Chemistry of Heterocyclic Compounds, Vol. 44, No. 8, 2008

SYNTHESIS OF UNNATURAL AMINO ACIDS CONTAINING THE 3,7-DIAZABICYCLO-[3,3,1]NONANE UNIT

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Unnatural amino acids containing the 3,7-diazabicyclo[3,3,1]nonane unit were synthesized in one step by the reaction of diethyl 3-oxoglutarate, bis(methoxycarbonylmethyl) sulfone, with formaldehyde and primary amino acids under conditions of the Mannich reaction.

Keywords: bis(methoxycarbonylmethyl) sulfone, 3,7-diazabicyclo[3,3,1]nonan-9-ones, diethyl 3-oxoglutarate, unnatural amino acids, 9-thia-3,7-diazabicyclo[3,3,1]nonane 9,9-dioxide, Mannich reaction.

An important direction at present in the area of organic and pharmaceutical chemistry is the synthesis of new confomationally rigid analogs of natural amino acids [1]. Showing similarities in a number of parameters with natural analogs, the twenty classical amino acids, these compounds possess a high potential for physiological activity. The limited conformational mobility of the molecules may bring about high activity and selectivity in reactions with receptors.

Many conformationally hindered and rigid amino acids, and peptide-mimics and synthetic peptides based on them, have been synthesized [1]. However there are few data on conformationally rigid cyclic amino acids containing the 3,7-diazabicyclo[3,3,1]nonane unit. Most of the publications are concerned with the synthesis of amino acids by functionalization of the natural alkaloid cytisine at the N-12 atom [2-4]. The paper [5] must also be noted in which two examples of unnatural amino acids of the 3,7-diazabicyclo[3,3,1]nonane series were synthesized by the reaction of glycine and L-alanine with paraformaldehyde and dibenzyl ketone.

The high physiological activity (anticancer [6], antiarrhythmic [7], insecticidal [8], etc.) of derivatives of 3,7-diazabicyclo[3,3,1]nonane predetermines the development of new methods and principles for the preparation of amino acids of unnatural origin, containing the 3,7-diazabicyclo[3.3.1]nonane unit which are of interest from the point of view of developing pharmaceutical preparations. One of the possible methods for the synthesis of nitrogenous heterocycles is the reaction of CH-acids with aldehydes and primary amines, on the basis of which we developed methods for the preparation of derivatives of 1,5-dihydro-3,7-diaza-bicyclo[3,3,1]nonane [9, 10] and 9-thia-3,7-diazabicylo[3,3,1]nonane 9,9-dioxide [11].

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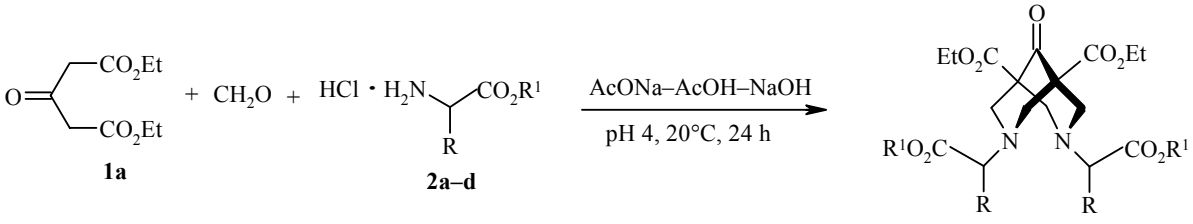
 0009-3122/08/4408-0996

In the present work the synthesis of unnatural amino acids, containing the 3,7-diazabicyclo-[3,3,1]nonane structure is presented, based on the condensation of diethyl oxoglutarate (**1a**), and bis(methoxy-carbonylmethyl) sulfone (**1b**) with formaldehyde and amino acids under Mannich reaction conditions. The hydrochlorides of ethyl glycinate (**2a**), methyl esters of α-alanine (L-isomer or racemate) **2b**, L-leucine **2c**, L-tyrosine **2d,** and also glycine **2e**.

It is known that the direction of the Mannich reaction is determined to a considerable degree by the acidity of the medium, the structure of the starting materials, and the nature of the solvent. During preliminary experiments it was established that amino acids of the 3,7-diazabicyclo[3,3,1]nonane series based on diethyl 3-oxoglutarate (**1a**) can be obtained in sufficiently high yields by carrying out the reaction in the system AcONa–AcOH–NaOH at pH 4. For example, reaction of ester **1a** with 32% aqueous formaldehyde and ethyl glycine hydrochloride (**2a**) (mol ratio 1:4:2) at room temperature for 24 h, gave 1,5-di(ethoxycarbonyl)-3,7-di-(ethoxycarbonylmethyl)-3,7-diazabicyclo[3,3,1]nonan-9-one (**3a**) in 76% yield. It should be noted that the reaction of ester **1a** with amino acid **2a** and formaldehyde in a 3:1 MeOH–H_2O medium at room temperature led to the formation of the ester of amino acid **3a** in 5% yield and increasing the temperature to 60°C gave a mixture of reaction products which was difficult to separate.



1a

2a–d

3a–d

2, 3 a R = H, R^1 = Et; **b–d** R^1 = Me, **b** R = Me, **c** R = CH_2CHMe_2, **d** R = 4-$HOC_6H_4CH_2$

In our chosen reaction conditions condensation of the diethyl ester **1a** with formaldehyde and the hydrochlorides of the esters of the racemate of α-alanine **2b**, L-leucine **2c**, and L-tyrosine **2d** led to the formation of 1,5-di(ethoxycarbonyl)-3,7-diazabicyclo[3,3,1]nonan-9-ones **3b-d** with two asymmetric centers in yields of 60, 85, and 79% respectively. According to ^{1}H and ^{13}C NMR data the product of the reaction of ester **1a** with formaldehyde and the racemate of the methyl ester of α-alanine **2b** was a mixture of the three D,D-, L,L-, and D,L-diastereomeric forms of 1,5-di(ethoxycarbonyl)-3,7-di(1-methoxycarbonylethyl)-3,7-diaza-bicyclo[3,3,1]nonan-9-one (**3b**) in a ratio of 1:1:2. It should be noted that we have never observed in the reaction mass piperidones – the possible intermediate products of the condensation reaction – even with a ratio of the starting materials **1a**–CH_2O–**2a** of 1:2:1 [10].

In the ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) of compound **3a** the signals of the methylene groups of the bicyclononane skeleton appear as a singlet at δ_C 57.5 ppm, but the protons form an AB system with ^2J = 11.1 Hz, which indicates the symmetrical structure of the heterocycle. Introduction of an asymmetric center in the substituent at N-3 and N-7 leads to the appearance diastereotopy of the NCH_2 group. In the ^{13}C NMR spectrum of compound **3c** there is a doubling of signals for the carbon atoms at δ_C 55.89 and 57.11 ppm, and for compound **3d** at δ_C 57.17 and 56.39 ppm (Table 1). The presence in the proton spectra of long distance coupling constants $^4J_{aa}$ = 1.8 and $^4J_{ee}$ = 1.3 Hz between the methylene protons shows that the 3,7-diazabicyclo[3,3,1]nonan-9-one has the *chair-chair* conformation and confirms that the substituents at atoms N-3 and N-7 have the same configuration of the chiral centers. In this case the axial and equatorial protons at atoms C-2, C-8, and C-4, C-6 are magnetically inequivalent and have a W-disposition. The D,D- and L,L-enantiomers of compound **3b** with the same D- or L-amino acid substituents at atoms N-3 and N-7 have analogous spectra as in the previous case.

Table 1. ^{1}H NMR Spectra of Amino Acids of the 3,7-diazabicyclo[3,3,1]nonane Series **3a-d** and **5**

Compound	Chemical shifts, δ, ppm (*J*, Hz*)								
	H-2		H-4		H-6		H-8		Other atoms H
	H_{ax}	H_{eq}	H_{ax}	H_{eq}	H_{ax}	H_{eq}	H_{ax}	H_{eq}	
3a	3.33 (d, *J* = 11.1)	3.42 (d, *J* = 11.1)	3.33 (d, *J* = 11.1)	3.42 (d *J* = 11.1)	3.33 (d, *J* = 11.1)	3.42 (d *J* = 11.1)	3.33 (d, *J* = 11.1)	3.42 (d, *J* = 11.1)	1.12, 1.14 (both 6H, t, ^3J = 7.1, $4CH_2C\underline{H}_3$) 3.21 (4H, s, $2NCH_2CO_2$); 4.01 (4H, q, ^3J = 7.1, $2OCH_2$); 4.09 (4H, q, ^3J = 7.1, $2NCH_2CO_2C\underline{H}_2CH_3$)
L,L-**3b**	3.21 (dd, *J* = 11.1, *J* = 1.7)	3.61 (dd, *J* = 11.1, *J* = 1.2)	3.34 (dd, *J* = 11.2, *J* = 1.7)	3.47 (dd, *J* = 11.1, *J* = 1.2)	3.21 (dd, *J* = 11.1, *J* = 1.7)	3.61 (dd, *J* = 11.1, *J* = 1.2)	3.34 (dd, *J* = 11.2, *J* = 1.7)	3.47 (dd *J* = 11.1, *J* = 1.2)	1.29 (6H, t, ^3J = 7.1, $2CH_2C\underline{H}_3$); 1.37 (6H, d, ^3J = 7.1, $2CHC\underline{H}_3$); 3.55 (2H, q, ^3J = 7.1, 2CH); 3.72 (6H, s, $2OCH_3$); 4.23 (4H, q, ^3J = 7.1, $2OCH_2$)
D,L-**3b**	3.59 (dd, *J* = 11.1, *J* = 1.4)	3.22 (dd, *J* = 11.2, *J* = 1.8)	3.48 (dd, *J* = 11.1, *J* = 1.4)	3.31 (dd, *J* = 11.1, *J* = 1.8)	3.48 (dd, *J* = 11.1, *J* = 1.4)	3.31 (dd, *J* = 11.1, *J* = 1.8)	3.59 (dd, *J* = 11.1, *J* = 1.4)	3.22 (dd, *J* = 11.2, *J* = 1.8)	1.288, 1.293 (both 3H, t, ^3J = 7.1, $2CH_2CH_3$); 1.37 (6H, d, ^3J = 7.1, $2CHC\underline{H}_3$); 3.55 (2H, q, ^3J = 7.5, 2CH); 3.73 (6H, s, $2OCH_3$); 4.23 (2H, q, ^3J = 7.1, CH_2); 4.24 (2H, q, ^3J = 7.1, CH_2)
3c	3.14 (dd, *J* = 11.3, *J* = 1.7)	3.59 (dd, *J* = 11.3, *J* = 1.3)	3.34 (dd, *J* = 11.3, *J* = 1.7)	3.43 (dd, *J* = 11.3, *J* = 1.3)	3.14 (dd, *J* = 11.3, *J* = 1.7)	3.59 (dd, *J* = 11.3, *J* = 1.3)	3.34 (dd, *J* = 11.3, *J* = 1.7)	3.43 (dd, *J* = 11.3, *J* = 1.3)	0.90, 0.94 (both 3H, d, ^3J = 6.5, $2CH_3$); 1.28 (6H, t, ^3J = 7.1, $2CH_2C\underline{H}_3$); 1.47 ($2H_A$, ddd, ^3J = 13.9, ^3J = 9.1, ^3J = 5.9, $2CH_2$); 1.72 ($2H_B$, ddd, ^3J = 13.9, ^3J = 9.6, ^3J = 5.3, $2CH_2$); 1.82 (2H, ddtt, ^3J = 9.1, ^3J = 6.5, ^3J = 6.5, ^3J = 5.3, 2CH); 3.42 (2H, dd, ^3J = 9.6, ^3J = 5.9, 2CHN); 3.70 (6H, s, $2OCH_3$); 4.23 (4H, q, ^3J = 7.1, OCH_2)
3d	3.09 (dd, *J* = 11.6 *J* = 1.5)	3.57 (dd, *J* = 11.6, *J* = 1.5)	3.24 (dd, *J* = 11.1, *J* = 1.5)	3.44 (dd, *J* = 11.1, *J* = 1.5)	3.09 (dd, *J* = 11.6, *J* = 1.5)	3.57 (dd, *J* = 11.6, *J* = 1.5)	3.24 (dd, *J* = 11.1, J = 1.5)	3.44 (dd, *J* = 11.1, *J* = 1.5)	1.26 (6H, t, ^3J = 7.1, $2CH_2C\underline{H}_3$); 2.85 ($2H_A$, dd, ^2J = 13.8, ^3J = 6.6, $2CH_2Ar$); 3.01 ($2H_B$, dd, ^2J = 13.8, ^3J = 8.5, $2CH_2Ar$); 3.53 (2H, dd, ^3J = 8.5, ^3J = 6.6, 2CHN); 3.63 (6H, s, $2OCH_3$); 4.22 (4H, q, ^3J = 7.1, $2OCH_2$); 6.73 (4H, d, ^3J = 8.5, $4CH_{Ar}$-*m*); 7.04 (4H, d, ^3J = 8.5, $4CH_{Ar}$-*o*)
5	3.55 (d, *J* = 14.0)	3.33 (d, *J* = 14.0)	3.55 (d *J* = 14.0)	3.33 (d, *J* = 14.0)	3.55 (d, *J* = 14.0)	3.33 (d, *J* = 14.0)	3.55 (d, *J* = 14.0)	3.33 (d, *J* = 14.0)	2.80 (2H, m, CH); 3.68 (6H, s, $2CH_3O$); 3.83 (4H, s, $2CH_2CO_2$)

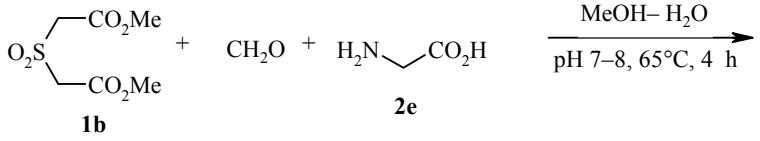
* ^{1}H NMR spectra were recorded in C_6D_6 (compound **3a**) and $CDCl_3$ (compounds **3b-d** and **5**).

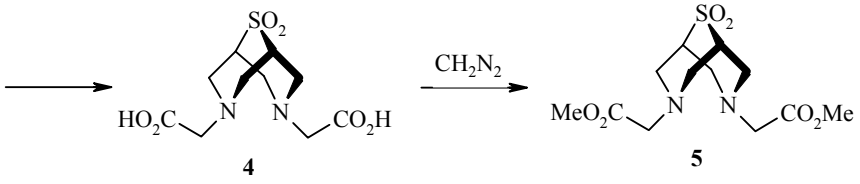
Table 2. ^{13}C NMR Spectra of the Esters of Amino Acids of the 3,7-Diazabicyclo[3,3,1]nonane Series **3a-d** and **5**

Com-pound	Chemical shifts, ($CDCl_3$), δ, ppm*						
	C-1	C-5	C-2	C-4	C-6	C-8	Others atoms C
3a	59.80	59.80	57.54	57.54	57.54	57.54	14.36 ($CO_2CH_2C\underline{H}_3$); 14.51 ($NCH_2CO_2CH_2\underline{C}H_3$); 57.54 ($CH_2N$); 59.39 ($\underline{C}H_2CO_2CH_2CH_3$); 60.26 ($NCH_2CO_2\underline{C}H_2CH_3$); 61.39 ($CO_2\underline{C}H_2CH_3$); 169.46 ($CO_2$); 169.56 ($CH_2\underline{C}O_2$); 202.57 (C=O)
L,L-**3b**	59.62	59.62	55.64	56.96	55.64	56.96	14.13 ($CH_2\underline{C}H_3$); 15.27 ($CH\underline{C}H_3$); 51.42 (OCH_3); 61.08 (CHN); 61.65 (OCH_2); 170.11 ($C\underline{C}O_2$); 172.89 ($CH\underline{C}O_2$); 202.88 (C=O)
D,L-**3b**	59.65	59.57	55.68	57.05	57.05	55.68	14.16 and 14.10 ($CH_2\underline{C}H_3$); 15.27 ($CH\underline{C}H_3$); 51.42 (OCH_3); 61.06 (CHN); 61.54 and 61.72 (OCH_2); 170.01 and 170.18 ($C\underline{C}O_2$); 172.84 ($CH\underline{C}O_2$); 202.92 (C=O)
3c	59.63	59.63	55.79	56.99	55.79	56.99	14.39 ($CH_2\underline{C}H_3$); 21.50, 23.10 (both $CH\underline{C}H_3$); 24.10 (CH); 37.88 (CH_2); 51.50 (OCH_3); 61.53 (OCH_2); 63.94 (CHN); 169.96 ($C\underline{C}O_2$); 172.31 ($CH\underline{C}O_2$); 202.50 (C=O)
3d	59.64	59.64	57.17	56.39	57.17	56.39	14.04 ($CH_2\underline{C}H_3$); 34.67 ($\underline{C}H_2Ar$); 51.53 (OCH_3); 61.96 (OCH_2); 68.35 (CHN); 115.53 (C(Ar)-*m*), 128.98 (C(Ar)-*i*); 130.14 (C(Ar)-*o*); 154.86 (C(Ar)-*p*); 170.11 ($C\underline{C}O_2$); 171.77 ($CH\underline{C}O_2$); 202.75 (C=O)
5	54.08	54.08	57.24	57.24	57.24	57.24	51.61 (OCH_3); 170.86 (CO_2)

* ^{13}C NMR Spectra were taken in (C_6D_6) (compound **3a**) and $CDCl_3$ (compounds **3b-d** and **5**).

In the case of the D,L-diastereomer, in which the atoms N-3 and N-7 have substituents with different chiral centers, 2 signals of the methylene carbon atoms of the NCH_2 groups are observed in the ^{13}C NMR spectrum, with corresponding signals of the pairs of protons on each carbon atom.





In distinction from the ester **1a,** the interaction of bis(methoxycarbonylmethyl) sulfone **1b** with formaldehyde and glycine **2e** (mole ratio 1:4:2) at pH 4 did not lead to the expected 9-thia-3,7-diaza-bicyclo[3,3,1]nonane 9,9-dioxide **4**. The starting sulfone **1b** was isolated from the reaction mass. The desired product (**4)** in the form of 3,7-di(methoxycarbonylmethyl)9-thia-3,7-diazabicyclo[3,3,1]nonane 9,9-dioxide [**5**] was obtained in ~10% yield by carrying out the reaction 2:1 MeOH-H_2O solution at 65°C for 4h.

As reported elsewhere [11], the formation of the sulfone **5** was accompanied by regioselective hydrolysis of the esters at positions 1 and 5 with subsequent decarboxylation. Hydrolysis and decarboxylation of the amino acid units did not occur in this case.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (300 and 75 MHz respectively) with Me_4Si as internal standard. IR spectra of thin films or nujol mulls were recorded with a Shimadzu IR Prestige-21 spectrometer and mass spectra on a MX-1300 with insertion *via* a temperature balloon at 100°C with ionization energy of 12 and 70 eV or a Shimadzu LCMS 2010. Analysis was carried out on Silufol chromatographic plastic plates (Merck). Preparative separation by column chromatography on SiO_2 (Alfa Aesar, 70-230 mesh). Melting points were determined on a Boetius apparatus. Elemental analysis was carried out on a HEKAlech GmbH –Technik's Euro-EA CHN analyzer. Optical rotations were measured with a Perkin-Elmer 341 (λ 589 nm) polarimeter at 20°C.

Synthesis of Compounds 3a-d (General Method). Diethyl 3-oxoglutarate **1** (0.5 g, 2.5 mmol), the hydrochloride of the ester of amino acids **2a-d** (5 mmol), acetate buffer (pH 4) (1.4 ml), and 32% aqueous formaldehyde (0.93 g, 10 mmol) were added with stirring to $AcONa{\cdot}3H_2O$ (0.68 g, 5 mmol). The mixture was kept at room temperature for 24 h and chloroform (20 ml) was added. The organic layer was separated, washed with water (3 x 10 ml), and dried over anhydrous Na_2SO_4. The solvent was removed in vacuum.

1,5-Di(ethoxycarbonyl)-3,7-di(ethoxycarbonylmethyl)-3,7-diazabicyclo[3,3,1]nonan-9-one (3a) was obtained in a yield of 0.86 g (76%) as a yellowish oil. IR spectrum (thin film), ν, cm^{-1}: 1195, 1265 (CO), 1716, 1743 (C=O). Mass spectrum (CI at atmospheric pressure), *m/z* (I_{rel}, %): 457 $[M+H]^+$, 455 $[M–H]^–$. Found, %: C 55.28; H 7.00; N 6.12. $C_{21}H_{32}N_2O_9$. Calculated, %: C 55.25; H 7.07; N 6.14.

L,L-1,5-Di(ethoxycarbonyl)-3,7-di(1-methoxycarbonylethyl)-3,7-diazabicyclo[3,3,1]nonan-9-one (3b) was obtained in 1.16 g (75%) yield as a red oil. $[\alpha]_D^{20}$ -23 (*c* 0.0085, $CHCl_3$). IR spectrum (thin film),

ν, cm^{-1}: 1165, 1195, 1228, 1273 (CO), 1732, 1743 (C=O). Mass spectrum (CI at atmospheric pressure), *m/z*; 457 $[M+H]^+$, 455 $[M–H]^–$. Found, %: C 55.30; H 6.98; N 6.15. $C_{21}H_{32}N_2O_9$. Calculated, %: C 55.25; H 7.07; N 6.14.

DL-1,5-Di(ethoxycarbonyl)-3,7-di(1-methoxycarbonylethyl)-3,7-diazabicyclo[3,3,1]nonan-9-one (3b) was obtained in 0.7g (60%) yield as a yellow oil. $[\alpha]_D^{20}$ +2.9 (*c* 0.46, $CHCl_3$). IR spectrum (thin film), ν, cm^{-1}: 1165, 1195, 1228, 1273 (CO), 1732, 1743 (C=O). Mass spectrum (CI at atmospheric pressure), *m/z*: 457 $[M+H]^+$, 455 $[M–H]^–$. Found, %: C 55.30; H 6.98; N 6.15. $C_{21}H_{32}N_2O_9$. Calculated, %: C 55.25; H 7.07; N 6.14.

L,L-1,5-Di(ethoxycarbonyl)-3,7-di(3-methyl-1-methoxycarbonylbutyl)-3,7-diazabicyclo[3,3,1]nonan-9-one (3c) was obtained in a yield of 0.9 g (85%) as a yellow oil, $[\alpha]_D^{20}$ -46 ± 1 (*c* 0.038, $CHCl_3$). IR spectrum (thin film), ν, cm^{-1}: 1165, 1192, 1222, 1269 (CO), 1735 (C=O). Mass spectrum (CI at atmospheric pressure), *m/z*: 541 $[M+H]^+$. Found, %: C 60.02; H 8.18; N 5.16. $C_{27}H_{44}N_2O_9$. Calculated, %: C 59.98; H 8.20; N 5.18.

L,L-1,5-Di(ethoxycarbonyl)-3,7-di(2-(4-hydroxyphenyl)-1-methoxycarbonylethyl)- 3,7-diazabicyclo-[3,3,1]nonan-9-one (3d) was obtained in a yield of 1.57 g (79%) as yellowish crystals; mp 65-67°C. $[\alpha]_D^{20}$ -16 ± 1 (*c* = 0.015, $CHCl_3$). IR spectrum (nujol mull), ν, cm^{-1}: 827, 1375, 1516, 1595, 1614 (Ar), 1172, 1201 (CO), 1734 (C=O), 3398 (OH). Mass spectrum (CI at atmospheric pressure), *m/z*: 641 $[M+H]^+$, 639 $[M-H]^+$. Found, %: C 61.90; H 6.31; N 4.35. $C_{33}H_{40}N_2O_{11}$. Calculated, %: C 61.86; H 6.29; N 4.37.

3,7-Di(1-methoxycarbonylmethyl)-9-thia-3,7-diazabicyclo[3,3,1]nonane 9,9-dioxide (5). 33% Aqueous formaldehyde (1.75 g, 19.2 mmol), bis(methoxycarbonylmethyl) sulfone **1b** (1.01 g, 4.8 mmol), and 20% aqueous NaOH to pH 7.5-8.0 were added with stirring to a solution of glycine **2e** (0.72 g, 9.6 mmol) in water (15 ml) and MeOH (30 ml) and boiled for 4 h. The solvent was evaporated in vacuum. The residue was dissolved in 1:1 aqueous methanol (15 ml) and treated with an ether solution of diazomethane by method [14]. After removal of the solvent in vacuum, 1 N HCl was added to the residue to pH 1, and washed with chloroform (3×25 ml). The acid aqueous layer after extraction was neutralized with 20% NaOH, extracted with chloroform (3×25 ml), and dried over anhydrous Na_2SO_4. The solvent was removed in vacuum. The residue was chromatographed on SiO_2 (9:1 $CHCl_3$–*i*-PrOH) to give 0.15 g (10%) of compound **5** as a yellow oil. IR spectrum (thin film), ν, cm^{-1}: 1110, 1292 (SO_2). Mass spectrum (EI, 70 eV), *m/z*: 320 $[M]^+$. Found, %: C 44.95; H 6.26; N 8.66; S 10.03. $C_{12}H_{20}N_2O_6S$. Calculated, %: C 44.99; H 6.29; N 8.74; S 10.01.

The authors acknowledge a grant form the Program of Fundamental Research of the Presidium of the Russian Academy of Sciences "Direct Synthesis of Organic Substances with Specific Properties and Specific Functional Materials Based on Them".

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