SEPARATION OF OPTICAL ISOMERS OF THE (±)-3--CARBOXY-4-OXO-6-METHYL-6,7,8,9-TETRAHYDRO-4-H--PYRIDO[1,2-a]PYRIMIDINE AND OF THE DL-THREO-1--(p-NITROPHENYL)-2-AMINO-PROPANDIOL-1,3 BY MUTUAL RESOLUTION

I. PREPARATION OF OPTICAL ISOMERS OF 3-CARBOXY-4-OXO-TETRAHYDRO-4-H--PYRIDO[1,2-a]PYRIMIDINE BY TREATMENT WITH OPTICALLY ACTIVE THREO-1-(*p*-NITROPHENYL)-2-AMINO-PROPANDIOL-1,3

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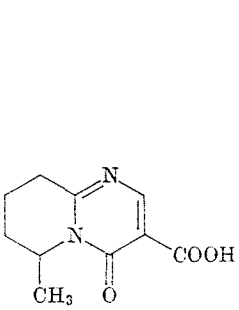
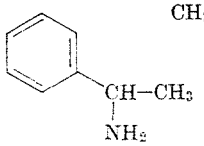
Introduction

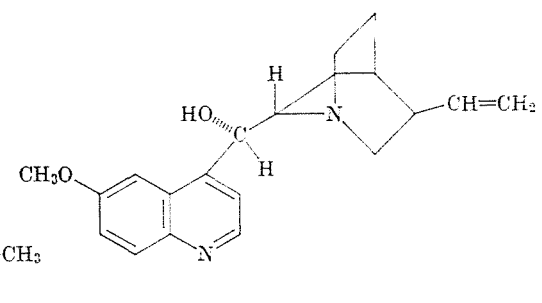
The optical isomers of 3-carboxy-4-oxo-6-methyl-6,7,8,9-tetrahydro-4-H--pyrido[1,2-a]pyrimidine (I) were prepared by the reaction of racemic I with optically active bases, such as (+) and (−)-phenylethyl-amine (II) or quinine (III) (1). Only the resolution accomplished with (+) and (−)-II will be written in detail.



I



II



III

The procedure is very complicated and uneconomical.

The mixture of one mol of racemic-I and one mol of (+)-II is refluxed in 95% dimethoxy-ethane, until a clear solution is formed. The solution is allowed to stand overnight at room temperature, and the crystalline salt is filtered. The crude salt of (−)-I-(+)-II is recrystallized three times from the same solvent. From this salt, the (−)-I is obtained at a yield of 25%.

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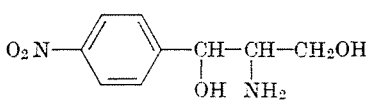
The residue obtained by the concentration of mother liquor is soluted in water and the mixture of 80% (±) and 20% (+)-acid precipitated by acidification with aq. cc. HCl. The (+)-isomer is extracted from the filtrate. This (+)-isomer is reacted with (−)-II in ethylacetate and the crude salt is recrystallized many times from ethylacetate. In this manner, the (+)-isomer is obtained at a yield of 13%. The procedure is not suitable for the production because of the cost of solvents, of the resolving agent, and of the low yield.

The compound I contains many free functional (imino, carboxyl and carbonyl) groups. The compound is amphoteric in character (isoelectric point 3.2). Therefore it is resolvable as a free amino acid in compounds of basic character, without blocking any functional group.

Experimental

A cheaper basic resolving agent as the one known from the cited paper had to be found, for the compound I.

The intermediate, otherwise useless compounds, L-(+)threo-1-(*p*-nitrophenyl)-2-amino-propan-1,3-diol (IV) of the production of Chlorocid gave good results.



IV

Several solvents (p.e. water, alcohols), have been tested best being water.

In general, the resolutions are realized in dilute solutions, because

1. the different solubilities eliminate concentrated solutions;

2. it is reasonable to start the crystallization from clear solutions (to obtain pure substances, see in 1), and the solubility of starting materials is mostly quite low.

Therefore the possibility of resolution of racemic-I with L-(+)-IV in dilute solution, has been examined but crystallization started only from concentrated solution. Without seed crystal, the obtained salt was impure. The yield of (−)-I-L-(+)-IV salt depending on the amount of water, at various molar ratios is done in Fig. 1.

The amount of water was further reduced by solving racemic-I in equ. cc. NH_4OH and adding solid L-(+)-IV. $HCl \cdot H_2O$. Decreasing the amount of solvent, eliminated the problem of handling big volumes.

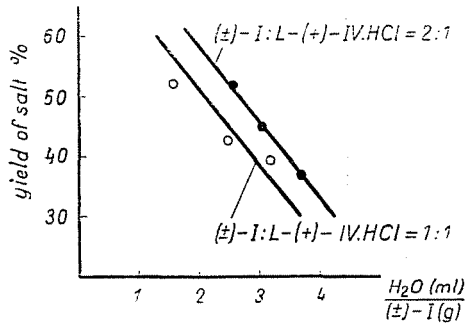


Fig. 1. Yield of (−)—I—L—(+)—IV salt vs. water quantity

Material quantities can further be reduced by adequate molar ratios. Based on the experiences with resolutions via diastereomer formation, the best separation of isomers results from one mol of resolving agent to 2 mols of racemic compounds. One salt formed from the resolving agent and an optically active isomer precipitates (in a ratio determined by the solubility in the said solvent). To the other isomer can be kept in solution in various ways.

1. Salt formation with some optically inactive base (or acid) (3).
2. It remains in the solution on free state (4).
3. It remains in a water-immiscible organic solvent (5) (stem 3 is valid to aqueous solutions alone, to the sense). Results of the resolution of racemic-I with L—(+)—IV are summarized in Fig. 2.

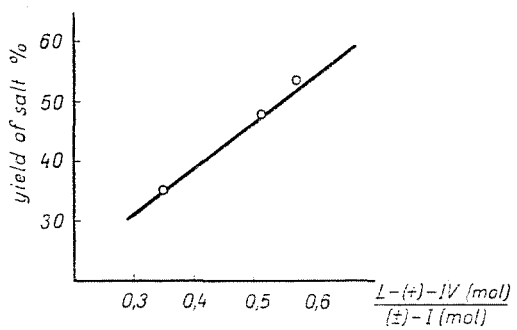


Fig. 2. Yield of (−)—I—L—(+)—IV salt vs. molar ratio

Comparison of Figs 1, 2. shows the yield to be independent of the molar ratio between the values 1—2, therefore compound purity, and other considerations induced us to the further experiments with 1 : 1 molar ratio.

Yield was at its maximum for pH 6.5, corresponding to that in mixing the two neutral solutions, as shown in Fig. 3.

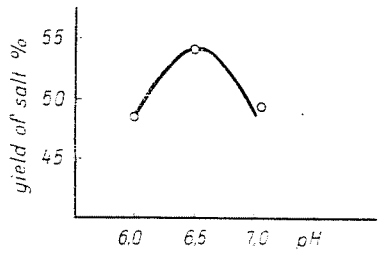


Fig. 3. Yield of (−)−I−L−(+)−IV salt vs. pH

The precipitated (−)−I−L−(+)−IV salt is impure with the salt of (+)-isomer, and so is the (+)−I−L−(+)−IV salt residue in the mother liquor, for this reason the problem of the purification of isomers had to be solved. Recrystallization of the precipitated salt is very lossy therefore purification of the liberated (−)−I isomer has been considered. For the preparation of (−)−I there are many possibilities.

1. Basification of the solution precipitates L−(+)−IV separable by filtration. The (−)−I is precipitable by acidification from the mother liquor.

2. Separation of the (−)−I, after then, of the L−(+)−IV from the salt dissolved in warm water.

The (−)−I is impure with (+)−I, hence a part is present in form of racemic molecule compound. The racemic compound is less soluble, therefore is precipitated first by acidification. Accordingly combining of the procedures of liberating and purifying (−)−I resulted in the following method: The (−)−I−L−(+)−IV salt is dissolved in warm water, acidified to pH 4. Upon to cooling, (+)−I precipitated. The pure (−)−L−(+)−IV salt remained in the solution. It was destructed and (−)−I was prepared by combined acidification and extraction with chloroform (acidification alone is not sufficient because at the pH 3.2, — isoelectric point of I — the L−(+)−IV hydrochloride precipitates too).

Recapitulation of the new procedure: Racemic−I is suspended in water, cc. NH_4OH added to the total solubilization (pH 7), then solid L−(+)−IV hydrochloride monohydrate is added. Temporarily a clear solution arises, then crystallization begins. The (−)−I−L−(+)−IV salt is filtered, redissolved in water, (and so is mother liquor) basification followed by extraction with chloroform yields (−) (or (+)−I. To purify the antipodes — since the racemic form is less soluble than the single isomers — selective precipitation (2) and extraction have been combined.

Applying — as resolving agent — the very expensive D−(−)−IV, then the precipitated salt is (+)−I−D−(−)−IV and the salt of (−) enantiomer remains in the solution.

(All the other parameters are idem with the described ones.)

Examples

1. *Preparation of* (−)−*I*−*L*−(+)−*IV salt*

368 g (1.77 mol) of racemic-I is suspended in 900 ml of water, warmed to 40 to 50 °C and basified to pH 7 with cc. NH_4OH.

To this stirred solution is added 460.5 g (1.73 mol) of solid L−(+)−IV. HCl · H_2O ($[\alpha]_D^{20} = +30°$ (c : 2; water)).

The arising clear solution (pH 6.5) is cooled to room temperature, seeded by (−)−I−L−(+)−IV salt. The crystallization is beginning. The precipitated salt is filtered, washed with 2×50 ml of water.

Yield: 290 g, 78%

$[\alpha]_D^{20} = -45°$ (c : 2; MeOH)

mp: 138°

2. *Preparation of* (−)−*I*

a) The salt obtained as in 1 is suspended in 2 l of water and warmed to 60 °C. The solution contains 4% of (−)−I. The solution is acidified to pH 2 with cc. HCl, then cooled in ice bath for two hours. The precipitate is filtered.

Yield: 22.1 g

$[\alpha]_D^{20} = -35°$ (c : 2; MeOH)

mp: 132°

b) The filtrate is extracted with 4×200 ml of chloroform, the organic phase is separated, dried with Na_2SO_4, and concentrated in vacuo. The residue is the (−)−I, a good pulverisable material.

Yield: 108.7 g, 58.9%

$[\alpha]_D^{20} = -93°$ (c : 2; MeOH)

mp: 119°
optical purity (o. p.): 91%

3. *Preparation of* (+)−*I*

The mother liquor of 1 is further diluted with 1 l of water. (The solution contains 4% (+)−I.) The further treatment is analog to the ones described in item 2.

a) yield: 118 g

$[\alpha]_D^{20} = -15°$ (c : 2; MeOH)

mp: 138 °C

b) yield: 107 g, 58.3%

$[\alpha]_D^{20} = +90°$ (c : 2; MeOH)

mp: 119 °C

op: 90.5%

4. *Recovery of* (±)—*I*

The combined materials (I) obtained according to 2)a ($[\alpha]_D^{20} = -35°$) and 3)a ($[\alpha]_D^{20} = -15°$) are resolvable again. The loss of one step of the procedure is 3—4% calculated for the (±)—I-acid.

5. *Purification of* (—)—*I*

a) 108.7 g of (—)—I ($[\alpha]_D^{20} = -93°$ (c : 2; MeOH)) is suspended in 500 ml of water and basified with cc. NH_4OH to pH 7, then acidified to pH 1.5 with cc. HCl, allowed to stand at room temperature, then the precipitated crystals are filtered.

Yield: 84.7 g, 78%

$[\alpha]_D^{20} = -68°$ (c : 2; MeOH)

mp: 128 °C

b) The filtrate is extracted with ×100 ml of chloroform, the combined organic phases are dried, concentrated in vacuo.

Yield of residue: 22.1 g, 20.5%

$[\alpha]_D^{20} = -115°$ (c : 2; MeOH)

mp: 114 °C

6. *Purification of* (+)—*I*

a) The 107 g ($[\alpha]_D^{20} = +90°$ (c : 2; MeOH)) of (+)—I obtained as 3)b is treated as described for 5)a.

Yield: 82.1 g, 76%

$[\alpha]_D^{20} = +65°$ (c : 2; MeOH)

mp: 130 °C

b) The filtrate obtained as in 6)a is treated as in 5)b.
Yield of residue: 20.4 g, 19%

$[\alpha]_D^{20} = +115°$ (c : 2; MeOH)

mp: 113—5 °C

7. *Recovery of L—(+)—IV*

The aqueous phase obtained by chloroform extraction according to 2)b and 3)b are combined, and basified with cc. NH_4OH to pH 9. The solution is allowed to stand overnight at room temperature and the crystalline salt is filtered, dried.

Yield of obtained L—(+)—IV: 320 g, 87% (calculated to L—(+)—IV. HCl. H_2O).

The base is suspended in 300 ml of water and to this suspension cc. HCl is added drop by drop to pH 1. The solution is allowed to stand overnight at room temperature. The L—(+)—IV. HCl · H_2O is filtered and dried.

$[\alpha]_D^{20} = +30°$ (c: 2; MeOH)

mp: 159—160 °C

Summary

The optical isomers of (±)-3-carboxy-4-oxo-6-methyl-6,7,8,9-tetrahydro-4GH--pyrido[1,2-a]pyrimidine are prepared by a new method. The resolution is accomplished with L-(+)— and D-(—)-threo-1-(*p*-nitrophenyl)-1-amino-propan-diol-1,3 in aqueous medium. Problems of recovery of all the involved substances have been solved.

References

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