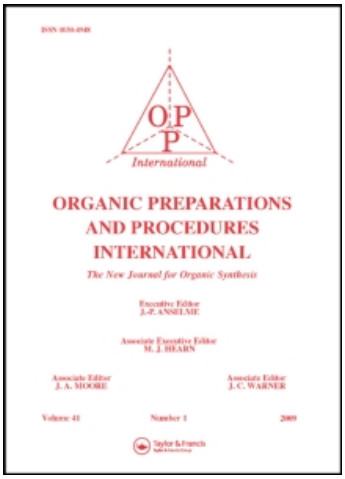

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AN IMPROVED RESOLUTION PROCESS FOR THE PREPARATION OF ANTIDE-PRESSANT DRUG: ESCITALOPRAM

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AN IMPROVED RESOLUTION PROCESS FOR THE PREPARATION OF ANTIDEPRESSANT DRUG: ESCITALOPRAM

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(11/18/05)

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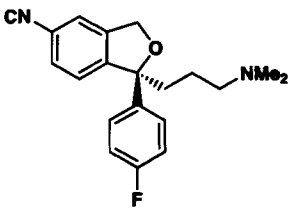
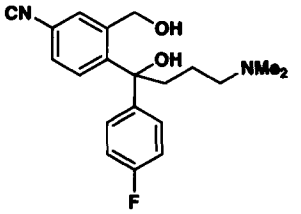
Depression is an extremely serious condition that can affect emotion, cognition, physical functioning and behavior of people at some time. It affects 7% of the world's population, including 10% of the people over the age of 18. Although the causes of this extreme disability are usually multifactorial, the neurochemical abnormalities are ultimately responsible for the emergence of depressive symptoms. There are currently three major classes of drugs available for the treatment of depression: tricyclic antidepressants (TCAs), monoamine oxidase (MAO) inhibitors and selective serotonin reuptake inhibitors (SSRIs),[1] the latter being advantageous compared to the other two classes.

Citalopram, an SSRI introduced in 1989 for the treatment of depression, is a racemic mixture whose entire inhibitory activity resides in the S-(+)-enantiomer,[2] also known as *escitalopram* **1**. Escitalopram can be prepared by different methods.[3-5] The most practical route is the resolution of 4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl) benzonitrile, the racemic diol **2**, a precursor for citalopram.[4] The S-enantiomer was obtained by stereoselective crystallization of the diastereomeric salts of the racemic (±) diol **2**, with (+)-di-p-toluoyl tartaric acid hydrate, or by the formation of the diastereomeric ester with (+)-α-methoxy-α-trifluoromethylphenylacetylchloride and subsequent crystallization.[4] However the R- or S-diol thus obtained are not pure and difficult to purify. Both these methods involve costly and enantiomerically pure reagents which give relatively low yields, thereby being economically unsuitable for industrial production. Consequently we recrystallised the precipitated enriched diastereomeric salt twice using a medium polar solvent, before it was isolated as a free base.



1
Escitalopram



± 2

Another route is by repeated HPLC purification of the enantiomers of the diastereomeric ester of the racemic diol **2** formed with (+)-a-methoxy-a-trifluoromethylphenylacetylchloride.[2] The enantiomers are separated by repeatedly collecting only 5-10% initial substance in the main peak. This is also a costly method as the chiral stationary phase used is very expensive.[6] The enzymatic resolution of (±) diol **2** with Candida enzyme has been reported in ES patent application P200302215, but this is yet to be proved practical on a large scale as it involves huge reaction volume (due to low titre value of the enzyme).[7] A recent patent reported[8] a process whereby, the enantiomeric purity of the S-citalopram obtained by earlier crystallization methods could be improved. Though this method gives the product of required purity, it requires two stages of purification. Thus, there is a need to develop a simple process whereby, enantiomerically pure S-citalopram may be produced that fulfils the market specifications.

We herein, report a convenient and efficient resolution process for the intermediate racemic diol **2**, wherein the S-diol is obtained in pure form, which is basified and then cyclized to give S-citalopram of >99% enantiomeric purity. The method provides an easy way to improve the enantiomeric purity of S-citalopram that is obtained by diastereomeric salt crystallization method as compared to the other processes. The novelty of this process is that the enriched diastereomeric salt is crystallized twice using a medium polar solvent, before it is released as a free base. This avoids the cumbersome two stage purification process of the other reported processes.

EXPERIMENTAL SECTION

All chemicals were obtained from Aldrich Chemical Company (USA) and racemic diol hydrobromide from Ind-swift Laboratories (INDIA). Proton magnetic resonance (NMR) spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$. The chemical shifts are reported in δ (ppm) relative to internal standard tetramethylsilane (TMS). Mass spectroscopy was conducted using Shimadzu QP 5000 mass spectrometer. Specific rotations were taken on Autopol IV automatic polarimeter.

Chromatographic Separation.- Chiral HPLC was done using Chiral AGP column (150 x 4.0 mm) and a mobile phase of 10 mM hexanoic acid and 3.0 mM SB-12 [dodecyldimethyl (3-sulfopropyl) ammonium hydroxide, inner salt, lauryl sulfobetaine] in phosphate buffer pH 6.5. The other conditions used for the chiral column are the flow rate being 0.5 mL /min, column temperature 30°C, injection volume 15 ml and UV detector wavelength 254 nm.

Resolution Method.- A solution of 20 g (0.0473 mole) of 4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile hydrobromide in 240 mL of water and toluene (1:1), was neutralized by addition of 100 mL of ice cooled 1M NaOH solution slowly. The mixture was stirred for 15 minutes; the toluene layer was separated, washed with (2 x 100 mL) water, dried over Na_2SO_4 and the toluene evaporated. The residual oil **2** (16 g) was

dissolved in 140 mL of 2-propanol at 40°C and 9.55 g (0.0236 moles) of (+)-di-p-toluoyl tartaric acid hydrate was added under vigorous stirring. After a short while (within an hour), crystallization began. After 5 hours of stirring, the slightly sticky precipitated salt was centrifuged and the solvent was decanted. The sticky precipitate is heated with ethyl acetate (50 mL), until it dissolves and then cooled in order to allow it to recrystallize. The precipitate was collected and washed with ethyl acetate (2 x 40 mL), and dried yielding 10.29 g (30.3%) of (-)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile hemi (+)-di-p-toluoyl tartaric acid salt, as a colorless solid, mp. 134-135°C, *lit.* mp.[4] 134-135°C. $[\alpha]_D$ = 10.02° (c = 1, MeOH), *lit.*[4] $[\alpha]_D$ = 10.00°.

Generation of S-Diol as Free base.- The 10.29 g of (+) acid salt was neutralized with 10 mL of 20% aq. $NaHCO_3$ at 20-25°C for 30 minutes. The aqueous solution was extracted with dichloromethane (2 x 25 mL). The dichloromethane layer was washed with water (2 x 25 mL), dried over Na_2SO_4 and concentrated to afford the (-) diol as colorless oil in quantitative yield 4.86g (100 %). $[\alpha]_D$ = –50.16° (c = 1, MeOH), $[\alpha]_D$ = –90.75° (c = 1, $CHCl_3$), *lit.*[7] $[\alpha]_D$ = –98.5° (c = 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.28 (s, 6H, CH_3), 2.38 (m, 6H, CH_2), 4.28 (dd, J = 12.15 Hz, 2H, CH_2), 5.4-5.8 (br s, 2H, OH), 6.98 (t, J = 8.69 Hz, 2H, CH), 7.40 (m, 3H, CH), 7.58 (d, J = 8.85 Hz, 2H, CH); MS (ESI^+, m/z): 365 $(M+Na)^+$, 343 $(M+H)^+$.

Preparation of S-Citalopram.- To an ice cooled solution of 2.5 g (7.43 mmol) of the (-) isomer of the diol, in 60 mL dry toluene was added 2.86 mL (20.5 mmol) of triethylamine. Methanesulfonyl chloride (0.64 mL, 8.26 mmol) in 5 mL dry toluene was added dropwise during 10 minutes. The reaction mixture was stirred for 3 hrs at 0°C, washed with brine, dried and the solvent concentrated to give 1.66 g (70%) of S-(+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile **1** as a viscous oil. $[\alpha]_D$ = 12.30° (c = 1, MeOH). *Lit.*[4] $[\alpha]_D$ = 12.33° (c = 1, MeOH). ^1H NMR ($CDCl_3$): δ 2.14 (s, 6H, CH_3), 2.24 (m, 6H, CH_2), 5.16 (d, J = 5.15 Hz, 2H, CH_2), 6.96 (t, J = 8.71 Hz, 2H, CH), 7.42 (m, 3H, CH), 7.56 (d, 2H, J = 8.69 Hz, CH); MS (ESI^+, m/z): 347 $(M+Na)^+$, 325 $(M+H)^+$. Chiral HPLC analysis showed a content of 99.7% of S-(+)-citalopram with retention time of 7.67 minute and 6.75 minute for R-(-) isomer, for a 30 minute elution time.

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