PREPARATION OF L-(-)-6-PHENYL-2,3,5,6-TETRAHYDRO-IMIDAZO [2,1-b] THIAZOLE

By

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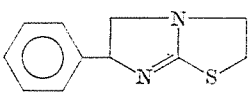
Introduction

The optically inactive racemate of 6-phenyl-2,3,5,6-tetrahydroimidazo-[2,1-b]thiazole (I) is known to be a potent drug for the treatment of helminthiasis in warm-blooded animals.



I

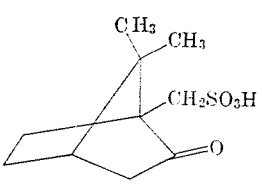
The laevo-isomer L-tetramisole (L—I, Levamisol) is known to be responsible for all of the pharmaceutical activity.

On the other hand the systemic toxicities of D and L-tetramisole are approximately of the same order. It follows that administration of pure L-tetramisole gives anthelmintic activity with substantially reduced risk of toxic reactions [1].

In the last decade, the separation of the isomers of synthetic Tetramisole (DL-I) is coming into prominence.

Chemists of the American Cyanamid Company [2] elaborated processes for the preparation of Levamisol (L-I) by the way of resolution.

They prepared the two isomers of Tetramisole (DL-I) by resolution with d-10-camphorsulfonic acid (II) in the presence of chloroform.



II

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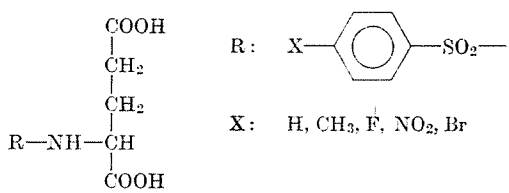
Their method is a very ingenious but very complicate solution. Tetramisole (DL-I) soluted in chloroform was reacted with camphorsulfonic acid, resulting camphorsulfonic acid salt and the insoluble complex camphorsulfonic acid salt was separated from the solution of the optically active compounds while the camphorsulfonic acid salts of the optically active isomers was by crystallization of the diastereometer salts obtained before.

The camphorsulfonic acid is simple to recover because the camphorsulfonic acid salt of Tetramisole precipitates from chloroform, but the camphorsulfonic acid salts of both the L and D-isomer are soluble in chloroform.

The D-(-)-isomer-camphorsulfonate soluted in double amount of chloroform is treated with 0,9 mol of Tetramisole dissolved in tenfold amount of toluene. A crystalline solid separates immediately — DL-I-d-10-camphorsulfonate — the solution contains the free D-(+)-isomer.

The precipitated DL-I-camphorsulfonate can be separated into its two diastereomers by chloroform treatment. Practical difficulties of this process arose from the recovery of the camphorsulfonic acid. Namely, this procedure can be repeated only four times (because of the impurity of the reactive mixture), furthermore the yields of the individual isomers amount to max. 80%, and the external temperature has to be kept below —10 °C.

A year later, Australian researchers (1) attempted to produce the Levamisol (L-I) in aqueous solution by the treatment of several N-acil derivatives of L and D glutamic acid (III).



III

The process is simpler as the above-mentioned, but the yield was by 20% lower, and the optical purity of the product was insufficient, too.

Recently, chemists of the firm RHONE—POULENC elaborated a new method for the resolution of the racemic bases (p. e. Tetramisole, DL-I) [3, 4]. They reacted 0,5 to 0,7 mol of dibenzoyl-d-tartaric acid disodium salt with one mol of DL-I hydrochlorid salt.

The yield was 57 to 60%, the end product was of very high optical purity.

Experimental

Our work started from the full knowledge of the existing patents. Our intention was to elaborate an economical procedure — of a high yield — with adequate optical purity of the product. We repeated the procedures mentioned before.

Experiments exhibited the quoted problems (low temperature, low yield, insufficient optical purity) and detected still others, p.e.: recovery of the solvents, of the resolving agent, the unresolved Tetramisol (DL-I), and the racemization of D-I, inactive in the pharmaceutical therapy. Our work (5) resulted in the economical resolution of Tetramisol (DL-I) with dibenzoyl--tartaric acid, in aqueous solution. One mol of DL-I-hydrochlorid was reacted with dibenzoyl-d-tartaric acid disodium salt, in aqueous solution. The neutral dibenzoyl-d-tartaric acid salt of the L-I, responsible for the pharmaceutical activity, precipitated immediately.

The yield depended on the tabulated molar ratios:

molar ratio	yield (%)
0.25	53.5
0.29	60.0
0.33	67.0
0.50	68.0

The molar ratio 0.33 is seen to practically provide the same yield as the value 0.5 known from the literature. By basic destruction and acidification the obtained neutral salt can be made to hydrochlorid salt of L-I. The unresolved Tetramisol (DL-I) is precipitable with a calculated quantity of NaOH — at a yield of 35 to 38% — and the residual D-I precipitates for further basification of the amount same as the L-I isomer.

From a comparison between our results and the published ones it is apparent that:

1. the loss is minimized (3 to 5%);
2. the resolving agent is recoverable;
3. only the D-I must be racemized;
4. the molar ratio is decreased and so is the volume of reaction mixture;
5. the reaction time decreases, too.

In course of further experiments a new procedure has been found for the resolution of Tetramisole, on a principle different from the published one.

The racemic base is suspended in the 1 : 1 mixture of water and water immiscible organic solvent and warmed until a clear solution is formed. To this mixture 0.33 mol of dibenzoyl-tartaric acid dissolved in the same solvent was added.

The precipitation of a solid mass begins immediately. The precipitated white mass is the neutral dibenzoyl-tartaric acid salt of L-I in a yield of 60%. This salt yields the L-I by basification (or in certain cases by acidification).

After separating the two solvents of the filtrate, the organic phase yields the DL and D-Tetramisole. (The D and DL-I are separable both by this and the first procedure, namely after acidification the basis becomes in form of hydrochlorid salt, to be separated by selective precipitation.)

The advantages of the new method are similar to those of the former (high purity, good yield, recovery of the resolving agent, the unresolved bases etc.).

The D-I-isomer obtained by resolution is racemized in a good yield in the mixture of dimethyl-formamid and benzene, by treatment with K-terc.-butylate — in absence of water. Dibenzoyl-d-tartaric acid has been recovered from the filtrate, obtained by destruction with NH_4OH of precipitated $(L\text{-}I)_2$-dibenzoyl-d-tartarate, adding cc. HCl — to pH = 1.

Examples

1. *Preparation of L-I-dibenzoyl-d-tartarate*

a) 48.0 g (0.2 mol) of DL-I hydrochlorid is soluted in 100 ml of water at 50 °C (pH 6.5). (solution I.) 25.0 g (0.066 mol) of dibenzoyl-d-tartaric acid monohydrate is suspended in 100 ml of water and cc. NaOH is added to the suspension to pH — 6.5. A clear solution is obtained (solution II). The first solution is mixed with the second one, during warming. After adding the last part of solution II., a crystalline mass begins to precipitate (pH 6.5). The reaction mixture is stirred and allowed to cool to room temperature (20 °C). The precipitated salt is filtered and washed with 20 ml of water. Yield (of L-I-dibenzoyl-d-tartarate): 28.3 g (74%)

$[\alpha]_D^{20} = -133°$ (c: 5; MeOH)

b) 40.8 g (0.2 mol) of DL-I-base is suspended in 100 ml of water and aq. cc. HCl is added to pH 6.5, during warmed to 50 °C. Subsequent procedures see in item 1.a.

c) 40.8 g (0.2 mol) of DL-I base (obtained by racemizing D-I, or by recovery: $[\alpha]_D^{20} = +3°$ (c : 5; MeOH))

is suspended in 100 ml of water. Subsequent procedures see in item 1.b.

d) 40.8 g (0.2 mol) of DL-I-base suspended in a mixture of 100 ml 1,2-dichlor-ethane and 80 ml of water and the mixture is warmed until a

clear solution is formed. This reaction mixture is treated with a solution of 25.0 g (0.066 mol) of dibenzoyl-d-tartaric acid monohydrate dissolved in 100 ml hot dichlorethane. A white crystalline mass begins to precipitate. The system is allowed to cool for 30 min. during stirring, to 10 °C. The obtained salt is filtered, washed with 20 ml of water.

Yield (of L-I-dibenzoyl-d-tartarate): 26.9 g (70.1%)

$[\alpha]_D^{20} = -132°$ (c : 5; MeOH)

2. *Recovery of DL-I*

a) To the filtrate (obtained as in 1. a, b, c) 1.4 g of NaOH dissolved in 10 ml of water is added drop by drop. The mixture is cooled to 10 °C, during a time of 30 min. The precipitate is filtered and washed with 15 ml of water.

Yield (of recovered DL-I) 9.4 g (23%)

$[\alpha]_D^{20} = 0°$ (c : 5; MeOH)

b) To the mother liquor obtained as in 1.d, cc. HCl is added drop by drop to pH 6.5 and the two phases are separated. The aqueous phase is treated according to 2.a.

c) To the mixture of 15 g of D-I-base and 9.8 g of DL-I-base 150 ml of water and cc. HCl is added — drop by drop — to pH 6.5, and subsequent procedures are as in item 2.a.

3. *Preparation of D-I*

To the filtrate obtained as in 2.a, or b. cc. NH_4OH is added to pH 9.5. The solution is cooled to 10 °C (during 30 min.), the precipitate is filtered, washed with 15 ml of water.

Yield (of D-I) 13.7 g (67.3%)

$[\alpha]_D^{20} = +72°$ (c : 5; MeOH)

4. *Racemization of D-I*

15 g of D-I is soluted in a mixture of 100 ml of dimethyl-formamid and of 100 ml of benzene. The solution is rectified in vacuo until the water content is decreased to 0.2% N_2 atmosphere, at max. 60 °C. The solution is treated with 1.5 g of K-terc.-butylate and stirred for 30 min. at max. 60 °C. The reaction mixture is clarified, filtered and acidified with cc. HCl to pH 2. The DL-I-hydrochloride precipitates. After stirring at 0 to 5° for 1 hour the precipitate is filtered, washed, and dried.

Yield (of DL-I-hydrochlorid) 14.4 g (96%)

$[\alpha]_D^{20} =$ 0° (c : 5; MeOH)

5. *Preparation of L-I*

The salt obtained as in 1.a, b, c, d is suspended in 100 ml of water, and cc. NH_4OH is added to pH 9.5. The reaction mixture is stirred for 30 min, and cooled to 10 °C. The base is filtered, washed with 2×10 ml of water.

Yield (of L-I) 13.7 g (67.3%)

$[\alpha]_D^{20} = -98°$ (c : 5; MeOH)

6. *Preparation of L-I-hydrochlorid*

a) 28.3 g of L-I-neutral-dibenzoyl-d-tartarate is suspended in 95 ml of water. 150 ml of toluene and cc. NH_4OH is added to pH 9.5. After extraction and separation of the two phases, the organic phase is clarified, desiccated and to this solution HCl dissolved in iso-propyl-alcohol is added. The precipitated L-I-hydrochloride is filtered, and washed with toluene containing iso-propyl-alcohol.

Yield (of L-I-HCl) 16 g (67% calculated as in 1.a, b, c)

$[\alpha]_D^{20} =$ −135° (c : 1; water)

b) The 13.7 g of L-I-base obtained as in 5 is soluted in 150 ml of toluene. Subsequent procedures see in item 6.a.

7. *Recovery of dibenzoyl-d-tartaric acid*

The mother liquor obtained as in an 5., or the aqueous phase obtained as 6.a are combined, and to this solution cc. HCl is added to pH 1 drop by drop during stirring and cooling.

The reaction mixture is stirred for 3 hours, filtered, washed with 3×15 ml of water.

Yield (of dibenzoyl-d-tartaric acid) 24.0 g (96%)

$[\alpha]_D^{20} =$ −116° (c : 5; MeOH)

Summary

Possibilities of the preparing L-isomer starting from DL-6-phenyl-2,3,5,6-tetrahydro--imidazo [2,1-b] thiazole (I) are examined.

The optical isomers are separated with dibenzoyl-d-tartaric acid, from aqueous solution, and from a mixture of water and water immiscible organic solvent.

The L-I-neutral- dibenzoyl-d-tartarate precipitates. The D-isomer remains in the solution as a salt of hydrogen chlorid or in free form in a water immiscible solvent. The separation is incomplete, therefore the impure base is purified by selective precipitation.

The D-isomer can be racemized with K-terc.-butylate in a mixture of dimethyl-formamid and benzene.

The recovered substances (racemic compound, racemized D-isomer, recovered dibenzoyl--d-tartaric acid) can be re-used.

References

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4. Ger. Offen 1, 908. 802
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