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Improved Industrial Synthesis of Antidepressant Sertraline

Krisztina Vukics,* Tamás Fodor, János Fischer, Irén Fellegvári, and Sándor Lévai
Gedeon Richter Ltd., H-1475 Budapest, 10, P.O.B. 27, Hungary

Abstract:
(*cis*-1*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine hydrochloride, or sertraline hydrochloride, is a very effective antidepressant. This report presents a novel industrial synthesis of sertraline hydrochloride that is in many respects more advantageous than processes reported thus far. *N*-[4-(3,4-Dichlorophenyl)-3,4-dihydro-1(2*H*)-naphthalenylidene]-methanamine *N*-oxide is used as intermediate in our process, which is a stable compound in normal conditions. It can be obtained in a simple reaction from the corresponding tetralone in good yield, using acceptable reagents with regard to environmental and safety respects. Its reduction to the desired *cis*-racemic amine is stereoselective, and thus it provides sertraline hydrochloride with a purity required for pharmaceutical ingredients.

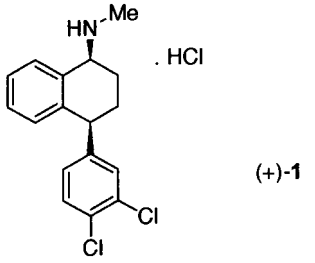
Introduction

Sertraline hydrochloride [(+)-**1**] selectively blocks serotonine reuptake and is used for the treatment of depression, as well as dependency- and other anxiety-related disorders.[1,2]

Sertraline belongs to those medicinal agents having one or more asymmetric centers in which the isomers show significant differences in their biological activity,[3] and therefore, it is necessary to produce the biologically active 1*S*,4*S*-enantiomer, sertraline, with high optical purity (Figure 1).

Results and Discussion

The key intermediate of the previous syntheses[4] of sertraline was tetralone **2**. In the original synthesis this compound was obtained in five steps, by classical reactions in low overall yield. Tetralone **2** was then reacted with 7 equiv of methylamine in the presence of $TiCl_4$ as catalyst, and the corresponding Schiff base was formed. $TiCl_4$ is an extremely corrosive material, requires special treatment during the reaction, and after workup, a large amount of hazardous material is formed. In an improved version,[5] $TiCl_4$ was replaced by molecular sieves, but in this case 17 equiv of methylamine was needed to achieve an acceptable yield. The latter reagent is a registered carcinogen, and protection against it is especially difficult because it is a gaseous



(+)-**1**

Figure 1.

material. The subsequent reduction of the Schiff base resulted in a mixture of amines, (±)-**1** and (±)-**3**, from which the useful *cis*-isomer was separated by crystallization as its hydrochloride salt. Using $NaBH_4$ as reducing agent the ratio of *cis*/*trans* isomers was 1:1, which was increased to 7:3 by catalytic hydrogenation on Pd/C. In the latter case the primary yield of (±)-**1** was 48%. After workup of the mother liquor a second crop was obtained, and the total yield was increased to 68%. Finally, resolution of (±)-**1** with *R*-(−)-mandelic acid provided the 1*S*,4*S*-isomer [(+)-**1**], which is the required active ingredient (Scheme 1).

In the synthesis of sertraline having two asymmetric centers, it would customarily be preferable to create the desired configurations as early as possible to minimize the loss generated from the unwanted isomer. Although enantioselective syntheses of the reqiured (*S*)-enantiomer of tetralone **2** have been achieved,[6−8] none of them has been commercially viable. On the other hand, the improvement of the synthesis of racemic tetralone **2** was so successful that with this simple industrial procedure[9,10] the late introduction of chirality has been possible without an unacceptable cost penalty (Scheme 2).

Our novel conversion of tetralone **2** to sertraline sought to improve upon the 3:1 *cis*/*trans* selectivity reported for the reduction of the *N*-methylimine,[4] and avoid the use of unacceptable reagents from the environmental and safety aspects ($TiCl_4$ and excess methylamine, respectively).

It is known from the literature that oxo compounds can easily be converted to oximes or nitrones with hydroxylamines, after which they can then be reduced to primary or secondary amines, respectively. Indeed, tetralone **2** easily forms the corresponding oxime **4** by reaction with hydroxylamine. However, conversion of **4** to sertraline requires

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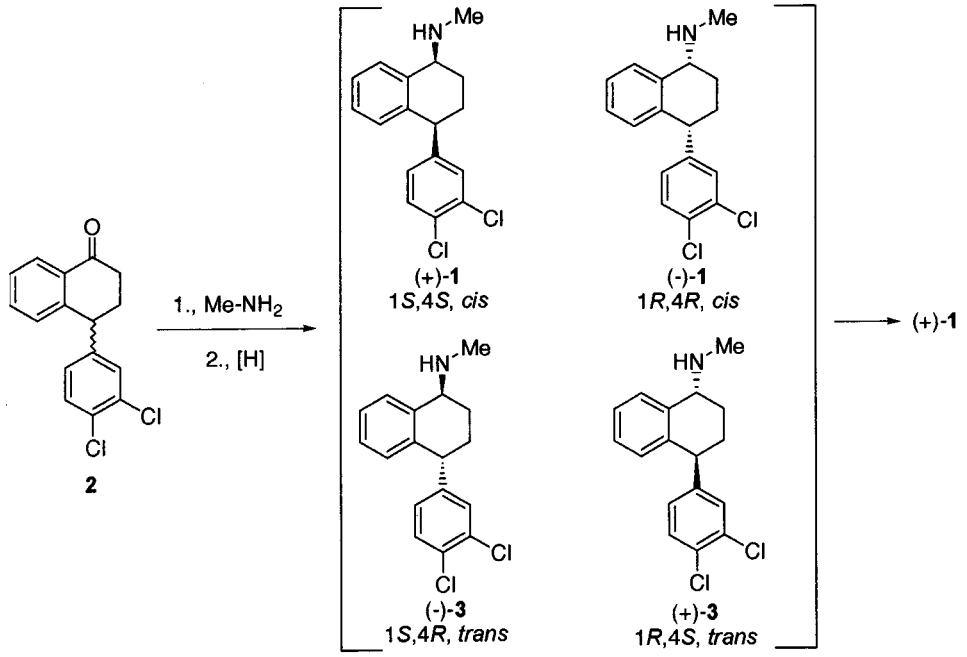
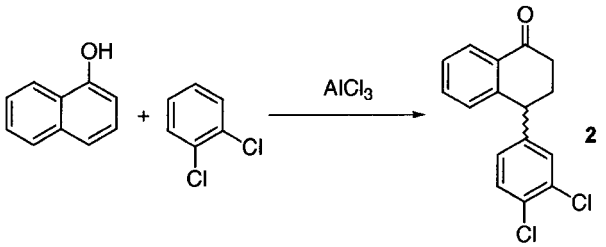
Scheme 1



Scheme 2



selective monomethylation of amine **5**, which may cause difficulties. Condensation of tetralone **2** with *N*-methylhydroxylamine results in nitrone **6**, whose reduction directly leads to amines **1** and **3** (Scheme 3). During the formation of nitrone **6** geometric isomerism takes place. In the reaction mixture the *E*/*Z* isomers are in equilibrium with each other, with the approximate ratio of 3:2. However, the isolation procedure provides only the thermodynamically more stable *Z* isomer.

Use of the above-mentioned nitrone intermediate **6** offers many advantages over the corresponding Schiff base applied in the previously known syntheses of sertraline. The reagent *N*-methylhydroxylamine hydrochloride is solid, easily treatable, and only 2 equiv of excess is needed in the reaction. Furthermore, there is no data of its possible carcinogenic or other toxic effects. Nitrone **6** obtained as described above can be isolated in stable crystalline form. After keeping it for months at room temperature, only slight coloration was observed.

The use of nitrone **6** was successful in respect to reduction as well. Reduction with $NaBH_4$ is partial, providing mainly the corresponding hydroxylamine. Catalytic hydrogenation on palladium-containing catalysts, even in deactivated cases, resulted in partial dehalogenation, which was reflected in the low yields as well (entries 1−3, Table 1). Hydrogenation on PtO_2 was not at all selective (entry 4, Table 1). Using

Table 1. **Summary of reductions[a] of nitrone 6**

entry	catalyst	yield of (±)−**1** **(%)**	ratio of *cis*/*trans* isomers
1	Pd/C	55	85:15
2	$Pd/CaCO_3$	52	86:14
3	$Pd/BaSO_4$	55	85:15
4	PtO_2	69	60:40
5	Raney Ni	81	92:8
6	Raney Ni	59[b]	92:8

[a] Reaction conditions: in methanol, atmospheric pressure, room temperature. [b] Experiment without isolation of nitrone **6**, yield calculated on tetralone **2**.

Raney-Ni as catalyst (entry 5, Table 1), a 92:8 *cis*/*trans* ratio was achieved, as determined by HPLC, and the *cis*-racemic amine hydrochloride (±)−**1** was isolated in 81% yield. Sertraline with required purity was obtained according to the literature by resolution of (±)−**1** with *R*-(−)-mandelic acid and then hydrogen chloride salt formation. This synthesis is described in our patent.[11]

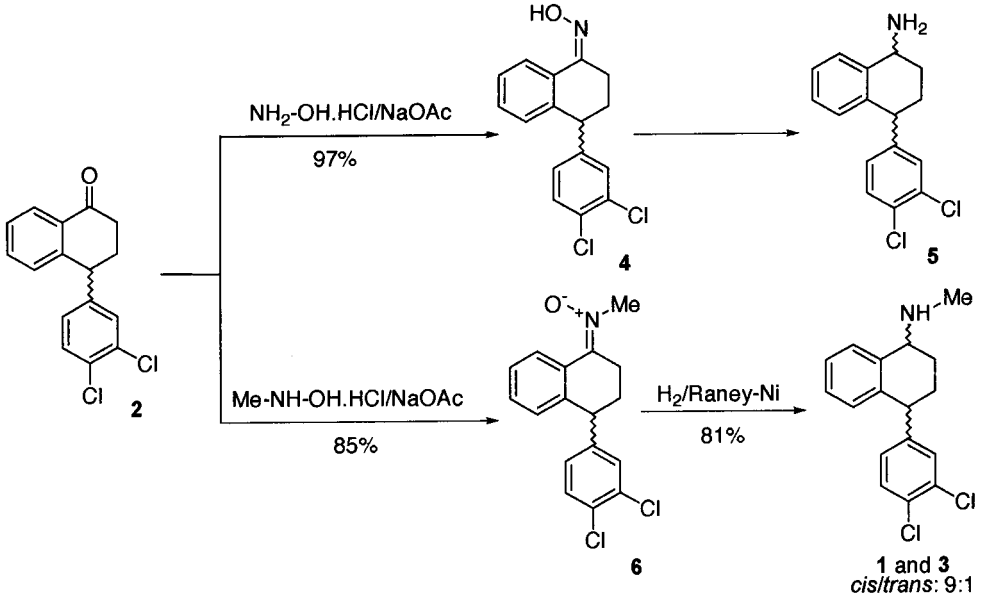
Experimental Section

Solvents and reagents were obtained from commercial sources. NMR spectra were recorded on a Varian VXR-300 spectrometer (^{1}H: 300 MHz) using $CDCl_3$ as solvent, temperature: 24 °C, reference: $\delta_{TMS} = 0.00$ ppm. MS spectra were obtained using a VG-TRIO-2 -spectrometer, ionization mode: EI, electron energy: 70 eV, ion source temperature: 250 °C. Infrared data were recorded on a PERKIN ELMER 1000 spectrophotometer, phase: KBr pellet, resolution: 4 cm^{-1}. Melting points were determined on a Büchi melting point apparatus.

4-(3,4-Dichlorophenyl)-3,4-dihydro-2*H*-naphthalen-1-one (2). To a stirred solution of 1-naphthol (21.62 g, 0.15 mol) in 1,2-dichlorobenzene (140 mL) anhydrous $AlCl_3$ (50

(11) Vukics, K.; Fodor, T.; Fischer, J.; Fellegvari, I.; Levai, S. PCT Int. Appl. WO 9827050 A1, 1998; *Chem. Abstr.* **1998**, *129*, 81571.

Scheme 3



g, 0.375 mol) was added. The reaction mixture was heated to 100 °C and stirred at this temperature for 1 h. The mixture was then cooled to room temperature and poured into ice (240 g) and concentrated hydrochloric acid (70 mL), followed by addition of CH_2Cl_2 (200 mL). The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2 (50 mL). The combined organic layers were washed with water (200 mL) and stirred with Celite (20 g) and activated carbon (10 g) and filtered; the solvents were then evaporated in vacuum. To the oily residue (45−50 g) methanol (44 mL) was added. The product was crystallized, filtered, and then washed twice with methanol. Yield: 34.9 g (80%). Mp: 99−101 °C.

4-(3,4-Dichlorophenyl)-3,4-dihydro-2*H*-naphthalen-1-one Oxime (4). Tetralone **2** (2.91 g, 0.01 mol), hydroxylamine hydrochloride (3.49 g, 0.05 mol) and NaOAc (4.11 g, 0.05 mol) were suspended in a mixture of ethanol (60 mL) and water (24 mL). The reaction mixture was stirred under reflux for 4 h. After cooling to room-temperature water (36 mL) was added. The precipitated product was filtered and washed with water. Yield: 2.98 g (97%). Mp.: 160−161.5 °C.

***N*-[4-(3,4-Dichlorophenyl)-3,4-dihydro-1(2*H*)-naphthalenylidene]-methanamine *N*-Oxide (6).** Tetralone **2** (46.08 g, 0.158 mol), *N*-methylhydroxylamine hydrochloride (26.45 g, 0.317 mol), and anhydrous NaOAc (25.98 g, 0.317 mol) in ethanol (600 mL) were stirred and heated until boiling. After 6 h heating under reflux the ethanol was evaporated in vacuum. To the residue, water (200 mL) and CH_2Cl_2 (200 mL) were added. The aqueous layer was washed with CH_2Cl_2 (100 mL), and then the combined organic layers were extracted with water (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was evaporated in vacuum. To the residue *tert*-butyl methyl ether (MTBE) (65 mL) was added. The product was filtered and washed with MTBE. Yield: 43.0 g (85%). Mp: 175−179 °C. ^{1}H NMR ($CDCl_3$): δ = 2.10−2.30 (m, 2H, H-3), 2.50−2.80 (m, 2H, H-2), 3.88 (s, 3H, *N*-Me), 4.12 (t, 1H, H-4), 6.83 (dd, 1H, H-6′), 6.97 (d, 1H, H-5′), 7.19 (d, 1H, H-2′), 7.25−7.50 (m, 3H, H-5,6,7), 9.63 (d, 1H, H-8). IR (KBr) (cm^{-1}): 1470, 1201 (N → O), 1642 (C═N), 1130, 1077 (Ar−Cl), 1588, 832, 767 (Ar), 2937, 1524, 1353, 1032, 949, 712, 560. MS *m*/*z* (rel int. %): 323 (6.0) $[M + 4]^+$; 321 (33.0) $[M + 2]^+$; 319 (49.0) $[M]^+$; 306 (18.0); 304 (68.0); 302 (100.0); 279 (3.0); 277 (13.0); 275 (21.0); 206 (4.0); 204 (23.0); 202 (29.0); 160 (20.0); 128 (30.0); 115 (33.0).

***cis*-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine Hydrochloride [(±)-1].** Nitrone **6** (11.2 g, 35 mmol) was suspended in methanol (200 mL) and hydrogenated over Raney-nickel catalyst (Degussa-Hüls, B 113 W) (3−4 g) washed to pH neutral at atmospheric pressure and 25 °C. After the theoretical hydrogen uptake had ceased (5−6 h), the catalyst was filtered, and the methanol was evaporated. The residue was dissolved in ethanol (60 mL), then 6.8 M HCl in ethanol (5.1 mL) was added dropwise to the stirred solution. The product was filtered and washed with ethanol. Yield: 11.5 g (81%) of the title compound. Mp: 290−291 °C.

(*cis*-1*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine Hydrochloride (Sertraline Hydrochloride) [(+)-1]. *Cis*-racemic amine hydrochloride (±)−**1** (10.27 g, 30 mmol) was suspended in CH_2Cl_2 (70 mL) and extracted with 10% aqueous Na_2CO_3 (40 mL). The aqueous layer was extracted with CH_2Cl_2 (30 mL), and then the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was evaporated in vacuum. The residue was then dissolved in ethanol (100 mL), and *R*-(−)-mandelic acid (4.56 g, 30 mmol) was added. The mandelic acid salt crystallized after a few minutes. The resulting suspension was stirred for 6 h at 25 °C and then filtered and washed with ethanol (50 mL). (*cis*-1*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine (*R*)-mandelate (5.65 g, 41%) was obtained. Mp: 189−191 °C.

The above-described mandelic acid salt (5.04 g, 11 mmol) was mixed with CH_2Cl_2 (50 mL) and 2 M aqueous NaOH

(30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was evaporated in vacuum. The residue was dissolved in ethanol (30 mL), and during stirring 6.8 M HCl in ethanol (1.62 mL) was added. The precipitated product was filtered and washed with ethanol. Yield: 3.2 g (85%). Mp: 246−249 °C. $[\alpha]^{25}_D = +38.9$ ($c = 2$, methanol).

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