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Preparation of highly enantiopure stereoisomers of 1-(2,6-dimethylphenoxy)-2-aminopropane (mexiletine)

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Abstract

Mexiletine [1-(2,6-dimethylphenoxy)-2-aminopropane], an orally effective antiarrhythmic agent, exhibits enantioselective pharmacokinetics and pharmacodynamics during mexiletine therapy. The purpose of this paper is to emphasize the advantage of tetrahydropyranyl-protected mandelic acid (THPMA) in the resolution of mexiletine enantiomers. Both enantiomers of mexiletine were obtained in 99% enantiomeric excess. Judging by the differential shielding effects in the ^{1}H and ^{13}C NMR analyses, we have observed the opposite predominant conformation for the mexiletine mandelates in comparison with the *O*-methylmandelates.

1. Introduction

Mexiletine **1** (Fig. 1), is an orally effective antiarrhythmic agent and is available for clinical use as the racemic mixture. It has been reported previously that mexiletine undergoes stereoselective disposition[1] in humans being associated with the selective binding of the (*R*)-(−)-mexiletine to a cardiac sodium channel[2] and the higher antiarrhythmic activity[3] of this enantiomer. Despite the extensive pharmacological[4] and analytical[5] studies over recent years, the mechanism of stereoselection in pharmacokinetics and pharmacodynamics for the individual enantiomers of mexiletine remains unclear. Consequently, there is a need for a multi-gram scale method for the preparation of both enantiomers of mexiletine in a high enantiomeric purity.

An elegant method has been shown to convert both commercially available enantiomers of the 2-amino-1-propanol into the target mexiletines via nucleophilic substitution of the 1,3-dimethyl-2-fluorobenzenetricarbonylchromium complex.[6] Also a method based on the relatively expensive chiral

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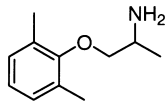


Figure 1. Chemical structure of 1-(2,6-dimethylphenoxy)-2-aminopropane (mexiletine) **1**

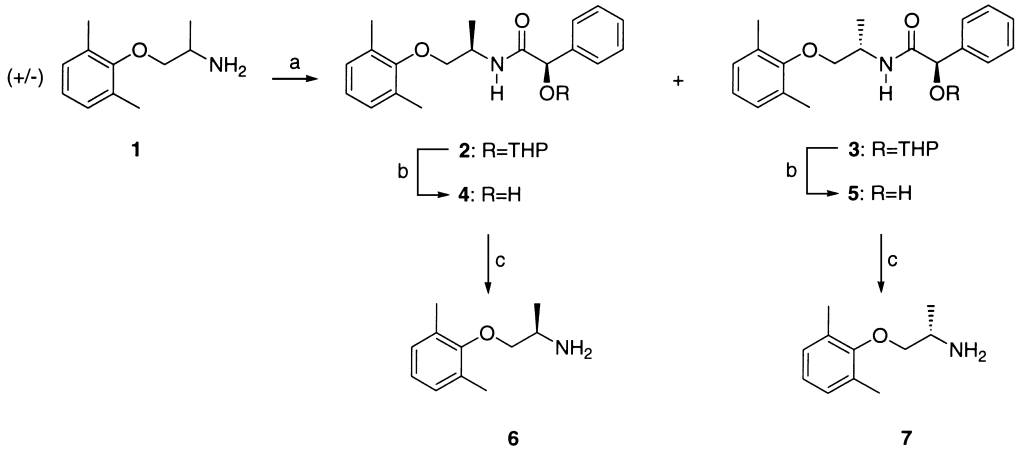
starting material, (*S*)-(+)-3-bromo-2-methyl-1-propanol, has been reported to allow the synthesis of (*R*)-(−)-mexiletine.[7] The resolution of mexiletine enantiomers from the racemic mixture by fractional crystallisation of *p*-toluoyl tartrate salts has been reported previously.[3] The process described needs large volumes of solvent and is time consuming which is the drawback of this method.

Recently, we have reported the application of tetrahydropyranyl-protected mandelic acid (THPMA) as a chiral derivatising agent for the absolute configurational assignment and semipreparative enantiomeric resolution of secondary alcohols.[8] Herein we wish to report the advantage of THPMA in the resolution of mexiletine enantiomers by the separation of their mandelic acid amides, which were synthesised by using THPMA. The unexpected results of the ^{1}H and ^{13}C NMR analyses of the mexiletine diastereomeric amides are also presented and discussed.

2. Results and discussion

The racemic mixture of mexiletine **1** was synthesised by the coupling of sodium 2,6-dimethylphenoxide with propylene oxide followed by azide synthesis with an overall yield of 64%. The chiral derivatising agent, tetrahydropyranyl-protected (*R*)-(−)-mandelic acid (THPMA), was prepared according to the reported procedure.[8] A diastereomeric mixture of the amides **4** and **5** (Scheme 1) was obtained by acylation of racemic mexiletine **1** with THPMA and subsequent hydrolytic cleavage of the tetrahydropyranyl (THP) protecting group. The better chromatographic separability of the deprotected amides **4** and **5** compared to the THP-protected ones **2** and **3** was observed by TLC. Thus, the chromatographic separation of **4** and **5** was accomplished by means of flash chromatography using silica gel 60 (240–400 mesh, Merck) and benzene:ethyl acetate (85:15).[9] As a result, (2*R*,2′*R*)-amide **4** (less polar) and (2*R*,2′*S*)-amide **5** (more polar) were obtained with diastereomeric purities greater than 98% for both according to HPLC analyses of the products. The amides **4** and **5** were further subjected to hydrolysis with the mixture of 8N H_2SO_4:dioxane (1:1) at 80°C thus giving rise to crude amines **6** and **7**, and offering a method to recover (*R*)-mandelic acid after workup procedures. Recrystallisation of the hydrochloric acid salts of the enantiomerically pure (*R*)-mexiletine **6** and (*S*)-mexiletine **7** from the 5 M methanolic HCl:diethyl ether (1:7) afforded nicely crystalline products. The enantiomeric purity for both mexiletine enantiomers was determined to be at least 99% ee by using HPLC analysis of the corresponding methoxy(trifluoromethyl)phenylacetyl (MTPA) derivatives in combination with ^{1}H and ^{13}C NMR experiments.

The application of MTPA and the related *O*-methylmandelate technique to the configurational analysis of chiral primary amines has been reported.[10,11] For the MTPA amides, the predominant conformation has been established to be analogous to that of esters of secondary alcohols: the methine hydrogen, the carbonyl oxygen, and the trifluoromethyl groups are coplanar and *syn*.[10] The differential shielding effects ($\Delta\delta$ values) obtained from the NMR analyses of the MTPA amides **8** and **9** (Table 1) are in good agreement with the previous findings. On the other hand, the conformations of *O*-methylmandelamides are known not to be analogous to those of the *O*-methylmandelate esters. The major conformation of *O*-methylmandelamides was deduced to have the methoxy group *anti*-periplanar to the carbonyl.[11] Somewhat unexpectedly, judging from the ^{1}H and ^{13}C NMR analyses, we have observed the opposite dominant



Scheme 1. Preparation of enantiomerically pure mexiletine enantiomers **6** and **7**. (a) DCC, THPMA, EtOAc; (b) HCl, H_2O/MeOH; (c) H_2SO_4, H_2O/dioxane

conformation for the mexiletine mandelates **4** and **5** in comparison with the *O*-methylmandelates **10** and **11** (Table 1). Thus, mandelic acid amides of mexiletine as well as mandelic acid esters of secondary alcohols behave according to the same conformational model in which the hydroxyl group is *syn*-coplanar to the carbonyl.

3. Experimental

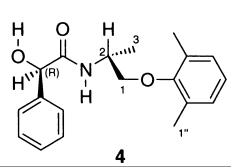
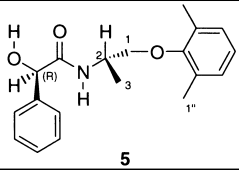
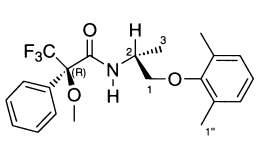
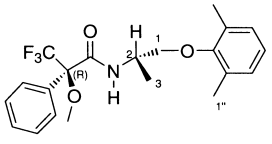
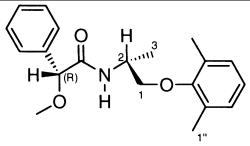
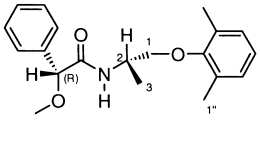
3.1. General

All solvents were reagent grade and were distilled before use. Ethyl acetate was dried over $CaCl_2$ and freshly distilled before use. Proton magnetic resonance spectra (^{1}H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker AMX-500 spectrometer operating at 500.13 MHz and 125.76 MHz, respectively. Chemical shifts are in parts per million (ppm) relative to the solvent as the internal reference. Optical rotations (in degrees) were measured with a Carl Zeiss Polamat A polarimeter at 546 nm. Melting points were determined on a Boetius melting point apparatus, and are uncorrected. Elemental analyses were performed on a Perkin–Elmer 2400 Series II CHNS/O analyser.

*3.2. (2*RS*)-1-(2,6-Dimethylphenoxy)-2-aminopropane (mexiletine) **1***

To a solution of propylene oxide (9.41 g, 0.162 mol) in 65 mL ethanol was added dropwise a mixture of 2,6-dimethylphenol (10.0 g, 0.081 mol) and sodium hydroxide (3.47 g, 0.085 mol) in 34 mL of water. The reaction mixture was cooled down to room temperature after stirring for 6 h at 60°C followed by the addition of water (150 mL). The mixture was extracted with 3×100 mL of chloroform. The combined organic layers were washed with 100 mL of 1% NaOH, 3×75 mL of water and dried over Na_2SO_4. Evaporation of solvents left 13.47 g (91% yield) of 1-(2,6-dimethylphenoxy)-2-propanol, which was dissolved in 110 mL of pyridine. To this solution, methanesulphonyl chloride (16.6 g, 0.145 mol) was added under an Ar atmosphere at 0°C. After stirring the mixture at room temperature for 4 h, it was poured on ice-water and extracted with chloroform (3×100 mL). The combined organic extracts were washed with water (3×100 mL), dried over Na_2SO_4 and concentrated to give 18.1 g (98% yield) of mesylate. To a mixture of this mesylate in DMF (230 mL), sodium azide (24.6 g, 0.375 mol) was added

Table 1
^{1}H and ^{13}C NMR differential shielding effects and the dominant conformations for mexiletine mandelates **4**–**5**, *O*-methyl(trifluoromethyl)mandelates **8**–**9** and *O*-methylmandelates **10**–**11**

Atom no.	^{13}C δ(ppm)	^{1}H δ(ppm)	^{13}C δ(ppm)	^{1}H δ(ppm)	^{13}C Δδ(ppm)	^{1}H Δδ(ppm)
					Δδ=δ(**R,R**)-**4** - δ(**R,S**)-**5**	
	4		**5**			
1"	15.94	2.09	16.14	2.22	-0.20	-0.13
1	73.54	3.69	74.24	3.73	-0.70	-0.04
3	17.65	1.41	17.52	1.38	+0.13	+0.03
					Δδ=δ(**R,R**)-**8** - δ(**R,S**)-**9**	
	8		**9**			
1"	16.05	2.29	15.99	2.16	+0.06	+0.13
1	73.57	3.85	73.56	3.78	+0.01	+0.07
3	17.59	1.44	17.63	1.49	-0.04	-0.05
					Δδ=δ(**R,R**)-**10** - δ(**R,S**)-**11**	
	10		**11**			
1"	16.00	2.32	16.04	2.24	-0.04	+0.08
1	73.77	3.84	73.72	3.74	+0.05	+0.10
3	17.49	1.41	17.68	1.50	-0.19	-0.09

under an Ar atmosphere. The mixture was stirred for 2.5 h at 100°C. Dilution of the reaction mixture in 500 mL water was followed by extraction with 3×150 mL of chloroform. The combined organic phases were washed with water (3×300 mL), dried over $MgSO_4$ and concentrated to give 12.02 g (84% yield) of azide which was dissolved in 220 mL of methanol. To this solution, a suspension of Raney nickel (1.17 g) was added. Hydrogenation (1 atm H_2) was carried out at room temperature for 5 h. The catalyst was removed by filtration and the methanol was evaporated under reduced pressure. The residue was taken up in 250 mL of chloroform and washed with 3×100 mL of aq. Na_2CO_3. The organic layer was dried over Na_2SO_4, solvents were removed under reduced pressure and the racemic mexiletine **1** (8.68 g, 86% yield) was obtained as an oil. The product obtained was identical in all respects to that described in the literature.[12]

*3.3. (2*RS*)-*N*-(1-(2′,6′-Dimethylphenoxy)-2-propyl)-tetrahydropyranyl-(*R*)-mandelamide **2** and **3***

To a solution of (2*R*)-2-phenyl-2-(tetrahydro-2-pyranyloxy)acetic acid (THPMA) (12.33 g, 0.052 mol) in dry ethyl acetate (180 mL) under an Ar atmosphere, a solution of dicyclohexylcarbodiimide (DCC) (11.34 g, 0.055 mol) in 90 mL of dry ethyl acetate was added at 0°C. The mixture was allowed to stir for 2 h at room temperature, then the solution of (±)-mexiletine **1** (9.85 g, 0.055 mol) in 90 mL of dry ethyl acetate was added. The reaction mixture was stirred at room temperature for 18 h, filtered, washed with 2×150 mL of water, 150 mL of brine and dried over Na_2SO_4. Removal of solvents under reduced

pressure afforded 20.15 g (97% yield) of a diastereomeric mixture of amides **2** and **3**. The crude complex mixture of four diastereomers was used in the next step without further purification.

*3.4. (2*R*)-N-(1-(2′,6′-Dimethylphenoxy)-2-propyl)-(*R*)-mandelamide **4** and (2*S*)-N-(1-(2′,6′-dimethylphenoxy)-2-propyl)-(*R*)-mandelamide **5***

To a solution of the mixture of amides **2** and **3** (20.15 g, 50.6 mmol) in 400 mL of methanol:water (4:1), conc. HCl (4.3 mL) was added at room temperature and stirred overnight. The reaction mixture was neutralised with $NaHCO_3$. Methanol was removed under reduced pressure, 250 mL of water was added and the products were extracted with 3×100 mL of ethyl acetate. The combined extracts were washed with 150 mL of water and 150 mL of brine and dried over Na_2SO_4. Removal of the solvents gave 13.48 g (85% yield) of an oily mixture of two diastereomers **4** and **5**. The chromatographic separation was accomplished by means of flash chromatography using silica gel 60 (240–400 mesh, Merck) and benzene:ethyl acetate (85:15) as an eluent.[9] As a result, 2.94 g of less polar (2*R*)-*N*-(1-(2′,6′-dimethylphenoxy)-2-propyl)-(*R*)-mandelamide **4** and 3.19 g of more polar (2*S*)-*N*-(1-(2′,6′-dimethylphenoxy)-2-propyl)-(*R*)-mandelamide **5** were obtained. **4**: $[\alpha]_{546}^{20}$ −7.8 (c=1.66, MeOH); ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ 1.41 (d, J=6.5 Hz, 3H, CH_3); 2.09 (s, 6H, aryl-CH_3); 3.67 (dd, J=9.0 Hz, 10.7 Hz, 1H, O-CH_a); 3.69 (dd, J=4.0 Hz, 10.7 Hz, 1H, O-CH_b); 4.28–4.38 (m, 1H, N-CH); 5.09 (s, 1H, O-CH); 6.70 (s, 1H, NH); 6.92 (t, J=7.5 Hz, 1H, *p*-O-aryl-H); 6.97 (d, J=7.5 Hz, 2H, *m*-O-aryl-H); 7.35 (m, 2H, *m*-C-aryl-H); 7.37 (t, J=7.2 Hz, 1H, *p*-C-aryl-H); 7.42 (d, J=7.8 Hz, 2H, *o*-C-aryl-H). ^{13}C NMR ($CDCl_3$, 125.76 MHz): δ 15.9, 17.7, 45.6, 73.5, 74.1, 124.1, 126.8, 128.6, 128.8, 128.9, 130.7, 139.5, 154.6, 171.5. Elemental analysis for $C_{19}H_{23}NO_3$: calcd C, 72.82; H, 7.40; N, 4.47; found C, 73.06; H, 7.40; N, 4.41. **5**: $[\alpha]_{546}^{20}$ −132.5 (c=1.28, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.38 (d, J=6.4 Hz, 3H, CH_3); 2.22 (s, 6H, aryl-CH_3); 3.69 (dd, J=8.8 Hz, 10.7 Hz, 1H, O-CH_a); 3.73 (dd, J=4.2 Hz, 10.7 Hz, 1H, O-CH_b); 4.26–4.36 (m, 1H, N-CH); 5.05 (s, 1H, O-CH); 6.78 (s, 1H, NH); 6.94 (t, J=7.5 Hz, 1H, *p*-O-aryl-H); 6.99 (d, J=7.5 Hz, 2H, *m*-O-aryl-H); 7.34 (m, 2H, *m*-C-aryl-H); 7.36 (t, J=7.2 Hz, 1H, *p*-C-aryl-H); 7.42 (d, J=7.8 Hz, 2H, *o*-C-aryl-H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 16.1, 17.5, 45.6, 73.7, 74.2, 124.1, 126.7, 128.6, 128.8, 129.0, 130.7, 139.4, 154.7, 171.5. Elemental analysis for $C_{19}H_{23}NO_3$: calcd C, 72.82; H, 7.40; N, 4.47; found C, 72.91; H, 7.40; N, 4.45.

*3.5. (2*R*)-1-(2′,6′-Dimethylphenoxy)-2-aminopropane hydrochloride*

To a solution of 2.94 g (9.39 mmol) of (2*R*)-*N*-(1-(2′,6′-dimethylphenoxy)-2-propyl)-(*R*)-mandelamide **4** in 94 mL dioxane, 75 mL of 4 M H_2SO_4 was added. The reaction mixture was stirred for 72 h at 80°C, then it was neutralised by the aqueous NaOH and alkalised by Na_2CO_3. The aqueous mixture was extracted with ethyl acetate (3×100 mL). The combined organic layer was washed with aqueous Na_2CO_3 and dried over Na_2SO_4. Evaporation of solvents left 1.48 g (88% yield) of (*R*)-(−)-mexiletine, which was dissolved in 35 mL of diethyl ether. To this solution, 4.8 mL of 20% HCl in methanol was added. The precipitate of hydrochloride was formed immediately. The crystals were taken up in methanol and recrystallised from methanol/diethyl ether to give 1.41 g (6.54 mmol, 70% yield) of the title compound as a white solid, mp 201–203°C. The enantiomeric purity of this material was determined to be 99% ee by using HPLC analysis of the corresponding MTPA derivative. $[\alpha]_{546}^{20}$ −2.98 (c=1.51, MeOH); ^{1}H NMR (CD_3OD, 500.13 MHz): δ 1.52 (d, J=6.8 Hz, 3H); 2.35 (s, 6H); 3.76–3.84 (m, 1H); 3.91 (dd, J=6.57 Hz, 10.1 Hz, 1H); 3.96 (dd, J=3.95 Hz, 10.1 Hz, 1H); 6.98 (t, J=7.55 Hz, 1H); 7.07 (d, J=7.55 Hz, 2H). ^{13}C NMR (CD_3OD, 125.76 MHz): δ 15.8, 16.8, 49.6, 73.1,

126.0, 130.4, 132.1, 156.1. Elemental analysis for $C_{11}H_{18}NClO$: calcd C, 61.25; H, 8.41; N, 6.49; found C, 61.48; H, 8.34; N, 6.45.

3.6. (2S)-1-(2′,6′-Dimethylphenoxy)-2-aminopropane hydrochloride

The procedure described above, applied to 3.19 g (10.2 mmol) of (2*S*)-*N*-(1-(2′,6′-dimethylphenoxy)-2-propyl)-(*R*)-mandelamide **5**, provided 1.2 g (5.56 mmol, 54.5% yield) of the title compound as a white solid, mp 201–203°C. The enantiomeric purity of this material was determined to be 99% ee by using HPLC analysis of the corresponding MTPA derivative. $[\alpha]_{546}^{20}$ +3.1 (c=1.47, MeOH). Elemental analysis for $C_{11}H_{18}NClO$: calcd C, 61.25; H, 8.41; N, 6.49; found C, 61.73; H, 8.62; N, 6.56.

Acknowledgements

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9. CAUTION! Benzene is carcinogenic! We took the risk in using highly toxic benzene as an eluent after thorough TLC and small-scale chromatographic separation studies in which the benzene/ethyl acetate eluent system gave the best resolution.
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