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sym-TRIAZINES. 7*. HYDROLYSIS AND CYCLIZATION OF 1,3,5-TRIAZINE SERIES MONONITRILES

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The routes of base and acid hydrolysis of sym-triazine mononitriles has been studied for aqueous or aqueous-alcohol media. Depending on the pH of the medium, the concentration of reagents, and the temperature it was found that the hydrolysis led to the formation of amides, oxo or alkoxy 1,3,5-triazines, or to an unstable sym-triazine carboxylic acid, the latter leading to formation of substituted sym-triazines. A novel series of tetrazolyltriazines has been prepared by the reaction of the mononitriles with sodium azide and their alkylation has been studied.

Keywords: 2-carbamoyl-*sym*-triazines, 2-[tetrazol-5-yl]-*sym*-triazines, 6H-*sym*-triazines, 2-cyano-*sym*-triazines.

The high biological activity and broad spectrum of possible areas of use of *sym*-triazine derivatives [2-4] are responsible for the increase in their interest. We have previously obtained a series of novel 2-cyano-4,6-disubstituted 1,3,5-*sym*-triazines **1** and investigated some of their reactions. Bearing in mind the availability of the starting compounds and simplicity of the synthesis of such mononitriles it was of interest to study routes of hydrolytic conversion of the cyano group in acid and base media and also to use these mononitriles as intermediate products in the preparation of related tetrazolotriazines *via* cyclization reactions with sodium azide.

With this in view we have investigated the base and acid hydrolysis of the mononitriles **1a-j** according to Scheme 1.

It was found that refluxing the starting nitrile **1a** with a solution of a two-fold excess of NaOH or KOH in 50% aqueous alcohols $C_nH_{2n+1}OH$ (n = 1-4) solutions gave the 4-alkoxy derivatives **2a-d** in about 85% yield in place of the expected *sym*-triazine-4-carboxylic acid salt. All of the constants and spectra were identical to the compounds prepared by alkylation of 2-oxo[1,2-dihydro]-4,6-disubstituted 1,3,5-triazines as reported by us previously [6].

Evidently, in base hydrolysis conditions using an aqueous alcohol medium the C–C≡N bond in position 2 of the *sym*-triazine ring becomes so labile that the cyano group of such a mononitrile behaves as a pseudohalogen and can be eliminated by the action of such active nucleophiles as alcohols.

* For Communication 6 see [1].

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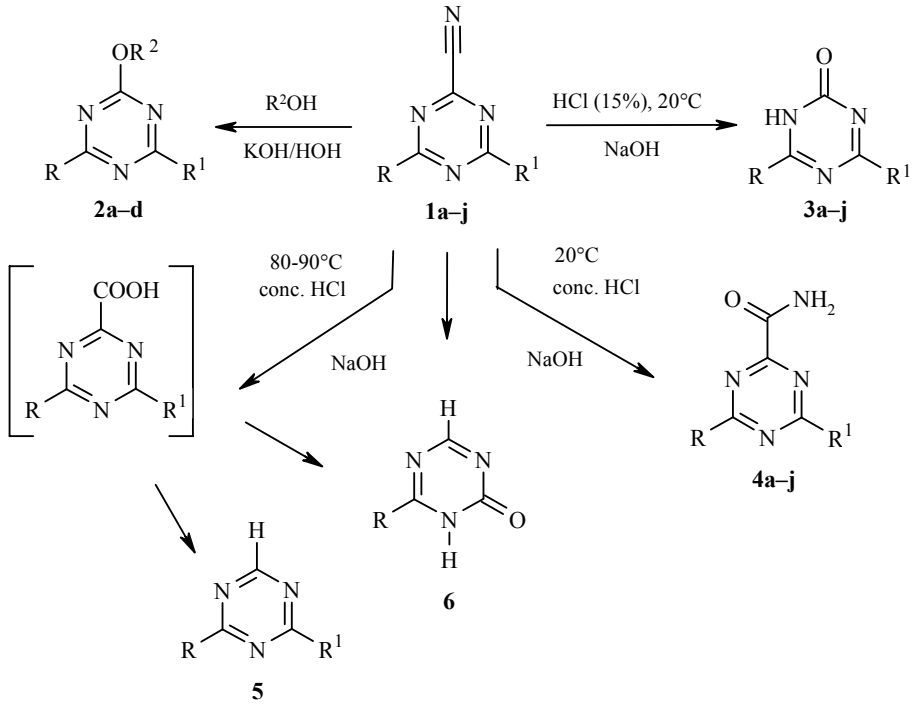
Scheme 1



1, 3, 4 a R = R^1 = morpholino, **b** R = R^1 = piperidino, **c** R = OEt, R^1 = piperidino; **d** R = OMe, R^1 = morpholino; **e** R = morpholino, R^1 = piperidino; **f** R = NHEt, R^1 = piperidino; **g** R = NHEt, R^1 = morpholino; **h** R = OMe, R^1 = piperidino; **i** R = R^1 = NEt_2; **j** R = OMe, R^1 = NEt_2; **5** R = R^1 = morpholino; **6** R = morpholino; **2 a–d** R = R^1 = morpholino; **a** R^2 = Me, **b** R^2 = Et, **c** R^2 = Pr, **d** R^2 = Bu

It was found that the nature of the hydrochloric acid hydrolysis of the nitriles **1** depends both on the concentration of acid and on the reaction temperature. Hence even simple solution of these nitriles in 15% hydrochloric acid at room temperature leads to formation of the 2-oxo derivatives **3a-j**, identical in properties to those reported before [6]. At the same time, the use of conc. HCl also at room temperature leads to formation of the 2-carbamoyl-substituted **4a-j** in 63-75% yield (Table 1) with the spectroscopic parameters given in Table 2. Finally, heating a solution of the nitrile **1a** in conc. HCl for 1-2 h at 80-95°C gave the 2,4-bis(1-morpholyl)-*sym*-triazine **5**, probably as a result of decarboxylation of the unstable intermediate acid. Acid hydrolysis of the starting nitrile **1d** containing a methoxy group in the triazine ring under analogous conditions gave the *sym*-triazinone **6**.

The amides **4a-j** and compounds **5, 6** obtained are white, finely crystalline powders which are higher melting and with lower solubility in organic solvents than the starting nitriles **1a-j**.

The composition and structure of the hydrolysis products were confirmed by a combination of their elemental analysis, IR, ^{1}H NMR , and mass spectroscopic data.

The IR spectra of compounds **4** show the presence of strong, narrow absorption bands at 1660-1695 cm^{-1} which are characteristic of $\nu_{C=O}$ and broad absorptions at 3240-3430 cm^{-1} for ν_{NH}. The IR spectra of compounds **5a,b** do not show the absorption bands characteristic of the amide or carboxyl groups while the spectrum of compound **6a** contains absorption bands for carbonyl and NH group stretching vibrations (Table 2). The ^{1}H NMR spectra show signals for the protons of all the substituents surrounding the *sym*-triazine ring, the number of which correspond to those expected from the integrated curve data. A common feature of the

TABLE 1. Characteristics of Compounds **4-8**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Molecular ion m/z (I_{rel}, %)	Yield, %
		C	H	N			
4a	$C_{12}H_{18}N_6O_3$	47.10 48.97	6.27 6.16	28.77 28.56	214-215	294 (45)	73
4b	$C_{14}H_{22}N_6O$	58.13 57.90	7.90 7.64	29.05 28.95	106-108	290 (57)	70
4c	$C_{11}H_{17}N_5O_2$	52.74 52.57	6.98 6.82	28.00 27.87	165-166	251 (58)	68
4d	$C_9H_{13}N_5O_3$	45.35 45.18	5.62 5.47	29.44 29.28	207-208	239 (28)	76
4e	$C_{13}H_{20}N_6O_2$	53.62 53.41	7.01 6.89	28.89 28.75	208-209	292 (72)	65
4f	$C_{11}H_{18}N_6O$	52.90 52.78	7.38 7.25	33.75 33.58	265-266	250 (58)	63
4g	$C_{10}H_{16}N_6O_2$	47.74 47.61	6.55 6.39	33.50 33.32	169-170	252 (42)	72
4h	$C_{10}H_{15}N_5O_2$	50.79 50.62	6.50 6.37	29.66 29.52	170-171	237 (77)	67
4i	$C_{12}H_{22}N_6O$	54.11 54.62	8.33 8.05	31.56 31.21	187-188	266 (75)	75
4j	$C_9H_{15}N_5O_2$	48.13 47.99	6.88 6.71	31.26 31.09	157-158	225 (63)	69
5	$C_{11}H_{17}N_5O_2$	52.79 52.57	7.06 6.82	28.00 27.87	167-168	251 (96)	40
6	$C_7H_{10}N_4O_2$	46.30 46.15	5.78 5.53	30.94 30.76	>190 (subl.)	182 (78)	35
7a	$C_{12}H_{17}N_9O_2$	45.00 45.13	5.52 5.37	39.31 39.48	269-270	319 (92)	61
7b	$C_{12}H_{21}N_9$	49.35 49.46	7.41 7.26	43.10 43.27	189-190	291 (78)	58
7c	$C_9H_{12}N_8O_2$	40.75 40.90	4.72 4.58	42.28 42.41	>210 (subl.)	264 (44)	49
7d	$C_9H_{14}N_8O$	43.00 43.19	5.81 5.64	44.55 44.78	233-234	250 700)	55
8a	$C_{16}H_{23}N_9O_4$	47.26 47.40	5.87 5.72	30.96 31.10	199-200	405 (51)	53
8b	$C_{13}H_{19}N_9O_2$	46.70 46.83	5.93 5.74	37.66 37.82	215-216	333 (100)	60
8c	$C_{16}H_{25}N_9O_2$	51.02 51.18	6.93 6.71	33.40 33.58	105-106	375 (75)	57
8d	$C_{16}H_{27}N_9O_2$	50.75 50.91	7.39 7.21	33.58 33.40	93-94	377 (52)	50

^{1}H NMR spectra of compounds **4a-e,h** is the appearance of the amide proton signal as two singlets at 7.43-7.62 and 7.80-7.94 ppm. Hence we can propose fixing of the carbamoyl group conformation *via* the formation of a hydrogen bond for one of the amino group protons with the heterocyclic nitrogen atom.

The mass spectra of all of the compound showed molecule ions with 45-96% intensity which also confirms their structure.

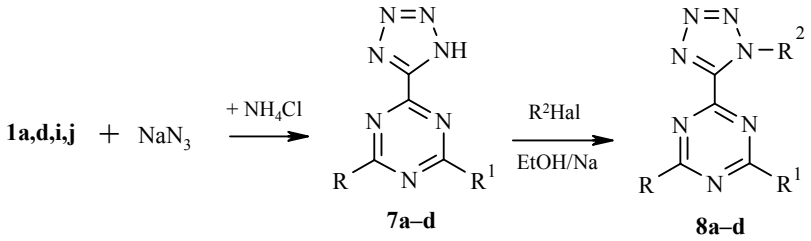
It is known that the reaction of sodium azide with cyanoarenes and -hetarenes give the corresponding tetrazole derivatives having marked biological activity [7]. In particular, Japanese authors [8] have shown that refluxing the cyano-*sym*-triazine **1i** with sodium azide in methanol for 10 h gives a low (~30%) yield of the tetrazolyl-*sym*-triazine **7b** (Scheme 2). Exchange of methanol for dry DMF and the addition to the reaction mixture of an equimolar amount of ammonium chloride allowed us to prepare a series of tetrazolyl-*sym*-triazines **7a-d** with better (46-91%) yields.

TABLE 2. Spectroscopic Characteristics of Compounds **4-8**

Compound	IR spectrum, ν, cm^{-1}			^{1}H NMR spectrum, δ, ppm (*J*, Hz)
	N=N, C=N, C=C conj.	NH	C=O	
4a	1510, 1560	3255, 3410	1698	3.60-3.85 (8H, m, 2-NCH_2, 2-OCH_2); 7.47, 7.88 (2H, s. s, NH_2)
4b	1540, 1570	3260, 3390	1680	1.45-1.70 (12H, m, CH_2-piperidine); 3.65-3.85 (8H, m, 4-NCH_2); 7.45, 7.80 (2H, s. s, NH_2)
4c	1500, 1565	3240, 3430	1690	1.30-1.38 (3H, t, *J* = 6.6, $\underline{CH_3}$ in Et); 1.55-1.77 (6H, m, 3-CH_2); 3.75-3.90 (4H, m, 2-NCH_2); 4.35-4.46 (2H, q, *J* = 6.6, $\underline{CH_2}$ in Et); 7.55, 7.85 (2H, s. s, NH_2)
4d	1500, 1580	3245, 3400	1695	3.64-3.93 (8H, m, 2-NCH_2, 2-OCH_2); 3.95 (3H, s, OCH_3); 7.63, 7.94 (2H, s. s, NH_2)
4e	1560, 1610	3250, 3385	1690	1.50-1.67 (6H, m, 3-CH_2); 3.60-3.85 (12H, m, 4-NCH_2, 2-OCH_2); 7.43, 7.80 (2H, s. s, NH_2)
4f	1520, 1570	3090, 3240, 3395	1690	1.12-1.20 (3H, t, *J* = 4.1, $NHCH_2\underline{CH_3}$); 1.53-1.73 (6H, m, 3-CH_2); 3.30-3.45 (2H, q, *J* = 4.1, $NH\underline{CH_2}CH_3$); 3.70-3.85 (4H, m, 2-NCH_2); 7.25-7.52 (3H, m, 1H-NH, 2H-NH_2)
4g	1510, 1580	3075, 3250, 3390	1685	1.13-1.20 (3H, t, *J* = 5.1, $NHCH_2\underline{CH_3}$); 3.30-3.46 (2H, q, *J* = 5.1, $NH\underline{CH_2}CH_3$); 3.60-3.83 (8H, m, 2-NCH_2, 2-OCH_2); 7.30-7.67 (3H, m, 1H-NH, 2H-NH_2)
4h	1580, 1610	3260, 3390	1670	1.55-1.72 (6H, m, 3-CH_2); 3.75-3.90 (4H, m, 2-NCH_2); 3.93 (3H, s, OCH_3); 7.62, 7.90 (2H, s. s, NH_2)
4i	1540, 1570	3270, 3420	1680	1.13-1.22 (12H, t, *J* = 8.0, $NCH_2\underline{CH_3}$); 3.49-3.60 (8H, m, $N\underline{CH_2}CH_3$); 7.45-7.55 (2H, br. s, NH_2)
4j	1520, 1575	3280, 3400	1675	1.18-1.25 (6H, t, *J* = 4.5, $NCH_2\underline{CH_3}$); 3.60-3.75 (4H, q, *J* = 4.5, $N\underline{CH_2}CH_3$); 4.29 (3H, s, OCH_3); 7.10-7.50 (2H, m, NH_2)
5	1550, 1600	—	—	3.55-3.80 (16H, m, –NCH_2 (8H), –OCH_2 (8H)); 8.12 (1H, s, CH)
6	1520, 1600	3100	1650	3.60-3.85 (8H, m, –NCH_2 (4H), –OCH_2 (4H)); 8.10 (1H, s, CH); 11.40-11.70 (1H, br. s, NH)
7a	1500, 1540, 1570	3340-3400 (br. s)	—	3.65-4.00 (16H, m, –NCH_2 (8H), –OCH_2 (8H)); 11.50-11.85 (1H, br. s, NH)
7b	1530, 1560, 1600	3240-3420 (br. s)	—	1.15-1.25 (12H, m, $NCH_2\underline{CH_3}$); 3.50-3.80 (8H, m, ΣNCH_2); 11.40-11.90 (1H, br. s, NH)
7c	1540, 1570, 1610	3250-3450 (br. s)	—	3.60-3.90 (8H, m, 4H-NCH_2, 4H-OCH_2); 4.40 (3H, s, OCH_3); 11.20-11.50 (1H, br. s, NH)
7d	1520, 1595, 1600	3220-3440 (br. s)	—	1.20-1.30 (6H, m, $NCH_2\underline{CH_3}$); 3.55-3.75 (4H, m, $N\underline{CH_2}CH_3$); 4.40 (3H, s, OCH_3); 11.90-12.10 (1H, br. s, NH)
8a	1515, 1560	—	1725	1.20-1.35 (3H, t, *J* = 5.75, $OCH_2\underline{CH_3}$); 3.65-3.85 (16H, m, Σ8H-NCH_2 + 8H-OCH_2); 4.15-4.23 (2H, q, *J* = 5.75, $O\underline{CH_2}CH_3$); 5.70 (2H, s, $N\underline{CH_2}COOEt$)
8b	1510, 1565, 1605	—	—	3.70-3.80 (16H, m, 8H-NCH_2, 8H-OCH_2); 4.36 (3H, s, NCH_3)
8c	1505, 1570, 1610	—	—	0.90-1.03 (3H, m, $N(CH_2)_3\underline{CH_3}$); 1.30-1.45 (2H, m, $N(CH_2)_2\underline{CH_2}CH_3$); 1.85-2.10 (2H, m, $NCH_2\underline{CH_2}CH_2CH_3$); 3.65-4.00 (16H, m, Σ8H-NCH_2 + + 8H-OCH_2); 4.67-4.83 (2H, m, $N\underline{CH_2}CH_2CH_2CH_3$)
8d	1520, 1570, 1595	—	1720	1.15-1.26 (15H, m, Σ$NCH_2\underline{CH_3}$, $OCH_2\underline{CH_3}$); 3.55-3.70 (8H, m, $N\underline{CH_2}CH_3$); 4.15-4.23 (2H, q, *J* = 6.3, *J* = 5.74, $O\underline{CH_2}CH_3$); 5.74 (2H, s, $N\underline{CH_2}COOEt$)

It is known that 2-substituted tetrazoles can be alkylated at position 1 [9]. We have carried out a similar reaction by refluxing the tetrazolyl-2-*sym*-triazines **7a,b** with alkyl bromides and iodides in EtOH in the presence of EtONa and obtained the 4,6-disubstituted 2-(α-alkyltetrazol-5-yl)-*sym*-triazines **8a-c** in 50-60% yields (Scheme 2).

Scheme 2



7a, 8a,c R = R^1 = morpholino; **8 a** R^2 = CH_2COOEt; **b** R^2 = Me; **c** R^2 = Bu;
7b, 8d R = R^1 = NEt_2; **8d** R^2 = CH_2COOEt; **7 c** R = OMe, R^1 = morpholino; **d** R = OMe, R^1 = NEt_2

The tetrazolyltriazines **7,8** synthesized are white, finely crystalline substances, readily soluble in polar organic solvents and insoluble in water and nonpolar organic solvents. Moreover, the N-alkyltetrazolyl-*sym*-triazines **8a-d** are rather lower melting and higher in solubility than the starting compounds **7** (Table 1). Their composition and structure were confirmed by combined elemental analysis and by IR, ^{1}H NMR, and mass spectroscopic data.

The IR spectra of compounds **7a-d** show both the characteristic bands for conjugated C=N bonds in the *sym*-triazine and tetrazole rings at 1660-1500 cm^{-1} and also broad stretching bands for the N–H groups at 3230-3450 cm^{-1} (Table 2). The latter is absent in the spectra of compounds **8a-d**. In the ^{1}H NMR spectra of compounds **7** the tetrazole ring proton is observed as a broad signal to low field in the range 11.20-16.50 ppm and this is evidently due to its ready migration to another nitrogen atom in the tetrazole ring.

The mass spectra of compounds **7,8** show molecular ions with intensities 44-100% which confirm their structure.

EXPERIMENTAL

IR spectra were taken for sample suspensions in vaseline oil on a Specord IR-75 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-500 (500 MHz) spectrometer using DMSO-d_6 and with TMS as internal standard. Mass spectra were recorded on a Finnigan MAT INCOS50 instrument with ionization energy 70 eV. Elemental analysis of the synthesized compounds was performed on a Carlo Erba 1106 analyser. Monitoring of the reaction course and purity of the compounds prepared was carried out by TLC using Silufol UV-254 plates in the system acetone–hexane (1:1).

The starting mononitriles **1** were prepared by the method in [5]. Solvents were purified as in [10].

2-Carbamoyl-4,6-dimorpholyl-*sym*-triazine (4a). Compound **1a** (36 mmol) was added to conc. HCl (5 ml). The reaction mixture was held for 12 h at 20°C and then basified to pH 8.0-8.5 using 40% NaOH. The precipitate was filtered off, washed with water to the absence of chloride ions in the water washings, and dried to constant weight. The amide **4a** prepared did not need further purification.

Amides 4b-j were prepared similarly.

2,4-Dimorpholyl-*sym*-triazine (5). A mixture of 2-cyano-4,6-dimorpholyl-1,3,5-triazine **1a** (36 mmol) in conc. HCl (5 ml) was heated with a reflux condenser at 80-90°C for 1 h. After cooling, the reaction mixture was treated with a 40% aqueous solution of NaOH to pH 7.0-7.5. The precipitate was filtered off, thoroughly washed with water, and dried to constant weight.

4-Morpholyl-2-oxo-1,2-dihydro-*sym*-triazine (6). A mixture of 2-cyano-4-methoxy-6-morpholyl-1,3,5-triazine **1d** (45 mmol) in conc. HCl (6 ml) was heated with a reflux condenser at 80-90°C for 1-1.5 h. 10% Aqueous NaOH solution was added to the reaction mixture stirred at 10-15°C to pH 7. The precipitate formed was filtered off, repeatedly washed with water, and dried to constant weight.

2,4-Dimorpholyl-2-[tetrazol(1'H)-5'-yl]-*sym*-triazine (7a). A mixture of compound **1a** (36 mmol), sodium azide (36 mmol), and ammonium chloride (36 mmol) in DMF (10 ml) was refluxed using a reflux condenser for 8 h. The mixture was cooled, poured into cold water (100 ml), and the precipitate formed was separated, thoroughly washed with water, and dried to give the tetrazolyltriazine **7a**.

Compounds 7b-d were prepared similarly.

4,6-Dimorpholyl-2-[1-carbethoxymethyltetrazol-5'-yl]-*sym*-triazine (8a). The tetrazolyltriazine **7a** (16 mmol) was added with stirring to a solution of metallic sodium (16 mmol) in absolute ethanol (10 ml). The mixture was heated to reflux and freshly distilled ethyl 2-bromoacetate (16 mmol) was added dropwise. Refluxing was continued for 10-11 h, solvent was removed in vacuo to dryness, and the precipitate formed was washed with water, dried, and purified by recrystallization from ethanol.

Compound 8d was prepared similarly but the synthesis of compounds **8b,c** used the corresponding methyl and butyl iodides.

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