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A Novel Synthetic Route to Enantiomers of ε-Hydroxynorleucine and ε-Chloronorleucine from *L*- and *D,L*-Lysine

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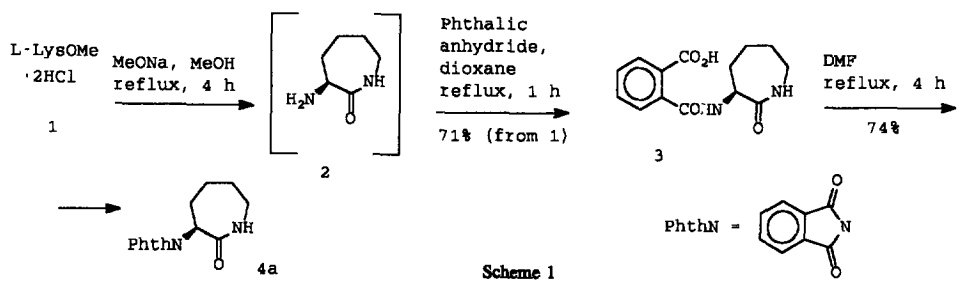
Abstract: Thermal rearrangement of *(S)*- or *(R)*-hexahydro-1-nitroso-3-phthalimido-2H-azepin-2-one to the corresponding lactone followed by nucleophilic ring opening of the latter gives ε-chloro- or ε-hydroxynorleucine.

The non-proteinogenic α-amino acid *L*-ε-hydroxynorleucine (**7a**) has been widely used for the synthesis of modified peptides[1-3], siderophores aerobactin and mycobactin[4,5], and *L*-α-aminoadipic acid derivatives[3,6]. In most cases, **7a** was obtained by enzymatic resolution of the racemic *N*-acylated derivatives with acylase[1-5]. Non-crystalline crude *N*-Cbz-*L*-ε-hydroxy-norleucine was prepared as an intermediate for the synthesis of *L*-α-aminoadipic acid derivative by treatment of N^2-Cbz-*L*-lysine with sodium nitroprusside[6]. Alkylation of dienolate derived from *(5S,6R)*- or *(5R,6S)*-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one with 1,4-diiodobutane followed by nucleophilic substitution of the second iodine atom gave derivatives of *L*- or *D*-ε-hydroxynorleucine, which were used for the synthesis of 2-amino-6-[(p-methoxybenzyl)-thio]hexanoic acid in both enantiomeric forms[7].

Recently, we reported the preparation of N^6-methyl-*L*-lysine[8] and *L*-α-aminoadipic acid[9] via the common intermediate - *(S)*-hexahydro-3-phthalimido-2H-azepin-2-one (**4a**). We now describe the simplified synthesis of the above lactam **4a** from *L*-lysine and its use for preparation of **7a** and *L*-ε-chloronorleucine (**8**).

Lactam **4a** was prepared earlier by treatment of *(S)*-3-aminohexahydro-2H-azepin-2-one (**2**) with *N*-carbomethoxyphthalimide[8]. The relatively high cost of the latter prompted us to look for a more economical pathway to **4a**. For this purpose, *L*-lysine methyl ester (**1**) was cyclized in the presence of sodium methoxide and, without isolation of the lactam **2**, acylated by phthalic anhydride. Phthalamic acid **3** thus obtained gave lactam **4a** upon heating in dimethylformamide solution (Scheme 1). No racemization was observed in this reaction sequence. Although yields were not very high, low cost of the starting materials and easy workup made this synthetic route satisfactory.

Unsubstituted ε-caprolactam can be *N*-nitrosated by nitrous gases in acetic acid[10], nitrosyl tetrafluoroborate



Scheme 1

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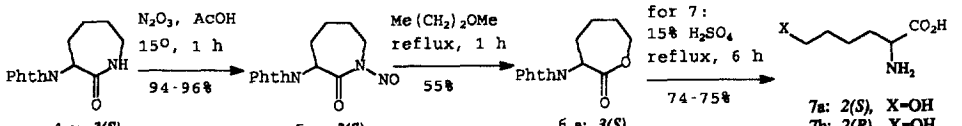
in pyridine[11] or dinitrogen tetroxide/sodium acetate in dichloromethane[12]. *N*-Nitrosolactam thus obtained was shown to undergo thermal rearrangement in the carbon tetrachloride solution at the room temperature to give the corresponding lactone[11,12]. Treatment of the phthalimido lactam **4a** with nitrous gases in acetic acid gave *N*-nitrosolactam **5a** in quantitative yield (mp 118° C (dec); $[\alpha]^{20}_D$ +185.0° (C=1, $CHCl_3$). Nitroso derivative **5a** appeared to be more stable as compared with unsubstituted *N*-nitroso-ε-caprolactam. Thus, heating of **5a** in dichloromethane solution under reflux for eight hours was shown by TLC to produce only traces of the desired lactone. The highest yield of the lactone **6a** was obtained upon heating of nitroso lactam **5a** in dry 1,2-dimethoxyethane under reflux for one hour (Scheme 2)[13]. Low concentration (ca. 3.4 mmol/L) of the nitroso lactam **5a** as well as lactone **6a** in the reaction mixture was critical for the yield of the latter. Thus, the increase of the **5a** concentration up to 34 mmol/L or slow addition of the concentrated lactam **5a** solution to the boiling dimethoxyethane with the same (ca. 34 mmol/L) final theoretical concentration of lactone **6a** lead to the formation of a very complex mixture of unidentified substances. Hydrolysis of the lactone **6a** in aqueous hydrochloric acid gave the mixture of **7a** and **8**, the latter can be isolated by crystallization from ethanol/water. The use of diluted sulfuric acid afforded pure **7a** (Scheme 2).



Scheme 2

(R)-Enantiomer of the lactam **2** can be readily prepared by resolution of racemic **2** with *L*-pyroglutamic acid or by kinetically controlled crystallization[14] . It is also commercially available. Application of the above procedure to *(R)*-phthalimido lactam **4b**, which was prepared from *(R)*-**2** similarly to **4a**[8] , allowed us to obtain *D*-ε-hydroxynorleucine (**7b**) via *N*-nitrosolactam **5b** and lactone **6b** (Scheme 2).

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13. All compounds described gave satisfactory analytical and spectroscopic data.
    (S)- and *(R)*-3-Phthalimidooxepan-2-one (**6a,b**): A solution of nitrosolactam **5a** or **5b** (0.5 g, 1.7 mmol) in dimethoxyethane (500 mL) was heated under reflux for one hour and evaporated under reduced pressure to dryness. The residue was recrystallized from 85% aq EtOH (10 mL) to give **6a** or **6b**.For **6a**: Yield: 0.25 g (55%); mp 203° C; $[\alpha]^{20}_D$ +95.0° (C=1, $CHCl_3$).^{1}H-NMR ($CDCl_3$ /TMS): δ = 1.2-2.9 (m, 6H, $CH_2CH_2CH_2$), 4.42 (m, 2H, OCH_2), 5.12 (dd, 1H, J=11.7, 1.6 Hz, CHCO), 7.80 (m, $4H_{arom}$). MS (70 eV): m/z (relative intensity)= 259 (M , 23), 186 (31), 173 (59), 148 (100), 130 (23), 104 (33), 76 (28), 67 (16).
    For **6b**: Yield: 0.25 g (55%); mp 201° C; $[\alpha]^{20}_D$ -95.0° (C=1, $CHCl_3$).
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