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An Investigation into the Formation of Impurity B during the Optimization of Naratriptan Hydrochloride†

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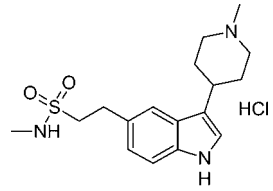
Abstract:

During the process development of naratriptan hydrochloride we have made an unusual observation about the enhanced levels of intermediate 3 as an impurity (impurity B) in the final stage. Detailed investigation has led to the conclusion that impurity B is not only a carried over but also formed via acid catalyzed dehydration of yet another process related impurity. The present work details a report of the journey towards the development of an efficient process for the commercial production of naratriptan hydrochloride substantially free from the impurity B.

Introduction

Naratriptan hydrochloride (trade name Amerge) exhibits selective vasoconstrictor activity as a serotonin 5-HT1-receptor agonist[1−3] and is widely used as an antimigraine agent.[4] It is chemically known as *N*-methyl-2-[3-(1-methylpiperidin-4-yl)-1*H*-indol-5-yl] ethanesulfonamide hydrochloride, which may be represented by the formula **5**.



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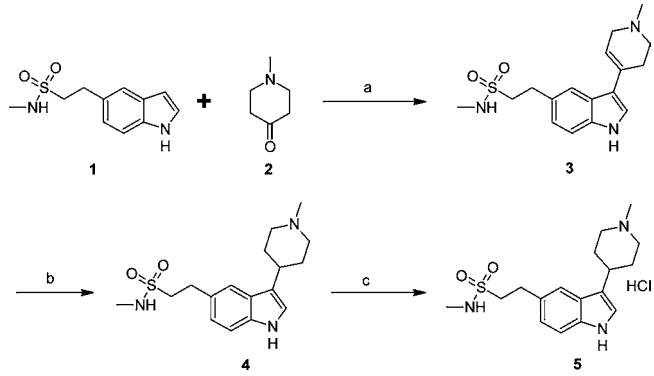
Literature study reveals several methods of synthesis for naratriptan hydrochloride,[5−8] of which the authors considered the reaction of 2-(1*H*-indol-5-yl)-*N*-methylethanesulfonamide **1** with *N*-methyl piperidin-4-one **2** by means of KOH in refluxing methanol, yielding *N*-methyl-2-[3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indol-5-yl]ethanesulfonamide (**3**), reducing the C=C double bond to give *N*-methyl-2-[3-(1-methylpiperidin-4-yl)-1*H*-indol-5-yl]ethanesulfonamide (**4**) and finally converting the naratriptan free base **4** to HCl salt **5** with hydrochloric acid as the method of synthesis[6] (Scheme 1) and studied to develop a laboratory process suitable for scale-up in a commercial plant. Herein we report our investigation on the role of solvent system on the rate of reaction and impurity profile during hydrogenation of alkene intermediate **3**.

Scheme 1[a]



[a] Reaction conditions: a) KOH, MeOH, reflux; b) MeOH/H_2O, AcOH, H_2, Pd/C 5% [50% wet]; c) MeOH, aq HCl.

Results and Discussion

Condensation of 2-(1*H*-indol-5-yl)-*N*-methylethanesulfonamide (**1**) with *N*-methyl piperidin-4-one (**2**) in the presence of KOH and methanol as solvent at reflux temperature was performed as per the recommended procedure[6] to afford *N*-methyl-2- [3-(1-methyl-1, 2, 3, 6-tetrahydropyridin-4-yl)-1*H*-indol-5-yl]ethanesulfonamide (**3**) with a yield of more than 75% and a purity of more than 99.5% by HPLC. Intermediate **3** obtained was subjected to catalytic hydrogenation followed by the isolation of the free base of naratriptan **4**.

During our preliminary optimization experiments involving the double bond reduction, we observed that the removal of unreduced material **3** from free base **4** and the final product **5** is cumbersome and often gives low yield. In addition to this, the rate of the reaction was hampered due to the presence of the sulfonamide group in the molecule. In order to obtain naratriptan hydrochloride (**5**) that was of pharmaceutically acceptable quality,[9] it was essential to drive the reaction to

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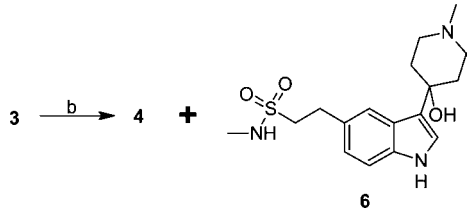
Table 1. **Effect of solvent ratio on the content of OH impurity during hydrogenation of 3 to naratriptan free base 4**

			HPLC purity		
entry	solvent	reaction time	**6** (OH-impurity) %	**4** %	**3** (alkene) %
1	methanol	8 h	0.01	99.42	0.08
2	water	30 min	1	98.62	0.02
3	MeOH (60%) water (40%)	2 h	0.14	99.31	0.01
4	MeOH (45%) water (55%)	2 h	0.25	99.35	0.01
5	MeOH (90%) water (10%)	3 h	0.01	99.41	0.01

Scheme 2

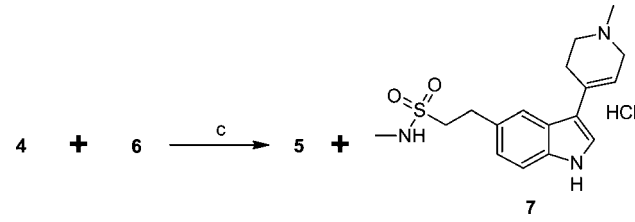


completion, leaving less than 0.1% of the unreduced **3**. We carried out several optimization experiments in order to improve the yield and to obtain product of better quality.

As a part of our optimization study, we studied various solvent systems such as methanol, methanol/dimethyl formamide, methanol/acetic acid and water/acetic acid for the reduction of alkene **3**. In methanol, the rate of reaction was slow due to the poor solubility of alkene **3**, and the same trend was observed with other organic solvents. Better solubility and rate of reaction were achieved with methanol/dimethyl formamide, but the workup procedure proved to be difficult. We observed that the rate of reaction was moderate with methanol/acetic acid (entry 1, Table 1) and highest with water/acetic acid (entry 2, Table 1). To our surprise, we have observed an unusual recurrence of intermediate **3** during the conversion of free base **4** to the final product **5** leading to pharmaceutically unqualified material. Detailed investigation and mapping of all the impurities present in both stages led to the observation that all the impurities of the free base were carried over intact to the hydrochloride stage except for one impurity. We observed not only that the level of this impurity decreased but that the level of impurity B increased during the conversion of free base **4** to hydrochloride **5**. On the basis of the available literature[6] on the synthetic route, the molecular weight analysis by LC−MS, and the above observation, the structure has been proposed as hydroxy compound **6**, which forms during the coupling of *N*-methyl piperidone **2** with indole **1** as an intermediate in the preparation of **3**. The identity was further confirmed by its synthesis[6] and by its spiking studies using HPLC. Although the purification at the condensation stage has taken enough care to control the hydroxy impurity below the level of 0.02%, the hydrogenation in the presence of water led to enhanced level of impurity **6** presumably due to the hydration of alkene **3,** by the influence of acidic condition (Scheme 2).

It is necessary to minimize the level of impurity **6** at the reduction stage, since it is converted to the corresponding hydrochloride salt **7** of unreduced intermediate **3**, via acid-

Scheme 3



catalyzed dehydration during the salt formation step, to end up with **5** of pharmaceutically inferior quality (Scheme 3).

On the other hand, we also noticed that the amount of OH impurity (**6**) was proportional to the water content of the solvent mixture. A better control of the impurity could therefore be achieved by a balanced combination of methanol and water. We found that MeOH/H_2O in a ratio of 9:1 was ideal to fulfill our requirements. Part of the data given in Table 1 shows the influence of solvent on the content of OH impurity **6**. Table 2 summarizes the impact of the content of **6** in free base.

Conclusion

It has been demonstrated through a series of experiments that not only is impurity B carried over from preceding stages, but it is also formed during the process. This allowed us to identify the optimal conditions for the transformation, so as to obtain a commercially scalable process. The present scalable process allowed us to prepare substantially pure naratriptan hydrochloride with more than 99.8% purity with less than 0.05% of unreduced alkene impurity **3**.

Experimental Section

General Procedures. Commercially available solvents and reagents were used without further purification. Reversed phased HPLC elutions were performed on a XTERRA RP C_{18} (150 mm × 6 mm) 3.5 μ column with acetonitrile buffer (5.75 g of $NH_4H_2PO_4$ in 1.0 L of water and pH 3.0 with ortho phosphoric acid) mixtures. ^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz spectrophotometer with multinuclear BBO probe with TMS as internal standard in DMSO-d_6/$CDCl_3$. Chemical shifts are reported in δ scale (ppm). Mass spectra were measured on a PE-SCIEX API-3000 LC/MS//MS with a Turbo ion spray mass spectrophotometer. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR spectrophotometer in KBr pellets.

***N*-Methyl-2-[3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indol-5-yl]ethanesulfonamide (3).** Mixtures of potassium hydroxide (42 g, 0.75 mol) flakes and methanol (300 mL) were stirred at 25−45 °C for 30 min to obtain a solution. To the solution was added 2-(1*H*-indol-5-yl)-*N*-methylethanesulfonamide **1**, (30 g, 0.13 mol), followed by *N*-methyl piperidin-4-one (**2**) (21.2 g, 0.19 mol) at 25−35 °C. The mixture was heated to reflux and maintained at reflux temperature for 4−5 h. The mixture was cooled to 25−35 °C, and 450 mL of water was added. The mixture was stirred at the same temperature for 30 min. The solid was filtered and washed with water and then dried under vacuum to afford 28 g, 67% yield of **3**. ^{1}H NMR (DMSO-d_6) δ: 2.28 (s, 3H), 2.57 (m, 2H), 2.62 (s, 3H), 3.02 (m, 4H), 3.28 (m, 2H), 3.43 (m, 2H), 6.15 (s, 1H), 7.0 (br s,

Table 2. **Acid-catalyzed conversion of 6 to 7 during the hydrochloride salt 5 formation of naratriptan free base 4**

	purity by HPLC of **4**			purity by HPLC of **5**		
entry	**6** (OH-impurity) %	**4** %	**3**(alkene) %	**6** (OH-impurity) %	**5** %	**7**(alkene) %
1	0.13	99.58	0.01	0.01	99.86	0.10
2	0.17	99.50	0.01	0.04	99.79	0.11
3	0.02	99.75	0.01	0.00	99.95	0.01
4	0.00	99.64	0.01	0.00	99.94	0.01

1H), 7.02 (d, 1H), 7.30 (d, 1H), 7.35 (d, 1H), 7.7 (s, 1H), 11.05 (s, 1H). IR (KBr) ν cm^{-1}: 3596, 2934, 1306, 1134; *m*/*z* 334 $[M + H]^+$.

***N*-Methyl-2-[3-(1-methylpiperidin-4-yl)-1*H*-indol-5-yl]-ethanesulfonamide (4).** *N*-Methyl-2-[3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indol-5-yl]ethanesulfonamide (**3**) (25 g, 0.075 mol) was suspended in methanol (300 mL) and water (50 mL) at 25−35 °C. To the stirred suspension was added acetic acid (9 g, 0.15 mol) at the same temperature and stirred to obtain clear solution. The solution obtained was treated with activated carbon at 25−35 °C. The filtrate obtained after carbon treatment was hydrogenated at 9−10 atm hydrogen pressure and 25−35 °C in the presence of Pd/C carbon 5% (50% wet) for 4−6 h. The reaction mass was filtered, and the volume of the mass was reduced to 250 mL under vacuum at 40−50 °C. To the stirred mass was added aq sodium hydroxide solution (6.3 g, 0.16 mol and 125 mL of water) at 25−35 °C. The mixture was filtered to obtain a solid. The solid was washed with water and dried under vacuum to afford 16 g, 64% yield of naratriptan free base (**4**). ^{1}H NMR (DMSO-d_6) δ: 1.66 (m 2H), 1.89 (m, 2H), 2.05 (m, 2H), 2.20 (m, 2H), 2.60 (m, 2H), 2.68 (m, 1H), 2.85 (m, 2H), 2.99 (m, 2H), 3.28 (m, 2H), 6.95 (m, 2H), 7.05 (d, 1H), 7.25 (d, 1H), 7.43 (s, 1H), 10.71 (s, 1H). IR (KBr) ν cm^{-1}: 3314, 2941, 1310, 1116; *m*/*z* 336 $[M + H]^+$.

***N*-Methyl-2-[3-(1-methylpiperidin-4-yl)-1*H*-indol-5-yl]-ethanesulfonamide Hydrochloride Salt (5).** A mixture of *N*-methyl-2-[3-(1-methylpiperidin-4-yl)-1*H*-indol-5-yl]ethanesulfonamide (**4**) (15 g, 0.045 mol) and methanol (225 mL) was stirred at 25−35 °C to obtain a clear solution. The solution was treated with 1.5 g of activated carbon, and the filtrate was treated with 20% aq hydrochloric acid (12.2 g, 0.067 mol) at 0−10 °C. The mixture was stirred and filtered to get **5** as solid. The solid was dried under vacuum to afford 14 g, 84% yield of naratriptan hydrochloride salt **5**. ^{1}H NMR (DMSO-d_6) δ: 2.09 (m, 4H), 2.62 (d, 3H), 2.76 (s, 3H), 3.02 (m, 3H), 3.09 (m, 2H), 3.30 (m, 2H), 3.44 (m, 2H), 7.0 (m, 2H), 7.10 (d, 1H), 7.28 (d, 1H), 7.58 (br s, 1H), 10.7 (br s, 1H), 10.9 (s, 1H). IR (KBr) ν cm^{-1}: 3227, 2965, 1314, 1153; *m*/*z* 336 $[M + H]^+$.

2-[3-(4-Hydroxy-1-methylpiperidin-4-yl)-1*H*-indol-5-yl]-*N*-methylethanesulfonamide (6). Mixtures of potassium hydroxide (1.77 g, 0.032 mol) flakes and ethanol (45 mL) were stirred at 25−45 °C for 30 min to obtain a solution. To the solution was added 2-(1*H*-indol-5-yl)-*N*-methylethanesulfonamide (**1**) (5.0 g, 0.029 mol), followed by *N*-methyl piperidin-4-one (**2**) (3.55 g, 0.032 mol) at 25−35 °C. The mixture was stirred at the same temperature for 24 h. The mixture was concentrated and the mass diluted with water (50 mL) and allowed to stand at 25−35 °C. The solid was filtered and washed with water (25 mL). The solid was dried under vacuum to afford 4.0 g, 54% yield of **6**. ^{1}H NMR (DMSO-d_6) δ: 1.84 (m, 2H), 2.00 (m, 2H), 2.2 (s, 3H), 2.40 (m, 2H), 2.62 (s, 3H), 3.00 (m, 2H), 3.07 (m, 2H), 3.27(m, 2H), 4.55 (br s, 1H), 6.95 (d, 1H), 7.12 (s, 1H), 7.28 (d, 1H), 7.64 (s, 1H), 10.78 (s, 1H). IR (KBr) ν cm^{-1}: 3317, 1637, 1401, and 1151. *m*/*z* 352 $[M + H]^+$.

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Supporting Information Available

Additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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