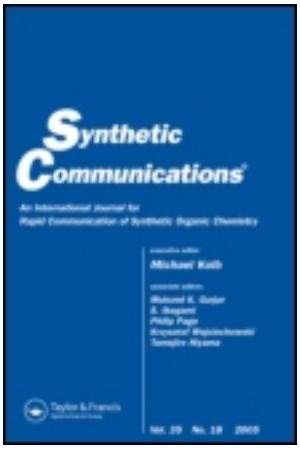

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IMPROVED PREPARATION OF (*R*) AND (*S*)-3-AMINOQUINUCLIDINE DIHYDROCHLORIDE

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Abstract: An improved procedure for the synthesis of either (*R*) or (*S*)-3-aminoquinuclidine was developed. Key intermediate imine **2** was made in a one pot process using lithium oxide as the base and molecular sieves.

Recently, 3-aminoquinuclidine has been incorporated into a wide variety of pharmacologically active compounds,[1-2] particularly 5-HT_3 receptor antagonists.[3-7] These antagonists are among the most potent compounds known in this important area and are useful in the treatment of nausea and vomiting caused by cancer chemotherapy. Two of the most potent 5-HT_3 receptor antagonists are RS-42358-197 and palonosetron which both require enantiomerically pure (*S*)-3-aminoquinuclidine for their synthesis.[8]

In producing palonosetron and RS-42358-197 to support clinical trials we required multi-kilo quantities of (*S*)-3-aminoquinuclidine dihydrochloride. Initially, small quantities were prepared using the procedure of Langlois but this was found inadequate as the scale increased.[9] The major problems with this route were

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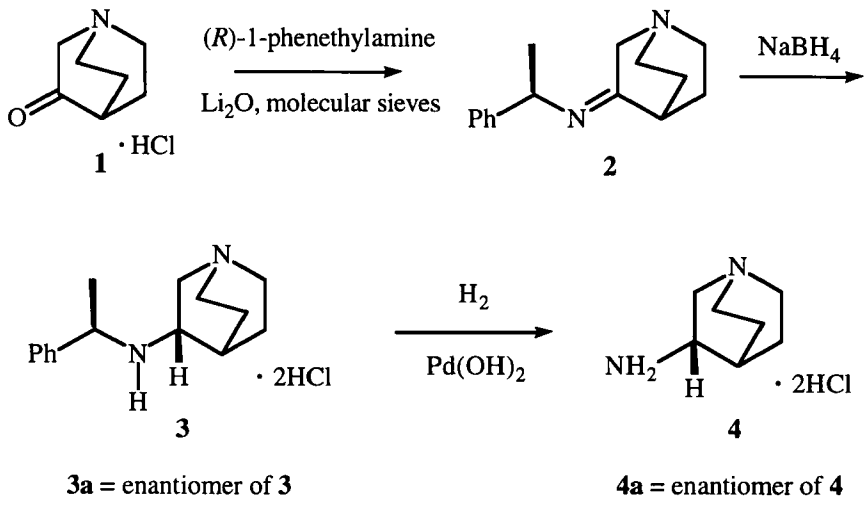
laborious and hazardous (large scale) ether extraction of 3-quinuclidinone free base, increasing polymeric material on scale-up during azeotropic removal of water during imine **2** formation, imine **2** requiring purification by distillation, boron complexed material carrying through the crystallization of **3**, and inefficient isolation of (*S*)-3-aminoquinuclidine dihydrochloride. In this communication we report an improved procedure for making either enantiomer of 3-aminoquinuclidine dihydrochloride.

The improved process is outlined in the Scheme. The procedure uses 3-quinuclidinone hydrochloride and inexpensive chiral 1-phenethylamine. Both enantiomers of 1-phenethylamine are readily available allowing either enantiomer of 3-aminoquinuclidine dihydrochloride to be produced. The first step from **1** to **2** was done in one pot using molecular sieves as the dehydrating agent/catalyst[10-12] and lithium oxide to neutralize the 3-quinuclidinone hydrochloride. It was very convenient to use the commercially available 3-quinuclidinone hydrochloride directly without the need for prior conversion to its free base. Lithium oxide was used as the base instead of lithium hydroxide to minimize the amount of water produced. After removal of the molecular sieves by filtration imine **2** was reduced *in situ* with sodium borohydride. In the quench it was important to warm the mixture to reflux while the solution was acidic to completely break up the boron complex of **3** which otherwise can be troublesome during the isolation of **3**. The purification of **3** required one recrystallization to bring the diastereomeric purity to 99.7-100.0 % by HPLC.

The second step was removal of the benzyl group by hydrogenolysis to give (*R*) or (*S*)-3-aminoquinuclidine dihydrochloride. The isolation of crystalline **4** was most easily achieved by slowly adding the filtered hydrogenolysis solution to



Scheme

distilling n-propanol. Removal of the water in the distillate maximized the recovery of crystalline **4**.

In summary, we have developed an efficient and safe process for making (*R*) or (*S*)-3-aminoquinuclidine dihydrochloride in 55 % overall yield from 3-quinuclidinone hydrochloride. The procedure exploits a one pot process using lithium oxide as a base and molecular sieves to produce imine **2**. The overall process overcomes the problems associated with the Langlois procedure and has been proven on multi-kilogram scale.

Experimental

General. All materials were purchased from commercial suppliers and used without further purification. The molecule sieves used were Linde 4Å as 1/16 inch pellets. All experiments have been successfully scaled to make 14 kilograms of **4** per batch.

(3*S*)-3-[(*R*)-(1-phenyl)ethylamino]-quinuclidine dihydrochloride (3). A mixture of 3-quinuclidinone hydrochloride (500 g, 3.1 mols), lithium oxide (46.1 g, 1.54 mols), and THF (4.0 L) was stirred under nitrogen in a 12-L flask. To the mixture was added (*R*)-1-phenethylamine (500 g, 4.1 mols) and the solution was stirred for 4-18 h. Molecular sieves (1.0 kg) were added to the solution and the stirring was maintained at 20-100 rpm. When the reaction was stirred too vigorously the sieves tended to break down and became difficult to remove by filtration. The completion of imine formation can be checked by sodium borohydride reduction in MeOH of a few drops of reaction mixture and then checking for the presence of 3-quinuclidinol by tlc (alumina, 89 % CH_2Cl_2/10 % MeOH/1 % NH_4OH as the eluent, R_f imine = 0.9, R_f 3-quinuclidinol = 0.5). After 66-90 h the reaction mixture was filtered through a filter containing a 1-2 inch bed of Celite and washed twice with THF (360 mL). A slurry of sodium borohydride (140.3 g, 3.7 mols) in ethanol (3.5 L) was stirred under nitrogen for 2-3 h. This slurry was added over 10 min to the THF filtrate contained in a 22-L flask. After stirring overnight, the reaction was quenched with a solution of conc. HCl (1.0 L) and water (2.9 L). During the first part of the HCl addition care should be taken as gas evolution (H_2) takes place. The solution was distilled until the vapor phase reached >95 °C. The residue was cooled to rt and 50 % NaOH (648 mL) was added to bring the pH to ≥ 12. The solution was cooled to rt and extracted with EtOAc (1.0 L) twice. The extracts were combined, dried over sodium sulfate (188 g), filtered and concentrated *in vacuo* to an oil. The oil was dissolved in ethanol (7.5 L) and HCl gas (263 g) was added directly to the stirred solution warming the solution to 45-50 °C. The solution was cooled slowly over ~18 h to <7 °C with stirring during which time crystallization took place. The

solution was filtered and the cake washed with ethanol (400 mL) to give crude **3** (683-885 g) after drying. To the crude material was added ethanol (5.7 L) and the solution was brought to reflux. While maintaining reflux MeOH (2.5-4.1 L) was added to clarify the solution. The solution was slowly cooled to <7 °C over ~18 h. The mixture was filtered and the cake washed with ethanol (400 mL) to give after drying **3** (556-612 g, 59-65 %) as white crystals: mp >285 °C (lit.[9] mp >260 °C); $[\alpha]^{20}_{D}$ = -2.1 ° (c = 2, H_2O) (lit.[9] $[\alpha]^{20}_{D}$ = -1.7 ° (c = 2, H_2O)); ^{1}H NMR spectrum was identical to the spectrum reported.[9]

(3*R*)-3-[(*S*)-(1-phenyl)ethylamino]-quinuclidine dihydrochloride (3a). **3a** was prepared identically to **3** except using (*S*)-phenethylamine: mp >285 °C (lit.[9] mp >260 °C); $[\alpha]^{20}_{D}$ = 1.8 ° (c = 2, H_2O) (lit.[9] $[\alpha]^{20}_{D}$ = 1.7 ° (c = 2, H_2O)); ^{1}H NMR spectrum was identical to the spectrum reported.[9]

(*S*)-3-aminoquinuclidine dihydrochloride (4). A mixture of **3** (100.0 g, 0.33 mol), 20 % $Pd(OH)_2$/C (15.0 g, 20 % water wet), *n*-PrOH (100 mL), and water (80 mL) was stirred at 40 °C under a hydrogen atmosphere for 18-40 h. Completion of reaction was determined by tlc (silica gel, 89 % CH_2Cl_2/10 % MeOH/1 % NH_4OH as the eluent, R_f of **3** = 0.3, R_f of **4** = 0.05). The solution was cooled to rt, filtered through a pad of celite, and the collected catalyst washed with a solution containing *n*-PrOH (20 mL) and water (20 mL). The lower layer of the filtrate was added dropwise over 50 min to a distilling solution of *n*-propanol (1.0 L). The addition rate was such that while each half of the solution was added 500 mL of distillate was collected. After the first half was added *n*-propanol (500 mL) was added. After the addition was complete the mixture was concentrated by distillation (75 mL distillate collected), cooled to rt, and futher cooled in an

ice/water bath for 1 h. The solid was collected by filtration, washed with *n*-propanol (30 mL), and dried to give **4** (55.6 g, 85 %) as a white crystalline powder: mp >285 °C (lit.[9] mp >260 °C); $[\alpha]^{20}_{D}$ = -24.5 ° (c = 1, H_2O) (lit.[9] $[\alpha]^{20}_{D}$ = -24.2 ° (c = 1, H_2O)); ^1H NMR spectrum was identical to the spectrum reported.[9]

(*R*)-3-aminoquinuclidine dihydrochloride (4a). 4a was prepared identically to **4** except using **3a**: mp >285 °C (lit.[9] mp >260 °C); $[\alpha]^{20}_{D}$ = 23.2 ° (c = 1, H_2O) (lit.[9] $[\alpha]^{20}_{D}$ = 24.0 ° (c = 1, H_2O)); ^1H NMR spectrum was identical to the spectrum reported.[9]

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