SYNTHESIS AND PROPERTIES OF *SYM*-TRIAZINE DERIVATIVES

9.* SYNTHESIS OF 2-AMINO- AND 2,4-DIAMINO-*SYM*-TRIAZINES CONTAINING FURAN FRAGMENTS

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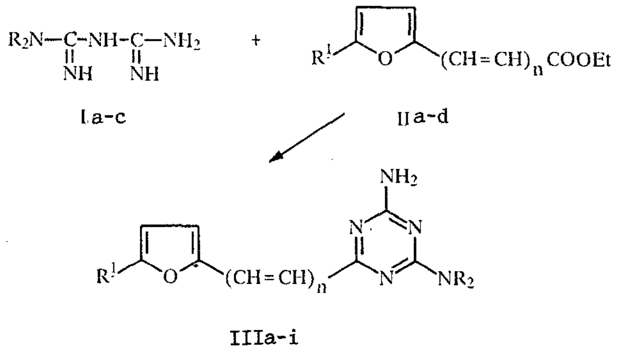
N-Substituted 2,4-diamino-6-furyl-sym-triazines were synthesized by cyclocondensation of furancarboxylic acid esters with biguanides. 2-Amino-4,6-disubstituted sym-triazines containing furyl residues were obtained by reacting furancarboxylic acid nitriles with guanidine or furancarboxylic acid esters with N-imidoylguanidines. Aminotriazines of this type are also formed in condensation of N-acylguanidines with nitriles or imino esters.

In continuing the research on synthesis of 2-amino- and 2,4-diamino-*sym*-triazines [1-4], we obtained compounds of this type containing furyl fragments. Such *sym*-triazine derivatives can be of interest as biologically active substances and antioxidants and stabilizers for polymeric materials, hydrocarbon fuels, and lubricants.

Condensation of nitriles, esters, and imino esters of acids of the furan series with guanidine and its derivatives was used in the present study.

N-substituted 2,4-diamino-6-alkyl(aryl, heteryl)-*sym*-triazines are formed [5] as a result of condensation of biguanides with esters. However, despite the wide use of different esters in this reaction, there is only one publication [6] concerning the participation of furan-2-carboxylic acid ethyl ester in the reaction with biguanide.

Condensation of N,N-disubstituted biguanides Ia-c with furan-2-carboxylic (IIa) and β-(5-R^1-furyl-2)acrylic acid (IIb-d) ethyl esters in the presence of bases was investigated in detail in the present study.



Ia, IIa, b R = Me; Ib, IIIc-f R_2N = piperidino; Ic, IIIg-i R_2N = morpholino; IIa, IIIa, c, g n = O, R^1 = H; IIb, IIIb, d, h n = 1, R^1 = H; IIc, IIIe n = 1, R^1 = Me; IId, IIIf-i n = 1, R^1 = NO_2.

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*See [1] for 8.

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TABLE 1. N,N-Disubstituted 2,4-Diamino-6-furyl-*sym*-triazines IIIa-i

Compound	Empirical formula	Mp, °C	R_f*	Yield, %
IIIa	$C_9H_{11}N_5O$	226...227	0,34(a)	75
IIIb	$C_{11}H_{13}N_5O$	> 320	0,82(в)	61
IIIc	$C_{12}H_{15}N_5O$	209...210	0,45(б)	46
IIId	$C_{14}H_{17}N_5O$	154...156	0,30(a)	52
IIIe	$C_{15}H_{19}N_5O$	166...167	0,54(a)	33
IIIf	$C_{14}H_{16}N_6O_3$	159...160	0,62(б)	41
III g	$C_{11}H_{13}N_5O_2$	184...185	0,58(в)	54
IIIh	$C_{13}H_{15}N_5O_2$	149...150	0,28(a)	68
III i	$C_{13}H_{14}N_6O_4$	> 320	0,52(б)	35

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*TLC on Al_2O_3; the system of solvents is indicated in parentheses (Experimental).

TABLE 2. 6-Substituted 2-Amino-4-furyl-*sym*-triazines VIIIa-d, IXa-m

Compound	Empirical formula	Mp, °C*	R_f**	Yield, % (method of preparation)
VIIIa	$C_{11}H_8N_4O_2$	238,5...240***	0,68(a)	92 (A), 70(B), 55 (C)
VIIIb	$C_{13}H_{12}N_4O_2$	247...248	0,62(a)	72 (A)
VIIIc	$C_{11}H_6Br_2N_4O_2$	255...256	0,54(b)	82 (A)
VIIId	$C_{11}H_6N_6O_6$	272...273	0,38(b)	82
IXa	$C_{13}H_{10}N_4O$	245...246	0,44(a)	68 (B), 52(C), 92 (D) 86 (E)
IXb	$C_{14}H_{12}N_4O$	243...244	0,56(a)	74 (B)
IXc	$C_{13}H_9BrN_4O$	250...251	0,64(c)	58 (B)
IXd	$C_8H_5Cl_3N_4O$	224...225	0,72(c)	62 (B), 45 (C), 81(D)
IXe	$C_9H_7Cl_3N_4O$	217...218	0,62(c)	56 (B)
IXf	$C_8H_4BrCl_3N_4O$	228...229	0,54(b)	42 (B)
IXg	$C_8H_8N_4O$	230...231	0,74(a)	42 (C)
IXh	$C_{12}H_{16}N_4O$	210 (decomp.)	0,36(a)	57 (C)
IXi	$C_{13}H_9N_5O_3$	185...186,5	0,48(b)	88 (D) 85 (E)
IXj	$C_8H_4ClN_5O_3$	165...167 (decomp.)	0,36(b)	83 (D)
IXk	$C_{12}H_9N_5O$	153...154	0,56(a)	82 (E)
IXl	$C_{15}H_{11}N_5O$	288...290	0,46(c)	76 (E)
IXm	$C_{15}H_{10}N_6O_3$	235...236 (decomp.)	0,41(c)	87 (E)

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*The compounds were purified by recrystallization: VIIIa-c: from benzene; VIIId, IXc, k, l: from alcohol; IXa, b, d-f, j: from aqueous alcohol; IXg-i, m: from aqueous DMF.

**TLC on Al_2O_3; the solvent systems are indicated in parentheses.

***Mp = 237-238°C [7].

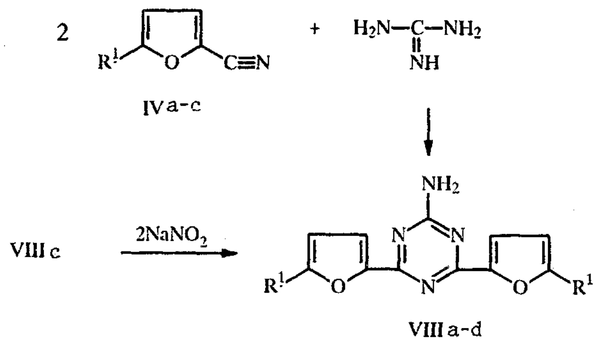
N,N-Disubstituted 2,4-diamino-6-furyl-*sym*-triazines IIIa-i are formed with a yield of 35-75% (Table 1).

We synthesized 4,6-disubstituted 2-amino-*sym*-triazines containing furyl fragments by several methods usually used for preparation of monoamino-*sym*-triazines: condensation of 5-R^1-furan-2-carboxylic acid nitriles IVa-c with guanidine [2, 3, 7] (method A); condensation of N-acylguanidines Va-c with nitriles IVa-g [3, 8] (methods B and C); condensation of N-acylguanidines Va, b with imino esters of 5-R^1-furan-2-carboxylic acids VIa, b [3, 9] (method D), and condensation of N-imidoylguanidines VIIa-c with 5-R^1-furan-2-carboxylic acid IIa, e esters [3, 10] (method E).

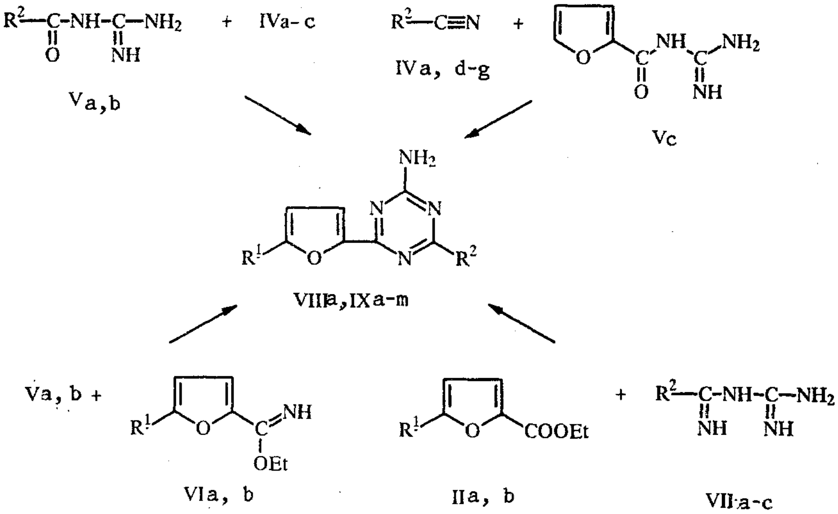
It should be noted that methods B-E can be used to synthesized amino-*sym*-triazines containing two different substituents in the ring.

2-Amino-4,6-di(5-R^1-furyl-2)-*sym*-triazines (VIIIa-c) are formed as a result of condensation of nitriles IVa-c with guanidine.

The best yield of *sym*-triazines VIIIa-c (72-92%) is obtained with intermittent heating of the reactants (2:1 molar ratio) in the presence of sodium ethylate. However, when 5-nitrofuran-2-carboxylic and β-(5-R^1-furyl-2)acrylic acid nitriles were added to the reaction with guanidine in these conditions, strong resinification occurred and we were unable to separate the individual compounds. We were not able to avoid resinification by varying the conditions and were unable to synthesize the corresponding 2-amino-*sym*-triazines by this method



IV, VIII a R^1 = H, b R^1 = Me, c R^1 = Br; VIII d R^1 = NO_2



IVd, Va, VIIa, IXa-c, i R^2 = Ph; IVe, Vb, IXd-f, j R^2 = Cl_3C; IVf, IXg, R^2 = Me; IVg, IXh R^2 = C_5H_{11}; VIIb, IXk R^2 = pyridyl-3; VIIc, IXl, m R^2 = indolyl-3; IIa, VIa, IXa, d, g, h, k, l R^1 = H; IXb, e R^1 = Me; IXc, f R^1 = Br; IIe, VIb, IXi, j, m R^1 = NO_2

2-Amino-4,6-di(5-nitrofuryl-2)-*sym*-triazine (VIIId) was obtained with a yield of 82% by substitution of the bromine atoms in compound VIIIc with sodium nitrite in glacial acetic acid [11].

In condensation of N-acylguanidines Va, b with nitriles IVa-c, the corresponding 2-amino-4-(5-R^1-furyl-2)-6-R^2-*sym*-triazines (IXa-f) are formed with a yield of 42-74% (Table 2) together with unidentified high-melting (mp 320°C) products of side reactions which are poorly soluble in most organic solvents. When 5-nitrofuran-2-carboxylic and β-(5-R^1-furyl-2)acrylic acid nitriles are added to this reaction, strong resinification of the reaction mixture takes place even at low temperatures.

We used an alternative method for synthesis of some compounds of this type (VIIIa, IXa, d, g, h): the reaction of N-(furoyl-2)guanidine (Vc) with the nitriles of different acids (IVa, d-g) (method C).

2-Amino-*sym*-triazines IXa, d, i, j are formed with a high yield as a result of condensation of N-acylguanidines Va, b with reactive imino esters VIa, b (see Table 2). Nitriles and amides of the corresponding 5-R^1-furan-2-carboxylic acids were determined as by-products with TLC.

Absorption maxima of variable intensity are observed in the 1575-1550, 1420-1405, 1115-1090, 1010-990, 815-805, and 715-695 cm^{-1} region, characteristic of stretching, out-of-plane, and plane deformation vibrations of the *sym*-triazine ring, in the IR spectra of all synthesized 2,4-diamino- (IIIa-i) and 2-amino-*sym*-triazines (VIIIa-d, IXa-m) [1-4, 12, 13]. In the spectra of *sym*-triazines containing trichloromethyl groups (IXd-f, j), these absorption bands are insignificantly shifted to the

TABLE 3. Parameters of the PMR Spectra of the Synthesized Compounds

Compound	Chemical shifts of protons,* ppm; SSCC, Hz								
	furan ring protons						NH_2 (2H, r.s	NR_2	other signals and SSCC
	3-H	4-H	5-H	J_{34}	J_{45}	J_{36}			
IIIa	6,34 d.d	6,68 d.d	7,36 d.d	3,5	1,9	0,7	5,84	3,08, 3,17 (6H)	—
IIIb	6,24 d.d	6,62 d.d	7,48 d.d	3,4	1,8	0,8	5,72	3,04, 3,13 (6H)	6,78 (1H,d, *J*=12,5, CH=CH); 7,22 (1H, d, *J*=12,5, CH=CH)
IIId	6,30 d.d	6,74 d.d	7,30 d.d	3,5	1,9	0,8	5,90	1,88...2,08 (6H, m, CH_2); 3,26 (4H, t, NCH_2)	6,92 (1H,d, *J*=13,0, CH=CH); 7,54 (1H, d, *J*=13,0, CH=CH)
IIIe	6,38 d	6,72 d	—	3,3	—	—	5,76	1,76...2,04 (6H, m, CH_2); 3,30 (4H, t, NCH_2)	2,40 (3H, s, 5-CH_3); 6,81 (1H, d, *J*=13,8, CH=CH); 7,37 (1H,d, *J*=13,8, CH=CH)
IIIi	6,51 d	7,16 d	—	4,0	—	—	5,58	3,36 (4H, t, NCH_2); 3,82 (4H, t, OCH_2)	7,27 (1H, d, *J*=14,0, CH=CH); 7,53 (1H, d, *J*=14,0, CH=CH)
VIIIa	6,59 (2H, d.d)	7,12 (2H, d.d)	7,66 (2H,d.d)	3,6	1,8	0,9	5,77	—	—
VIIIb	6,80 (2H, d)	7,38 (2H, d)	—	3,4	—	—	6,03	—	2,43 (6H, s, 5-CH_3)
VIIIc	6,38 (2H, d)	6,62 (2H, d)	—	3,4	—	—	5,68	—	—
VIIId	6,25 (2H, d)	6,74 (2H, d)	—	3,7	—	—	5,74	—	—
IXa	6,33 d.d	7,04 d.d	7,74 d.d	3,6	1,7	0,9	5,68	—	7,35...7,48 (5H, m, arom.)
IXb	6,54 d	6,92 d	—	3,5	—	—	5,70	—	2,48 (3H, s, 5-CH_3); 7,16...7,32 (5H, arom.)
IXd	6,39 d.d	6,79 d.d	7,66 d.d	3,5	1,7	0,9	5,78	—	—
IXh	6,42 d.d	6,83 d.d	7,55 d.d	3,4	1,8	0,7	5,64	—	1,24 (3H, s, CH_3); 1,36...2,04 (6H, m, CH_2); 2,92 (2H, t, CH_2)
IXj	6,54 d	7,28 d	—	3,9	—	—	5,92	—	—
IXk	6,38 d.d	6,74 d.d	7,48 d.d	3,6	1,9	0,8	5,76	—	7,12...7,26 (4H, m, arom)
IXm	6,74 d	7,32 d	—	4,0	—	—	5,72	—	7,51 (1H, d, *J*=2,5, 2-H indole; 7,63...7,82 (4H, m, arom.); 8,14 (1H, s, NH indole)

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*The spectra of compounds IIIa, b, d, e, i, IXh, m were made in DMSO-D_6; VIIIa, c, IXa, d were made in $CDCl_3$; VIIIb, IXb were made in CD_3OD; VIIId, IXj, k were made in acetone-D_6.

low-frequency region in comparison to the spectra of other aminotriazines. There are two broad absorption bands in the region of stretching vibrations of NH in the spectra of all compounds: one of them is observed in the 3335-3285 cm^{-1} range (ν_{asNH}), and the other appears in the 3190-3150 cm^{-1} region (ν_{sNH}). This position and shape of the doublet of NH stretching vibrations indicates the presence of a strong hydrogen bond in these compounds in the crystalline state [4, 12]. The intense absorption bands in the 1670-1635 cm^{-1} region belong to scissor vibrations of NH bonds in the primary amino groups of amino-*sym*-triazines [3, 4, 14].

In addition to these vibrations, there are also absorption bands caused by furan fragments [12]: 3150-3080 (ν_{CH}), 1590-1560, 1515-1495, 1395-1370 (ν_{ring}), 1140-1030 (β_{CH}), 1005-990 (ring "breathing" vibrations), 955-945 (γ_{CH}), 890-880 and 780-760 cm^{-1} (β_{ring}).

The signals in the PMR spectra of these compounds (Table 3) were assigned with consideration of the data on furan derivatives [12, 15] and *sym*-triazine [2-4, 16]. In the spectra of *sym*-triazines IIIb,d-f, h, i containing β-furylvinyl fragments, the signals of ethylene protons are observed as doublets in the 6.74-7.37 and 7.22-7.54 ppm regions with SSCC of 12.5-14.0 Hz, which indicates the *trans*-configuration of these fragments [15].

In the spectra of *sym*-triazines IIIa, b containing dimethylamino groups, the signals of the protons of these groups appear as two singlets ($\Delta\nu$ = 7.0-7.2 Hz), which could be attributed to hindered rotation around the C—N bond caused by conjugation of the π-electrons of the exocyclic nitrogen atom with the *sym*-triazine ring. These doublets converge into one singlet when the spectra are recorded at a high temperature (45°C).

EXPERIMENTAL

The IR spectra were made on UR-20 and Specord IR-75 instruments in KBr pellets. The PMR spectra were obtained on a Bruker WP spectrometer (80 MHz), TMS internal standard. The course of the reactions and purity of the compounds obtained were monitored with TLC on Al_2O_3 with Brockmann degree II activity in CCl_4—ethanol, 15:1 (a); benzene—methanol, 20:1 (b); chloroform—acetone, 10:1 (c) solvent systems; and on Silufol UV-254 plates in chloroform—acetone, 5:1 (d) and benzene—acetone, 5:1 (e) solvent systems; development with iodine vapors.

The starting N,N-pentamethylene- (Ib) and N,N-3-oxapentamethylenebiguanide (Ic) hydrochlorides [17]; N-benzoyl- (Va) [18], N-trichloracetyl- (Vb) [18], and N-(furoyl-2)guanidine (Vc) [19]; furan-2-carboxylic (VIa) [20] and 5-nitrofuran-2-carboxylic acid (VIb) [21] ethyl imino esters, and N-benzimidoylguanidine (VIIa) [22] were prepared with existing methods. N,N-dimethylbiguanide hydrochloride (Ia) [4], N-(pyridyl-3-imidoyl)- (VIIb), and N-(indolyl-3-imidoyl)guanidine (VIIc) [3] were synthesized previously.

The properties of the synthesized compounds are reported in Tables 1 and 2. The data from elemental analysis of the synthesized compounds for C, H, and N correspond to the calculated data.

N,N-Disubstituted 2,4-diamino-6-furyl-*sym*-triazines (IIIa-i). At 0°C, 0.12 mole of biguanide hydrochloride Ia-c was added by portions to a solution of sodium ethylate prepared from 3.5 g (0.16 mole) of sodium in 120 ml of absolute ethanol. The reaction mixture was stirred for 1 h at 20°C, cooled to −5°C, the precipitated NaCl sediment was filtered off and washed on the filter with 15 ml of cold absolute ethanol. A solution of 0.12 mole of IIa-d ethyl ester in 25 ml of absolute ethanol was added by drops to the solution of biguanide base obtained while stirring. The reaction mixture was boiled while stirring for 12-16 h (monitoring with TLC until the initial ester disappeared) and evaporated dry at reduced pressure. The sediment was washed with hot hexane (3 × 20 ml) and crystallized from absolute ethanol (see Table 1).

6-Substituted 2-amino-4-(5-R^1-furyl-2)-*sym*-triazines (VIII, IX). A. Here 3.0 g (30 mmole) of guanidine nitrate was added by portions to a solution of sodium ethylate prepared from 0.74 g (32 mmole) of sodium in 50 ml of absolute ethanol. The reaction mixture was boiled while stirring for 0.5 h, cooled to −10°C, the precipitated $NaNO_3$ sediment was filtered off and washed on the filter with 10 ml of absolute ethanol. Then 60 mmole of IVa-c nitrile was added to the filtrate, the solution obtained was boiled for 3-5 h while stirring (monitored with TLC until the starting nitrile disappeared). The reaction mixture was evaporated dry at reduced pressure, and the residue was extracted with hot ethanol (3 × 35 ml), the extract was evaporated, and *sym*-triazines VIIIa-c were obtained (Table 2).

B. A mixture of 12 mmole of N-acylguanidine Va, b and 50 mmole of IVa-c nitrile in 30 ml of DMF was boiled while stirring for 4-5 h. The reaction mixture was evaporated dry at reduced pressure, the residue was washed with ether (3 × 15 ml), chromatographed in a column with Al_2O_3 (4.5 × 60 cm), and eluted with benzene—ethanol mixture, 10:1, yielding *sym*-triazines IXa-f (see Table 2).

C. A mixture of 1.53 g (10 mmole) of N-acylguanidine Vc and 70 mmole of IVa, d-g nitrile was stirred for 8 h at 160°C (for IVe, f nitriles, the mixture was boiled while stirring for 22 h). The reaction mixture was then treated similar to method B, yielding *sym*-triazines VIIIa, IXa, d, g, h (see Table 2).

D. A mixture of 15 mmole of N-acylguanidine Va, b and 15 mmole of VIa, b ethyl imino ester in 40 ml of absolute ethanol was boiled while stirring for 2 h, cooled to 20°C, and poured in 200 ml of cold water. The sediment was filtered off, washed on the filter with water, vacuum dried over P_2O_5, and crystallized from the appropriate solvents (see Table 2), yielding *sym*-triazines IXa, d, i, j.

E. A solution of 12 mmole of IIa, e ester in 10 ml of absolute ethanol was added by drops to a stirred solution of 10 mmole of N-imidoylguanidine VIIa-c in 25 ml of absolute ethanol. The reaction mixture was boiled while stirring for 2 h, cooled to 20°C, and poured in 200 ml of cold water. The sediment was filtered off, washed on the filter with water, vacuum dried over P_2O_5, and crystallized from the appropriate solvents (see Table 2), yielding *sym*-triazines IXa, i, k-m.

Samples from mixing of *sym*-triazines VIII and IX, prepared by different methods, did not depress the melting point, and their IR spectra were identical.

2-Amino-4,6-di(5-nitrofuryl-2)-*sym*-triazine (VIIId). Here 2.85 g (41.4 mmole) of $NaNO_2$ was added by portions to a stirred solution of 5.32 g (13.8 mmole) of *sym*-triazine VIIIc in 60 ml of glacial acetic acid. The reaction mixture was stirred for 3 h at 20°C, poured in 200 ml of cold water, the precipitated sediment was filtered off, washed on the filter with water, dried, and crystallized from ethanol, yielding 3.75 g (85%) of *sym*-triazine VIIId.

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