Kinetic resolution of (±)-2-methyl-1,2,3,4-tetrahydroquinoline and (±)-2-methylindoline

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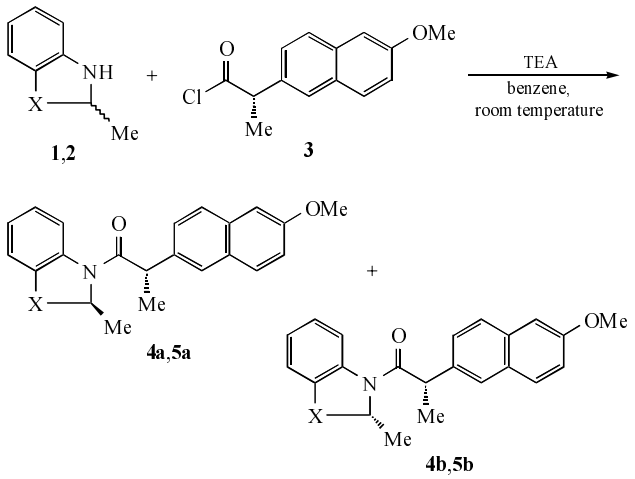
The acylation of racemic 2-methyl-1,2,3,4-tetrahydroquinoline and 2-methylindoline by (*S*)-naproxen acyl chloride resulted in their kinetic resolution with the predominant formation of (*S*,*S*)-diastereoisomeric amides (*de* 78–76%), recrystallisation of which followed by acid hydrolysis gave individual (*S*)-isomers of heterocyclic amines.

The kinetic resolution of racemic compounds from various classes is an effective method for obtaining individual stereoisomers.[1] We found previously that the kinetic resolution of 2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine derivatives by (*S*)-2-(6-methoxynaphthyl-2)propionyl chloride [(*S*)-naproxen acyl chloride] gave (*S*)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazines of high optical purity.[2]

In this paper, we report on the use of the above resolving agent for the preparation of individual (*S*)-stereoisomers of 2-methyl-1,2,3,4-tetrahydroquinoline **1** and 2-methylindoline **2**, close structural analogues of 2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine.

As the first step, the diastereomeric mixtures of amides **4a**,**b** and **5a**,**b** were obtained by the interaction of acyl chloride **3** with racemic amines **1** and **2** in the stoichiometric ratio in the presence of TEA (Scheme 1).† In both cases, the compositions of diastereoisomeric mixtures **4a**,**b** (**5a**,**b**) were 1:1 according to the ^{1}H NMR spectra‡ and HPLC data.§

When the molar ratio between starting amine **1** (or **2**) and acyl chloride **3** was 2:1, without any tertiary amine present in the reaction mixture, the resulting products **4a**,**b** (**5a**,**b**) were found to be significantly enriched with (*S*,*S*)-diastereoisomers **4a** (**5a**).¶ In the case of amide **4a**, *de* was 78%; in the case of **5a**, *de* was 76%. The (*S*,*S*)-diastereoisomers **4a** and **5a** of high diastereoisomeric purity (*de* > 99%) were obtained after recrystallisation from hexane in yields about 75%.†† The (*R*)-isomers of amines **1** and **2** can be isolated from acidic solutions in *ee* 78 and 76%, respectively.‡‡



Scheme 1

(*S*,*S*)-Amides **4a** and **5a** were hydrolysed on heating under reflux in a mixture of concentrated HCl and glacial acetic acid[2] to give individual (*S*)-isomers of amines **1** and **2** (Scheme 2).§§ The yields of (*S*)-(–)-isomers of amines **1** and **2** were 30 and

† To a stirred solution of amine **1** or **2** (1 mmol) and TEA (1 mmol) in dry benzene (5 ml) a solution of acyl chloride **3** (1 mmol) in dry benzene (5 ml) was added dropwise. The reaction mixture was stirred at room temperature for 24 h. Then, it was washed successively with 1 M HCl, water, 5% $NaHCO_3$ and water and dried ($MgSO_4$). The resulting solution was evaporated to dryness to give a yellow oily residue, which was treated with hexane to yield amides **4a**,**b** (82%), **5a**,**b** (86%) as yellow oil.

‡ ^{1}H NMR spectra were recorded on a Bruker DRX 400 spectrometer, the spectra of amides **4a**,**b** and **5a**,**b** were measured in [$^2H_6$]DMSO at 100 °C; the spectra of amines *S*-**1** and *S*-**2** were measured in $CDCl_3$ at ambient temperature. All signals are given in ppm (δ) with TMS as an internal standard.

4a,**b**: 7.79–6.96 (m, 10H, arom.), 4.79 (m) and 4.66 (m) (1H, CH–quinoline), 4.42 (q) and 4.15 (q) (1H, CH–naproxen, *J* 6.9 Hz), 3.89 (s) and 3.84 (s) (3H, OMe), 2.63 (ddd) and 2.30 (ddd) (1H, C^4–H_A–quinoline, *J* 15.0, 5.3 and 5.2 Hz), 2.12 (dddd, 1H, C^3–H_A–quinoline, *J* 13.0, 7.6, 5.4 and 5.2 Hz), 1.79 (ddd) and ~1.29 (m) (1H, C^4–H_B–quinoline, *J* 15.0, 10.1 and 5.4 Hz), 1.47 (d) and 1.37 (d) (3H, Me–naproxen, *J* 6.9 Hz), ~1.29 (m) and 1.16 (dddd) (1H, C^3–H_B–quinoline, *J* 13.0, 10.1, 6.7 and 5.3 Hz), 1.04 (d) and 0.93 (d) (3H, Me–quinoline, *J* 6.6 Hz).

5a,**b**: 7.98–6.94 (m, 10H, arom.), 4.85 (dqd) and 4.66 (dqd) (1H, CH–indoline, *J* 8.8, 6.4 and 1.4 Hz), 4.35 (q) and 4.21 (q) (1H, CH–naproxen, *J* 6.8 Hz), 3.864 (s) and 3.858 (s) (3H, OMe), 3.38 (dd) and 3.12 (dd) (1H, C^3–H_A–indoline, *J* 15.9 and 8.7 Hz), 2.59 (dd) and 2.58 (dd) (1H, C^3–H_B–indoline, *J* 15.9 and 0.6 Hz), 1.53 (d) and 1.52 (d) (3H, Me–naproxen, *J* 6.8 Hz), 1.32 (d) and 0.97 (d) (3H, Me–indoline, *J* 6.5 Hz).

§ The *de* values of amides **4** and **5** were measured by HPLC on a Merck-Hitachi chromatograph with an L-4000A Intelligent Pump, an L-4000A UV Detector, and a D-2500A Chromato-Integrator [Hibar Pre-packed Column RT250-4, Lichrosorb Si-60]; mobile phase: hexane–Pr^{i}OH, 200:1 (A), hexane–Pr^{i}OH, 80:1 (B), flow rate of 1 cm^3 min^{-1}; UV detection at 230 nm; $\tau_{\mathbf{4a}}$ 17.0 min, $\tau_{\mathbf{4b}}$ 15.4 min (A); $\tau_{\mathbf{5a}}$ 6.8 min, $\tau_{\mathbf{5b}}$ 5.4 min (B).

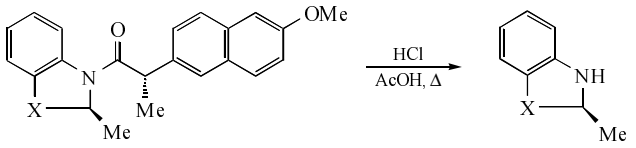
¶ To a stirred solution of amine **1** or **2** (1 mmol) in dry benzene (5 ml) a solution of acid chloride **3** (0.5 mmol) in dry benzene (3 mmol) was added. The reaction mixture was stirred for 24 h at room temperature; then, it was washed sequentially with 1 M HCl, water, 5% $NaHCO_3$ and water and dried ($MgSO_4$). The solution was evaporated to dryness to give (*S*,*S*)-diastereoisomer **4a** (*de* 78%) in 90% yield or (*S*,*S*)-diastereoisomer **5a** (*de* 76%) in 86% yield.

†† **4a**: mp 57–59 °C; $[\alpha]_D$ +66.8° (*c* 1.3, $CHCl_3$); *de* 99.0%. HPLC: τ_R 17.0 min (A). ^{1}H NMR, δ: 7.79–6.96 (m, 10H, arom.), 4.79 (ddq, 1H, CH–quinoline, *J* 7.6, 6.7 and 6.6 Hz), 4.42 (q, 1H, CH–naproxen, *J* 6.9 Hz), 3.84 (s, 3H, OMe), 2.30 (ddd, 1H, C^4–H_A–quinoline, *J* 15.0, 5.3 and 5.2 Hz), 2.12 (dddd, 1H, C^3–H_A–quinoline, *J* 13.0, 7.6, 5.4 and 5.2 Hz), 1.79 (ddd, 1H, C^4–H_B–quinoline, *J* 15.0, 10.1 and 5.4 Hz), 1.47 (d, 3H, Me–naproxen, *J* 6.9 Hz), 1.16 (dddd, 1H, C^3–HB–quinoline, *J* 13.0, 10.1, 6.7 and 5.3 Hz), 0.93 (d, 3H, Me–quinoline, *J* 6.6 Hz).

5a: mp 106–107 °C; $[\alpha]_D$ +82.8° (*c* 1.9, $CHCl_3$); *de* 99.3%. HPLC: τ_R 6.8 min (B). ^{1}H NMR, δ: 7.98–6.94 (m, 10H, arom.), 4.85 (dqd, 1H, CH–indoline, *J* 8.7, 6.5 and 1.4 Hz), 4.35 (q, 1H, CH–naproxen, *J* 6.9 Hz), 3.864 (s, 3H, OMe), 3.38 (dd, 1H, C^3–H_A–indoline, *J* 15.9 and 8.7 Hz), 2.59 (dd, 1H, C_3–H_B–indoline, *J* 15.9 and 0.6 Hz), 1.53 (d, 3H, Me–naproxen, *J* 6.8 Hz), 0.97 (d, 3H, Me–indoline, *J* 6.5 Hz).

‡‡ The aqueous acid layers after preparing amide **4a** or **5a** were treated with NaOH up to pH 9–10 under ice cooling, extracted by chloroform, washed with brine, and dried ($MgSO_4$). The solution was evaporated to dryness to give amines (*R*)-**1** in 90% yield or (*R*)-**2** in 86% yield as colourless oils. Optical purity was determined by HPLC with the pre-column derivatization of amines by acyl chloride **3**.

27%, respectively, relative to the starting racemic amines. The optical purity of the obtained stereoisomers was confirmed by HPLC after the derivatization of amines by acyl chloride **3**.



4a,**5a** **1**,**2**

1, **4**: X = $(CH_2)_2$
2, **5**: X = CH_2

Scheme 2

The stereochemical configuration of compound (*S*)-(–)-**1** was determined by a comparison of the $[\alpha]_D$ sign with published data[3] for (*R*)-(+)-**1**. The absolute configuration of (*S*)-**2** has not been determined before our study. Assignment of the absolute configuration for the 2-methylindoline fragment of amide **5a** was performed by X-ray diffraction analysis, taking into account the known absolute configuration of the starting (*S*)-naproxen (Figure 1).

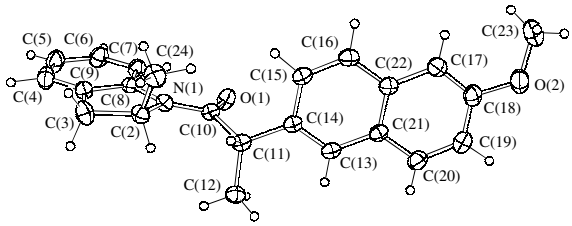


Figure 1 Crystal structure of (*S*,*S*)-amide **5a**.

In conclusion, note that the use of (*S*)-naproxen acyl chloride as a resolving agent in the kinetic resolution of racemic heterocyclic amines appears to be a good general procedure for obtaining individual stereoisomers of high optical purity.

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§§ Amide **4a** or **5a** (1 mmol) was heated under reflux in a mixture of glacial acetic acid (5 ml) and conc. HCl (5 ml) for 15 h. The reaction mixture was evaporated to dryness. Water (10 ml) was added to the residue; the precipitate was filtered off and washed with water. The combined filtrates were made alkaline with 10 M NaOH to pH 10 at +5 °C and extracted with CH_2Cl_2. The organic layer was washed with brine and dried ($MgSO_4$). The solution was evaporated to dryness to give amines (*S*)-**1** in 90% yield or (*S*)-**2** in 85% yield as colourless oils.

(*S*)-(–)-**1**: $[\alpha]_D$ –85° (*c* 1.5, benzene). Lit.,[3] (*R*)-**1**: $[\alpha]_D$ +85° (*c* 2, benzene). ^{1}H NMR, δ: 6.96–6.92 (m, 2H, C^5H, C^7H), 6.58 (t, 1H, C^6H, *J* 7.4 and 1.2 Hz), 6.44 (dd, 1H, C^8H, *J* 8.3 and 1.2 Hz), 3.63 (br. s, 1H, NH), 3.38 (dqd, 1H, C^2H, *J* 9.8, 6.3 and 2.8 Hz), 2.82 (ddd, 1H, C^4–H_A, *J* 16.4, 11.4 and 5.6 Hz), 2.71 (ddd, 1H, C^4–H_B, *J* 16.4, 5.4 and 3.7 Hz), 1.91 (dddd, 1H, C^3–H_A, *J* 12.8, 5.7, 3.5 and 2.9 Hz), 1.57 (dddd, 1H, C^3–H_B, *J* 12.8, 11.4, 9.9 and 5.4 Hz), 1.19 (d, 3H, Me, *J* 6.3 Hz).

(*S*)-(–)-**2**: $[\alpha]_D$ –12.2° (*c* 2.6, benzene). ^{1}H NMR, δ: 7.07 (dd, 1H, C^4H, *J* 7.2 and 0.3 Hz), 7.00 (ddd, 1H, C^5H, *J* 7.5, 7.4 and 0.4 Hz), 6.68 (ddd, 1H, C^6H, *J* 7.5, 7.3 and 0.8 Hz), 6.59 (dd, 1H, C^7H, *J* 7.8 and 0.3 Hz), 3.98 (ddq, 1H, C^2H, *J* 8.5, 7.8 and 6.2 Hz), 3.62 (br. s, 1H, NH), 3.13 (dd, 1H, C^3–H_A, *J* 15.4 and 8.5 Hz), 2.62 (dd, 1H, C^3–H_B, *J* 15.4 and 7.8 Hz), 1.28 (d, 3H, Me, *J* 6.2 Hz).