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Resolution of 1-phenyl-2-(*p*-tolyl)ethylamine via diastereomeric salt formation

Marco Pallavicini,[a,*] Cristiano Bolchi,[a] Barbara Moroni,[a] Ermanno Valoti[a] and Oreste Piccolo[b]

[a] *Istituto di Chimica Farmaceutica e Tossicologica, Università di Milano, viale Abruzzi 42, I-20131 Milan, Italy*
[b] *Studio di Consulenza Scientifica, via Bornò 5, I-23896 Sirtori (LC), Italy*

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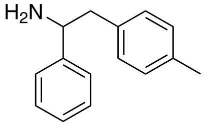
Abstract—(*S*)-1-Phenyl-2-(*p*-tolyl)ethylamine (*S*)-**1**, used for the industrial scale resolution of chrysanthemic acids, was obtained via resolution of the racemate with the hemiphthalate of (*S*)-isopropylidene glycerol (*R*)-**2**. The maximum experimental efficiency [69% yield and >99% e.e. of (*S*)-**1**] was achieved by a simple precipitation of (*S*)-**1**·(*R*)-**2** from the solution of the 1:1 diastereomeric salt mixture in 93/7 isopropanol/water at saturation of the more soluble (*R*)-**1**·(*R*)-**2** salt. Such an experimental efficiency was consistent with 0.79 maximum theoretical resolvability, derived from the solubilities of the two diastereomeric salts, and with DSC data, which indicated that the (*S*)-**1**·(*R*)-**2**/(*R*)-**1**·(*R*)-**2** system is a binary mixture exhibiting an eutectic with composition approximately corresponding to a 0.2 molar ratio of (*S*)-**1**·(*R*)-**2**.

1. Introduction

(*S*)-1-Phenyl-2-(*p*-tolyl)ethylamine (*S*)-**1** is widely used for the large scale resolution of cyclopropanecarboxylic acid pyrethroids[1] and has proved to resolve other acids efficiently, such as atrolactic,[2] 2-methylpentanoic,[3] α-isopropyl-*p*-fluorophenylacetic[4] and α-isopropyl-*p*-chlorophenylacetic acid.[5] On an industrial scale, (*S*)-**1** and (*R*)-**1** are in turn obtained from the racemate via resolution with optically active acids. To our knowledge, four selective precipitations of diastereomeric salts of **1** have been claimed in patents to date: (i) of (*S*)-**1** L-aspartate,[6] (ii) of (*R*)-**1** L-tartrate, from *R* enriched solutions of the amine,[7] (iii) of (*R*)-**1** (*R*)-mandelate[8] and (iv) of (*R*)-**1** L-lactate.[9] Apart from these patents, however, the only resolutions of **1** described in the literature are the preferential crystallization of its cinnamate[10] and the fractional crystallization of the salts with optically active α-isopropyl-*p*-chlorophenylacetic acid.[11]



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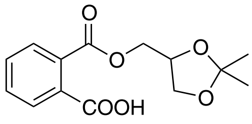

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Therefore, it seemed worthwhile to develop and to optimise an alternative resolution procedure. For this purpose, we decided to verify the resolvability of **1** with isopropylidene glycerol hydrogen phthalate **2**, a new acid we had previously shown to resolve 1-phenylethylamine and many other primary amines with high efficiencies.[12–15] Herein, the results of such an investigation are reported with emphasis on the relationship between the experimental resolution efficiencies and the difference in physical properties of the diastereomeric salts (*S*)-**1**·(*R*)-**2** and (*R*)-**1**·(*R*)-**2**.

2. Results

We decided to utilise the (*R*)-enantiomer of **2**, prepared from readily available (*S*)-isopropylidene glycerol and phthalic anhydride, and to combine the racemic amine **1** with a stoichiometric quantity of such a resolving acid in alcoholic solvents. Initial experiments were performed in methanol and in ethanol (Table 1, entries 1 and 2). Due to its high dissolving ability, methanol was used in a low ratio to the diastereomeric salt mixture (2.3 mL/g) and cooled to 0°C in order to obtain a precipitate in good yield (68.4% of the theoretical amount). Chiral HPLC analysis allowed us to establish the prevalence of the second eluted (*S*)-enantiomer of **1** in the precipitated salt, but only with a moderate 41.3% e.e. From ethanol, used in a higher ratio to the

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* Corresponding author. E-mail: marco.pallavicini@unimi.it

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Table 1. Resolution of amine **1** by diastereoselective precipitation of (*S*)-**1**·(*R*)-**2** salt

Entry	Solvent	$\frac{1}{2}C_0$[a]	Solv./salt[b]	Yield of (*S*)-**1**·(*R*)-**2** (%)[c]	E.e. of (*S*)-**1** (%)[d]	S_{exp}[e]
1	MeOH	0.219	2.3	68.4	41.3	0.28
2	EtOH	0.110	4.6	91.2	30.8	0.28
3	*i*-PrOH	0.029	17.4	63.0	96.1	0.61
4	*i*-PrOH	0.029	17.1	61.6	96.5	0.59
5[f]	*i*-PrOH		6.0	65.6	68.0	0.45
6[f]	*i*-PrOH		9.0	50.0	92.4	0.46
7	*i*-PrOH/H_2O	0.067	7.4	68.0	>99	0.68
8	*i*-PrOH/H_2O	0.074	6.7	69.0	>99	0.69
9	*i*-PrOH/H_2O	0.083	6.0	84.9	68.1	0.58
10	*i*-PrOH/H_2O	0.094	5.3	104.8	36.1	0.38
11	*i*-PrOH/H_2O	0.120	4.2	128.1	27.9	0.36

[a] Half the initial concentration (g/mL) of the 1:1 diastereomeric salt mixture, i.e. before precipitation.

[b] Ratio of the solvent to the diastereomeric salt mixture in mL/g.

[c] Relative to the theoretical amount, i.e. half of the starting racemic amine.

[d] Enantiomeric excess (determined by HPLC) of the amine liberated from the salt.

[e] Experimental resolution efficiency or experimental resolvability, calculated from the chemical yield of the precipitated salt and the enantiomeric excess of the amine liberated from the same.

[f] The experiment was carried out using 0.55 equiv. of resolving agent.

diastereomeric mixture (4.6 mL/g) at room temperature, precipitation of (*S*)-**1**·(*R*)-**2** occurred in 91.2% yield (45.6% of the starting **1**) and with 30.8% e.e. of (*S*)-**1**. On the basis of the resultant modest resolvabilities, 0.28 for both procedures, the use of methanol and ethanol as resolution solvents was dropped. Subsequent experiments were carried out in 2-propanol (Table 1, entry 3 and 4). Equivalent amounts of the racemic amine **1** and (*R*)-**2** were combined in a relatively large volume of this latter alcohol (17.4 mL/g diastereomeric salt mixture). After stirring for 2 hours at room temperature, a precipitate of (*S*)-**1**·(*R*)-**2** was collected in 63% yield (31.5% of the starting **1**) and with 96.1% e.e. of (*S*)-**1**. These data were confirmed by a further experiment under nearly identical conditions (61.6% yield and 96.5% e.e.). The high resolution efficiency, about 0.60, achieved by a single precipitation from 2-propanol, prompted us to search for conditions which allowed the solvent/salts ratio to be considerably lower without decreasing the resolvability. To this end, the use of less than 1 equiv. of resolving agent was attempted. In the presence of 0.55 equiv. of (*R*)-**2** and of 6 and 9 mL of 2-propanol per gram of diastereomeric salt mixture, the precipitation of (*S*)-**1**·(*R*)-**2** took place in 65.6% and 50% yield and with 68% and 92.4% d.e., respectively (Table 1, entries 5 and 6). The corresponding 0.45 and 0.46 resolvabilities indicated that such procedures were much less efficient than the previous ones from larger volumes of 2-propanol and with stoichiometric resolving acid. We then reconsidered the use of equimolar (*R*)-**2**, but in aqueous isopropanol, hoping that the addition of a small percentage of water would sensibly enhance the solubilities of both the diastereomeric salts leaving the resolution efficiency unaltered. Indeed, the results of the first experiment (Table 1, entry 7), carried out in 93/7 (v/v) 2-propanol/water (7.4 mL/g diastereomeric salt mixture), exceeded our expectations: (*S*)-**1**·(*R*)-**2** precipitated in 68% yield and with >99% e.e. of (*S*)-**1**, resulting in a sensibly higher resolvability (0.68 versus 0.60 in anhydrous isopropanol).

In order to verify if this procedure was susceptible to optimisation, further experiments were performed precipitating (*S*)-**1**·(*R*)-**2** from solutions with higher C_0 (initial concentration of the 1:1 diastereomeric salt mixture, i.e. before crystallisation). The reduction of the volume of aqueous isopropanol per gram of diastereomeric mixture from 7.4 mL to 6.7, 6.0, 5.3 and 4.2 mL led to 0.69, 0.58, 0.38 and 0.36 resolution efficiencies, respectively (Table 1, entries 8–11). All the experimental resolvabilities shown by the crystallisations from 2-propanol–water were plotted against $\frac{1}{2}C_0$ (see Fig. 1). On the basis of measured k_n (0.071 g/mL) and k_p (0.015 g/mL) (solubilities in 93/7 isopropanol/water, at 20°C, of (*R*)-**1**·(*R*)-**2** and (*S*)-**1**·(*R*)-**2**, respectively), the theoretical resolvability was calculated at different C_0 values according to van der Haest, Wynberg et al.[16] The resultant correlation with $\frac{1}{2}C_0$ is represented by the solid curve depicted in the same diagram where the experimentally determined resolvabilities are reported.

By DSC analysis, the melting points of the less soluble p-salt (*S*)-**1**·(*R*)-**2** and of the more soluble n-salt (*R*)-**1**·(*R*)-**2** were estimated to be 140.5 and 131.2°C, respectively (see Fig. 2). The corresponding heats of fusion could not be accurately evaluated, because of the thermal decomposition, which started before the fusion was complete. In the case of (*S*)-**1**·(*R*)-**2**, TG analysis indicated a 5% weight loss at the temperature of the DSC melting curve maximum (140.5°C). Such a loss increased with temperature, reaching a 30% value 20°C above the melting point.

In addition, we recorded the DSC data for two precipitated diastereomeric salt mixtures (Table 1, entries 9 and 10) containing 68 and 84% of (*S*)-**1**·(*R*)-**2**, respectively. Two clearly distinct peaks, preceding the ultimate decomposition, characterised their melting profiles, the first, at 124°C, representing the fusion of the eutectic and the second, at 130 and 131°C for the less and the more enriched diastereomeric mixture,

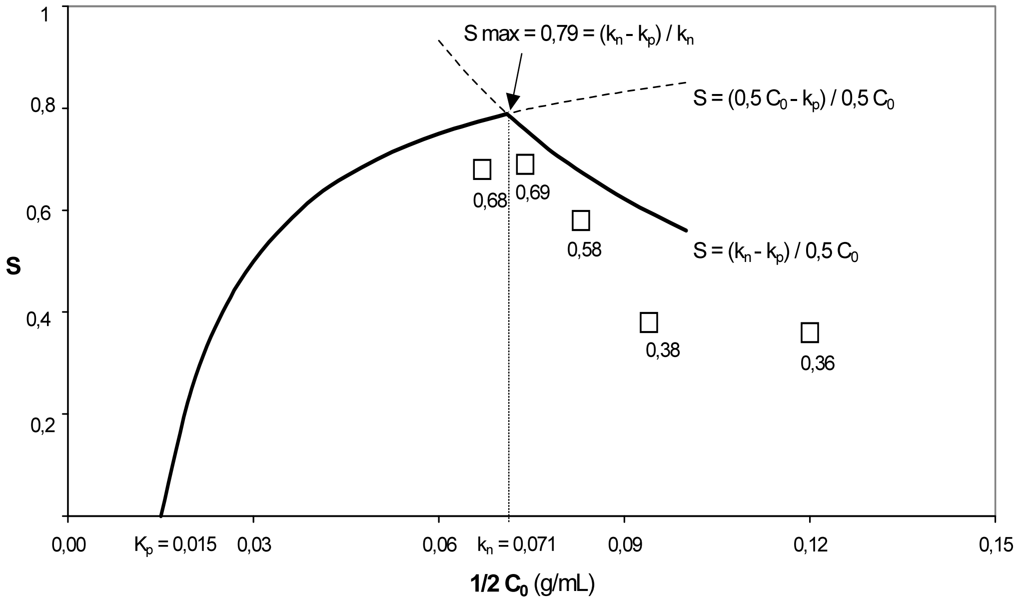

Figure 1. Resolvability (S) plotted against half of the initial concentration of the 1:1 (S)-**1**·(R)-**2**/(R)-**1**·(R)-**2** mixture ($\frac{1}{2}C_0$) in 93/7 isopropanol/water. The solid curve represents the theoretical resolvabilities, i.e. the values calculated on the basis of the solubilities of (S)-**1**·(R)-**2** (k_p) and (R)-**1**·(R)-**2** (k_n). The squares represent the experimental resolvabilities, obtained by multiplying the yields of the precipitated salts by the enantiomeric excess of the liberated amine (see Table 1).

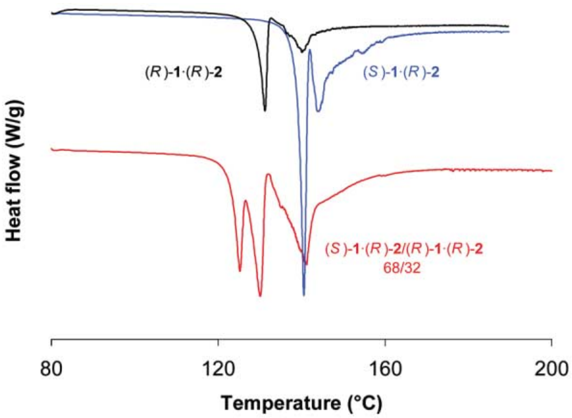

Figure 2. DSC traces of the pure salts (S)-**1**·(R)-**2** and (R)-**1**·(R)-**2** (upper curves) and of their mixture precipitated in the resolution experiment corresponding to entry 10 of Table 1 (lower curve).

respectively, belonging to the residual (S)-**1**·(R)-**2** salt (see Fig. 2). Finally, the DSC curve of a 80/20 (R)-**1**·(R)-**2**/(S)-**1**·(R)-**2** mixture, prepared by combining the pure salts, was recorded. In this case, the DSC trace showed a single peak, corresponding to the melting of the eutectic.

3. Discussion and conclusion

As shown in Table 1 (entries 3, 4, 7 and 8), isopropanol and isopropanol–water proved the best solvents for the resolution of **1** with **2**. In both cases, a simple precipitation from the solution of the 1:1 diastereomeric mixture led to the isolation of (S)-**1**·(R)-**2** in good yield and with very high enantiomeric excess of (S)-**1**. In particular, the use of isopropanol added with water resulted in nearly 70% yields and >99% enantiomeric excesses, while allowing the volume of the mother liquors to be reduced considerably. The higher efficiency achieved in aqueous isopropanol was presumably due to the more favourable ratio between the solubilities of the two diastereomeric salts in this latter solvent system (4.7 versus 3 in pure isopropanol).

The trend of the experimental efficiencies of the resolutions in isopropanol–water is meaningful. In fact, as shown in Figure 1, it parallels, within experimental error, the ideal correlation between resolvability and $\frac{1}{2}C_0$, derived from the solubility data k_n, k_p, reaching the maximum in proximity to the saturation of the more soluble n-salt (i.e. $\frac{1}{2}C_0 = k_n = 0.071$ g/mL), where the utmost theoretical efficiency (0.79) is located. This suggests that the two highest experimental resolvabilities (0.68 and 0.69) are optimal.

Inspection of the DSC traces (see Fig. 2) of the pure salts (S)-**1**·(R)-**2** and (R)-**1**·(R)-**2** and of two precipitated mixtures with 0.84 and 0.68 mole fraction of (S)-**1**·(R)-**2** indicate that the (S)-**1**·(R)-**2**/(R)-**1**·(R)-**2** system forms a binary mixture exhibiting an eutectic. The whole binary (melting point–mole fraction) diagram of such a system was not experimentally constructed, neither was it calculated by the Schroeder–van Laar equation, the heats of fusion of the pure salts as well as the final temperatures of their fusion and of the fusion of their mixtures not being accurately measured. Consequently, the eutectic composition (χ_{eu}) was not determined. This notwithstanding, it could be presumed to lie in proximity to 0.18 mole fraction of (S)-**1**·(R)-**2**. In fact, a 0.174 value of χ_{eu} is obtained equating the two expressions of the maximum theoretical resolvability, i.e. $S=(k_n-k_p)/k_n$ and $S=(1-2\chi_{eu})/(1-\chi_{eu})$. On the other hand, the DSC analysis of a diastereomeric mixture with 0.2 mole fraction of (*S*)-**1**·(*R*)-**2** substantiated such an hypothesis, yielding a trace where only a single melting peak, that of the eutectic, was detectable.

In summary, a new resolution of **1** has been developed and optimised utilising the hemiphthalate **2** as a resolving agent. The (*R*)-form of the acid, easily obtained from the more available enantiomer of glycerol acetonide, selectively precipitated (*S*)-**1**, the more requested stereoisomer of the amine. The highest found resolvability, near 0.7 in aqueous isopropanol, was close to the theoretical maximum (0.79), resulting from both solubility and DSC data of the (*S*)-**1**·(*R*)-**2**/(*R*)-**1**·(*R*)-**2** system. On the basis of these results, we have investigated and disclosed a further interesting application of the novel resolving acid **2**, concerning a valuable racemic amine, whose few known resolutions are mostly claimed in patents.

4. Experimental

^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz) instrument. Optical rotations were measured in a 1 dm cell of 1 mL capacity using a Perkin–Elmer 241 polarimeter. HPLC analyses were performed on a Chiralcel OD-R column (250×4.6 mm i.d.) from Daicel using a Hitachi 7100 pump, a Hitachi L-7400 UV detector ($\lambda=225$ nm) and a Hitachi D-7000 HPLC System Manager software. Melting points were determined by DSC analysis, taking the temperature of the maximum of the peak. The DSC curves were recorded and integrated with the aid of a TA Instruments DSC 2010 apparatus. The thermogravimetric measurements were carried out on a TA Instruments TG 2050 system. Elemental analyses are indicated by the symbols of the elemets only. Analytical results for these elements were within 0.4% of the theoretical value.

(*RS*)-**1** and two samples of (*S*)- and (*R*)-**1** were provided by Endura S.p.a. (Bologna, Italy). (*R*)-**2** was prepared by the reaction of phthalic anhydride with (*S*)-isopropylidene glycerol, purchased from Chemi S.p.a. (Cinisello Balsamo, MI, Italy), according to the method previously reported.[12]

4.1. (*S*)-1-Phenyl-2-(*p*-tolyl)ethylamine (*S*)-1

The optimal resolution procedure was as follows:(*R*)-**2** (2.46 g, 8.78 mmol) and (*RS*)-**1** (1.855 g, 8.78 mmol) were combined in 93/7 (v/v) isopropanol/water (29 mL). The resulting clear solution was stirred at room temperature for 4 h. Over this period, a white precipitate progressively separated, to give a suspension which was finally filtrated isolating (*S*)-**1**·(*R*)-**2** salt (1.49 g, 69% of the theoretical amount): mp 140.5°C; e.e. of (*S*)-**1** >99% (determined by HPLC of the amine liberated from a sample of the salt; 75/25 0.5 M $NaClO_4$/CH_3CN, 1.5 ml/min); ^{1}H NMR (DMSO-d_6) δ 1.21 (s, 3 H), 1.30 (s, 3 H), 2.20 (s, 3 H), 2.98 (dd, 1 H), 3.24 (dd, 1 H), 3.76 (dd, 1 H), 3.99 (pseudo t, 1 H), 4.15 (d, 2 H), 4.30 (m, 2 H), 6.91 (d, 2 H), 6.97 (d, 2 H), 7.20–7.50 (m, 8 H), 7.73 (d, 2 H); anal. ($C_{29}H_{33}NO_6$) C, H, N. The salt was decomposed by treatment with 1 M H_2SO_4 and ethyl acetate. The aqueous phase was separated, made alkaline with NaOH and extracted with dichloromethane. Removal of the solvent from the extract, previously dried over Na_2SO_4, gave a colourless oil (620 mg), which was distilled under vacuum yielding (*S*)-**1** (600 mg, 64.7% of the theoretical amount): $[\alpha]_D^{25}=+62.2$ (*c* 1, methanol); lit.[10] $[\alpha]_D^{25}=+62.9$ (*c* 1, methanol); e.e. identical to that previously determined for the amine liberated from a sample of the salt with (*R*)-**2**; ^{1}H NMR ($CDCl_3$) δ 1.53 (bs, 2 H), 2.34 (s, 3 H), 2.78 (dd, 1 H, $J=13.4$, 9.0), 2.99 (dd, 1 H, $J=13.4$, 4.8), 4.18 (dd, 1 H, $J=9.0$, 4.8), 7.06–7.13 (2 d, 4 H), 7.23–7.39 (m, 5 H).

4.2. Thermal analyses

For DSC analyses, samples of 2–5 mg were run in crimped aluminium pans with a heating rate of 2.5 K min^{-1}. The samples were drawn from the precipitates resulting from the resolution experiments corresponding to the entries 9 and 10 of Table 1. In addition, two samples were prepared, one of (*R*)-**1**·(*R*)-**2**, combining the enantiomer of the amine with that of the hydrogen ester, the other, with 0.8 molar fraction of (*R*)-**1**·(*R*)-**2**, mixing this latter salt with >99% diastereomerically pure (*S*)-**1**·(*R*)-**2** isolated from the resolution experiments. The loss of weight of (*S*)-**1**·(*R*)-**2** due to thermal decomposition was determined by TG measurements at the same heating rate of DSC analyses (2.5 K min^{-1}).

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