sym-TRIAZINE DERIVATIVES

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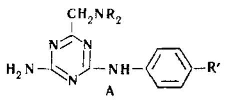
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 1, pp. 154–156, 1969

UDC 547.491.8

A number of potentially biologically active derivatives of sym-triazine are described.

There is much information in the literature indicating the interesting biological properties of some sym-triazine derivatives. Among the substituted aminomethyl-sym-triazines, compounds have been obtained which possess tranquillizing, anti-inflammatory, and analgesic properties [1]. The introduction of appropriate groups into the molecule of sym-triazine has led to compounds with antimalarial [2] or diuretic [3] action: urotropine, khlorazinin, ornidan. In a number of cases the replacement of amino groups of some biologically active substances by a hydrazine residue has led to substances with a more pronounced and prolonged action. Among these there are, in particular, substances stimulating the central nervous system [4].

This information induced us to undertake the synthesis of a number of potentially biologically active derivatives of sym-triazine. In this work we synthesized a number of compounds with the general formula:



A

$R' = H, OCH_3, Cl$

$NR_2 = HNCH_2CH_2OH;$
$N(CH_2CH_2OH)_2;$
$N(CH_2CH_2Cl)_2;$
$N(CH_3)NH_2;$
$NNHC_6H_5$

We started from the chloromethyl-sym-triazines (B) obtained from the corresponding biguanides and ethyl chloroacetate [5]. Compounds **A** with $NR_2 = —NHCH_2CH_2OH$ and $—N(CH_2CH_2OH)_2$ were obtained by the reaction of **B** with mono- and diethanolamine, respectively. The reaction may be carried out both in the amine [1] and in a suitable solvent. To bind the hydrogen chloride liberated, an excess of amine was used. The resulting hydroxyethyl derivatives were subjected to chlorination. In an attempt to carry out chlorination with hydrochloric acid in a sealed tube at 120–140° C, the triazine ring was completely destroyed, and the main reaction product isolated was ammonium chloride. In an attempt to perform chlorination with the aid of phosphorus pentachloride, only resinous products of undetermined composition were isolated. But the reaction of the hydrochloride of **A** $[NR_2 = N(CH_2CH_2OH)_2]$ with an excess of thionyl chloride in the cold or with gentle heating with subsequent decomposition of the thionyl chloride with water or methanol yielded the hydrochloride of the chloroethyl derivative **A** $[NR_2 = N(CH_2CH_2Cl)_2]$.

To obtain hydrazine derivatives, a hot solution of **B** in a suitable solvent (ethanol, dioxane) was added slowly to a solution of a three- to fivefold excess of the corresponding hydrazine in a small amount of the same solvent, and the reaction mixture was stirred at 80–100° C for 2–4 hr. Under these conditions practically no formation of disubstituted or quaternary salts took place. The phenylhydrazine derivatives were yellow and all the other compounds were colorless crystalline substances. The formulas, melting points, and analytical results of the compounds obtained are given in the table.

EXPERIMENTAL

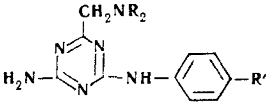
2-Amino-4-(p-chlorophenylamino)-6-(β-hydroxyethylaminomethyl)-sym-triazine III. A mixture of 5.4 g (0.02 mole) of 2-amino-6-chloromethyl-4-(p-chlorophenylamino)-sym-triazine and 15 g (0.25 mole) of ethanolamine was heated in an oil bath with stirring at 100–110° C for 1 hr 30 min and was then cooled and treated with 75 ml of cold water. The oily product that separated was gradually converted on rubbing into a powder. After filtration, washing with water, and drying, 5.1 g of a gray substance was obtained; after crystallization from dioxane, 3.4 g (62%).

2-Amino-6-[bis-(β-hydroxyethyl)aminomethyl]-4-(p-methoxyphenylamino)-sym-triazine (V). A mixture of 9.55 g (0.036 mole) of 2-amino-6-chloromethyl-4-(p-methoxyphenylamino)-sym-triazine, 7.6 g (0.072 mole) of diethanolamine, and 30 ml of n-butanol was heated in the boiling water bath with stirring. The solid matter dissolved, and after 4 hr crystals began to separate. The reaction mixture was stirred with heating for another 1 hr and cooled, after which the precipitate was filtered off, washed with cold n-butanol, dried, and recrystallized from ethanol. Found, %: C 54.28; H 6.78. Calculated for $C_{15}H_{22}N_6O_3$, %: C 54.00; H 6.60.

2-Amino-6-[bis(β-chloroethyl)aminomethyl]-4-(p-methoxyphenylamino)-sym-triazine (VII). With water cooling 1.85 g (0.005 mole) of the hydrochloride of 2-amino-6-[bis(β-hydroxyethyl)aminomethyl]-4-(p-methoxyphenylamino)-sym-triazine was dissolved in 8 ml of thionyl chloride and the solution was heated at 40–50° C for 30 min. The cooled solution was treated in drops with cold water. The product that precipitated was filtered off and crystallized from 10 ml of ethanol to give 1.1 g of product. Found, %: C 44.17; H 5.20. Calculated for $C_{15}H_{21}N_6OCl_3$, %: C 44.20; H 5.16.

2-Amino-4-(p-chlorophenylamino)-6-(α-methylhydrazinomethyl)-sym-triazine (XI). A solution of 5.4 g (0.02 mole) of 2-amino-6-chloromethyl-4-(p-chlorophenylamino)-sym-triazine in 55 ml of hot absolute ethanol was added in drops to a boiling solution of 4.6 g (0.1 mole) of methylhydrazine in 10 ml of absolute ethanol during 30 min, the mixture was stirred at the boil for 2 hr, and the ethanol and excess of methylhydrazine were distilled off in vacuum. The residual clear viscous mass was triturated with 50 ml of water and filtered to give 4.6 g of a white powder. After two crystallizations from dimethylformamide the yield was 3.1 g. Found, %: C 47.26; H 4.73. Calculated for $C_{11}H_{14}N_7Cl$, %: C 47.20; H 5.02.

2-Amino-4-(p-methoxyphenylamino)-6-(phenylhydrazinomethyl)-sym-triazine (XIII). A solution of 3.98 g (0.015 mole) of 2-amino-6-chloromethyl-4-(p-methoxyphenylamino)-sym-triazine and 4.9 g (0.045 mole) of phenylhydrazine in 80 ml of isopropanol was stirred with heating in the boiling water bath. After 30 min, colorless crystals



Compound	NR₂	R′	Mp, °C (solvent)	Empirical formula	N, %		Yield, %
					found	calculated	
I	$HNCH_2CH_2OH$	H	206—208 (dioxane)	$C_{12}H_{16}N_6O$	32.81	32.30	71
II	$HNCH_2CH_2OH$	OCH_3	152—154 (dioxane)	$C_{13}H_{18}N_6O_2$	28.81	29.00	64
III	$HNCH_2CH_2OH$	Cl	152—154 (dioxane)	$C_{12}H_{15}N_6OCl$	28.44	28.50	62
IV	$N(CH_2CH_2OH)_2$	H	121—123 (ethanol)	$C_{14}H_{20}N_6O_2$*	27.81	27.61	69.5
V	$N(CH_2CH_2OH)_2$	OCH_3	159—161	$C_{15}H_{22}N_6O_3$	25.18	25.15	66.6
VI	$N(CH_2CH_2OH)_2$	HCl	159—160 (ethanol)	$C_{14}H_{19}N_6O_2Cl$	25.09	24.80	68
VII	$N(CH_2CH_2OH)_2$	OCH_3	180 (95% ethanol)	$C_{15}H_{21}N_6OCl_3$	20.52	20.60	54
VIII	$N(CH_2CH_2Cl)_2$	Cl	183—184 (95% ethanol)	$C_{14}H_{18}N_6Cl_4$	20.63	20.40	57.5
IX	NCH_3NH_2	H	192—194 (methanol)	$C_{11}H_{15}N_7$	40.09	40.05	57.2
X	NCH_3NH_2	OCH_3	199—201 (dioxane)	$C_{12}H_{17}N_7O$	37.21	37.40	54
XI	NCH_3NH_2	Cl	200—202 (dioxane)	$C_{11}H_{14}N_7Cl$	34.66	35.00	55.4
XII	$HNHNC_6H_5$	H	205—207 (dioxane + + water)	$C_{16}H_{17}N_7$	31.73	31.90	69.4
XIII	$HNHNC_6H_5$	OCH_3	226—227 (dioxane + + water)	$C_{17}H_{19}N_7O$	29.83	29.10	68.3
XIV	$HNHNC_6H_5$	Cl	218—219 (butanol)	$C_{16}H_{16}N_7Cl$	28.48	28.80	72.1

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* Found, %: C 55.63; H 6.37. Calculated, %: C 55.30; H 6.59.

of phenylhydrazine hydrochloride appeared and then yellow crystals separated out. The mixture was stirred with boiling for another 1 hr 30 min and was left at room temperature overnight. On the following day the precipitate was filtered off and was washed with a small amount of isopropanol and then with water until chlorine was absent from the wash-water. After crystallization from a mixture of dioxane and water (3 : 1), 3.46 g of a yellow crystalline substance was obtained. Found, %: C 60.97; H 5.88. Calculated for $C_{17}H_{19}N_7O$, %: C 60.70; H. 5.70.

REFERENCES

1. S. L. Shapiro, E. S. Isaaks, and L. Freedman, J. Org. Chem., **26**, 74, 1961.
2. A. B. Sen and P. G. Singh, J. Ind. Chem. Soc., **38**, 187, 1961.
3. S. L. Shapiro, V. A. Parrino, K. Geiger, S. Kobrin, and L. Freedman, J. Am. Chem. Soc., **79**, 5064, 1957.
4. I. H. Biel, A. E. Drukker, T. F. Mitchell, P. Sprengeler, P. A. Nahfer, A. C. Conweg, and A. Horita, J. Am. Chem. Soc., **81**, 2805, 1959.
5. Organic Syntheses, Vol. 10 [Russian translation], 5.

13 February 1966

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