Tetrahedron Letters,Vol.27,No.48,pp 5865-5868,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SIMPLE OPTICAL RESOLUTION OF TERLEUCINE

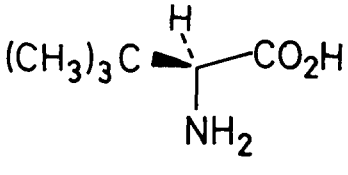
Joëlle Viret, Heiko Patzelt, and André Collet
Chimie des Interactions moléculaires, E.R. C.N.R.S. 285, Collège de France
11, place Marcelin-Berthelot, 75005 Paris, France

Summary : Underivatized terleucine (1) can be conveniently resolved into its L- and D-enantiomers by recrystallization of its diastereoisomeric 10-camphorsulfonate salts.

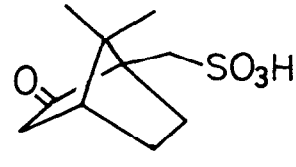
We report the first simple optical resolution of terleucine (1) into its L- and D-enantiomers. This unusual amino acid has recently proved to be a valuable chiral inducer in various asymmetric syntheses.[1-4] It has also been employed as a substitute for leucine or other amino acids in modified peptides (enkephalin, vasopressin and oxytoxin analogues).[5-7]

Since the first synthesis of DL-1 in 1914,[8] several optical resolution procedures have been reported, in which the amino or acidic function has to be protected prior to interaction with the resolving agent. The N-formyl[9] and N-tosyl[10] derivatives have been resolved by crystallization of their brucine salts, the N-acetyl[11] and N-benzyloxycarbonyl[12] compounds by their cinchonidine and quinine (or quinidine) salts, respectively, whereas the methyl[13] and ethyl[10] esters have been separated as their dibenzoyltartrate salts. Apart from these methods which often have been reported to be tedious and/or inefficient,[3] there is an ingenious asymmetric transformation whereby DL-1 can be converted to L-1 (60%) in four steps through dipeptide formation with L-methyl glutamate,[14] and two enzymatic processes,[15,16] in which DL-terleucinamide or DL-N-phenylacetyl-1 are hydrolyzed to L-1 in the presence of hog kidney amylase or penicillin-G-amidase, respectively.

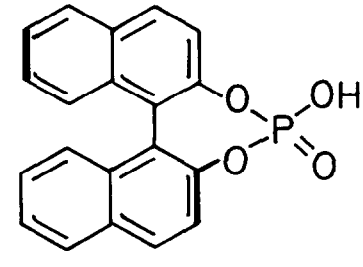
The direct resolution of free amino acids is obviously a more attractive process than that involving prior introduction and subsequent cleavage of a protecting group.[17a] Strong acidic resolving agents are sometimes capable of forming, with neutral, unprotected amino acids, nicely crystalline



L-1



(+)-2

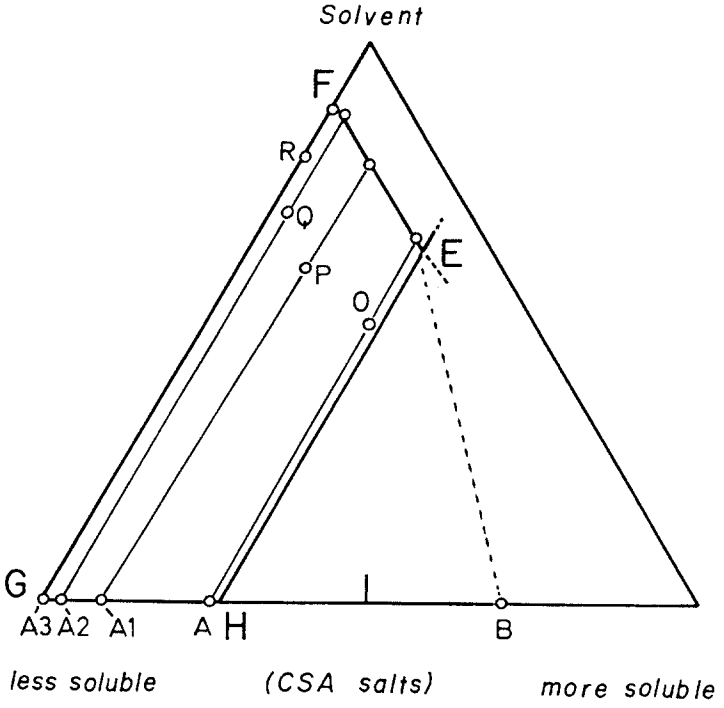


S-(+)-3

salts that are analogous in nature to amino acid hydrochlorides. For instance DL-phenylglycine[18] and DL-o-tyrosine[19] have been efficiently resolved by formation of diastereoisomeric salts with 10-camphorsulfonic acid (CSA, 2) and binaphthylphosporic acid (BNP, 3), respectively. We have found that DL-1 readily formed crystalline salts with both these chiral reagents in ethanol. BNP, however, revealed to be unsuitable for a complete separation, presumably due to the formation of unfavorable solid solutions between the diastereoisomeric salts. On the contrary, separation of the CSA salts proved quite satisfactory.

In order to optimize the resolution we first seeked for the main features of the ternary phase diagram of the diastereoisomeric CSA salts in 95% ethanol, at 20°C (Figure 1).[17b,21] From the eutectic location (E), the solubility curve of the less soluble [(+)-CSA L-1] salt (EF) and the terminal solid solution range (GH), the procedure described below was set up. In such a situation, the philosophy is to separate, at the very first crystallization, about 50% of a salt (A) whose composition would then roughly correspond to that of the solid solution boundary (H), from approximately the same weight of a salt (B) of nearly symmetrical composition in the mother liquors. Then A is recrystallized (two or three times) until the desired enantiomeric purity is attained, while B is cleaved back to partially resolved I; the latter is combined with CSA of opposite sign to give new salt C, which is worked up like A.

Figure 1[21]



Illustrative procedure. DL-Terleucine[20] (20 g, 0.153 mol) and (+)-CSA (35.44 g, 0.153 mol) were dissolved in hot 95% ethanol (55.4 g) and the solution (point O in Figure 1) was stirred in a thermostatted water bath (20°C) overnight (minimum crystallization duration 10 h). The solid was collected by suction filtration, washed with a small amount of absolute ethanol, and dried in air. Yield 23.5 g (43 %) of salt A, m.p. ca. 188-195°C (by DSC).[22] In order to determine the e.e.[23] of **1** in this salt, ca. 150 mg were cleaved by percolation through a Dowex 1X2 column (OH form) using 1N acetic acid as the eluant; the recovered **1** showed $[\alpha]_D^{25}$ +14.5° (AcOH, c=1), e.e. ∿47%. The mother liquors evaporated to dryness (B in Figure 1) and cleaved back to terleucine by the same procedure yielded 10.8 g (54%) of **1** with $[\alpha]_D^{25}$ -13.2° (AcOH, c=1), e.e. ∿43%.

Recrystallization of A (23.2 g) in 95% ethanol (34.8 g, P in Figure 1) at 20°C (overnight stirring) gave salt **A1** (14.2 g, 61%), m.p. 189-198°C, e.e. of **1** 85%; recrystallization of **A1** (13.9 g) in 32.4 g of ethanol (Q) yielded **A2** (9.5 g, 68%), m.p. 204-207°C, e.e. 95%. Finally, recrystallization of **A2** (9.4 g) from 36.4 g of ethanol (R) afforded **A3** (4.5 g), m.p. 209-211°C, which on cleavage (Dowex 1X2 (OH), 1N AcOH) furnished 1.5 g (95%) of L-**1**, $[\alpha]_D^{25}$ +30.0°, $[\alpha]_{546}^{25}$ +36.0°, $[\alpha]_{365}^{25}$ +110.1° (AcOH, c=1), e.e. ⩾98%.[24,25]

On the other hand, the sample of terleucine recovered from the original mother liquors (B) (10.2 g) was combined with (-)-CSA (18.1 g) in 34.6 g of 95% ethanol, giving 17.6 g of salt **C1**, e.e. ca. 80%. Two recrystallizations of this salt as described above for **A1** eventually afforded salt **C3** (6.6 g), m.p. 208-210°C, from which D-terleucine was recovered in 98% yield (2.3 g); $[\alpha]_D^{25}$ -31.4°, $[\alpha]_{546}^{25}$ -37.4°, $[\alpha]_{365}^{25}$ -111.6° (AcOH, c=1), e.e. ⩾98%.[24,25]

The overall yield of pure L- and D-**1** from DL-**1** is ca. 23%, without taking into account the partially resolved **1** which can be recovered in ca. 90% yield from the mother liquors by using the ion exchange procedure. The (+)- and (-)-CSA can be easily recovered from the resin by elution with dilute ammonia. This method is especially suitable for obtaining gram quantities (1-10 g) of resolved **1** in a short time (ca. 3 days overall) on a laboratory scale.

References and Notes

1) S. Hashimoto and K. Koga Chem. Pharm. Bull. 1979, **27**, 2760.
2) H. Kogen, K. Tomioka, S. Hashimoto and K. Koga Tetrahedron 1983, **37**, 3951.
3) U. Schöllkopf Tetrahedron 1983, **39**, 2085.
4) U. Schöllkopf and R. Schever Liebigs Ann. Chem. 1984, 939.
5) J.-L. Fauchère and C. Peterman Helv. Chim. Acta 1980, **63**, 825.
6) J. Pospisek and K. Blaha Coll. Czechoslov. Chem. Commun. 1977, **42**, 1069.
7) M. Lebl, J. Pospisek, J. Hlavacek, T. Barth, P. Malon, L. Servitova, K. Hauser and and K. Jost Coll. Czechoslov. Chem. Commun. 1982, **47**, 689.
8) F. Knoop and G. Landmann Z. physiol. Chem. 1914, **89**, 157.
9) E. Abderhalden, W. Faust and E. Haase Z. physiol. Chem. 1934, **228**, 187.

10) D.A. Jaeger, M.D. Broadhurst and D.J. Cram J. Am. Chem. Soc. 1979, **101**, 717.
11) T. Tanabe, S. Yajima and M. Imaida Chem. Pharm. Bull. 1968, **41**, 2178.
12) T. Miyazawa, K. Takashima, Y. Mitsuda, T. Yamada, S. Kuwaka and H. Watanabe Bull. Chem. Soc. Jpn. 1979, **52**, 1539.
13) H. Pracejus and S. Winter Chem. Ber. 1964, **97**, 3173.
14) W. Steglich, E. Frauendorfer and F. Weygand Chem. Ber. 1971, **104**, 687.
15) N. Izumiya, Shou-Cheng J. Fu, S.M. Birnbaum and J.P. Greenstein J. Biol. Chem. 1953, **205**, 221.
16) S. Grabley, M. Schlingmann (Hoechst A.-G.) **Ger. Offen.** DE 3,334,848; Chem. Abstr. 1986, **104**, 34334.
17) J. Jacques, A. Collet and S.H. Wilen "Enantiomers, Racemates and Resolutions", J. Wiley & Sons ed., New York, 1981; (a) p. 261; (b) p. 389.
18) A.W. Ingersoll J. Am. Chem. Soc. 1925, **47**, 1168.
19) A. Garnier-Suillerot, J.-P. Albertini, A. Collet, L. Faury, J.-M. Pastor and L. Tosi J. Chem. Soc., Dalton trans. 1981, 2544.

20) A combination of several reported procedures[8,10,12] was found convenient for the synthesis of DL-1. To a well stirred mixture of $KMnO_4$ (155 g), NaOH (50 g) and water (500 ml), cooled in an ice-salt bath, was added dropwise 62.5 ml of pinacolone at such a rate that the temperature did not exceed 0°C. This operation was repeated three additional times in the same (5 l) flask. After MnO_2 had been separated off, the aqueous solution was acidified (HCl), and a solution of phenylhydrazine (220 ml) in acetic acid (400 ml) was slowly added with stirring. After 24 h standing the yellow precipitate was collected and recrystallized from 70% ethanol, yielding 356 g (87%) of trimethylpyruvic acid phenylhydrazone, m.p. 172°C. This phenylhydrazone was then hydrogenated to DL-1 as described.[12]

21) In the isothermal solubility diagram of figure 1, the compositions are expressed in g per 100 g of the whole mixture (g%); solubility of the less soluble salt (**F**) in 95% ethanol, 20°C, ca. 11 g%; eutectic composition (E), concentration ca. 34 g%, with 40% excess of the more soluble salt; solid solution boundary (**H**) ca. 45% excess of the less soluble salt.

22) Melting point were recorded on a Perkin Elmer DSC2 differential microcalorimeter connected to a HP86 computer for data acquisition and processing; scanning rate 5 K/min, sample size ca. 1.5 mg.

23) The maximum rotation of **1** was considered to be $[\alpha]_D^{25}$ 30.7±0.7° in glacial acetic acid, c=1, based on the chiral g.l.c. analysis of the final samples (see note 24); lit. $[\alpha]_D^{26}$ +30° (acetic acid, c=1),[12] and $[\alpha]_D^{25}$ +36° (acetic acid, c=2),[14] for L-terleucine.

24) The N-trifluoroacetyl-isopropyl ester of this sample showed a single peak by g.l.c. analysis on a Chrompack S-Valine-S-phenylethylamide capillary column, 50 m length, 110°C, carrier gas He 1.5 bar; a racemic sample was fully resolved under these conditions, with $\alpha \simeq 1.037$ and the D isomer first eluted; 1% of the other enantiomer in the resolved samples would have been detected. We thank Dr R. Azerad (Faculté de Médecine, Paris) for these measurements.

25) No m.p. could be recorded by DSC for L-, D-, or DL-1, due to sublimation above 200°C.

(Received in France 9 October 1986)