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PREPARATION OF SOME SUBSTITUTED 1,2,4-TRIAZINES

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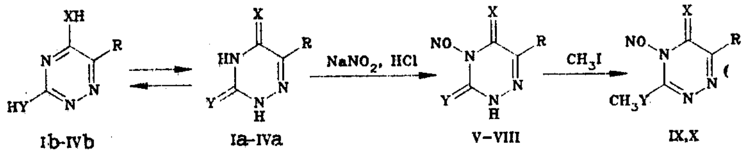
By nitrosating 6-R-1,2,4-triazine-3,5-diones(thiones) the corresponding 4-nitroso derivatives are obtained. On reacting methyl iodide with 3-thio-4-nitroso-6-R-1,2,4-triazin-5-ones their methyl analogs are obtained. The influence of structural factors on the course of the reactions has been examined.

Interest in the chemistry of 1,2,4-triazines has been stimulated by the possibility of obtaining compounds possessing biological activity. Certain 4-substituted 1,2,4-triazin-5-ones [1], obtained by condensation of α-dicarbonyl compounds with thiocarbohydrazides [1, 2] or of hydrazine with acylhydrazones of glyoxylic acid esters [3], have found application as herbicides. Utilization of reactions for replacement of hydrogen in the triazine ring in preparing 4-substituted 1,2,4-triazin-5-ones has been little investigated except for methylation of 1,2,4-triazine-3,5-diones (thiones) by various reagents [4].

The aim of the present work was to investigate the nitrosation of 1,2,4-triazine-3,5-diones(thiones) for synthesis of the 4-nitroso derivatives.

The starting compounds — 3-thio-6-tert-butyl-1,2,4-triazin-5-one (I), 3-thio-6-phenyl-1,2,4-triazin-5-one (II), 6-phenyl-1,2,4-triazine-3,5-dione (III), and 6-phenyl-1,2,4-triazine-3,5-dithione (IV) — were synthesized according to [5, 6]. The products were identified from the data of elemental analysis and IR spectroscopy.

On nitrosation of compounds I-IV with sodium nitrite in an acid medium, the 4-nitroso-6-R-1,2,4-triazine-3,5-diones(thiones) (V-VIII) were obtained respectively.



I—III, V—VII, IX, X X=O, IV, VIII X=S; I, II, IV—VI, VIII Y=S, III, VII Y=O, IX, X Y=$-SCH_3$; I, V, IX R=$-C(CH_3)_3$, II—IV, VI—VIII, X R=$-C_6H_5$

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TABLE 1. Spectral Properties of Compounds V-X

Compound	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm
V	1200 (C=S), 1675 (C=O), 1485 ((N—N=O), 3408 (N_2—H)	1,32 s, $C(CH_3)_3$], 13—14 [s, SH (0,5H), s, NH (0,5H)]
VI	1185 (C=S), 1620 (C=O), 1500 (N—N=O), 3430 (N_2—H)	7,27—7,78 (m, Ar), 10,72—11,04 [s, SH (0,5H), s, NH (0,5H)]
VII	1680, 1720 (C=O), 1490 (N—N=O), 3410 (N_2—H)	7,38—7,78 (m, Ar), 12,2 s NH)
VIII	1190, 1240 (C=S), 1490 (N—N=O), 3415 (N_2—H)	7,33—7,78 (m, Ar), 11,96—12,3 [s, SH (0,5H), s, NH (0,5H)]
IX	1680 (C=O), 1350 (CH_3—S), 1480 (N—N=O)	1,28 [s, $C(CH_3)_3$], 2,47 (s, CH_3S)
X	1620 (C=O), 1355 (CH_3S), 1495 (N—N=O)	

TABLE 2. Properties of Compounds V-X

Compound	mp, °C (decomp.)	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	N	S		C	H	N	S	
V	235—250	39,4	4,8	26,3	15,1	$C_7H_{10}N_4O_2S$	39,3	4,7	26,1	14,9	57
VI	183—210	46,2	2,5	23,8	13,6	$C_9H_6N_4O_2S$	46,1	2,6	23,9	13,7	72
VII	238—252	49,8	2,8	25,5	—	$C_9H_6N_4O_3$	49,6	2,7	25,7	—	63
VIII	168—186	43,1	2,4	22,5	25,7	$C_9H_6N_4OS_2$	43,2	2,4	22,4	25,6	56
IX	182—215	41,9	5,4	24,6	14,2	$C_8H_{12}N_4O_2S$	42,1	5,3	24,5	14,1	92
X	192—221	43,5	3,4	22,8	13,1	$C_{10}H_8N_4O_2S$	48,4	3,3	22,6	12,9	94

It is known [7] that in neutral and acid media the equilibrium Ia,b—IVa,b is strongly displaced towards the a form. The nitrosation reaction in this case, like the nitrosation of mixed amides, leads to the formation of N-nitrosamines. Derivation of 4-nitroso-6-R-1,2,4-triazine-3,5-diones(thiones) (I-IV), and not a mixture of 4- and 2-nitroso-substituted 1,2,4-triazines, is evidently caused by the greater reactivity of the N-4 atom in the triazine ring in combination with the kinetic control for product formation. Since the active nitrosating agent (N_2O_3) is electrophilic, a greater reactivity is to be expected for the nitrogen atom having a greater π-electron density value. Calculations of π-electron density [8] show that for the N_4 atom of 1,2,4-triazine-3,5-diones(thiones) this value is always higher than that for the N_2 atom in the triazone ring. Thus, the direction of substitution in the triazine ring on nitrosation, under the experimental conditions adopted, corresponds to the expected. The data from IR spectroscopy confirm the structure of the synthesized compounds. In all the spectra distinctive absorption bands of ν(N—N=O) at 1480-1580 cm^{-1} are observed. In the spectrum of compound V the N_4—H band at 3380 cm^{-1}, which is present in initial compound I, is absent, but the ν(N_2—H) absorption band at 3408 cm^{-1} remains. Assignment of the N_4—H and N_2—H absorption bands (Table 1) was carried out in accordance with the data in the literature for 1,2,4-triazine-3,5-diones(thiones) [9].

The causes of the stability of the substituents (especially sulfur) in 1,2,4-triazines in the presence of the strong oxidizing agents HNO_2 and N_2O_3, present a certain interest. It is possible that the acid medium, by further displacing the tautomeric equilibrium Ia,b—IVa,b towards a, plays the role of protecting agent, owing to the lower susceptibility to oxidation of thione groups in comparison with —SH groups and particularly $—S^-$ anions.

In view of the practical importance of 3-methylmercapto-4-substituted 6-R-1,2,4-triazin-5-ones, we conducted the methylation of compounds V and VI using methyl iodide in an aqueous alcoholic solution of alkali. Compounds IX and X obtained were, in fact, 3-methylmercapto-4-nitroso-absorption bands of ν(C=S) at 1185-1200 cm^{-1}, which are present in the spectrum of compounds V and VI, are absent, and ν(CH_3—S) absorption bands at 1350-1355 cm^{-1} appear. The N—CH_3 absorption bands at 2800-2990 cm^{-1}[9] are absent, and the N_2H band, characteristic of compounds V and VI, have disappeared. Unlike the methylation of 3-thio-6-R-1,2,4-triazin-5-ones, which gives, under the experimental conditions adopted, a mixture of 3-methylmercapto and N_2-methyl derivatives (the small quantity of the 2-methyl derivative, determined by PMR, amounts to a few percent [10]), the methylation of 3-thio-4-nitroso-6-R-1,2,4-triazin-5-ones gives the 3-methylmercapto derivative of 1,2,4-triazine. The greater reactivity of the —SH group compared to N_2—H in the methylation reactions with CH_3I in aqueous alcoholic alkali can be explained by the greater nucleophilicity of the $-S^-$ anion, formed in an alkali medium. This is confirmed by a comparison of nucleophilicity constants (n_{CH_3I}) from the Swain—Scott equation for compounds analogous with relation to S^- and N—H. Thus, for example, for $C_6H_5S^-$ $n_{CH_3I} = 9.9$, and for $(C_2H_5)_3N$ $n_{CH_3I} = 6.7$ [11]. The data from the PMR spectrum of compound IX confirm the process of methylation on the thio group, as the signal from the protons of the CH_3—S group at 2.37 ppm is observed, and the signal from an N—CH_3 group at 3.5-4 ppm is absent. The signals from the protons at 13-14 ppm, characteristic of compound V, and having two different components, have disappeared. On increasing the temperature of the run, a broadening of these lines occurs and at 50°C (in DMSO-d_6) they merge. In comparison with the methylation of 4-amino-3-thio-6-R-1,2,4-triazin-5-ones [10], the methylation of 4-nitroso-3-thio-6-R-1,2,4-triazin-5-ones is more selective, and there are no by-products from methylation on the N_2 atom in the triazine ring.

EXPERIMENTAL

IR spectra were obtained on a Specord IR-75 instrument using KBr pellets; PMR spectra were obtained on a Tesla BS-487B instrument with working frequency 80 MHz in DMSO-d_6 with internal standard TMS of HMDS. The properties of the compounds synthesized are presented in Tables 1 and 2.

4-Nitroso-6-R-1,2,4-triazine-3,5-diones(thiones) (V-VIII). To a suspension of 0.05 mole initial 1,2,4-triazine in 50 ml 2 N HCl at 0°C and with stirring in such a manner that the formation of nitrous gases was not observed (1.5-2 h). On completion of the addition of $NaNO_2$ solution, the mixture was stirred for 15-20 min. The precipitate was filtered off, washed with water to neutral pH, and dried in air. The product was purified by recrystallization from acetone.

3-Methylthio-4-nitroso-6-R-1,2,4-triazin-5-ones (IX, X). 0.02 mole compound V (VI) was dissolved on stirring in 20 ml of an aqueous methanol solution of 1 N NaOH (methanol—water 1:1). To the solution at room temperature was added dropwise 0.02 mole CH_3I; the mixture was stirred for 2-2.5 h and left overnight. The precipitate was filtered off and dried in air. The product was purified by recrystallization from 0.1 N NaOH.

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