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A Large Scale Preparation of the Cognitive Enhancer Linopirdine

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A LARGE SCALE PREPARATION OF THE COGNITIVE ENHANCER LINOPIRDINE

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Abstract: Linopirdine is a pharmacologically potent drug which stimulates central nervous system neurotransmitter release. A facile process used to synthesize linopirdine on a commercial manufacturing scale consisting of seven chemical steps with only a single isolated intermediate is described.

Linopirdine (3,3-Bis(4-pyridinylmethyl)-1-phenyl-2H-indolin-2-one, DuP 996) is a pharmacologically potent and orally active cognitive enhancer targeted to ameliorate cognitive deficiencies associated with Alzheimer's

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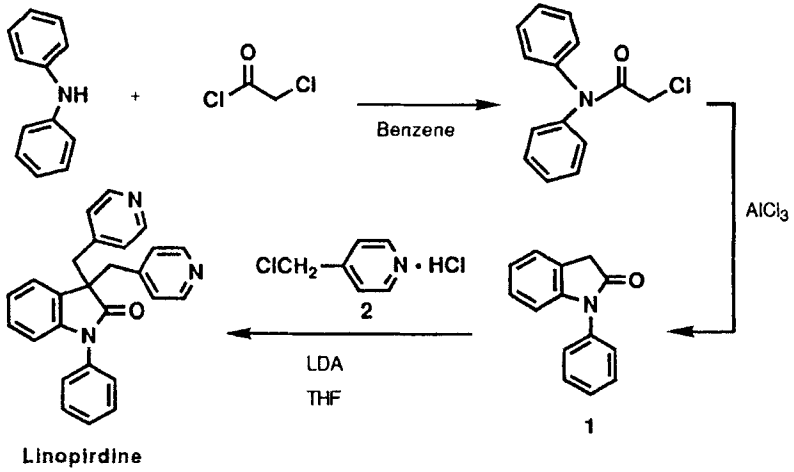

Scheme 1

disease by stimulating central nervous system neurotransmitter release such as acetylcholine, dopamine, and serotonin.[1,2,3] We have developed a facile process which has been used to manufacture ton quantities of linopirdine. The process involves seven chemical steps with a single isolated intermediate followed by decolorization and recrystallization.

Linopirdine was originally prepared via the three step synthesis illustrated in Scheme 1.[4] From the perspective of a commercial manufacturing process, this route had several disadvantages. For example, the ring closing step to form 1-phenyloxindole (**1**) is highly exothermic, and we wanted to avoid handling large quantities of reactive aluminum chloride catalyst. In the final step, we wanted to avoid using lithium diisopropylamide (LDA) on a large scale and find an alternative to using two equivalents of 4-picolyl chloride hydrochloride (**2**), an expensive and scarce raw material which represented greater than 90% of the original raw material cost. Finally, we wanted a process which did not require a chromatographic purification of the final product.

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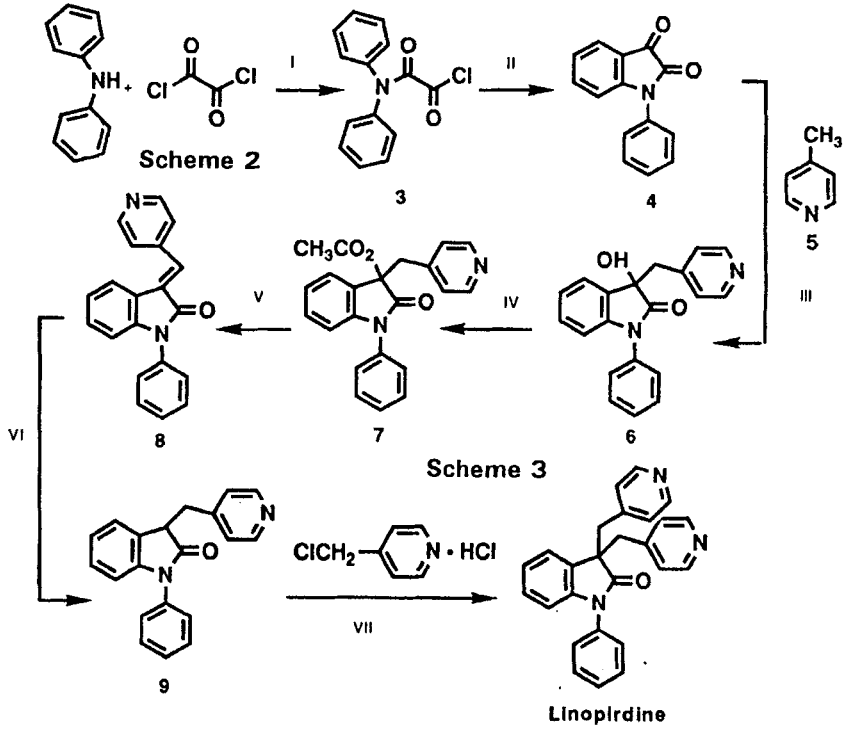

Scheme 2: I: Toluene; II: Toluene; III: 4-Picoline (neat), Methylene chloride to precipitate; IV: Acetic anhydride, acetic acid; V: Water to precipitate; VI: 5% Palladium on carbon, formic acid, 2-propanol, then HCl; VII: Methanol, water, NaOH

Scheme 3: I: Toluene; II: Toluene; III: Acetic acid; IV: Acetic anhydride; V: Water and 2-propanol to precipitate; VI: Methanol, water, $NaBH_4$, NaOH; VII: Methanol, water, NaOH

Other workers later demonstrated the alkylation of 1 using 2-equivalents of 4-picolyl chloride hydrochloride under phase transfer conditions.[5] We also successfully prepared linopirdine under phase transfer conditions and consistently obtained yields of approximately 70% of theory. However, this method still requires 2 equivalents of expensive 4-picolyl chloride hydrochloride.

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We have developed two processes, illustrated in Schemes 2 and 3, from a seven chemical step synthesis.[6] These processes have significant advantages over the original synthesis.

Linopirdine was first prepared by this synthetic route using a process in which the intermediates **6, 8,** and **9** were isolated (Scheme 2). The ring closure to form 1-phenylisatin (**4**) as first described by Stolle[7] is much more facile and does not require a catalyst as compared to the analogous 1-phenyloxindole synthesis. Based on the work of Akkerman and Veldstra,[8] who demonstrated that isatins could condense in an aldol fashion with pyridine derivatives containing active methyl and methylene substituents, we condensed 1-phenylisatin with 4-picoline (**5**) to form **6**. 4-picoline is considerably less expensive and more readily available than 4-picolyl chloride hydrochloride. Although we tried to reduce **6** to **9** directly using catalytic hydrogenation and several other methods, we were unable to find conditions which would selectively reduce the tertiary alcohol and not the pyridine ring. Therefore, we dehydrated **6** using acetic anhydride in acetic acid. The dehydration product **8** was then easily reduced via catalytic transfer hydrogenation in 2-propanol using formic acid as the hydride donor, and then crystallized from the reaction mass as the hydrochloride salt. Finally, **9** was alkylated in aqueous methanol with only a slight excess of 4-picolyl chloride hydrochloride and using sodium hydroxide to generate the reactive anion. The material was purified by recrystallizing from 2-propanol.

The final manufacturing process uses the same synthetic route, but, by combining several of the steps in one vessel and changing the reduction conditions, requires isolation of only intermediate **8** (Scheme 3). Instead of isolating **6**, the toluene is solvent-exchanged with acetic acid during the 4-picoline condensation reaction, and then the aldol adduct is dehydrated in situ by adding acetic anhydride. After adding water and 2-propanol, the mixture is slowly cooled to yield **8** in 75-80 % yields and purity of greater than 99%. Similar to the work of Long, Richards, and Ross,[9] we have found that slow cooling of the crystallization mass yields primarily the *E*-isomer of **8** (illustrated with the pyridine ring "up"). After recrystallization

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and drying, **8** is slurried in methanol, water, and sodium hydroxide and reduced by adding a slightly basic aqueous solution of sodium borohydride. After additional sodium hydroxide and water are added, **9** is alkylated in situ by adding an aqueous solution of 4-picolyl chloride hydrochloride. The product crystallizes from the reaction mass as a coarse brown to purple solid in 85-90 % yield, and the purity is approximately 95%.

The crude linopirdine is purified and decolorized by dissolving in hot toluene, treating with basic alumina and activated carbon, and cooling to crystallize. This product is then recrystallized from 2-propanol. The overall yield of pure linopirdine from diphenylamine is 45-55%.

EXPERIMENTAL

All raw materials and solvents are commercially available. ^{1}H NMR and ^{13}C NMR spectra were recorded using either a Varian VXR-400S or a Varian Unity-400 NMR spectrometer operating at 399.95 MHz for proton and 100.59 MHz for carbon-13. High resolution mass spectroscopy was performed on a VG 70-VSG Mass Spectrometer using electron ionization with a full scanning or magnetic scanning method.

General Procedures

3-(4-pyridinylmethylene)-1-phenyl-2H-indolin-2-one (8)

A 2-liter 4-neck round-bottom flask is fitted with an overhead stirrer, temperature controller, nitrogen sweep, 1-liter pressure equalizing addition funnel, condenser, and acid scrubber. The flask is charged with toluene (302 mL) and oxalyl chloride (216 g, 1.70 mol). The mixture is cooled to maintain the temperature below 40°C while a solution of diphenylamine (266 g, 1.57 mol) dissolved in toluene (438 mL) is added. The addition funnel is rinsed with toluene (45 mL). The slurry is then heated to 55-65°C for 30-60 minutes until a clear brown solution forms and HCl evolution slows considerably. The mixture is then distilled until approximately

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580 mL of distillate is collected and a pot temperature of 120-125 °C is reached. (The distillate contains unreacted oxalyl chloride, and should be carefully hydrolyzed before disposal. It may develop pressure in a sealed container.) The mass is then held under gentle reflux (118-125°C) for 17-20 hours, and then cooled to 100-110°C. Acetic acid (700 mL) and 4-picoline (172 g, 1.85 mol) are added, and the mass is distilled until approximately 470 mL of distillate is collected and a temperature of 125-130°C is reached. The mixture is cooled to 90-100 °C and acetic anhydride (326 g, 3.20 mol) is added. The mass is then heated to 120-125°C for 1-2 hours, cooled to 80-90°C, and water (460 mL) is added followed by 2-propanol (330 mL) while maintaining the temperature between 60°C and 80°C. The mixture is then cooled over not less than 4 hours to 5-10°C. (If crystals have not formed by approximately 50°C, a small sample of the reaction mass should be removed, cooled to form seed crystals, and added back to the reaction.) The mixture is filtered, washed with 2-propanol (150 mL), sucked down well, and recrystallized directly by heating to reflux in a mixture of 2-propanol (1520 mL), water (1400 mL), and acetic acid (4 mL). After cooling over not less than 4 hours to 10-15°C, the orange crystals are dried under vacuum at 60-90°C. Yield is approximately 325-350 g of orange crystalline solid (70-75 % of theoretical, starting from diphenylamine). ^{1}H NMR (E-isomer) [δ TMS, CDCl3]:6.87 (d, 1H), 6.95 (t, 1H), 7.26(t, 1H), 7.46-7.60 (m, 7H), 7.84 (s, 1H), 8.81 (m, 2H). ^{13}C NMR [δ TMS, CDCl3]: 166.98. 150.36, 144.62, 142.91, 134.21,133.39, 130.62, 129.83, 129.60, 128.11, 126.57, 123.24, 122.89, 122.47, 120.32, 109.74. High resolution mass spectrum: Calculated Mass ($C_{20}H_{14}N_2O$): 298.1106; Measured Mass: 298.1106. UV/VIS (CH_2Cl_2): λ_{Max}= 255 nm, ε_{Max}= 20843 L Mol^{-1} cm^{-1}

Linopirdine

Synthesis: A 2-liter 4-neck round-bottom flask fitted with an overhead stirrer, temperature controller, nitrogen sweep, 1-liter pressure equalizing addition funnel, and condenser is charged with **8** (200 g, 0.67 mol), 50% sodium hydroxide (5.4 g, 0.68 mol), and methanol (600 mL). Separately, a solution of 50 % sodium hydroxide (0.64 g, 8 mMol), sodium borohydride

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(10.16 g, 0.27 mol), and water (53 mL) is prepared and charged to the addition funnel (This solution slowly decomposes and should be used immediately). After purging the system well with nitrogen, the sodium borohydride solution is added to the reaction mass over 30-60 minutes while maintaining the temperature between 20°C and 30°C (Caution: hydrogen evolution). The reaction is then heated to 35°C for 30 to 60 minutes. The mass is cooled to 10-15°C, and water (160 mL) and 50% sodium hydroxide (118 g, 1.47 mol) are added. A solution of 4-picolyl chloride hydrochloride (110.4 g, 0.67 mol) in water (166 mL) is prepared, charged to an addition funnel, and added to the reaction mass over 45-90 minutes while cooling to maintain the temperature between 15-25°C. The addition funnel is rinsed with water (40 mL), and the mass stirred at ambient temperature for 2-3 hours. Additional water (400 mL) is added over 15-30 minutes, the mixture stirred 1.5-2.5 hours, cooled to 5-10°C, and filtered. The product is washed with water (200 mL), and sucked down well. Yield is 233-249 g dry-weight equivalent (89-95 %) of purple-to-brown crystalline solid (approximately 266 g wet).

Decolorization/recrystallization: A 2-liter 4-neck round-bottom flask fitted with an overhead stirrer, temperature controller, nitrogen sweep, Dean-Stark trap and condenser is charged with crude damp linopirdine (~266 g damp or ~240 g dry-weight equivalent) and toluene (1075 mL). The mixture is heated to reflux and distilled until all the water has been removed from the solution and then approximately 125 mL of toluene is distilled. The mass is cooled to approximately 80°C, and activity I basic alumina (27 g) and activated carbon (5.4, Norit® A) are added. The mass is heated to 90-100°C for 30 minutes, filtered hot, and the residue washed with toluene (80 mL). The combined filtrate and wash are charged to a 2-liter 4-neck round-bottom flask, fitted with an overhead stirrer, temperature controller, nitrogen sweep, and distillation apparatus, and distilled to collect approximately 635 mL of distillate. The mass is cooled to 0-5°C, filtered, and the product washed with toluene (165 mL). The product is dried in a vacuum oven at 60-90°C. Recovery is approximately 206 g of off-white to light yellow solid. To recrystallize, a 2-liter 4-neck round-bottom flask fitted with an overhead stirrer, temperature controller,

nitrogen sweep, and condenser is charged with linopirdine (206 g) and 2-propanol (580 mL). The mass is heated to reflux until a solution is obtained, filtered hot to remove any trace insolubles, and then the filtrate is concentrated by atmospheric distillation to collect approximately 354 mL of distillate. The mixture is then cooled to 0-5°C, filtered, and washed with 2-propanol (100 mL). After drying in a vacuum oven at 60-90°C, the yield is approximately 188 g (91 % of theory) of white to off-white crystalline solid. MP: 185-187°C. ^{1}H NMR [δ TMS, CDCl3]: 3.26 (d, 2H), 3.47 (d, 2H), 6.26 (m, 1H), 6.62 (m, 2H), 6.87 (m, 4H), 7.07 (m, 1H), 7.15 (m, 1H), 7.34 (m,1H), 7.38 (m, 2H), 7.46 (m,1H), 8.29 (m, 4H). ^{13}C NMR [δ TMS, CDCl3]: 176.95, 149.57, 144.95, 144.26, 134.34, 129.93, 128.98, 128.94, 128.68, 126.84, 125.53, 124.46, 123.15, 109.62, 55.83, 43.48. High resolution mass spectrum: Calculated Mass ($C_{26}H_{21}N_3O$): 391.1685; Measured Mass: 391.1677. UV/VIS (CH_3OH): λ_{Max}= 246 nm, ε_{Max}= 12892 L Mol^{-1} cm^{-1}

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