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SHORT COMMUNICATIONS

Dedicated to the Full Member of the Russian Academy of Sciences V.A.Tartakovsky on occasion of his 75th birthday

Pyridine-Containing Pyrrolidonecarboxylate: Synthesis and Reactions with Nitroethenes

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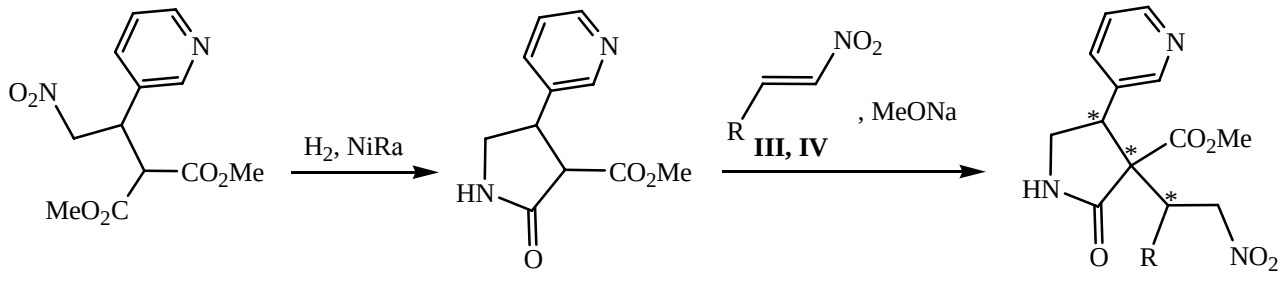
The product of intramolecular heterocyclization of γ-aminobutyric acid, γ-butyrolactam (or 2-pyrrolidone) is known to be a structural fragment of many drugs. For instance, the pyrrolidone ring is a part of piracetam composition [1] and of its phenyl analog, carphedon [2]; poly-*N*-vinylpyrrolidone is used as substitute of blood plasma, to remove toxic substances from the body and prolonging the action of some drugs [3]. Another nitrogen-containing heterocycle, pyridine, is contained in the composition of coramin, sulphidine, ftivazide, piroxicam, and other pharmaceuticals widely used in medical practice [1, 4, 5]. Therefore the development of a procedure for preparation of a pyridine-containing pyrrolidonecarboxylate and a study of its reactions with electron-deficient compounds like nitroethenes is not only of theoretical but also of practical interest for it opens the way to the synthesis of β-nitroethyl-substituted pyrrolidonecarboxylates, precursors of a totally new series of derivatives of γ-aminobutyric acid and piracetam.

We developed a convenient preparative method of the synthesis of pyridine-containing pyrrolidonecarnoxylic acid ester based on the reduction of methyl (2-methoxycarbonyl)-4-nitro-3-(3-pyridyl)butanoate (**I**). Initial nitrobutanoate **I** prepared formerly by procedure [6] was hydrogenated by electrolytical hydrogen on a skeleton nickel catalyst. The process was accompanied by an intramolecular acylation of the primarily formed amino group to give 3-methoxycarbonyl-4-(3-pyridyl)-2-pyrrolidone (**II**) in 70% yield.

The reactions of compound **II** with β-nitrostyrene (**III**) and pyridylnitroethene (**IV**) were carried out at equimolar reagents ratio in the presence of sodium alcoholate in the alcohol. In the former case the nitroethyl pyrrolidonecarboxylate was isolated as a mixture of



I **II**

R = Ph (**III, Va, Vb**), 3-pyridyl (**IV, VI**).

diastereomers **Va** and **Vb** easily separated by fractional recrystallization. Reaction with nitroethene **IV** resulted in a single product **VI**.

The structure of compounds obtained was proved by spectral methods. For instance, the IR spectra of compounds **II, Va, Vb**, and **VI** contained the characteristic absorption bands of the stretching vibrations of carbonyl groups of ester (1740 cm^{-1}) and lactam [1710 (**II**), 1705, 1670 (**Va**), 1710 (**Vb**), and 1700, 1665 cm^{-1} (**VI**)]. In the ^1H NMR spectra of compounds **II, Va, Vb**, and **VI** proton signals of all structural fragments were observed. For instance, in the ^1H NMR spectrum of compound **II** the following signals appeared: 3.67 s (OCH_3), 3.33 m, 3.95 m (CH–CH), 3.67 m (CH_2N), 8.13 (NH), 7.32–8.47 (C_5H_4N) ppm. ^1H NMR spectrum of compounds **Va** and **Vb** evidently contains a double set of methylene protons signals from the CH_2NO_2 moiety: (4.23, 4.85 ppm) and (4.08, 5.17 ppm) belonging to diastereomers **Va** and **Vb** respectively (the ratio **Va:Vb** = 1:1); it is important that the signals of nitromethylene protons of compound **VI** (4.25 m, 4.90 m) practically coincide with the respective signals of diastereomer **Va**.

3-Methoxycarbonyl-4-(3-pyridyl)-2-pyrrolidone (II). Into a dispersion of 11 g of skeleton nickel catalyst in 50 ml of methanol saturated with electrolytic hydrogen was added a dispersion of 8.46 g (0.03 mol) of ester I in 100 ml of methanol, and at vigorous stirring was performed the reduction of nitroester **I** till the calculated amount of hydrogen was completely consumed (2 l). The catalyst was separated, the filtrate was evaporated in a vacuum of a water-jet pump. The residue was recrystallized from ethyl acetate. Yield 4.62 g (70%), mp 145–147°C. Found, %: C 59.92, 59.88; H 5.70, 5.69; N 12.93, 12.90. $C_{11}H_{12}N_2O_3$. Calculated, %: C 60.00; H 5.45; N 12.73.

3-Methoxycarbonyl-3-(2-nitro-1-phenylethyl)-4-(3-pyridyl)-2-pyrrolidone (Va and **Vb).** To a methanol solution of sodium methylate prepared from 5 ml of methanol and 0.46 g (0.02 mol) of sodium was added 4.4 g (0.02 mol) of compound **II**. The mixture was cooled to 0°C and at stirring was added by portions a dispersion of 3 g (0.02 mol)of β-nitrostyrene (**III**) in 14 ml of methanol maintaining the temperature at 0–5°C. The reaction mixture was kept for 2 h at 16–18°C, then it was poured on crushed ice containing acetic acid in amount equivalent to the taken sodium (1.15 ml). The separated precipitate was filtered off, washed with cold water, and dried in air. We isolated 6.7 g (91%) of isomers **Va** and **Vb** mixture that was separated by fractional recrystallization from methanol. Yield of isomer **Va** 3.1 g (42%), mp 178–180°C (from methanol). Found, %: C 61.81, 61.78; H 5.23, 5.28; N 11.35, 11.39. $C_{19}H_{19}N_3O_5$. Calculated, %: C 61.79; H 5.15; N 11.38. Yield of isomer **Vb** 2.9 g (40%), mp 165–167°C (from methanol). Found, %: C 61.82, 61.89; H 5.29, 5.27; N 11.32, 11.30. $C_{19}H_{19}N_3O_5$. Calculated, %: C 61.79; H 5.15; N 11.38.

3-Methoxycarbonyl-3-[2-nitro-1-(3-pyridyl)ethyl]-4-(3-pyridyl)-2-pyrrolidone (VI) was prepared analogously to compounds **Va** and **Vb**. Yield 50%, mp 170–172°C (from methanol). Found %: C 58.47, 58.45; H 4.91, 4.91; N 15.00, 15.01. $C_{18}H_{18}N_4O_5$. Calculated %: C 58.38; H 4.86; N 15.13.

IR spectra wqere recorded on a spectrophotometer InfraLUM FT-02 [chloroform, C 0.1 – 0.001 mol l^{-1} (**II**), mulls in mineral oil (**Va, Vb, VI**)]. ^1H NMR spectra were registerd on a spectrometer Bruker AC-200 (200 MHz), solvent $CDCl_3$; chemical shifts were measured with respect to external reference HMDS with an accuracy ± 0.5 Hz.

Initial 1-nitro-2-phenyl and 2-(3-pyridyl)ethenes **III** and **IV** were prepared by procedures [7] and [8] respectively.

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REFERENCES

1. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2006, 1200 p.
2. Tyurenkov, I.N., Uvarov, A.V., Tyukhteneva, Z.I., Galenko-Yaroshevskii, P.A., Perfilova, V.N., Berestovitskaya, V.M., Zobacheva, M.M., Vasil'eva, O.S., Usik, N.V., and Novikov, B.M., European Patent 002379, 2002; *Byull. Izobr.*, 2001, no. 1.
3. Soldatenkov, A.T., Kolyadina, N.M., and Shendrik, I.V., *Osnovy organicheskoi khimii lekarstvennykh veshchestv* (Fundamentals of Organic Chemistry of Medicines), Moscow: Khimiya, 2001, p. 96.
4. Vidal', *Lekarstvennye preparaty v Rossii.* Spravochnik (Medicines in Russia. Handbook), Moscow: AstraFarm-Servis, 2003, 1488 p.
5. Gilchrist, T.L., *Heterocyclic Chemistry*, Harlow: Longman Scientific & Technical, 1992.
6. Berestovitskaya, V.M., Ostroglyadov, E.S., and Vasil'eva, O.S., *Zh. Org. Khim.*, 2002, vol. 39, p. 304.
7. *Sint. Org. Prep.*, 1949, vol. 2, p. 37.
8. Berestovitskaya, V.M., Ishmaeva, E.A., Litvinov, I.A., Vasil'eva, O.S., Vereshchagina, Ya.A., Ostroglyadov, E.S., Fattakhova, G.R., Beskrovnyi, D.V., and Aleksandrova, S.M., *Zh. Obshch. Khim.*, 2004, vol. 74, p. 1198.