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Note on the Resolution of DL-Norvaline

P. Alaupović

Department of Chemistry, Faculty of Medicine, University of Zagreb, Šalata 3, Croatia, Yugoslavia

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For the stereospecific synthesis of necrosamine (4,5-diaminoeicosane) and similar diamines which has been carried out in this laboratory[1] it was necessary to develop a simple chemical method for the resolution of DL-norvaline.

Both enantiomers of norvaline were first prepared by Abderhalden and Kürten[2] by the resolving of *N*-formyl derivative with brucine. Recently, Velluz et al.[3] resolved successfully *N,N*-dibenzyl-DL-norvaline by means of D- and L-*threo*-1-*p*-nitrophenyl-2-amino-propandiol-1,3. Norvaline was also resolved enzymatically with acylase by Greenstein et al.[4] and with papain by Albertson[5].

In this note the resolution of *N*-acetyl-DL-norvaline by means of (-)- and (+)-α-phenylethylamine is reported following the analogous procedure applied for the resolution of norleucine by Huffman and Ingersoll[6]. Both enantiomeric salts *N*-acetyl-L-norvaline — (+)-α-phenylethylamine and *N*-acetyl-D-norvaline — (-)-α-phenylethylamine were obtained in an average yield of 60—70% and 30—35% respectively. Since (+)- and (-)-α-phenylethylamine became readily available[7] and N-acetyl-DL-norvaline is found to be more stable against hydrolysis — which occurs during the crystallization[8] — than the *N*-formyl derivative this method represents a favourable source for L- and D-norvaline.

EXPERIMENTAL

The melting points are uncorrected.

N-*Acetyl*-DL-*norvaline*

The substance was prepared in 65—70% yield according to the procedure given for the preparation of *N*-acetyl-DL-leucine by DeWitt and Ingersoll[9], and melted at 118—119°.

N-*Acetyl*-L-*norvaline* — (+)-α-*Phenylethylamine Salt*

N-Acetyl-DL-norvaline (5.20 g., 0.032 mole) and (+)-α-phenylethylamine (3.97 g., 0.032 mole) were dissolved in a boiling mixture of acetone (500 ml.) and methanol (30 ml.) and the solution allowed to stand at 0° overnight. The separated salt was collected (4.9 g., m.p. 165—168°) and recrystallized from a mixture of acetone (400 ml.) and methanol (30 ml.). By cooling the solution colourless crystals were obtained (2.42 g., m.p. 184—186°). The second crop (0.34 g., m.p. 184—186°) crystallized after evaporation of the mother liquid to half of its volume. The total yield on the less soluble diastereomeric salt was 2.76 g. (60.2%). A sample for analysis was recrystallized from acetone; colourless leaflets, m.p. 185—186°, $[\alpha]_D^{20}$ — 15.3° (c 2.6, in water).

Anal. 5.490 mg. subst.: 0.470 ml. N_2 (26.5°, 745 mm)
$C_{15}H_{24}O_3N_2$ (280.36) calc'd.: N 9.99%
found: N 9.57%

L-(+)-Norvaline

The less soluble salt was dissolved in water (100 ml.) and shaken with concentrated hydrochloric acid (25 ml.). In order to remove (+)-α-phenylethylamine hydrochloride the solution was extracted with chloroform (400 ml.). The aqueous layer was evaporated *in vacuo* to dryness. The crude, oily residue — which could not be crystallized from the usual solvents — was dissolved in 12% hydrobromic acid (100 ml.) and refluxed for 3 hrs. After evaporation to dryness, the residue was dissolved in methanol (100 ml.) and the solution made alkaline (to *p*H 8) with concentrated ammonia. Thereby a crystalline precipitate of L-norvaline was obtained (3.0 g., 85.7%), $[\alpha]_D^{20}$ + 20.5° (c 2.53, in 20% hydrochloric acid). One crystallization from a mixture methanol-water gave a product with $[\alpha]_D^{20}$ + 23.4 (c 2.40, in water).

N-Acetyl-D-norvaline-(-)-α-Phenylethylamine Salt

From 5.20 g. (0.032 mole) of *N*-acetyl-DL-norvaline and 3.97 g. (0.032 mole) of (-)-α-phyenylethylamine following exactly the same procedure as described above 5.0 g. of crystalline product (m. p. 158—160°) were obtained. Recrystallization from a mixture acetone-methanol gave 1.52 g. (33.2%) of the pure salt, m. p. 182—184°, $[\alpha]_D^{20}$ +12.6° (c 2.52, in water)

Anal. 6.135 mg. subst.: 0.547 ml. N_2 (26.5°, 745 mm.)
$C_{15}H_{24}O_3N_2$ (280.36) calc'd.: N 9.99%
found: N 9.96%

D-(-)-Norvaline

The substance prepared from the other enantiomeric salt in the same manner showed $[\alpha]_D^{20}$ — 25.1° (c 2.98, in 20% hydrochloric acid).

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IZVOD

Bilješka o cijepanju DL-norvalina

P. Alaupović

Opisano je cijepanje *N*-acetil-DL-norvalina pomoću (-)- i (+)-α-feniletilamina provedeno u smjesi acetona i metanola. Enantiomerne soli *N*-acetil-L-norvalin-(+)-α-feniletilamina i *N*-acetil-D-norvalin-(-)-α-feniletilamina dobivene su u prosječnom iskorištenju od 60—70%, odn. 30—35%. Iz tih soli izolirani su na uobičajeni način L- i D-norvalin u 85—90%-tnom iskorištenju.

ZAVOD ZA KEMIJU
MEDICINSKI FAKULTET
ZAGREB

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