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Resolution of the flumequine intermediate 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline

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Abstract

Racemic 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (FTHQ) was resolved by the *N*-phthaloyl derivative of the (*R*)-enantiomer. The enantiomeric mixture was very effectively enriched by recrystallisation from either the melt (working best for mixtures of relatively high starting enantiomeric purities) or from solution of its hydrochloride salt (giving good results when applied for mixtures of moderate to medium enantiomeric purities).

1. Introduction

9-Fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic acid (flumequine, **2**) is an antibacterial agent, the (*S*)-enantiomer being more effective than the (*R*)-isomer.[1] Recently we have reported on the resolution of 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (FTHQ, **1**) and the synthesis of (*S*)-flumequine[2] from (*S*)-FTHQ (Fig. 1). However, the price of the resolving agent 3-bromocamphor-8-sulfonic acid urged us to find a more economic way for producing enantiomerically pure flumequine.

A special case of resolution methodologies is when some derivative of one single enantiomer is used as resolving agent for the racemate. This derivative should be of opposite acid–base character to the racemate. In the literature only a few examples are cited for this type of resolution. Such molecules are: β-lactam;[3] amino acids: phenylglycine,[4] phenylalanine;[5] and amines: phenylethylamine,[6] chloramphenicol base.[7] Except for the β-lactam the crystallising diastereomeric salt contains the enantiomer of absolute configuration opposite to the one in its derivative used as resolving agent. An advantageous feature of the above mentioned process is that it can make use of the undesired enantiomer. In this paper we present our results on the resolution of FTHQ by its *N*-phthaloyl derivative.

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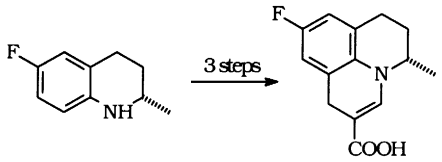

Fig. 1. 6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (FTHQ, **1**) and 9-fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-benzo-[*i*,*j*]quinolizine-2-carboxylic acid (flumequine, **2**)

2. Results and discussion

First, *N*-phthaloyl-(*R*)-FTHQ was synthesised from (*R*)-FTHQ and phthalic anhydride. The analysis of the ^{1}H NMR spectra taken at different temperatures shows that the restricted rotation around the CO–NH bond together with the large moieties on both sides of the bond results in a rigid structure, which hopefully has a favourable effect on the selectivity as resolving agent.

As for the resolution, the process is not as simple as the classical diastereoisomeric salt formation: 1 mol of base crystallises with 2 mol of resolving agent (confirmed by NMR and elemental analysis, see Fig. 2).

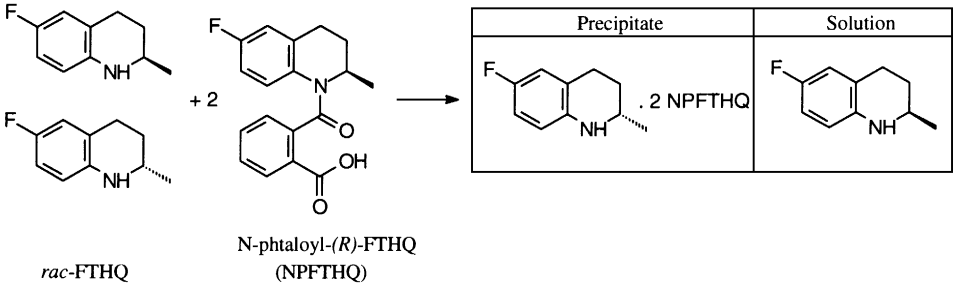

Fig. 2. Resolution of FTHQ by *N*-phthaloyl-FTHQ

Among the solvents tested hexane was the one which produced the best results. When using water (dissolving the salts of the reagents), the diastereoisomeric complex formed oily clumps of moderate enantiomeric excess, while in the case of organic solvents the high solubility made the process troublesome.

The resolution was carried out as follows: the racemic FTHQ was dissolved in hexane and the resolving agent was added. The resolving agent did not dissolve in hexane, but after seeding recrystallisation took place resulting in precipitated diastereoisomer of 75% enantiomeric excess and 85% yield of the (*S*)-FTHQ base after workup, while the (*R*)-FTHQ was recovered from the mother liquor at 90% yield and 74% ee.

This method is similar to that reported by Toda et al.[8] and later by Kozma et al.[9] They carried out resolutions in hexane without dissolving the reagents (e.g. racemic alcohols and *O*,*O*′-dibenzoyl-(2*R*,3*R*)-tartaric acid) by simple precipitation of the diastereoisomeric complex.

The resulting enantiomeric mixture needed further enrichment. The first attempt by the most usual method — recrystallisation of the diastereoisomeric salt — failed even in several solvents, so another method was required. First, recrystallisation of the FTHQ melt was tested and gave good results when the starting enantiomeric excess of the FTHQ enantiomeric mixture was higher than 50%. The high enantiomeric excess portion solidified while the portion of low enantiomeric excess stayed in the melt (Table 1).

For medium to moderate optical purities this method did not work but we found that recrystallisation

Table 1
Enantiomeric enrichment by crystallisation from melt

Starting FTHQ mixture	Solidified portion		Melt	
ee %*	Y %	ee %	Y %	ee %
81.4	58.0	92.8	41.6	69.5
69.5	29.5	93.7	68.6	57.4
57.4	16.6	92.5	82.8	50.2
50.2	10.4	91.9	86.1	46.5
42.4	42.2	40.0	57.7	44.5

*A sample of specific rotation of $[\alpha]_{D,20}$= +70.2 (c=1, ethanol) proved to be enantiomerically pure by NMR method: 6.3 equivalent of *(R)*-(-)-(9-anthryl)-2,2,2-trifluoroethanol as a chiral solvating agent was applied. In all other cases, enantiomeric excesses were determined by relating the specific rotation to the above mentioned sample.

of the FTHQ hydrochloric salt from water was quite efficient. In this case the enantiomerically more pure portion stayed in the solution and the one of low enantiomeric excess crystallised (Table 2).

Table 2
Enantiomeric enrichment by crystallisation of the hydrochloric salt

Starting FTHQ mixture	Crystalline portion		Solution	
ee %	Y %	ee %	Y %	ee %
95.7	72.8	97.0	24.1	93.8
42.1	51.2	10.3	44.0	81.4
10.3	72.7	1.4	21.1	36.8

Combining these two enrichment processes an enantiomeric mixture of practically any enantiomeric excesses can be separated to an almost racemic sample and a portion of high enantiomeric excess.

3. Conclusion

Racemic 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (FTHQ) was resolved by the *N*-phthaloyl derivative of the undesired enantiomer. For the enantiomeric enrichment of the resulting enantiomeric mixture two simple processes are reported: selective precipitation of the FTHQ from the melt and recrystallisation of its hydrochloric salt from water. As a result, (*S*)-FTHQ of high optical purity can be manufactured in a simple and economical way.

4. Experimental

4.1. Materials and methods

The ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer operating at 500 MHz. All spectra were taken in DMSO-d_6 solution and chemical shift values are expressed in ppm from DMSO (2.49 ppm) as internal standard on δ scale. IR spectra were taken on a Specord 2000 spectrometer. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. FTHQ was manufactured in Chinoin. All solvents used were freshly distilled.

4.2. Preparation of the resolving agent N-phtaloyl-(R)-FTHQ

(*R*)-FTHQ (10.0 g, 60.5 mmol, $[\alpha]_D^{20}$=+70.2 (c=1, ethanol)), phthalic anhydride (9.0 g, 60.8 mmol) and *N*,*N*-dimethylaminopyridine (catalytic amount) were dissolved in methylene chloride (50 ml) and the mixture was kept under reflux for 1.5 h, then the solvent was evaporated. Ethyl acetate (10 ml) was added and the solution was seeded. The mixture was left to crystallise overnight and then it was cooled to −10°C. The crystals were filtered, washed with ethyl acetate (2×4 ml) and dried: 14.4 g (76%) of white crystals, mp: 143–145°C, $[\alpha]_D^{20}$=−236 (c=1, methanol). ^{1}H NMR (DMSO-d_6, at 410 K): 1.09 (d, 3H), 1.50 (m, 1H), 2.35 (m, 1H), 2.75 (m, 1H), 4.49 (s, br, 1H), 6.71–8.05 (ms, 7H). FT-IR (KBr, cm^{-1}): 3461, 2996, 1721, 1605, 1570, 1494, 1447, 1392, 1364, 1270, 1223, 1202, 1149, 1140, 1124, 1074, 1046, 956, 870, 815, 775, 743, 676, 644, 618. Anal. calcd for $C_{18}H_{16}FNO_3$: C 69.00, H 5.15, F 6.06, N 4.47; found: C 68.78, H 5.17, F 6.04, N 4.47.

4.3. Resolution of racemic FTHQ by N-phthaloyl-(R)-FTHQ

Racemic FTHQ (3.70 g, 22.4 mmol) was dissolved in hexane (35 ml) and *N*-phthaloyl-(*R*)-FTHQ (7.0 g, 22.3 mmol) was added. After seeding it was left at room temperature for 24 h with occasional stirring. The mixture was filtered, washed with hexane (4×3.5 ml) and dried: 8.71 g of white powder, mp: 117–119°C, $[\alpha]_D^{20}$=−199.2 (c=1, methanol). ^{1}H NMR (DMSO-d_6, at 410 K): The ratio of a selected peak of the base (3.22, m, 1H) and of the resolving agent (6.95, s, 1H) is 0.95 to 2, corresponding to assumed base/resolving agent ratio of 1 to 2. FT-IR (KBr, cm^{-1}): 3446, 1648, 1616, 1436, 1394, 1330, 1209, 1145, 866, 815, 779, 723. Anal. calcd for $C_{46}H_{44}F_3N_3O_6$: C 69.77, H 5.60, F 7.20, N 5.31; found: C 69.44, H 5.59, F 7.18, N 5.33.

Water (35 ml), 37% HCl solution (3.5 ml) and methylene chloride (10 ml) were added and the mixture was stirred for 10 min. The phases were separated, the aqueous phase was washed with methylene chloride (2×5 ml). NaOH (2.5 g) was dissolved in the aqueous phase and it was extracted with methylene chloride (3×20 ml). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated: 1.58 g (85.4%) of semi-solid oil, $[\alpha]_D^{20}$=−52.5 (c=1, ethanol), ee: 74.7%. The mother liquor of the resolution was evaporated. The further workup was the same as above: 1.66 g (89.7%) of semi-solid oil, $[\alpha]_D^{20}$=+51.6 (c=1, ethanol), ee: 73.5%.

4.4. Enantiomeric enrichment by crystallisation from melt (representative example)

FTHQ base (22.0 g, 133.2 mmol, $[\alpha]_D^{20}$=−48.8 (c=1, ethanol), ee: 69.5%) was cooled to 0–5°C and seeded by the (−)-enantiomer. The crystalline mass was homogenised and filtered on a glass filter cooled to 0°C. During continuous filtration the mass was left to warm up to room temperature (22°C). The

white crystalline FTHQ base left on the filter: 6.5 g (39.3 mmol, 29.5%), $[\alpha]_D^{20}=-65.8$ (c=1, ethanol), ee: 93.7%; the filtrate: 15.1 g (91.4 mmol, 68.6%) of oily FTHQ base, $[\alpha]_D^{20}=-40.3$ (c=1, ethanol), ee: 57.4%.

For results at other starting enantiomeric excess values see Table 1.

4.5. Enantiomeric enrichment by recrystallisation of the FTHQ HCl salt (represenative example)

FTHQ (66.0 g, 399.5 mmol, $[\alpha]_D^{20}=-7.2$ (c=1, ethanol), ee: 10.3%) and 37% HCl solution (35 ml, 419.0 mmol, d=1.18) were dissolved in hot water (200 ml). After cooling and scratching, white crystals precipitated. The so obtained thick suspension was filtered at 20°C and washed with 0°C water (3×15 ml).

The wet FTHQ·HCl was suspended in water (150 ml), NaOH (13.0 g, 325 mmol) was dissolved and the solution was extracted with methylene chloride (3×50 ml). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated in vacuo: 48.0 g (290.5 mmol, 72.7%) of FTHQ base, $[\alpha]_D^{20}=-1.0$ (c=1, ethanol), ee: 1.4%.

In the mother liquor NaOH (7.0 g, 175.0 mmol) was dissolved and the solution was extracted with methylene chloride (3×50 ml). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated in vacuo: 13.9 g (84.1 mmol, 21.1%) of FTHQ base, $[\alpha]_D^{20}=-25.8$ (c=1, ethanol), ee: 36.8%.

For results at other starting enantiomeric excess values see Table 2.

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