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DERIVATIVES OF *sym*-TRIAZINES.
6*. SOME SPECIAL FEATURES OF THE ADDITION OF SUBSTITUTED ACETYLENES TO TRIAZINE MONOAZIDES

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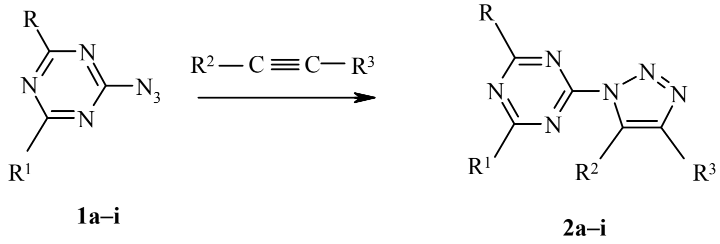
The special features of the interaction of 2-azido-4-R-6-R'-sym-triazines with some acetylenic compounds have been investigated. A series of new derivatives of sym-triazine linked at position 2 with a 1,2,3-triazole ring has been synthesized.

Keywords: 2-azido-4-R-6-R'-*sym*-triazines, substituted 2-(1,2,3-triazol-1-yl)-*sym*-triazines.

We have described the synthesis and some conversions of oxygen- and nitrogen-containing derivatives of *sym*-triazines and have shown their promise as reactive and convenient intermediates for the synthesis of nitrogen-containing heterocyclic compounds [1,2].

It is known that azidoazolopyridazines, monoazidofurazans, and monoazidotriazines [2-4] form coupled biheterocyclic systems with 1,3-dicarbonyl compounds, which display high antibacterial and antidote activity, but 1,3-dipolar components (such as azides) add to acetylenes with the formation of five-membered heterocycles, the triazoles [5]. Since these reactions have still not been studied for monoazides of the *sym*-triazine series, it seemed of interest to investigate such reactions and the possibility of obtaining C–N linked heterocyclic systems of triazolyl-*sym*-triazines.

With this aim azides **1**, synthesized by us previously, were used as starting materials in cycloaddition reactions with certain substituted acetylenes, which were carried out according to the following scheme.



1, 2 a,b,i R = OMe, R^1 = 4-morpholino; **c** R = R^1 = 1-piperidino;
d,g,h R = R^1 = 4-morpholino; **e** R = OEt, R^1 = 1-piperidino; **f** R = R^1 = OEt;
2 a–f R^2 = H, R^3 = Ph; **g** R^2 = R^3 = CH_2OH; **h,i** R^2 = H, R^3 = CH_2OH

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* For Part 5 see [1].

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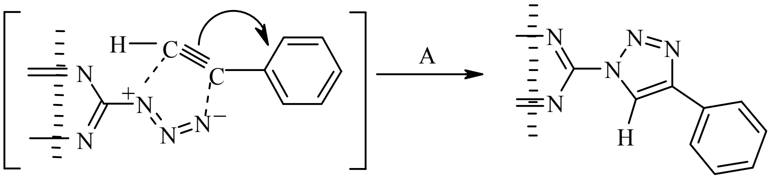
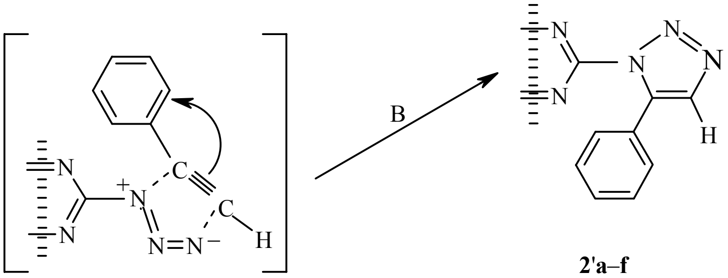
The reaction was carried out in dry toluene or benzene at the boiling point of the solvent. It turned out that the reaction rate depends significantly both on the type, character, and structure of the substituents in positions 4 and 6 of the triazine ring and on the structure of the acetylenic compound used. On interacting monoazides **1** with propargyl alcohol, which is inclined to polarize and is more reactive, in benzene at 80°C the reaction time did not exceed 5 h. The symmetrical and nonpolar molecules of 2-butyne-1,4-diol are so less reactive that far longer heating in toluene at 110°C was required, but the reaction was accompanied by resinification. With the sterically hindered molecules of phenylacetylene the cyclization reaction with monoazides **1** containing alkoxy substituents in positions 4 and 6 of the triazine ring is complete after 48-72 h. In the case of amides **1c,d,g,h**, containing the bulky substituents morpholino or piperidino, the reaction time with phenylacetylene is increased.

The application of catalysts, complex compounds and mercury salts [6], proved to have no significant effect on the cycloaddition reaction rate, as also UV irradiation of the reaction mixture, even on conducting the reaction in a quartz reactor. Probably this reaction takes place by a typical cycloaddition mechanism according to the following scheme.



2a–f

In view of the lower steric hindrance the probability of carrying out the process by scheme A is far higher than by the alternative route B.



2'a–f

In reality analysis of the reaction mixture by high resolution ^{1}H NMR and TLC showed that, together with the 4'-substituted cycloadducts **2a-f**, a small quantity of the 5'-substituted triazolyltriazines **2'a-f** are formed in the reaction process. Comparison of the integral intensities of the signals of the appropriate protons shows that the ratio of the **2** and **2'** isomers in the reaction mixture was in all cases ~9:1. Regretably, due to the instability of the liquid **2'** adducts we were unable to isolate and characterize them. Yields of the **4'**-substituted triazoles **2a-f** were 59-84%.

In the case of propargyl alcohol the cycloaddition reaction also proceeds by the two alternative routes A and B with the formation of compounds **2'h,i** as minor products.

Compounds **2a-i** synthesized in this way were relatively high melting white finely crystalline powders, readily soluble in many polar organic solvents, insoluble in hydrocarbons and in water (Tables 1, 2). The composition and structure of triazolyltriazines **2a-i** were confirmed by data of elemental analysis, IR, ^{1}H NMR and mass spectra. The homogeneity of all the compounds was confirmed by TLC.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % Calculated, %			mp, °C	Mol. ion, *m/z* *	Yield, %
		C	H	N			
2a	$C_{16}H_{17}N_7O_2$	56.40 56.62	5.13 5.05	28.93 28.89	176-177	339	80
2b	$C_{17}H_{19}N_7O$	60.39 60.52	5.73 5.68	29.12 29.06	174-175	337	78
2c	$C_{21}H_{26}N_8$	64.43 64.59	6.80 6.71	28.79 28.70	189-190	390	82
2d	$C_{19}H_{22}N_8O_2$	57.63 57.85	5.80 5.62	28.55 28.41	309-310	394	84
2e	$C_{18}H_{21}N_7O$	61.70 61.52	6.29 6.02	28.12 27.90	172-173	351	59
2f	$C_{15}H_{16}N_6O_2$	57.39 57.68	4.98 5.16	26.94 26.88	138-139	312	63
2g	$C_{15}H_{22}N_8O_4$	47.49 47.61	6.03 5.89	29.80 29.62	232-233	378	62
2h	$C_{14}H_{20}N_8O_3$	48.04 48.26	5.93 5.79	32.30 32.17	235-236	348	65
2i	$C_{11}H_{15}N_7O_3$	44.95 45.09	5.32 5.16	33.59 33.43	184-185	293	55

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* Mass spectral data may be obtained from the authors.

TABLE 2. Spectral Characteristics of the Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm (SSCC, *J*, Hz)
	C=C–, C=N– and N=N– conj.	Other groups	
2a	1630, 1610, 1510	1020, 1140 (C–O–C)	3.65-3.90 (8H, m, $2NCH_2$, $2OCH_2$); 4.03 (3H, s, OCH_3); 7.32-8.00 (5H, m, H_{Ph}); 9.28 (1H, s, =CH)
2b	1600, 1620, 1515	1060, 1095 (C–O–C)	1.60-1.75 (6H, m, $3CH_{2\,\text{piperid.}}$); 3.85-4.00 (4H, m, $2NCH_2$); 4.02 (3H, s, OCH_3); 7.35-8.05 (5H, m, H_{Ph}); 9.28 (1H, s, =CH)
2c	1595, 1500, 1485	—	1.50-1.70 (12H, m, $6CH_{2\,\text{piperid.}}$); 3.70-3.92 (8H, m, $4NCH_2$); 7.35-8.05 (5H, m, H_{Ph}); 9.30 (1H, s, =CH)
2d	1605, 1550, 1510	—	3.67-4.00 (16H, m, $4NCH_2$, $4OCH_2$); 7.30-7.97 (5H, m, H_{Ph}); 8.98 (1H, s, =CH)
2e	1610, 1590, 1530	1030, 1055 (C–O–C)	1.43 (3H, t, *J* = 5.5, $OCH_2\underline{CH_3}$); 1.60-1.80 (6H, m, $3CH_{2\,\text{piperid.}}$); 3.85-4.03 (4H, m, $2NCH_2$); 4.49 (2H, q, *J* = 5.5, $O\underline{CH_2}CH_3$); 7.30-8.00 (5H, m, H_{Ph}); 9.02 (1H, s, =CH)
2f	1600, 1580, 1540	1130, 1050 (C–O–C)	1.49 (6H, t, *J* = 7.0, $2OCH_2\underline{CH_3}$); 4.60 (4H, q, *J* = 7.0, $2O\underline{CH_2}CH_3$); 7.30-8.05 (5H, m, H_{Ph}); 9.12 (1H, s, =CH)
2g	1600, 1550, 1505	3470-3300 (br. s, OH)	3.65-3.85 (16H, m, $4NCH_2$, $4OCH_2$); 4.60-5.00 (6H, m, $2\underline{CH_2}O$, $2O\underline{H}$)
2h	1615, 1575, 1515	3400-3250 (br. s, OH)	3.65-3.85 (16H, m, $4NCH_2$, $4OCH_2$); 4.89 (2H, d, *J* = 5.7, $\underline{CH_2}O$); 5.19 (1H, br. s, $O\underline{H}$); 7.62 (1H, s, =CH)
2i	1600, 1530, 1500	3420-3280 (br. s, OH), 1110, 1050 (C–O–C)	3.65-3.85 (8H, m, $2NCH_2$, $2OCH_2$); 4.03 (3H, s, $O\underline{CH_3}$); 4.89 (2H, d, *J* = 5.5, $\underline{CH_2}O$); 5.19 (1H, br. s, $O\underline{H}$); 7.62 (1H, s, =CH)

In difference to the initial azides **1**, the intense absorption band at 2100-2110 cm^{-1} for the stretching vibrations of the azide group disappears from the IR spectra of triazolyltriazines **2**. However the strong bands for the stretching vibrations of the conjugated C=C–, C=N–, and N=N– bonds at 1500-1630 cm^{-1} are retained (Table 2).

Characteristic signals were detected in the ^{1}H NMR spectra of compounds **2a-i** for all the protons of the substituents located at positions 4 and 6 of the triazine ring. Multiplets were detected in the spectra of compounds **2a-f** for the phenyl ring protons at 7.30-8.05 ppm and singlets for the proton at position 5 of the triazole ring at 8.98-9.28 ppm. The protons of symmetrical $HOCH_2$ substituents in positions 4 and 5 of the triazole ring (in compound **2g**) were displayed as multiplets at 4.60-5.00 ppm, but unsymmetrical C-H and CH_2OH substituents in the same positions of the triazole ring (compounds **2h,i**) appeared as doublets at 4.60-4.93 ppm ($C\underline{H_2}OH$) and as broadened signals at 5.15-5.23 ppm ($CH_2O\underline{H}$), with a singlet at 7.62 ppm (C–H in position 5).

The homogeneity and structures of the synthesized triazolyltriazines were also confirmed by mass spectrometry.

The reaction of monoazides of *sym*-triazines with acetylenic compounds has been investigated. New triazolyltriazines, linked in position 2 of the triazine and position 1 of the triazole, have been obtained for the first time by cycloaddition. These compounds have the prospect of being biologically active.

EXPERIMENTAL

The IR spectra were recorded for suspensions of samples in nujol with a Specord IR 75 Spectrometer. The ^{1}H NMR spectra were taken on a Bruker WM 500 spectrometer (500 MHz) in DMSO-d$_6$. The mass spectra were recorded on a Finnigan MAT INCOS 50 instrument (energy of ionizing electrons 70 eV). Elemental analysis of the synthesized compounds was carried out with a Carlo-Erba model 1106 analyzer. A check on the progress of reactions and the purity of the compounds obtained was effected by TLC on Silufol UV 250 plates in acetone–hexane, 1:1.

4,6-Disubstituted 2-chloro-*sym*-triazines and (2-*sym*-triazinyl)trimethylammonium chlorides (DTTA) were obtained by the known procedure of [7, 8]. Azides **1** were synthesized by the reaction of DTTA with sodium azide according to [1]. Solvents were purified and dried directly before use according to the procedure of [9].

2-Methoxy-4-morpholino-6-(5-phenyl-4H-1,2,3-triazol-1-yl)-*sym*-triazine (2a). Phenylacetylene (10.2 mmol) was rapidly added dropwise to a solution of azide **1a** (5.1 mmol) in dry toluene (10 ml) and the mixture was then refluxed for 48 h. The reaction mixture was evaporated to dryness in the vacuum of a water-jet pump, washed thoroughly with water, and dried. After purification by crystallization from alcohol, triazolyltriazine **2a** (1.39 g, 80%) was obtained.

Compounds 2b-f were obtained analogously.

2,4-Dimorpholino-6-(4-hydroxymethyl-5H-1,2,3-triazol-1-yl)-*sym*-triazine (2h). Propargyl alcohol (4.8 mmol) in dry benzene (5 ml) was added with stirring to a solution of azide **1h** (2.4 mmol) in dry benzene (10 ml) and the reaction mixture was refluxed for 5 h. Benzene was distilled off to 1/2 volume, the mixture was cooled, the precipitated solid was rapidly filtered off, washed sequentially with cold benzene (2 × 2 ml), methylene chloride (2 × 2 ml), and cold water (15 ml). After purification by crystallization from alcohol triazolyltriazine **2h** (0.54 g, 65%) was obtained.

Compound 2i was obtained analogously, but in the case of **compound 2g** the reaction mixture was boiled for 72 h.

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