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(54) Title: PROCESS FOR THE PREPARATION OF DEXMETHYLPHENIDATE HYDROCHLORIDE

(57) Abstract: The present invention provides a new and efficient process for the preparation of the dexamethylphenidate hydrochloride with high optical purity, the process comprising: (a) reacting a solution of *threo*-N-Boc-ritalinic acid with (*S*)-1-phenylethylamine, separating precipitated solid salt of (*R,R*)-enriched N-Boc-ritalinic acid with (*S*)-1-phenylethylamine from the reaction mixture and recrystallizing, reslurring and/or triturating of said salt; (b) mixing the solid salt of (*R,R*)-N-Boc-ritalinic acid and (*S*)-1-phenylethylamine obtained in step (a) with aqueous acid and separating (*R,R*)-N-Boc-ritalinic acid from the mixture; and (c) reacting the (*R,R*)-N-Boc-ritalinic acid prepared in step (b) with hydrogen chloride and methanol to give dexamethylphenidate hydrochloride with optical purity of at least 99% ee. The present invention further provides salt of (*R,R*)-N-Boc-ritalinic acid with (*S*)-1-phenylethylamine as new intermediate in the preparation of dexamethylphenidate hydrochloride.

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**PROCESS FOR THE PREPARATION OF  
DEXMETHYLPHENIDATE HYDROCHLORIDE**

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**FIELD OF THE INVENTION**

The present invention relates to a process for the preparation of  
10 dexmethylphenidate hydrochloride and to novel intermediates used in this  
process.

**LIST OF REFERENCES**

15 The following references are considered to be pertinent for the purpose of  
understanding the background of the present invention:

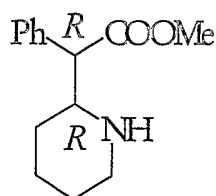
- J.A. Axten et al., *J. Org. Chem.*, 1998, v. 63, 9628-9 and Supporting Info.;
- E.J. Corey and A.M. Felix, *J. Am. Chem. Soc.*, 1965, v. 87, 2518-9;
- H.M. Deutsch et al., *J. Med. Chem.*, 1996, v. 39, 1201-9;
- 20 Y.-S. Ding et al., *Psychopharmacology*, 1997, v. 131, 71-8;
- R.H. Earle et al., *J. Chem. Soc. (C)*, 1969, 2093-8;
- L. Panizzon, *Helv. Chim. Acta*, 1944, v. 27, 1748-56;
- K. Patric et al., *J. Labelled Compd. Radiopharm.*, 1982, v. 19, 485-90;
- K.S. Patric et al., *J. Pharm. Exp. Therap.*, 1987, v. 241, 152-8;
- 25 M. Prashad et al., *Tetrahedron: Asymmetry*, 1998, v. 9, 2133-6;
- M. Prashad et al., *Tetrahedron: Asymmetry*, 1999, v. 10, 3479-82;
- M. Prashad et al., *Organic Process R&D*, 2000, v.4, 55-9;
- L. Szporny et al., *Biochem. Pharmacol.*, 1961, v. 8, 263-8;
- U.S. Patent No. 2,507,631;

- U.S. Patent No. 2,838,519;  
U.S. Patent No. 2,957,880;  
U.S. Patent No. 5,936,091;  
U.S. Patent No. 5,965,734;  
5 U.S. Patent No. 6,100,401;  
U.S. Patent No. 6,121,453;  
U.S. Patent No. 6,162,919;  
U.S. Patent No. 6,242,464;  
U.S. Patent Application No.2002/0019535  
10 WO 98/25902;  
WO 99/36403; and  
WO 01/27070.

## BACKGROUND OF THE INVENTION

15

Dexmethylphenidate, also known as *d-threo*-methylphenidate, (*R,R*)-methylphenidate or (*R,R*)- $\alpha$ -phenyl-2-piperidineacetic acid methyl ester, having the formula:



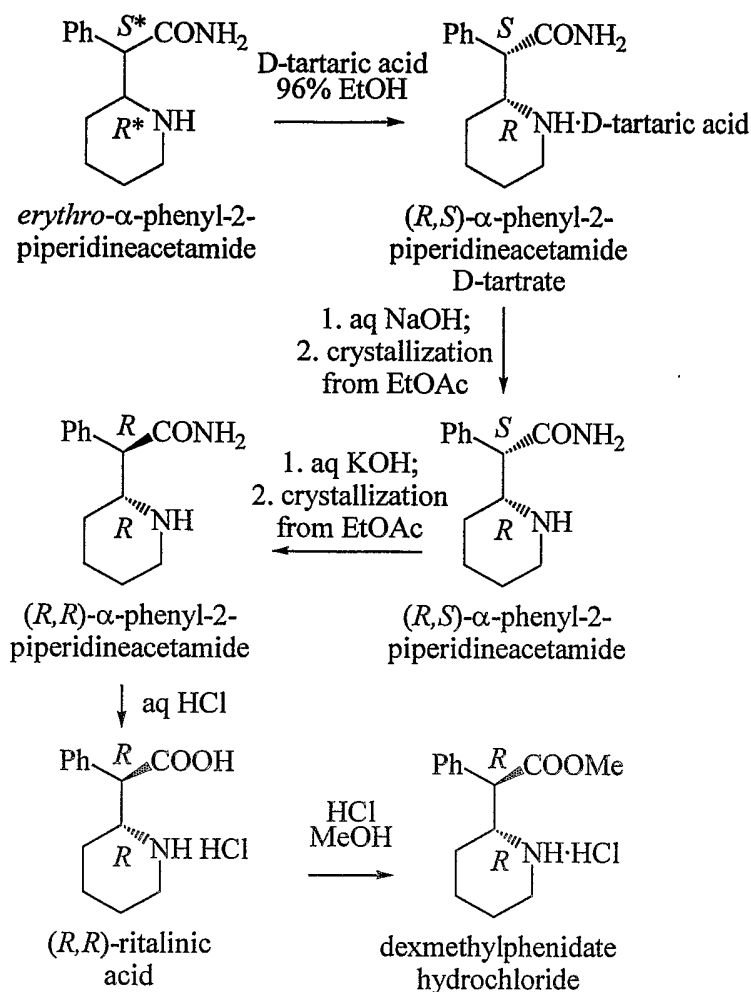
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is CNS (central nervous system) stimulant that is chemically and pharmacologically similar to the amphetamines. Dexmethylphenidate's CNS actions is milder than those of the amphetamines and have more noticeable  
25 effects on mental activities than on motor activities.

It has been reported by Szporny (1961) that among racemic mixtures of *threo* and *erythro* diastereomers of methylphenidate, only *threo*-isomer displays stimulant properties. Dexmethylphenidate hydrochloride (i.e. the d-*threo* enantiomer of methylphenidate hydrochloride) has been reported to be 5 to 38 times more active than the corresponding (*S,S*)-methylphenidate hydrochloride (Prashad 2000).

A commercially available drug is sold under the name Focalin<sup>TM</sup> (Novartis) and it consists of dexmethylphenidate in the form of the hydrochloride salt. This product is orally administered and clinically used in the treatment of narcolepsy and as adjunctive treatment in children with attention deficit disorder (ADD) and attention-deficit hyperactivity disorder (ADHD).

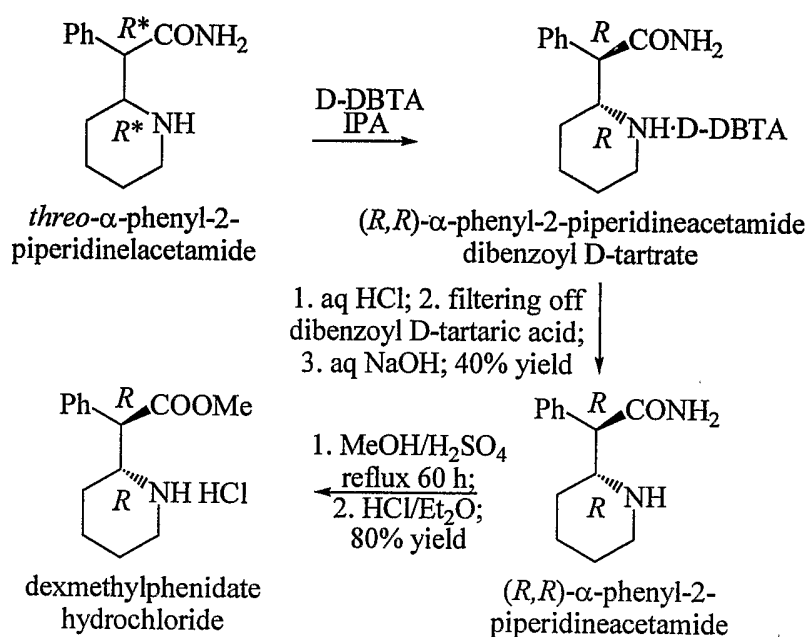
A synthesis of dexmethylphenidate hydrochloride was firstly described in U.S. Patent No. 2,838,519 and include resolution of *erythro*- $\alpha$ -phenyl-2-piperidineacetamide to obtain enantiopure (*2R,2'S*)- $\alpha$ -phenyl-2-piperidineacetamide, which was subjected to epimerization, hydrolysis, and esterification as shown in Scheme 1:



Scheme 1

Related example of preparation of dexmethylphenidate from *erythro*- $\alpha$ -phenyl-2-piperidineacetamide was described in US 5,936,091.

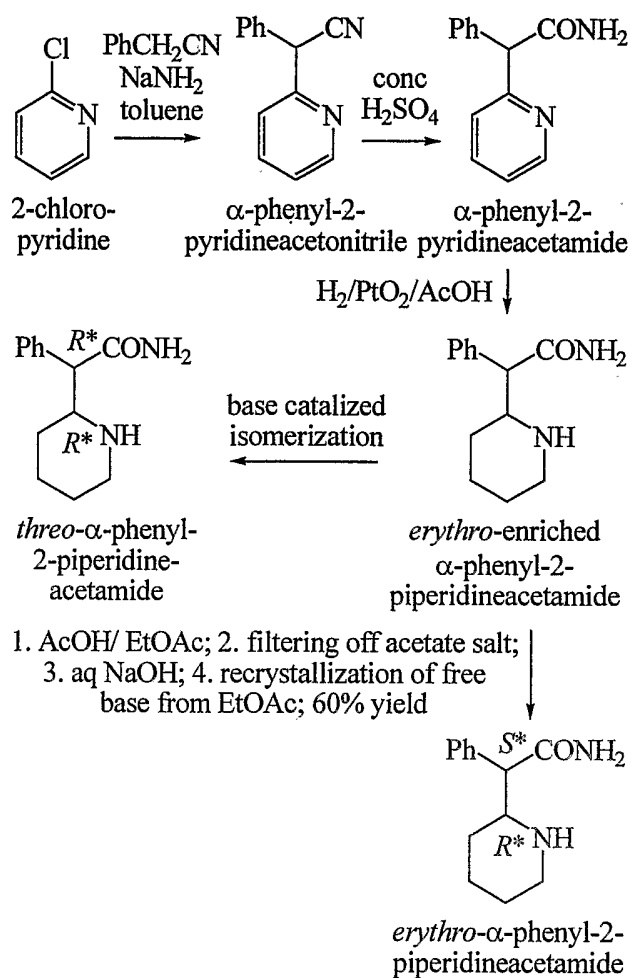
Preparation of dexmethylphenidate through optical resolution of *threo*- $\alpha$ -phenyl-2-piperidineacetamide was described in US 5,965,734, as shown in Scheme 2:



D-DBTA = dibenzoyl D-tartaric acid

### Scheme 2

Synthetic methods for the preparation of racemic mixture of *threo*- and *erythro*- $\alpha$ -phenyl-2-piperidineacetamides as raw materials for the preparation of dexmethylphenidate were described by Panizzon (1944) and Patric (1982) and in U.S. Patent Nos. 2,507,631, 2,838,519, 2,957,880 and 5,936,091, and in WO 01/27070. These methods include using sodium amide as base in the nucleophilic substitution of chlorine in 2-chloropyridine with phenylacetonitrile followed by hydrolysis of the formed nitrile and reduction of a pyridine ring to a piperidine one by hydrogenation on PtO<sub>2</sub> catalyst, as shown in Scheme 3:

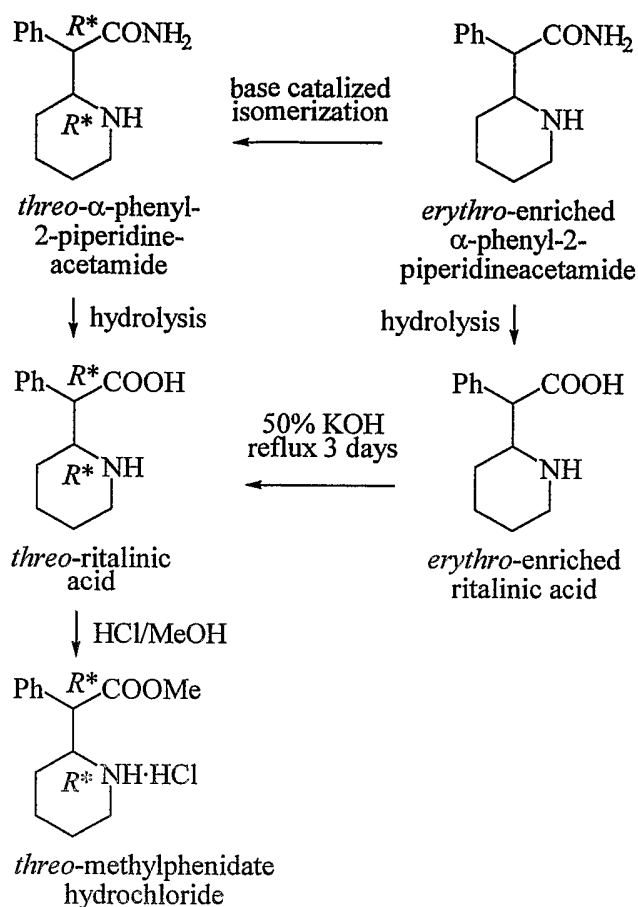


Scheme 3

Alternatively, 2-bromopyridine was used instead of 2-chloropyridine by  
 5 Deutsch (1996).

In some other methods *threo*-methylphenidate was used as the raw material for the preparation of dexmethylphenidate. *Threo*-methylphenidate may be prepared by a several routes, *inter alia* by the following two processes:

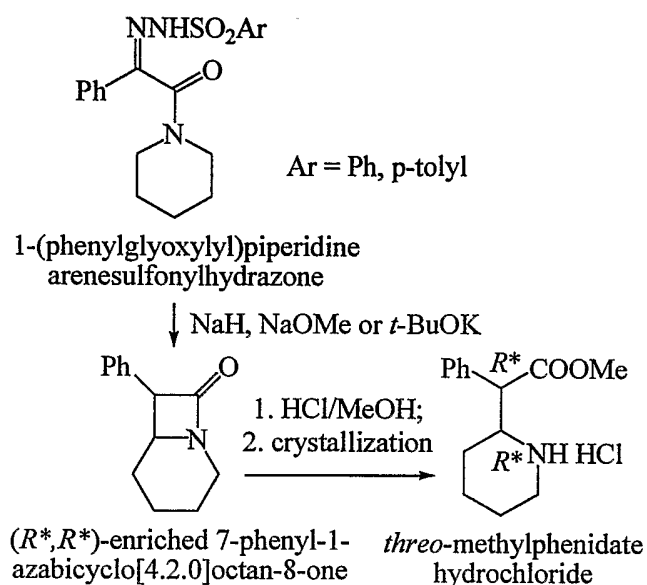
i) by esterification of *threo*-ritalinic acid which may be prepared from  
 10 *erythro*-enriched and *threo*- $\alpha$ -phenyl-2-piperidineacetamides as shown in Scheme 4:



#### Scheme 4

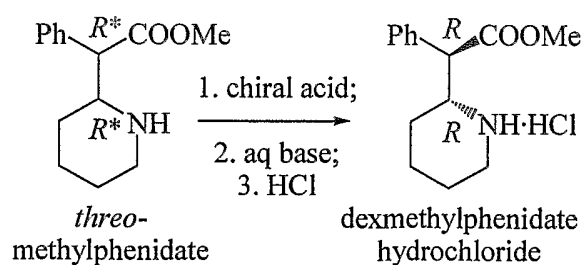
ii) by cyclization of easily available 1-(phenylglyoxylyl)piperidine  
 5 arenesulfonylhydrazone to ( $R^*,R^*$ )-enriched 7-phenyl-1-azabicyclo[4.2.0]octan-  
 8-one and further converting the  $\beta$ -lactam to *threo*-methylphenidate  
 hydrochloride, as described by Axten (1998), Corey (1965) and Earle (1969) and  
 in WO 99/36403 and shown in Scheme 5:



**Scheme 5**

The resolution of *threo*-methylphenidate to afford dexmethylphenidate was first reported by Patric (1987) which used (*R*)-(-)-binaphthyl-2,2'-diyl hydrogen phosphate as the resolving agent. Several new resolutions of *threo*-methylphenidate have been reported recently by Prashad (1999) and in U.S. Patent Nos. 6,100,401, 6,121,453, 6,162,919 and 6,242,464 as described in Scheme 6:

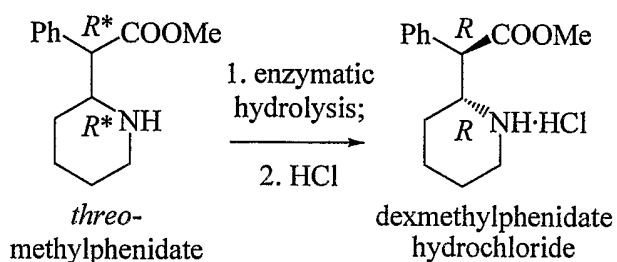
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**Scheme 6**

15

wherein the chiral acid is one of the following: (*R*)-(-)-binaphthyl-2,2'-diyl hydrogen phosphate, (-)-menthoxyacetic acid, ditoluoyl-D-tartaric acid or dibenzoyl-D-tartaric acid.

Resolution of *threo*-methylphenidate may be also achieved by enzymatic hydrolysis methods as proposed by Prashad (1998) and in WO 98/25902. Such resolution is described in Scheme 7:

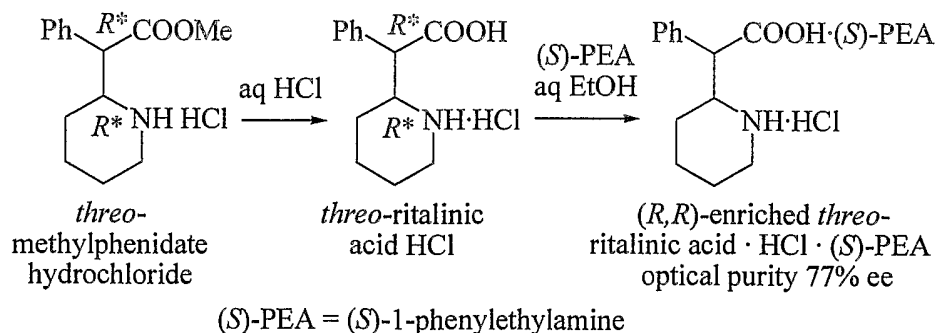


**Scheme 7**

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Resolution of *threo*-ritalinic acid hydrochloride with (*S*)-1-phenylethylamine give complex salt (*R,R*)-enriched *threo*-ritalinic acid · HCl · (*S*)-1-phenylethylamine with 77% ee optical purity of ritalinic acid (US 2002/0019535), Scheme 8:

15



**Scheme 8**

## SUMMARY OF THE INVENTION

It is an object of this invention to provide new and efficient process for the preparation of dexmethylphenidate or its salts, in particular dexmethylphenidate hydrochloride, with high optical purity, which excludes the use of expensive resolving agents.

It is a further object of this invention to provide novel intermediates for the above process.

The above objects are achieved in accordance with the present invention, which in one aspect thereof, provides a process for the preparation of dexmethylphenidate hydrochloride with high optical purity, the process comprising:

- (a) reacting a solution of *N*-protected *threo*-ritalinic acid with optically active 1-arylethylamine, separating precipitated salt of *N*-protected (*R,R*)-enriched ritalinic acid with optically active 1-arylethylamine from the reaction mixture and recrystallizing, reslurring and/or triturating of said salt;
- (b) mixing the salt of *N*-protected (*R,R*)-ritalinic acid and optically active 1-arylethylamine obtained in step (a) with aqueous acid and separating *N*-protected (*R,R*)-ritalinic acid from the mixture; and
- (c) deprotecting and esterifying the *N*-protected (*R,R*)-ritalinic acid prepared in step (b) to give dexmethylphenidate hydrochloride with optical purity of at least 99% ee.

Optical purity is defined by the percent of enantiomeric excess (ee) and in the present case the proportion of the (*R,R*) isomer in the product is at least 99%. The aryl group of 1-arylethylamine is preferably selected from phenyl, *p*-tolyl, *p*-bromophenyl, *p*-nitrophenyl and naphthyl. More preferably, the resolving agent is (*S*)-1-phenylethylamine.

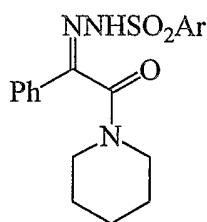
*Threo*-ritalinic acid is preferably N-protected by a group selected from methyl, benzyl, allyl, acyl, alkoxycarbonyl, haloalkoxycarbonyl, arylmethylcarbonyl, allylcarbonyl and vinylcarbonyl. More preferably the N-protecting group is *tert*-butoxycarbonyl (Boc) group.

5 In a preferred embodiment, the present invention provides a process for the preparation of dexmethylphenidate hydrochloride having high optical purity, the process comprising:

- (i) reacting a solution of *threo*-*N*-Boc-ritalinic acid with (*S*)-1-phenylethylamine, separating precipitated salt of (*R,R*)-enriched *N*-Boc-ritalinic  
10 acid with (*S*)-1-phenylethylamine from the reaction mixture and recrystallizing, reslurring and/or triturating of said salt in crystalline form;
- (ii) mixing the solid salt of (*R,R*)-*N*-Boc-ritalinic acid and (*S*)-1-phenylethylamine obtained in step (ii) with aqueous acid and separating (*R,R*)-*N*-Boc-ritalinic acid from the mixture; and
- 15 (iii) deprotecting and esterifying the (*R,R*)-*N*-Boc-ritalinic acid prepared in step (ii) to give dexmethylphenidate hydrochloride with optical purity of at least 99% ee.

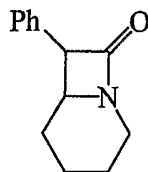
*Threo*-*N*-Boc-ritalinic acid is prepared by a process comprising:

- (1) contacting a solution of 1-(phenylglyoxylyl)piperidine  
20 arenesulfonylhydrazone of the formula



wherein Ar is an aryl group, in a water immiscible organic solvent, with an inorganic base, in the presence of phase transfer catalyst to obtain 7-phenyl-1-  
25 azabicyclo[4.2.0]octan-8-one;

(2) reacting the 7-phenyl-1-azabicyclo[4.2.0]octan-8-one of the formula



obtained in step (1) with a solution of hydrogen chloride in methanol to give  
5 methylphenidate;

(3) reacting the methylphenidate prepared in step (2) with di-tert-butyl dicarbonate to give *N*-Boc-methylphenidate;

(4) reacting *N*-Boc-methylphenidate with sodium hydroxide in an alcohol solution or aqueous alcohol solution and separating precipitated solid  
10 sodium salt of *threo*-*N*-Boc-ritalinic acid from the reaction mixture;

(5) mixing the salt obtained in step (4) with an aqueous acid and separating *threo*-*N*-Boc-ritalinic acid from the obtained mixture.

The above process is more efficient if a recycling procedure is carried out after step (4) and before step (5). Such procedure includes:

15 (ai) acidifying the mother liquor of step (4) and isolating *erythro*-enriched *N*-Boc-ritalinic acid from the obtained mixture;

(aii) esterifying of the *erythro*-enriched acid obtained in step (ai);

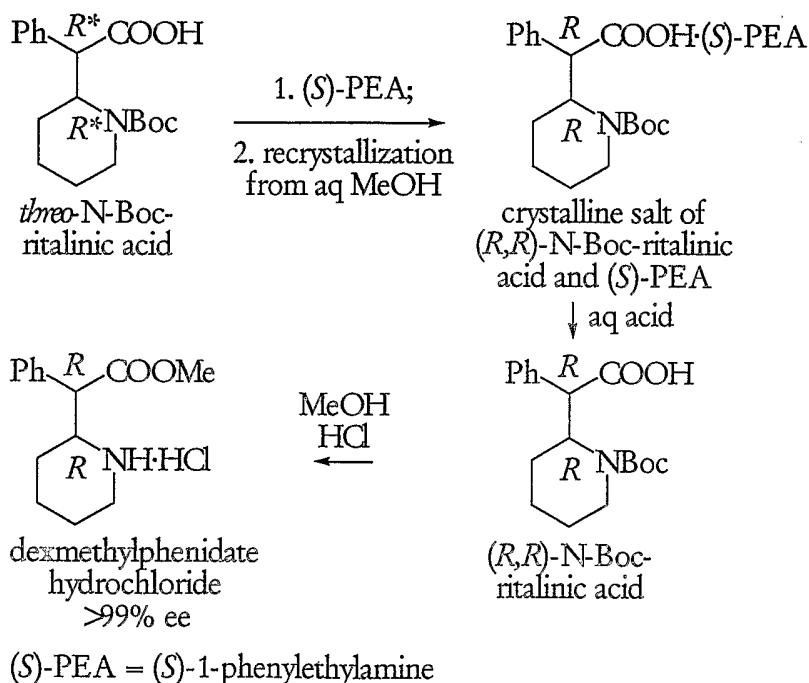
(aiii) recycling the *N*-Boc-methylphenidate obtained in step (aiii) to act as the starting material for step (4).

20 In accordance with a further aspect of this invention there is provided a novel compound which are salts of (*R,R*)-*N*-Boc-ritalinic acid with (*S*)-1-phenylethylamine and sodium *threo*-*N*-Boc-ritalinate. The novel intermediates of the present invention are a stable solid compounds, obtainable in high yield, which can be easily purified by re-crystallizing, reslurrig or trituring and stored  
25 for long periods of time.

## DETAILED DESCRIPTION OF THE INVENTION

The benefit of the process of the present invention is, *inter alia*, a process for the optical resolution of racemic N-protected *threo*-ritalinic acid. According to a preferred embodiment of the invention the process is carried out using  
5 optically active 1-arylethylamine as resolving agent.

The process for preparing dexmethylphenidate hydrochloride according to the present invention is schematically shown in Scheme 9 below, starting with *threo*-N-Boc-ritalinic acid:



10

**Scheme 9**

A solution of *threo*-N-Boc-ritalinic acid is reacted with a resolving agent, e.g. with (S)-1-phenylethylamine, and the salt of (R,R)-N-enriched-Boc-ritalinic  
15 acid with (S)-1-phenylethylamine is separated in solid form from the reaction mixture. The purification of the salt includes recrystallizing, reslurring and/or triturating procedures to give the salt of (R,R)-N-Boc-ritalinic acid with (S)-1-

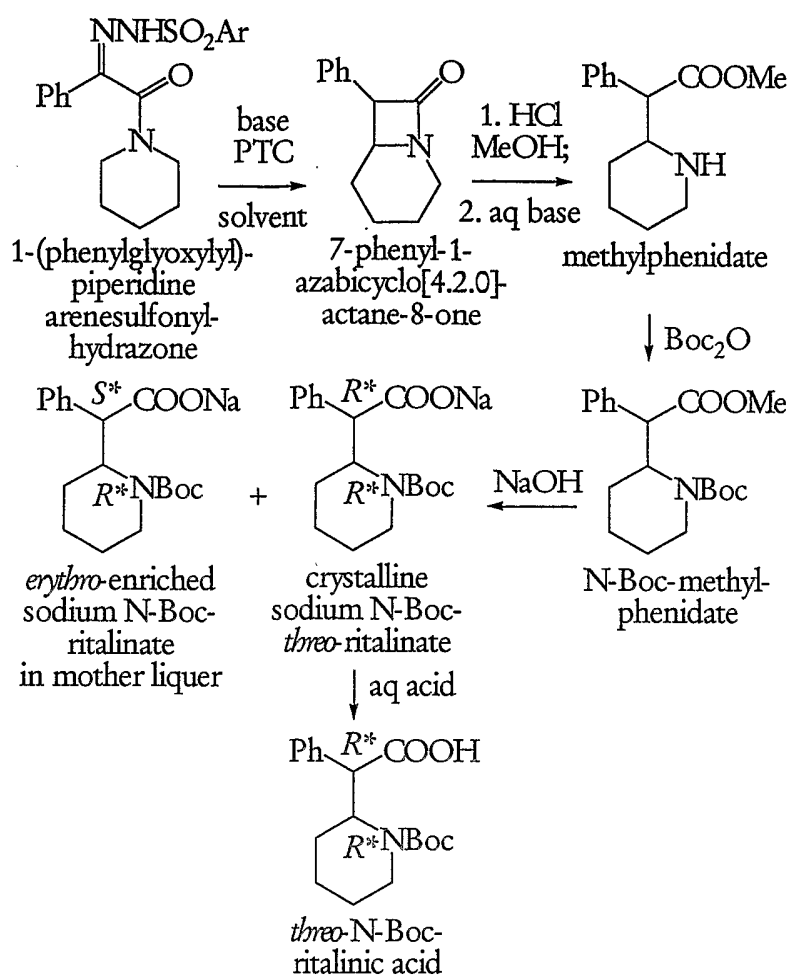
phenylethylamine. Upon acidification, (*R,R*)-*N*-Boc-ritalinic acid is formed and separated. The reaction of (*R,R*)-*N*-Boc-ritalinic acid with hydrogen chloride and methanol gives pure dexmethylphenidate hydrochloride in crystalline form.

*N*-Protected *threo*-ritalinic acid may be prepared by *N*-protecting and  
5 hydrolyzing of *threo*-methylphenidate. For example, *N*-Boc-*threo*-ritalinic acid may be prepared by reacting *threo*-methylphenidate with di-*tert*-butyl dicarbonate and following hydrolyzing the ester group of obtained *N*-Boc-*threo*-methylphenidate.

Preferably *threo-N*-Boc-ritalinic acid can be prepared by a process  
10 comprising:

- (i) contacting a solution of 1-(phenylglyoxylyl)piperidine arenesulfonylhydrazone in a water immiscible organic solvent with an inorganic base, in the presence of phase transfer catalyst to obtain 7-phenyl-1-azabicyclo[4.2.0]octan-8-one;
- 15 (ii) reacting the 7-phenyl-1-azabicyclo[4.2.0]octan-8-one obtained in step (i) with a solution of hydrogen chloride in methanol to give methylphenidate;
- (iii) reacting the methylphenidate prepared in step (ii) with di-*tert*-butyl dicarbonate to give *N*-Boc-methylphenidate;
- 20 (iv) reacting *N*-Boc-methylphenidate with solution of sodium hydroxide and separating precipitated solid sodium salt of *N*-Boc-*threo*-ritalinic acid from the reaction mixture;
- (v) mixing the salt obtained in step (iv) with an aqueous acid and separating *threo-N*-Boc-ritalinic acid from the obtained mixture;

25 The above process for preparing starting material *N*-Boc-*threo*-ritalinic acid is schematically shown in Scheme 10 below:



Scheme 10

According to a preferred embodiment, the said solution in step (iv) is alcohol or aqueous alcohol solution, wherein the alcohol preferably is methanol, ethanol or isopropanol.

Examples of the aryl group of 1-(phenylglyoxylyl)piperidine arenesulfonylhydrazones are phenyl, *p*-tolyl, *p*-chlorophenyl or *p*-nitrophenyl group. More preferably, 1-(phenylglyoxylyl)piperidine arenesulfonylhydrazones is 1-(phenylglyoxylyl)piperidine *p*-toluenesulfonylhydrazones.



The phase transfer catalyst is selected from the group consisting of quaternary ammonium and phosphonium salts, polyglycols, crown ethers and podans. Preferably, the phase transfer catalyst is methyltrioctylammonium chloride.

5 As mentioned above, the reaction is carried out in a water-immiscible organic solvent such as for example halogenated hydrocarbons, e.g. dichloromethane and aromatics, e.g. toluene.

Preferably, the inorganic base is used in solid state or in an aqueous solution and is selected from sodium hydroxide, potassium hydroxide, sodium  
10 carbonate or potassium carbonate. More preferably, the said inorganic base is sodium hydroxide.

The present invention further provides sodium salt of N-Boc-*threo*-ritalinic acid as new intermediate in the preparation of dexmethylphenidate hydrochloride. Sodium N-Boc-*threo*-ritalinic acid is stable solid compound which  
15 can be easily purified by re-crystallizing, reslurring or triturating and stored for long period of time.

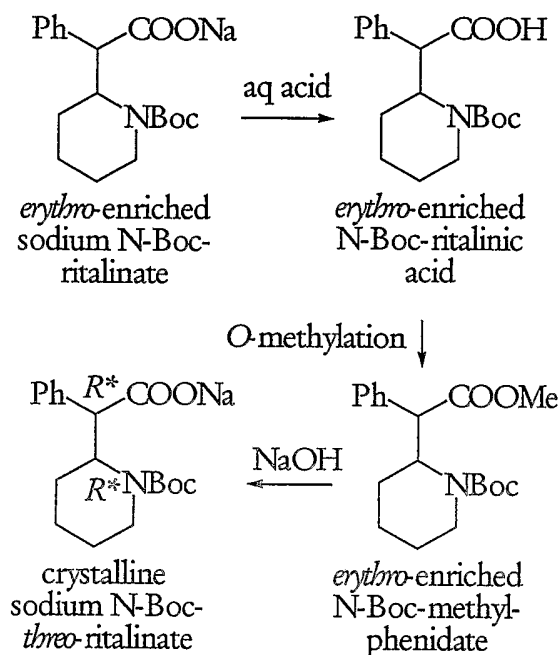
The sodium salt of *threo*-N-Boc-ritalinic acid precipitates and is separated as a white powder, while the *erythro*-enriched sodium salt of N-Boc-ritalinic acid remains dissolved in the mother liquor and may be converted into the *threo*-  
20 isomer and recycled back into the process as the starting material for the second step.

According to a preferred embodiment of the present invention, the process further comprises the recycling of the *erythro*-enriched N-Boc-ritalinic acid obtained after step (iv) back into step (iv) as a starting material. The following  
25 steps constitute the recycling process which is described with reference to the *erythro*-enriched N-Boc-ritalinic acid:

- (ai) acidifying the mother liquor of step (iv) and isolating *erythro*-enriched N-Boc-ritalinic acid from the obtained mixture;
- (aii) esterifying of the *erythro*-enriched acid obtained in step (ai);

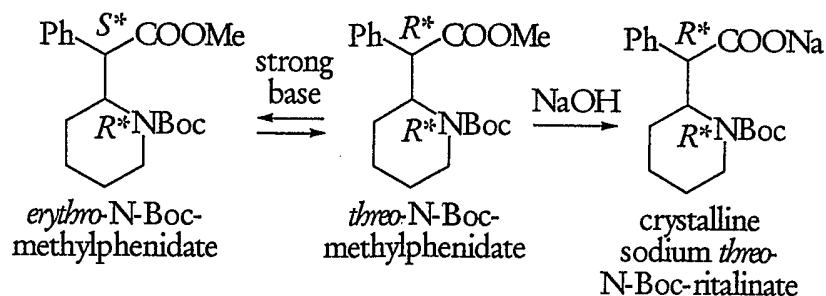
(aiii) recycling the N-Boc-methylphenidate obtained in step (aiii) to act as the starting material for step (iv).

The process for preparing sodium N-Boc-*threo*-ritalininate from *erythro*-enriched N-Boc-ritalinic acid sodium salt according to the present invention is schematically shown in Scheme 11 below:



**Scheme 11**

10 A mixture of about 1:1 *threo/erythro*-N-Boc-methylphenidate may be prepared by base catalyzed isomerizing of *erythro*-N-Boc-methylphenidate. Sodium hydroxide play role of strong base and saponifying agent in the conversion of *erythro*-N-Boc-methylphenidate to sodium *threo*-N-Boc-ritalininate according to Scheme 12:



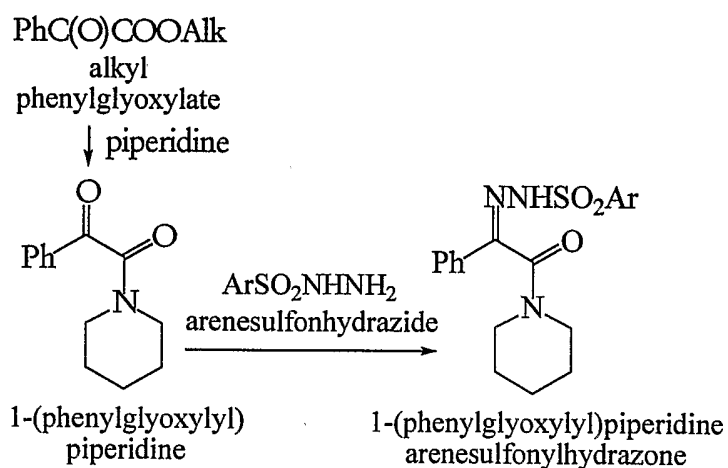
### Scheme 12

So, *erythro*-enriched N-Boc-methylphenidate or even *erythro*-N-Boc-methylphenidate may be used as starting material for preparing  
 5 dexmethylphenidate according of the process of our invention. *erythro*-Enriched or *erythro*-N-Boc-methylphenidate may be obtained by reacting an *erythro*-enriched or *erythro*-methylphenidate with di-tert-butyl dicarbonate.

The term “*enriched*” used in the context of the present invention denotes a higher amount of one entity over others in the mixture. In a similar manner,  
 10 “*threo-enriched*” refers to a mixture where the amount of the threo isomer is higher than that of the erythro and “*erythro-enriched*” refers to a mixture where the amount of the erythro isomer is higher than that of the threo.

The term “*substantially pure threo-methylphenidate*” relates to a mixture that contains at least 95% of threo-isomer of methylphenidate. By analogy, the  
 15 term “*substantially pure erythro-methylphenidate*” describes a mixture that contains at least 95% of erythro-isomer of methylphenidate.

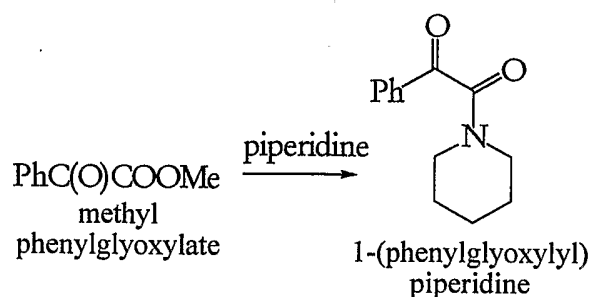
1-(Phenylglyoxylyl)piperidine arenesulfonylhydrazone may be readily prepared by a reaction between 1-(phenylglyoxylyl)piperidine and arenesulfonylhydrazide according to Scheme 13:

**Scheme 13**

1-(Phenylglyoxylyl)piperidine may be prepared by reaction of alkyl  
5 phenylglyoxylate with piperidine. Preferably the alkyl group is methyl or ethyl  
group.

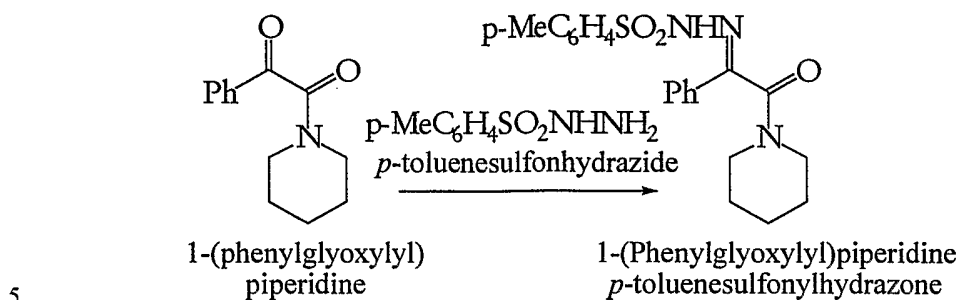
**EXAMPLES**

10 In order to understand the invention and to see how it may be carried out  
in practice, preferred embodiments will now be described, by way of non-limiting  
examples only.

**Example 1****1-(Phenylglyoxylyl)piperidine**

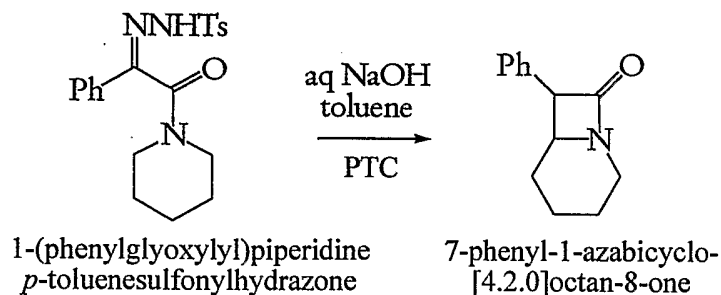
5

Methyl phenylglyoxylate (12.50 Kg, 76.1 mol, 1 eq) was added dropwise to a stirred mixture of piperidine (19.45 Kg, 228 mol, 3 eq) and methanol (5.0 L) for 3.5 hours to maintain the temperature at 45 - 55 °C. The mixture was stirred at the same temperature for 0.5 hour and kept overnight at +4 °C. The precipitated solid was filtered off, washed on the filter with cold methanol (5 L) and dried under reduced pressure to a constant weight to give 15.90 Kg (96 %) of 1-(phenylglyoxylyl)piperidine with 99.9 % purity by GC.

**Example 2**1-(Phenylglyoxylyl)piperidine *p*-toluenesulfonylhydrazone

A solution of 98% sulfuric acid (121.7 g, 1.22 mol, 0.02 eq) in abs ethanol (1.0 L) was added dropwise to a stirred mixture of 1-(phenylglyoxylyl)piperidine (17.58 Kg, 80.9 mol, 1 eq), *p*-toluenesulfonylhydrazide (16.20 Kg, 87.0 mol, 1.08 eq) and abs ethanol (50 L) at 20 – 30 °C. The obtained mixture was stirred under reflux conditions until 1-(phenylglyoxylyl)piperidine disappeared (~7 hours, TLC control). The mixture was stirred for 1 hour at 20 – 30 °C and kept overnight at 4 – 6 °C. The precipitated solid was filtered off, washed on the filter with cold methanol and cold hexane and dried under reduced pressure to a constant weight to yield 28.25 Kg (90.6%) of 1-(phenylglyoxylyl)piperidine *p*-toluenesulfonylhydrazone with 99.9% purity by HPLC.

15

**Example 3****7-Phenyl-1-azabicyclo[4.2.0]octan-8-one**

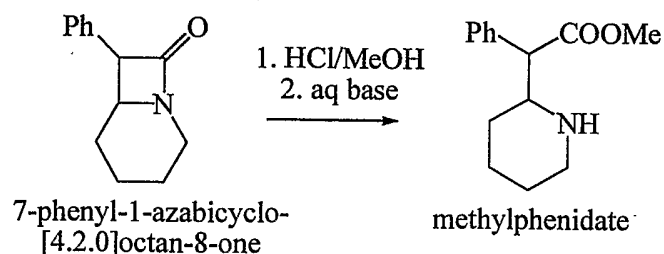
5

Sodium hydroxide, 50% aqueous solution (1.09 Kg, 13.6 mol, 1.05 eq) was added to a stirred mixture of 1-(phenylglyoxylyl)piperidine *p*-toluenesulfonylhydrazone (5.00 Kg, 13.0 mol, 1 eq), phase transfer catalyst (PTC) trioctylmethylammonium chloride (aliquat 336) (60.0 g, 0.15 mol, 0.01 eq) and toluene (50 L) at 20 - 30 °C. The mixture was heated to reflux and monitored by both TLC and the color of the reaction mixture. The originally yellow solution in 10 minutes turned bright orange as the diazo compound was formed. After 6.5 hours at reflux, the solution re-assumed a yellow color and TLC indicated that no starting material and intermediate were present. Crushed ice (20 Kg) was added to the reaction mixture (temperature of the mixture was dropped to 15 °C). The organic layer was separated, washed with brine (15 L) and evaporated under reduced pressure to give 2.69 Kg (quantitative yield) of 7-phenyl-1-azabicyclo[4.2.0]octan-8-one with *R*\**R*\*/*S*\**R*\* 3.3:1 by GC.

20

**Example 4**

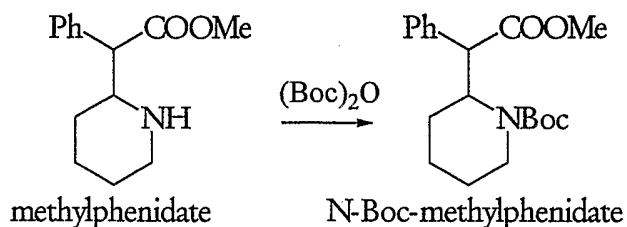
## Methylphenidate



5

Hydrogen chloride (gas) was passed through a stirred solution of 7-phenyl-1-azabicyclo[4.2.0]octan-8-one with *R*\**R*\*/*S*\**R*\* 3.3:1 by GC (2.61 Kg, 13.0 mol) in methanol (13 L) under reflux conditions for 60 hour until TLC indicated that all starting material had been consumed. The mixture was  
10 evaporated under reduced pressure. The residue was treated with hot water (8 L) for 0.5 h. The hot mixture was filtered, cooled to 50 °C, washed with toluene (2 x 1.2 L), cooled to the room temperature, basified with sodium carbonate to pH 10 - 11 and extracted with dichloromethane (3 x 2.5 L). The combined organic extracts were dried over sodium sulfate, filtered and evaporated under reduced  
15 pressure to give 2.33 Kg (76.9%) of methylphenidate with *threo/erythro* 3.5:1 by GC.



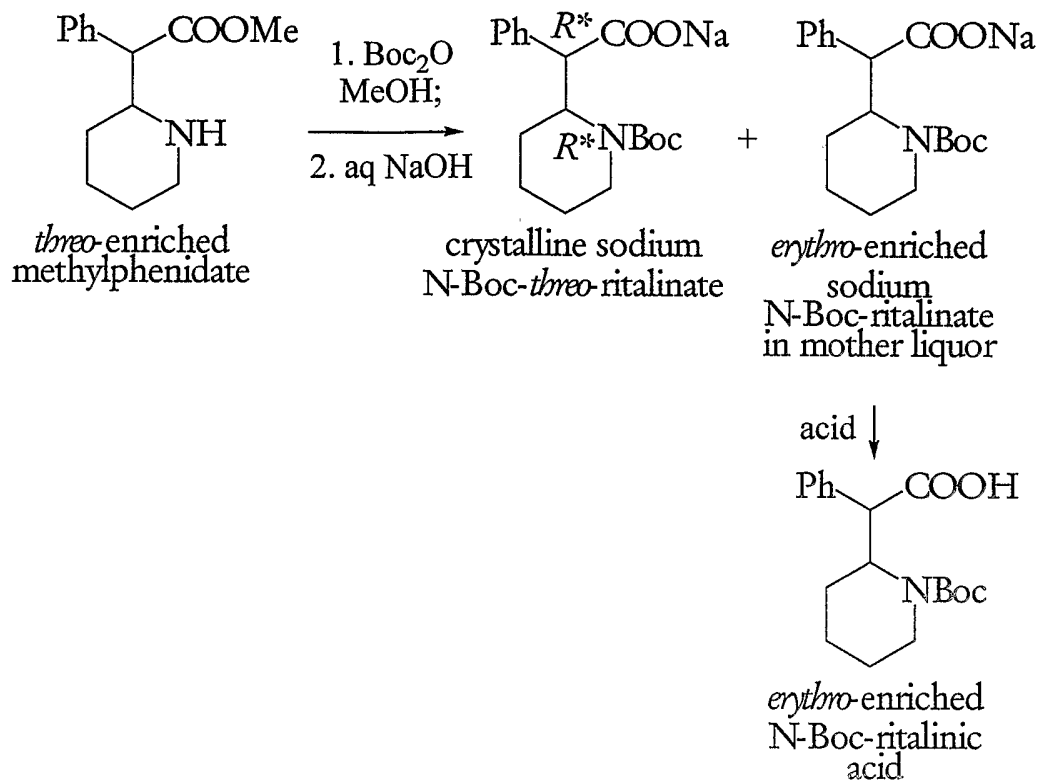
**Example 5****N-Boc-methylphenidate**

5

A solution of di-*tert*-butyl dicarbonate (50.5 g, 0.23 mol, 1 eq) in methanol (115 mL) was added dropwise to a stirred solution of methylphenidate with *threo/erythro* 3.2:1 by GC (54.0 g, 0.23 mol, 1 eq) in methanol (115 mL) with such rate to maintain the temperature at 15 - 20 °C. The mixture was stirred for 6  
10 hours at 20 - 25 °C (TLC control). Methanol was evaporated from the mixture under reduced pressure. Water (100 mL) and dichloromethane (100 mL) were added to the residue. The aqueous layer was separated and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated under reduced pressure to give 70.8 g  
15 (91.7 %) of N-Boc-methylphenidate as off white solidified oil with *threo/erythro* 3.2:1 by HPLC.

**Example 6**

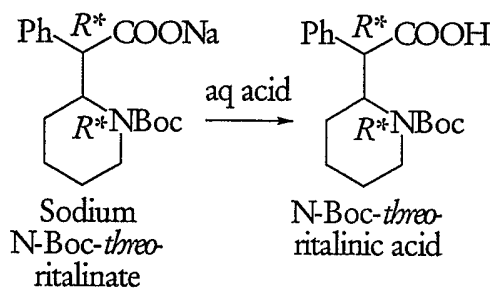
N-Boc-*threo*-ritalinic acid sodium salt and *erythro*-enriched N-Boc-ritalinic acid from *threo*-enriched methylphenidates



A solution of di-*tert*-butyl dicarbonate (1459 g, 6.69 mol, 1.0 eq) in methanol (3.3 L) was added dropwise (3.5 h) to a stirred solution of methylphenidate with *threo/erythro* 4:1 by GC (1560 g, 6.69 mol, 1.0 eq) in  
5 methanol (3.3 L) to maintain by cooling ice water the temperature at 10 - 20 °C. The mixture was stirred overnight at 20 - 25 °C (TLC control). A solution of sodium hydroxide (374.4 g, 9.36 mol, 1.4 eq) in water (3.3 L) was added to the mixture in one portion. The obtained mixture stirred under reflux conditions for  
10 9 hours (TLC control). Methanol was evaporated from the mixture under reduced pressure. Water (2.7 L) was added to the stirred residue. The obtained mixture was kept overnight at 4 °C. Precipitated solid was filtered off (Note 1), washed on the filter with ice water (3 x 1 L) and hexane (2 x 0.5 L) and dried azeotropically with toluene under reduced pressure to a constant weight to give  
15 1700 g (74.5 % yield) of N-Boc-*threo*-ritalinic acid sodium salt as white powder with *threo/erythro* 97.5:0.5 by HPLC.

Note:

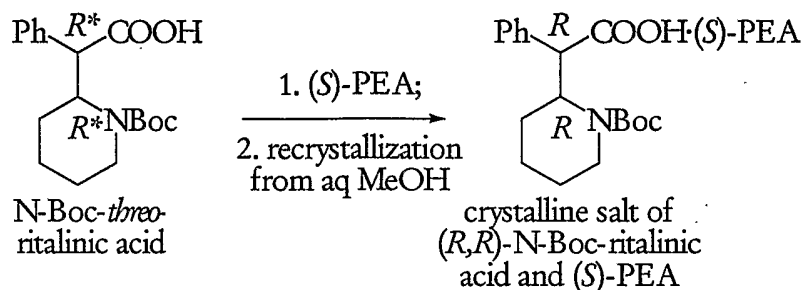
The mother liquor was acidified by 20 % aqueous citric acid to pH 4 and  
20 thoroughly extracted with ethyl acetate (3 x 1 L), combined organic extracts were washed with brine (2 x 0.5 L), dried over sodium sulfate, filtered and evaporated under reduced pressure to constant weight to give 455 g (21.4 % yield) of N-Boc-ritalinic acid as off white solidified oil with *threo/erythro* 5.5/94.5 by HPLC. Analytical sample of N-Boc-*erythro*-ritalinic acid with mp 170-172 °C was  
25 prepared by crystallization of the *erythro*-enriched N-Boc-ritalinic acid from EtOAc/hexane.

**Example 7**N-Boc-*threo*-ritalinic acid

5

A mixture of solution of N-Boc-*threo*-ritalinic acid sodium salt (1700 g, 4.98 mmol), citric acid (1150 g, 5.98 mmol) and water (5 mL) was stirred at 15 - 25 °C for 0.5 hour and extracted with ethyl acetate (3 x 4 L). Combined organic  
10 extracts were washed with brine (2 x 3 L), dried over sodium sulfate, filtered and evaporated under reduced pressure to constant weight to give 1560 g (98.1 % yield) of N-Boc-*threo*-ritalinic acid with mp 133 - 134 °C (EtOAc/hexane) and 99.8 % purity by HPLC.

15

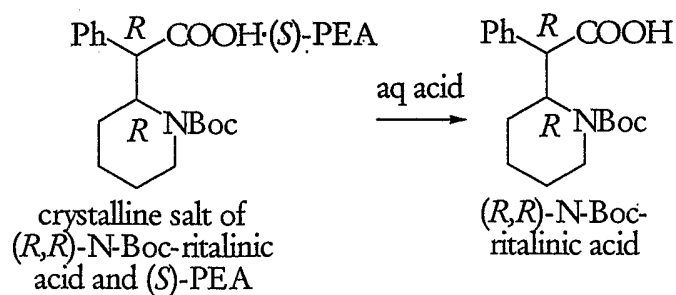
**Example 8**Salt of (*R,R*)-*N*-Boc-ritalinic acid and (*S*)-1-phenylamine ((*S*)-PEA)

5

(*S*)-1-Phenylethylamine (113.8 g, 0.94 mol, 0.6 eq) was added dropwise to a stirred solution of *N*-Boc-*threo*-ritalinic acid (500 g, 1.57 mol, 1 eq) in ethyl acetate (5 L) for 1 hour at 20 - 40 °C. The mixture was stirred for 1 hour at 40 °C and overnight at 5 °C. The precipitated solids were filtered off, washed on the

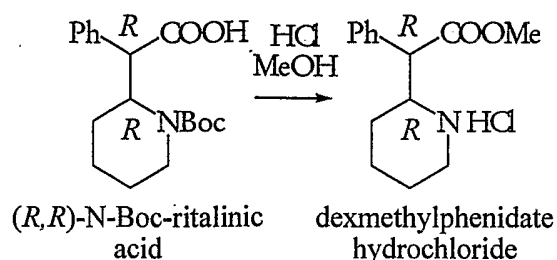
10 filter with cold ethyl acetate (2 x 500 mL) and dried under reduced pressure to give 380 g of white crystals with  $[\alpha]_{\text{D}}^{20} -23.3^\circ$  ( $c = 1$ , MeOH). The salt was twice recrystallized from aqueous methanol. The precipitated crystals were filtered off, washed on the filter with cold aqueous methanol and dried under reduced pressure to a constant weight to give 265 g (33.5 % yield) of salt of

15 (*R,R*)-*N*-Boc-ritalinic acid and (*S*)-1-phenylamine as white crystals with  $[\alpha]_{\text{D}}^{20} -28.6^\circ$  ( $c = 1$ , MeOH).

**Example 9****(*R,R*)-N-Boc-ritalinic acid**

5

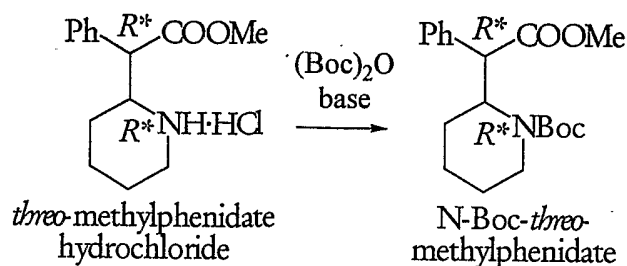
A mixture of crystalline salt of (*R,R*)-N-Boc-ritalinic acid and (*S*)-1-phenylamine with  $[\alpha]_D^{20}$   $-28.6^\circ$  ( $c = 1$ , MeOH) (133.0 g, 302 mmol), ethyl acetate (1.3 L) and solution of citric acid (164.0 g, 845 mmol) in water (1.3 L) was stirred at 15 - 25 °C for 1.5 hours. The organic layer was separated, washed  
10 with brine (20 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure to give 95.4 g (99 %) of (*R,R*)-N-Boc-ritalinic acid as white solid with mp 117-119 °C (EtOAc/hexane).

**Example 10****Dexmethylphenidate hydrochloride**

5

Gaseous hydrogen chloride was passed through a boiling solution of *(R,R)*-N-Boc-ritalinic acid (95.4 g, 299 mmol) in methanol (1.5 L). The mixture was stirred for 12 hours under reflux conditions and concentrated to the volume of 250 mL. Toluene (750 mL) was added to the stirred residue, then methanol  
10 was removed from boiling suspension under normal pressure. The obtained mixture was stirred overnight at 0 – 5 °C. The precipitated solids were filtered off, washed on the filter with toluene (3 x 50 mL) and dried under reduced pressure to give 78.4 g (97.2 % yield) of dexmethylphenidate hydrochloride as white crystals with mp 222-224 °C and  $[\alpha]_{\text{D}}^{25} 87.0^\circ$  ( $c = 1, \text{MeOH}$ ).

15

**Example 11****N-Boc-*threo*-Methylphenidate**

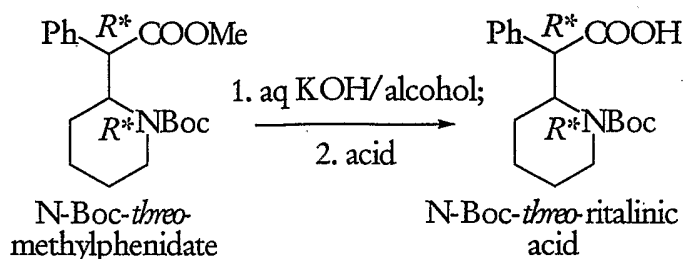
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A solution of di-*tert*-butyl dicarbonate (24.0 g, 0.11 mol, 1.1 eq) in dichloromethane (50 mL) was added dropwise to a stirred mixture of *threo*-methylphenidate hydrochloride (27.0 g, 0.1 mol, 1 eq), dichloromethane (50 mL) and solution of sodium carbonate (10.6 g, 0.1 mol, 2 eq) in water (100 mL) at 0 – 5 °C. The mixture was stirred overnight at a room temperature. The aqueous layer was separated and extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was dissolved in hot hexane (150 mL) and stirred for 1 hour at 0 – 5 °C. The precipitated solids were filtered off, washed on the filter with hexane (30 mL) and dried under reduced pressure to give 27.5 g (82.1%) of N-Boc-*threo*-methylphenidate with mp 83 – 84 °C.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.33 (m, 5H), 4.86 (m, 1H), 4.01 (d,  $J = 12$  Hz, 1H), 3.96 (m, 1H), 3.58 (s, 3H), 1.47 (m, 16H)

20



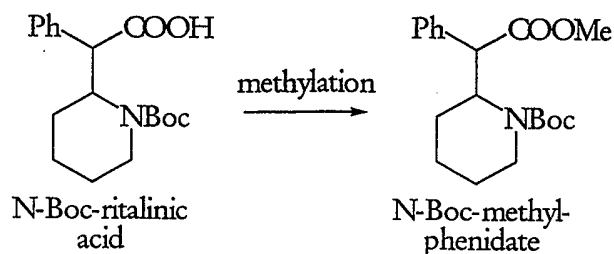
**Example 12**N-Boc-*threo*-ritalinic acid

5

A mixture of N-Boc-*threo*-methylphenidate (25.0 g, 75.0 mmol, 1 eq), 96% ethanol (50 mL), potassium hydroxide 85% (5.93 g, 90.0 mmol, 1.2 eq) and water (50 mL) was stirred under reflux conditions for 2 hours (TLC monitoring on silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1). Ethanol was evaporated from the mixture.

10 Ethyl acetate (200 mL) and 10% aqueous solution of citric acid (200 g, 104 mmol, 4.2 eq) were added to the stirred resulting aqueous solution of potassium salt at room temperature. The mixture was stirred for 0.5 hour. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried

15 over sodium sulfate, filtered and evaporated under reduced pressure to give 23.0 g (96% yield) of N-Boc-*threo*-ritalinic acid.

**Example 13****N-Boc-Methylphenidate**

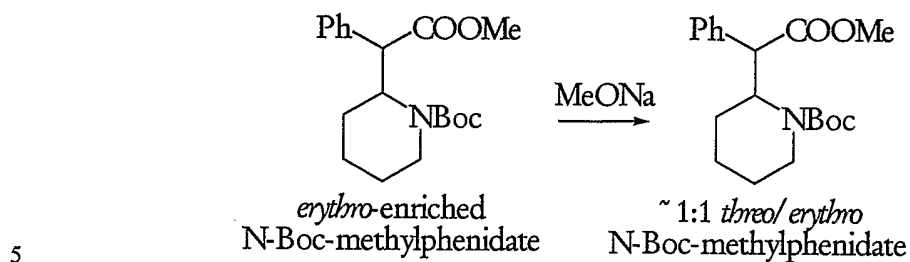
5

A mixture of N-Boc-ritalinic acid, *threo/erythro* 5.5:94.5 by HPLC (455.0 g, 1.43 mol, 1 eq), dimethylsulfate (215.6 g, 1.71 mol, 1.2 eq), methyl ethyl ketone (3 L) and potassium carbonate (295.0 g, 2.14 mol, 1.5 eq) was stirred under reflux conditions for 2 hour (TLC control), cooled to 0 °C, filtered and  
10 washed on the filter with methyl ethyl ketone (3 x 250 mL). Combined organic filtrates were evaporated under reduced pressure, dissolved in dichloromethane (2.5 L), washed with brine, dried over anhydrous sodium sulfate, filtered off and evaporated under reduced pressure (oil pump) to give 463.0 g (97.5 % yield) of N-Boc-methylphenidate with *threo/erythro* 6.9:93.1 by GC.

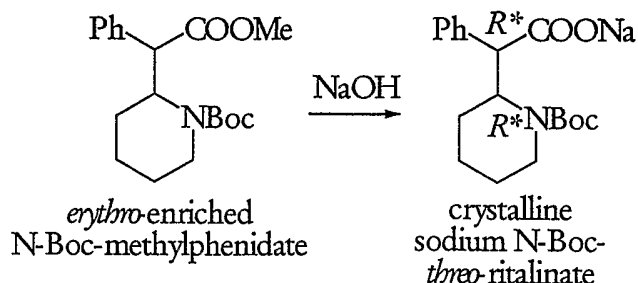
15

**Example 14**

~1:1 *threo/erythro* N-Boc-methylphenidate from *erythro*-enriched N-Boc-methylphenidate



A mixture of N-Boc-*erythro*-methylphenidate with *threo/erythro* 7:93 (10.0 g, 30.0 mmol, 1 eq), methanol (100 mL) and sodium methoxide (30.0 mmol, 1 eq) was stirred for 3 hours at 20 -30 °C and evaporated under reduced  
10 pressure. The residue was dissolved in dichloromethane (50 mL), washed with brine, dried over sodium sulfate, filtered, passed through short silica gel column and evaporated under reduced pressure to give 8.9 g (89.0 % yield) of N-Boc-methylphenidate with *threo/erythro* 51.2:48.9 by HPLC.

**Example 15**N-Boc-*threo*-ritalinic acid sodium salt

5

A mixture of N-Boc-methylphenidate, *threo/erythro* 7:93 (10.0 g, 30.0 mmol, 1.0 eq), methanol (100 mL) and sodium hydroxide (3.6 g, 90.0 mmol, 3.0 eq) was stirred for 90 hour at 25 °C until the isomerization and hydrolysis had completed (HPLC control). The mixture was evaporated under reduced pressure.

10 A mixture of the residue and water (50 mL) was stirred for 0.5 hour at 60 °C, then kept overnight at 5 °C. Precipitated solids were filtered off, washed on the filter with cold water (3 x 10 mL), hexane (2 x 10 mL) and dried azeotropically with toluene under reduced pressure to give 3.2 g (62.7 % yield,) of N-Boc-ritalinic acid sodium salt as white powder with *threo/erythro* 95:5 by HPLC.

15

**CLAIMS:**

1. A process for the preparation of dexmethylphenidate hydrochloride having high optical purity, the process comprising:
  - 5 (a) reacting a solution of *N*-protected *threo*-ritalinic acid with optically active 1-arylethylamine, separating precipitated salt of *N*-protected (*R,R*)-enriched ritalinic acid with optically active 1-arylethylamine from the reaction mixture and recrystallizing, reslurring and/or triturating of said salt;
  - (b) mixing the salt of *N*-protected (*R,R*)-ritalinic acid and optically active 1-  
10 arylethylamine obtained in step (a) with aqueous acid and separating *N*-protected (*R,R*)-ritalinic acid from the mixture; and
  - (c) deprotecting and esterifying the *N*-protected (*R,R*)-ritalinic acid prepared in step (b) to give dexmethylphenidate hydrochloride with optical purity of at least 99% ee.
- 15 2. The process of claim 1 wherein the aryl group in the said 1-arylethylamine is selected from phenyl, *p*-tolyl, *p*-bromophenyl, *p*-nitrophenyl and naphthyl.
3. The process of claim 1, wherein said optically active 1-arylethylamine is  
20 (*S*)-1-phenylethylamine.
4. The process of claim 1, wherein said *N*-protected *threo*-ritalinic acid is prepared by *N*-protecting and hydrolyzing of *threo*-methylphenidate.

5. The process of claims 1 or 4, wherein said N-protecting group is selected from methyl, benzyl, allyl, acyl, alkoxycarbonyl, haloalkoxycarbonyl, arylmethylcarbonyl, allylcarbonyl or vinylcarbonyl.

5

6. The process of claim 5, wherein said N-protecting group is *tert*-butoxycarbonyl (Boc) group.

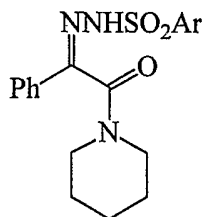
7. A process for the preparation of dexmethylphenidate hydrochloride having  
10 high optical purity, the process comprising:

- (i) reacting a solution of *threo*-*N*-Boc-ritalinic acid with (*S*)-1-phenylethylamine, separating precipitated salt of (*R,R*)-enriched *N*-Boc-ritalinic acid with (*S*)-1-phenylethylamine from the reaction mixture and recrystallizing, reslurring and/or triturating of said salt in crystalline form;
- 15 (ii) mixing the solid salt of (*R,R*)-*N*-Boc-ritalinic acid and (*S*)-1-phenylethylamine obtained in step (i) with aqueous acid and separating (*R,R*)-*N*-Boc-ritalinic acid from the mixture; and
- (iii) deprotecting and esterifying the (*R,R*)-*N*-Boc-ritalinic acid prepared in step (ii) to give dexmethylphenidate hydrochloride with optical purity of at least 99%.

20 ee.

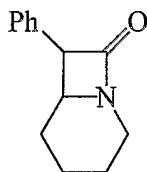
8. The process of claim 7, wherein said *threo*-*N*-Boc-ritalinic acid is prepared by a process comprising:

(1) contacting a solution of 1-(phenylglyoxylyl)piperidine  
5 arenesulfonylhydrazone of the formula



wherein Ar is an aryl group, in a water immiscible organic solvent, with an inorganic base, in the presence of phase transfer catalyst to obtain 7-phenyl-1-azabicyclo[4.2.0]octan-8-one;

(2) reacting the 7-phenyl-1-azabicyclo[4.2.0]octan-8-one of the  
10 formula



obtained in step (1) with a solution of hydrogen chloride in methanol to give methylphenidate;

(3) reacting the methylphenidate prepared in step (2) with di-tert-butyl  
15 dicarbonate to give *N*-Boc-methylphenidate;

(4) reacting *N*-Boc-methylphenidate with sodium hydroxide in an alcohol solution or aqueous alcohol solution and separating precipitated solid sodium salt of *threo*-*N*-Boc-ritalinic acid from the reaction mixture;

(5) mixing the salt obtained in step (4) with an aqueous acid and  
20 separating *threo*-*N*-Boc-ritalinic acid from the obtained mixture.

9. The process of claim 8, further comprising the following steps after step (4) and before step (5):
- (ai) acidifying the mother liquor of step (4) and isolating *erythro*-enriched N-Boc-ritalinic acid from the obtained mixture;
  - 5 (aii) esterifying of the *erythro*-enriched acid obtained in step (ai);
  - (aiii) recycling the N-Boc-methylphenidate obtained in step (aiii) to act as the starting material for step (4).
10. The process of claim 8, wherein said alcohol used in step (iv) is methanol,  
10 ethanol or isopropanol.
11. A salt of (*R,R*)-N-Boc-ritalinic acid with (*S*)-1-phenylethylamine in a substantially pure solid form.
- 15 12. A salt of (*R,R*)-N-Boc-ritalinic acid with (*S*)-1-phenylethylamine for use in the preparation of dexmethylphenidate hydrochloride.
13. Sodium salt of N-Boc-*threo*-ritalinic acid in a substantially pure solid form.  
20
14. The process of claim 8, wherein said phase transfer catalyst is selected from quaternary ammonium and phosphonium salts, polyglycols, crown ethers and podans.
- 25 15. The process of claim 8 wherein said phase transfer catalyst is methyltrioctylammonium chloride.
16. The process of claim 8 wherein said water-immiscible organic solvent is dichloromethane or toluene.



17. The process of claim 8 wherein said inorganic base is used in solid state or in an aqueous solution.
- 5 18. The process of claim 8 wherein said inorganic base is selected from sodium hydroxide, potassium hydroxide, sodium carbonate and potassium carbonate.
- 10 19. The process of claim 8 wherein the aryl group is selected from phenyl, *p*-tolyl, *p*-chlorophenyl and *p*-nitrophenyl.