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INTERACTION OF HYDROXYLAMINE WITH ESTERS OF 2-OXOBUTENOIC ACIDS. SYNTHESIS OF 3-HYDROXIMINO-1-HYDROXY-2-PYRROLIDINONES

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New 3-hydroximino-1-hydroxy-2-pyrrolidinones have been synthesized by the interaction of NH_2OH and NH_2OBn with the methyl esters of 2-oxo-3-butenoic acid derivatives. Some intermediate compounds have been isolated and identified and the reaction mechanism is discussed.

Keywords: hydroxylamine, 3-hydroximino-1-hydroxy-2-pyrrolidinone, cyclic hydroxamic acids, 2-oxo-3-butenoic acid esters.

Hydroxamic acids display a broad spectrum of biological activity, such as antibacterial [1,2], antitumor [3-5], antitubercular, and fungicidal [6], and are inhibitors of metalloenzymes [7,8]. The unique activity of hydroxamic acids is caused by their chelate-forming properties [6,9,10] and by the ability to generate NO in cells [11].

Various methods have been proposed for obtaining hydroxamic acids [12-15]. One of the known methods of obtaining them is the acylation of hydroxylamine with esters [16]. On interacting hydroxylamine with esters of saturated β-keto acids isoxazolin-5-one (the oxime of the corresponding ester was detected spectroscopically in the reaction mixture as an intermediate) and/or isoxazolin-3-one are formed [17]. The intermediate compounds for the latter, 5-hydroxy-3-isoxazolidinone and the linear hydroxamic acid, are found in equilibrium, however the sequence of their formation was not clarified. Unsaturated δ-keto esters interact with hydroxylamine with the formation of oximes, which, depending on the presence of a substituent, are converted into oxazolines or 1-hydroxy-2-pyridones [18]. It was shown that in reactions with α,β-unsaturated esters the first step is a Michael type addition at the double bond, and not acylation of hydroxylamine by the ester group [19].

The reaction of hydroxylamine with esters of 2-oxo-3-butenoic acids has not been studied up to the present time. The latter are valuable starting materials for the synthesis of biologically active compounds. In continuing investigations on the use of the esters mentioned as synthons [20], we have studied the interaction of them with hydroxylamine.

2-Oxo-3-butenoic acid ester has three centers for nucleophilic attack. The use of an excess of hydroxylamine in the investigated reaction, interacting with all the functional groups of the ester, theoretically suggests the formation of 3-hydroximino-1-hydroxy-2-pyrrolidinone **1**, two oxazinone isomers **2** and **3**, and the linear hydroxamic acid **4** (X = H).

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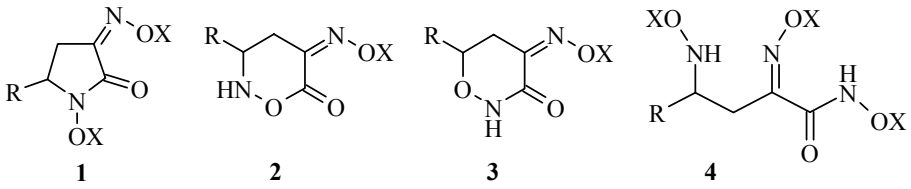


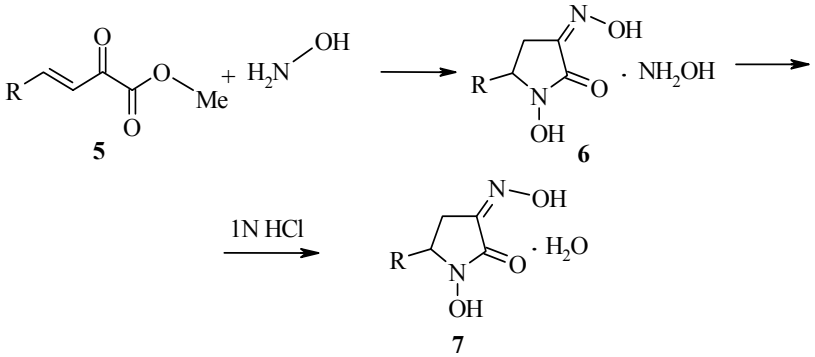
1 **2** **3** **4**

The interaction of NH_2OH with 2-oxo-4-(2-thienyl)-3-butenoic acid ester (**5b**) was studied at ~20°C and pH 8. In the ^1H NMR spectrum (DMSO-d_6) of the isolated substance three double doublet signals were observed at 5.12 (1H, dd, J = 8.2, 3.8 Hz), 3.35 (1H, dd, J = 18.6, 8.2 Hz), and 2.66 ppm (1H, dd, J = 18.6, 3.8 Hz), which may correspond to compounds **1**, **2**, and **4** (X = H), but according to elemental composition (the presence of three hydroxylamine fragments) this substance corresponds to structure **4**.

Additional confirmation of the structure of this compound is the reaction of **5b** with NH_2OBn, since on interaction with an O-substituted hydroxylamine the formation is possible of only compounds **1** and **4**. The ^1H NMR spectrum and elemental composition of the product isolated from the reaction of ester **5b** with NH_2OBn at pH 7 and ~20°C showed the presence of only two NH_2OBn fragments in the molecule. The compound was identified as the derivative of 5-(2-thienyl)-2-pyrrolidinone **1b** (X = Bn).

To define more precisely the structure of the compound obtained on interaction of the initial ester with NH_2OH it was alkylated with benzyl bromide. The compound isolated was identical to compound **1b** (X = Bn) in all analytical characteristics. This confirms unequivocally that in reactions with NH_2OH 3-hydroxyiminopyrrolidinone derivatives **1** are also formed. It has been established that compound **6** crystallizes from the reaction mixture as the 3-hydroximino-1-hydroxy-2-pyrrolidinone and hydroxylamine salt (Scheme 1). After acidification with 1N HCl to pH 2 the monohydrate **7** was isolated. The characteristics of the 3-hydroximinopyrrolidinones **7a-f** synthesized are given in Tables 1-3.

Scheme 1

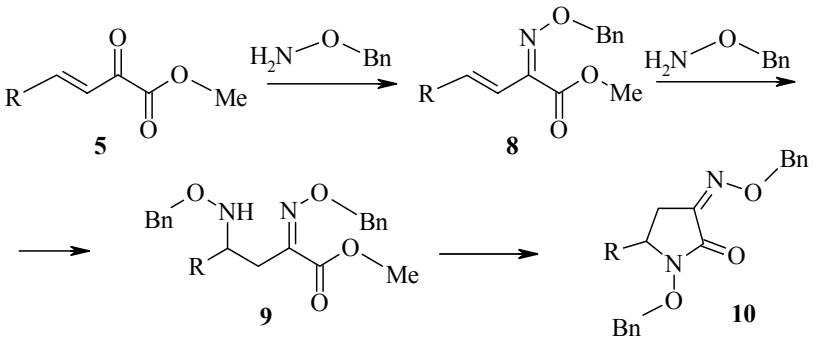


5 **6** **7**

a R = Ph, **b** R = 2-thienyl, **c** R = 2-furyl, **d** R = 3,4-$(MeO)_2C_6H_3$, **e** R = 4-ClC_6H_4, **f** R = 4-$O_2NC_6H_4$

The intermediate compounds, isolated and identified by us for certain derivatives (**5d** and **5f**), enabled the sequence of reactions of NH_2OBn with the functional groups of the initial ester to be determined. The interaction of NH_2OBn with 2-oxobutenoic acid occurs in three stages (Scheme 2). It is apparent that at pH 7-8 NH_2OBn reacts initially with the α-keto group with the formation of oxime **8**. Addition of a second molecule of NH_2OBn to the double bond then follows (compound **9**). The last stage is a 5-exo-*trig* cyclization with the formation of derivatives of 3-benzyloximinopyrrolidinone **10**.

Scheme 2



a R = Ph, **b** R = 2-thienyl, **c** R = 2-furyl, **d** R = 3,4-$(MeO)_2C_6H_3$, **e** R = 4-ClC_6H_4, **f** R = 4-$O_2NC_6H_4$

The rate of cyclization varies significantly depending on the character of the substituent in the initial ester. In the case of phenyl and thienyl derivatives we did not succeed in isolating the intermediate compounds **9a** and **9b**. After chromatographic purification ester **9c** is cyclized both in methanol solution at 0°C and without a solvent. However the cyclization of derivatives with a substituted phenyl group **9d-f** occurs only on extended heating of a methanolic solution at 60°C. The reaction conditions and the characteristics of some isolated intermediate compounds **9c,d**, **8f**, and **9f** are given in Experimental.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %*
		C	H	N		
7a	$C_{10}H_{12}N_2O_4$	53.61 / 53.57	5.34 / 5.39	12.45 / 12.49	232 (dec.)	54
7b	$C_8H_{10}N_2O_4S$	41.74 / 41.73	4.15 / 4.38	12.11 / 12.17	245 (dec.)	66
7c	$C_8H_{10}N_2O_5$	44.65 / 44.86	4.64 / 4.71	12.78 / 13.08	236 (dec.)	46
7d	$C_{12}H_{16}N_2O_6$	50.54 / 50.70	5.61 / 5.67	9.60 / 9.85	116 (dec.)	98
7e	$C_{10}H_{11}ClN_2O_4$	46.67 / 46.43	4.13 / 4.29	10.60 / 10.83	235 (dec.)	63
7f	$C_{10}H_{11}N_3O_6$	44.48 / 44.62	3.92 / 4.12	15.20 / 15.61	212 (dec.)	49
10a	$C_{24}H_{22}N_2O_3$	74.42 / 74.59	5.76 / 5.74	7.23 / 7.25	122-123	87
10b	$C_{22}H_{20}N_2O_3S$	67.06 / 67.33	5.08 / 5.14	7.02 / 7.14	140-142	58
10c	$C_{22}H_{20}N_2O_4$	69.94 / 70.20	5.28 / 5.36	7.37 / 7.44	124-126	76
10d	$C_{26}H_{26}N_2O_5$	69.92 / 69.94	5.81 / 5.87	6.22 / 6.27	115-117	44
10e	$C_{24}H_{21}ClN_2O_3$	68.43 / 68.49	4.93 / 5.03	6.58 / 6.66	111-112	31
10f	$C_{24}H_{21}N_3O_5$	66.50 / 66.81	4.85 / 4.91	9.68 / 9.74	178-179	42

***** Compounds **10d-f** were obtained by heating the corresponding compounds **9** at 60°C in MeOH for 72 h (**10d,f**) and 4 h (**10e**).

TABLE 2. ^{1}H NMR Spectra of Compounds **7a-f** and **10a-f**

Compound	Chemical shifts, δ, ppm. (*J*, Hz)*			
	H-4 (1H, dd)	H-5 (1H, dd)	R	N–OBn or N–OH
7a	2.44 (*J* = 18.8 and 3.7), 3.29 (*J* = 18.8 and 8.1)	4.83 (*J* = 8.1 and 3.7)	7.22-7.41 (5H, m)	12.00 (1H, s), 10.20 (1H, s)
7b	2.66 (*J* = 18.7 and 3.9), 3.35 (*J* = 18.7 and 8.1)	5.12 (*J* = 8.1 and 3.9)	7.01 (1H, dd, *J* = 5.0 and 3.4); 7.13 (1H, dd, *J* = 3.4 and 1.0), 7.53 (1H, dd, *J* = 5.0 and 1.0)	12.10 (1H, s), 10.28 (1H, s)
7c	2.73 (*J* = 18.8 and 3.8), 3.18 (*J* = 18.8 and 8.2)	4.90 (*J* = 8.2 and 3.8)	6.43 (1H, dd, *J* = 3.6 and 1.8), 6.50 (1H, d, *J* = 3.6), 7.65 (1H, d, *J* = 1.8)	12.04 (1H, s), 10.19 (1H, s)
7d	2.46 (*J* = 18.8 and 4.0), 3.26 (*J* = 18.8 and 7.9)	4.76 (*J* = 7.9 and 4.0)	3.74 (6H, s), 6.78 (1H, d, *J* = 8.3), 6.83 (1H), 6.93 (1H, d, *J* = 8.3)	11.97 (1H, s), 10.11 (1H, s)
7e	2.43 (*J* = 19.0 and 3.7), 3.27 (*J* = 19.0 and 8.0)	4.86 (*J* = 8.0 and 3.7)	7.43-7.47 (2H, m), 7.27-7.21 (2H, m)	12.03 (1H, s), 10.23 (1H, s)
7f	2.49 (*J* = 18.7 and 3.9), 3.37 (*J* = 18.7 and 8.3)	5.04 (*J* = 8.3 and 3.9)	8.23-8.28 (2H, m), 7.55-7.60 (2H, m)	12.01 (1H, s), 10.38 (1H, s)
10a	2.67 (*J* = 18.9 and 3.7), 3.36 (*J* = 18.9 and 8.0)	4.96 (*J* = 8.0 and 3.7)	7.18-7.42 (5H, m)	4.71 (1H, d, *J* = 10.1), 4.99 (1H, d, *J* = 10.1), 5.25 (2H, s), 7.18-7.42 (10H, m)
10b	2.82 (*J* = 19.0 and 4.0), 3.42 (*J* = 19.0 and 7.9)	5.29 (*J* = 7.9 and 4.0)	7.03 (1H, dd, *J* = 5.0 and 3.5), 7.22 (1H, d, *J* = 3.5), 7.57 (1H, d, *J* = 5.0)	4.67 (1H, d, *J* = 9.7), 4.99 (1H, d, *J* = 9.7), 5.25 (2H, s), 7.25-7.40 (10H, m)
10c	2.87 (*J* = 18.9 and 3.9), 3.26 (*J* = 18.9 and 8.2)	5.08 (*J* = 8.2 and 3.9)	6.47 (1H, dd, *J* = 3.2 and 1.8); 6.61 (1H, d, *J* = 3.2); 7.69 (1H, d, *J* = 1.8)	4.54 (1H, d, *J* = 10.1), 4.93 (1H, d, *J* = 10.1); 5.25 (2H, s); 7.26-7.49 (10H, m)
10d	2.70 (*J* = 19.0 and 4.1), 3.30 (*J* =19.0 and 8.0)	4.87 (*J* = 8.0 and 4.1)	3.71 (3H, s); 3.73 (3H, s); 6.83 (1H, dd, *J* = 8.2 and 1.7); 6.92 (1H, d, *J* = 1.7); 6.93 (1H, d, *J* = 8.2)	4.67 (1H, d, *J* = 10.2), 4.97 (1H, d, *J* = 10.2); 5.24 (2H, s); 7.17-7.38 (10H, m)
10e	2.64 (*J* = 19.0 and 3.8), 3.35 (*J* = 19.0 and 8.0)	4.98 (*J* = 8.0 and 3.8)	7.31-7.45 (4H, m)	4.74 (1H, d, *J* = 10.3), 4.98 (1H, d, *J* = 10.3); 5.24 (2H, s); 7.18-7.37 (10H, m)
10f	2.67 (*J*=19.1 and 3.8), 3.41 (*J* = 19.1 and 8.3)	5.02 (*J* = 8.3 and 3.8)	7.55-7.63 (2H, m); 8.17-8.24 (2H, m);	4.82 (1H, d, *J* = 10.3), 5.02 (1H, d, *J* = 10.3); 5.25 (2H, s); 7.20-7.41 (10H, m)

* Compounds **7a-f** were taken in DMSO-d_6, compounds **10a-f** in $CDCl_3$.

Derivatives of 3-hydroximino-1-hydroxypyrrolidinone are therefore formed on interaction of esters of 2-oxo-3-butenoic acids with NH_2OH. It is apparent that the reaction proceeds by the sequential interaction of NH_2OH with the α-keto group and the double bond with subsequent intramolecular acylation of the hydroxylamine nitrogen by the ester group.

TABLE 3. ^{13}C NMR Spectra of Compounds **7a-f** and **10a-f**

Compound	Chemical shifts, δ, ppm					
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	R	Bn
7a	148.4	159.1	30.4	59.5	126.4; 128.0; 128.7; 140.2	
7b	147.9	158.6	30.5	55.3	126.1; 126.4; 126.9; 143.1	
7c	148.1	158.6	26.5	53.2	109.3; 110.6; 143.4; 151.0	
7d	148.7	159.3	30.5	59.4	55.5; 55.6; 109.9; 111.8; 118.9; 132.3; 148.6; 149.0	
7e	148.2	159.2	30.2	58.9	128.5; 128.7; 132.6; 139.1	
7f	147.74	159.4	29.9	58.9	123.9; 127.9; 147.70; 147.3	
10a	149.1	158.2	30.7	57.7	126.9; 127.9; 128.7; 138.9	76.35; 76.43; 128.0; 128.26; 128.29; 128.4; 128.6; 129.1; 134.5; 137.1
10b	148.6	157.9	31.1	53.4	126.8; 127.2; 127.5; 141.8	76.5; 76.6; 128.0; 128.05; 128.4; 128.4; 128.7; 129.2; 134.4; 137.1
10c	148.7	157.8	27.1	51.2	110.2; 110.8; 143.7; 149.8	76.5; 76.6; 127.95; 128.0; 128.3; 128.3; 128.7; 129.1; 134.3; 137.0
10d	149.5	158.3	30.7	57.8	55.5; 55.5; 110.6; 111.7; 119.6; 130.9; 148.96; 149.0	76.5; 76.5; 127.9; 128.0; 128.2; 128.6; 129.1; 134.6; 137.1
10e	148.2	159.2	30.6	57.1	128.3; 128.7; 137.9; 132.9	76.4; 76.5; 127.9; 128.0; 128.3; 128.6; 128.9; 129.0; 134.5; 137.0
10f	148.5	158.6	30.5	57.1	123.8; 127.96; 146.5; 147.3;	76.4; 76.6; 127.95; 128.0; 128.2; 128.3; 128.7; 129.1; 134.4; 137.0

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Varian 200 Mercury spectrometer (200 and 50 MHz respectively) in $CDCl_3$ (NH_2OBn derivatives) and DMSO-d_6 (NH_2OH derivatives), internal standard was TMS. Column chromatography was carried out on Acros silica gel (0.035-0.07 mm), using gradient elution with petroleum ether–ethyl acetate 10:1 to 2:1 (for compounds **5a-f** and **10a-f**). Reaction products **7a-f** were isolated by crystallization from water at pH 2. All the synthesized compounds **7a-f** gave a characteristic lilac coloration with $FeCl_3$ solution. The reactions were checked by TLC, using Merck silica gel (F_{254}) plates. Systems were petroleum ether–ethyl acetate 2:1 (for compounds **5-10**), and $CHCl_3$–MeOH–AcOH 85:10:5 (for compounds **7a-f**). The initial methyl esters of 2-oxo-3-butenoic acids **5** were obtained by alkylation with methyl iodide of the potassium salts of the appropriate acids, obtained by the procedure of [21] [MeI (3 equiv.), 18-crown-6 (2 mol %), solvent DMF, 22°C, 3 h]. Solutions of NH_2OH and NH_2OBn in methanol were prepared by the standard procedure of [16].

Hydroxylamine Salt of 3-Hydroximino-1-hydroxy-2-oxo-5-(2-thienyl)pyrrolidine (6b). A solution of NH_2OH (4.31 g, 0.13 mol) in MeOH (pH 8) (50 ml) was added dropwise to a solution of 2-oxo-4-(2-thienyl)-3-butenoic acid methyl ester (**5b**) (3 g, 15.3 mmol) in MeOH (10 ml) at 0-5°C. The reaction mixture was stirred for 1 day at 20-22°C. The precipitated solid was filtered off, washed with water, and dried in vacuum. Compound **6b** (3.2 g, 85%) was obtained as colorless crystals of mp 235°C (decomp.). ^1H NMR spectrum

(DMSO-d_6), δ, ppm (*J*, Hz): 7.53 (1H, d, *J* = 4.8, α-Th); 7.13 (1H, d, *J* = 3.0, β-Th); 7.01 (1H, dd, *J* = 4.8, 3.0, β-Th); 5.12 (1H, dd, *J* = 8.2, 3.8, Th-CH); 3.35 (1H, dd, *J* = 18.6, 8.2, CH_2); 2.66 (1H, dd, 18.6, 3.8, CH_2). Found, %: C 39.05; H 4.44; N 16.92; S 12.90. $C_8H_{11}N_3O_4S$. Calculated, %: C 39.18; H 4.52; N 17.13; S 13.07.

3-Hydroximino-1-hydroxy-2-oxo-5-phenylpyrrolidine Monohydrate (7a) (typical procedure A). A solution of NH_2OH (0.189 g, 5.71 mmol) in methanol (pH 8) (1 ml) was added dropwise to a 1.5 M solution (1.1 ml) in methanol of 2-oxo-4-phenylbutenoic acid methyl ester **5a** (0.32 g, 1.68 mmol) at 0-5°C. The reaction mixture was stirred at 20-22°C for 1 day. The precipitated solid was filtered off, and to it was added water (30 ml), the mixture was acidified with 1 N HCl to pH 2, the solid was filtered off, washed with water, and dried. Compound **7a** (0.205 g, 54%) was obtained as colorless crystals.

3-Hydroximino-1-hydroxy-2-oxo-5-(2-thienyl)pyrrolidine (7b) Monohydrate was obtained by the general procedure A from compound **5b** (0.192 g, 0.98 mmol) in methanol (0.64 ml) and NH_2OH (0.27 g, 8.1 mmol) in methanol (pH 8) (3.4 ml) as colorless crystals in a yield of 0.15 g (66%).

5-(2-Furyl)-3-hydroximino-1-hydroxy-2-oxopyrrolidine Monohydrate (7c) was obtained by general procedure A from compound **5c** (0.22 g, 1.22 mmol) in methanol (0.8 ml) and NH_2OH (0.13 g, 4 mmol) in methanol (pH 8) (1.7 ml) as colorless crystals in a yield of 0.12 g (46%).

5-(3,4-Dimethoxyphenyl)-3-hydroximino-1-hydroxy-2-oxopyrrolidine Monohydrate (7d) was obtained by general procedure A from compound **5d** (0.18 g, 0.72 mmol) in methanol (0.8 ml) and NH_2OH (0.071 g, 2.158 mmol) in methanol (pH 7) (1.7 ml) as colorless crystals in a yield of 0.20 g (98%).

5-(4-Chlorophenyl)-3-hydroximino-1-hydroxy-2-oxopyrrolidine Monohydrate (7e) was obtained by general procedure A from compound **5e** (0.18 g, 0.80 mmol) in methanol (0.8 ml) and NH_2OH (0.093 g, 2.804 mmol) in methanol (pH 7) (1.7 ml) as colorless crystals in a yield of 0.13 g (63%).

3-Hydroximino-1-hydroxy-5-(4-nitrophenyl)-2-oxopyrrolidine Monohydrate (7f) was obtained by general procedure A from compound **5f** (0.19 g, 0.807 mmol) in methanol (0.8 ml) and NH_2OH (0.093 g, 2.827 mmol) in methanol (pH 7) (1.7 ml) as colorless crystals in a yield of 0.108 g (49%).

3-Benzyloximino-1-benzyloxy-2-oxo-5-phenylpyrrolidine (10a) (Typical Procedure B). A solution (~24%) of NH_2OBn (0.97 g, 7.87 mmol) in MeOH (pH 7) (4 ml) was added dropwise to a 1.5 M solution of 2-oxo-4-phenylbutenoic acid methyl ester (**5a**) (0.49 g, 2.58 mmol) in MeOH (1.7 ml) at 0-5°C. The reaction mixture was stirred at 20-22°C for 1 day. The precipitated solid was filtered off and recrystallized from ethyl acetate–petroleum ether. Compound **10a** (0.87 g, 87%) was obtained as colorless crystals.

3-Benzyloximino-1-benzyloxy-2-oxo-5-(2-thienyl)pyrrolidine (10b) was obtained by general procedure B from compound **5b** (0.57 g, 2.9 mmol) in methanol (1.9 ml) and NH_2OBn (1.07 g, 8.7 mmol) in methanol (pH 7) (4.5 ml) as colorless crystals in a yield of 0.66 g (58%).

3-Benzyloximino-1-benzyloxy-5-(2-furyl)-2-oxopyrrolidine (10c). B. Compound **5c** (0.49 g, 2.72 mmol) in methanol (1.6 ml) and NH_2OBn (1.90 g, 15.45 mmol) in methanol (pH 7) (7.8 ml) were stirred for 1 day. The methanol was evaporated, and the obtained mixture was chromatographed. A mixture of colorless crystals of compound **10c** (0.35 g, 34%) R_f 0.38 (Merck silica gel F_{254}, petroleum ether–ethyl acetate, 2:1), and compound **9c** (0.42 g, 38 %), R_f 0.62 was obtained. A colorless oil, which crystallized during several hours at 22°C into compound **10c** (overall yield 72%) was also obtained. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz) of compound **9c**: 7.19-7.36 (11H, m, Ph, Fur); 6.26 (1H, dd, *J* = 3.2, 1.9, β-Fur); 6.18 (1H, d, *J* = 3.2, α-Fur); 5.4-5.9 (1H, br. s, NH); 5.26 (2H, s, O-CH_2-Ph); 4.55 (2H, d, *J* = 1.6, O-CH_2-Ph); 4.40-4.53 (1H, m, Fur-CH); 3.77 (3H, s, O-CH_3); 3.17 (1H, dd, *J* = 13.2, 8.0, CH_2); 3.02 (1H, dd, *J* = 13.2, 6.9, CH_2).

3-Benzyloximino-1-benzyloxy-5-(3,4-dimethoxyphenyl)-2-oxopyrrolidine (10d) (General Procedure B). A mixture of compound **5d** (0.18 g, 0.719 mmol) in methanol (0.8 ml) and NH_2OBn (0.217 g, 1.758 mmol) in methanol (pH 7) (1.8 ml) was stirred for 1 day, the methanol was evaporated, and the obtained mixture was chromatographed. Compound **10d** (0.094 g, 28%), R_f 0.43 (Merck silica gel F_{254}, petroleum ether–ethyl acetate, 2:1) was isolated as colorless crystals and also compound **9d** (0.17 g, 67%), R_f 0.56 as a colorless oil. The latter was partially converted on heating in methanol at 60°C for 3 days into compound **10d** (overall yield of **10d** was 44%. Chromato-mass spectrum of compound **9d**, *m/z* (I_{rel}, %): 355 (6) $[M]^+$, 296 (2) $[M\text{-}COOCH_3]^+$, 248 (11)

$[M\text{-}OCH_2C_6H_5]^+$, 234 (6) $[M\text{-}OCH_2C_6H_5\text{-}N]^+$, 188 (14) $[M\text{-}OCH_2C_6H_5\text{-}COOCH_3\text{-}H]^+$, 165 (2) $[(CH_3O)_2C_6H_3CH{=}CH{+}2H]^+$, 151 (9) $[(CH_3O)_2C_6H_3CH{+}H]^+$, 91 (100), $[CH_2C_6H_5]^+$, 77 (14) $[C_6H_5]^+$, 59 (15).

3-Benzyloximino-1-benzyloxy-5-(4-chlorophenyl)-2-oxopyrrolidine (10e). B. A mixture of compound **5e** (0.178 g, 0.792 mmol) in methanol (1 ml) and NH_2OBn (0.244 g, 2.226 mmol) in methanol (pH 8) (1.8 ml) was stirred for 1 day, the methanol was evaporated, and the residue obtained was chromatographed. A mixture of compounds **9e** and **10e** was obtained, which was not separated. After heating the mixture at 60°C for 4 h crystalline compound **10e** (0.104 g, 31%) was obtained, R_f 0.37 (Merck silica gel F_{254}, petroleum ether–ethyl acetate, 2 : 1).

3-Benzyloximino-1-benzyloxy-5-(4-nitrophenyl)-2-oxopyrrolidine (10f). B. A mixture of compound **5f** (0.19 g, 0.808 mmol) in methanol (1 ml) and NH_2OBn (0.219 g, 1.777 mmol) in methanol (pH 7) (1.8 ml) was stirred for 1 day, the methanol was evaporated, and the resulting residue was chromatographed. Compound **8f** (0.018 g, 12%) was obtained with R_f 0.5 (Merck silica gel F_{254}, petroleum ether–ethyl acetate, 2:1), also compound **9f** (0.16 g, 43%) with R_f 0.43, and compound **10f** (0.034 g, 9.8%), R_f 0.23, all as cream-colored crystals. On heating a methanolic solution of compound **9f** for 72 h at 60°C the compound partially cyclized into **10f**. The overall yield of compound **10f** was 42%.

Compound **8f**; mp 118-120°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.16-8.24 (2H, m, Ph-NO_2); 7.72 (1H, d, *J* = 16.8, =CH); 7.58-7.67 (2H, m, Ph-NO_2); 7.38-7.44 (5H, m, C_6H_5); 7.34 (1H, d, *J* = 16.8, CH=); 5.40 (2H, s, O-$\underline{CH_2}$-Ph); 3.93 (3H, s, O-CH_3). Fouind, %: C 63.46; H 4.65; N 8.00. $C_{18}H_{16}N_2O_5$. Calculated, %: C 63.53; H 4.74; N 8.23.

Compound **9f**; mp 148-150°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.04-8.09 (2H, m, Ph-NO_2); 7.15-7.42 (12H, m, Ph, Ph-NO_2); 5.7 (1H, br. s, NH); 5.21 (2H, s, O-$\underline{CH_2}$-Ph); 4.53 (2H, d, *J* = 2.8, O-$\underline{CH_2}$-Ph); 4.29-4.50 (1H, m, O_2N-Ph-$\underline{CH}$); 3.78 (3H, s, OCH_3); 2.82-3.03 (2H, m, CH_2).

Alkylation of Compound 6b. Benzyl bromide (0.855 g, 0.59 ml, 5.0 mmol) and K_2CO_3 (0.76 g, 5.5 mmol) were added to a solution of compound **6b** (0.245 g, 1.0 mmol) in DMF (11ml) and the mixture heated at 80°C for 6 h. The mixture was filtered, and the solvent distilled off in vacuum. The reaction product was isolated by chromatography in the system petroleum ether–ethyl acetate, 3:1. The ^{1}H NMR spectrum, elemental analysis, and melting point of the obtained compound were identical with those of compound **10b**, yield was 0.19 g (50%) of colorless crystals.

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