

# Optical Resolution of N-methylamphetamine Via Diastereoisomeric Salt Formation With 2R,3R-O,O'-Di-p-toluoyltartaric Acid

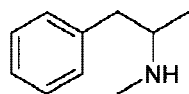
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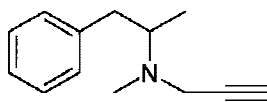
**ABSTRACT** Racemic N-methylamphetamine can be resolved by O,O'-di-p-toluoyltartaric acid in methanol either by the classic Pasteurian method by fractional crystallization of the neutral diastereoisomeric salt pair (molar ratio of the base:acid 2:1) or by the Marckwald or the Pope-Peachey method by fractional crystallization of the enantiomer (or its hydrochloride) from the diastereoisomeric salt (molar ratio of the base:acid 4:1). The optical purity of the precipitated salt could be increased slightly by performing the resolution in a water-water immiscible solvent system (water-dichloroethane). We found that the O,O'-Di-p-toluoyltartaric acid forms exclusively neutral salts with the N-methylamphetamine. This resolution may have practical application because the efficiency of the resolution is in the same range as with tartaric acid but only 0.25 molar equivalent of resolving agent is required for the resolution of 1 mol base. Chirality 11:373–375, 1999. © 1999 Wiley-Liss, Inc.

**KEY WORDS:** enantiomer separation; neutral salt; acidic salt; tartrate; efficiency of the resolution

N-Methylamphetamine is the key intermediate of some chiral drugs, for example Jumex® the antiparkinson agent.



N-methyl-amphetamine



Jumex<sup>R</sup>

On the industrial scale, the optically active forms of N-methylamphetamine are prepared by optical resolution via diastereoisomeric salt formation with tartaric acid or with O,O'-dibenzoyltartaric acid.<sup>1,2</sup>

In a recent study, we investigated the optical resolution of racemic N-methylamphetamine by distillation after partial salt formation with several chiral acids.<sup>3</sup> We found that despite the fact that tartaric acid is the most effective resolving agent for N-methylamphetamine by fractional crystallization, distillation results in no enantiomer separation. The two O-acyl derivatives of the tartaric acid, O,O'-dibenzoyl- and O,O'-di-p-toluoyl-tartaric acid gave efficient resolution by this method. Because the optical resolution of N-methylamphetamine with O,O'-di-p-toluoyltartaric by fractional crystallization had not been reported, we decided to investigate this resolution process in detail.

## EXPERIMENTAL

All the chemicals were purchased from Merck. The specific rotations were measured on a Perkin Elmer 241 po-

larimeter. The specific rotation of the optically pure (R)-N-methylamphetamine is  $[\alpha]_D^{20} = -18.90$  ( $c = 1$ ; 1N HCl).

### General Procedure for Optical Resolution of N-methylamphetamine by O,O'-Di-p-toluoyltartaric Acid

3.0 g (0.02 mol) N-methylamphetamine was dissolved in half of the solvent and mixed at room temperature with given amount of O,O'-di-p-toluoyltartaric acid dissolved in the other half of the solvent. (In the third experiment cHCl was added to the cooled solution of N-methylamphetamine, before adding the solution of the resolving agent.) The mixture was stirred at room temperature for 30 min while the precipitation started. The mixture was stored at 10°C for 2 h without stirring and then was filtered. The salt was dried in air; the mother liquor was evaporated to dryness in vacuum. Both fractions were reacted by 15 ml 2N NaOH and extracted three times with 25 ml of dichloromethane. After drying over MgSO<sub>4</sub>, the solvent was evaporated and the specific rotation was measured.

The results of the experiments are summarised in Table 1.

## RESULTS AND DISCUSSION

The optical resolution via diastereoisomeric salt formation usually is accomplished three different ways.<sup>4</sup> During

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TABLE 1. Summary of the experimental results\*

Exp. No.	Molar ratio B:A:HCl	Amount of resolving agent g	Solvent (ml)	Y <sub>(P salt)</sub> g	Y <sub>(P)</sub> g (%)	OP <sub>(P)</sub> [α] <sub>D</sub> <sup>20</sup> (%)	S	Y <sub>(ML)</sub> g (%)	OP <sub>(ML)</sub> [α] <sub>D</sub> <sup>20</sup> (%)
1	4:1:0	1.9	Methanol (10)	2.4	1.1 (73)	-14.9 (78.8)	0.575	1.7 (113)	+8.0 (42.3)
2	2:1:0	3.9	Methanol (10)	3.6	1.5 (100)	-11.5 (60.9)	0.609	1.2 (80)	+11.6 (61.4)
3	4:1:2	1.9	Methanol (8); ccHCl (0.84)	2.2	1.0 (67)	-13.0 (68.8)	0.461	1.8 (120)	+6.7 (35.5)
4	4:1:0	1.9	ClC <sub>2</sub> H <sub>4</sub> Cl (12); water (3)	2.4	1.1 (73)	-15.5 (82.0)	0.599	1.6 (107)	+10.1 (53.4)

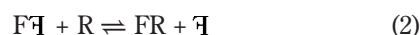
\*Values measured of the base liberated from precipitated salts (P), from the mother liquor (ML).

the classic Pasteurian resolution, 1 mol racemate is reacted with 1 mol resolving agent (Eq. 1).

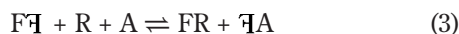


$\mathfrak{I}$  and F represent the enantiomer of the racemate R represent the resolving agent.

The use of nonstoichiometric amounts (0.5 mol) of resolving agent is called the Marckwald method (Eq. 2).



When solubility problems occur during the use of the Marckwald method, an achiral salt of the unreacted enantiomer can be formed. This is the Pope-Peachy method (Eq. 3).



O,O'-Di-p-toluoyltartaric acid is able to form either acidic or neutral salts because like the tartaric acid it also has two carboxylic groups. This makes several molar ratios possible for the resolution. In Table 2 the most obvious possibilities are summarised.

From Table 2 it can be seen that resolution is not possible when the diastereoisomeric salts form a 1:1 molecular compound. By formation of an eutectic mixture, the resolution is theoretically possible in all cases.<sup>5</sup> At a 1:1 molar ratio an efficient separation is not likely, because one of the diastereoisomeric salts must be separated from both the mixture of the free acid and the other diastereoisomeric salt.

In case of eutectic mixture forming acidic salts at a 1:4 molar ratio the efficiency of the resolution is limited, while either the optically active acidic salt is separated by maximum 50% yield or the unreacted enantiomer with a maximum of 33% optical purity.

Theoretically, optical resolution with 100% can be expected in cases of acidic salt formation at 1:1 or 1:2 or in the case of neutral salt formation, at 1:2 or 1:4 molar ratio. The Marckwald method can be more effective than the Pasteurian method, since the physicochemical differences between an enantiomer and the salt of the enantiomer with the resolving agent are larger than between a diastereoisomeric salt pair. Based on these considerations, we selected 1:2 and 1:4 molar ratios for the resolution by the Marck-

wald method, the former for resolution if acidic salt formation took place, the latter for neutral salt formation.

As a first choice of solvent, methanol proved to be a suitable solvent. In both experiments the diastereoisomeric salts precipitated readily. The resolution results are summarised in Table 1.

The yield of the precipitate in the case of 1:2 molar ratio was quantitative, but the optical purity of the precipitated salt was about 20% lower than in the case of 1:4 molar ratio when the yield was lower.

Considering the experimental error, the efficiency of the two resolutions were practically equal. [The efficiency ( $0 < S < 1$ ) of the optical resolution has been defined as the product of the optical purity ( $0 < OP < 1$ ) and the yield ( $0 < Y < 1$ ) of the precipitated salt:  $S = OP \times Y$ .]<sup>6</sup> From the material balance it is obvious that in both cases neutral salts are formed. The resolution with 1:2 molar ratio was Pasteurian, while with 1:4 molar ratio it was a Marckwald type resolution. These results were in accordance with our expectations, since the Marckwald method resulted in the highest optical purity.

The Pope-Peachy method was also applied, using hydrochloric acid as achiral salt forming agent in 0.5 molar equivalent amount. Not only the yield but also the optical purity of the precipitated neutral salt was lower than in case of the Marckwald method.

We tried to increase the efficiency of the resolution by using a water-dichloroethane solvent mixture, since according to our experience during optical resolutions by the Marckwald method in water-water immiscible organic solvent mixtures, usually the diastereoisomeric salt with higher optical purity precipitates.<sup>7</sup>

We obtained really the highest optical purity by this method, but the increase was not substantial and the efficiency of the resolution was only slightly higher than in methanol.

## CONCLUSIONS

Tartaric acid forms only acidic salts with N-methylamphetamine. From crystallographical studies, it is known that the crystal structure of the diastereoisomeric salt is dominated by hydrogen tartrate chains.<sup>8</sup> We found that O,O'-di-p-toluoyltartaric acid forms neutral salts exclusively with N-methylamphetamine.

TABLE 2. Resolution possibilities by reacting a chiral dicarboxylic acid with a racemic base\*

	Molar ratio (acid:base)					
	1:1			1:2		
	Diastereoisomeric salt	Racemic enantiomer	Active enantiomer	Diastereoisomeric salt	Racemic enantiomer	Active enantiomer
Acidic salt formation eutectic mixture	$\begin{bmatrix} B \\ B \end{bmatrix} \begin{bmatrix} A \\ A \end{bmatrix}$	—	—	$\begin{bmatrix} B \\ B \end{bmatrix} \begin{bmatrix} B \\ B \end{bmatrix}$	—	2 <b>B</b>
1:1 molecular compound		—	—		<b>B</b> B	—
Neutral salt formation eutectic mixture	$\begin{bmatrix} B \\ 1/2 B \end{bmatrix} \begin{bmatrix} B \\ 1/2 B \end{bmatrix}$	—	—	$\begin{bmatrix} B \\ B \end{bmatrix} \begin{bmatrix} B \\ B \end{bmatrix}$	—	—
1:1 molecular compound	$\begin{bmatrix} B \\ B \end{bmatrix} \begin{bmatrix} B \\ B \end{bmatrix}$	—	—	$\begin{bmatrix} B \\ B \end{bmatrix} \begin{bmatrix} B \\ B \end{bmatrix}$	—	—

\***B** and B represents the enantiomers of the base, [ represents the optically active chiral dicarboxylic acid.

In case of neutral salt formation there is no possibility for hydrogen tartrate chain formation, from which we can conclude that, despite the structural similarity of the two resolving agents, the mechanism of the resolution must be completely different.

This resolution may have practical application because the efficiency of the resolution is in the same range as with tartaric acid but only 0.25 molar equivalent amount of resolving agent is required for the resolution of 1 mol base.

#### ACKNOWLEDGMENTS

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