



Resolution of Racemic 1,3-disubstituted Propanols by (R,R)-Di-(4-toluoyl)-tartaric Acid: Similar Conditions for Similar Structures

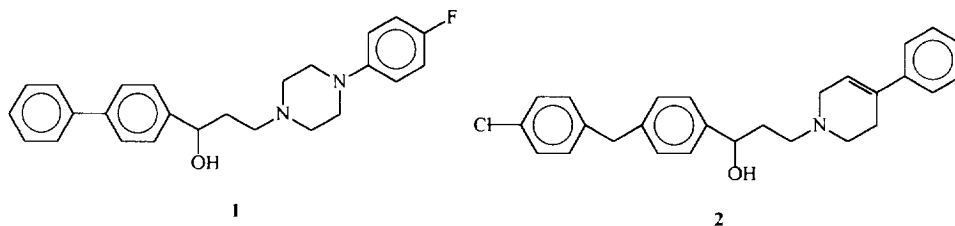
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Abstract: The resolution of structurally similar (\pm)-1-[4-(4-chlorobenzyl)-phenyl]-3-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)-1-propanol and (\pm)-1-(1,1'-biphenyl-4-yl)-3-[4-(4-fluorophenyl)-piperazin-1-yl]-1-propanol was accomplished by (R,R)-di-(4-toluoyl)-tartaric acid in methanol. The experiments illustrate the possibilities for selecting the resolving agent for a racemate which is available in insufficient quantity by making the trial experiments on a structurally similar racemates. Copyright © 1996 Elsevier Science Ltd

The resolving agent for the resolution via diastereoisomeric salt formation is still selected by trial and error method¹, since neither the physico-chemical² nor the computational³ selection can be generally applied. The trial and error method -depending on the success of the experiments- requires at least 3-10 g of racemates. Recently we faced the problem, how we can develop a preparative scale resolution having only about 0.5 g racemate available. The compound to be resolved was the (\pm)-1-(1,1'-biphenyl-4-yl)-3-[4-(4-fluorophenyl)-piperazin-1-yl]-1-propanol (\pm)-1, which during pharmacological investigations proved to be a potent atypical antipsychotic agent⁴. The optically active form of the compound was not known.



Since it was obvious that this small amount of racemate is not enough for the series of trial experiments for selecting the resolving agent and the solvent, we decided to make the trial experiments on a structurally related compound, which is available in substantial amounts. The (\pm)-1-[4-(4-chlorobenzyl)-phenyl]-3-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)-1-propanol (\pm)-2⁵ was selected since the centre of both molecules are practically identical. For the resolution of **2** tartaric acid, R,R-dibenzoyl-tartaric acid, (R,R)-di-(4-toluoyl)-tartaric acid (**DTTA**), mandelic acid, malic acid, camphor-10-sulphonic acid was tested in water, methanol, ethanol, ethylacetate. We found that the **DTTA** provides the most efficient resolution⁶ by using methanol as solvent⁷. Under the optimal conditions found for **2**, **1** was easily resolved for the first attempt.⁸ The efficiency of the separation was practically the same for both resolution ($S=0.77$ for **1** and $S=0.74$ for **2**).

It was already known, that a homologous series of racemates may be resolved by the same resolving agent.¹⁰ Our experiments illustrate the possibility of extending this concept for selecting the resolving agent, for a racemate available in insufficient quantity by making the trial experiments on a structurally similar racemates.

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References and Notes

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- 6.) The efficiency ($0 < S < 1$) of the resolution has been defined as the product of the enantiomeric excess ($0 < OP < 1$) and the yield ($0 < Y < 1$) of the precipitated salt: $S = OP \times Y$.^{3a}
- 7.) Resolution of (\pm)-2: 3.50 g (0.00837 mol) of (\pm)-2 and 3.38 g (0.00837 mol) of (R,R)-di-(4-toluoyl)-tartaric acid monohydrate were dissolved in 120 ml of methanol by heating. Then the reaction mixture was allowed to stand at 5 °C for two days. The crystalline product was filtered off and washed with 2x2 ml of methanol. Yield: 3.4 g (100%). The product was dissolved in 10 ml of 2N sodium hydroxide solution, and the mixture was extracted with 3x20 ml of dichloromethane. The organic layer was evaporated. Yield: 1.75 g (100%); $[\alpha]_D^{20} = +20.3^{\circ}$ (c=1, methanol). The product was recrystallized from 110 ml of isopropanol. Yield: 0.7 g (40%) (+)-2; mp: 100-101 °C; $[\alpha]_D^{20} = +26.5$ (c= 1, methanol).⁹ The filtrate containing the diastereomeric salt was evaporated. To the residue, 10 ml of 2 N sodium hydroxide solution was added. The mixture was extracted with 3x20 ml of dichloromethane. The organic layer was evaporated. Yield: 1.7 g (97%); $[\alpha]_D^{20} = -20^{\circ}$ (c=1 methanol). The product was recrystallized from isopropanol. Yield: 0.7 g (40%) of (-)-2; mp: 98-101 °C; $[\alpha]_D^{20} = -26$ (c=1 methanol).
- 8.) The resolution of (\pm)-1 were accomplished similarly except 0.48 g (0.00125 mol) (\pm)-1 racemate were resolved in 40 ml of methanol. Yield: 0.18 g (74.2%) (-)-1; mp: 163-164 °C; $[\alpha]_D^{20} = -31$ (c=1 methanol).⁹ The other enantiomer separated from the mother liquor Yield: 0.21 g (87.7%) (+)-1; mp: 160-4 °C; $[\alpha]_D^{20} = +30$ (c=1 methanol). The optical rotations were measured on a Perkin Elmer 241 polarimeter.
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