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SYNTHESIS AND MUTAGENIC PROPERTIES OF 6-CHLOROMETHYL, CYANOMETHYL, AND β-AMINOETHYL DERIVATIVES OF 1,3,5-TRIAZINES

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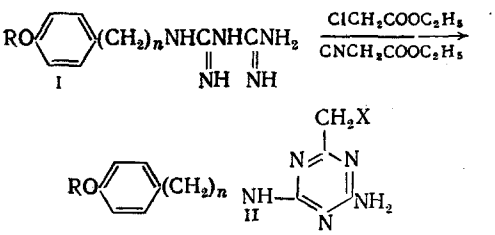
UDC 615.31:547.873

The available literature data show some interesting biological properties of symm-triazine derivatives. Some diamino-symm-triazines exhibit antipyretic, vasodilatory, antiviral, diuretic, and hypoglycemic activity [1-3].

We prepared some substituted diamino-symm-triazines based on biguanidines reported earlier [4, 5] in order to study their biological properties.

It is known that acidic reagents can cyclize biguanidines to 1,3,5-triazines. It was, therefore, of some interest to study the chemical behavior of the starting biguanidines (I) in the condensation reactions with chloroacetic and cyanoacetic esters.

For the cyclization of biguanidines with chloroacetic ester we took into account the fact that a similar reaction takes place in low-boiling alcohols with the use of alcoholates of alkaline metals [6]. This synthesis was accomplished in methanol in the presence of sodium methylate as catalyst according to the following scheme:

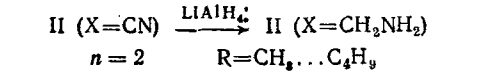


R=CH_3,..., iso-C_4H_9; $n = 1, 2$; X=Cl, CH.

The structure II (X = Cl) was confirmed by mass spectroscopy (see Fig. 1a). The spectrum of II where R = CH_3, n = 1, X = Cl shows an intensive peak of the molecular ion (M^+ 279) and ion peaks at 243, 161, 147, 136, 121, and 77.

Triazines II where X = CN were prepared by cyclizing biguanidine I with cyanoacetic ester in methanol on prolong keeping. The compounds (X = CN) are obtained as colorless stable crystals. The mass spectra of II where X = CN and R = CH_3, n = 1 and R = C_2H_5, and n = 2 showed peaks corresponding to the molecular ions together with the characteristic fragmentation pattern (see Fig. 1b, c).

The reduction of the cyano group in triazines II (X = CN) with lithium aluminum hydride in ether did not take place apparently due to a low solubility of the starting nitriles in absolute ether. Better results were obtained when tetrahydrofuran was used as a solvent.



Amines II were treated with an ether solution of hydrogen chloride to give the corresponding hydrochlorides. The hydrochlorides were hygroscopic. The mutagenic activity of triazines II was studied using biochemical mutants: *Escherichia coli* P678 for threonine, leucine, and

*Deceased.

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 11, No. 12, pp. 35-39, December, 1977. Original article submitted June 27, 1977.

0091-150X/77/1112-1617$07.50

TABLE 1. Mutagenic and Lethal Properties of Triazine Derivatives II

R	n	X	Dosage		E. coli P=678 (Thr⁻→Thr⁺)			Dosage		Act. rimosus (Lys⁻→Lys+)		
			M	time, h	survival, %	frequency of inverted products occurrence		M	time, h	survival, %	frequency of inverted products occurrence	
						abs.	%				abs.	%
CH_3	1	CH_2Cl	0,1	4	0,03	6 825	97 500	0,1	24	40	20	500
C_2H_5	1	CH_2Cl	0,1	1	0,34	2 702	28 600	0,2	24	10	172	4 300
C_2H_5	1	CH_2CN	0,1	0,5	1	1 000	14 300	0,2	24	0,7	428	10 700
CH_3	2	CH_2Cl	0,2	1	17	26	370	0,2	24	12	116	2 900
C_2H_5	2	CH_2Cl	0,1	4	0,4	1 750	25 000	0,2	24	8,3	48	1 200
CH_3	2	CH_2CN	0,1	2	0,24	2 380	34 000	0,2	24	23	16	400
CH_3	2	CH_2NH_2	0,05	0,5	0,4	20	280	0,2	24	7,4	110	1 000
C_2H_5	2	CH_2NH_2	0,01	1	0,3	8 155	116 500	0,1	0,5	0,74	384	9 600
Control (spontaneous mutation)			—	1	100	7	100	—	24	100	4	100
ethylenimine			0,1	20	0,1	2769	39 550	0,1	30	1,0	1215	30 400

Note. Values given as percent relative to the control.

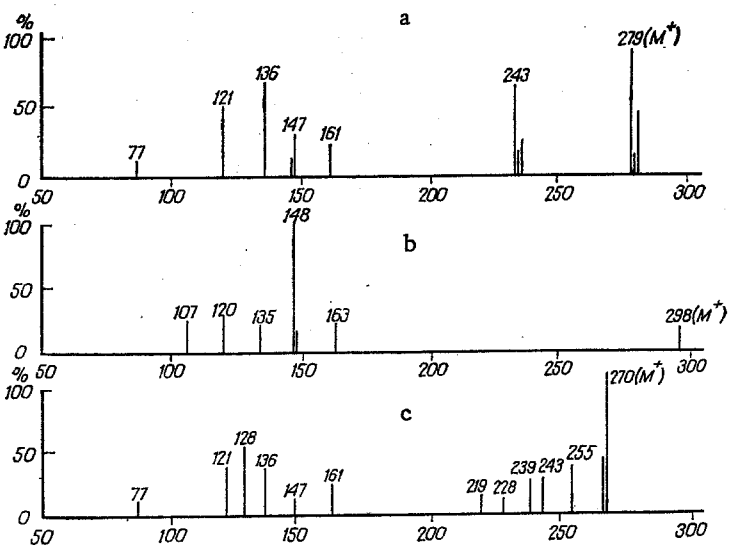


Fig. 1. Mass spectra of compounds II.

vitamin B_1 and *Actinomyces rimosus* 222 for lysine. The mutagenic activity was determined from the frequency with which the induced inversion of oxotropic to prototropic configuration, responsible for the threonine and lysine amino acid synthesis, occurred. The method of studying the mutagenic activity and the lethal action of the compounds was described earlier [7]. Table 1 shows results with compounds that exhibited notable mutagenic properties.

The most active of the compounds studied were triazines II (R = CH_3, n = 1, X = Cl) and II (R = C_2H_5, n = 2, X = CH_2NH_2), that induced the reverse mutation along the threonine locus that was 975- and 1165-fold larger, respectively, than that of the control.

EXPERIMENTAL

Chemical

The TLC analyses were carried out on Silufol UV 254 plates in the ether–ethanol (2:1) system, and the plates developed with iodine vapors. The melting point values of all the compounds were determined using a Boetius bench. The MX-1303 instrument with the direct introduction probe using the energy of ionization 50 eV and with the inlet temperature about 20-30°C lower than the melting point of the compound studied recorded the mass spectra.

TABLE 2. Triazine Derivatives II

R	n	Yield, %	mp, °C	R_f	Found, %				Empirical formula	Calculated, %			
					C	H	N	Cl		C	H	N	Cl
							X=Cl						
CH_3	1	74,1	122—5	0,64	51,25	5,48	24,49	12,61	$C_{12}H_{14}N_5OCl$	51,52	5,42	25,03	12,67
C_2H_5	1	83,3	134—5	0,67	53,54	5,32	23,68	12,40	$C_{13}H_{16}N_5OCl$	53,33	5,16	23,92	12,11
C_3H_7	1	72,2	137—8	0,67	54,38	5,63	22,85	11,77	$C_{14}H_{18}N_5OCl$	54,63	5,89	22,70	11,51
Iso-C_3H_7	1	71,4	139—40	0,68	54,81	5,77	22,42	11,19	$Cl_{14}H_{18}N_5OCl$	54,63	5,89	22,70	11,51
C_4H_9	1	83,3	150—2	0,69	56,09	5,91	22,05	10,82	$C_{15}H_{20}N_5OCl$	55,98	6,02	21,79	11,01
Iso-C_4H_9	1	69,14	147—8	0,71	56,21	6,29	22,38	10,93	$C_{15}H_{20}N_5OCl$	55,98	6,02	21,79	11,01
CH_3	2	68,3	103—5	0,63	53,47	5,20	23,71	12,26	$C_{13}H_{16}N_5OCl$	53,33	5,16	23,92	12,11
C_2H_5	2	63,2	119—21	0,65	54,38	5,63	22,85	11,77	$C_{14}H_{18}N_5OCl$	54,63	5,89	22,70	11,51
C_3H_7	2	79,3	128—30	0,67	55,69	5,97	21,48	11,15	$C_{15}H_{20}N_5OCl$	55,98	6,02	21,79	11,01
Iso-C_3H_7	2	61,1	125—7	0,68	56,07	6,23	21,93	10,78	$C_{15}H_{20}N_5OCl$	55,98	6,02	21,79	11,01
C_4H_9	2	75,3	146—8	0,69	57,48	6,83	20,59	10,83	$C_{16}H_{22}N_5OCl$	57,21	6,60	20,84	10,56
Iso-C_4H_9	2	58,4	151—3	0,70	57,34	6,41	20,98	10,34	$C_{16}H_{22}N_5OCl$	57,21	6,60	20,84	10,56
							X=CN						
CH_3	1	73,2	172—4	0,49	57,48	4,98	30,81		$C_{13}H_{14}N_6O$	57,76	5,22	31,09	
C_2H_5	1	68,4	149—51	0,55	59,37	5,38	29,77		$C_{14}H_{16}N_6O$	59,14	5,67	29,56	
C_3H_7	1	63,3	152	0,56	60,59	5,82	28,42		$C_{15}H_{18}N_6O$	60,38	6,08	28,17	
Iso-C_3H_7	1	71,1	168—70	0,58	60,43	6,27	27,88		$C_{15}H_{18}N_6O$	60,38	6,08	28,17	
C_4H_9	1	66,3	135—7	0,61	61,90	6,71	26,63		$C_{16}H_{20}N_6O$	61,51	6,45	26,90	
Iso-C_4H_9	1	65,9	133—4	0,62	61,82	6,62	27,08		$C_{16}H_{20}N_6O$	61,51	6,45	26,90	
CH_3	2	68,3	110—3	0,61	58,83	4,98	29,25		$C_{14}H_{16}N_6O$	59,14	5,67	29,56	
C_2H_5	2	79,2	130—1	0,63	59,9	6,05	28,08		$C_{15}H_{18}N_6O$	60,38	6,08	28,17	
C_3H_7	2	63,8	139—41	0,64	61,24	6,13	26,78		$C_{16}H_{20}N_6O$	61,51	6,45	26,90	
Iso-C_3H_7	2	54,9	134—6	0,66	61,38	6,94	26,80		$C_{16}H_{20}N_6O$	61,51	6,45	26,90	
C_4H_9	2	80,1	150—2	0,68	62,48	7,06	25,63		$C_{17}H_{20}N_6O$	62,58	6,79	25,44	
Iso-C_4H_9	2	72,7	158—60	0,69	62,26	7,00	25,08		$C_{17}H_{20}N_6O$	62,58	6,79	25,44	
							$X=CH_2NH_2$						
CH_3*	2	48,3	168—70		57,88	7,13	29,56		$C_{14}H_{20}N_6O$	58,29	6,99	29,15	
C_2H_5	2	42,2	196—8		59,34	7,49	27,86		$C_{15}H_{22}N_6O$	59,60	7,33	27,80	
C_3H_7 †	2	37,2	220—2		60,61	7,93	26,88		$C_{16}H_{24}N_6O$	60,73	7,64	26,57	
C_4H_9 ‡	2	35,4	233—4		61,47	8,22	25,73		$C_{17}H_{26}N_6O$	61,80	7,93	25,45	

*Hydrochloride: mp 202-204°C. Found, %: Cl 10.79. Calculated, %: Cl 10.91.

†Hydrochloride: mp 243-245°C. Found, %: Cl 10.08. Calculated, %: Cl 10.46.

‡Hydrochlorides are hygroscopic.

2-(4-Alkoxybenzylamino- or Phenethylamino)-4-amino-6-chloromethyl-1,3,5-triazines (II, X = Cl). The alcoholate prepared from sodium (3 g, 0.16 mole) and absolute methanol (20 ml) was cooled to −70°C and methyl chloroacetate (2.7 g, 0.025 mole) was added dropwise with stirring. Compound I (0.025 mole) was then added, the mixture was stirred till it warmed up to room temperature and then left standing for another 5 h. The precipitate was filtered off and recrystallized from ethanol (Table 2).

2-(4-Alkoxybenzylamino- or Phenethylamino)-4-amino-6-cyanomethyl-1,3,5-triazines (II, X = CN). A solution of I (0.03 mole) and ethyl cyanoacetate (3.5 g, 0.03 mole) in methanol (25 ml) was left standing at room temperature for 35 h. The precipitate was filtered off and recrystallized from water (see Table 2).

2-(4-Alkoxyphenethylamino)-4-amino-6-β-aminoethyl-1,3,5-triazines (II, X = CH_2NH_2). To a mixture of lithium aluminum hydride (3.8 g, 0.1 mole) in tetrahydrofuran (100 ml) was added dropwise with stirring a solution of II (X = CN, n = 2) (17 g, 0.06 mole) in tetrahydrofuran (100 ml). The mixture was heated on a water bath for 30 h, and 40% sodium hydroxide solution (50 ml) was then added dropwise. The ether layer was separated, the solvent was evaporated, and the residue was recrystallized from ethanol (see Table 2).

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SYNTHESIS AND THE BACTERIOCIDAL ACTIVITY OF FERROCENYLAMINOMETHYLPHOSPHONATES

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UDC 615.28:547.558.1

Organophosphorous compounds are widely used as insecticides. However, the physiological activity of these compounds is far from limited just to the insecticidal action. Organophosphorous compounds having herbicidal and fungicidal activity have been prepared and also used in both veterinary and medical practice [1]. Of particular interest is the possibility of obtaining bacteriocidal aminoalkyl organophosphorous compounds, the biological activity of which has not been studied much. The low toxicity of the aminoalkylphosphonic acids and their esters towards warm-blooded animals makes them particularly suitable for use as bacteriocidal agents [2].

In this work, we prepared and studied the bacteriocidal activity of a group of new organophosphorous compounds, i.e., ferrocenylaminomethylphosphonates. The synthesis of 22 compounds of this type was comparatively easy; they were prepared by condensing the readily available formyl- and acetylferrocenes with the phosphorous acid dialkylesters in the presence of various primary and secondary amines. The reaction was carried out by keeping the reaction mixture, containing equimolar quantities of the aldehyde or ketone, phosphorous acid dialkyl ester, and the amine for 7-10 days at room temperature. The corresponding ferrocenylaminomethylphosphonates are obtained under these conditions in quantitative yields. With heating, the yields of the expected compounds decreased considerably and a large quantity of resinous product formed instead.

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 11, No. 12, pp. 39-43, December, 1977. Original article submitted June 20, 1977.

0091-150X/77/1112-1620$07.50