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DERIVATIVES OF *sym*-TRIAZINE.

3*. SYNTHESIS AND SOME CONVERSIONS OF MONOAZIDES OF THE TRIAZINE SERIES

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A convenient preparative route has been developed for the synthesis of 2-azido-4-R-6-R'-sym-triazines, which are promising synthons in organic synthesis. A series of 2-(1-triazolyl)-sym-triazine derivatives has been synthesized for the first time from the obtained azides and acetylacetone or acetoacetic ester.

Keywords: 2-azido-4-R-6-R'-*sym*-triazines, substituted 2-(1-triazolyl)-*sym*-triazines, (4-R-6-R'-*sym*-2-triazinyl)trimethylammonium chlorides.

Organic azides are extremely reactive and convenient synthons for the synthesis of many heterocyclic compounds promising for practical use [2]. However, azides of the *sym*-triazine series have not been described up to the present time. The problem of the present work consists of the development of a synthetic route and the study of certain properties of such compounds.

Our numerous attempts at the synthesis of 4,6-disubstituted 2-azido-*sym*-triazines by the traditional method, the nucleophilic substitution of the chlorine atom in disubstituted monochloro-*sym*-triazines with the aid of sodium and potassium azides by the known procedure [3], were not crowned with success, in spite of a comprehensive variation of the conditions of carrying out the reaction. This is probably linked with the extremely weak lability of the chlorine atom in the indicated compounds and the complexity of obtaining diazonium salts from them.

Previously [1,4] we synthesized and reported the relatively stable and simultaneously highly reactive (4-R-6-R'-*sym*-2-triazinyl)trimethylammonium chlorides of the type of **1**. We have discovered that salts **1a-k** react readily with sodium azide in aqueous solution even at room temperature. The desired previously unavailable monoazides of the *sym*-triazine series **2a-k** were formed smoothly in good yield (65-94%) (Scheme 1).

The synthesized azides **2a-k** are extremely stable on extended storage, and are explosion-proof finely crystalline white powders, readily soluble in aromatic hydrocarbons and the usual polar organic solvents, poorly soluble in aliphatic hydrocarbons in the cold, and insoluble in water. Their homogeneity was verified by TLC and their composition and structures were confirmed by results of elemental analysis, and by data of IR, ^{1}H NMR, and mass spectra (Tables 1, 2).

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* For Part 2 see [1].

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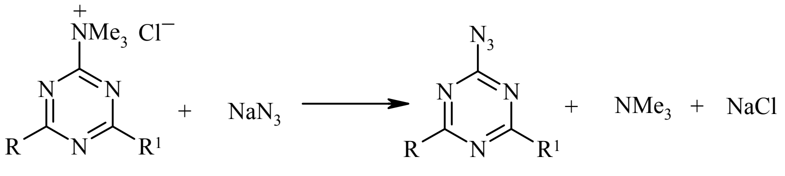
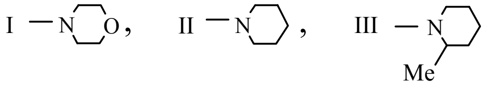
Scheme 1



1a–k **2a–k**

1, **2 a–d**, **k** R = I, **e–g** R = II, **h** R = OMe, **i**, **j** R = III, **a** R^1 = I, **b, g, h** R^1 = OMe, **c, e** R^1 = OEt, **d, f** R^1 = II, **i** R^1 = OMe, **j** R^1 = III, **k** R^1 = NPh_2



Intense absorption bands were present in the IR spectra of azides **2** characteristic of the stretching vibrations of the azide group at 2100-2110, and of the conjugated C=N bond of the triazine ring at 1505-1620 cm^{-1}. In the ^1H NMR spectra (Table 2) the resonance signals for the protons of all the substituents of the heterocycle were also sharply differentiated, however the singlet signal for the protons of the N^+Me_3 group, characteristic of the initial salts **1**, was absent [4].

TABLE 1. Characteristics of Compounds **2-4**

Compound	Empirical formula	Found, % / Calculated, % C	H	N	mp, °C	Mol. ion, *m/z**	Yield, %
1	2	3	4	5	6	7	8
2a	$C_{11}H_{16}N_8O_2$	45.49 45.20	5.68 5.52	38.48 38.39	185-185.5	292	68
2b	$C_8H_{11}N_7O_2$	40.77 40.50	4.83 4.67	41.43 41.33	116-17	237	94
2c	$C_9H_{13}N_7O_2$	43.19 43.02	5.38 5.21	39.12 39.03	104-105	251	84
2d	$C_{12}H_{18}N_8O$	49.83 49.63	6.39 6.25	38.67 38.59	113-114	290	72
2e	$C_{10}H_{15}N_7O$	48.29 48.18	6.23 6.07	39.40 39.34	74-75	249	90
2f	$C_{13}H_{20}N_8$	54.33 54.14	7.22 6.99	38.96 38.88	96-97	288	65
2g	$C_9H_{13}N_7O$	46.23 45.95	5.68 5.57	41.78 41.68	85-86	235	91
2h	$C_5H_6N_6O_2$	33.20 32.97	3.45 3.32	46.28 46.14	82-83	182	69
2i	$C_{10}H_{15}N_7O_2$	45.42 45.27	5.87 5.69	37.10 36.96	92-93	265	75
2j	$C_{15}H_{24}N_8$	57.09 56.94	7.80 7.65	35.58 35.42	116-117	316	75
2k	$C_{19}H_{18}N_8O$	61.13 60.95	4.98 4.84	30.06 29.93	161-162	374	80
3a	$C_{16}H_{22}N_8O_3$	51.49 51.32	6.15 5.92	29.32 29.23	203-204	374	79
3b	$C_{13}H_{17}N_7O_3$	49.04 48.89	5.49 5.44	30.83 30.83	198-199	319	85
3c	$C_{14}H_{19}N_7O_3$	50.58 50.44	5.83 5.74	29.55 29.42	192-193	333	76
3d	$C_{17}H_{24}N_8O_2$	54.99 54.82	6.67 6.50	30.21 30.09	178-179	372	86
3e	$C_{15}H_{21}N_7O_2$	50.48 50.36	6.51 6.38	29.68 29.59	140-141	331	85
3f	$C_{18}H_{26}N_8O$	58.46 58.35	7.16 7.07	30.35 30.25	184-185	370	75

TABLE 1 (continued)

1	2	3	4	5	6	7	8
3g	$C_{14}H_{19}N_7O_2$	53.16 52.98	6.20 6.17	31.02 31.03	133-134	317	91
3h	$C_{10}H_{12}N_6O_3$	45.57 45.45	4.71 4.58	31.95 31.81	175-176	264	89
3i	$C_{15}H_{21}N_7O_2$	54.47 54.36	6.49 6.38	29.74 29.59	132-133	331	87
4a	$C_{17}H_{24}N_8O_4$	50.59 50.48	6.13 5.98	27.85 27.71	188-189	404	70
4b	$C_{14}H_{19}N_7O_4$	48.29 48.13	5.63 5.48	28.16 28.07	155-156	349	85
4c	$C_{15}H_{21}N_7O_4$	49.76 49.58	5.99 5.83	27.08 26.98	110-111	363	81
4d	$C_{18}H_{26}N_8O_3$	53.81 53.71	6.67 6.51	27.95 27.85	198-199	402	83
4e	$C_{16}H_{23}N_7O_3$	53.01 52.17	6.29 6.41	27.20 27.13	119-120	361	85
4f	$C_{19}H_{28}N_8O_2$	56.81 56.98	6.91 7.05	28.07 27.98	168-169	400	71
4g	$C_{15}H_{21}N_7O_3$	51.98 51.86	6.25 6.09	28.32 28.23	114-115	347	82
4h	$C_{11}H_{14}N_6O_4$	44.98 44.89	4.87 4.79	28.64 28.56	147-148	294	87
4i	$C_{25}H_{26}N_8O_3$	61.58 61.71	5.27 5.39	23.14 23.03	212-213	486	73

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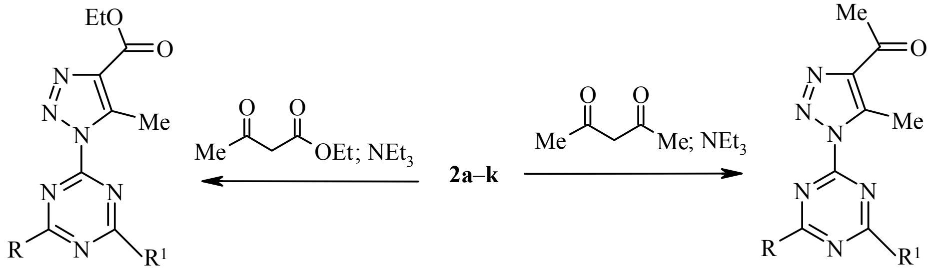
* Mass spectral data may be obtained from the authors.

It is known that azidoazolopyridazines [5] and monoazidofurazans [6] form biheterocyclic systems with 1,3-dicarbonyl compounds. Since substances including similar systems display high biological activity [6], it seemed of interest to clarify the possibility of obtaining still unreported compounds with a single bond linking the *sym*-triazine and triazole rings.

For this purpose we have studied the interaction of the synthesized azides **2a-k** with such widely available dicarbonyl compounds as acetylacetone and acetoacetic ester. As a result, the corresponding products **3a-i** and **4a-i** were obtained in high yield (71-91%) (Scheme 2).

Scheme 2



4a–i

3a–i

3a–d, **4a–d**, **i** R = I, **3e–g**, **4e–g** R = II, **3i** R = OMe; **3**,**4** **a** R^1 = I, **b** R^1 = OMe, **c,e** R^1 = OEt, **d**,**f** R^1 = II, **3i** R^1 = III

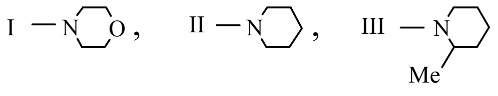


TABLE 2. Spectral Characteristics of Compounds **2-4**

Com-pound	IR spectrum, ν, cm^{-1}		^1H NMR spectrum, δ, ppm (SSCC, *J*, Hz)
	N_3 or C=O	N=N–, C=N– and C=C-conj.	
1	2	3	4
2a	2110	1570, 1550	3.55-3.75 (16H, m, $4NCH_2$, $4OCH_2$)
2b	2105	1565, 1505	3.60-3.80 (8H, m, $2NCH_2$, $2OCH_2$); 3.85 (3H, s, OCH_3)
2c	2100	1560, 1505	1.30 (3H, t, $J = 7.85$, $\underline{CH_3}$ in OEt); 3.60-3.80 (8H, m, 2 NCH_2, $2OCH_2$); 4.35 (2H, q, $J = 7.85$, $\underline{CH_2}$ in OEt)
2d	2110	1550, 1530	1.47-1.70 (6H, m, $3CH_2$); 3.55-3.75 (12H, m, $4NCH_2$, $2OCH_2$)
2e	2105	1500, 1580	1.33 (3H, t, $J = 7.4$, $\underline{CH_3}$ in OEt); 1.50-1.73 (6H, m, $3CH_2$); 3.70-3.80 (4H, m, $2NCH_2$); 4.34 (2H, q, $J = 7.4$, CH_2 in OEt)
2f	2100	1620, 1550, 1505	1.40-1.62 (12H, m, $6CH_2$); 3.55-3.70 (8H, m, $4NCH_2$)
2g	2110	1510, 1570	1.53-1.70 (6H, m, $3CH_2$); 3.70-3.80 (4H, m, $2NCH_2$); 3.86 (3H, s, OCH_3)
2h	2100	1580, 1540	3.85 (6H, s, $2OCH_3$)
2i	2100	1560, 1500	1.19 (3H, d, $J = 7.4$, $CHCH_3$); 1.32-1.80 (6H, m, $3CH_2$); 2.92-3.03 (1H, m, $N\underline{CH}$); 3.87 (3H, s, OCH_3); 4.44-4.99 (2H, m, $N\underline{CH_2}$)
2j	2110	1575, 1530	1.19 (6H, d, $J = 7.35$, $2CH\underline{CH_3}$); 1.32-1.80 (12H, m, $6CH_2$); 2.97-3.04 (2H, m, $2N\underline{CH}$); 4.48-4.98 (4H, m, $2N\underline{CH_2}$)
2k	2100	1550, 1520	3.25-3.75 (8H, m, $2OCH_2$, $2NCH_2$); 7.20-7.40 (10H, m, $2C_6H_5$)
3a	1680	1530, 1560	2.80 (3H, s, 5'-$\underline{CH_3}$); 2.62 (3H, s, $CO\underline{CH_3}$); 3.60-3.85 (16H, m, $4OCH_2$, $4NCH_2$)
3b	1685	1540, 1565, 1595	2.63 (3H, s, $CO\underline{CH_3}$); 2.85 (3H, s, 5'-$\underline{CH_3}$); 3.65-3.90 (8H, m, $2OCH_2$-, $2NCH_2$-); 4.00 (3H, s, OCH_3)
3c	1705	1590, 1550, 1505	1.36 (3H, t, $J = 7.0$, $\underline{CH_3}$ in OEt); 2.63 (3H, s, $COCH_3$); 2.82 (3H, s, 5'-$\underline{CH_3}$); 3.65-3.85 (8H, m, $2OCH_2$, $2NCH_2$); 4.43 (2H, q, $J = 7.0$, $\underline{CH_2}$ in OEt)
3d	1670	1590, 1535, 1510	1.55-1.72 (6H, m, $3CH_2$), 2.65 (3H, s, $COCH_3$), 2.80 (3H, s, 5′-$\underline{CH_3}$), 3.63-3.84 (12H, m, $4NCH_2$, $2OCH_2$)
3e	1665	1590, 1550, 1530	1.39 (3H, t, $J = 7.0$, $\underline{CH_3}$ in OEt); 1.57-1.75 (6H, m, $3CH_2$); 2.64 (3H, s, $COCH_3$); 2.85 (3H, s, 5'-$\underline{CH_3}$); 3.80-3.88 (4H, m, $2NCH_2$); 4.44 (2H, q, $J = 7.0$, $\underline{CH_2}$ in OEt)
3f	1680	1620, 1590, 1535	1.45-1.70 (12H, m, $6CH_2$); 2.63 (3H, s, $COCH_3$); 2.80 (3H, s, 5'-$\underline{CH_3}$); 3.70-3.82 (8H, m, $4NCH_2$)
3g	1685	1590, 1560, 1535	1.62-1.80 (6H, m, $3CH_2$); 2.65 (3H, s, $CO\underline{CH_3}$); 2.87 (3H, s, 5'-$\underline{CH_3}$); 3.85-3.95 (4H, m, $2NCH_2$); 4.03 (3H, s, OCH_3)
3h	1690	1580, 1550	2.65 (3H, s, $COCH_3$); 2.70 (3H, s, 5'-$\underline{CH_3}$); 4.08 (6H, s, $2OCH_3$)
3i	1680	1595, 1550, 1535	1.28 (3H, d, $J = 7.3$, $CH\underline{CH_3}$); 1.37-1.48 (1H, m, $N\underline{CH}$); 1.62-1.83 (6H, m, $3CH_2$); 2.65 (3H, s, $COCH_3$); 2.85 (3H, s, 5'-$\underline{CH_3}$); 3.87 (3H, s, OCH_3); 4.55-5.11 (2H, m, NCH_2)
4a	1710	1550, 1510	1.36 (3H, t, $J = 6.6$, $\underline{CH_3}$ in COOEt), 2.81 (3H, s, 5′-$\underline{CH_3}$); 3.61-3.86 (16H, m, $4OCH_2$, $4NCH_2$); 4.39 (2H, q, $J = 6.6$, $\underline{CH_2}$ in COOEt)
4b	1715	1600, 1560, 1505	1.34 (3H, t, $J = 7.4$, $\underline{CH_3}$ in COOEt); 2.85 (3H, s, 5'-$\underline{CH_3}$); 3.65-3.87 (8H, m, $2OCH_2$, $2NCH_2$); 3.97 (3H, s, OCH_3); 4.37 (2H, q, $J = 7.4$, $\underline{OCH_2}$ in COOEt)
4c	1705	1590, 1550, 1505	1.30-1.40 (6H, m, $\underline{CH_3}$ in OEt and COOEt); 2.85 (3H, s, 5'-$\underline{CH_3}$); 3.65-3.83 (8H, m, $2OCH_2$, $2NCH_2$); 4.35 (2H, q, $J = 7.5$, $\underline{CH_2}$ in COOEt); 4.45 (2H, q, $J = 7.35$, $\underline{CH_2}$ in OEt)
4d	1710	1600, 1550	1.36 (3H, t, $J = 7.4$, $\underline{CH_3}$ in COOEt); 1.53-1.73 (6H, m, $3CH_2$); 2.83 (3H, s, 5'-$\underline{CH_3}$); 3.65-3.85 (12H, m, $2OCH_2$, $4NCH_2$); 4.36 (2H, q, $J = 7.4$, $\underline{CH_2}$ in COOEt)

TABLE 2 (continued)

1	2	3	4
4e	1700	1600, 1575, 1505	1.37 (6H, m, $\underline{CH_3}$ in OEt and COOEt); 1.57-1.75 (6H, m, 3CH_2); 2.85 (3H, s, 5'-$\underline{CH_3}$); 3.80-3.88 (4H, m, 2NCH_2); 4.38 (2H, q, *J* = 7.0, $\underline{CH_2}$ in COOEt); 4.45 (2H, q, *J* = 7.0, $\underline{CH_2}$ in OEt)
4f	1705	1600, 1545	1.34 (3H, t, *J* = 7.35, $\underline{CH_3}$ in COOEt); 1.50-1.70 (12H, m, 6CH_2); 2.80 (3H, s, 5'-$\underline{CH_3}$); 3.70-3.85 (8H, m, 4NCH_2); 4.35 (2H, q, *J* = 7.35, $\underline{CH_2}$ in COOEt)
4g	1708	1605, 1580, 1510	1.37 (3H, t, *J* = 7.4, $\underline{CH_3}$ in COOEt); 1.57-1.75 (6H, m, 3CH_2); 2.85 (3H, s, 5'-$\underline{CH_3}$); 3.80-3.90 (4H, m, 2NCH_2); 3.98 (3H, s, OCH_3); 4.36 (2H, q, *J* = 7.4, $\underline{CH_2}$ in COOEt)
4h	1715	1595, 1535	1.39 (3H, t, *J* = 7.4, $\underline{CH_3}$ in COOEt); 2.56 (3H, s, 5'-$\underline{CH_3}$); 4.07 (6H, s, 2OCH_3); 4.37 (2H, q, *J* = 7.4, $\underline{CH_2}$ in COOEt)
4i	1720	1580, 1540, 1510	1.32 (3H, t, *J* = 7.35, $\underline{CH_3}$ in COOEt); 2.42 (3H, s, 5'-$\underline{CH_3}$); 3.55-3.82 (8H, m, 2OCH_2, 2NCH_2); 4.32 (2H, q, *J* = 7.3, $\underline{CH_2}$ in COOEt); 7.25-7.45 (10H, m, 2C_6H_5)

It turned out that the reaction rate depended significantly on the type of dicarbonyl compound used. On interacting monoazides **2** with the more reactive acetylacetone the time for the synthesis at room temperature varied from 0.5-14 h. To obtain the same desired products **4a-i** in the reaction with acetoacetic ester required far more time (in some cases up to 72 h) at 30-40°C.

As was to be expected the structure of the initial azide influences the reaction rate. The most reactive turned out to be azide **2h**, containing the small volume OMe substituent in positions 4 and 6 of the triazine ring. The least reactive were azides **2j,k** having residues of the sterically hindering diphenylamine and 2-methylpiperidine at the indicated positions.

The synthesized triazolyltriazines **3a-i**, **4a-i** were white, finely crystalline powders, readily soluble in polar organic solvents and aromatic hydrocarbons, poorly soluble in petroleum ether in the cold, and insoluble in water. Their melting points always somewhat exceeded those of the corresponding initial azides **2**. The homogeneity of the obtained compounds was confirmed by TLC, and their composition and structure by the results of elemental analysis, and data of IR, ^{1}H NMR, and mass spectra.

The absorption band for the stretching vibrations of the azide group at 2100-2110 was absent from the IR spectra of triazolyltriazines **3a-i**, **4a-i**, but there were intense absorption bands characteristic of the C=O group at 1665-1720, and also for conjugated C=C and C=N bonds at 1505-1630 cm^{-1} (Table 2).

In all the ^{1}H NMR spectra of compounds **3a-i**, **4a-i** (Table 2) signals were present for the protons of the substituents in positions 4 and 6 of the triazine ring, a singlet for the protons of the 5'-Me group of the triazole ring at 2.70-2.87 for compounds **4a-g**, and at 2.42-2.56 ppm for compounds **4h,i** (the displacement of the signal towards high field is probably linked with the effect of the substituents in positions 4 and 6 of the triazine ring). The singlet signal for the protons of the 4'-COMe group of the triazole ring of compounds **3a-i** was observed at 2.62-2.65 ppm. There were characteristic signals in the spectra of compounds **4a-i** for the 4'-COOEt group, a triplet at 1.30-1.42 (CH_3) and a quartet at 4.28-4.48 ppm (CH_2). The structures of the synthesized products **2-4** were also confirmed by data of mass spectroscopy.

A simple and reliable procedure is proposed for the synthesis of the difficultly available monoazides of *sym*-triazines. An addition-cyclization reaction of these azides with dicarbonyl compounds has been studied and the dependence of reaction time on reactant structure has been shown. A series of substituted 2-(1-triazolyl)triazines has been obtained for the first time. These are promising as biologically active compounds.

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 for solutions of samples in DMSO-d_6 on a Bruker WM-500 (500 MHz) radiospectrometer. The mass spectra were recorded on a Finnigan MAT INCOS 50 instrument (energy of ionizing electrons was 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-254 plates in acetone–hexane, 1:1.

The initial 2-chloro-*sym*-triazines and salts **1a-k** were obtained by the known procedures of [4, 8]. Triethylamine was dried over KOH directly before use, then subjected to fractional distillation. The main fraction was distilled once more over metallic sodium. DMF was purified and dried by the known procedure of [9].

2-Azido-4,6-dimorpholino-*sym*-triazine (2a). A solution of sodium azide (30 mmol) in water (10 ml) was slowly added dropwise with stirring at 5-10°C to a solution of compound **1a** (15 mmol) in water (20 ml) . The reaction mixture was then stirred at room temperature for 3 h. The precipitated solid was filtered off, washed with water until chloride ion was absent from the washings, and dried to constant weight. Azide **2a** was obtained having category A purity (content of main substance >99%), and did not require further purification.

Monoazides 2b-k were obtained analogously.

6-(4-Acetyl-5-methyl-1,2,3-triazol-1-yl)-2,4-dimorpholino-*sym*-triazine (3a). A mixture of acetylacetone (68 mmol) and triethylamine (68 mmol) was added dropwise with stirring at room temperature to a solution of azide **2a** (34 mmol) in dry DMF (10 ml). The reaction mixture was stirred at the same temperature for 0.5 h and then poured into cold water (100 ml) as a fine stream with continuous stirring. The precipitated solid of the desired product was filtered off, washed repeatedly with water, and dried. Triazolyltriazine **3a** was obtained with category A degree of purity.

Compounds 3b-i were obtained analogously.

6-(4-Ethoxycarbonyl-5-methyl-1,2,3-triazol-1-yl)-2,4-dimorpholino-*sym*-triazine (4a). A mixture of acetoacetic ester (68 mmol) and triethylamine (68 mmol) was added dropwise with stirring at room temperature to a solution of azide **2a** (34 mmol) in dry DMF (10 ml). The reaction mixture was stirred at 30-40°C for 48 h and after treatment as described above for compound **3a** triazolyltriazine **4a** was obtained with category A degree of purity.

Compounds 4b-i were obtained analogously.

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