# Procedures for the Resolution of Racemic Amphetamines

[ Back to the Chemistry Archive ]

#### Methamphetamine Optical Resolution by Distillation After Partial Diastereoisomeric Salt Formation

Solvent-free optical resolution of N-methylamphetamine was developed by distillation after partial diastereoisomeric salt formation.

From the 18 chiral acids tested by this method, five provide by this method resolution: O,O'-dibenzoyltartaric acid, O,O'-di-p-toluoyltartaric acid, 6-methoxy-*alpha*-methyl-2-naphthaleneacetic acid (Naproxen), the cis-permetrinic acid, and the 2-phenoxypropionic acid. Among them the O,O'-dibenzoyltartaric acid in water-free form provided the more effective resolution. The efficiency of this resolution S = 0.74 is in the range of the industrial-scale resolutions and not worse than the efficiency achieved by optical resolution via fractional crystallization.

Chirality 13, 428-430 (2001).

#### FEATURE ARTICLE:

#### Dutch Resolution: Separation of Enantiomers with Families of Resolving Agents. A Status Report

*Richard M. Kellogg et. al.* Synthesis (10), 1626-1638 (2003) **DOI:** <u>10.1055/s-2003-40508</u>

#### Abstract

Dutch Resolution is the term given to the use of mixtures (families) of resolving agents in classical resolutions. In this status report an overview is given of the latest results and new (possible) families of resolving agents are introduced. The concept of families is discussed as well as the factors that come into play on use of families. Practical aspects of Dutch Resolution in particular and resolutions in general are discussed.

## **Resolution of racemic Amphetamine**

My invention relates to a novel method for the separation of the optically active isomers of amphetamine and it compromises methods wherein the laevo and dextro isomers, in the form of their neutral salts with d-tartaric acid, are separated by the fractional crystallisation from an alcohol solution of such salts, the neutral d-tartrate of the laevo amine being obtained as a crystalline material, and it more particularly relates to the separation of the laevo-isomer, in the form of its neutral salt with d-tartaric acid, and the recovery of the laevo amine, as free base, from such neutral salt; all as more fully hereinafter set forth and as claimed.

It is known in the art (Ber. D. Chem. Gesell. (1932) p664) that d-amphetamine d-bitartrate may be obtained as a crystalline acid tartrate, from the racemic (- methylphenethylamine, by reacting the racemic amine with sufficient d-tartaric acid to form a mixture of the tartrates of the d- and I- amine and then fractionally crystallising the bitartrate of the d-amine from an alcohol solution of the mixture of acid tartrates so obtained. To obtain the d-amine as the free base, the acid tartrate may be decomposed with caustic alkali and the free base recovered by distillation in vacuo. By using I-tartaric acid in such method, the I-amphetamine I-bitartrate is obtained as a crystalline material by fractional crystallisation. This acid tartrate may likewise be decomposed with alkali to obtain the I-amine as a free base.

That is, either dextro or laevo -amphetamine have been previously obtained from the racemic form by certain known prior methods. But in such prior methods, the separation of the desired isomer is effected by the fractional crystallisation of acid tartrates. And in those methods, d-tartaric acid is used to obtain the dextro amine and I-tartaric acid to prepare the laevo amine. However while those processes are operable chemically, they have serious disadvantages, particularly with regard to the separation of I-amphetamine by means of d-tartaric acid, in that while d-tartaric acid is readily available and comparatively cheap, I-tartaric acid at the present time is both difficult to obtain and expensive in pure form (d tartaric acid comes from fruit, I-tartaric acid is 'unnatural'). Thus by the method outlined above d-amphetamine may be readily and cheaply prepared while the laevo form can only be obtained at great expense.

I have discovered a method whereby both optically active forms of amphetamine, and especially the laevo form may be prepared by the use of d-tartaric acid alone. This novel method greatly simplifies the process and makes the

therapeutically useful isomers readily available.

Broadly, the method according to this invention comprises the separation of I-amphetamine from dI-amphetamine by treatment with d-tartaric acid for the production of a mixture of neutral d-tartrates and crystallisation from a solution, it having been found that I-amphetamine may be readily separated by crystallisation from a solution of the neutral d-tartrates.

The method according to this invention may be applied to, for example, racemic amphetamine, or to any mixture of the optically active isomers thereof in which the laevo form is present in amount not substantially less than the dextro form.

Again, the method according to this invention is applicable to mixtures rich in the laevo form, such as result from initial separation of the dextro form by methods heretofore known, as, for example, by crystallisation from a solution of a mixture of acid d-tartrates.

Where it is desired to effect separation of the laevo form from a mixture a mixture rich in the dextro form, it will usually be necessary to first effect separation of a part of the dextro form by methods heretofore known and then to apply the method in accordance with this invention to the remaining mixture.

As will be appreciated, the method in accordance with this invention, while primarily of the greatest advantage for effecting separation of I-(-methylphenethylamine, provides also procedure for the separation of d-amphetamine.

As more specifically illustrative of the method in accordance with this invention for the separation of the l-enantiomorph form, for example, racemic amphetamine, by the use of d-tartaric acid alone and with separation also of d-amphetamine, the following procedure may be employed and will be found to be efficient.

Two mols, for example, 270 grams, of racemic amphetamine base are reacted with one mol (150 grams) of d-tartaric acid, thereby forming a dl-amphetamine d-tartrate, a neutral salt. The neutral salt thus obtained is fully dissolved by the addition of sufficient, say about 1 litre, of absolute ethanol, and heating to about boiling point. The solution is then allowed to cool to room temperature with occasional stirring to effect crystallisation. The crystals are filtered off and will be found to contain a preponderance of the laevo enantiomorph. On recrystallisation the preponderance of the l-enantiomorph is increased and the process is repeated until no further change in optical rotation is effected and a reading of [(]20(D = -6.5 is obtained in a concentration of 8 grams per 100 cc of aqueous solution. The product thus obtained is l-amphetamine d-tartrate. The residual solid in the mother liquors is repeatedly and systematically crystallised, yielding a further fraction of l-amphetamine d-tartrate which may be purified by recrystallization. d-amphetamine may be readily recovered from the mother liquors by the addition of tartaric acid thereto for the formation of acid tartrates and separation of d-amphetamine d-bitartrate by crystallisation.

The free base of either optically active isomer may be obtained by addition to the d-tartrate in the case of the laevo isomer and the d-bitartrate in the case of the dextro isomer of alkali in excess, as for example, by the addition of an aqueous solution of caustic soda, which will cause the base to separate as an oil which may be recovered and purified by any well known procedure.

As a further example, one mol of racemic amphetamine base is reacted with 1.2 mols of tartaric acid and the resulting bitartrate is dissolved in, for example, 80% ethanol, with heating almost to the boiling point. The solution is then allowed to cool to about 60(C and filtered hot. Repeated crystallisation is then carried out until crystals having an optical rotation  $[(]20(D = +30.8 \text{ are obtained in a concentration of 8 grams per 100cc of aqueous solution. The product thus obtained is pure d-amphetamine d-bitartrate. The residual solid in the mother liquors is repeatedly and systematically crystallised, yielding a further fraction of d-amphetamine d-bitartrate which may be purified by recrystallisation.$ 

The residual solid in the mother liquors now remaining comprises a preponderance of l-amphetamine d-bitartrate, which may now be separated by effecting neutralisation of the excess of d-tartaric acid present with production of neutral tartrates and effecting separation of the l-amphetamine d-tartrate by crystallisation.

Neutralisation of the excess tartaric acid may be effected where, as in the case of the example above, the mother liquors comprise alcoholic solutions by dividing the total volume of the mother liquors into equal parts, removing, for example, by evaporation, the alcohol from one part, adding excess alkali, liberating the free base, which, as has been indicated, separates as an oil, separating and drying the free base with for example, caustic potash and then adding the free base to the other portion of the mother liquors with heating to forma solution. Such procedure will result in the formation of a neutral d-tartrate solution. From the solution so formed I-amphetamine d-tartrate may be separated by repeated crystallisation and the free base may be recovered as described above.

Following the procedure in accordance with this invention, other salts of the optically active isomers may be obtained from the free bases of the isomers by exact neutralisation of either base, with an organic or inorganic acid corresponding to the salt desired. Thus, by way of example, any desired organic or inorganic salt of the optically active isomers, in addition to the tartrates initially obtained, as for example, sulphates, hydrochlorides, oleates, etc., may be obtained by exact neutralisation of either optically active base with the acid corresponding to the desired salt. Following the procedure according to this invention it will be apparent that the I-enantiomorph may be initially separated from the racemic amphetamine, or from any mixture of the optically active isomers in which the dextro form is not in substantial excess; and that following the separation of the laevo form the dextro form may be recovered from the mother liquors by the addition thereto of d-tartaric acid for the formation of acid d-tartrates and crystallisation.

Again, as will now be evident, where the I-amphetamine is to be separated from a mixture of the optically active isomers in which the dextro form is in substantial excess, or in preponderance, the dextro form will first be separated by crystallisation following treatment with d-tartaric acid to form d-bitartrates and the laevo form will then be recovered by crystallisation following neutralisation with the formation of neutral d-tartrates.

Thus, it will now be understood that the method in accordance with this invention comprises essentially the separation of I-amphetamine from a racemic amphetamine and from the various mixtures of d- and I-amphetamine in which the laevo form is present in amount not substantially less than the dextro form with the use of d-tartaric acid for the formation of neutral d-tartrates and separation of I-amphetamine d-tartrate by crystallisation, whether the procedure be for the initial separation of the I-amphetamine d-tartrate, as from racemic amphetamine, or a mixture in which the dextro form is not in substantial excess, or is preceded by preliminary separation of the dextro form by known methods, as in the case of mixtures in which the dextro form predominates.

It will be understood that proceeding in accordance with this invention the free base, I-amphetamine may be readily obtained from the I-amphetamine d-tartrate by treatment of the d-tartrate with alkali in excess, resulting in separation of the free base as an oil which may be recovered and purified by any well known method.

Reference: US patent 2,276,508

## **Resolution of racemic Methamphetamine**

85 parts of racemic methamphetamine are introduced into a solution of 100 parts of d-tartaric acid in 1000 parts of methyl alcohol. After protracted standing about 100 parts of the precipitated salt are aspirated off and extracted with hot ethyl alcohol. Since the d-tartrate of dextrorotary methamphetamine is readily soluble in both methyl and ethyl alcohol whereas the d-tartrate of levorotary methamphetamine is sparingly soluble both in methyl alcohol and hot ethyl alcohol an extremely simple separation of the d-tartrates of the optical antipodes of the base is effected.

Reference: British Patent 508,757

## **Resolution of racemic Amphetamine**

Two mols, for example, 270 grams, of racemic amphetamine base are reacted with one mol (150 grams) of d-tartaric acid, thereby forming dl-amphetamine d-tartrate, a neutral salt. The neutral salt thus obtained is fully dissolved by the addition of sufficient, say about 1 liter, of absolute ethanol, and heating to about the boiling point. The solution is then allowed to cool to room temperature with occasional stirring to effect crystallization. The crystals are filtered off and will be found to contain a preponderance of the levo enantiomorph.

The residual solid in the mother liquors is repeatedly and systematically crystallized, yielding a further fraction of amphetamine d-tartrate which may be purified by recrystallization. d-amphetamine may be readily recovered from the mother liquors by the addition of tartaric acid thereto for the formation of acid tartrates and separation of d-amphetamine d-bitartrate by crystallization.

The free base of either optical isomer may be obtained by addition to the d-tartrate in the case of the levo isomer and the d-bitartrate in the case of the dextro isomer of alkali in excess, as, for example, by the addition of an aqueous solution of caustic soda, which will cause the base to separate as an oil which may be recovered and purified by any well-known procedure. The base is exactly neutralized with sulfuric acid to give the sulfate.

#### References

- Merck Index 2918 PDR pp. 1450, 1711
- OCDS Vol. 1 p.70 (1977)
- I.N. p. 301
- REM p.881
- Nabenhauer, F.P.; U.S. Patent 2,276,508; March 17, 1942.

## Resolution of racemic Methamphetamine using selective extraction

The dextro isomer of amphetamine and methamphetamine is the d, (+), D or S isomer; the levo isomer is the I, (-), L or R isomer. The racemic mixtures may be referred to as d, I or (+,-) or DL or (R)(S). Classical resolution techniques are often tedious and usually afford poor yields. The best published procedure seems to be that of Rusznak et al. below which utilizes a selective extraction rather than the usual crystallization.

## Selective Extraction of d-Methamphetamine with d-Tartaric Acid:

Rusznak et al., Resolution of Phenylisopropylamines, Hung. Teljes, 12,208 (CI.C07B), 28 Sep. 1976, Appl. 1,516, 08 Nov. 1974; C.A. 85: 192337q, p. 518 (1976).

Phenylisopropylamines and phenylisopropylmethylamines and various substituted amines were resolved with 0.5 mole tartaric acid in benzene-water containing 0.5 mole sodium hydroxide or potassium hydroxide by selective extraction of either enantiomer.

A mixture of 0.1 mole (13.52 g.) phenylisopropylamine (or 14.92 g. methamphetamine base) in 60 ml benzene, 0.05 mole d-tartaric acid (7.50 g.) in 30 ml water, and 2 g sodium hydroxide (reagent grade or titrated equivalent) in 3 ml water was kept 4 hours with intermittent shaking, and the organic phase evaporated to give 98% L-phenylisopropylamine. The aqueous phase was extracted with benzene at pH 13 and evaporated to give 96% D-enantiomer.

## Selective Crystallization of Methamphetamine with d-Tartaric Acid:

Rusznak et al., Resolution of 1-Phenylisopropyl methyl amine, Hung. Teljes, 12,210 (Cl. C07B), 28 Sep. 1976, Appl. 1,520, 04 Dec. 1974; C.A. 85: 192335n, p. 518 (1976).

Phenylisopropylmethylamine was resolved by treatment with 0.4-6 moles of dextro tartaric acid in water or aqueous ethanol containing 0.4-6 moles hydrogen chloride.

A mixture of phenylisopropylmethylamine 150, d-tartaric acid 82.5, and H2O 330 g was treated with HCl to pH 4 to deposit 120 g L-phenylisopropylmethylamine-d-tartrate salt, which gave 88 g L-phenylisopropylmethylamine. The D-enantiomer (58 g as the HCl salt) was isolated from the filtrate.

## Resolution of racemic Methamphetamine using O,O-DibenzoyI-R,R-Tartaric Acid

Using O,O-Dibenzoyl-2R,3R-Tartaric Acid (made by acylating L(+)-tartaric acid with benzoyl chloride) in dichloroethane/methanol/water, racemic methamphetamine can be resolved in 80-95% yield, with an optical purity of 85-98%.

## Experimental

15.0g (100 mmol) of racemic methamphetamine freebase was dissolved in a mixture of 20ml dichloroethane and 15ml water. A solution of 9.4g (25 mmol) 0,0-Dibenzoyl-*2R*,*3R*-tartaric acid in 40ml of dichloroethane and methanol (see amounts below) was added to the two-phase solution during 30 minutes at room temp. From the stirred solution the crystallization starts in 10-15 minutes. The resulting suspension was stirred at 5°C overnight, then filtered. The precipitate was washed on the filter three times with 5°C dichloroethane and air dried under a heat lamp. The precipitated salt were dissolved in 30ml 2N NaOH and extracted with 3x25ml dichloromethane. After drying over MgSO4, filtering and evaporation of the solvent, the methamphetamine freebase was obtained, which can be dissolved in diethyl ether and bubbled with dry HCl gas to obtain the crystalline hydrochloride salt.

Using 3ml methanol in the above procedure gave d(+)-methamphetamine in 93% yield and 85% optical purity, and 18.8ml methanol gave 78% yield in 98% optical purity.

Reference: Synthetic Communications 29(24), 4315-4319 (1999)