Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1323–1329

TETRAHEDRON: *ASYMMETRY*

Synthesis and resolution of a Tolperisone metabolite

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Received 20 January 2000; accepted 27 January 2000

Abstract

The synthesis and resolution of a Tolperisone metabolite ((3′-hydroxy-4′-methylphenyl)-2-methyl-3-(piperidine-1-yl)-1-propane-1-one, **M1**) is described. Racemic **M1** was subjected to resolution by the enantiomers of camphor-10-sulfonic acid. Absolute configuration was determined by X-ray diffraction analysis. Enantiomeric excesses were determined by ^{1}H NMR spectroscopy.

1. Introduction

Tolperisone (2-methyl-3-(piperidino-1-yl)-1-*p*-toluenyl-propane-1-one, Fig. 1) had been found to be effective as a central muscle relaxant.[1] The enantiomers of Tolperisone have different biological activities: while (+)-Tolperisone is a central muscle relaxant, the (–)-enantiomer has bronchodilatory peripheral activity.

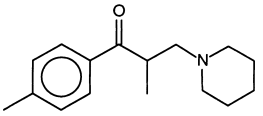

Figure 1. 2-Methyl-3-(piperidino-1-yl)-1-*p*-toluenyl-propane-1-one (Tolperisone)

1.1. Metabolism of Tolperisone

Japanese researchers[2] have reported on Tolperisone metabolism, but the chemical structure of the metabolites remains unknown. Other Japanese researchers[3] observed metabolism of Tolperisone

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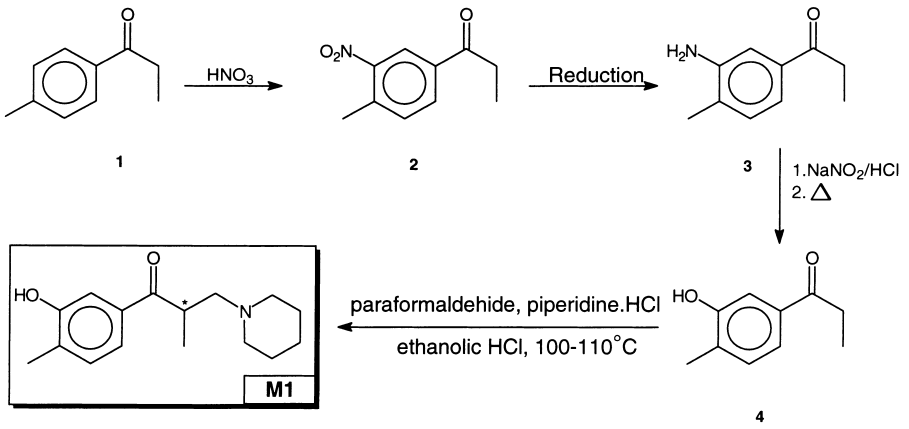
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00047-1

in human objects and rats after oral administration. In this case the structures were submitted. So in the urine of rats 13 metabolites were found while in human urine 11 were present. The human organism can oxygenate the methyl group of the aromatic ring to a hydroxymethyl group and even to a carboxylic group; it can reduce the carbonyl group, generate an *N*-oxide in the piperidine ring and can oxygenate the aromatic ring at position 3. This last compound (3′-hydroxy-tolperisone) is racemic (**M1**) and its optically active forms were of interest to us; thus its synthesis and resolution are discussed.

2. Results and discussion

2.1. Synthesis of *M1* (Scheme 1)

A suitable way to form the desired hydroxy group at position 3 was the following: after nitration of the aromatic ring the nitro group is reduced to amine, which is then diazotized and the diazonium salt hydrolyzed. The product **4** yields **M1** after Mannich reaction with piperidine. For nitration,[4,5] reduction[5–7] and diazotation[5,8] several methods were tested and the most effective ones are described in the Experimental. The Mannich reaction could only be carried out well when no solvent was applied.

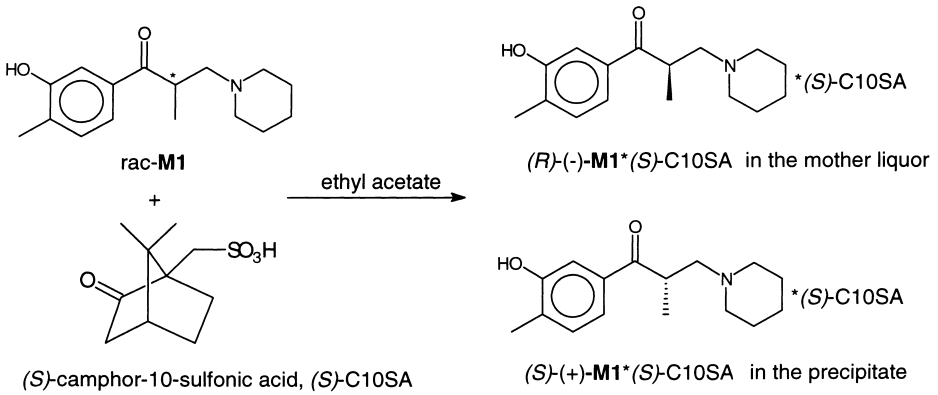


Scheme 1. Preparation of **M1**

Resolution of **M1** was accomplished by (*S*)-(+)-camphor-10-sulfonic acid in ethyl acetate (Scheme 2). The solid diastereoisomeric salt gave enantiomerically pure (*S*)-**M1** after cleavage following two resolution steps from ethyl acetate. The other enantiomer was obtained from the mother liquor by diastereoisomeric salt formation with (*R*)-(–)-camphor-10-sulfonic acid.

2.2. Determination of the absolute configuration of (S)-(+)-*M1*

The X-ray diffraction analysis showed that the absolute configuration of the (+)-enantiomer is (*S*) (see Fig. 2). In the crystal structure of the diastereomeric salt a water molecule with a site occupation of 0.22 is included in the asymmetric unit. A final check was made by removing the



Scheme 2. Optical resolution of **M1**

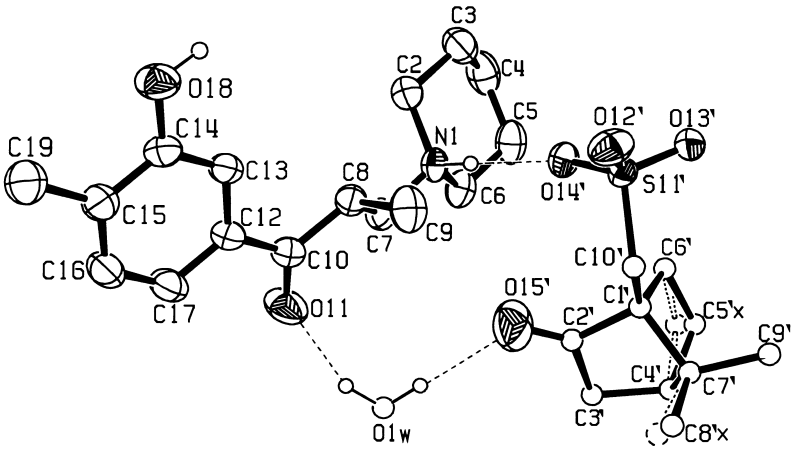


Figure 2. Structure of diastereomeric salt

water molecule and repeating the refinement, which resulted in a higher R factor. We could therefore establish that the water molecules do not form cavities through the crystal. A disordered carbon atom was found in the cyclohexane ring at position 6.

3. Experimental

3.1. Materials and methods

The ^{1}H NMR spectra were recorded at 250 MHz on a Bruker WM250 spectrometer. Chemical shift values are expressed in ppm values on the δ scale. IR spectra of thin film samples were taken on a Perkin–Elmer 1600 series FTIR spectrophotometer. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. Thin layer chromatography was carried out using Polygram® SIL G/UV$_{254}$ sheets. Spots were visualized by UV light or by treatment with 5% ethanolic phosphomolybdic acid solution and heating of the dried plates. (*S*)- and (*R*)-Camphor-10-sulfonic acids were products of Aldrich. All solvents used were freshly distilled.

3.2. Preparation of 1-(4′-methyl-3′-nitrophenyl)-propane-1-one **2**

Compound **1** (25 g, 0.16 mol) was added into cold nitric acid (125 ml) during stirring, the temperature being kept below +10°C. After the addition the mixture was stirred for 1 h then poured into excess ice water. The phases were separated, the organic phase was washed with sodium bicarbonate solution and water, dried over Na_2SO_4 and solvent was evaporated in vacuo: 26 g of yellow crystals. The crystals were recrystallized from hexane. Yield: 20.0 g of white crystals (0.10 mol, 60%), mp 46.5–47.0°C [lit.[4] 51°C]. ^{1}H NMR ($CDCl_3$) 1.25 (t, 3H, H_3, 7.22 Hz), 2.67 (s, 3H, $H_{4'Me}$), 3.03 (q, 2H, H_2, 7.2 Hz), 7.47 (d, 1H, $H_{5'}$, 7.94 Hz), 8.09 (m, 1H, $H_{6'}$, 1.55 Hz, 7.91 Hz), 8.52 (m, 1H, $H_{2'}$, 1.55 Hz). FT-IR (KBr, cm^{-1}): 3450, 2984, 2941, 2906, 1954, 1687, 1313, 1536, 1400, 1356, 1220, 914, 800; calcd for $C_{10}H_{11}NO_3$: C 62.17, H 5.74, N 7.25; found: C 62.36, H 5.73, N 7.23.

3.3. Preparation of 1-(3′-amino-4′-methylphenyl)-propane-1-one **3**

Into a mixture of water (320 ml) and iron powder (94 g, 1.68 mol) cc. HCl (5.7 ml) was added at 80°C and then **2** (45.7 g, 0.24 mol) was also added at 95–100°C. The reaction mixture was refluxed for 2.5 h and the hot mixture was filtered; the precipitate was washed with acetone (300 ml). From the filtrate the acetone was removed, the aqueous phase was washed with dichloromethane (4×50 ml). The organic phase was clarified by charcoal, dried over Na_2SO_4 and evaporated. Yield: 34.26 g (0.21 mol, 89%) of brown crystals. It was recrystallized from a mixture of toluene and hexane. Yield: 23.23 g (0.14 mol, 59%), mp 76.5–77.0°C [lit.[6] 85.5–86°C]. ^{1}H NMR ($CDCl_3$) 1.19 (t, 3H, H_3, 7.27 Hz), 2.20 (s, 3H, H_4), 2.93 (q, 2H, H_2, 7.27 Hz), 3.85 (s, 2H, $H_{3'}$), 7.10 (d, 1H, $H_{5'}$, 8.11 Hz), 7.27 (s, 1H, $H_{6'}$), 7.28 (d, 1H, $H_{2'}$, 8.11 Hz). FT-IR (KBr, cm^{-1}): 3486, 3375, 3247, 3028, 2978, 2936, 2898, 1901, 1663, 1625, 1570, 1510, 1452, 1416, 1359, 1290, 1221, 1188, 1149, 971, 796; calcd for $C_{10}H_{13}NO$: C 73.59, H 8.03, N 8.58; found: C 73.88, H 8.06, N 8.56.

3.4. Preparation of 1-(3-hydroxy-4-methylphenyl)-propane-1-one **4**

To the cooled mixture of water (170 ml) and 96% sulfuric acid (38 ml) **3** (22.06 g, 0.135 mol) was added, the temperature being kept below 10°C and then $NaNO_2$ (9.79 g, 0.142 mol) was also added below 10°C. The reaction mixture was stirred at 70°C for 1 h. The reaction mixture was cooled, the precipitate was filtered and washed until the pH of the dripped solution was less than 6. Yield: 21.17 g (0.13 ml, 96%), which was recrystallized from toluene. Yield: 17.42 g (0.11 mol, 79%), mp 119–121°C [lit.[8] 120–122°C]. ^{1}H NMR ($CDCl_3$) 2.22 (t, 3H, H_3, 7.27 Hz), 2.31 (s, 3H, $H_{4'Me}$), 2.98 (q, 2H, H_2, 7.25 Hz), 4.50 (s, 1H, OH), 7.18 (d, 1H, $H_{5'}$, 8.11 Hz), 7.42 (d, 1H, $H_{6'}$, 7.73 Hz), 7.60 (s, 1H, $H_{2'}$). FT-IR (KBr, cm^{-1}): 3412, 3076, 2988, 2933, 1671, 1608, 1582, 1450, 1421, 1408, 1379, 1274, 1243, 1197, 1176, 1129, 879, 785, 713, 612; calcd for $C_{10}H_{12}O_2$: C 73.15, H 7.37; found: C 73.12, H 7.34.

3.5. Preparation of 2-methyl-3-(piperidine-1-yl)-1-(3′-hydroxy-4′-methylphenyl)-propane 1-one **M1**

A mixture of **4** (3.7 g, 0.023 mol), piperidine hydrochloride (2.96 g) and ethanolic HCl (1.2 ml) was stirred at 100–110°C for 3 hours. To the cooled reaction mixture water was added and the mixture was extracted with dichloromethane (3×20 ml). The pH of the aqueous solution was set

to 8 by 1 M solution of Na_2CO_3, then it was extracted with dichloromethane (3×50 ml), the organic phase dried over Na_2SO_4 and evaporated. Yield: 4.3 g of brown oil, to which maleic acid (2.0 g) was added in isopropanol (7.7 ml) and it was recrystallized twice. Yield: 2.0 g (5.2 mmol, 22.6%), mp 147.5–148.5°C. ^{1}H NMR ($CDCl_3$) 1.22 (m, 3H, H_{2Me}), 1.28 (m, 1H, $H_{4''}$), 1.80 (m, 5H, $H_{4'}$, 2×$H_{2'}$, 2×$H_{3''b}$), 2.30 (s, 3H, $H_{4'Me}$), 2.55 (m, 1H, $H_{2''b}$), 2.77 (m, 1H, $H_{2''}$), 3.01 (m, 1H, H_3), 3.31 (m, 1H, $H_{2''b}$), 3.61 (m, 1H, $H_{2''}$), 3.80 (m, 1H, H_3), 4.29 (m, 1H, H_2), 6.26 (s, 2H, maleic acid), 7.21 (d, 1H, $H_{5'}$, 7.77 Hz), 7.45 (d, 1H, $H_{6'}$, 7.69 Hz), 7.57 (s, 1H, $H_{2'}$). FT-IR (KBr, cm^{-1}): 3405, 3050, 2940, 1863, 2780, 1673, 1582, 1458, 1353, 1280, 1245, 1202, 1174, 1112, 1013, 864, 728; calcd for $C_{20}H_{27}NO_6$: C 63.65, H 7.21, N 3.71; found: C 63.60, H 7.24, N 3.72.

3.5.1. Preparation of the free bases

M1-Maleate (5.0 g, 13.25 mmol) was dissolved in a solution of NaOH (1.3 g, 32.5 mmol) in water (15 ml). The mixture was extracted with ethyl acetate (3×5 ml), the organic phase was dried over Na_2SO_4 and the solvent was evaporated. Yield: 3.36 g (12.85 mmol, 97%) of oil, which solidified slowly [mp 62–65°C (recryst. from hexane: 65–67°C)]. ^{1}H NMR ($CDCl_3$) 1.14 (d, 3H, H_{2Me}, 7.13 Hz), 1.38 (m, 2H), 1.52 (m, 4H), 2.27 (s, 3H, $H_{4'Me}$), 2.43 (m, 5H), 3.02 (m, 1H), 3.74 (m, 1H), 7.14 (d, 1H, H_5, 7.74 Hz), 7.41 (d, 1H, $H_{6'}$, 7.79 Hz), 7.45 (s, 1H, $H_{2'}$). FT-IR (KBr, cm^{-1}): 3424, 2935, 2852, 2814, 1670, 1608, 1584, 1449, 1423, 1282, 1258, 1174, 1104, 993, 762; calcd for $C_{16}H_{23}NO_2$: C 73.53, H 8.87, N 5.36; found: C 73.32, H 8.90, N 5.38.

3.6. Resolution of *M1*

3.6.1. Preparation of S-(+)-*M1*

To the solution of **M1** (3.3 g, 12.63 mmol) in ethyl acetate (10 ml) (*S*)-camphor-10-sulfonic acid monohydrate (3.16 g, 12.6 mmol) in 15 ml ethyl acetate was added. The solution was cooled to 0–5°C, then it was inoculated and the mixture was left to crystallize for 40 min. It was filtered, washed with ethyl acetate (3×1 ml) and dried: 1.55 g, 3.14 mmol. The precipitate was dissolved in ethyl acetate (10 ml) and washed with 1 M bicarbonate solution. The organic phase was dried and evaporated. Yield: 0.81 g (3.1 mmol, $[\alpha]_D = +29.0$ (c = 1, methanol)) of oil.

This procedure was repeated twice. Yield: 1.03 g of white crystals, $[\alpha]_D = +50.3$ (c = 1, methanol), mp 173–174°C, after cleavage 0.52 g (2.0 mmol, 31.5%) of white crystalline base, $[\alpha]_D = +34.1$ (c = 1, methanol), mp 102–104°C. Its enantiomeric excess was determined with the aid of *R*-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol. In the ^{1}H NMR spectrum of **M1** and the chiral solvating agent (excess: 2.73) it is recognizable that the signal of H_{2Me} was split into two doublets (0.92 ppm, 1.07 ppm, $\Delta = 76.7$ Hz). In the case of the spectrum of (*S*)-(+)-enantiomer and chiral solvating agent (excess: 3.13) the peaks at 0.92 ppm were missing, so we could establish that the optical purity of the sample is higher than 95%.

3.6.2. Preparation of (R)-(–)-*M1*

The mother liquor of the resolution was washed with 3×15 ml 1 M solution of Na_2CO_3. The organic phase was dried and evaporated: 2.26 g of oil (8.65 mmol, $[\alpha]_D = -9.9$ (c = 1, methanol)). The (*R*)-(–)-enantiomer was retrieved like the other, but using (*R*)-camphor-10-sulfonic acid monohydrate. Yield: 1.68 g (3.4 mmol) of white crystals, $[\alpha]_D = -49.8$ (c = 1, methanol), mp 170–172°C, after cleavage 0.81 g (3.10 mmol, 49.1%) of white crystalline base, $[\alpha]_D = -33.8$ (c = 1, methanol), mp 101–103°C.

In the case of the spectrum of (*R*)-(–)-enantiomer and chiral solvating agent (excess: 2.77) the peaks at 1.1 ppm were missing, so we could establish that the enantiomeric excess of the sample is higher than 95%.

3.7. X-Ray crystallography

Crystals were obtained as follows: the diastereoisomeric salt ($[\alpha]_D = +50.3$ (c = 1, methanol)) of (*S*)-(+)-**M1** ($[\alpha]_D = +34.1$ (c = 1, methanol)) and (*S*)-camphor-10-sulfonic acid monohydrate (1.71 g, 3.46 mmol) was dissolved in hot ethyl acetate (7.5 ml). The solution was cooled to room temperature, inoculated and left to crystallize overnight. The crystals were filtered and air-dried: white needles (0.54 g, 1.1 mmol, 32%), $[\alpha]_D^{20}$ +50.3 (c = 1, methanol), mp 174–175°C. Intensity data were collected on an Enraf–Nonius CAD4 diffractometer (graphite monochromator; Cu–Kα radiation, $\lambda = 1.54180$ Å) at 293(2) K in the range $3.60 \leq \theta \leq 75.00°$ using ω–2θ scans. The intensities of three standard reflections were monitored regularly every 60 min. The intensities of the standard reflections remained constant within experimental error throughout the data collection.

Hydrogen atomic positions were calculated from assumed geometry except H18, which was located in difference maps. The obvious hydrogen bonding contacts generated hydrogen atomic positions of the disordered water molecule. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the *U* (equiv.) value of the atom they bonded. The riding model was applied to the hydrogen atoms.

Full matrix refinement on F^2 was performed using all reflections. A final check was made with removing the water molecule and repeating the refinement that resulted in $R1 = 0.0386$ versus 0.0329, $wR2 = 0.1119$ versus 0.0903 for the observed reflections. The water molecule with partial occupancy was therefore retained.

Crystal data, experimental and refinement details: empirical formula, $C_{26}H_{39}NO_6S \cdot 0.22H_2O$; formula weight, 511.68; temperature, 293(2) K; wavelength, 1.54184 Å; crystal system, orthorhombic; space group, $P2_12_12_1$; unit cell dimensions, $a = 8.537(1)$ Å, $b = 13.180(1)$ Å, $c = 24.556(1)$ Å, volume, 2763.0(4) Å^3; Z, 4; density (calculated), 1.196 Mg/m^3; absorption coefficient, μ, 1.361 mm^{-1}; $F(000)$, 1073; crystal size, $0.30 \times 0.20 \times 0.15$ mm; θ range for data collection, $3.60 \leq \theta \leq 75.00°$; index ranges, $-9 \leq h \leq 10$, $-16 \leq k \leq 16$, $-30 \leq l \leq 30$; reflections collected, 6428; independent reflections, 5537 [R(int.) = 0.0140]; absorption correction, semi-empirical absorption correction; refinement method, full-matrix least-squares anisotropic on F^2; data/restraints/parameters 5537/58/337; goodness-of-fit on F^2, 1.051; final R indices [$I > 2\sigma(I)$], $R1 = 0.0329$, $wR2 = 0.0903$; R indices (all data), $R1 = 0.0411$, $wR2 = 0.0939$; absolute structure parameter, 0.012(3); extinction coefficient, 0.0051(3); largest diff. peak, 0.152 eA^{-3}; largest diff. hole, –0.233 eA^{-3}.

Neutral atomic scattering factors and anomalous scattering factors were taken from the International Tables for X-ray Crystallography, Vol. C (Vol. IV).[9–13]

Acknowledgements

The Hungarian OTKA Foundation (Project Nos: T29251) is gratefully acknowledged for financial support. J.B. thanks the Zoltán Magyary Foundation and OTKA (D 32705) for a postdoctoral fellowship.

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