium on carbon catalyst. The (+)- and (−)-camphorsulfonic acid salts of the 1*H*-benz[*de*]isoquinolin-1-one and the complex of the 1*H*-benz[*de*]isoquinolin-1-one with Mg^{2+} upon catalytic hydrogenation gave the greatest preference for the undesired diastereomer. An equilibration of the undesired diastereomer from hydrogenation and palonosetron as hydrochloride salts using hydrogen-activated palladium on carbon catalyst under a nitrogen atmosphere was developed. The procedure was used to recycle the hydrochloride salt of the undesired diastereomer from hydrogenation into pure palonosetron hydrochloride.

Introduction

There has been a great deal of interest in 5-HT$_3$ receptor antagonists for the treatment of nausea and vomiting often accompanying cancer chemotherapy[1] and for other potential therapeutic uses.[2] Palonosetron (**2**) is one of the most potent 5-HT$_3$ receptor antagonists known and is currently in clinical trials.[3]

The synthesis of palonosetron is based on the hydrogenation of the 3,3a double bond of chiral 2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one **1** (Scheme 1).[3−5] It was hypothesized that the chiral 3-quinuclidine portion of the molecule might guide the hydrogenation to the desired **2** and not its diastereomer **3**. Since this hydrogenation is the last step in the synthetic route, it is very important for the efficient synthesis of **1**. In this paper, we report the details of the optimization of selectivity for the hydrogenation of **1**, and an equilibration between diastereomers **2a** and **3a** using palladium catalyst.

Scheme 1



1
1a = **1**•HCl

2
2a = **2**•HCl

3
3a = **3**•HCl

Results and Discussion

The optimization of catalytic hydrogenations is often a challenging problem due to the difficulty in predicting the changes that will occur from even minor variations in experimental conditions.[6] However, a systematic approach can lead to significant improvements in important processes. Our optimization experiments began with the hydrogenation of various salts of **1** using 10% Pd/C as the catalyst and are reported in Table 1. There was only modest selectivity for **2** in several of the entries (2, 3, 7 and 8). The difference in both the conversion of **1** and the ratio of **2**:**3** for the various salts indicated that the ion pairs may be tight during the hydrogenation. The most intriguing results were with the (+)- and (−)-camphorsulfonic acid (CSA) salts (entries 5 and 6), which were relatively selective for **3**. The similarity in the results from both enantiomers of CSA suggests that the CSA/**1** ion pairs with both enantiomers of CSA are composed of **1** in a similar conformation which is preferentially blocked from one face.

The catalytic hydrogenation of **1** was investigated with a wide selection of catalysts, and the successful results are tabulated in Table 2. Reactions with several other catalysts (PdO, Pt/C, Ra-Ni, Ru/C, and Ru/Al$_2$O$_3$) were attempted but produced little **2** or **3**. The platinum- and rhodium-based catalysts (entries 1−3) all gave modest selectivity for **2**. The palladium catalysts on a support other than carbon (entries 4−6) gave somewhat better selectivity for **2**, with 5% Pd/BaSO$_4$ (entry 4) having an encouraging ratio of 2.7:1 for **2**:**3**. Palladium on carbon catalyst was tried in a selection of solvents (entries 7−12), with the ratio of **2**:**3** up to 3.2:1 in EtOAc using an unreduced catalyst (entry 11). When Pearlman's catalyst was used (entry 13), the ratio was equally high at 3.3:1 for **2**:**3**. In entries 14−17 magnesium perchlorate or lithium perchlorate was added in an attempt to coordinate the Li$^+$ or Mg^{2+} with **1**. The experiments containing magnesium perchlorate (entries 14−16) all had

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Table 1. **Catalytic hydrogenations (10% Pd/C[a]) of various salts of 1**

entry	salt	solvent	conversion of **1** (%)	ratio of **2**:**3**
1	HOAc	EtOAc	97	0.85:1
2	benzoic	EtOAc	36	1.4:1
3	*d*-tartaric	EtOAc	6	1.2:1
4	(+)-mandelic	EtOAc	53	1.0:1
5	(+)-CSA	EtOAc	99	0.35:1
6	(−)-CSA	EtOAc	99	0.34:1
7	HCl	EtOAc	3	1.5:1
8	HCl	EtOH/H_2O	99	1.2:1

[a] Engelhard reduced, dry.

Table 2. **Catalytic hydrogenations of 1**

entry	catalyst	solvent	conversion of **1** (%)	ratio of **2**:**3**
1	PtO_2	EtOAc	91	1.6:1
2	5% Rh/Al_2O_3	EtOAc	8	1.2:1
3	5% Rh/Al_2O_3	EtOH	75	1.1:1
4	5% Pd/$BaSO_4$	EtOAc	45	2.7:1
5	5% Pd/$SrCO_3$	EtOAc	99	2.1:1
6	5% Pd/Al_2O_3	EtOAc	20	1.7:1
7	10% Pd/C[a]	toluene	88	2.5:1
8	10% Pd/C[a]	EtOAc	67	2.3:1
9	10% Pd/C[a]	EtOH	95	1.5:1
10	10% Pd/C,[b] w[c]	toluene	98	2.1:1
11	10% Pd/C,[b] w	EtOAc	95	3.2:1
12	10% Pd/C,[b] w	THF	97	3.0:1
13	20% Pd(OH)$_2$/C, w	EtOAc	97	3.3:1
14	10% Pd/C,[a] Mg[d]	acetone	70	0.48:1
15	10% Pd/C,[a] Mg	EtOAc	32	0.45:1
16	10% Pd/C,[a] Mg	EtOH	22	0.56:1
17	10% Pd/C,[a] Li[e]	acetone	14	2.2:1

[a] Engelhard reduced. [b] Degussa Type E101 N/W. [c] w = water wet. [d] Mg = Mg(ClO_4)$_2$. [e] Li = $LiClO_4$.

a substantial lowering of the ratio of **2**:**3**. The Mg^{2+} was probably coordinated to the tertiary nitrogen of **1**, which holds **1** in a conformation in which one face was preferentially hindered.

Since the highest ratio of **2**:**3** was with palladium on carbon catalysts, a detailed investigation was undertaken (Table 3). A series of Engelhard Escat catalysts were chosen for their commercial availability and variety. All of the experiments were performed in THF to keep the conditions uniform. The palladium catalysts which were reduced (entries 1−4, 5, 8, and 10) consistently gave ratios of 2.1:1 to 2.5:1 for **2**:**3**. The best results were with unreduced catalysts (entries 6, 7, 9, and 11), which gave ratios of 2.8:1 to 3.3:1 for **2**:**3**. The conversion of **1** to **2**/**3** was also the highest for the unreduced catalysts. The unreduced palladium catalysts which become reduced under the hydrogen atmosphere must have a different surface than the reduced catalysts. The best results from Table 2 (entries 11−13) were consistent, on reexamination, with the use of unreduced palladium on carbon catalysts in those examples.

With even the best ratio of **2**:**3** at 3.3:1, a large buildup of **3** was anticipated during production of **2**. The purification of **2** from **3** was achieved in good yield by crystallization of the hydrochloride salts (**2a** and **3a**).[3,4] The transformation of **3** into **2** was highly desirable to improve the overall efficiency of the process. The interconversion of **3a** and **2a** was achieved using hydrogen-activated palladium on carbon catalyst under a nitrogen atmosphere (Scheme 2).[7] The equilibration of **3a** and **2a** using this unique equilibration procedure is demonstrated in Figure 1. To investigate the equilibration, the process was started with either pure **2a** or pure **3a** and after five hydrogen/nitrogen cycles had fully equilibrated to a final ratio of **2a**:**3a** of 1.26:1 (55.8% of **2a**). The equilibration took place under the nitrogen atmosphere and not under the hydrogen atmosphere part of the cycle. The hydrogen part of the cycle served to activate the catalyst and hydrogenate any **1a** formed. There was only 0.5−2.0% leakage to **1a** during the nitrogen atmosphere part of the cycle.

The mechanism is speculated to be dehydrogenation at the 3a position of either **2a** or **3a** followed by unselective hydrogenation of the 3a position, all while on the catalyst surface. The interconversion occurred only under the nitrogen atmosphere, because the catalyst became hydrogen starved and had free sites for dehydrogenation to take place. The leakage to **1a** is by dehydrogenation of both the 3a and 3 positions of **2a** or **3a**. The very small amount of leakage to **1a** indicates that hydrogenation of a molecule dehydrogenated at the 3a position must be fast compared to further dehydrogenation of the 3 position leading to **1a**.

The interconversion was conducted on the free base of **2** and **3**, but it was much slower and not fully to equilibrium even after several months. The interconversion also generated up to 20% leakage to **1**.

For the practical production of **2a** the equilibration was typically carried out on the mother liquors obtained from the crystallization of **2a**, which contained a mixture of **2a** and **3a** but enriched in **3a** (see Figure 1, typical recycle). The full equilibration of this mixture in pilot plant facilities took only one cycle of hydrogen (activation of the catalyst), nitrogen (equilibration), and hydrogen (hydrogenation of the small amount of **1a** produced). Pharmaceutical quality **2a** was obtained from the fully equilibrated mixture by selective crystallization, thus achieving recycle of **3a** into desired **2a**. The mother liquors generated in the equilibration were effectively used as starting material for a new equilibration procedure and could be done repeatedly. The equilibration process has become an important part of the efficient synthesis of **2a**.

In summary, the most selective hydrogenations of **1** into the desired **2** were carried out with unreduced palladium on carbon catalyst. The (+)- and (−)-CSA salts of **1** and the complex of **1** with Mg^{2+} gave the greatest preference for the undesired **3**. An equilibration of **2a** and **3a** under a nitrogen atmosphere using hydrogen-activated palladium on carbon catalyst was used in a process to convert **3a** into pure **2a**.

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Table 3. **Optimization of the hydrogenation of 1 using Engelhard Escat catalysts**

entry	Escat no.	catalyst[a]	distribn[a]	type[a]	surface area (m^2/g)[a]	mean particle size (μm)[a]	conversion of **1** (%)	ratio of **2**:**3**
1	10	5% Pd/C	mixed	R/W	850	21	40	2.3:1
2	11	5% Pd/C	mixed	R/W	950	28	54	2.2:1
3	12	5% Pd/C	mixed	R/W	1350	27	32	2.5:1
4	13	5% Pd/C	mixed	R/W	900	28	53	2.2:1
5	101	5% Pd/C	edge	R/W	850	21	49	2.3:1
6	103	5% Pd/C	edge	U/W	850	21	77	3.3:1
7	110	5% Pd/C	edge	U/W	950	28	73	2.8:1
8	111	5% Pd/C	edge	R/W	950	28	48	2.1:1
9	112	5% Pd/C	edge	U/W	950	28	89	3.2:1
10	120	3% Pd/C	mixed	R/W	850	21	16	2.3:1
11	122	3% Pd/C	edge	U/W	850	21	67	3.2:1

[a] Engelhard data. R = reduced, U = unreduced, W = water wet.

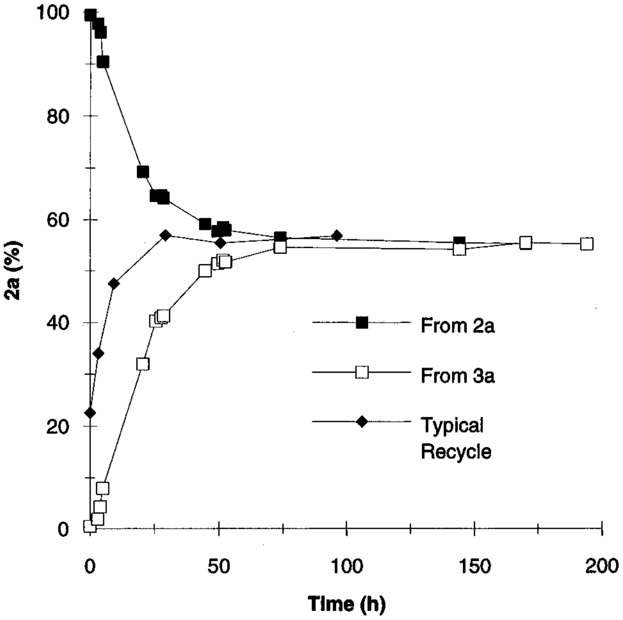
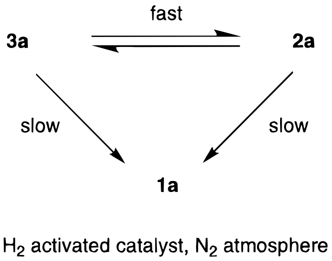


Figure 1. **Equilibration of 2a and 3a using Pd/C catalyst.**

Scheme 2



Experimental Section

General. All materials were purchased from commercial suppliers and used without further purification. For the ^{1}H NMR data *J* values are in hertz. HPLC analysis was performed on a Zorbax Sil column (4.6 mm × 25 cm) using NH_4OH_{aq}/MeOH/CH_2Cl_2 (0.4:10:89.6, v/v/v) as the mobile phase. All atmospheric changes were performed by evacuation and filling with nitrogen or hydrogen three times. **1a** and **2a** were identical to material reported previously.[3-5]

(*S*)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one (1). A solution of **1a** (170 g, 0.51 mol), water (1.0 L), and 50% NaOH (62 g) was extracted three times with EtOAc (1.0 L, 0.75 L, and 0.50 L). The extracts were combined, dried over sodium sulfate (310 g), filtered, and concentrated *in vacuo*. The residue was dissolved in EtOAc (650 mL) at reflux, and hexane (2.0 L) was added while reflux was maintained. The solution was stirred at rt overnight and further cooled in an ice/water bath for 2 h. The resulting crystals were filtered, washed with hexane (300 mL), and dried to give **1** (134.5 g, 89%) as off-white crystals: mp 143.8−144.6 °C; $[\alpha]^{25}_D$ 43.1° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47−1.55 (m, 1), 1.68−2.10 (m, 6), 2.71−3.15 (m, 9), 3.48 (ddd, 1, *J* = 2.2, 10.4, 14.6), 5.14−5.20 (m, 1), 7.15 (s, 1), 7.33−7.45 (m, 2), 8.27 (dd, 1, *J* = 2.3, 7.1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.36, 22.90, 25.98, 27.56, 27.69, 29.88, 47.26, 47.51, 51.85, 52.45, 113.31, 122.74, 125.71, 125.90, 126.36, 130.91, 133.21, 135.14, 162.53. Anal. Calcd for $C_{19}H_{22}ON_2$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.63; H, 7.49; N, 9.60.

General Hydrogenation of 1. A mixture of **1** (45 mg, 0.15 mmol), catalyst (22 mg dry weight), additive if appropriate (0.16 mmol), and solvent (2 mL) was stirred under a hydrogen atmosphere for 48 h (for Table 2 all were for 72 h). The reaction mixture was filtered through a plug of Celite, and the catalyst cake was washed with solvent (2 mL). The total filtrate was analyzed by HPLC.

(3a*R*)-2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1*H*-benz[*de*]isoquinolin-1-one Hydrochloride (3a). A portion of the mother liquor solution from the crystallization of **2a** which was composed of **2a** (13.3%), **3a** (86.3%), and **1a** (0.4%) was concentrated *in vacuo* to a thick oil (357 g). The oil was dissolved in *i*-PrOH (1.2 L) and brought to reflux, and hexane (4.0 L) was added while the mixture was at reflux. The solution was cooled overnight to rt. The resulting crystals were filtered and dried to give crude **3a** (244 g). The crude material was dissolved in refluxing *i*-PrOH (1.1 L), and hexane (2.0 L) was added while the mixture was at reflux. The solution was cooled overnight at rt. The resulting crystals were filtered and dried to give crude **3a** (220 g). The dried material was dissolved in water (1.0 L), and 50% NaOH (73 g) was added. The mixture was extracted twice with toluene (2 L and 1 L) at 45−50 °C. The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was dissolved in toluene (350 mL) at reflux, and hexane (1.7 L) was added while reflux was maintained. The solution was cooled at rt overnight. The crystallization was further cooled in an ice/water bath for 2 h. The crystals were filtered, washed with hexane (450 mL), and dried to give **3** (143.4

g). A portion of **3** (90.0 g) was dissolved in *i*-PrOH (300 mL), and 3.5 M HCl/*i*-PrOH (100 mL) was added. The solution was stirred at rt overnight and further cooled in an ice/water bath for 2 h. The crystals were filtered, washed with *i*-PrOH (100 mL), and dried to give **3a** (91.1 g) as white crystals: mp 274−276 °C; $[\alpha]^{25}_{D}$ 95° ($c = 0.9$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.35−1.47 (m, 1), 1.68−2.27 (m, 7), 2.39−2.42 (m, 1), 2.74−2.93 (m, 2), 3.07−3.16 (m, 1), 3.26−3.38 (m, 4), 3.58−3.85 (m, 4), 4.83−4.91 (m, 1), 7.25−7.28 (m, 2), 7.80−7.85 (m, 1), 12.19 [s(br), 1]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.28, 21.92, 23.66, 25.99, 26.33, 28.15, 34.89, 46.43, 47.88, 50.53, 50.76, 125.93, 126.86, 128.84, 132.76, 135.06, 136.56, 165.74; IR (KBr) 1645, 1591 cm^{-1}. Anal. Calcd for $C_{19}H_{25}N_2OCl$: C, 68.56; H, 7.57; N, 8.42. Found: C, 68.59; H, 7.52; N, 8.26.

Equilibration of (3a*S*)-2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1*H*-benz[*de*]isoquinolin-1-one Hydrochloride (2a). A mixture of **2a** (5.6 g), 10% palladium on carbon (3.7 g, Degussa Type E101 N/W, 54% water), ethanol (72 mL), and water (23 mL) was stirred under a hydrogen atmosphere for 3 h. The atmosphere was switched to nitrogen for an average of 31 h. The atmosphere was cycled through hydrogen and nitrogen atmospheres a total of four more times as above. The atmosphere was switched to hydrogen for 24 h. Samples for HPLC analysis were taken from the reaction mixture by withdrawing a small sample through a rubber septum using a needle and syringe. The final mixture contained **2a** (55.3%), **3a** (43.8%), and **1a** (0.9%). See Figure 1 for process results.

Equilibration of (3a*R*)-2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1*H*-benz[*de*]isoquinolin-1-one Hydrochloride (3a). The procedure was the same as the equilibration of **2a** except starting with **3a**.

Synthesis of 2a from a Typical Mixture of Enriched 3a. The mother liquors from the isolation of **2a** were combined and concentrated *in vacuo*, and the residue (12.0 kg, 36.1 mol) contained **3a** (79.6%), **2a** (20.2%), and **1a** (0.2%). The residue was dissolved in ethanol (163 L) and water (53 L). The solution was stirred with 10% palladium on carbon (8.1 kg, Degussa Type E101 N/W, 54% water) for 4 h under a hydrogen atmosphere. The atmosphere was switched to nitrogen for 96 h. A reaction sample was composed of **3a** (42.7%), **2a** (56.8%), and **1a** (0.5%). The atmosphere was switched to hydrogen for 24 h. A product sample contained **3a** (43.4%), **2a** (56.5%), and **1a** (0.1%). A solution of sodium bisulfite (500 g) dissolved in water (2.3 kg) was added to the hydrogenation mixture. After 1h, the mixture was filtered through a pad of Solka Floc[8] and the collected catalyst washed with a solution of ethanol (4 L) and water (4 L). The filtrate was concentrated *in vacuo* to a volume of 55 L, and 50% NaOH (5.7 kg) was added. The solution was extracted three times with EtOAc (75 L, 2 × 37.5 L). The extracts were combined, dried over sodium sulfate (13.7 kg), filtered, and concentrated *in vacuo*. The residue was dissolved in 2-propanol (96 L), and concentrated HCl (3.3 L) was added. The solution was concentrated by distillation removing 40.9 kg of solvent. The solution was aged at rt overnight and further cooled for 4 h at 5 °C. The resulting crystals were filtered off, washed with 2-propanol (12 L), and dried to give crude **2a** (3.43 kg). The crude material was dissolved in refluxing 2-propanol (117 L) and water (5.0 L). The solution was concentrated by distillation removing 59 kg of solvent, then aged at rt overnight, and further cooled at 5 °C for 4 h. The resulting crystals were filtered, washed with 2-propanol (12 L), and dried to give **2a** (3.05 kg, 25%) as white crystals: HPLC, 99.2%.

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(8) Powdered cellulose, CAS No. 9004-34-6, available from Fiber Sales and Development Corp.

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1997.