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Unusual phenomena during the resolution of 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (FTHQ): thermodynamic-kinetic control

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Abstract—6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (FTHQ) was resolved in several different solvents by tartaric acid derivatives as the most common acidic resolving agents available in industrial quantities. Strong reaction kinetics and solvent dependence were observed, curiously without solvation. In possession of these findings, an economic resolution process is proposed, which is completed by the incorporation of a racemization step. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

9-Fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-benzo-[*i*,*j*]quinolizine-2-carboxylic acid (Flumequine, Fig. 1) is an antibacterial agent of the quinolone family (like Cyprofloxacine), the (*S*)-enantiomer is in the main responsible for the antibiotic effect.[1] Hence, finding an appropriately efficient and economic way to the enantiopure (*S*)-enantiomer is of interest. Herein we report on some interesting phenomena experienced during the resolution of its intermediate 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (FTHQ, **1**, Fig. 1) with tartaric acid and its derivatives: dibenzoyl and di-*p*-toluoyl tartaric acid (DPTTA).

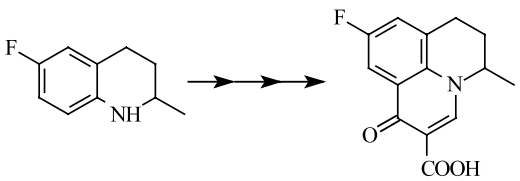

Figure 1. 6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (FTHQ, **1**) and Flumequine.

Resolution of 2,6-dimethyl-1,2,3,4-tetrahydroquinoline was attempted by Reichardt et al.[2] They used dibenzoyl tartaric acid and the results were quite moderate. However, dibenzoyl tartaric acid proved to be suitable for the resolution of the 2,6-difluoro derivative: Japanese authors described conditions and also the single-crystal X-ray diffraction structure.[3,4] As for the 2-methyl-1,2,3,4-tetrahydroquinoline, it has been successfully resolved with tartaric acid.[5,6] The process was carried out in aqueous medium. Resolving agents of 6-fluoro-1,2,3,4-tetrahydroquinoline include 3-bromocamphor-8-sulfonic acid and the *N*-phthaloyl derivative of the (*R*)-enantiomer.[7,8] In this paper we focus on the use of commercially available resolving agents in order to economize the production of the desired enantiomer.

2. Results and discussion

Preliminary experiments showed that tartaric acid and its derivatives form crystalline diastereoisomeric salts with FTHQ so these experiments were repeated at 2 g scale. The results are shown in Table 1. The results vary from 57% e.e. of the (*R*)-enantiomer to 59% e.e. of the (*S*)-enantiomer. Curiously, dibenzoyl tartaric acid acted as the weakest resolving agent, while di-*p*-toluoyl tartaric acid gave acceptable results. Between these two derivatives underived tartaric acid afforded moderate enantiomeric excesses.

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Table 1. Resolution of FTHQ by tartaric acid derivatives in several different solvents

Entry	Resolving agent	Solvent		FTHQ in the crystallized salt			
			Volume (mL)	Abs. conf.	Yield (%)	E.e.[a] (%)	S[b]
1	Tartaric acid (1 equiv.)	Acetonitrile	60	*R*	97	12	0.12
2	Tartaric acid (1 equiv.)	Methanol:water	15:15	*S*	75	6	0.05
3	Dibenzoyl tartaric acid (0.5 equiv.)	Chloroform	25	*R*	89	2	0.02
4	Dibenzoyl tartaric acid (0.5 equiv.)	Ethyl acetate	12	*S*	86	2	0.02
5	Dibenzoyl tartaric acid (0.5 equiv.)	Methanol	10	*S*	88	3	0.03
6	Di-*p*-toluoyl tartaric acid (0.5 equiv.)	Ethyl acetate	15	*R*	91	48	0.44
7	Di-*p*-toluoyl tartaric acid (0.5 equiv.)	Chloroform	20	*R*	98	37	0.37
8	Di-*p*-toluoyl tartaric acid (0.5 equiv.)	Acetonitrile	15	*R*	99	35	0.35
9	Di-*p*-toluoyl tartaric acid (0.5 equiv.)	Toluene	30	*R*	98	26	0.26
10	Di-*p*-toluoyl tartaric acid (0.5 equiv.)	Acetic acid	10	*R*	85	57	0.48
11	Di-*p*-toluoyl tartaric acid (0.5 equiv.)	Acetone	15	*R*	63	20	0.13
12	Di-*p*-toluoyl tartaric acid (0.5 equiv.)	Ethyl acetate:methanol	12:3	~*rac*	87	–	–
13	Di-*p*-toluoyl tartaric acid (0.5 equiv.)	*i*-Propanol	8	*S*	96	51	0.49
14	Di-*p*-toluoyl tartaric acid (0.5 equiv.)	Methanol	10	*S*	70	59	0.41
15	Di-*p*-toluoyl tartaric acid (0.5 equiv.)	Ethanol	8	*S*	91	44	0.40
16	Di-*p*-toluoyl tartaric acid (0.5 equiv.)	Propanol	8	*S*	92	18	0.17

[a] Determined by chromatography (see Section 4).
[b] S (efficiency) = (yield×e.e.)/10000.

Such strong solvent dependence is not unknown in the literature,[9] but in these cases solvation is always presumed. In our case, however, solvation could be excluded by elemental analysis and DSC/TG measurements.

For an economical resolution it is desirable to employ common solvents so we decided to optimize the process in methanol or ethyl acetate. The latter solvent seemed more advantageous because it favors an extractive workup of the reaction mixture. Therefore, the first solvent examined was ethyl acetate. Surprisingly, on trying to reproduce our preliminary results at 10 g scale, we encountered unexpected difficulties: repeating the experiments generated a number of different enantiomeric excess values. This fact suggested us that reaction kinetics may play some role. To check this, experiments were conducted in methanol and ethyl acetate with a set of 2 g scale FTHQ resolutions using DPTTA. Aliquots were worked up at periods from 5 min to 3 weeks. The results are shown in Table 2.

As Table 2 shows, time-scale experiments justified the presumption: in methanol the enantiomeric excess of the (*S*)-enantiomer showed continuous increase, while in ethyl acetate first the less stable diastereoisomeric salt containing the (*R*)-enantiomer precipitated and after some days redissolved and the salt containing the (*S*)-FTHQ precipitated. Such a kinetic effect in resolution processes has no precedent in the literature.

Hereafter, we tried to speculate how to overcome this phenomenon in terms of the resolution process and thus increase the enantiomeric excess and efficiency of the reaction. It soon became apparent that the achiral additive also plays a crucial role in the outcome of the experiment: when applying half an equivalent of DPTTA and half an equivalent of cc. aqueous hydrochloric acid in methanol, after a short time (10 min) the diastereoisomeric salt containing the desired (*S*)-FTHQ crystallizes and after a single recrystallization of this salt almost enantiomerically pure (e.e. 99.2%) *S*-FTHQ can be produced in good yield (54%).

Table 2. Resolution of FTHQ shows definite thermodynamic-kinetic control[a]

Solvent	Time	FTHQ in the crystalline diastereoisomeric salt					
		(*R*)			(*S*)		
		Yield (%)	E.e. (%)	S	Yield (%)	E.e. (%)	S
Methanol	5 min				70	59	0.41
	4 days				74	67	0.50
	3 weeks				75	68	0.51
Ethyl acetate	5 min	91	48	0.44			
	4 days	99	7	0.07			
	3 weeks				92	41	0.38

[a] 0.5 molar equiv. of di-*p*-toluoyl tartaric acid was used as resolving agent.

For an economic resolution it is advantageous to make use of the unwanted enantiomer. One possibility is its racemization, which, in theory, allows complete transformation of the racemate to the desired enantiomer.

An FTHQ derivative, (*S*)-5,6-difluoro-2-methyl-1,2,3,4-tetrahydroquinoline is reported[10] to undergo racemization by stirring for 7 h at 120°C in methanesulfonic acid. However, similar conditions (150°C, 8 h) in our experiment for FTHQ did not result in any racemization. Therefore, we sought an indirect method and the possibility of aromatization was considered. As for the appropriate methods, strong catalytic dehydrogenation cannot be applied because of the fluorine substituent; the quinone type agents[11,12] are expensive and manganese dioxide[13] is complicated to apply. Finally, oxygen[14] and sulfur[15] seemed to be practical so we focused on these two agents.

When applying a stream of air at normal pressure (hot acetic acid solution, cobalt acetate and sodium bromide catalyst), the rate of the reaction was not satisfactory and side products also formed. Next, higher temperature and pressure (8 bar) was applied and aromatization took place in good yield. Similarly, elemental sulfur (2.2 equiv.) at 200°C yielded aromatic quinoline (Fig. 2).

This aromatization can be integrated into the FTHQ production, as 6-fluoro-2-methyl-quinoline is an existing industrial intermediate and therefore it can be recycled without any further transformation. As for the overall process to produce (*S*)-FTHQ the route presented in Fig. 3 is proposed.

3. Conclusions

In the search for an economically viable process to provide enantiomerically pure (*S*)-FTHQ, the resolution manifested unusual behavior: although there is no solvation in any of the tested solvents, they still affected results both in terms of enantiomeric purity and configuration. The solvent type (protic or aprotic) and nature of achiral additive (weak acid, no additive or strong acid) apparently influences the experimental outcome. A good combination resulted in the isolation of (*S*)-FTHQ in good yield and high enantiomeric purity. Two racemization protocols are also presented, which allow recycling of the unwanted enantiomer. The overall process thus provides an economic way to obtain the desired active enantiomer of FTHQ.

4. Experimental

4.1. Materials and methods

The ^{1}H NMR spectra were recorded at 500 MHz on a Bruker DRX-500 spectrometer. Chemical shift values are expressed in ppm values on δ scale. Optical rotations were determined on a Perkin Elmer 241 polarimeter. Resolving agents were purchased from Aldrich. FTHQ was manufactured in Chinoin. All solvents used were freshly distilled.

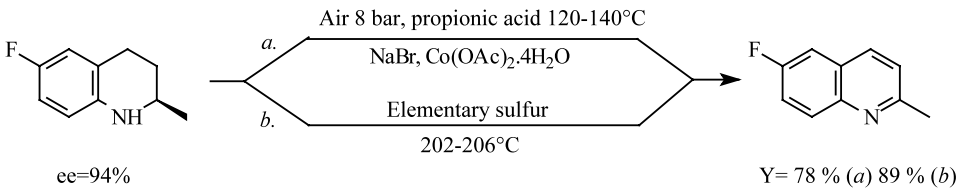

Figure 2. Aromatization of (*R*)-FTHQ.

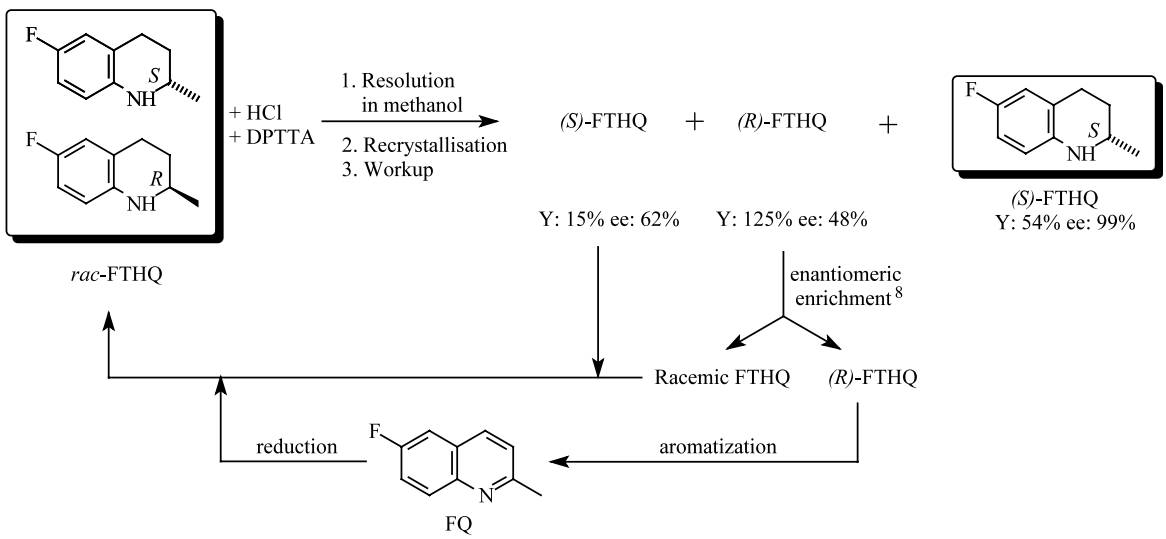

Figure 3. Production of (*S*)-FTHQ.

4.2. Determination of the enantiomeric excess by gas chromatography

Gas chromatographic measurements were completed on a Hewlett-Packard HP 5890/II instrument using FID. Separations were achieved on a 12 m×0.1 mm fused silica open tubular column coated with Chirasil-Dex (methyl silicone polymer substituted with permethylated β-cyclodextrin) chiral stationery phase.[16] H_2 carrier gas was used (1 mL/min), with split injection and 150°C analysis temperature. Acetate derivatives were analyzed, which were synthesized by the generally used method (acetic acid anhydride with triethylamine, 80°C, 2 h).[17]

4.3. Small scale resolution of FTHQ (general procedure)

Racemic FTHQ **1** (2.0 g) and the resolving agent (tartaric acid, dibenzoyl-tartaric acid or di-*p*-toluoyl tartaric acid, 1.0 or 0.5 molar equiv.) were dissolved in the given solvent (see Table 1) with heating. The solution was cooled to room temperature. Crystallization was induced by scratching. The crystals were filtered after 5 minutes (Table 1) or given time (Table 2). In the case of the time-scale experiments stirring was only occasional. The diastereoisomeric salt and the mother liquor were worked up separately.

Workup of the diastereoisomeric salt is as follows: The crystals were suspended in water (20 mL) and NaOH (1 g) was added. After adding dichloromethane (10 mL), the mixture was stirred for 5 min. The phases were separated. The aqueous phase was extracted again with dichloromethane (3×10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo. FTHQ is an oily substance, which, depending on its enantiomeric excess, may crystallize upon scratching. The NMR and FT-IR spectra and the elemental composition are identical to those of the racemate.

4.4. Resolution of FTHQ by di-*p*-toluoyl tartaric acid in the presence of HCl

A solution of (*R*,*R*)-di-*p*-toluoyl tartaric acid (19.50 g, 50.5 mmol) in methanol (60 mL) at about 50°C was treated with FTHQ (16.60 g, 100.5 mmol) and 37% aqueous HCl solution (4 mL, 49 mmol). After cooling to room temperature, crystallization was initiated by scratching. The thick suspension was stirred for 10 min, then filtered. The filter cake was washed with methanol (4×5 mL) and dried to afford the solid diastereoisomeric salt (20.04 g). The salt was dissolved in hot methanol (100 mL) and cooled slowly to −5°C. After stirring for 1 h at −5°C the mixture was filtered, washed with methanol (4×5 mL) and dried to afford white crystalline diastereoisomeric salt (15.5 g), $[\alpha]_D^{20} = -124.0$ ($c = 1$ methanol).

The crystals were suspended in water (150 mL) and NaOH (4 g) was added. After adding dichloromethane (25 mL), the mixture was stirred for 5 min. The phases were separated. The aqueous phase was extracted again by dichloromethane (3×25 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford an oil (4.73 g). Vacuum distillation afforded an oil of (*S*)-6-fluoro-2-methyl-quinoline (4.46 g, 54%,), which solidified on standing or scratching $[\alpha]_D^{20} = -69.5$ ($c = 1$, ethanol) $e.e._{GC} = 99.2\%$, mp: 40–42°C.

Workup of the resolution mother liquor was similar to that of the diastereoisomeric salt after evaporation of the solvent, yielding an oil of (*R*)-6-fluoro-2-methyl-quinoline, (10.41 g, 125%), $[\alpha]_D^{20} = +33.8$ ($c = 1$, ethanol) $e.e._{GC} = 48.1\%$.

Similarly, workup of the recrystallization mother liquor gave (*S*)-6-fluoro-2-methyl-quinoline (oil, 1.21 g, 15%), $[\alpha]_D^{20} = -43.9$ ($c = 1$, ethanol) $e.e._{GC} = 62.5\%$.

4.5. Aromatization of (*R*)-FTHQ by oxygenation

Propionic acid (40 mL) was stirred for 15 min with NaBr (0.25 g, 2.43 mmol) and $Co(AcO)_2 \cdot 4H_2O$ 0.60 g, 2.41 mmol). To the purplish solution was added (*R*)-FTHQ (7.80 g, 47.2 mmol, e.e. = 94%). The mixture was kept under air pressure (8 bar) at 120–140°C for 8 h. Propionic acid was removed in vacuo (10 mmHg) then the product was purified by vacuum distillation (0.3 mmHg). Yield: 6.00 g of oily substance (6-fluoro-2-methyl-quinoline, 37 mmol, 78%, $[\alpha]_D^{20} = 0$ ($c = 1$ ethanol). ^1H NMR ($CDCl_3$): 2.7 (s, 3H, CH_3), 1.50 (m, 1H), 7.3–7.4 (m, 3H, Ar), 7.9–8.0 (m, 2H, Ar).

The product contained 12% (mol/mol) of propionic acid: 1.2 (t, 3H, CH_3), 2.4 (d, 2H, CH_2).

4.6. Aromatization of (*R*)-FTHQ by elemental sulfur

FTHQ (7.80 g, 47.2 mmol, $[\alpha]_D^{20} = +66.1$ ($c = 1$, ethanol) and sulfur (3.30 g, 103 mmol) were kept at 202–206°C for 40 min. Following heavy gas evolution the mixture became dark brownish-red. After this time, the mixture was cooled to 80°C and distilled in vacuo (0.3 mmHg) to yield a dark yellow oil of 6-fluoro-2-methyl-quinoline (6.84 g, ca. 42 mmol, ca. 89%) which solidified on standing $[\alpha]_D^{20} = +4.0$ ($c = 1$ ethanol) mp 40–46°C. The ^1H NMR spectrum of the product is identical to that described in Section 4.5. The product contained ca. 7% of unreacted FTHQ.

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