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ACYLATION OF 3-SUBSTITUTED 1-AMINOTHIOHYDANTOINS

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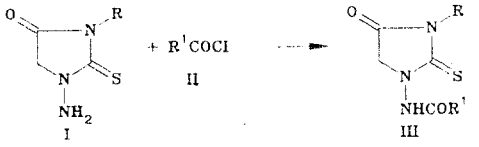
1-Monoacylamino-3-aryl(alkenyl)thiohydantoins were obtained by the acylation of 3-R-1-aminothiohydantoins by acid chlorides in various solvents and also under the conditions of phase-transfer catalysis.

Plant growth regulators [1,2], herbicides [3,4], and fungicides [5,6] have recently been found among derivatives of hydantoin, which have been the subject of searches for effective pesticides. The acylation of 3-substituted 1-aminothiohydantoins was investigated in order to find new physiologically active substances in the hydantoin series.

The synthesis of these compounds was realized comparatively recently, and their properties have been studied little with the single exception of the acylation of 1-amino-3-phenylthiohydantoin by acetic anhydride in the presence of anhydrous sodium acetate [7].

In the present work we investigated the acylation of 3-substituted 1-aminothiohydantoins (I) by carboxylic acid chlorides (II) (acetic, chloroacetic, benzoic) in aprotic (benzene) and protophilic (pyridine) solvents and also in a two-phase system (benzene—aqueous sodium hydroxide solution).



III a $R=C_6H_5$, $R^1=CH_3$; b $R=C_6H_5$, $R^1=CH_2Cl$; c $R=R^1=C_6H_5$; d $R=CH_2=CH-CH_2-$, $R^1=CH_3$; e $R=CH_2=CH-CH_2-$, $R^1=CH_2Cl$; f $R=CH_2=CH-CH_2-$, $R^1=C_6H_5$; g R=α-Naphthyl $R^1=CH_3$; h R=α-Naphthyl $R^1=CH_2Cl$; and R=α-Naphthyl $R^1=C_6H_5$

During acylation of the aminothiohydantoins (I) by acetyl chloride, chloroacetyl chloride, and benzoyl chloride in dry benzene in the presence of triethylamine (amine—acyl chloride—triethylamine ratios 1:1:1, method A [8]) we isolated the monoacylation products (III) with yields of 35-40% and also a large part of the initial compound (I). Increase in the amount of acyl chlorides did not change the yield of the product (III) and led to the formation of trace quantities of diacylation products. 3-Phenyl-1-diacetylaminothiohydantoin was synthesized for identification by the method in [7].

Realization of acylation in pyridine (method B [9]), which was at the same time solvent and hydrogen chloride acceptor, also did not help to increase the yields of compounds (III).

The acylation of the aminothiohydantoins (I) in the two-phase system, where the acyl chloride and aminothiohydantoin are present in the nonaqueous phase (benzene) while the sodium hydroxide is in the aqueous phase (method C [10]), increased the yield of the required products (III) to 70%. On account, clearly, of the fact that the amine hydrochloride formed in the reaction dissolves in the water and is converted into the amine by the action of alkali it then passes into the nonaqueous phase and reenters the reaction.

The nature of the substituents at position 3 of the aminothiohydantoins (I) does not substantially affect the yields of the final products (III).

The IR spectra of compounds (IIIa-i) contain absorption bands for the hydantoin ring at 1195 cm^{-1}, for the thiohydantoin carbonyl group at 1765 cm^{-1}, and for the carbonyl fragment of the acyl group at 1695-1700 cm^{-1}.

In the mass spectra of compounds (III) there are clearly defined peaks corresponding to the molecular ions (M^+), and there are also strong peaks formed as a result of the successive elimination of the acyl and aminoacyl fragments and the sulfur atom from the molecular ion. One of the main processes in the dissociation of the molecular ions is the elimination of the NR—C=S and O=C—NR—C=S fragments.

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TABLE 1. 1-Monoacylamino-3-aryl(alkenyl)thiohydantoins (IIIa-i)

Compound	Molecular formula	R	R^1	mp, °C*	M+**	R_f	Yield, %***
IIIa	$C_{11}H_{11}H_3O_2S$	C_6H_5	CH_3	210...211	249	0,05	68
IIIb	$C_{11}H_{10}ClN_3O_2S$	C_6H_5	CH_2Cl	166...167	283	0,21	70
IIIc	$C_{16}H_{13}N_3O_2S$	C_6H_5	C_6H_5	230...231	311	0,34	70
IIId	$C_{15}H_{13}N_3O_2S$	$CH_2CH—CH_2—$	CH_3	100...102	213	0,09	69
IIIe	$C_{15}H_{12}ClN_3O_2S$	$CH_2=CH—CH_2—$	CH_2Cl	Oil	247	0,26	67
IIIf	$C_{20}H_{15}N_3O_2S$	$CH_2=CH—CH_2—$	C_6H_5	95...96	275	0,44	71
IIIg	$C_8H_{11}N_3O_2S$	α-Naphthyl	CH_3	275...276	299	0,12	69
IIIh	$C_8H_{10}ClN_3O_2S$	α-Naphthyl	CH_2Cl	177...178	333	0,20	70
IIIi	$C_{13}H_{13}N_3O_2S$	α-Naphthyl	C_6H_5	204...205	361	0,35	70

*Compounds (IIIa, b, d, g) were crystallized from ethanol, compound (IIIh) from methanol, compound (IIIc) from toluene, compound (IIIf) from ethyl acetate, and compound (IIIi) from chloroform. **For the chlorine-containing ions their masses with the ^{35}Cl isotope are given. ***By method C.

EXPERIMENTAL

The mass spectra were recorded on an MX-1303 spectrometer at 30 eV and 150-210°C with direct injection of the sample into the ion source. The IR spectra were recorded in tablets with potassium bromide on a UR-20 spectrometer.

The individuality of the obtained substances was monitored by TLC on Silufol 254 plates in the 7:5:9 hexane—ethyl acetate—methylene chloride system.

The characteristics of the obtained compounds are given in Table 1. The elemental analyses corresponded to the calculated data.

Acylation of Aminothiohydantoins (I) by Acid Chlorides (General Procedures). A. To 0.02 mole of the aminothiohydantoin (I) in 100 ml of dry benzene we added 0.02 mole of triethylamine. The reaction mixture was cooled to 0°C, and 0.02 mole of the acylating agent (II) in 10 ml of dry benzene was added drop by drop so that the reaction temperature did not rise above 5°C. When the acylating agent had been added, the reaction mixture was stirred at room temperature for 30 min and at the boiling point of benzene for 10-15 min. The precipitated triethylamine hydrochloride was filtered off, the excess of the solvent was distilled, the residue was washed with water, and the product was treated with chloroform. The chloroform was evaporated, and the impure products (III) were recrystallized from an appropriate solvent.

B. To 0.01 mole of the aminothiohydantoin (I) in 50 ml of pyridine we added 0.01 mole of the acylating agent (II) in portions. The reaction mixture was stirred at room temperature for 1 h and diluted with an equal volume of water. The precipitate that separated after standing for several hours was filtered off.

C. To a solution of 0.02 mole of the aminothiohydantoin (I) in 100 ml of benzene, containing 0.05 mole of sodium hydroxide in 10 ml of water, we added with cooling and stirring 0.05 mole of the acylating agent (II). The obtained reaction mixture was stirred at room temperature for 1 h. The benzene layer was separated and evaporated, and the residue was treated by method A.

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RING—CHAIN TAUTOMERISM OF 3-ALKYLTHIO-1,5-DIHYDRO-1,2,4-TRIAZOLIUM SALTS

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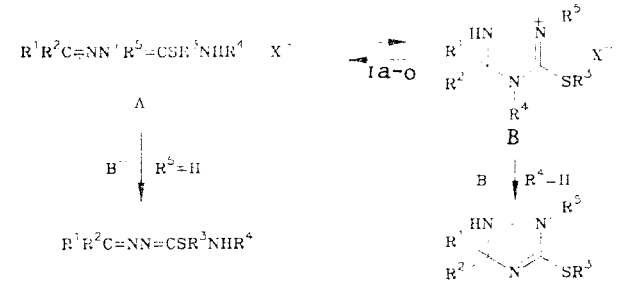
Ring—chain tautomerism in S-alkylisothiosemicarbazonium salts was detected for the first time by PMR and ^{13}C NMR spectroscopy. It was shown that substitution at the nitrogen atoms stabilizes the cyclic 1,5-dihydro-1,2,4-triazolium form. The data from the mass spectra are given.

The ability to undergo ring—chain tautomerism with the formation of 1,2,4-triazole derivatives with specific structural parameters of the same type is a characteristic feature of 1-alkylidene(arylidene)amidrazonium [1-3] and 1-alkylidene(arylidene)aminoguanidinium salts [4] and also thiosemicarbazone S,S,S-trioxides [5]. There are no data in this respect on their analogs, the isothiosemicarbazonium salts, which are easily synthesized by the alkylation of thiosemicarbazones. Only data on the stereoisomerism of their free bases, i.e., isothiosemicarbazones, have been described [6].

In the present work we examine the structure of S-alkylisothiosemicarbazonium salts (Ia-o) in DMSO-d_6 solution by PMR and ^{13}C NMR spectroscopy (Table 1). The previously obtained criteria for choosing between the linear and ring tautomers A and B were used [1-4].



IIc,e,j III h,i

Ia—e,h,j—o X=I; f,i,k X=Br; g X=Cl; a $R^1=R^4=R^5=H$, $R^2=R^3=CH_3$; b $R^1=H$, $R^2=R^3=R^4=R^5=CH_3$; c $R^1=R^4=R^5=H$, $R^2=C_6H_5$, $R^3=CH_3$; d $R^1=H$, $R^2=4\text{-}OCH_3C_6H_4$, $R^3=R^4=R^5=CH_3$; e $R^1=R^2=R^3=CH_3$, $R^4=R^5=H$; f $R^1=R^2=CH_3$, $R^3=C_2H_5$, $R^4=R^5=H$; g $R^1=R^2=CH_3$, $R^3=CH_2C_6H_5$, $R^4=R^5=H$; h $R^1=R^2=R^3=R^5=CH_3$, $R^4=H$; i $R^1=R^2=R^5=CH_3$, $R^3=C_2H_5$, $R^4=H$; j $R^1=R^2=R^3=R^4=CH_3$, $R^5=H$; k $R^1=R^2=R^4=CH_3$, $R^3=C_2H_5$, $R^5=H$; l $R^1=R^2=R^3=CH_3$, $R^4=C_2H_5$, $R^5=H$; m $R^1=R^2=R^3=CH_3$, $R^4=CH_2C_6H_5$, $R^5=H$; n $R^1=R^2=CH_3$, $R^3=R^4=CH_2C_6H_5$, $R^5=H$; o $R^1=R^2=R^3=R^4=R^5=CH_3$; IIc $R^1=R^4=H$, $R^2=C_6H_5$, $R^3=CH_3$; e, $R^1=R^2=R^3=CH_3$, $R^4=H$; j $R^1=R^2=R^3=R^4=CH_3$; IIIh $R^1=R^2=R^3=R^5=CH_3$; i $R^1=R^2=R^5=CH_3$, $R^3=C_2H_5$

It was found that even such a well known compound as S-methylacetoneisothiosemicarbazonium iodide (Ie) is represented by the ring tautomer to the extent of 3%, as follows from the data from both the PMR (Table 1) and the ^{13}C NMR (see the Experimental section) spectra. Variation in the structure of the salts not having substituents at the nitrogen atoms, i.e., change of the substituents R^3 in the acetone derivatives [the salts (If, g)] and the transition to derivatives of acetaldehyde and benzaldehyde [the salts (Ia, c)], gives rise to stabilization of the linear form. It is interesting to note that the salt (Ig) is a mixture of stereoisomers with respect to the $C{=}N_{(2)}$ bond, as observed earlier for certain isothiosemicarbazones [6]. We did not make structural assignments of these isomers, like determination of the structure of other linear salts, represented by one geometric isomer.

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