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DERIVATIVES OF *sym*-TRIAZINE.

1. SYNTHESIS AND CONVERSIONS OF QUATERNARY METHYLAMMONIUM SALTS OF 2-CHLORO-4,6-DISUBSTITUTED 1,3,5-TRIAZINES IN NUCLEOPHILIC SUBSTITUTION REACTIONS

A. A. Chesniuk, S. N. Mikhailichenko, V. S. Zavodnov, and V. N. Zaplishny

New quaternary ammonium salts of monochloro-4,6-disubstituted 1,3,5-triazines have been obtained. These compounds are convenient synthons for the synthesis of new cyano, alkoxy, and other derivatives of sym-triazine. Some conversions of the synthesized salts have been studied. An elimination–isomerization reaction of the sym-triazine ring into a 2-oxo-1,2-dihydro-sym-triazine ring was discovered.

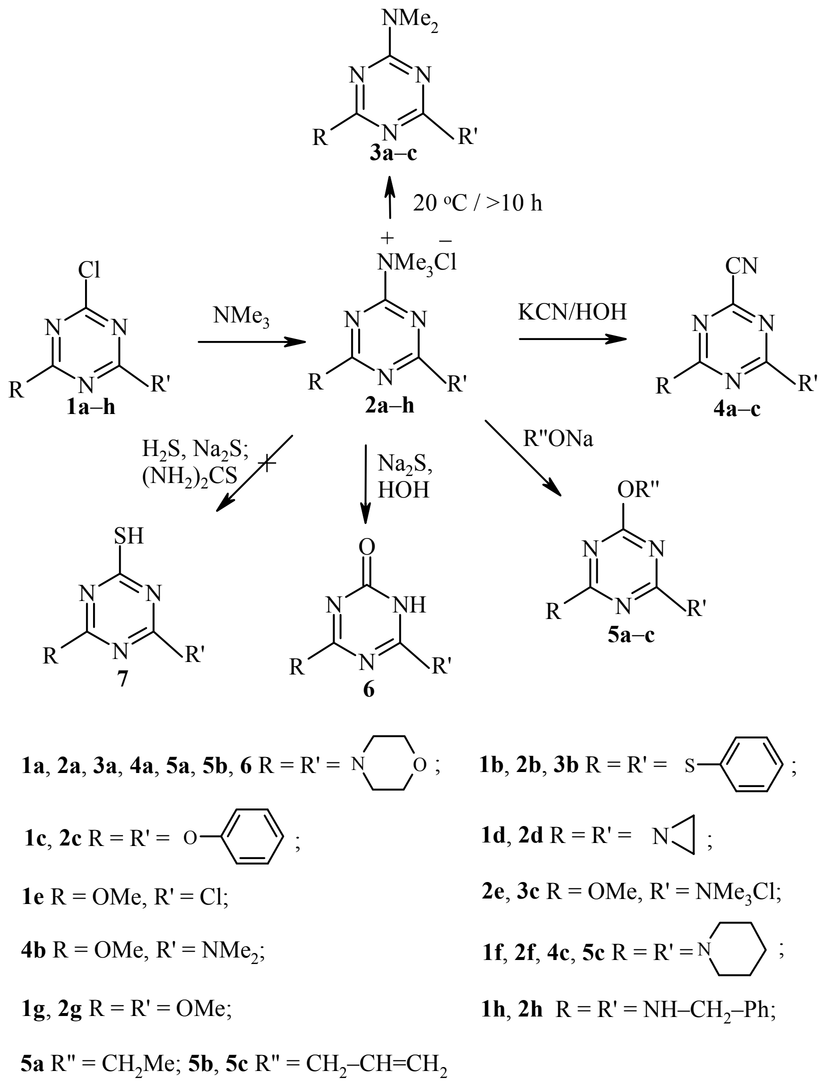
Keywords: 4,6-dimorpholyl-2-oxo-1,2-dihydro-*sym*-triazine, 2-trimethylammonio-*sym*-triazine chloride, 2-cyano-*sym*-triazines.

Functionally substituted 1,3,5-triazines possessing various physiological activity are widely used in industry as antioxidants, antiscorching agents, hardeners, and modifiers of reagents, monomers, etc. [1-3]. The nature and structure of the substituents in the *sym*-triazine ring in the main determine the properties of these compounds.

Most frequently the starting material in the synthesis of compounds of the *sym*-triazine series is the available industrial product, the acid chloride of cyanuric acid or cyanuric chloride (CC). The latter reacts readily by nucleophilic substitution, however the stepwise substitution of the chlorine atoms in CC occurs smoothly only for the first two atoms. Substitution of the third chlorine atom is a problem [1]. One solution is the use of quaternary methylammonium salts, on which there are only individual reports of synthesis and properties [2,3]. Such salts are reactive substances, but are extremely unstable [4,5], which hinders work on them.

In view of this we undertook the synthesis of new synthons, quaternary methylammonium salts from 2-chloro-4,6-disubstituted *sym*-triazines, and investigated their reactivity in certain nucleophilic substitution reactions according to the scheme shown.

Kuban State Agricultural University, Krasnodar 350044, Russia; e-mail: vlad_zpl@mail.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 197-203, February, 2002. Original article submitted November 1, 1999; revision submitted June 14, 2000.



Salts **2a-h** were obtained by the modified procedure [4,5] from 2-chloro-4,6-disubstituted *sym*-triazines **1a-h** by treatment of solutions with dry trimethylamine. Compounds **2a-h** were white finely crystalline substances readily soluble in water and other polar solvents. Their composition and structure were confirmed by elemental analysis, IR and ^{1}H NMR spectroscopy (Tables 1-3).

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, % C	H	N	mp, °C	Yield, %
1	2	3	4	5	6	7
2a	$C_{14}H_{25}ClN_6O_2$	48.89 48.77	7.40 7.31	24.52 24.38	194-195	98
2b	$C_{18}H_{19}ClN_4S_2$	55.41 55.30	4.97 4.90	14.54 14.33	185-186	60
2c	$C_{18}H_{19}ClN_4O_2$	60.32 60.25	5.45 5.34	15.73 15.61	178-179	96

TABLE 1 (continued)

1	2	3	4	5	6	7
2d	$C_{10}H_{17}ClN_6$	46.81 46.78	6.76 6.68	32.81 32.74	266-267	95
2e	$C_{10}H_{21}Cl_2N_5O$	40.33 40.27	7.36 7.10	23.62 23.49	>60 (decomp.)	95
2f	$C_{16}H_{29}ClN_6$	56.45 56.37	8.53 8.57	24.83 24.65	135-136	93
2g	$C_8H_{15}ClN_4O_2$	41.06 40.93	2.23 2.15	23.93 23.87	>95 (decomp.)	95
2h	$C_{20}H_{25}ClN_6$	62.62 62.58	6.60 6.56	21.98 21.89	>120 (decomp.)	96
3a	$C_{13}H_{22}N_6O_2$	53.10 52.96	7.64 7.52	28.54 28.51	197-198	70
3b	$C_{17}H_{16}N_4S_2$	60.15 59.97	4.89 4.74	16.59 16.46	235-236	61
3c	$C_9H_{18}ClN_5O$	43.61 43.49	7.55 7.30	28.36 28.18	210-211	64
4a	$C_{12}H_{16}N_6O_2$	52.31 52.16	5.95 5.84	30.57 30.41	205-206	75
4b	$C_7H_9N_5O$	47.00 46.92	5.31 5.06	39.31 39.09	144-145	40
4c	$C_{14}H_{20}N_6$	61.85 61.74	7.52 7.40	31.05 30.80	130-131	93
5a	$C_{13}H_{21}N_5O_3$	52.98 52.86	7.29 7.17	23.86 23.72	144-145	65
5b	$C_{14}H_{21}N_5O_3$	54.88 54.71	6.93 6.89	22.83 22.79	131-132	60
5c	$C_{16}H_{25}N_5O$	63.65 63.33	8.47 8.30	23.31 23.08	76-77	70
6	$C_{11}H_{17}N_5O_3$	49.57 49.42	6.63 6.41	26.45 26.20	310-311	62

TABLE 2. IR Spectra of the Synthesized Compounds

Compound	ν, cm^{-1}			
	C=C, C=N	C–N, C–O–C	C=N	Other signals
2a	1580, 1560	1220, 1150, 1040	—	—
2b	1640, 1620	1260, 1170, 1110	—	—
2c	1630, 1615	1240, 1190	—	—
2d	1580, 1520	1190, 1130	—	—
2e	1630, 1580	1240, 1160, 1080	—	—
2f	1590, 1570, 1500	1240, 1190	—	—
2g	1610, 1580	1220, 1180, 1050	—	—
2h	1590, 1550, 1520	1230	—	3340 (N–H)
3a	1520	1230, 1180, 1090	—	—
3b	1640, 1520	1270, 1210, 1130	—	—
3c	1610, 1560	1220, 1180, 1050	—	—
4a	1550, 1525	1220, 1100, 1070	2330	—
4b	1620, 1590, 1550	1260, 1240, 1200, 1070	2320	—
4c	1610, 1525	1260, 1200, 1105	2305	
5a	1550, 1510	1230, 1120, 1080, 1050	—	—
5b	1560, 1505	1240, 1110, 1080	—	1675 (C=C)
5c	1550, 1505	1220, 1140, 1100, 1070	—	1670 (C=C)
6	1590, 1540	1150, 1070	—	1660 (C=O)

TABLE 3. ^{1}H NMR Spectra of the Synthesized Compounds

Compound	δ, ppm (coupling constant, *J*, Hz)				
	$N–CH_3$, s	$N–CH_2$, (8H, m)	$O–CH_2$	H_{Ar}, (10H, m)	Other protons
2a	3.2	3.39-3.65 (16H, m)		—	—
2b	2.82	—	—	6.91-7.12	—
2c	2.87	—	—	6.85-7.06	—
2d	2.83-3.05 (17H, m)		—	—	—
2e	2.86	—	3.27 (3H, s, OCH_3)	—	—
2f	1.89	2.94-3.5	—	—	1.28-1.62 (12H, m CH_2)
2g	1.94	—	2.87 (6H, s, OCH_3)	—	—
2h	2.6	—	—	6.72-7.08	2.9 (4H, *J* = 6, $NH–\underline{CH_2}–C_6H_5$); 4.4 (2H, br. s, $\underline{NH}–CH_2–C_6H_5$)
3a	2.79	3.3-3.68 (16H, m)		—	—
3b	2.63	—	—	6.85-7.0	—
3c	2.67, 2.86	—	3.28 (3H, s, OCH_3)	—	—
4a	—	3.42-3.76 (16H, m)		—	—
4b	2.67	—	3.27 (3H, s, OCH_3)	—	—
4c	—	3.49-3.65 (8H, m)			1.34-1.57 (12H, m, CH_2)
5a	—	3.35-3.7 (16H, m)		—	1.0 (3H, t, *J* = 7.1, $OCH_2\underline{CH_3}$); 4.2 (2H, q, *J* = 7.1, $O\underline{CH_2}CH_3$)
5b	—	3.4-3.8 (16H, m)		—	4.59 (2H, d, *J* = 5, $O–\underline{CH_2}–CH{=}CH_2$); 4.8-5.26 (3H, m, $O–CH_2–\underline{CH{=}CH_2}$)
5c	—	3.54-3.8	4.65-4.71 (2H, d, *J* = 5, $O–\underline{CH_2}CH{=}CH_2$)	—	1.41-1.69 (12H, m, CH_2); 5.15-5.48 (2H, dd, *J* = 7, $O–CH_2–CH{=}\underline{CH_2}$); 5.94-6.05 (1H, m, $O–CH_2–\underline{CH}{=}CH_2$)
6	—	3.53-3.73 (16H, m)		—	10.52 (1H, br. s, N–H)

It was shown that the stability of such salts depends to a significant extent on the character of the substituents in positions 4,6 of the triazine ring. Compounds **2b,c,e,g,h** were extremely unstable and may be stored for a prolonged time only under a layer of benzene at 5-10°C. At room temperature in air they rapidly (1-3 h) eliminate methyl chloride with the formation of 2-(dimethylamino)-4-R-6-R'-*sym*-triazines **3a-c**. To form the same side product from the stable salt **2a** it was necessary to use extended refluxing (up to 20 h) in butanol or storage for more than 20 days in the air under the usual conditions. In the ^{1}H NMR spectra of compounds **3a-c** (Table 3) a high-field shift of 0.2-0.4 ppm was observed for the singlet signal of the N-methyl group protons, which is characteristic for the $N(CH_3)_2$ group and is in agreement with the data of [6].

The synthesized quaternary salts **2a-h** are reactive substances entering readily into various nucleophilic substitution reactions. The corresponding cyano derivatives **4a-c** were obtained smoothly on interaction of **2a-h** with KCN in water or acetonitrile. The IR spectra of such compounds contain an additional intense absorption band characteristic of the nitrile group at 2230-2340 cm^{-1} and strong absorption bands in the 1500-1610 cm^{-1} region characteristic of conjugated C=C and C=N bonds (Table 2). The ^{1}H NMR spectra revealed the only signals for the protons of the substituents at positions 4 and 6 of the triazine ring (Table 3).

The interaction of salts **2** with alkali metal alcoholates in ethyl or allyl alcohol leads smoothly to the corresponding alkoxy derivatives **5a-c** (Tables 1-3). It is interesting that the 2-allyloxy-4-R-6-R'-*sym*-triazines **5b,c** are also formed fairly readily in this way but are not formed from the corresponding 2-chloro-4-R-6-R'-*sym*-triazines **1** and allyl alcohol due to the low lability of the third chlorine atom in such compounds [1].

In view of the increased interest of investigators towards nitrogen-containing heterocyclic compounds with an exocyclic sulfur atom, it seemed of interest to replace the chlorine atom in compounds **1** by sulfur with the aim of obtaining thiones **7**. As was to be expected in spite of wide variations in synthetic conditions attempts to obtain 2-mercapto-4,6-disubstituted *sym*-triazines **7,** or the thiones isomeric with them, by the direct substitution of the chlorine atom in the corresponding initial **1a-h,** were unsuccessful, which is in agreement with the data of [1]. It was unexpected that it was impossible to make structure **7** even on using the highly reactive quaternary methylammonium salts **2**. In the case of the relatively stable salt **2a** the initial compound was isolated after extended (over 50 h) stirring with saturated H_2S solution. Continued refluxing of this salt with a small (0.1 mol) excess of thiourea in butanol under conditions analogous to [7] leads to decomposition of the salt and the formation of compound **3a**. Refluxing the same salt **2a** in saturated aqueous sodium sulfide solution led unexpectedly to the oxo compound **6**, the structure of which was confirmed by data of elemental analysis, IR and ^{1}H NMR spectroscopy (Tables 1-3). The formation of compound **6** is probably the result of isomerization–elimination of the exocyclic group from position 2 of the triazine ring, and the unusual nature of such an isomerization is linked with the alkaline character of the reaction mixture in the presence of water and Na_2S. A similar conversion of a *sym*-triazine ring was observed previously [8] in acidic medium under the conditions of the Friedel–Craft reaction on acylation of toluene and xylenes with monosubstituted dichlorotriazines.

Quaternary ammonium salts of 4,6-disubstituted *sym*-triazines have consequently been synthesized in good yield using a modified procedure. Some conversions of these salts have been investigated and a series of new potentially bioactive derivatives of *sym*-triazine have been obtained.

EXPERIMENTAL

The initial 2-chloro-4,6-disubstituted 1,3,5-triazines were obtained by known methods [1] from CC purified by crystallization from CCl_4 (mp 146°C). Organic solvents were purified and dried by the procedure of [9]. The IR spectra were recorded on a Specord IR 75 instrument in nujol. The ^{1}H NMR spectra were taken in DMSO-d$_6$, $(CH_3)_2CO$-d$_6$, and in CF_3COOH for compound **6** on Bruker AC 200, DRX500, and Tesla 60 instruments (internal standard was HMDS) at 30°C. The purity of the compounds synthesized was checked by TLC (Silufol UV-vis, acetone–hexane, 1:1, visualization with iodine vapor in UV light).

4,6-Dimorpholino-2-trimethylammonio-*sym*-triazine Chloride (2a). A stream of dry $N(CH_3)_3$ in a current of nitrogen was passed through a stirred solution of 2-chloro-4,4-dimorpholino-*sym*-triazine (**1a**) (5 g, 18 mmol) in abs. benzene (30 ml) at 10°C. Saturation with trimethylamine was continued for 1 h and the reaction mixture was then left for 12 h at this temperature. The abundant precipitate formed was filtered off, washed with abs. benzene (3 × 25 ml), and dried to constant weight in a vacuum desiccator. Product **2a** (5.4 g, 98%) was obtained as a white finely crystalline powder; mp 194-195°C.

Salts **2b-h** were obtained analogously.

2-(Dimethylamino)-4,6-dimorpholino-*sym*-triazine (3a). A solution of salt **2a** (1.9 g, 6 mmol) in *n*-butanol (10-15 ml) was refluxed for 20 h. The reaction mixture was cooled, the precipitated solid filtered off, washed with cold ethanol, then with water, and dried. Product **3a** (1.33 g, 70%) was obtained in the form of a white finely crystalline powder; mp 197-198°C.

Compounds **3b,c** were obtained analogously.

2-Cyano-4,6-dimorpholino-*sym*-triazine (4a). Salt **2a** (1.9 g, 6 mmol) was added rapidly to a solution of KCN (0.78 g, 12 mmol) in water (5 ml) and the mixture stirred for 1 h at 50°C. The resulting precipitate was filtered off, washed with water until chloride ion was absent from the washings, and dried. Compound **4a** (0.6 g, 76%) was obtained as a white finely crystalline powder; mp 205-206°C, insoluble in water and hexane, and readily soluble in polar organic solvents.

Compounds **4b,c** were obtained analogously.

2-Allyloxy-4,6-dimorpholino-*sym*-triazine (5b). Salt **2a** (1.0 g, 3 mmol) was added in small portions with stirring at 10°C to a solution of metallic sodium (0.069 g, 3 mmol) in allyl alcohol (10 ml), and the mixture stirred for 0.5 h. The reaction mixture was evaporated to dryness using a water-pump vacuum. Water (25 ml) was added to the residue, the solid was filtered off, washed with water until chloride ion was absent from the washings, and dried. Compound **5b** (0.55 g, 60%) was obtained as a white finely crystalline powder; mp 131-132°C, insoluble in water and hexane, readily soluble in aromatic hydrocarbons and in polar organic solvents.

Compounds **5a,c** were obtained analogously.

4,6-Dimorpholino-2-oxo-1,2-dihydro-*sym*-triazine (6). Salt **2a** (0.7 g, 2 mmol) was added to a solution of Na_2S (0.312 g, 4 mmol) in water (10 ml) and the mixture was heated for 1.5 h at 60°C. The reaction mixture was acidified to pH 6 with acetic acid, the precipitated solid filtered off, washed with water until the absence of chloride ion in the washings, and dried. Compound **6** (0.3 g, 55%) was obtained as a white finely crystalline powder; mp 310-311°C, insoluble in water and the usual organic solvents, soluble in DMSO and DMF, and satisfactorily soluble in chloroform on heating.

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