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Technical Notes

A Practical Procedure for the Resolution of (+)- and (−)-Tramadol

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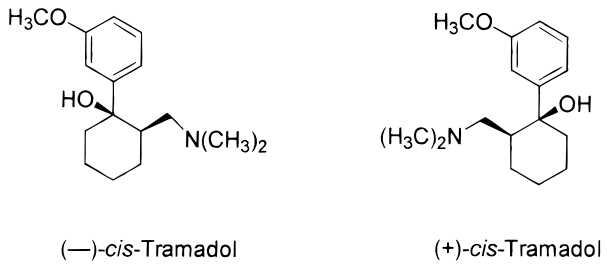
Abstract:

A practical procedure for the efficient resolution of *cis*-tramadol [*cis*-2-(dimethylaminomethyl)-1-(3-methoxyphenyl)cyclohexanol] has been developed. This process was based on the observation that *cis*-tramadol free base selectively formed mandelic acid salts at different rates, affording a readily scalable kinetic resolution of each enantiomer. The key to the process was the observation that the resolving salt needed to be broken and re-formed to ultimately improve the optical purity. The mandalate salt of each *cis*-enantiomer was found to be >99% optically pure after three cycles through the salt formation process. A sample of each mandelate salt enantiomer was successfully converted to the known, optically active hydrochloride salt.

Introduction

Tramadol [2-(dimethylaminomethyl)-1-(3-methoxyphenyl)cyclohexanol] is a mild, non-addictive, centrally acting binary analgesic agent, introduced in Germany in the late 1970s by Grunenthal.[1] It was approved for use in the United States in 1995 and is currently marketed as Ultram by Ortho-McNeil Pharmaceuticals, Inc. While the marketed form is the racemic hydrochloride salt of the *cis*-isomer[2,3] (separated from the minor, *trans*-isomer[2,3] by crystallization of the hydrochloride salt during the production process), it is known that the (+)-enantiomer of the *cis*-isomer exhibits analgesic activity 10-fold higher than that of the (−)-enantiomer.[4,5] Recently we required a ready supply of both enantiomers of *cis*-tramadol. While a chiral synthesis of each enantiomer was a tantalizing challenge, the quickest method to produce appreciable quantities of each enantiomer appeared to be the classical resolution of the readily prepared racemate (Figure 1).



(—)-*cis*-Tramadol (+)-*cis*-Tramadol

Figure 1.

The synthesis and purification of the racemic material was described in 1978.[6] A later article[4] described the resolution of both enantiomers by the use of dibenzoyl-D-tartaric acid. Enantiomers were isolated from the racemic salt by a tedious fractional digestion, followed by fractional crystallization. While an isolated yield was provided for the preparation of the racemate salt, no yields were provided for the ultimate isolation of the resolved salts and subsequent conversion back to the respective hydrochlorides. Later, a brief description was published for the resolution of *cis*-tramadol by fractional crystallization with mandelic acid,[7] but no experimental procedures were provided. Our material requirements for the resolved crystalline salt (the acid component was not particularly specified or required) were to be >99% optically pure (by chiral HPLC analysis) and to match the literature data of both corresponding hydrochloride salt isomers.

Discussion

In our hands, the method of Frankus and co-workers[4] readily afforded the racemate salt with dibenzoyl-D-tartaric acid. However, all attempts to separate the enantiomers by sequential digestion of the solids in ethyl acetate (to dissolve the (+)-enantiomer), followed by digestion of the remaining solids in 2-propanol (to dissolve the (−)-enantiomer) failed. Tramadol isolated by this procedure was, at best, only slightly enriched in either enantiomer, and this method was judged impractical for the preparation of the required quantities of each resolved isomer.

While the mandelic acid procedure of Elsing and Blaschke[7] successfully afforded partially resolved tramadol after multiple fractional recrystallizations, these salts failed to meet the desired specifications of >99% optical purity.

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(1) (a) Flick, K.; Frankus, E. U.S. Patent 3,652,589, March 28, 1972; *Chem. Abstr.* **1972**, *76*, 153321. (b) Flick, K.; Frankus, E. U.S. 3,830,934, August 20, 1974; *Chem. Abstr.* **1974**, *82*, 21817 (both to Grunenthal G.m.b.H.).

(2) The biologically active isomer which was developed by Grunenthal was originally described in the patent[1] and journal[4,6] citations as the *trans*-isomer. As the drug was developed in the United States, this name was revised to the *cis*-isomer.[3]

(3) *Physicians Desk Reference*; Medical Economics Data: Oradell, NJ, 2000; Vol. 54, pp 2218−2219.

(4) Frankus, E. v.; Friedrichs, E.; Kim, S. M.; Osterloh, G. *Arzneim.-Forsch./Drug Res.* **1978**, *28 (I)*, 114−121.

(5) Goeringer, K. E.; Logan, B. K.; Christian, G. D. *J. Anal. Toxicol.* **1997**, *21*, 529−537.

(6) Flick, K.; Frankus, E. v.; Friedrichs, E. *Arzneim.-Forsch./Drug Res.* **1978**, *28 (I)*, 107−113.

(7) Elsing, B.; Blaschke, G. *Arch. Pharm. (Weinheim, Ger.)* **1991**, *324*, 719.

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Additionally, the isolated yields were very low (<5% yield as the mandelate salt) and the necessity of ultimately preparing multi 100-g quantities required the detailed reevaluation of this method in an attempt to improve the yield and purity of each of the separated enantiomers.

Early in the process of attempting to optimize the fractional crystallization, it was noted that the enantiomers of *cis*-tramadol free base formed mandelic acid salts at different rates. When (*R*)-(−)-mandelic acid was used, the solid product was enriched in the (−)-enantiomer. When (*S*)-(+)-mandelic acid was used, the solids were enriched in the (+)-enantiomer. The respective mother liquors were correspondingly enriched in the opposite enantiomer (affording the possibility of recycling and recovering the mother liquor concentrates). When 1 mol equiv of (*R*)-(−)-mandelic acid was used, the extremely rapid crystallization afforded an 87% yield of the salt of which the −:+ ratio was 54.8:45.2. When the theoretically optimal charge of mandelic acid was utilized (0.5 mol equiv of (*R*)-(−)-mandelic acid) the initial isolated yield of crystalline salt was <15%. The solids isolated were 81.4% of the (−)-enantiomer of *cis*-tramadol. Attempts to improve the isolated yield by conducting the resolution more concentrated or to concentrate the filtrate following the first crop isolation, afforded a solid of which the −:+ ratio was about 60:40. A quick examination of the molar charge of (*R*)-(−)-mandelic acid to tramadol free base in a fixed volume of acetate solvent indicated that when a 70−75% mol % charge was used, the white solid isolated was significantly enriched in one enantiomer at a maximized isolated yield of about 50%. Resolution by differential salt solubilities is not a new concept, but the specific undercharge of the chiral resolving acid to maximize the resolution was a concept we were unable to locate in the chemical literature. However, recently this concept was elegantly demonstrated in the efficient resolution of (±)-*threo*-methylphenidate with (*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate.[8] With *cis*-tramadol free base, this generalized procedure worked surprisingly well. The first crystallization (40−50% absolute yield) typically afforded a 75:25 to 94:6 mixture of each enantiomer.

Attempts to improve the optical purity of the first crystallization products to acceptable purity levels by simple recrystallizations, fractional recrystallizations, or selective solvent digestions were only marginally successful, as the enantiomer ratio remained virtually unchanged. When the partially resolved salt was converted to the free base and the salt reformed with a charge of fresh mandelic acid which matched the % of the desired enantiomer present in the sample, the crystallized product was typically >95% in optical purity of the desired enantiomer. Since the (+) and (−) enantiomers of mandelic acid are each readily commercially available and relatively inexpensive, it was a quick effort to show that this procedure worked equally well to produce either enantiomer of *cis*-tramadol from the racemic free base. One more repetition of the free base and salt reformation sequence (again using the diminished mol % of mandelic acid) afforded either salt in >99% optical purity as determined by chiral HPLC analyses (Tables 1 and 2).[9]

Table 1. **Resolution of (−)-*cis*-tramadol**

crystallization	(*R*)-(−)-mandelic acid (equiv)	% recovery	HPLC purity
1	0.75	49.3	75.3% (−)-enantiomer 24.7% (+)-enantiomer
2	0.70	65.0	96.8% (−)-enantiomer 3.2% (+)-enantiomer
3	0.95	85.2	99.4% (−)-enantiomer 0.6% (+)-enantiomer

Table 2. **Resolution of (+)-*cis*-tramadol**

crystallization	(*S*)-(−)-mandelic acid (equiv)	% recovery	HPLC purity
1	0.75	43.2	6% (−)-enantiomer 94% (+)-enantiomer
2	0.95	83.0	1.9% (−)-enantiomer 98.1% (+)-enantiomer
3	0.98	94.0	100% (+)-enantiomer (no (−)-enantiomer detected)

To complete the comparison to the known data for resolved tramadol, a small sample of each resolved enantiomer was converted to the free base after which the respective hydrochloride salts were prepared. In both cases, each salt compared very favorably to the literature data (melting point and optical rotation).

Conclusions

The observation that the two enantiomers of tramadol selectively form optically active salts of mandelic acid has afforded a process to prepare each of the separated enantiomers. This process was successfully scaled up to prepare 100+ g of each enantiomer in >99% optical purity. A sample of each enantiomer was converted to the known optically active hydrochloride salts (via the free base) with excellent agreement with the published data.

Experimental Section

All non-aqueous reactions were performed under a dry nitrogen atmosphere. Racemic *cis*-tramadol hydrochloride was prepared following the literature procedure.[1,6] Reagents and solvents were obtained from commercial sources and used as received. Proton magnetic resonance spectra were obtained on a Bruker AC 300 MHz NMR, using either tetramethylsilane or chloroform as an internal reference. Infrared spectra were obtained as KBr pellets on a Perkin-Elmer Spectrum 1000 Infrared Spectrophotometer. Mass spectra analyses were performed on a Shimadzu QP-5000 GC/MS (CI mass spectrometry). Melting points were obtained using a Perkin-Elmer model DSC-4 differential scanning calorimeter. HPLC analyses were performed on a Waters 600 E HPLC system equipped with a Waters 440 UV detector and Hewlett-Packard 3396A integrator.

(8) Prashad, M.; Hu, B.; Repiè, O.; Blacklock, T. J.; Giannousis, P. P. *Org. Process Res. Devel.* **2000**, *4*, 55−59.

(9) Elsing, B.; Blaschke, G. *J. Chromatogr.* **1993**, *612*, 223−230.

Chiral HPLC Method for the Analysis of *cis*-Tramadol. The chiral HPLC analysis of *cis*-tramadol was carried out using a modified version of the method of Elsing and Baschke.[9] A sample (about 1 mg of any salt or free base in 5 mL of 2-propanol) was eluted on a Chiralpak AD column (4.6 mm × 25 cm) with an isocratic mobile phase of hexane/2-propanol/diethylamine (97.5:2.5:0.01) at 1 mL/minute. The system was monitored by UV at 280 nm. The (+)-cis enantiomer eluted at 7.0 min and the (−)-cis enantiomer eluted at 11.4 min.

Preparation of *cis*-Tramadol Free Base. To a vigorously stirred mixture of saturated aqueous sodium bicarbonate solution (2.0 L) and solid sodium carbonate (50 g, 0.47 mol) was added, portionwise, racemic *cis*-tramadol hydrochloride (254.4 g, 0.85 mol). Once the solids had dissolved, the aqueous solution was extracted with methylene chloride (3 × 1.2 L). The combined organic extracts were washed with saturated aqueous sodium chloride solution (2 × 2.0 L), dried over anhydrous sodium sulfate, clarified, and concentrated under reduced pressure to afford the free base with 98.7% recovery as a viscous oil (221.4 g, 0.84 mol). This material was used without purification in the following resolution procedures.

Preparation of (−)-*cis*-Tramadol (*R*)-(−)-Mandelate. A stirred biphasic mixture of tramadol free base (66.0 g, 0.25 mol) in a mixture of isopropyl acetate (300 mL) and ethyl acetate (200 mL) was heated at 70 °C until a clear solution was obtained. A solution of (*R*)-(−)-mandelic acid (28.6 g, 0.188 mol, 0.75 equiv) in ethyl acetate (100 mL) was prepared with heating at 40 °C. The mandelic acid solution was added to the free base solution, and the resulting mixture was stirred at 35 °C until crystallization began. The crystallizing mixture was allowed to cool to room temperature and stirred overnight. The resulting slurry was cooled to −5 °C, with stirring, for 3.5 h, and the solids were collected by vacuum filtration. The filter cake was washed with isopropyl acetate (2 × 50 mL) and diethyl ether (2 × 50 mL) and dried to a constant weight to afford 72.2 g of a white crystalline solid. Chiral HPLC analysis of the solid showed a 40:60 mixture of (+)- and (−)-*cis*-tramadol enantiomers. Chiral HPLC analysis of the filtrate showed an 88.7:11.3 mixture of the (+)- and (−)-*cis*-tramadol enantiomers. The solid crystalline material was mostly dissolved in boiling ethyl acetate (1.2 L), and the solution was clarified and cooled to room temperature. The solution was then concentrated to a volume of about 500 mL and cooled to 0 °C with stirring for about 4 h. The resulting crystals were collected by vacuum filtration, washed with cold ethyl acetate (50 mL), and dried to a constant weight to afford a 49.3% yield (57.3 g) of the (−)-mandelate salt of *cis*-tramadol as white crystalline solid. This solid contained 75.3% of the (−)- and 24.7% of the (+)-enantiomer (by chiral HPLC analysis).

This sample of partially resolved (−)-*cis*-tramadol was combined with several additional samples of the same 3:1 mixture of enantiomers (75.0 g total) and was dissolved in water (500 mL). The solution was acidified (pH ≈ 2) with concentrated hydrochloric acid (15 mL) and the mandelic acid was extracted with diethyl ether (3 × 300 mL). The aqueous solution was neutralized with solid sodium bicarbonate (34.2 g) and then extracted with methylene chloride (3 × 300 mL). The combined organic extracts were dried over sodium sulfate, filtered, and the solvents were removed under reduced pressure to afford 46.5 g (0.18 mol) of free base as a thick oil. This oil was dissolved, with vigorous stirring, in ethyl acetate (200 mL) and a warm solution of (*R*)-(−)-mandelic acid (18.8 g, 0.12 mol, 0.7 equiv) in ethyl acetate (50 mL) was added in one portion. Crystallization occurred very quickly and the resulting slurry was stirred at room-temperature overnight. The resulting solids were collected by vacuum filtration, washed with cold ethyl acetate (20 mL), and dried to a constant weight to afford a 65% recovery of *cis*-tramadol (*R*)-(−)-mandelate salt (48.6 g). This salt was a mixture of 96.8% of the (−)-enantiomer and 3.2% of the (+)-enantiomer (by chiral HPLC analysis).

This salt was combined with another sample of the same enantiomeric purity (89.5 g total) and the mixture was dissolved in water (1 L). The solution was acidified (pH ≈ 2) with concentrated hydrochloric acid (25 mL), and the mandelic acid was washed out with diethyl ether (3 × 500 mL). The aqueous solution was neutralized with solid sodium bicarbonate (34.4 g) and then extracted with methylene chloride (3 × 400 mL). The combined organic extracts were dried over sodium sulfate and filtered, and the solvents were removed under reduced pressure to afford 54.5 g (0.21 mol) of free base as a thick oil. This oil [98.1% (−)-enantiomer] was dissolved, with vigorous stirring, in ethyl acetate (50 mL), and a warm solution of R−(−)-mandelic acid (29.9 g, 0.20 mol, 0.95 equiv) in ethyl acetate (50 mL) was added in one portion. Crystallization occurred very quickly, and the resulting slurry was stirred at room temperature overnight. The resulting solids were collected by vacuum filtration, washed with cold diethyl ether (40 mL), and dried to a constant weight to afford a 85% recovery of (−)-*cis*-tramadol (*R*)-(−)-mandelate salt (74.6 g). This salt was composed of 99.4% of the (−)-enantiomer and 0.6% of the (+)-enantiomer (by chiral HPLC analysis), mp = 153−155 °C, $[\alpha]_D^{25°C}$ = −57.2° (*c* = 1.02, methanol), ^{1}H NMR, δ (CD_3OD): 1.40−1.90 (m, 8H), 2.20 (m, 1H), 2.55 (s, 6H), 2.75−2.95 (m, 1H), 3.30 (m, 1H), 3.80 (s, 3H), 4.85 (s, 1H), 4.90 (s, 3H, exchanges with D_2O), 6.80 (d, 1H), 7.10 (m, 2H), 7.25 (m, 4H) and 7.45 (m, 2H) ppm. IR (KBr, cm^{-1}): 3400 (ν, OH, S), 3237 (ν, H-bonding, S, br), 2926 (ν, CH_3, CH_2, S), 1616 (ν, carboxylate, VS), 1580 (ν, aromatic C = C, M), 1351 (δ, OH, M); 1253, 1216 (ν, C−O−CH_3, S). Anal. Calcd for $C_{24}H_{33}NO_5$: C, 69.37; H, 8.01; N, 3.37. Found: C, 69.23; H, 7.82; N, 3.33.

A small sample of this mandelate salt was converted to the free base and then to the known (−)-*cis*-tramadol hydrochloride salt following literature procedures.[4] The melting point and optical rotation were comparable to the literature values: mp = 172−174 °C, $[\alpha]_D^{26°C}$ = −28.8° (*c* = 1.0, water), [lit:[4] mp = 169−170 °C, $[\alpha]_D^{20°C}$ = −28° (*c* = 1.0, water)].

Preparation of (+)-*cis*-Tramadol (*S*)-(+)-Mandelate. A stirred biphasic mixture of racemic *cis*-tramadol free base

(66.0 g, 0.25 mol) in ethyl acetate (200 mL) was heated at 70 °C until a clear solution was obtained. A solution of (*S*)-(+)-mandelic acid (28.6 g, 0.188 mol, 0.75 equiv) in ethyl acetate (150 mL) was prepared with warming at 40 °C. The mandelic acid solution was added in one portion to the free base solution and the resulting mixture was stirred at about 40 °C until crystallization began. The crystallizing mixture was allowed to cool to room temperature and stirred overnight. The resulting slurry was cooled to −5 °C and stirred for 4.5 h, at which point the solids were collected by vacuum filtration. The filter cake was washed with isopropyl acetate (50 mL) and diethyl ether (50 mL) and was dried to a constant weight to afford 43.2% yield (50.3 g) of a white crystalline solid. Chiral HPLC analysis of the solid showed a 94:6 mixture of the (+)- and (−)-cis-tramadol enantiomers. Chiral HPLC analysis of the filtrate showed a 4.3:95.7 mixture of the (+)- and (−)-cis-tramadol enantiomers.

This sample of partially resolved (+)-*cis*-tramadol was combined with two additional small samples of a 95:5 mixture of enantiomers (54.8. g total), and the mixture was dissolved in water (600 mL). The solution was acidified (pH ≈ 2) with concentrated hydrochloric acid (15 mL), and the mandelic acid was extracted with diethyl ether (3 × 300 mL). The aqueous solution was neutralized with solid sodium bicarbonate (34 g) and then extracted with methylene chloride (3 × 300 mL). The combined organic extracts were dried over sodium sulfate and filtered, and the solvents were removed under reduced pressure to afford 40.5 g (0.15 mol) of free base as a thick oil. This oil was dissolved, with vigorous stirring, in ethyl acetate (30 mL), and a warm solution of (*S*)-(+)-mandelic acid (22.2 g, 0.146 mol, 0.95 equiv) in ethyl acetate (60 mL) was added in one portion. Crystallization occurred very quickly, and the resulting slurry was stirred at room temperature overnight. The solid was collected by vacuum filtration, washed with cold ethyl acetate (20 mL), and dried to a constant weight to afford a 83% recovery of *cis*-tramadol (*S*)-(+)-mandelate salt (51.6 g). This salt was 98.1% (+)-enantiomer and 1.9% (−)-enantiomer (HPLC).

This salt was dissolved in water (600 mL) and the solution was acidified (pH ≈ 2) with concentrated hydrochloric acid (15 mL). The mandelic acid was washed out with diethyl ether (3 × 300 mL). The aqueous solution was neutralized with solid sodium bicarbonate (24 g) and extracted with methylene chloride (3 × 300 mL). The combined organic extracts were dried over sodium sulfate, filtered, and the solvents were removed under reduced pressure to afford 33.4 g (0.13 mol) of free base as a thick oil. This oil was dissolved, with vigorous stirring, in ethyl acetate (20 mL) and a warm solution of (*S*)-(+)-mandelic acid (19.3 g, 0.12 mol, 0.98 equiv) in ethyl acetate (55 mL) was added in one portion. Crystallization occurred very quickly and the resulting slurry was stirred at room temperature for 7 h. The solids were collected by vacuum filtration, washed with cold ethyl acetate (25 mL), and dried to a constant weight to afford a 94% recovery of (+)-*cis*-tramadol S−(+)-mandelate salt (48.5 g). This salt was entirely the (+)-enantiomer by chiral HPLC analysis, mp = 153−155 °C, $[\alpha]_D^{25°C} = +57.8°$ (*c* = 1.07, methanol), ^{1}H NMR, δ (CD_3OD): 1.40−1.90 (m, 8H), 2.20 (m, 1H), 2.55 (s, 6H), 2.75−2.95 (m, 1H), 3.30 (m, 1H), 3.80 (s, 3H), 4.85 (s, 1H), 4.90(s, 3H), 6.80 (d, 1H), 7.10 (m, 2H), 7.25 (m, 4H) and 7.45 (m, 2H) ppm. IR (KBr, cm^{-1}): 3400 (ν, OH, S), 3237 (ν, H-bonding, S, br), 2927 (ν, CH_3, CH_2, S), 1615 (ν, carboxylate, VS), 1580 (ν, aromatic C = C, M), 1351 (δ, OH, M), 1253, 1216 (ν, C−O−CH_3, S). Anal. Calcd for $C_{24}H_{33}NO_5$: C, 69.37; H, 8.01; N, 3.37. Found: C, 69.42; H, 7.87; N, 3.34.

A small sample of this mandelate salt was converted to the free base and then to the known (+)-cis tramadol hydrochloride salt following literature procedures.[4] The melting point and optical rotation were comparable to the literature values: mp = 172−175 °C, $[\alpha]_D^{26\ °C} = +27.8°$ (*c* = 1.0, water), [lit.:[4] mp = 169−170 °C, $[\alpha]_D^{20°C} = +27.5°$ (*c* = 1.0, water)].

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