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Resolution of methyl-1-phenylethylamines by acidic derivatives of 1-phenylethylamine

József Bálint,[a] József Schindler,[a] Gabriella Egri,[a,*] Miklós Hanusz,[b] Katalin Marthi,[c] Zoltán Juvancz[d] and Elemér Fogassy[a]

[a]*Department of Organic Chemical Technology, Budapest University of Technology and Economics, H-1521 Budapest, PO Box 91, Hungary*
[b]*CHINOIN Co Ltd—Member of Sanofi Aventis Group, Budapest H-1325, PO Box 110, Hungary*
[c]*Hungarian Academy of Sciences—Budapest University of Technology and Economics, Research Group of Technical Analytical Chemistry, H-1111 Budapest, Szt. Gellért tér 4, Hungary*
[d]*VITUKI Plc., H-1095, Budapest, Kvassay J. u.1, Hungary*

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Abstract—Methyl-1-phenylethylamines were resolved by phenylethylamine derivatives formed with a homologous series of dicarboxylic acids. The structure of the 4-methyl-1-phenylethylamine *N*-(1-phenylethylamine) succinic acid monoamide diastereoisomeric salt was investigated by single crystal X-ray diffraction.

1. Introduction

Separation of the diastereoisomeric salts of a given compound is the leading method for resolution.[1–3] A special case is the resolution by its own derivative: the resolving agent is manufactured from one of the enantiomers of the target compound to give the derivative of opposite acid–base characteristics. Although this is quite a promising method, which makes use of the undesired enantiomer, only a few examples are known from literature.[4–7]

In a recent paper[8] we reported the optical resolution of 1-phenylethylamine by its acidic derivatives formed by the homologous series of three dicarboxylic acids: oxalic, malonic and succinic acid.

Herein we report on how this phenomenon can be applied on a wider scope. The above described three resolving agents are suitable for studying how some structural differences in the resolving agents influence the outcome of the resolution process.

The methylated phenylethylamines have been selected for the resolution studies, as this allows towards investigations of the model compound structure as well. Also, economical considerations come into the picture: an expensive racemate could in this way be resolved by a cost-effective resolving agent.

2. Results and discussion

2.1. Resolution and enantiomeric enrichment

The resolving agents were synthesized by known method.[8] The optical resolution was carried out by applying the resolving agent in equivalent quantity. In each case resolution by the (*R*)-monoamide yielded (*S*)-methylphenylethylamine. That is, the (*S*,*R*)-diastereoisomeric salt is more stable than the (*R*,*R*)-diastereoisomer, which indicates molecular compound-like behaviour of the diastereoisomeric mixture—as in the case of molecular compounds heterochiral interactions, are usually stronger than homochiral ones.

The resolution process can be seen in Figure 1.

The resulting diastereoisomeric salts were enriched in one diastereomer by recrystallization. The resolution

* Corresponding author. Tel.: +36 1 4631884; fax: +36 1 4633648; e-mail: egrig@ella.hu

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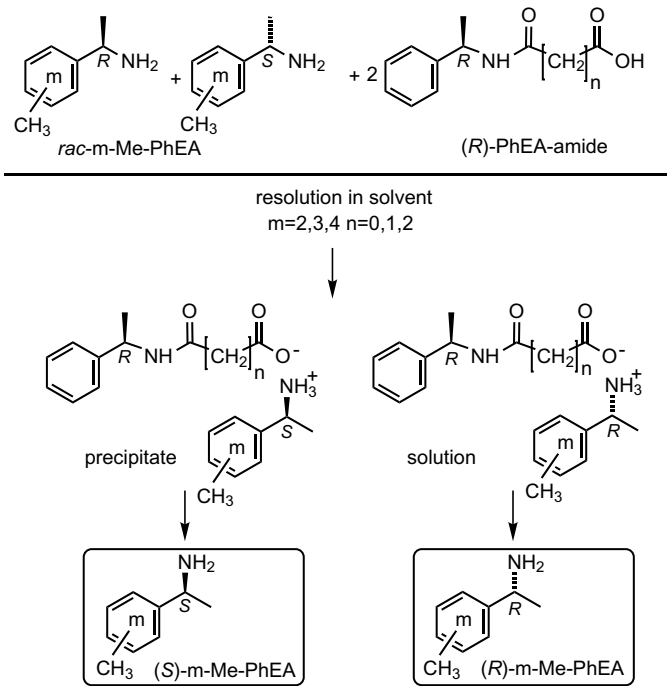


Figure 1. Resolution of methyl-phenylethylamines by α-phenylethylamine monoamides.

and enrichment results (compared to the resolution of underivatized α-phenylethylamine) are summarized in Table 1.

Of the nine possible combinations, the empty cells in Table 1 (4) show that in some cases it was not possible to find suitable conditions for crystallization. In the five crystal-resulting combinations one gave poor enantiomeric excess, but in four cases the yields were satisfactory and enantiomeric excesses were high.

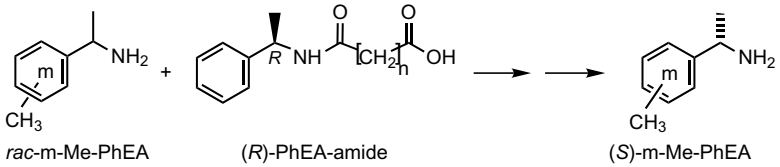
This deviation (cp. first line, PhEA[8]) probably indicates the structural difference between the methyl-phenylethylamines and the underivatized α-phenylethylamine. Obviously a small structural difference (methyl group in different positions) can influence the experimental outcome at great extent. However, it was possible to find a resolving agent for each of the target racemates with satisfactory yield (36–55%) and high enantiomeric excess (98–100%).

2.2. X-ray crystallography

For a better interpretation of the resolution results, single crystal X-ray structure determinations were undertaken for (*S*)-4-methyl-PhEA·(*R*)-PhEA-succinamic acid. Unfortunately the crystals of the other salts were not suitable for single crystal X-ray diffraction experiments, but this structure is itself interesting and can be compared to (*S*)- and (*R*)-PhEA·(*R*)-PhEA-oxalamic acid[8] diastereoisomeric salts.

The crystal structure of (*S*)-4′-methyl-1-phenylethylamine (*R*)-1-phenylethylamine succinic acid monoamide

Table 1. Resolution of methyl-phenylethylamines by phenylethylamine monoamides



Base/resolving agent	(*R*)-PhEA-oxalamic acid (*n* = 0)		(*R*)-PhEA-malonamic acid (*n* = 1)		(*R*)-PhEA-succinamic acid (*n* = 2)	
	Y [%]	Ee[c] [%]	Y [%]	Ee[c] [%]	Y [%]	Ee[c] [%]
PhEA[a,b]	38	98	56	99	61	100
2-Methyl-PhEA (*m* = 2)	46	98	—	—	76	19
3-Methyl-PhEA (*m* = 3)	—	—	—	—	54	99
4-Methyl-PhEA (*m* = 4)	—	—	55	100	36	100

[a] PhEA = α-phenylethylamine.
[b] See lit. 8.
[c] Enantiomeric excesses have been measured by chiral GC.

salt was determined by single crystal X-ray diffraction. Its absolute configuration has been established based on the known absolute configuration of the used 1-phenylethylamine succinic acid monoamide, that is, (*R*).

In Figure 2 we present the configuration and the conformation of the cation and the anion. The conformation of the amide along the N2–C20 bond resembles that in the crystal structure of (*S*)-1-phenylethylamine-(*R*)-1-phenylethylamine oxalic acid monoamide salt,[8] which was found to be quite different from its diastereomeric salt.

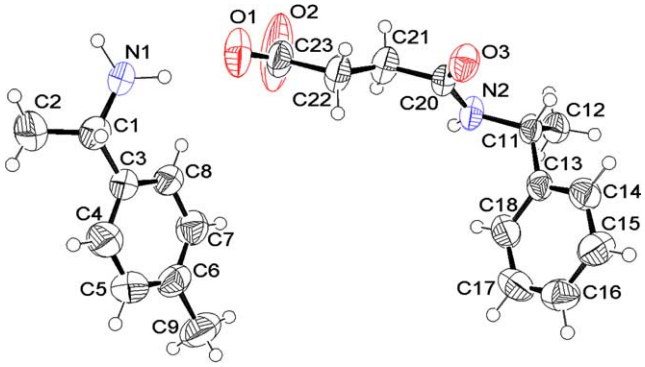


Figure 2. Molecular structure of (*S*)-4′-methyl-1-phenylethylamine (*R*)-1-phenylethylamine succinic acid monoamide salt.

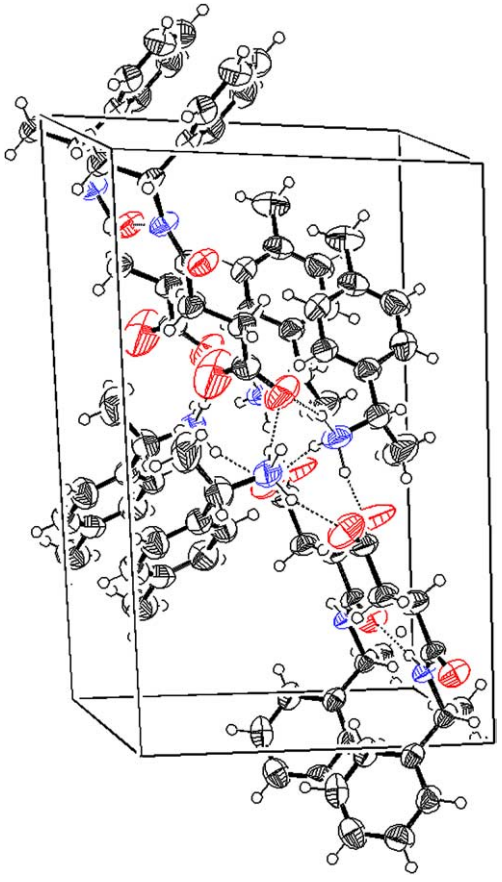


Figure 3. Hydrogen bonds and packing in the crystal structure of (*S*)-4′-methyl-1-phenylethylamine (*R*)-1-phenylethylamine succinic acid monoamide salt.

The hydrogen bond pattern shown in Figure 3 is quite different from that found in the oxalic acid analogues mentioned above. No intramolecular N–H···O hydrogen bond was observed, instead the amide N–H is hydrogen bonded to the O3 atom of another amide group related by translational symmetry along the **b** axis.

The three H atoms of the ammonium group form hydrogen bonds to the carboxylate oxygen atoms of three different molecules, with O1 being acceptor for two different hydrogen bonds. Two of the anions hydrogen bonded to the same ammonium group are also hydrogen bonded by the amide N–H···O (amide) hydrogen bond as described above. The third anion bonded to the same ammonium group is related by a 2-fold screw axis to the other two anions. The three hydrogen bonds connecting the ammonium groups with the carboxylate groups form two types of 10-membered rings, with four hydrogen bonds between two donor and three acceptor atoms.

3. Conclusion

An extended applicability of the 'resolution by similar structures' has been investigated. We found that all of the target compounds could be resolved by an α-phenylethylamine monoamide; however, it was not the same monoamide working for all the target amines. These results show that it can be worth searching not only just among identical structures but also similar ones. An economical aspect has been added in our case: expensive target racemates (methyl-phenylethylamines) were separated by a resolving agent made from α-phenylethylamine, an inexpensive and easily available chemical. The applicability of this method for other PhEA and naphthylethylamine derivatives is currently under investigation.

4. Experimental

4.1. Materials and methods

Optical rotations were determined on a Perkin–Elmer 241 polarimeter. Chemicals were purchased from Aldrich. All solvents used were freshly distilled. GC analyses were done on Hewlett–Packard 5890/II instrument equipped with FID at 120 °C. Column was a 20 m × 0.200 mm I.D. fused silica tubing, coated with ChNEB (naphthylethylamide chiral group containing silicone polymer[xy]) stationary phase at 0.2 μm film thickness. Carrier gas was H_2 with 1:100 split ratio. Samples were derivatized with trifluoroacetyl anhydride according to standard procedures.[9,10] Methyl-phenylethylamines were synthesized from the corresponding acetophenones by a known method.[11]

4.2. Resolution of 4-methyl-phenylethylamine by (*R*)-*N*-(1-phenylethyl)-succinamic acid

Racemic 4-methyl-phenylethylamine (6.80 g, 50 mmol) and *N*-(1-(*R*)-phenylethyl)-succinamic acid (11.1 g, 50 mmol) dissolved in hot acetone (30 mL), were seeded[12] and left to crystallize overnight. The crystals were filtered, washed by ethyl acetate (3 × 3 mL) and

dried: 7.38 g; after two recrystallizations from acetone (55 and 35 mL): 3.54 g (39.5%), $[\alpha]_D^{20} = +50.3$ (*c* 1, methanol), mp: 138–140 °C. The diastereoisomeric salt was dissolved in water (6 mL), 20% HCl (3 mL) added and the mixture washed by dichloromethane (3 × 10 ml). To the aqueous phase, NaOH (1.5 g) was added and extracted by dichloromethane (4 × 10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent evaporated, yielding (*S*)-4-methyl-phenylethylamine: 1.23 g (36.2%) of oil, $[\alpha]_D^{20} = -28.6$ (*c* 2.5, methanol).

4.3. The other resolutions

Here the other resolutions are summarized in brief. All resolutions were carried out by 50 mmol of base. Solvent, yield, specific rotation and melting point of the pure diastereoisomeric salts are given in brackets. Table 1 contains the data of the bases isolated from the below salts.

- (*S*)-2-Methyl-PhEA·(*R*)-PhEA-oxalamic acid: 20 mL of acetone, recryst. from 70 and 60 mL of acetone, yield 52.8%, $[\alpha]_D^{20} = +76.4$ (*c* 1, methanol), mp: 147–150 °C;
- (*S*)-2-Methyl-PhEA·(*R*)-PhEA-succinamic acid: 40 mL of acetone, yield 82.1%, $[\alpha]_D^{20}$ -, mp: - (not isolated in pure form);
- (*S*)-3-Methyl-PhEA·(*R*)-PhEA-succinamic acid: 34 mL of acetone, recryst. from 90 mL of acetone, yield 59.9%, $[\alpha]_D^{20} = +42.4$ (*c* 1, methanol), mp: 138–141 °C;
- (*S*)-4-Methyl-PhEA·(*R*)-PhEA-malonamic acid: 34 mL of ethyl acetate, recryst. from 20 mL of acetone, yield 59.9%, $[\alpha]_D^{20} = +45.9$ (*c* 1, methanol), mp: 128–131 °C;
- (*S*)-4-Methyl-PhEA·(*R*)-PhEA-succinamic acid: 30 mL of acetone, recryst. from 55 and 35 mL of acetone, yield 39.5%, $[\alpha]_D^{20} = +50.3$ (*c* 1, methanol), mp: 138–140 °C.

4.4. X-ray crystallography

Single crystals were picked from the resolution mixture.

A crystal of (*S*)-4′-methyl-1-phenylethylamine (*R*)-1-phenylethylamine succinic acid monoamide salt was mounted on a glass fibre. Cell parameters were determined by least squares of the setting angles of 25 ($25.44° \leqslant 2\theta \leqslant 47.96°$) reflections.

Crystal data, experimental and refinement details. CCDC No. 250449. Empirical formula: $C_9H_{14}N^+ C_{12}H_{14}NO_3^-$, formula weight: 356.45, colourless, block crystals, size: 0.25 × 0.20 × 0.50 mm, crystal system: monoclinic, space group $P2_1$, unit cell dimensions: $a = 11.197(2)$ Å, $b = 5.163(3)$ Å, $c = 17.2836(12)$ Å, $\beta = 99.250(9)°$, $V = 986.1(6)$ Å^3, $T = 293(2)$ K, $Z = 2$, $F(000) = 384$, $D_x = 1.201$ Mg/m^3, $\mu = 0.642$ mm^{-1}.

Intensity data were collected on a Rigaku AFC6S diffractometer (graphite monochromator; CuKα radiation, $\lambda = 1.54178$ Å) at 293(2) K in the range $2.59° \leqslant \theta \leqslant 62.55°$ using $\omega/2\theta$ scans. Backgrounds were measured 1/2 the total time of the peak scans. The intensities of three standard reflections were monitored regularly (every 150 refl.). No decay correction had to be applied.

A total of 3341 reflections were collected of which 2779 were unique [R(int) = 0.034, $R(\sigma) = 0.053$].

The initial structure model was obtained by direct methods.[13]

Anisotropic full-matrix least-squares refinement on F^2 for all nonhydrogen atoms yielded $R_1 = 0.0528$ and $wR_2 = 0.1407$ for 1872 [$I > 2\sigma(I)$] and $R_1 = 0.0957$ and $wR_2 = 0.1690$ for all (2779) intensity data (number of parameters = 244, goodness-of-fit = 1.068, absolute structure parameter $x = 0.3(6)$, the maximum and mean shift/esd is 0.001 and 0.000).

The maximum and minimum residual electron density in the final difference map was 0.273 and −0.215 e Å^{-3} (the applied weighting scheme was $w = 1/[\sigma^2(F_o^2) + (0.0831P)^2 + 0.3044P]$ where $P = (F_o^2 + 2F_c^2)/3$).[14]

Hydrogen atomic positions were calculated from assumed geometries except those of the ammonium group, which were located in difference maps. Hydrogen atoms were included in structure factor calculations but were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the U(eq) value of the atom they were bonded to.

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