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REACTIONS OF 1,3,5-TRIAZINYLNITROFORMALDOXIMES 3*. INTERACTION OF 1,3,5-TRIAZINYLNITROFORMALDOXIMES WITH MALONIC ACID ESTERS

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The reaction of 6-R-4-methoxy-1,3,5-triazin-2-ylnitroformaldoximes with dimethyl malonate gives the zwitterionic 4-methoxycarbonyl-3-(4-R-6-methoxy-1,3,5-triazin-2-yl)-4,5-dihydroisoxazol-5-ones. X-ray structural analysis has been carried out on the zwitterionic 4-methoxycarbonyl-3-(4-methoxy-6-piperidino-1,3,5-triazin-2-yl)- 4,5-dihydroisoxazol-5-one.

Keywords: 3,4-disubstituted 4,5-dihydroisoxazol-5-ones, dimethyl malonate, 1,3,5-triazinylnitrile oxides, 1,3,5-triazinylnitroformaldoximes.

Base treatment of 1,3,5-triazinylnitroformaldoximes generates 1,3,5-triazinylnitrile oxides which can react with diketones or keto esters enolates *via* a dipolar [3+2] cycloaddition to form 3,4,5-trisubstituted isoxazole derivatives [2]. However, examples of the reactions of nitrile oxides with malonic acid esters have not been reported. In trying to fill this gap we have studied the reaction of 1,3,5-triazinylnitroformaldoximes with dimethyl malonate.

The reaction of the 4-R-6-methoxy-1,3,5-triazin-2-ylnitroformaldoximes **1a-d** with dimethyl malonate **2** in the presence of alkali occurs through formation of a series of intermediates and their mutual interactions. The action of alkali on compounds **1a-d** gives nitrile oxides but compound **2** gives a carbanion. Their dipolar [3+2] cycloaddition interaction leads to splitting off methanol and to the closure of an isoxazole ring. After the treatment with an acid zwitterionic 4-methoxycarbonyl-3-(6-R-4-methoxy-1,3,5-triazin-2-yl)-4,5-dihydro-isoxazol-5-ones **3a-d** were formed in 59-75% yield.

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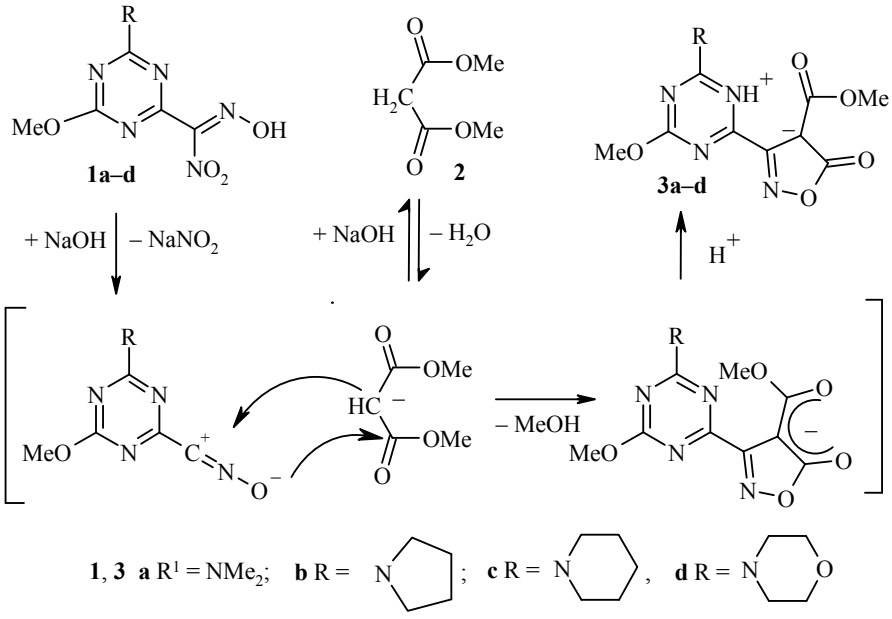
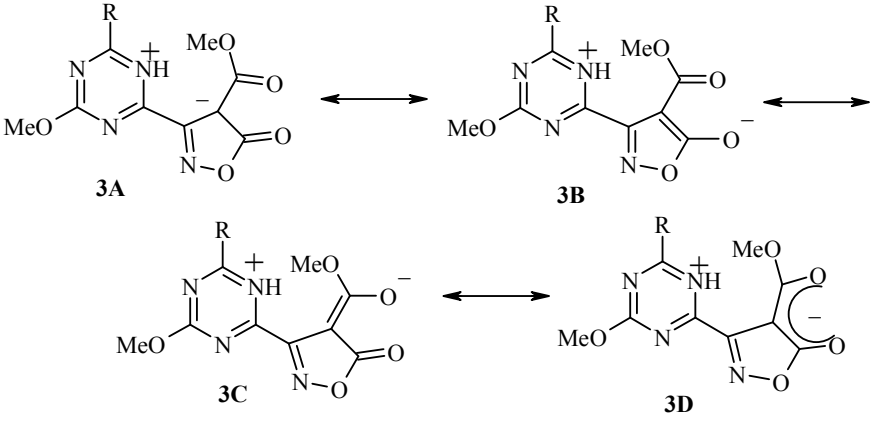


The carbonyl group absorptions in isoxazoles **3a-d** appear as a single peak in the region 1716-1720 cm^{-1}. This averaging and somewhat lowering in frequency of the carbonyl group absorptions in compounds **3a-d** when compared to 4-ethoxycarbonyl-3-(6-R-4-methoxy-1,3,5-triazin-2-yl)-5-methylisoxazoles [2] is likely due to a decreased multiplicity of the C=O bonds in carbonyl groups as represented by the overall structures **3A-D**:



The structure confirmation of of the compounds obtained and the assignment of their ^{1}H and ^{13}C NMR signals came from their ^{1}H and ^{13}C spectra and from the two-dimensional gs-HMBC and gs-HSQC proton-carbon correlations. In particular, cross peaks are observed due to the presence of long range interactions of the C(2) and C(4) atoms of the triazine ring, the carbonyl carbon atom of the ester function, and the protons of the corresponding substituents and this unambiguously leads to their assignment. Proof of the presence of a carbanion center at atom C(4) of the isoxazole ring comes from the chemical shift of 76-80 ppm which is a characteristic of an sp^3-hybridized carbon atom. The shift of the ^{13}C NMR signal for this atom to high field when compared to 4-ethoxycarbonyl-3-(6-R-4-methoxy-1,3,5-triazin-2-yl)-5-methylisoxazoles is about 29-32 ppm (δ C(4) = 108-109 ppm). Additionally, the C(4) isoxasole ring atom does not have any cross peaks with the protons in the gs-HSQC spectra hence this also confirms the absence of a covalent bond with protons and points to its carbanion character.

TABLE 1. ^{13}C NMR Spectroscopic Data for the Zwitterionic 4-Methoxycarbonyl-3-(6-R-4-methoxy-1,3,5-triazin-2-yl)-4,5-dihydroisoxazol-5-ones **3a-d** and 4-ethoxycarbonyl-3-(6-R-4-methoxy-1,3,5-triazin-2-yl)-5-methylisoxazoles

Compound	Chemical shifts, δ, ppm							
	1,3,5-Triazine ring			Isoxazole ring			COOMe, COOEt	Other signals
	C(2)	C(4)	C(6)	C(3)	C(4)	C(5)		
3a	164.9	163.1	163.1	158.0	80.7	173.3	164.7	36.9, 37.1 ($N(CH_3)_2$); 50.6 ($COOCH_3$); 55.5 (OCH_3)
3b	165.3	161.3	163.4	158.1	79.9	173.1	167.6	24.8, 25.1 (CH_2); 47.6, 47.8 (CH_2N); 50.8 ($COOCH_3$); 56.0 (OCH_3)
3c	164.9	162.4	162.8	157.6	76.6	172.8	164.8	23.7, 23.3, 25.4 (CH_2); 44.9, 45.2 (CH_2N); 50.5 ($COOCH_3$); 55.6 (OCH_3)
3d	165.1	164.5	163.5	159.3	80.2	172.9	165.1	43.4, 43.8 (CH_2N); 50.0 ($COOCH_3$); 55.0 (OCH_3); 65.7 (OCH_2)
3-(6-Dimethylamino-4-methoxy-1,3,5-triazin-2-yl)-4-ethoxycarbonyl-5-methylisoxazole	169.78	165.74	164.99	160.16	108.45	174.40	159.29	12.01 (CH_3); 13.28 (CH_3); 35.50, 35.75 ($N(CH_3)_2$); 53.98 (OCH_3); 60.23 (OCH_2)
4-Ethoxycarbonyl-3-(4-methoxy-6-pyrrolidinyl-1,3,5-triazin-2-yl)-5-methylisoxazole	169.58	165.66	162.84	160.15	108.44	174.38	159.29	12.03 (CH_3); 13.28 (CH_3); 24.13, 24.29 (CH_2); 45.84, 46.08 (CH_2N); 53.94 (OCH_3); 60.21 (OCH_2)
4-Ethoxycarbonyl-3-(4-methoxy-6-piperidino-1,3,5-triazin-2-yl)-5-methylisoxazole	170.07	166.06	163.99	160.18	108.46	174.35	159.26	11.97 (CH_3); 13.28 (CH_3); 23.51, 24.83, 24.91 (CH_2); 43.48, 43.83 (CH_2N); 53.99 (OCH_3); 60.23 (OCH_2)
4-Ethoxycarbonyl 3-(4-methoxy-6-morpholino-1,3,5-triazin-2-yl)-5-methylisoxazole	170.07	166.15	164.47	160.14	108.45	174.50	159.16	11.99 (CH_3); 13.30 (CH_3); 43.02, 43.38 (CH_2N); 54.16 (OCH_3); 60.27 (OCH_2); 65.37 (OCH_2)

The structure of isoxazole **3c** was confirmed by X-ray structural analysis (Figure 1 and Tables 2-4).

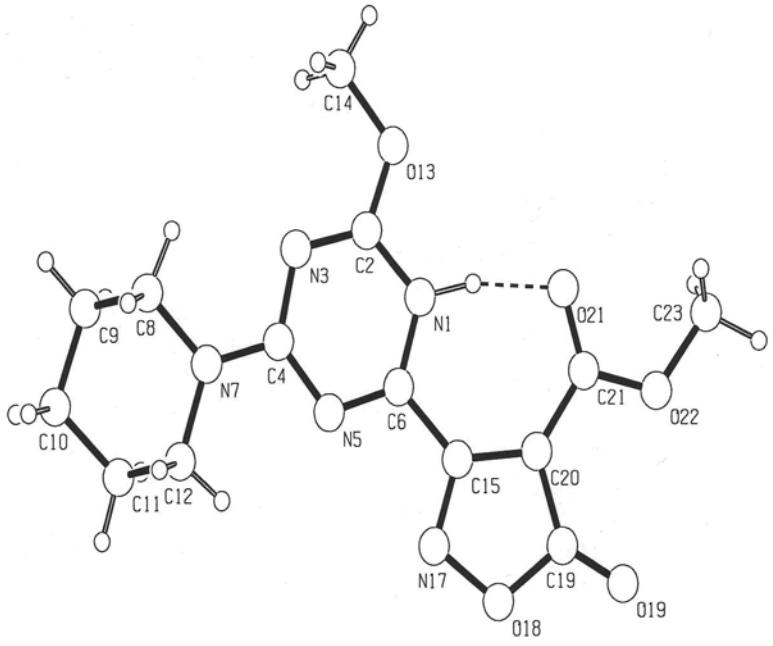


Fig. 1. Molecular structure of 3-(4-methoxy-6-piperidino-1,3,5-triazin-2-yl)-4-methoxycarbonyl-4,5-dihydroisoxazol-5-one **3c**.

Despite the presence of a substituent at the 4 position of the isoxazole ring (comparison with X-ray data for ethyl 3-(4-methoxy-6-pyrrolidinyl-1,3,5-triazin-2-yl)-5-methylisoxazole-4-carboxylate [2]) all of the molecule is planar with the exception of the piperidine ring which has a *chair* conformation. The molecular planarity is achieved through the intramolecular hydrogen bond O(21)–H(1)–N(1) (hydrogen bond parameters: N(1)–H(1) 0.972, H(1)···O(21) 1.616, N(1)···O(21) 2.567 Å, N(1)–H(1)···O(21) angle 165.72º). The 1,3,5-triazine ring is symmetrically deformed: the C(2)–N(3) and C(6)–N(5) bonds are shortened to 1.290-1.310 Å and the C(4)–N(3), C(4)–N(5), C(2)–N(1), and C(6)–N(1) bonds are lengthened to 1.35-1.37 Å. The C(20) atom basically bears the negative charge and has a trigonal configuration: all of the bonds C(15)–C(20), C(21)–C(20), and C(19)–C(20)

TABLE 2. Bond Lengths (*d*) in Compound **3c**

Bond	*d*, Å	Bond	*d*, Å
N(1)–C(2)	1.356(2)	C(10)–C(11)	1.513(3)
N(1)–C(6)	1.348(2)	C(11)–C(12)	1.512(3)
N(5)–C(4)	1.367(2)	C(6)–C(15)	1.480(2)
N(5)–C(6)	1.304(2)	C(15)–N(17)	1.309(2)
N(3)–C(2)	1.297(2)	O(18)–N(17)	1.404(2)
N(3)–C(4)	1.360(2)	O(18)–C(19)	1.402(2)
O(13)–C(2)	1.309(2)	O(19)–C(19)	1.215(2)
O(13)–C(14)	1.452(2)	C(20)–C(19)	1.426(2)
C(4)–N(7)	1.324(2)	C(20)–C(21)	1.427(2)
N(7)–C(8)	1.475(2)	O(22)–C(21)	1.335(2)
N(7)–C(12)	1.468(2)	O(22)–C(23)	1.440(2)
C(8)–C(9)	1.500(3)	O(21)–C(21)	1.235(2)
C(9)–C(10)	1.508(3)	C(15)–C(20)	1.427(2)

are identical at 1.427 Å. The angle deviations from 120º are C(15)–C(20)–C(21) 130.72º, C(21)–C(20)–C(19) 124.74º, and C(19)–C(20)–C(15) 104.53º and this is associated with the fact that atom C(20) is part of the cyclic isoxazole system.

TABLE 3. Valence Angles (ω) in Compound **3c**

Angle	ω, deg	Angle	ω, deg
C(2)–N(1)–C(6)	117.82(11)	C(12)–N(7)–C(8)	114.66(13)
C(2)–N(3)–C(4)	115.45(12)	N(1)–C(6)–C(15)	117.26(10)
C(4)–N(5)–C(6)	115.58(11)	N(5)–C(6)–C(15)	119.68(11)
N(1)–C(6)–N(5)	123.06(12)	C(6)–C(15)–N(17)	115.43(11)
N(1)–C(2)–N(3)	123.46(12)	C(6)–C(15)–C(20)	131.33(11)
N(3)–C(4)–N(5)	124.61(11)	C(15)–N(17)–O(18)	105.92(10)
C(2)–O(13)–C(14)	117.48(11)	N(17)–O(18)–C(19)	110.56(10)
O(13)–C(2)–N(1)	113.12(11)	O(18)–C(19)–O(19)	118.61(13)
O(13)–C(2)–N(3)	123.41(13)	O(18)–C(19)–C(20)	105.80(11)
N(3)–C(4)–N(7)	117.80(12)	O(19)–C(19)–C(20)	135.59(12)
C(4)–N(7)–C(8)	122.19(13)	N(17)–C(15)–C(20)	113.17(12)
N(5)–C(4)–N(7)	117.59(12)	C(19)–C(20)–C(15)	104.53(11)
C(4)–N(7)–C(12)	123.04(12)	C(15)–C(20)–C(21)	130.72(12)
N(7)–C(8)–C(9)	111.26(15)	C(19)–C(20)–C(21)	124.74(12)
C(8)–C(9)–C(10)	111.39(15)	C(20)–C(21)–O(21)	126.09(12)
C(9)–C(10)–C(11)	110.38(16)	C(20)–C(21)–O(22)	113.84(11)
C(10)–C(11)–C(12)	111.37(16)	C(21)–O(22)–C(23)	116.28(12)
C(11)–C(12)–N(7)	109.89(14)	O(21)–C(21)–O(22)	120.06(12)

TABLE 4. Torsional Angles (θ) in Compound **3c**

Angle	θ, deg	Angle	θ, deg
C(14)–O(13)–C(2)–N(3)	1.6(2)	N(1)–C(6)–C(15)–C(20)	-2.2(2)
C(14)–O(13)–C(2)–N(1)	-177.4(1)	N(1)–C(6)–C(15)–N(17)	-179.0(1)
O(13)–C(2)–N(3)–C(4)	-179.9(1)	N(5)–C(6)–C(15)–N(17)	0.7(2)
O(13)–C(2)–N(1)–C(6)	-179.1(1)	N(5)–C(6)–C(15)–C(20)	177.5(1)
C(2)–N(3)–C(4)–N(5)	-0.5(2)	C(6)–C(15)–C(20)–C(21)	2.4(2)
N(3)–C(4)–N(5)–C(6)	1.0(2)	C(6)–C(15)–N(17)–O(18)	177.5(1)
C(4)–N(5)–C(6)–N(1)	-0.0(2)	C(6)–C(15)–C(20)–C(19)	-176.0(1)
N(5)–C(6)–N(1)–C(2)	-1.3(2)	C(15)–N(17)–O(18)–C(19)	-1.1(1)
C(6)–N(1)–C(2)–N(3)	1.9(2)	N(17)–O(18)–C(19)–O(19)	-178.1(1)
N(1)–C(2)–N(3)–C(4)	-1.0(2)	N(17)–O(18)–C(19)–C(20)	1.6(1)
N(3)–C(4)–N(7)–C(8)	-6.1(2)	O(18)–C(19)–C(20)–C(21)	-180.0(1)
N(3)–C(4)–N(7)–C(12)	178.1(1)	O(18)–C(19)–C(20)–C(15)	-1.4(1)
N(5)–C(4)–N(7)–C(12)	-2.5(2)	C(15)–C(20)–C(19)–O(19)	178.2(2)
N(5)–C(4)–N(7)–C(8)	173.4(1)	C(15)–C(20)–C(21)–O(22)	-176.6(1)
C(4)–N(7)–C(8)–C(9)	129.7(2)	C(19)–C(20)–C(15)–N(17)	0.8(2)
C(4)–N(7)–C(12)–C(11)	129.3(2)	C(20)–C(21)–O(22)–C(23)	175.7(1)
N(7)–C(12)–C(11)–C(10)	55.0(2)	C(15)–C(20)–C(21)–O(21)	3.7(2)
C(12)–C(11)–C(10)–C(9)	56.2(2)	C(19)–C(20)–C(21)–O(21)	-178.1(1)
C(11)–C(10)–C(9)–C(8)	-55.0(2)	C(19)–C(20)–C(21)–O(22)	1.5(2)
C(10)–C(9)–C(8)–N(7)	53.2(2)	O(21)–C(21)–C(20)–C(19)	-178.1(1)
C(9)–C(8)–N(7)–C(12)	-54.1(2)	C(21)–C(20)–C(19)–O(19)	-0.3(3)
C(8)–N(7)–C(12)–C(11)	54.6(2)	O(21)–C(21)–C(20)–C(15)	3.7(2)

EXPERIMENTAL

IR spectra were recorded on an Avatar 360ESP spectrophotometer in KBr tablets and ^{1}H and ^{13}C NMR spectra on a Bruker Avance II spectrometer (400 and 100 MHz respectively) using DMSO-d_6 with TMS as internal standard. Elemental analysis was carried out on a Eurovector EA 3000 instrument.

X-ray Structural Analysis of Compound 3c was carried out at 20ºC on a Bruker Smart APEX2 automatic diffractometer (λ MoKα, graphite monochromator, ω-scanning). Calculation of absorption was not carried out because it was very small. The structure was solved by the direct method using the SIR program [3] and refined initially in the isotropic and then the anisotropic approximation using the SHELXL-97 program [4]. The hydrogen atom coordinates were revealed in Fourier difference synthesis and refined isotropically. All of the calculations were carried out using the WinGX [5] and APEX2 [6] programs. Figure 1 and the analysis of hydrogen bonds were carried out through the PLATON [7] program.

Crystals of compounds **3c** are colorless, transparent, tricyclic prisms: $C_{14}H_{17}N_5O_5$, M = 335.33, a = 7.0908(5), b = 10.5571(7), c = 11.1432(8) Å, α = 98.552(1), β = 107.493(1), γ = 97.187(1)º, V = 773.88(9) Å^3, d_{calc} = 1.44 g/cm^3, Z = 2, space group $P\bar{1}$. Scanning angle 2.0º ≤ θ ≤ 27.0º. 3361 Independent reflections were measured, 2806 of which had $I > 2\sigma(I)$. Calculation of the absorption was not carried out because it was very small (μ(Mo) = 0.112 cm^{-1}). The final difference factors were R_{1obs} = 0.037 and R_{wobs} = 0.0978 for 2806 reflections.

The study of the compound **3c** monocrystal was carried out in the X-ray structural research department of JUC SAC based on the Laboratory of the Diffraction Research Methods of the A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center of the Russian Academy of Sciences.

The atomic coordinates and structural parameters for compound **3c** have been placed in the Cambridge Structural Database as deposit CCDC 736560.

Compounds **1a-d** were prepared by method [8]. 4-Ethoxycarbonyl-3-(6-R-4-methoxy-1,3,5-triazin-2-yl)- 5-methylisoxazoles were synthesized by method [1].

Zwitterionic 3-(6-Dimethylamino-4-methoxy-1,3,5-triazin-2-yl)-4-methoxycarbonyl-4,5-dihydro-isoxazol-5-one (3a). Dimethyl malonate (2.3 ml, 2 mmol) was added to a stirring solution of sodium hydroxide (1.6 g, 4 mmol) in methanol (20 ml) at 20-25ºC followed by compound **1a** (2.42 g, 1 mmol). The reaction mixture stirred at 20-25ºC until disappearance of the starting compound **1a** (1 to 1.5 h according to TLC). It was then cooled to 5-10ºC and the precipitate was filtered off and washed with cold methanol (5 ml). The precipitate was dissolved in water (20 ml) and acidified with dilute hydrochloric acid. The precipitated compound **3a** was filtered off and washed with cold water. Yield 2.12 g (72%); mp175-177ºC (decomp.). IR spectrum, ν, cm^{-1}: 3018, 2958, 1720, 1648, 1618, 1502, 1467, 1413, 1214, 1193, 1083, 1024, 935, 906, 885, 781, 732. ^{1}H NMR spectrum, δ, ppm (J, Hz): 3.21 and 3.33 (6H, two s, NCH_3); 3.51 (3H, s, $COOCH_3$); 3.99 (3H, s, OCH_3); 11.07 (br. s, NH^+). Found, %: C 44.88; H 4.28; N 23.60. $C_{11}H_{13}N_5O_5$. Calculated, %: C 44.75; H 4.44; N 23.72.

Zwitterionic 3-(4-Methoxy-6-pyrrolidinyl-1,3,5-triazin-2-yl)-4-methoxycarbonyl-4,5-dihydroisoxazol-5-one (3b) was prepared similarly from compound **1b** (2.68 g, 1 mmol). Yield 1.9 g (59%); mp140-142ºC (decomp.). IR spectrum, ν, cm^{-1}: 2958, 2887, 2439, 1716, 1648, 1608, 1500, 1459, 1378, 1213, 1122, 1078, 1037, 1027, 908, 885, 781, 659. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.96 (4H, m, CH_2); 3.55 (3H, s, $COOCH_3$); 3.61 (4H, t, J = 8.0, NCH_2); 4.02 (3H, s, OCH_3); 10.13 (1H, br. s, NH^+). Found, %: C 48.54; H 4.87; N 21.91. $C_{13}H_{15}N_5O_5$. Calculated, %: C 48.60; H 4.71; N 21.80.

Zwitterionic 3-(4-Methoxy-6-piperidino-1,3,5-triazin-2-yl)-4-methoxycarbonyl-4,5-dihydroisoxazol-5-one (3c) was prepared similarly from compound **1c** (2.82 g, 1 mmol). Yield 2.25 g (67%); mp 145-147ºC (decomp.). IR spectrum, ν, cm^{-1}: 3432, 3012, 2863, 1718, 1710, 1652, 1612, 1560, 1498, 1467, 1450, 1382, 1290, 1214, 1180, 1153, 1093, 1035, 910, 779, 673. ^{1}H NMR spectrum, δ, ppm; 1.08-1.15 (6H, m, CH_2); 3.53 (3H, s, $COOCH_3$); 3.87 (4H, m, NCH_2); 4.00 (3H, s, OCH_3); 11.83 (br. s, NH^+). Found, %: C 50.32; H 5.17; N 20.75. $C_{14}H_{17}N_5O_5$. Calculated, %: C 50.15; H 5.11; N 20.89.

Zwitterionic 3-(4-Methoxy-6-morpholino-1,3,5-triazin-2-yl)-4-methoxycarbonyl-4,5-dihydroisoxazol-5-one (3d) was prepared similarly from compound **1d** (2.84 g, 1 mmol). Yield 2.53 g (75%); mp 155-157ºC (decomp.). IR spectrum, ν, cm^{-1}: 3012, 2954, 2860, 1718, 1646, 1602, 1500, 1465, 1448, 1380, 1303, 1284, 1211, 1116, 1078, 1016, 904, 881, 783, 622. ^{1}H NMR spectrum, δ, ppm: 3.51 (3H, s, $COOCH_3$); 3.66-3.84 (8H, m, NCH_2CH_2O); 3.97 (3H, s, OCH_3); 10.50 (br. s, NH^+). Found, %: C 46.13; H 4.41; N 20.57. $C_{13}H_{15}N_5O_6$. Calculated, %: C 46.29; H 4.48; N 20.76.

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