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

PREPARATION OF THE OPTICAL ISOMERS OF DL-THREO-1-(P-NITROPHENYL)-2-AMINO-PROPANEDIOL USING OPTICALLY ACTIVE 3-CARBOXY-4-OXO-6-METHYL-6,7,8,9-TETRAHYDRO-4H-PYRIDO(1,2-a)PYRIMIDINE

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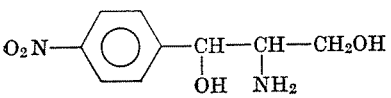
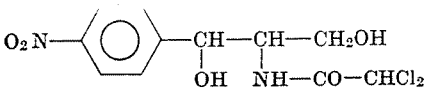
D-(—)-threo-2-amino-1-(p-NO_2-phenyl)-propanediol-1,3 (*I*) is an intermediate product in the manufacture of Chlorocide (II).



I



II

Owing to the difference in the biological activity of D-II and L-II' it is necessary to separate the optical antipodes.

Different synthesis paths have been effectuated resolving different compounds in different stages of the synthesis. One of these consists in the separation of the antipodes of *I*. The first paper discussing the resolution of *I* appeared in 1949. Numerous methods have been reported since, with the common disadvantage that *I* cannot be racemized without further transformation. In some of these methods, no optically active auxiliary agent is utilized (so-called spontaneous crystallization methods), while in other methods diastereomer salt formation is being used, utilizing various resolving acids, or — after some transformations — various resolving bases.

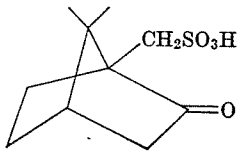
Velluz and co-workers [1] stated, based on thermal analysis and IR spectroscopic results, that DL-threo-*I* is a racemic (racemic solid solution) (1:1) of the D and L forms.

According to Collet and co-workers [2], in such cases the optical antipodes can be separated by spontaneous crystallization in any required purity grade (depending on the purity of the seed crystal, cf. Marckwald principle [3]).

* CHINOIN Pharmaceutical and Chemical Products Co.

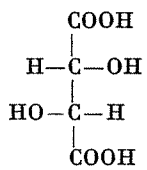
D-*I* and L-*I* can be separated without adding an optically active agent [4, 5]. When a solution of *I* in aqueous hydrochloric acid is inoculated with the pure L-*I* base, addition of alkali will precipitate the L-base from the solution with a yield of 24%.

One of the first methods based on diastereomer salt formation was reported by CONTROULIS and co-workers [6]. They resolved *I* in isopropanolic solution using camphor-10-sulphonic acid (III).



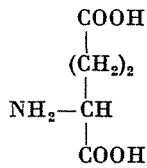
III

Simpler and less expensive methods for resolving *I* also exist. Tartaric acid (IV) proved successful in aqueous solution [7].



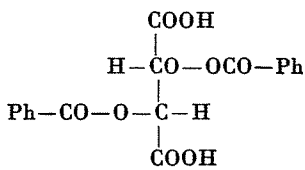
IV

Glutamic acid (V) has been applied in aqueous ethanolic [8] and in ethanolic [9] solution



V

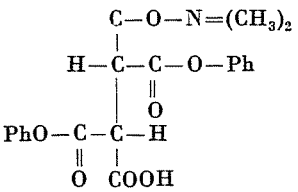
The sodium salt of dibenzoyl-tartaric acid (VI) has been utilized to resolve the neutral salt of *I* [10].



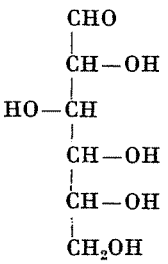
VI

Hungarian researchers also developed several methods for resolving this intermediate product of Chlorocide manufacture. Researchers of the CHINOIN Pharmaceutical and Chemical Products Co. utilized dibenzoyltartaric acid-dimethylsemiamide (VII) [11], researchers of the United Pharmaceuticals and Nutriments Co. its calcium salt [12] to separate the optical isomers of *I*.

It is interesting to note that even glucose (VIII) — which is rarely used for such purposes — was a successful agent in absolute ethanolic solution [13].



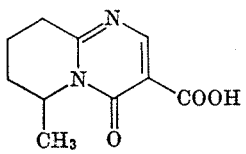
VII



VIII

Experimental

In an earlier paper [14] we reported that *I* is a successful resolving agent for 3-carboxy-4-oxo-6-methyl-6,7,8,9-tetrahydro-4H-pyrido(1,2-a)pyrimidine (IX) in aqueous solution.



IX

Accordingly, the question presented itself whether this process is reversible, that is, could DL-*I* be resolved with (+)-IX and (—)-IX, these latter having been obtained by using L(+)-threo-*I*.

In the literature relatively few examples for such "cross-resolving" or mutual resolution could be found.

MISLOW [16] maintains that reversibility is not imperative. He supports his argumentation by simple sequence of equations. (D, L, D' and L' stand for optically active compounds, DL and D'L' for racemic compounds.)

When DL is successfully resolved with D' and L', resp., the following equilibria, largely shifted to the right-hand side, will be established:

(i) $DL + D' \rightleftharpoons DD' + LD'$ the two reaction mixtures are enantiomeric
(ii) $DL + L' \rightleftharpoons DL' + LL''$

When D'L' is being resolved with D and L, resp., the corresponding equations will be

(iii) $D'L' + D \rightleftharpoons D'D + L'D$
(iv) $D'L' + L \rightleftharpoons D'L + L'L$

A comparison of the right-hand sides demonstrates that whereas (i) and (ii), and (iii) and (iv), resp., are enantiomeric, (i) and (iii), (ii) and (iv), (i) and (iv), (ii) and (iii) are diastereomers, that is at least two asymmetry centres are different (e.g. LD' and L'D in (i) and (iii)). Hence, while DL can necessarily be resolved with D', if it could be resolved with L', D'L' is not necessarily resolvable with the isomers of DL.

In MISLOW's statement he disregarded PASTEUR's observation [15] that asymmetric systems behave identically towards symmetric systems, but differently towards asymmetric systems. Hence it may be concluded that D'L' might be resolvable with D and L, resp., perhaps requiring a slight variation of the conditions. We therefore attempted to resolve *I* with d-IX and l-IX.

The method, answering our expectation, proved succesful. The optical isomers of *I* could be separated using 1 mol resolving agent per mol.

In a 50% aqueous solution of 1 mol *I* HCl we dissolved 1 mol (—)-IX and adjusted the pH value to 7 with NH_4OH. Seed crystals were added to accelerate precipitation. As expected, L(+)-threo-*I* was obtained with (—)-IX, and correspondingly D(—)-threo-*I* with (+)-IX.

After filtering off the diastereomer salt, the mother liquor is further processed in the following way:

After adjusting pH to 9 with NH_4OH, precipitation of D(—)-threo-*I* that had remained in the solution will start. The resolving agent, i.e. (—)-IX can be recovered from the filtrate by acidifying it with conc. HCl to pH 2 and subsequent extraction with chloroform repeated four times. Evaporation of the chloroform yields (—)-IX suitable for further resolving operations. From the diastereomer salt, a 20% solution is made and processed similarly to the mother liquor.

The obtained D(—)-threo-*I* and L(+)-threo-*I* compounds are not pure. This can be due to two reasons:

(i) It follows from the MISLOW principle that if the resolving agent is not 100% pure, the precipitated salt cannot be pure either, as shown by the followings.

R is the optically active resolving agent, and *r* is the contaminating modification, namely the optical antipode of R. We then have

$$DL + Rr \rightarrow DR + LR + Dr + Lr \quad (R : r \gg 1)$$

DR and Lr as well as LR and Dr are pairs of optical antipodes, so that the probability of their precipitation is identical.

(ii) Solubility conditions do not result either in complete solubility of LR or in complete insolubility of DR.

Procedures

1. Resolving of DL-threo-I with (—)-IX

In a 50% aqueous solution of 460 g (1.73 mol) DL-threo-I · HCl, 368 g (1.77 mol) (l)-IX ($[\alpha]_D^{20} = -100°$, c = 2; MeOH) are dissolved at 60—70 °C under constant stirring. pH is adjusted to 7 with conc. NH_4OH. In the cooled solution (eventually effected by adding seed crystals of the L(+)-I-(—)-IX salt) crystallization will start. This is made complete by cooling with ice. The crystals are filtered, washed with water and dried.
Yield: 154 g

2. Preparation of D(—)-threo-I

The mother liquor obtained after filtering off the diastereomer salt L(+)-I-(—)-IX is made alkaline with conc.NH_4OH to pH 9. At this value D(—)-threo-I crystallizes. The crystals are filtered, washed with water and dried.
Yield: 193 g
M.p.: 127 °C.
$[\alpha]_D^{20} = -6.5°$ (c = 2; nHCl)

3. Preparation of L(+)-threo-I

The diastereomer salt L-(+)-I-(—)-IX obtained according to paragraph 1 is dissolved in 2000 cm^3 water. Further processing is the same as described in paragraph 2.
Yield: 92 g
M.p.: 161.5 °C
$[\alpha]_D^{20} = +17.5$ (c = 2; nHCl)

4. Preparation of (—)-IX

The mother liquor obtained after filtering of D(—)-threo-I and L(+)-threo-I, resp., as described in paragraphs 2 and 3, is acidified with conc. HCl to pH 2. The resolving agent is recovered by extraction with 4×100 ml chloroform. The united extracts are dried over anhydrous Na_2SO_4 and chloroform is removed by evaporation.
Residue: 95 g
M.p.: 116 °C.
$[\alpha]_D^{20} = -94°$ (c = 2; MeOH)

5. Resolving of DL-threo-I with (+)-IX

The procedure is the same as described in paragraph 1. (Characteristics of (+)-IX: $[\alpha]_D^{20} = 94.5°$, c = 2; MeOH.)
Yield: 166 g

6. Preparation of L(+)-threo-I

Cf. paragraph 2.
Yield: 197.0 g
M.p.: 135 °C
$[\alpha]_D^{20} = +7.8°$ (c = 2; nHCl)

7. Preparation of D(—)-threo-I

Cf. paragraph 3.
Yield: 93.5 g
M.p.: 161 °C
$[\alpha]_D^{20} = -17.5°$ (c = 2; nHCl)

Summary

Racemic threo-2-amino-1(p-nitrophenyl)-propanediol-1,3 can be resolved with the optical isomers of 3-carboxy-4-oxo-6-methyl-6,7,8,9-tetrahydro-4H-pyrido(1,2-a)pyrimidine at molar ratios of 1:1 in aqueous solutions at pH 6.5. The point of interest of this method is that the two compounds can mutually serve as resolving agents for one another.

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