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Resolution of amines with isopropylidene glycerol hydrogen phthalate

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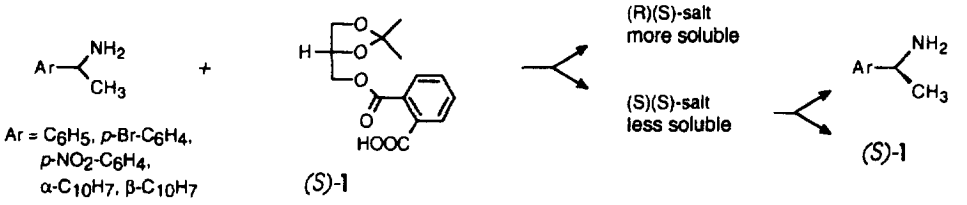
Abstract: The hydrogen phthalate of isopropylidene glycerol has been recently described as an efficient resolving agent of 1-arylethylamines. In order to gain more information on its versatility and to develop a rationale which accounts for its effectiveness, further 1-arylethylamines and other racemic amines were subjected to the same resolution process. A preliminary qualitative analysis of the results reported herein allows to identify some structural features of the aminic substrates conditioning the feasibility of the resolution.

Recently, we have developed a new acidic resolving agent, the hydrogen phthalate of isopropylidene glycerol **1**, which has proved to be very efficient in resolving a range of 1-arylethylamines.[1] In particular, the salts between (*S*)-**1** and the *S* isomer of 1-phenyl-, 1-(4-bromophenyl)-, 1-(4-nitrophenyl)-, 1-(1-naphthyl)- and 1-(2 naphthyl)ethylamine selectively crystallized from methanol or 2-propanol allowing to recover the (*S*)-1-arylethylamines from the corresponding racemates in high chemical yields and enantiomeric excesses (Scheme 1).



Scheme 1.

On the basis of these results it seemed worthwhile to gain more information on the versatility of **1** as a resolving agent subjecting other racemic amines to the same resolution process. Firstly, amines **2–5** were selected with the aim of confirming the capability of efficiently resolving 1-arylethylamines. Secondly, we considered amines **6–14**, in which the 1-phenylethylamine framework is differently modified, in order to verify the retention of the resolving ability in spite of structural modifications of the substrate and in the hope of successively providing a theoretical basis for understanding the outcome of the resolutions.

As previously described for the resolutions of 1-phenylethylamine and its *para*-bromo and *para*-nitro derivatives, treatment of amines **2–4** with stoichiometric (*S*)-**1** in methanol yielded white crystalline precipitates, which afforded, after usual extractive procedures and without the necessity of performing recrystallizations, the corresponding *S* amines with very high enantiomeric excesses (Table 1, entries 1–3). In particular, (*S*)-**4** was obtained with >99% e.e. and in an excellent 77% yield (38.5% of the starting **4**).

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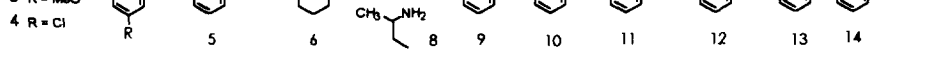
Table 1. Preparation of (*S*)-1-arylalkylamines from the corresponding racemates by selective crystallization of the respective salts with (*S*)-**1**[a] according to Scheme 1[2–6]

entry	amine	solvent	yield,[b] %			ee,[c] %		$[\alpha]_D$,[d]
			1st cryst.[e]	2nd cryst.	recovered amine	1st cryst.	2nd cryst.	
1	(*S*)-**2**	methanol	51.2	-[f]	46.1	97.7	-	-32.9 [g]
2	(*S*)-**3**	"	61.8	-[f]	53.2	>99	-	-29.4 [h]
3	(*S*)-**4**	"	81.0	-[f]	77.0	>99	-	-23.7 [i]
4	(*S*)-**10**	"	62.3	-[f]	56.1	96.8	-	-19.8 [j]
5	(*S*)-**11**	2-propanol	96.2	76.9	63.1	64.1	>99	-15.1 [k]

a) All crystallizations were performed using equivalent amounts of racemic amine and (*S*)-**1**. b) Relative to the theoretical amount, i.e., half of starting racemate. c) Enantiomeric excess of the amines determined by reversed-phase chiral HPLC analysis of the corresponding salts with (*S*)-**1** on a Chiralcel OD-R column from *Daicel* (el. $NaClO_4$ aq./CH_3CN mixtures). d) Of the recovered amine. e) From the solution of racemic amine and (*S*)-**1**. f) The recrystallizaion was not performed, since unnecessary. g) At 25°C; neat (lit.[2] -34.0). h) At 27°C; *c* 8, benzene (lit.[3] -29.79). i) At 20°C, *c* 2, MeOH (lit.[4] +26.5, for the *R* isomer). j) At 24°C; neat (lit.[5] +21.2, for the *R* isomer). k) At 20°C; *c* 1, $CHCl_3$ (lit.[6] -11.5).



The results of trial resolution of amines **5–14** can be summarized as follows: (a) attempts at obtaining crystalline precipitates by treatment of **5**, **6**, **8**, **9**, **12** and **13** with equimolar (*S*)-**1** were unsuccessful; (b) **14** gave rise, upon reaction with (*S*)-**1** in 2-propanol, to a crystalline salt, in which, however, the two diastereoisomers were present in about equal amounts; (c) on the contrary, **7** was partially resolved under the same conditions, the *S* and the *R* amines being recoverable 53% and 39% enantiomerically pure from the precipitate and from the mother liquor, respectively; (d) finally, **10** and **11** were efficiently resolved by (*S*)-**1**, one recrystallization being necessary in the only case of **11** (Table 1, entries 4 and 5).

We are presently attempting to develop a rationale which accounts for the behaviour of amines **2–14** and of those previously resolved. A detailed computational analysis aimed at modelling the intermolecular interactions between (*S*)-**1** and the enantiomeric pairs of the considered amines has been therefore initiated and its results will be successively reported. However, some significant trends can be already identified on the basis of a preliminary qualitative evaluation of the experimental data: (i) All the successful resolutions showed the same stereochemical course. (ii) 1-Phenylethylamines proved to be ideal substrates; the presence of *para* substituents or of a second condensed phenyl ring (1-(1-naphthyl)ethylamine and 1-(2-naphthyl)ethylamine) did not preclude the feasibility of the resolutions, on the contrary, in some cases, increased their efficiency. (iii) The phenyl group or, instead of this, another unsaturated moiety seems to play a critical role in the interaction with (*S*)-**1**, as shown by the fact that 1-phenylethylamine and, partially, **7** could be resolved by (*S*)-**1**, while the corresponding saturated amines **6** and **8** failed to form solid precipitates upon treatment with (*S*)-**1**. Consistent with such an assumption, **13**, in which the phenyl group is present, but separated from the ethylamine framework by one methylene, behaved in the same way as **6** and **8**. (iv) The contiguity of the nitrogen atom to the stereogenic centre is a determinant factor in regard to the solubility difference of the two diastereomeric salts. Indeed, **14** formed a precipitate with (*S*)-**1**, but the crystallization was not selective. (v) The modifications of the alkyl chain bound to the stereogenic carbon are not so critical as the previous ones. **10** and **11** could be still resolved, contrarily to **9** and **12**, in which the alkyl is further extended.

In summary, we have investigated the applicability of **1** to the resolution of a range of eighteen amines, including those previously reported. Half of these were 1-arylethylamines and all resolvable by **1**, with the exception of the only secondary amine **5**. Of the residual nine, **1** resolved **7**, **10** and **11**. On the basis of these results and of the above remarks, we can presently conclude that **1** shows a high and specific capability of resolving 1-arylethylamines. On the other hand, its versatility seems to be limited, as shown by the fact that slight modifications of these lead substrates, expecially in proximity to the stereogenic centre, often result in the loss of the resolvability with **1**.

Experimental section

^{1}H NMR spectra were recorded on a Bruker 200 (200 MHz) instrument. Melting points were recorded on a Gallenkamp capillary melting point apparatus and are uncorrected. Optical rotations were measured in a 1-dm cell of 1 ml capacity using a Perkin–Elmer 1310 instrument. HPLC analyses were performed on a Chiralcel OD-R column (250×4.6 mm I.D.) from *Daicel*. Racemic amines **2**, **3**, **4**, **10** and **11** were readily synthesized by the Leuckart reaction from the corresponding ketones according to the experimental procedure described for 1-phenylethylamine.[7] **7** was synthesized from racemic 3-chloro-1-butene according to a literature procedure.[8]

(S)-1-(4-Methylphenyl)ethylamine (S)-2

(*S*)-**1** (11.77 g, 42 mmol) and **2** (5.68 g, 42 mmol) were combined in methanol (50 ml) and heated to boiling temperature. The resulting solution was allowed to cool slowly to about 5°C to yield a white precipitate of (*S*)-**1**–(*S*)-**2** salt (4.47 g), which was collected by filtration and rinsed with cold methanol: m.p. 136–138°C; e.e. of (*S*)-**2** 97.7% (by HPLC of the salt; 85/15 0.4 M $NaClO_4/CH_3CN$, 0.8 ml/min); ^{1}H NMR (DMSO) δ 1.31 (s, 3 H), 1.36 (s, 3 H), 1.49 (d, 3 H), 2.33 (s, 3 H), 3.84 (dd, 1 H), 4.06 (pseudo t, 1 H), 4.19 (d, 2 H), 4.33 (m, 2 H), 7.23 (d, 2 H), 7.39–7.48 (m, 5 H), 7.74 (d, 1 H). The salt was decomposed by treatment with 10% HCl and CH_2Cl_2. The aqueous phase was separated, made alkaline with 1 N NaOH and extracted with ethyl acetate. Removal of the solvent from the extract, previously dried over Na_2SO_4, gave (*S*)-**2** (1.31 g, 46.1% of the theoretical amount) as an oil: $[\alpha]_D^{25}=-32.9$ (neat, d=0.917); ^{1}H NMR ($CDCl_3$) δ 1.38 (d, 3 H), 1.59 (s, 2 H), 4.09 (q, 1 H), 7.15 (d, 2 H), 7.25 (d, 2 H).

(S)-1-(4-Methoxyphenyl)ethylamine (S)-3

(*S*)-**1** (3.7 g, 13.2 mmol) and **3** (2 g, 13.2 mmol) were combined in methanol (12 ml) and heated to boiling temperature. The resulting solution was treated as described above for the resolution of (*S*)-**2** to give (*S*)-**1**–(*S*)-**3** salt (1.76 g): m.p. 136–137°C; e.e. of (*S*)-**3** >99% (by HPLC of the salt; 85/15 0.4 M $NaClO_4/CH_3CN$, 0.5 ml/min); ^{1}H NMR (DMSO) δ 1.30 (s, 3 H), 1.36 (s, 3 H), 1.50 (d, 3 H), 3.79 (s, 3 H), 3.84 (dd, 1 H), 4.06 (pseudo t, 1 H), 4.19 (d, 2 H), 4.33 (m, 2 H), 6.98 (d, 2 H), 7.35–7.50 (m, 5 H), 7.74 (d, 1 H). The salt was decomposed in the same way as described for the hydrogen phthalate of (*S*)-**2** yielding (*S*)-**3** (0.532 g, 53.2% of the theoretical amount) as an oil: $[\alpha]_D^{27}=-29.4$ (*c* 8, benzene); ^{1}H NMR ($CDCl_3$) δ 1.37 (d, 3 H), 1.58 (br s, 2 H), 3.80 (s, 3 H), 4.09 (q, 1 H), 6.87 (δ, 2 H), 7.27 (δ, 2 H).

(S)-1-(4-Chlorophenyl)ethylamine (S)-4

(*S*)-**1** (14.59 g, 52.1 mmol) and **4** (8.1 g, 52.1 mmol) were combined in methanol (80 ml) and heated to boiling temperature. The resulting solution was treated as described above for the resolution of (*S*)-**2** to give (*S*)-**1**–(*S*)-**4** salt (9.2 g): m.p. 144–146°C; e.e. of (*S*)-**4** >99% (by HPLC of the salt; 85/15 1.5 M $NaClO_4/CH_3CN$, 0.8 ml/min); ^{1}H NMR (DMSO) δ 1.31 (s, 3 H), 1.36 (s, 3 H), 1.48 (d, 3 H), 3.83 (dd, 1 H), 4.07 (dd, 1 H), 4.20 (d, 2 H), 4.36 (m, 2 H), 7.40–7.60 (m, 7 H), 7.74 (dd, 1 H). The salt was decomposed in the same way as described for the hydrogen phthalate of (*S*)-**2** yielding (*S*)-**4** (3.12 g, 77% of the theoretical amount) as an oil: $[\alpha]_D^{20}=-23.7$ (*c* 2, MeOH); ^{1}H NMR ($CDCl^3$) δ 1.34 (d, 3 H), 1.39 (s, 2 H), 4.08 (q, 1 H), 7.27 (s, 4 H).

*(S)-1-Phenylpropylamine (S)-**10***

(*S*)-**1** (12.23 g, 43.6 mmol) and **10** (5.9 g, 43.6 mmol) were combined in methanol (53 ml). The resulting solution was treated as described above for the resolution of (*S*)-**2** to give (*S*)-**1**–(*S*)-**10** salt (5.65 g): m.p. 138–139°C; e.e. of (*S*)-**10** 96.8% (by HPLC of the salt; 85/15 1 M $NaClO_4/CH_3CN$, 0.7 ml/min); ^1H NMR (DMSO) δ 0.78 (t, 3 H), 1.31 (s, 3 H), 1.36 (s, 3 H), 1.82 (m, 1 H), 1.94 (m, 1 H), 3.84 (dd, 1 H), 4.06 (m, 2 H), 4.19 (d, 2 H), 4.36 (m, 1 H), 7.35–7.50 (m, 8 H), 7.74 (d, 1 H). The salt was decomposed in the same way as described for the hydrogen phthalate of (*S*)-**2** yielding (*S*)-**10** (1.65 g, 56.1% of the theoretical amount) as an oil: $[\alpha]_D^{24}=-19.8$ (neat, d=0.936); ^1H NMR ($CDCl^3$) δ 0.87 (t, 3 H), 1.57 (s, 2 H), 1.70 (m, 2 H), 3.80 (t, 1 H), 7.15–7.40 (m, 5 H).

*(S)-1-Phenylisobutylamine (S)-**11***

(*S*)-**1** (9.39 g, 33.5 mmol) and (*S*)-**11** (5 g, 33.5 mmol) were combined in 2-propanol (40 ml). Crystallization at room temperature gave a white crystalline solid (6.92 g), which was recrystallized from 2-propanol (22 ml) yielding (*S*)-**1**–(*S*)-**11** salt (5.53 g): m.p. 120–121°C; e.e. of (*S*)-**11** >99% (64.1%, before the recrystallization) (by HPLC of the salts; 85/15 0.4 M $NaClO_4/CH_3CN$, 0.5 ml/min); ^1H NMR (DMSO) δ 0.74 (d, 3H), 1.00 (d, 3 H), 1.30 (s, 3 H), 1.35 (s, 3 H), 2.02 (m, 1 H), 3.82 (pseudo t, 2 H), 4.08 (pseudo t, 1 H), 4.20 (d, 2 H), 4.36 (m, 1 H), 7.30–7.55 (m, 8 H), 7.74 (dd, 1 H). The salt was decomposed in the same way as described for the hydrogen phthalate of (*S*)-**2** yielding (*S*)-**11** (1.58 g, 63.1% of the theoretical amount) as an oil: $[\alpha]_D^{20}=-15.1$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.78 (d, 3 H), 0.98 (d, 3 H), 1.53 (s, 2 H), 1.86 (m, 1 H), 3.60 (d, 1 H), 7.15–7.35 (m, 5 H).

*Partial resolution of 1-methylallylamine **7***

(*S*)-**1** (26.46 g, 94.4 mmol) and **7** (6.71 g, 94.4 mmol) were combined in diethyl ether (50 ml). The resulting white precipitate (29.37 g) was collected by filtration and crystallized from 2-propanol, yielding (*S*)-**1**–(*S*)-**7** salt (12.26 g): ^1H NMR (DMSO) δ 1.29 (d, 3 H), 1.31 (s, 3 H), 1.36 (s, 3 H), 3.70–3.90 (m, 2 H), 4.07 (dd, 1 H), 4.19 (d, 2 H), 4.36 (m, 1 H), 5.22 (d, 1 H), 5.32 (d, 1 H), 5.85–6.05 (m, 1 H), 7.30–7.50 (m, 3 H), 7.73 (dd, 1 H). The salt was dissolved in a small quantity of water and excess solid potassium hydroxide added. The liberated amine was extracted with diethyl ether and the extract concentrated at atmospheric pressure below 50°C. Distillation of the residue gave 0.9 g of (*S*)-**7**: b.p. 62–64°C; $[\alpha]_D^{22}=+17.81$ (*c* 1.1, ethanol) [lit.[9] $[\alpha]_D^{22}=-33.8$ (*c* 1.1, ethanol; for the *R* isomer)]; ^1H NMR ($CDCl_3$) δ 1.13 (d, 3 H), 1.47 (br s, 2 H), 3.44 (m, 1 H), 4.94 (d, 1 H), 5.06 (d,1 H), 5.70–5.95 (m, 1 H).

The 2-propanol mother liquor was concentrated. The resulting residue (17.08 g) was dissolved in a small quantity of water and excess solid potassium hydroxide added. Fractional distillation at atmospheric pressure of the basified solution afforded (*R*)-**7** (2.53 g): $[\alpha]_D^{22}=-13.24$ (*c* 1, ethanol).

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