

THERMAL BEHAVIOUR OF 1,2,4-TRIAZOLE AND 1,2,4-TRIAZINE DERIVATIVES

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Process of thermal decomposition and stability of the methyl esters of 3-(2-pyridyl)-4-phenyl-1,2,4-triazol-5-carboxylic acid (**I**), 3-(2-pyridyl)-4-(4-methyl-phenyl)-1,2,4-triazol-5-carboxylic acid (**II**), 3-(2-pyridyl)-4-(4-methyl-phenyl)-5-oxo-1,2,4-triazine-6-acetic acid (**III**) and 3-(2-pyridyl)-4-phenyl-5-oxo-1,2,4-triazine-6-acetic acid (**IV**) were studied. The compounds are stable up to fusion point. Next they decompose in several overlapping stages. Among the decomposition products CO₂, H₂O, NH₃ and CH₃OH molecules are presented. When kept in air under atmospheric pressure at temperature over the range of 20–80°C and relative humidity over the range of 50–90% the esters do not change their structure and composition.

Keywords: antiviral and antimycotic activity, TG-DSC, TG-DTA, TG-FTIR, 1,2,4-triazine derivatives, 1,2,4-triazole derivatives

Introduction

Manufacturing processes of drug may involve the presence of water in the crystallization of the drug substance or in manufacturing or in the composition of the drug product through excipients. Furthermore, drug substances and drug products are submitted to different temperatures and relative humidities, due to various manufacturing or storage conditions. Changes of the solid state may have a considerable effect on activity, toxicity and stability of compounds. For the patient it is very important that the product remains identical through its shelf life in order to maintain the action without unexpected side effects [1–3]. Currently, there is an increasing interest of thermal techniques in the pharmaceutical area. Combined thermal techniques (e.g. TG-DTA or TG-DSC) give the possibility to study every phenomenon where energy or mass changes occur [4].

The research of new compounds possessing biological activity requires of the accomplishing of two fundamental conditions: a given compound should prove clear pharmacological activity and it should exhibit also limited toxicity and a weak effect on human or animal organisms. Some new active antiviral compounds are structurally based on the 1,2,4-triazole (Ribavirine, Vibunazole) or 1,2,4-triazine (Azaribine) heterocyclic systems [5]. This paper presents the results of thermal investigations of representatives of both 1,2,4-triazole and 1,2,4-triazine groups: the methyl esters of 3-(2-pyridyl)-4-phenyl-1,2,4-triazol-

5-carboxylic acid (**I**), 3-(2-pyridyl)-4-(4-methyl-phenyl)-1,2,4-triazol-5-carboxylic acid (**II**), 3-(2-pyridyl)-4-(4-methyl-phenyl)-5-oxo-1,2,4-triazine-6-acetic acid (**III**) and 3-(2-pyridyl)-4-phenyl-5-oxo-1,2,4-triazine-6-acetic acid (**IV**). The compounds **I–IV**, depending on their concentration and growing conditions, exhibit antiviral activity and they can inhibit early steps of viral replication. Compounds also exhibit moderate antibacterial and antimycotic activity against yeasts. It was found that the tested compounds did not inhibit the growth of bacteria and fungi of some species of the human digestive tract microflora. They show no effect on the central nervous system, only compound **I** exhibits weak analgesic activity [6, 7].

Experimental

Preparation, structure and properties of studied compounds, i.e. the methyl esters of 3-(2-pyridyl)-4-phenyl-1,2,4-triazol-5-carboxylic acid (**I**), 3-(2-pyridyl)-4-(4-methyl-phenyl)-1,2,4-triazol-5-carboxylic acid (**II**), 3-(2-pyridyl)-4-(4-methyl-phenyl)-5-oxo-1,2,4-triazine-6-acetic acid (**III**) and 3-(2-pyridyl)-4-phenyl-5-oxo-1,2,4-triazine-6-acetic acid (**IV**) were described early [5–9].

Thermal analyses experiments, including thermogravimetry (TG), differential thermal analysis (DTA), and differential scanning calorimetry (DSC), were performed using a Setaram thermal analyzer

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Table 1 Temperatures of the beginning (T_b) and the end (T_e) of thermal decomposition of **I–IV** compounds heated in air and argon atmosphere

Compound	Air		Argon	
	$T_b/^\circ\text{C}$	$T_e/^\circ\text{C}$	$T_b/^\circ\text{C}$	$T_e/^\circ\text{C}$
I	195	645	195	930
II	160	630	165	>990
III	200	660	200	>990
IV	200	675	195	>990

Table 2 X-ray diffraction data for **I–IV** starting compounds ('dry') and for **I–IV** compounds kept for 120 h at 80°C and 90% of relative humidity under atmospheric pressure ('humid')

Compound I				Compound II			
'Dry'		'Humid'		'Dry'		'Humid'	
$2\theta/^\circ$	Intensity/%	$2\theta/^\circ$	Intensity/%	$2\theta/^\circ$	Intensity/%	$2\theta/^\circ$	Intensity/%
9.75	100	9.70	100	7.8	63	7.85	80
11.40	12	11.40	18	8.35	84	8.45	96
14.65	8	14.60	12	13.65	47	13.7	43
15.65	15	15.60	25	15.60	55	16.65	53
16.45	12	16.45	12	16.90	62	16.95	62
16.95	15	16.95	26	17.80	48	17.85	40
18.60	18	18.50	28	18.70	60	18.75	40
21.35	18	21.35	20	19.25	65	19.50	55
22.10	15	22.10	20	20.45	95	20.60	92
23.75	20	23.75	32	21.90	80	22.05	48
24.30	76	24.30	80	22.70	100	22.80	100
26.35	30	26.35	32	25.30	52	25.45	52
27.00	18	27.05	18	26.60	43		
29.50	52	29.55	60	28.35	83	28.50	80
33.85	42	33.95	40	29.50	50	29.65	48
39.70	16	39.70	22				
Compound III				Compound IV			
'Dry'		'Humid'		'Dry'		'Humid'	
$2\theta/^\circ$	Intensity/%	$2\theta/^\circ$	Intensity/%	$2\theta/^\circ$	Intensity/%	$2\theta/^\circ$	Intensity/%
9.95	100	9.95	100	10.60	48	10.50	40
11.70	30	11.70	30	11.40	95	11.45	90
11.95	45	12.00	30	11.75	55	11.75	40
19.90	24	19.80	24	13.35	25	13.35	20
20.40	57	20.40	80	17.65	18	17.60	20
23.45	45	23.20	45	20.75	60	20.75	60
23.95	28	23.90	33	22.75	100	22.75	100
24.75	13	24.75	16	23.25	30	23.15	40
25.85	12	25.80	18	24.25	15	24.25	15
27.80	10	27.65	10	24.95	22	25.00	20
35.20	15	35.20	12	27.45	15	27.45	15
38.35	10			29.75	20	29.75	20
				32.25	12		
				34.50	10	34.50	10

Setsys 16/18. Experiments were carried out in a dynamic atmosphere of argon ($0.6 \text{ dm}^3 \text{ h}^{-1}$) or air ($0.75 \text{ dm}^3 \text{ h}^{-1}$). Equal masses (ca. 3 mg) of powder samples were heated in ceramic crucibles. The products of thermal decomposition were identified using Netzsch TG 209 apparatus coupled with a Bruker FTIR IFSS spectrophotometer. The samples of ca. 5 mg were heated in dynamic argon atmosphere up to 600°C at a heating rate of $10^\circ\text{C min}^{-1}$.

To study the stability, the samples of compounds were held by 120 h inside of Binder KBF115 climatic chamber where the constant temperature over the range of $20\text{--}80^\circ\text{C}$ and the constant relative humidity over the range of $50\text{--}90\%$ were kept.

The X-ray patterns of esters were recorded on a HZG 4 diffractometer, using Ni filtered $\text{CuK}\alpha$ radiation. Measurements were taken over the range of $2\theta = 5\text{--}70^\circ$.

Results and discussion

The Fig. 1 presents the structural formula of methyl esters of 3-(2-pyridyl)-4-phenyl-1,2,4-triazol-5-carboxylic acid (**I**), 3-(2-pyridyl)-4-(4-methylphenyl)-1,2,4-triazol-5-carboxylic acid (**II**), 3-(2-pyridyl)-4-(4-methylphenyl)-5-oxo-1,2,4-triazine-6-acetic acid (**III**) and 3-(2-pyridyl)-4-phenyl-5-oxo-1,2,4-triazine-6-acetic acid (**IV**).

In order to study thermal stability of **I**, **II**, **III** and **IV** the samples were examined by TG-DTA method. At first, we decided to examine the thermal decomposition of compounds. The 3 mg samples were heated up to 1000°C at a heating rate of $10^\circ\text{C min}^{-1}$ in dynamic air and argon atmosphere, Figs 2 and 3, respectively. It results from the figures that the compounds are stable up to fusion point. Melting process is connected with an endothermic peak on DTA curve. The onset point is equal to: $T(\text{I})=192.0\pm 0.2^\circ\text{C}$; $T(\text{II})=150.2\pm 1.0^\circ\text{C}$; $T(\text{III})=195.1\pm 0.2^\circ\text{C}$; $T(\text{IV})=147.4\pm 0.2^\circ\text{C}$ in air and $T(\text{I})=192.2\pm 0.2^\circ\text{C}$; $T(\text{II})=152.1\pm 1.0^\circ\text{C}$; $T(\text{III})=195.5\pm 0.2^\circ\text{C}$; $T(\text{IV})=146.6\pm 0.2^\circ\text{C}$ in argon. The values of onset point are burdened with an error. The melting process is followed by decomposition one. The DTA peaks of

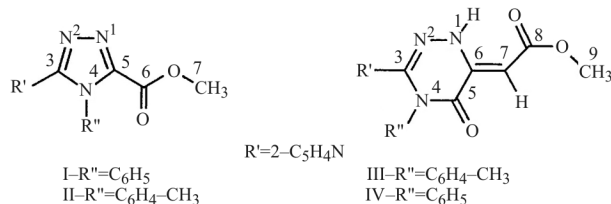


Fig. 1 Structural formula of studied compounds

melting and decomposition overlap and it makes difficult to determine the limits of peaks.

The crystal structure of the methyl esters of 3-(2-pyridyl)-4-phenyl-1,2,4-triazol-5-carboxylic acid (**I**) and 3-(2-pyridyl)-4-phenyl-5-oxo-1,2,4-triazine-6-acetic acid (**IV**) was detailed described in [9]. The crystals of **I** are triclinic (P1 space group) and

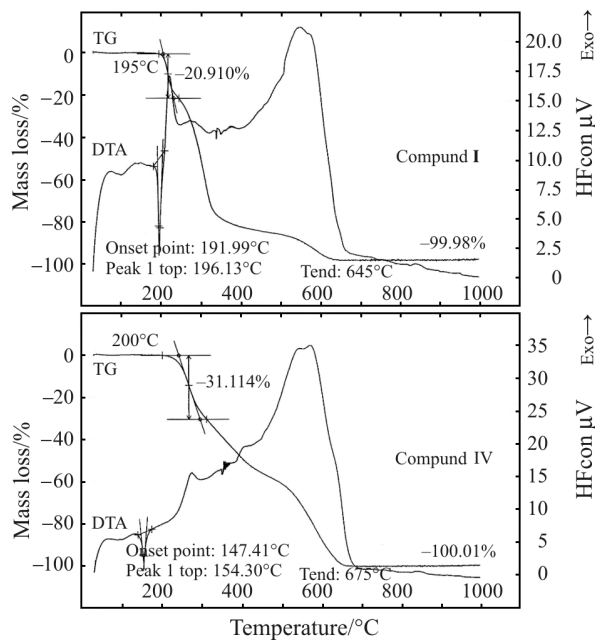


Fig. 2 TG and DTA curves of **I** and **IV** compounds heated in air atmosphere ($\beta=10^\circ\text{C min}^{-1}$; $m\approx 3 \text{ mg}$; ceramic crucible)

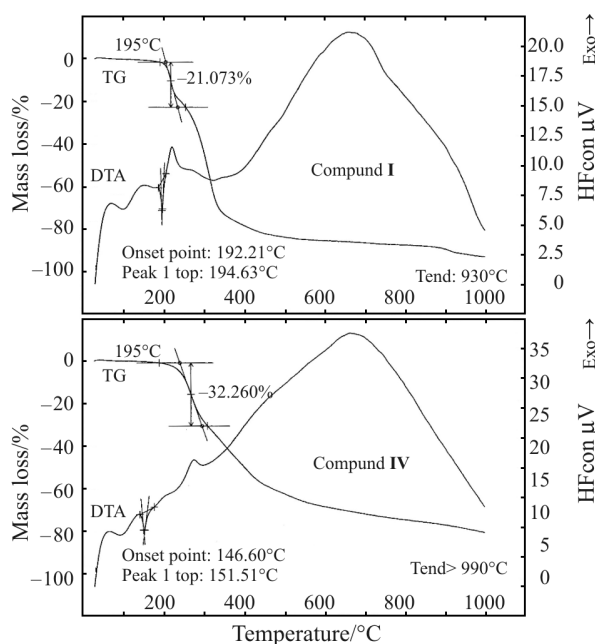


Fig. 3 TG and DTA curves of **I** and **IV** compounds heated in argon atmosphere ($\beta=10^\circ\text{C min}^{-1}$; $m\approx 3 \text{ mg}$; ceramic crucible)

crystals of **IV** - monoclinic ($P2_1/c$ space group). The both structures do not reveal any strong intermolecular hydrogen bonds. The crystal structure of **II** and **III** are not known yet. Much higher value of melting point of **III** may suggest the existence of stronger interactions in crystal lattice in comparison with **IV** compound.

The **I–III** compounds decompose immediately after melting. Only the **IV** compound is relatively stable in melting form and it begins to decompose at 195°C . All esters decompose in several overlapping stages. Temperatures of the beginning and the end of decomposition in air and argon atmosphere are given in Table 1. We can state that furnace atmosphere does not influence the beginning of thermal decomposition. The decomposition process in air ends at much lower temperature than in argon atmosphere. The oxidizing atmosphere causes the quick combustion of organic residues. The shape of DTA curves obtained in air atmosphere suggests that over the range of $300\text{--}500^\circ\text{C}$ the endothermic processes of decomposition and the exothermic processes of combustion of decomposition products overlap (Fig. 2).

The FTIR spectrophotometry was applied to identify of the gaseous products of thermal decomposition of esters. The results are presented on Figs 4 and 5. The respective gaseous products were identified on the ground of characteristic bands: H_2O – $3500\text{--}3900$, $1750\text{--}1250\text{ cm}^{-1}$ [10], NH_3 – 3320 , 960 , 920 cm^{-1} [11, 12], CO_2 – 2360 , 2330 cm^{-1} [13], 668 cm^{-1} [14], CO – 2180 , 2100 cm^{-1} [11], CH_3OH – 3800 (νOH), ~ 3000 (νCH_3), 1280 (δOH), 1050 cm^{-1} [15, 16], pyridine – 3080 , 1900 , 1600 , 1400 , 780 cm^{-1} [17]. The complex structure of studied esters and multistage decomposition process cause that complex IR spectra have been obtained. The TGFTIR technique provides evidence for no decomposition reaction below the fusion point. Next the molecules of CO_2 and small quantities of CO appear, and in the case of **II**, **III** and **IV** compounds the bands of H_2O appear, too. The presence of NH_3 and pyridine among gaseous products of decomposition is observed above 280°C . The thermal decomposition of **I** ester occurs with delivery of CH_3OH molecules over the range of $200\text{--}240^\circ\text{C}$. It is very probably that the first stage of decomposition is connected with the loss of $-\text{C}(\text{O})\text{OCH}_3$ groups as a mixture of CO_2 and CH_3OH molecules. The theoretical loss of mass is in good agreement with the found one ($\Delta m_{\text{theor.}} = 21.07\%$, $\Delta m_{\text{found}} = 22\%$).

The samples of **I–IV** esters were kept for 120 h in constant conditions of temperature and relative humidity. The experiments were carried out under atmospheric pressure at temperature of 20 , 50 or 80°C and at relative humidity of 50 , 70 or 90% . After each experiment the TG-DSC curves of dehydration in dynamic air were recorded. The DSC curves allowed for calcula-

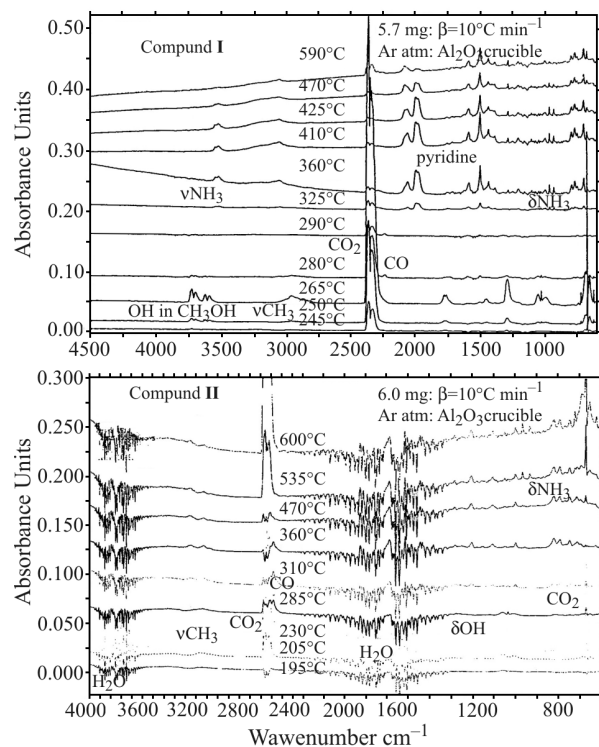


Fig 4 FTIR spectra of gaseous products of thermal decomposition of **I** and **II** compounds

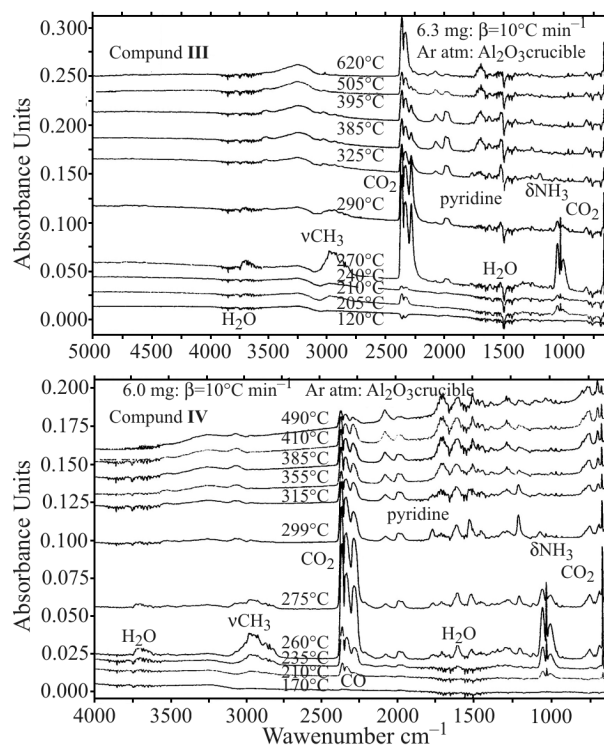


Fig 5 FTIR spectra of gaseous products of thermal decomposition of **III** and **IV** compounds

tion of enthalpy of fusion of studied compounds. The ΔH values are equal: $\Delta H(\text{I})=98.0 \text{ J g}^{-1}=27.44 \text{ kJ mol}^{-1}$; $\Delta H(\text{II})=130.0 \text{ J g}^{-1}=38.2 \text{ kJ mol}^{-1}$; $\Delta H(\text{III})=127.0 \text{ J g}^{-1}=42.80 \text{ kJ mol}^{-1}$, $\Delta H(\text{IV})=67.0 \text{ J g}^{-1}=21.64 \text{ kJ mol}^{-1}$. The X-ray diffraction patterns were recorded, too. The results were compared with those obtained for starting compounds (Table 2). It was found that the mentioned experiment conditions have not caused any changes in composition or structure of starting esters. The TG-DSC curves pointed that the studied esters neither adsorbed water molecules nor bound them in crystal structure. The comparison of X-ray diffraction patterns of starting compounds and compounds after experiments in climatic chamber provided evidence for stability of crystal structure of studied esters.

Conclusions

The methyl esters of 3-(2-pyridyl)-4-phenyl-1,2,4-triazol-5-carboxylic acid (**I**), 3-(2-pyridyl)-4-(4-methyl-phenyl)-1,2,4-triazol-5-carboxylic acid (**II**), 3-(2-pyridyl)-4-(4-methyl-phenyl)-5-oxo-1,2,4-triazin-6-acetic acid (**III**) and 3-(2-pyridyl)-4-phenyl-5-oxo-1,2,4-triazine-6-acetic acid (**IV**) are stable in air and inner atmosphere up to fusion point.

The thermal decomposition is multistage and the product of decomposition are difficult to identify. One can observe the presence of CO_2 , CO , H_2O , NH_3 , pyridine molecules among the gaseous products of decomposition, and in the case of **I** compound the presence of CH_3OH molecules is observed.

When kept in air under atmospheric pressure the studied esters are stable over the range of temperature of 20–80°C and of relative humidity of 50–90%. Any structural and composition changes were observed. It follows from the experiments the compound **I–IV** do not require a special condition of storage.

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Received: October 1, 2004

In revised form: December 22, 2004

DOI: 10.1007/s10973-005-6496-z