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Functionally Substituted Isocyanurates with Heteroatoms (O, S) in the *N*-Alkyl Chain

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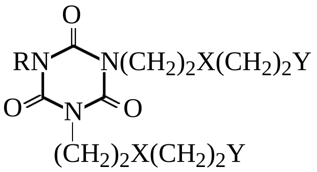
Abstract—Alkylation of disodium benzyl and disodium methyl isocyanurates with β,β'-dichlorodiethyl and β,β'-dibromodiethyl ethers was used to prepare 1-benzyl and 1-methyl 3,5-bis[2-(2-haloethoxy)ethyl] isocyanurates whose reaction with thiourea followed by hydrolysis gave the corresponding 1-alkyl 3,5-bis[2-(2-mercaptoethoxy)ethyl] isocyanurates. 1-Benzyl and 1-methyl 3,5-bis[2-(2-chloroethyl)ethyl] isocyanurates were reacted with $NaSCH_2CH_2OH$ to obtain the corresponding 1-alkyl 3,5-bis[2-(2-hydroxyethylthio)ethyl] isocyanurates. Treatment of the latter two esters with thionyl chloride gave 1-benzyl and 1-methyl 3,5-bis-[2-(2-chloroethylthio)ethyl] isocyanurates, respectively.

Earlier [1] we reported the synthesis of a series of 1-alkyl 3,5-bis(ω-haloalkyl)-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-triones whose reaction with thiourea followed by hydrolysis of the resulting isothiuronium salts gave rise to 1-alkyl 3,5-bis(ω-mercaptoalkyl) isocyanurates [2]. Proceeding with these studies, we developed in the present work methods for synthesis of a series of ω-functionally substituted isocyanurates with heteroatoms (O, S) in the *N*-alkyl chain, which are of interest as starting materials for subsequent syntheses and as building blocks for constructing macrorings with isocyanurate fragments [3].

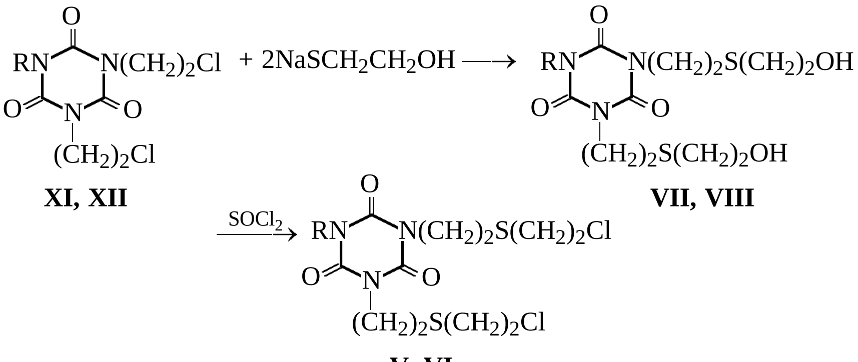
1-Benzyl and 1-methyl 3,5-bis[2-(2-haloethoxy)-ethyl] isocyanurates **I**–**IV** in yields of 46–71% were prepared similarly to bis(ω-haloalkyl) isocyanurates [1] by alkylation of anhydrous disodium alkyl isocyanurates with excess β,β'-dichlorodiethyl or β,β'-dibromodiethyl ethers (Chlorex and Bromex) (Table 1).



I–**X**

R = $C_6H_5CH_2$, CH_3; X = O, S; Y = Cl, Br, OH, SH (for R, X, Y, see Table 1).

The disodium salts could also be alkylated with bis(2-chloroethyl) sulfide (yperite) [4], but we considered this approach hardly practicable because of the high toxicity of yperite. Therefore, 1-alkyl 3,5-bis-[2-(2-chloethylthio)ethyl] isocyanurates **V** and **VI** were obtained by reaction of 1-alkyl 3,5-bis(2-chloroethyl) isocyanurates **XI** and **XII** with $NaSCH_2CH_2OH$ with subsequent treatment of the resulting 1-alkyl 3,5-bis[2-(2-hydroxyethylthio)ethyl] isocyanurates **VII** and **VIII** with thionyl chloride.

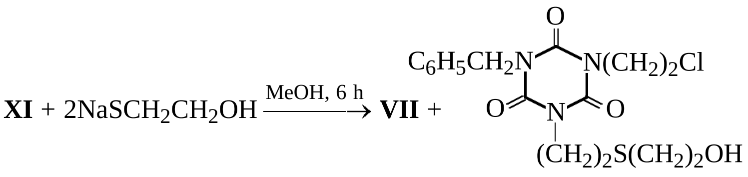


XI, XII **VII, VIII** **V, VI**

Table 1. Yields, R_f values, and elemental analyses of compounds **I**–**X**

Comp. no.	R	X	Y	Yield, %	R_f (solvent for crystallization)	Found, % C	H	Hlg	N	S
I	$C_6H_5CH_2$	O	Cl	70	0.33 (benzene–ethyl acetate, 10:1)	49.84	5.24	15.91	9.66	–
II	CH_3	O	Cl	49	0.20 (benzene–ethyl acetate, 10:1)	40.29	5.04	11.47	19.68	–
III	$C_6H_5CH_2$	O	Br	71	0.33 (benzene–ethyl acetate, 10:1)	41.47	4.47	30.63	8.03	–
IV	CH_3	O	Br	46	0.39 (benzene–ethyl acetate, 5:1)	32.86	4.43	35.64	9.24	–
V	$C_6H_5CH_2$	S	Cl	61	0.50 (benzene–ethyl acetate, 1:1)	46.29	5.01	14.85	9.37	14.02
VI	CH_3	S	Cl	65	0.35 (diethyl ether–hexane, 1:1)	37.45	5.00	18.18	10.85	16.77
VII	$C_6H_5CH_2$	S	OH	60	0.38 (benzene–methanol, 5:1) 0.29 (ethyl acetate)	49.79	6.33	–	10.16	15.25
VIII	CH_3	S	OH	85	0.39 (benzene–methanol, 5:1)	40.79	6.03	–	12.23	18.46
IX	$C_6H_5CH_2$	O	SH	50	0.31 (benzene–ethyl acetate , 5:1)	50.00	6.32	–	9.37	14.98
X	CH_3	O	SH	57	0.31 (diethyl ether–hexane, 2:1) 0.71 (diethyl ether)	40.36	6.10	–	11.26	18.58

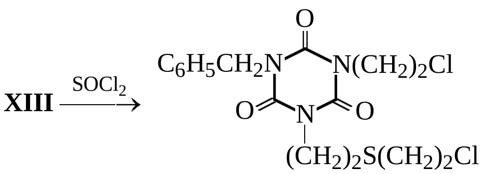
Compound no.	Formula	Calculated, % C	H	Hlg	N	S
I	$C_{18}H_{23}Cl_2N_3O_5$	50.01	5.36	16.40	9.66	–
II	$C_{12}H_{19}Cl_2N_3O_5$	40.46	5.38	11.18	19.91	–
III	$C_{18}H_{23}Br_2N_3O_5$	41.48	4.45	30.66	8.06	–
IV	$C_{12}H_{19}Br_2N_3O_5$	32.38	4.30	35.90	9.44	–
V	$C_{18}H_{23}Cl_2N_3O_5S_2$	46.55	4.99	15.28	9.05	13.81
VI	$C_{12}H_{19}Cl_2N_3O_5S_2$	37.12	4.93	18.26	10.82	16.51
VII	$C_{18}H_{25}N_3O_5S_2$	50.57	5.89	–	9.83	15.00
VIII	$C_{12}H_{21}N_3O_5S_2$	41.01	6.02	–	11.96	18.25
IX	$C_{18}H_{25}N_3O_5S_2$	50.57	5.89	–	9.83	15.00
X	$C_{12}H_{21}N_3O_5S_2$	41.01	6.02	–	11.96	18.25



XIII

R = $C_6H_5CH_2$ (**XI**), CH_3 (**XII**).

The reaction of 1-benzyl 3,5-bis(2-chloroethyl) isocyanurate (**XI**) with $NaSCH_2CH_2OH$ in methanol (boiling, 6 h) gave, along with compound **VII**, a monosubstitution product, 1-benzyl 3-(2-chloroethyl) 5-[2-(2-hydroxyethylthio)ethyl] isocyanurate (**XIII**) in 19% yield. The same reaction in DMF resulted in exclusive formation of a disubstitution product (Table 1, compound **VIII**). Treatment of compound **XIII** with thionyl chloride provided 1-benzyl 3-(2-chloroethyl) 5-[2-(2-chloroethylthio)ethyl] isocyanurate (**XIV**).



XIV

Table 2. IR and ^{1}H NMR spectra of compounds **I**–**X**

Compound no.	IR spectrum[a] (thin layer), ν, cm^{-1}				
	triazine ring [5]	C=O	CO	OH	SH
I	753 s	1740 m, 1675 s	1115 s	–	–
II	755 s	1740 s, 1675 s	1110 s	–	–
III	750 s	1740 m, 1675 s	1114 s	–	–
IV	750 s	1750 m, 1686 s	1114 s	–	–
V	750 s	1690 s	–	–	–
VI	745 s	1740 m, 1675 s	–	–	–
VII	745 s	1664 s	1033 s	3340 s	–
VIII	750 s	1740 m, 1673 s	1040 s	3350 s	–
IX	750 s	1675 s	1100 s	–	2557 m
X	745 s	1748 m, 1686 s	1100 s	–	2557 m

Comp. no.	^{1}H NMR spectrum (CCl$_4$), δ, ppm[b]							
	CH$_3$	C$_6$H$_5$	C$_6$H$_5$CH_2	NCH$_2$ ($^3J_{HH}$ 6 Hz)	OCH$_2$	CH$_2$Hlg	SCH$_2$	SH ($^3J_{HH}$ 8 Hz)
I	–	7.16 m	4.92 s	4.00 t	3.30–3.72 m		–	–
II	3.30 s	–	–	4.02 t	3.26–3.75 m		–	–
III	–	7.21 m	4.95 s	4.03 t	3.58–3.80 m	3.26 t ($^3J_{HH}$ 6 Hz)	–	–
IV	3.27 s	–	–	4.04 t	3.53–3.83 m	3.26 t ($^3J_{HH}$ 6 Hz)	–	–
V	–	7.21 m	4.95 s	4.00 t	–	3.74 t ($^3J_{HH}$ 8 Hz)	2.95 m	–
VI	3.30 s	–	–	4.00 t	–	3.60 t ($^3J_{HH}$ 8 Hz)	3.00 m	–
VII	–	7.28 m	5.03 s	4.08 t	3.73 t ($^3J_{HH}$ 5.5 Hz)	–	2.65–2.95 m	–
VIII	3.37 s	–	–	4.14 t	3.81 t ($^3J_{HH}$ 5.5 Hz)	–	2.68–2.95 m	–
IX	–	7.27 m	4.95 s	4.00 t	3.37–3.83 m	–	2.50 q ($^4J_{HH}$ 7 Hz)	1.38 t
X	3.28 s	–	–	4.00 t	3.43–3.68 m	–	2.40–2.83 m	1.40 t

[a] Along with the listed bands, the spectra of compounds **I**–**X** contain strong bands at, cm^{-1}, 2960–2860 [ν(CH)] and 1450 [δ(CH$_2$)], as well as 3030 m, 1600 w, 1570 w, 694 s (benzene ring) or 1370–1360 s [δ(CH$_3$)].

[b] The ^{1}H NMR spectra of compounds **VII** and **VIII** were obtained in CDCl$_3$.

Compounds **III** and **IV** were reacted with thiourea, and the resulting isothiuronium salts were hydrolyzed to obtain thiols **IX** and **X** in 50–60% yields (Table 1). The reactions of chloro derivatives **I** and **II** with thiorea (boiling in isopropanol, 16–18 h) gave no isothiuronium salts.

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 instrument in thin film or in suspensions in mineral oil. The ^{1}H NMR spectra were measured on a Varian T-60 at 60 MHz, internal reference tetramethylsilane.

The ^{1}H NMR and IR spectra of compounds **I**–**X** are given in Table 2.

1-Benzyl and 1-methyl 3,5-bis[2-(2-chloroethoxy)ethyl]-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-triones (I, II). Benzyl isocyanurate **VII** or methyl isocyanurate **VIII**, 0.05 mol, was added with stirring to sodium butylate obtained from 0.1 mol of sodium in 300 ml of absolute butanol, and the mixture was boiled for 8 h. The butanol was distilled off in a vacuum, the residual solvent was removed by azeotropic distillation with toluene, and the residual toluene was distilled off in a vacuum. The dry disodium salt that remained was treated with 300 ml of absolute DMF and 0.5 mol (5-fold excess) of $Cl(CH_2)_2O(CH_2)_2Cl$, the mixture was stirred at 85–90°C for 4–5 h (to pH 7), and the precipitate was filtered off. The DMF and Chlorex were removed in a vacuum, and the residue was subjected to column chromatography on silica gel, eluent benzene–ethyl acetate, 10 : 1. Compounds **I** and **II** are transparent yellowish thick oils.

1-Benzyl and 1-methyl 3,5-bis[2-(2-bromoethoxy)ethyl]-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-triones (III, IV) were obtained in a similar way. The reactions were performed at 45–50°C. Compounds **III** and **IV** are transparent yellowish thick oils.

1-Benzyl and 1-methyl 3,5-bis[2-(2-chloroethylthio)ethyl]-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-triones (V, VI). Thionyl chloride, a 5-fold molar excess, was slowly added at 10–15°C to a solution of compound **VII** or **VIII** in absolute 1,2-dichloroethane, and the mixture was boiled for 3 h. After cooling, it was treated with water, the organic layer was dried with $MgSO_4$, the solvent was removed, and the residue was subjected to column chromatography on silica gel, eluent benzene–ethyl acetate (first 10 : 1 and then 5 : 1). Compounds **V** and **VI** were isolated as transparent oils, and compound **V** crystallized on standing.

1-Benzyl-3-(2-chloroethyl)-5-[2-(2-chloroethylthio)ethyl]-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (XIV) was obtained in a similar way by treatment with thionyl chloride of compound **XIII**. The eluent for chromatography was benzene. Yield 65%, transparent tar. R_f 0.33 (ether–hexane, 1 : 1). IR spectrum (thin film), ν, cm^{-1} : 3030 m, 1580 w, 1600 w, 700 s, 680 s (benzene ring), 2960 s, 2920 s (CH), 1690 s (C=O), 1464 s [$\delta(CH_2)$], 747 m (triazine ring). ^1H NMR spectrum (CCl_4), δ, ppm : 2.63–2.95 m (4H, SCH_2), 3.42–3.73 m (4H, CH_2Cl), 4.00 t (4H, NCH_2, $^3J_{HH}$ 6 Hz), 4.95 s (2H, $C_6H_5CH_2$), 7.22 m (5H, C_6H_5). Found, %: C 47.68; H 4.81; Cl 17.36; N 10.18; S 8.08. $C_{16}H_{19}Cl_2N_3O_3S$. Calculated, %: C 47.53; H 4.74; Cl 17.54; N 10.39; S 7.93.

1-Benzyl-3,5-bis[2-(2-hydroxyethylthio)ethyl]-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (VII). 2-Mercaptoethanol, 2 g, and 4.3 g of 1-benzyl-3,5-bis-(2-chloroethyl)-1,3,5-triazine-2,4,6(1*H*,31*H*,51*H*)-trione (**XI**) were added to sodium methylate obtained from 0.57 g of sodium in 50 ml of absolute methanol, and the mixture was boiled for 6 h. The precipitate was filtered off, and the filtrate was evaporated in a vacuum. The residue was subjected to column chromatography on silica gel, eluents benzene–ethyl acetate, 5 : 1, and benzene–methanol, 5 : 1, in succession. From the benzene–ethyl acetate fraction we obtained 1 g (19%) of **1-benzyl-3-(2-chloroethyl)-5-[2-(2-hydroxyethylthio)ethyl]-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (XIII)** as a transparent oil. R_f 0.45 (benzene–ethyl acetate, 1 : 1). IR spectrum (thin film), ν, cm^{-1}: 3425 m (OH), 3030 m, 1580 w, 1600 w, 694 s, 670 s (benzene ring), 2906 s, 2940 s (CH), 1740 m, 1680 s (C=O), 1440 s [$\delta(CH_2)$], 1040 m (CO), 750 m (triazine ring). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.53–2.83 m (4H, SCH_2), 3.53–3.73 m (4H, CH_2Cl and CH_2O), 4.00 t (4H, NCH_2, $^3J_{HH}$ 6 Hz), 4.93 s (2H, $C_6H_5CH_2$), 7.18 m (5H, C_6H_5). Found, %: C 50.01; H 5.13; Cl 8.95; N 10.45; S 8.41. $C_{16}H_{20}ClN_3O_4S$. Calculated, %: C 49.80; H 5.22; Cl 9.19; N 10.89; S 8.31.

From the benzene–methanol fraction we isolated 3.15 g (60%) of compound **VII** as an oil that crystallized on standing.

1-Methyl-3,5-bis[2-(2-hydroxyethylthio)ethyl]-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (VIII). 2-Mercaptoethanol, 1.1 g, was added to sodium methylate obtained from 0.31 g of sodium in 40 ml of absolute methanol, and the mixture was stirred for 15 min. The methanol was removed in a vacuum, and the residue was treated with 30 ml of absolute DMF and 1.8 g of 1-methyl-3,5-bis(2-chloroethyl)-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (**XII**). The mixture was stirred for 1 h at 30°C, cooled, the precipitate was filtered off, the DMF was removed in a vacuum, and the residue was subjected to column chromatography in the above-described conditions to isolate 2 g (85%) of compound **VIII** as a transparent thick oil.

1-Benzyl and 1-methyl-3,5-bis[2-(2-mercaptoethoxy)ethyl]-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-triones (IX, X). Equimolar amounts of compound **III** or **IV** and thiourea were boiled in isopropanol for 4–12 h. The alcohol was removed in a vacuum, and the residue was treated with aqueous K_2CO_3, stirred for 90°C (on a water bath) for 2 h, and extracted with methylene chloride. The aqueous layer was acidified with HCl, and extracted with methylene chloride. The extract was dried with $MgSO_4$ and purified on a column of silica gel. Compound **IX**: eluent benzene–ethyl acetate, 10 : 1. Yield 50%, transparent yellowish oil. Compound **X**: eluent benzene–ethyl acetate, 7.5 : 1. Yield 57%, transparent yellowish oil, crystallizes on standing, mp 103–105°C (from benzene).

1-Methyl-3,5-bis(2-chloroethyl)-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (XII) was obtained by treatment with thionyl chloride of 1-methyl 3,5-bis-(2-hydroxyethyl) isocyanurate similarly to compound **XIII** [1]. Yield 56%, mp 114–115°C (from benzene). R_f 0.25 (ether–hexane, 1 : 1). IR spectrum (Vaseline), ν, cm^{-1}: 1750 m, 1665 v.s (C=O), 747 m (triazine ring). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.32 s (3H, CH_3), 3.68 t (4H, CH_2Cl, $^3J_{HH}$ 7 Hz), 4.21 t (4H, NCH_2, $^3J_{HH}$ 6.5 Hz). Found, %: C 35.80; H 4.06; Cl 25.15; N 15.52. $C_8H_{11}Cl_2N_3O_3$. Calculated, %: C 35.84; H 4.14; Cl 25.45; N 15.67.

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