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O-NITRATES OF HYDROXYAMINO ACIDS SERINE AND THREONINE

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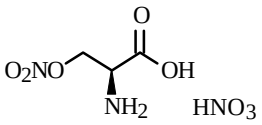
The synthesis of O*-nitrates of natural hydroxyamino acids serine and threonine was described for the first time.*

Key words: serine, threonine, nitration, *O*-nitrates of hydroxyamino acids.

Herein the synthesis of nitrate esters of L- and D-serine and L-threonine is described for the first time.

Hydroxyamino acids are rather stable to the action of ordinary nitrating mixtures. They can be nitrated in conc. HNO_3 or its mixtures with H_2SO_4 or acetic anhydride, i.e., standard conditions for preparing nitrate esters can be used [1]. However, using a mixture of HNO_3 and H_2SO_4 produces sulfates as side products; acetic anhydride, acetates [2]. By experimenting with various nitrating mixtures, we found that the main problem in preparing *O*-nitrates of hydroxyamino acids is not the chemical nitration process, which occurs in good yield, but the isolation of the products from the reaction mixture. The lability of the nitrate ester under alkaline conditions and its reduction in hydrogenolysis reactions prohibits its use to protect carboxyl and amino groups of standard groups that are stable under the acidic conditions of the nitration reaction. This could increase the lipophilicity of the starting amino acids and facilitate the extraction of the products by organic solvents.

The most efficient nitrating mixture for synthesizing **1**-**3** was a solution of HNO_3 (100%) in CH_2Cl_2, which was used earlier to prepare *O*-nitrates of monoethanolamine, 3-amino-1-propanol, and 1,3-diamino-2-propanol [3]. Monoethanolamine and its analogs are very soluble in CH_2Cl_2. This enabled a homogeneous reaction mixture to be used with slow addition of a solution of the aminoalcohol to the nitrating mixture [3]. In our instance, the starting amino acids can be dissolved only in water. Unfortunately, this would dilute the HNO_3 and layer the aqueous and organic phases. Therefore, we added to the nitrating solution the dry amino acid. The initially heterogeneous mixture became homogeneous as the reaction proceeded. The water that formed during the reaction dissolved the nitrate salts of the hydroxyamino acid nitrates of serine (**1** and **2**) and threonine (**3**). This water was destroyed after the reaction was finished by adding acetic anhydride. Then the crystalline products precipitated. Adding acetic anhydride at the beginning of the reaction led to the formation of acetates, which were difficult to separate from the desired products.



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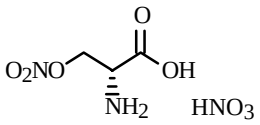

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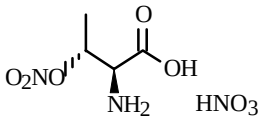

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Thus, we described for the first time the synthesis of *O*-nitrates of natural hydroxyamino acids, which can be viewed as new members of the family of organic nitrates that are derivatives of biogenic alcohols.

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EXPERIMENTAL

L-Serine, D-serine, and L-threonine were purchased from Acros Organics (Belgium). All solvents were purified by standard methods. Melting points were determined on a Boetius heating stage and are uncorrected. Specific rotation of compounds in ethanol solution was measured on a Jasco DIP360 spectropolarimeter (Tokyo, Japan) at 25°C. PMR spectra were recorded on a Bruker CXP-200 instrument (Germany) in trifluoroacetic acid solution. Chemical shifts are given on the δ-scale relative to TMS. IR spectra were recorded on a Bruker IFS-113V instrument (Germany); mass spectra, in an MX-5303 time-of-flight mass spectrometer (IAP, RAS) using electrospray ionization.

General Method for Synthesizing Nitrate Salts of *O*-Nitrates of Serine and Threonine. A solution of HNO_3 (3 mL, 100%) in CH_2Cl_2 (20 mL) at 0°C was stirred vigorously, treated with hydroxyamino acid (serine or threonine, 16 mmol) over 10 min, stirred at this temperature for 50 min, treated dropwise with Ac_2O (2 mL), and stirred for 40 min at 25°C. The resulting precipitate of the nitrate salt of amino acid *O*-nitrates (**1**-**3**) was filtered off and recrystallized from C_2H_5OH:$CHCl_3$. All compounds had practically identical IR spectra (KBr, ν, cm^{-1}): 1285 (NO_2, sym), 1382, 1482, 1644 (NO_2, asym), 1733 (CO), 2905.

Nitrate Salt of (L)-2-Amino-3-nitroxypropionic Acid (1). L-Serine (1.68 g) produced the nitrate salt of (L)-2-amino-3-nitroxypropionic acid (**1**, 2.14 g, 63%), white crystals, mp 111-113°C, $[\alpha]_D$ +5.0° (*c* 2.6). PMR (δ, ppm): 4.93 (1H, br.s, CH), 5.25 (2H, m, CH_2), 7.87 (3H, br.s, NH_2, CO_2H). Mass spectrum (*m*/*z*): 151.0584, $[M + H]^+$, $C_3H_7N_2O_5$.

Nitrate Salt of (D)-2-Amino-3-nitroxypropionic Acid (2). D-Serine (0.84 g) produced the nitrate salt of (D)-2-amino-3-nitroxypropionic acid (**2**, 1.3 g, 75%), white crystals, mp 113-115°C, $[\alpha]_D$ –8.2° (*c* 2.6). The PMR spectrum was identical to that of the L-isomer (**1**). Mass spectrum (*m*/*z*): 151.0154, $[M + H]^+$, $C_3H_7N_2O_5$.

Nitrate Salt of (L)-2-Amino-3-nitroxybutanoic Acid (3). L-Threonine (1.904 g) produced the nitrate salt of (L)-2-amino-3-nitroxybutanoic acid (**3**, 2.27 g, 64%), white crystals, mp 121.5-122.5°C (dec.), $[\alpha]_D$ +4.4° (*c* 1.6). PMR spectrum (δ, ppm): 1.79 (3H, d, CH_3), 4.7 (1H, m, $NH_2\underline{CH}$), 5.88 (1H, br.s, MeCH), 7.80 (3H, br.s, NH_2, CO_2H). Mass spectrum (*m*/*z*): 165.0679, $[M + H]^+$, $C_4H_9N_2O_5$.

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