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SYNTHESIS OF ACYLATED (2'-HYDROXYETHYL)AMINO- AND (2'-AMINOETHYL)AMINO-1,3,5-TRIAZINES

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UDC 547.873:542.951

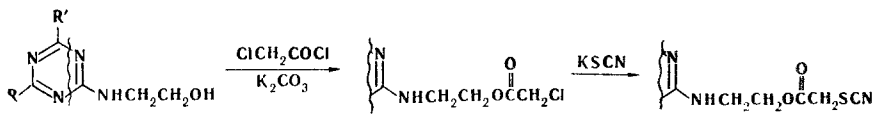
The acylation of (2'-hydroxyethyl)amino-1,3,5-triazines with chloroacetyl chloride with subsequent reaction of the resulting (2'-chloroacetoxyethyl)aminotriazines with potassium thiocyanate is described. Acylated derivatives of substituted (2'-aminoethyl)aminotriazines were obtained by the reaction of the chlorotriazines with monoacylethylenediamines.

1,3,5-Triazines are finding wide application as herbicides. The disadvantages of this class of compounds include their high persistence in environmental objects and the low selectivity of their herbicidal action. The introduction of labile (2'-hydroxyethyl)amino and (2'-aminoethyl)amino groupings in the triazine molecule makes it possible to obtain compounds that have selectivity with respect to their action and more rapid detoxication in the soil and plants.

In order to obtain biologically active compounds and in a continuation of our earlier research [1, 2] on the chemical behavior of (2'-hydroxyethyl)amino- and (2'-aminoethyl)aminotriazines in reactions with electrophilic reagents we accomplished the synthesis of their acylated derivatives.

Chloroacetyl chloride was used as the acylating agent in reactions with (2'-hydroxyethyl)-aminotriazines (I). (2'-Chloroacetoxyethyl)amino-1,3,5-triazines (II) were obtained by the reaction of triazines I with chloroacetyl chloride in acetone in the presence of potassium carbonate.

Starting triazines I contain two reaction centers that are capable of undergoing acylation, viz., the NH and OH groups.



I a-i II a-i III a-d, f

I a-h, II a-h, III a-d, f R=Cl; I i, II i R=OCH_3; I—III a R'=NHC_2H_5; b R'=NHC_3H_7-*n*; c R'=NHC_4H_9-*i*; d R'=NHC_6H_{13}-*n*; e R'=$NHC_{12}H_{25}$-*n*; f R'=$NHCH_2CH{=}CH_2$; g R'=OC_2H_5; h R'=SCH_3; i R'=NHC_3H_7-*i*

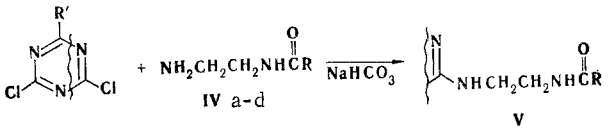
The absence in the IR spectra of II of an absorption band of an OH group and the presence of an absorption band of an ester carbonyl group at 1740-1750 cm^{-1}, as well as the absence in the PMR spectra of signals of one or two NH protons (depending on substituent R') at 6-7.8 ppm, confirm that acylation takes place at the OH group. A comparision of data from the PMR spectra of II with the data in [3] makes it possible to conclude that the acyl chloride chlorine atom participates in acylation. The triplet of the most characteristic $CH_2OC(O)$ group in the investigated compounds appears at 4.2-4.3 ppm, while the singlet of the $ClCH_2$ group is observed at 4.2 ppm.

All-Union Scientific-Research Institute of Chemical Agents for the Protection of Plants, Moscow 109088. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 260-263, February, 1982. Original article submitted February 11, 1981.

The presence of an active chlorine atom in II makes it possible to subject them to some nucleophilic substitution reactions. Thus the corresponding (2'-thiocyanoacetoxyethyl)amino-1,3,5-triazines (III) were obtained by the reaction of II with potassium thiocyanate.

An absorption band of a CO group is observed in the IR spectra of III at 1740-1760 cm^{-1}, while the NCS group shows up in the form of a narrow band of medium intensity at 2160 cm^{-1}, which is in agreement with the data in [4]. A triplet of $CH_2OC(O)$ group at 4.16-4.37 ppm, a singlet of a CH_2SCN group at 4.0 ppm, and a multiplet of CH_2N protons of the $HNCH_2CH_2OC(O)$ fragment at 3.26-3.86 ppm are present in the PMR spectra of III.

In contrast to triazines I, monosubstituted triazinylethylenediamines cannot be obtained. Some of us have previously shown [5] that substituted chlorotriazines react with ethylenediamine to give bis(triazinyl)ethylenediamines even when a large excess of ethylenediamine is present. For (2'-acylaminoethyl)amino-1,3,5-triazines (V) we therefore selected a method that consists in the reaction of substituted chlorotriazines with monoacylethylenediamines (IV), the synthesis of which was realized by the method in [6] extended to esters of propionic, butyric, and benzoic acids. The acylation of a fourfold amount of ethylenediamine with ethyl esters of carboxylic acids takes place at room temperature in periods ranging from a few hours to a few weeks, depending on the acylating agent used; diacylethylenediamines are formed in up to 40% yields in this case. Heating also leads to an increase in the yields of disubstitution products.



IV a R=CH_3; b R=C_2H_5; c R=p-C_3H_7; d R=C_6H_5; V a-g, R=C_2H_5; h-k R=p-C_3H_7; *l* R=C_6H_5; a R'=NHC_3H_7-*i*; b, i R'=NHC_4H_9-p; c R'=NHC_4H_9-*t*; d R'=$NHCH_2CH{=}CH_2$; e R'=NHC_6H_{13}-p; f, j R'=$N(CH_3)_2$; g, k R'=$N(C_2H_5)_2$; h R'=NH_2; *l* R'=$NHCH_3$

The reaction of the chlorotriazines with monoacylethylenediamines IV takes place in acetone at 40-50°C in the presence of sodium bicarbonate as the hydrogen chloride acceptor.

In addition to absorption bands of the starting chlorotriazines (triazine ring at 800, 1400-1600 cm^{-1}, 3440-3460 cm^{-1} and 3250-3260 cm^{-1} for free and associated NH), an absorption band of a C=O group at 1630-1650 cm^{-1} is observed in the IR spectra of V. In the PMR spectra of V the methylene protons of the $HNCH_2CH_2NHC(O)$ fragment show up in the form of a broad multiplet at 3.07-3.56 ppm, while the signals of the NH protons show up in the form of a broad multiplet at 7.0-7.9 ppm. The integral intensities in all cases correspond to the numbers of protons of the substituting groups.

EXPERIMENTAL

The IR spectra of KBr pellets and solutions in CCl_4 (c ~ 0.01%) were obtained with a Perkin-Elmer 577 spectrometer. The PMR spectra of solutions of the compounds in DMSO and $(CD_3)_2CO$ were recorded with an FT-80A spectrometer (80 MHz) with tetramethylsilane as the internal standard. The purity of the compounds was verified by chromatography on Silufol plates in a hexane–acetone system (4:1) with Bromphenol blue as the developer.

2-Chloro-4-alkylamino-6-(2'-chloroacetoxyethyl)amino-1,3,5-triazines (IIa-i, Table 1). A 0.015-mole sample of chloroacetyl chloride was added dropwise at 25°C in the course of 20 min to a solution of 0.015 mole of I in 40 ml of acetone, after which 0.015 mole of freshly calcined K_2CO_3 was added, and the mixture was maintained at 40-45°C for 2 h. The completion of the reaction was monitored by chromatography. The precipitate was removed by filtration, the acetone solution was diluted to twice its original volume with water, and the precipitated crystals were removed by filtration and dried. If an oil was liberated when the mixture was diluted with water, it was extracted with methylene chloride or chloroform, the solvent was removed by distillation, and the product began to crystallize when the residue was cooled. The product was purified by recrystallization from absolute ethanol. The products were obtained in 60-80% yields.

2-Chloro-4-alkylamino-6-(2'-thiocyanoacetoxyethyl)amino-1,3,5-triazines (IIIa-d,f, Table 1). A solution of 0.01 mole of KSCN in 10 ml of acetone was added dropwise at 20°C in

TABLE 1. (2'-Acyloxyethyl)amino-1,3,5-triazines

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		Cl	N	S		Cl	N	S	
IIa	165—166	24,6	24,3	—	$C_9H_{13}Cl_2N_5O_2$	24,1	23,8	—	80
IIb	167—168	22,6	23,2	—	$C_{10}H_{15}Cl_2N_5O_2$	23,0	22,7	—	75
IIc	144—145	22,2	21,9	—	$C_{11}H_{17}Cl_2N_5O_2$	22,0	21,7	—	80
IId	239—240	19,8	20,1	—	$C_{13}H_{21}Cl_2N_5O_2$	20,2	20,0	—	68
IIe	183—184	16,3	16,2	—	$C_{19}H_{33}Cl_2N_5O_2$	16,3	16,1	—	70
IIf	184—185	23,1	23,5	—	$C_{10}H_{13}Cl_2N_5O_2$	23,2	23,0	—	83
IIg	115—116	24,6	18,6	—	$C_9H_{12}Cl_2N_4O_3$	24,1	19,1	—	65
IIh	74—75	24,2	18,4	11,2	$C_8H_{10}Cl_2N_4O_2S$	23,8	18,9	10,8	60
IIi	88—89	12,1	23,8	—	$C_{11}H_{18}ClN_5O_3$	11,6	23,4	—	63
IIIa	150—151	11,0	26,5	10,2	$C_{10}H_{13}ClN_6O_2S$	11,2	26,5	10,1	92
IIIb	134—135	10,3	25,0	10,0	$C_{11}H_{15}ClN_6O_2S$	10,7	25,4	9,7	82
IIIc	167—168	10,1	24,3	9,3	$C_{12}H_{17}ClN_6O_2S$	10,3	24,4	9,3	89
IId	178—179	9,8	22,2	9,0	$C_{14}H_{21}ClN_6O_2S$	9,5	22,5	8,6	68
IIIf	142—143	11,3	25,5	9,5	$C_{11}H_{13}ClN_6O_2S$	10,8	25,6	9,8	78

TABLE 2. Monoacylethylenediamines

Compound	bp, °C (hPa)	n_D^{20}	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IVa*	130—135 (13)	1,4825	46,7	10,3	28,0	$C_4H_{10}N_2O$	47,1	9,9	27,5	70
IVb	153—154 (33)	1,4775	51,8	10,5	24,5	$C_5H_{12}N_2O$	52,1	10,0	24,1	76
IVc	156—157 (27)	1,4755	55,2	10,6	21,7	$C_6H_{14}N_2O$	55,5	10,8	21,5	60
IVd	150—160 (1)†	—	66,6	7,8	17,4	$C_9H_{12}N_2O \cdot H_2O$	66,2	7,3	17,0	42

*According to [6], this compound had bp 125-130°C (5 mm).
†This compound had mp 135-137°C.

TABLE 3. 2-Chloro-4-alkyl(dialkyl)amino-6-(2'-acylaminoethyl)-amino-1,3,5-triazines

Compound	mp, °C	Found, %		Empirical formula	Calc., %		Yield, %
		Cl	N		Cl	N	
Va	109—110	11,9	28,9	$C_{11}H_{19}ClN_6O$	12,4	29,3	70
Vb	209—210	12,1	28,4	$C_{12}H_{21}ClN_6O$	11,8	27,9	76
Vc	120—122	11,3	27,6	$C_{12}H_{21}ClN_6O$	11,8	27,9	71
Vd	204—205	12,2	30,0	$C_{11}H_{17}ClN_6O$	12,5	29,6	73
Ve	100—101	11,0	25,1	$C_{14}H_{25}ClN_6O$	10,8	25,6	76
Vf	168—169	13,5	31,4	$C_{10}H_{17}ClN_6O$	13,0	31,0	74
Vg	116—118	12,2	28,4	$C_{12}H_{21}ClN_6O$	11,8	27,9	78
Vh	174—175	14,1	32,0	$C_9H_{15}ClN_6O$	13,7	32,5	71
Vi	200—201	11,7	26,2	$C_{13}H_{23}ClN_6O$	11,3	26,7	78
Vj	194—195	11,8	28,9	$C_{11}H_{19}ClN_6O$	12,4	29,3	68
Vk	189—190	10,9	27,0	$C_{13}H_{23}ClN_6O$	11,3	26,7	71
Vl	183—184	12,0	28,0	$C_{13}H_{15}ClN_6O$	11,6	27,5	60

the course of 15 min to a solution or suspension of 0.01 mole of II in 30 ml of acetone, and the reaction mixture was maintained at 35-40°C for 6-7 h with chromatographic monitoring of the course of the reaction. The resulting precipitate was removed by filtration, the filtrate was evaporated, and the crystalline product was recrystallized from absolute ethanol. The products were obtained in 68-92% yields.

Monoacylethylenediamines (IVa-d, Table 2). A 4-mole sample of a 70% aqueous solution of ethylenediamine was mixed at 20°C with 1 mole of ethyl carboxylate. The reaction was considered to be complete when the solution became homogeneous (5-6 h for the reaction with ethyl acetate and 2 weeks for the reaction with ethyl butyrate). The reaction mixture was distilled *in vacuo* (water aspirator).

2-Chloro-4-alkyl(dialkyl)amino-6-(2'-acylaminoethyl)amino-1,3,5-triazines (Va-l, Table 3). A solution of 0.015 mole of N-acylethylenediamine in 15 ml of acetone was added at 15-20°C in the course of 30 min to a solution of 0.015 mole of 2-alkyl(dialkyl)amino-4,6-dichloro-1,3,5-triazine in 40 ml of acetone, and the mixture was stirred at ~20°C for 15-20 min, after which it was treated with an aqueous solution of 0.015 mole of $NaHCO_3$ at such a rate that the

pH did not exceed eight. It was then maintained at 45-50°C for 5-7 h, after which it was cooled and diluted with water, and the resulting crystals were separated, dried, and recrystallized from methanol (Vd, i, j), absolute ethanol (Vb, f, g, h, l), and ethanol–hexane (1:3) (Va, c, e, k).

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TETRAZOLES.

11.* ACIDITIES OF TETRAZOLYLACETIC ACIDS

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UDC 547.796.1

The acidities of two series of substituted 1- and 2-tetrazolylacetic acids, as well as some 1- and 2-substituted 5-tetrazolylacetic acids, in water and 50% ethanol were investigated. All of the investigated compounds are stronger acids than acetic acid and are comparable to haloacetic acids. The induction constants (σ_I) of the 1-, 2-, and 5-tetrazolyl groups (0.65, 0.62, and 0.41, respectively) were calculated from data on the acidities of tetrazolylacetic acids.

Tetrazolylacetic acids are used to obtain new semisynthetic antibiotics [2], growth regulators, and chemical agents for the protection of plants [3, 4], whereas very little information regarding the reactivities and acid-base properties of these compounds is available. In this connection we studied the acidities of a series of tetrazolylacetic acids and calculated the induction constants (σ_I) of the tetrazolyl group.

A σ_I value of 0.57 was previously found for the 1-tetrazolyl group from data on the basicities of m- and p-(1-tetrazolyl)dimethylanilines [5]. However, the calculation of the σ_I substituent induction constants by estimating the reactivities of aromatic compounds entails a number of assumptions [6, 7]. The method for the determination of the σ_I substituent induction constants in which aliphatic carboxylic acids of the XCH_2COOH type, for which the dependence $\sigma_I = -0.251\ pK_a + 1.186$ (1) with correlation coefficient 0.99 is observed for a large number of substituents, is more valid [8].

In conformity with this the σ_I induction constants of the tetrazolyl group can be calculated from the pK_a values of isomeric tetrazolylacetic acids. For this, we studied the acidities of 1-, 2-, and 5-tetrazolylacetic acids in water and calculated the σ_I constants by means of Eq. (1) (Table 1). It is apparent that the σ_I values for the 1-tetrazolyl group found by various methods agree satisfactorily. The dissociation constants of 1- and 2-tetrazolylacetic acids differ only slightly, whereas 5-tetrazolylacetic acid is weaker; this once again confirms the data in [9] regarding the weak aromatic character of the tetrazole ring.

*See [1] for communication 10.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 264-266, February, 1982. Original article submitted March 10, 1981.

0009-3122/82/1802-0208$07.50