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Separation of Diastereomers Taking Advantage for the Kinetic Control and Structure of Resolving Agent

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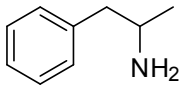
Abstract

The preparation of pure enantiomers of (1-methyl-2-phenyl)-ethylamine (A) is described. The resolution of racemic compound (A) was accomplished using half equivalent of tartaric acid. The purification of enantiomeric mixtures by a non-usual method are also described.

Introduction

The enantiomers of (1-methyl-2-phenyl)-ethylamine (A) (Figure 1) have not only therapeutical effect, but they could be important base material both for the pharmacetical industry and the organic chemical research (eg. for preparation of the Selegiline [1], Tamsulozine [2], or for other types of molecules). Our aim was to work out an effective, quick and practicable resolution method of racemic compound 1-phenylpropane-amine (A) to obtain the pure enantiomers.



R,S-**A**

Figure 1: Racemic (1-methyl-2-phenyl)-ethylamine (**A**).

According to earlier literature, the resolution was accomplished using (R,R)-Tartaric Acid (TA), or N-acetyl-aminoacids in 25 volumes of ethanol [3] and i-propyl alcohol [4,5]. In case of the above mentioned methods were used an equivalent amount of resolving agent and, not rare, 25-fold of solvent, obtaining the pure enantiomers after recrystallisation of diastereomers one or more times. The crystallization time was often over 12 hours in each case. The yield was under 60% referring to one of the enantiomers in the racemate.

Results and Discussion

The method described in this paper is based on our earlier works when we examined the possibilities of resolution of the racemic N-acyl amino acids with the structurally similar bases (PhEA, and its derivative MEA) in aqueous solution (Table 1) [6-11]. The applied resolving agents didn't work for acetyl-phenyl glycine, but in case of acetyl-phenylalanine enantiomeric enrichment was obtained.

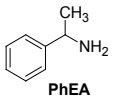
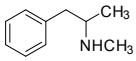
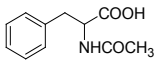
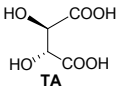
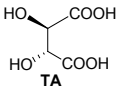
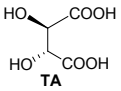
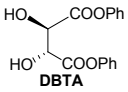
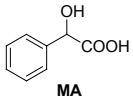
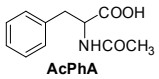
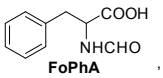
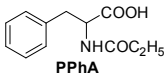
Racemic compounds	Resolving agents					
	 PhEA			 MEA		
	ee	Y	F	ee	Y	F
 AcPhA	5.0	102	0.05	71.8	26.4	0.19

Table 1: Results of resolutions of racemic N-acyl amino acids with structurally similar derivatives.

Based on our earlier findings [12] we have attempted the reciprocal resolution of A using enantiomers of N-acyl amino acids. An influence of the applied solvent was also observed in these processes The obtained results are shown in the Table 2.

Resolving agents	Solvent/The ratio solvent –racemic compound	Y (%)	ee (%)	F
Na salt of Tartaric acid and the racemic base acidified with HCl **	water/ 3x	28.3	69.0	0.195
 TA	ethanol/ 12x	71.1	60.0	0.427
 TA	IPA/ 2x	100	54.8	0.548
 TA	IPA/ 2.4x	70.0	89.1	0.624
 DBTA	IPA/ 10x	120	10.9	0.130
 MA	IPA/ 4x	85.7	0	0
 AcPhA	IPA/ 7x	75.2	50.0	0.375
 FoPhA	IPA/ 3x	43.8	46.8	0.205
 PPhA	IPA/ 3x	50.0	14.2	0.071

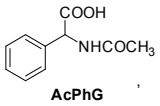
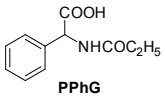
 AcPhG	IPA/ 3x	16.3	42.2	0.069
 PPhG	IPA/ 3x	43.8	16.9	0.074
ee: enantiomeric excess Y: yield calculed refering to the pure enantiomer rate in the racemic compound (50% of the total material). F= efficiency of the resolution F=ee * Y * the results refer to the reaction between 1 mol racemic compound 0.5 mol diluted hydrochlorid acid (37%) ad 0.5 mol resolving agent ** 1 mol racemic compound 1 mol HCl (37%) 0.5 mol TA.Na salt				

Table 2: Results* of the resolution of A**.**

Was observed that using structurally similar resolving agents (N-substituted A, FoPhA (1), AcPhA (2), PPhA (3)) the increase of the length of the N-substituents don't produces a linear change in the resolution results (ee, F). The correlation between substituents and the results obtained are plotted in Figure 2.

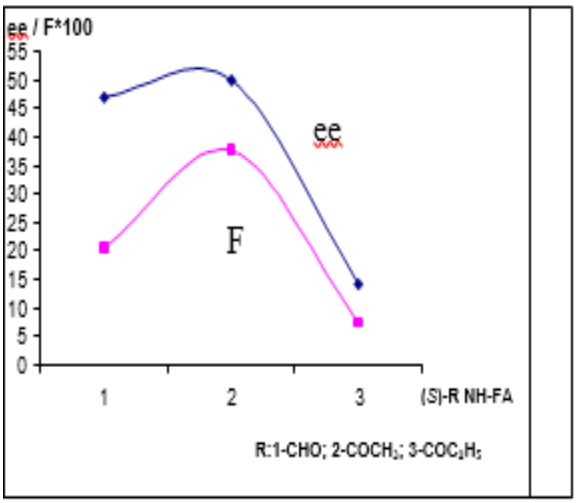


Figure 2: Tendency of correlation between the NH-substituents of **A** and the ee and F.

The Tartaric Acid (TA) was also applied as resolving agent for enantiomeric separation of A**,** in isopropanol, using 0.5 eq. of TA, 0.5 eq of sulfuric acid, since A had been successfully resolved under similar conditions.

The resolution of the racemic 1-methyl-2-phenyl-ethylamine (A) was effectuated by half equivalent of (S, S)-TA (the other half part was replaced with hydrochloric acid) and as solvent was applied IPA. Since the crystallization time and temperature could influence significantly the results of separation, these resolutions were effectuated in different conditions, varying the crystallization time and temperature. Was examined the influence of temperature and time of crystallization. If the solution is inoculated hot (about 60 °C) with the pure diastereomer or the enantiomeric hydrochloride after mixing the reagents, crystallization almost complete within a few minutes. If it is frozen (-7 °C) or the filtration is started in approximatively 15 minutes the enantiomeric purity remains high (83.5-89.1%). However, keeping overnight at 5 °C gives low enantiomeric purity (44.0%) with a high (97.0%) yield. The best results are shown below (Table 3, Figure 3).

Crystallization Time	Temperature °C	Y (%)	ee (%)	F
12 hours	5	97.0	44.0	0.427
12 min.	-7	70.0	89.1	0.624
15 min.	25	87.5	83.5	0.716

Table 3: Influence of crystallization time and temperature.

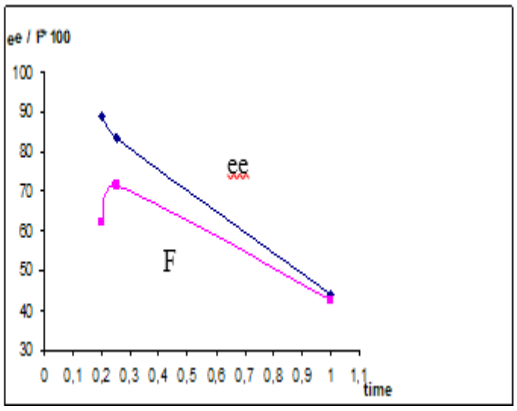


Figure 3: Tendency of correlation between crystallization time, ee and F.

So not only the influence of temperature but that of the kinetic controll was also observed, as the (S)-(+)-A*(S,S)-TA diastereomeric salt crystallizesd faster than the other corresponding salt. So the crystalls obtained must be filtrated quickly (less than one hour after start of crystallization) to obtain the wanted higher results. In this case the yield was about 90% as well as the ee (90%). These values of resolvabilty (F=ee*Y) are much higher (0.8) than the results described in literature.

In most cases a purity of enantiomers of almost 100% is needed. The purification of enantiomeric mixture can be effectuated by recrystalization (utilized in literature as mentioned above) or by re-resolution. The latter method resulted in high losses in our hands (Table 4).

ee_0 (%)	Ratio of TA	Ratio of HCl	Y (%)	ee (%)	ee-ee_0 (%)	F
57.0	0.75	0.25	55.0	77.6	20.6	0.113
40.0	0.70	0.30	105.6	55.0	15.0	0.158
ee_0: the starting enantiomeric excess						

Table 4: The results of re-resolution of the mixture of enantiomers of **A** by **TA.**

In this case the purification of enantiomeric mixture was not achieved by the usual method (multiple recrystallization) but by using a digestion process. The crystalls were boiled for a short period (1-2 minutes) in a mixture of aqueous hydrochloric acid (37%) and IPA (in equivalent amount with the racemic proportion of the diastereomeric salt).

The filtration must be effectuated quickly (preferably in no more than one hour), and so the purity of enantiomer can reach ee>80%. (If higher purity is required, this step can be repeated.) The results of purification by digestion are shown in the Table 5.

ee_0 (%)	Molar ratio HCl/diast. salt	RatioIPA /diast. salt	Y (%)	ee (%)	ee-ee_0 (%)	F
45.0	0.44	2.4	49.3	64.0	19.0	0.094
64.0	0.27	4.6	69.4	76.0	12.0	0.083
76.0	0.19	4.2	77.6	89.4	13.4	0.104
83.5	0.15	2.4	81.2	93.1	9.6	0.078
89.1	0.20	2.8	78.4	95.4	6.3	0.049

Table 5: Purification of diastereomeric salts by digestion.

During the resolution, the unusually fast crystallization of the diastereomeric salt is enabled by the kinetic control, and the ratio is assured by the rapid separation of the diastereomeric salt. By increasing the crystallization time the system is moved to thermodynamic control. As a consequencethe efficacy of resolution decreased in 12 hours from 0.716 to 0.427, and the enantiomeric purity (ee diastereomer) from 89 to 44.0 % as well.

The enantiomer A was eliberated by aqueous sodium hydroxide from the diastereomeric salt. After liberation the enantiomer was extracted with an solvent unmiscible with water (e.g. DCM) followed by the distillation of the solvent. To the remained enantiomer was added hydrochlorid acid in solution of

ethylacetate, followed by filtration of the precipitated hydrochloride salt. With this method the enantiomeric excess was increased to ee ~ 97%.

Experimental

Chemicals were the products of Aldrich (Steinheim, Germany).

Optical rotation data were measured with a Perkin-Elmer 241 automatic polarimeter.

The preparation of pure enantiomers of (-) -(1-methyl-2-phenyl) ethylamine is shown in the Figure 4.

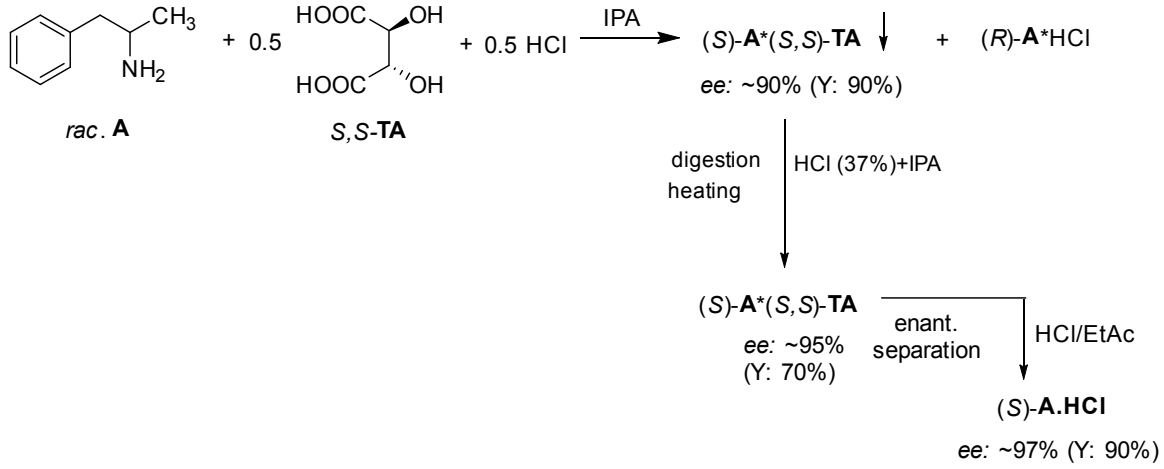


Figure 4: The general scheme for preparation of pure enantiomers of (-) -(1-methyl-2-phenyl) ethylamine.

The preparation of (-) (1-methyl-2-phenyl)ethylamine*(-)-Tartric acid diastereomeric salt

Was dissolved 5 g of the racemic compound (2-phenyl-1methyl)-ethylamine in a mixture of 12 $cm^3$of IPA and 1,53 cm^3 of aquaeous hydrochloric acid (37%), and it was heated to boiling. Was added 2,81 g (-)-tartaric acid to the hot mixture. The obtained diastereomeric salt was filtrated quickly and washed with 2x4 cm^3 IPA. The obtained salt was suspended with 10 cm^3 hexane, filtrated and dried on air.

The weight of the obtained salt 4.62 g (87.5%), [α]D= -25..3 (c=1, water), ee: 83.5%.

The purification of the diastereomeric salt

The diastereomeric salt obtained was suspended in a solution of 11 cm^3 IPA and 0,3 cm^3 diluted hydrochlorid acid (37%) and stirring heat to boiling twice (the diastereomeric salt remained suspension). The mixture was cooled to 30 ˚C in 10 minutes. The obtained salt was suspended with 10 cm^3 hexane, filtrated and dried on air.

The weight of the obtained salt 3.7 g (70.0%), $[\alpha]_D$= -28.8 (c=1, water), ee: 95%.

The preparation of (-) (1-methyl-2-phenyl)ethylamine hydrochlorid salt

To the (-)**A***(-)-**TA** diastereomeric salt (3.7g $[\alpha]_D$= -28.8 (c=1, water), ee: 95%) was added 14 cm^3 solution of NaOH (1 molar) and 6 cm^3 water. The emulsion obtained was extracted with 3x20 cm^3 Dichloromethane (DCM). The combined organic phases were dried on Na_2SO_4, filtrated and evaporated. The remained base (1.69g) was dissolved in 21 cm^3 ether and to this solution was added 2.7 cm^3 (8,7 molar) a mixture of hydrochlorid acid and ethyl acetate under stirring. After 20 minutes continue stirring the crystals were separated by filtration and washed with 2x3 cm^3 ether followed by 2x5 cm^3 hexane. The weight of (-)-**A**. HCl salt: 1.17 g (66.7%, counted on diastereomeric salt), $[\alpha]_D$= -23,9 (c=5, water), ee: 96.4%.

Acknowledgments

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