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Thermochimica Acta 343 (2000) 69–79

thermochimica acta

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Thermal characterization of some new xanthine derivatives

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Received 6 April 1999; accepted 25 June 1999

Abstract

In order to enhance and multiply the pharmacological properties of theophylline, the 8-substituted-7-[2-hydroxy-3-(4-acetyl-amino)-fenoxy-propyl]-1,3-dimethyl-xanthine derivatives with various substituents have been synthesized.

Their chemical structures have been assessed by IR and ^{1}H NMR spectroscopy and elemental analysis.

The influence of the non-cyclic and cyclic substituents on the thermal and thermo-oxidative behaviours has been followed by thermogravimetry and differential scanning calorimetry. These methods are useful to determine thermal stability, the purity of the compounds and crystallinity.

The pharmacological tests have proved their action both on bronchopulmonary and cardiovascular systems.

Keywords: Xanthine derivatives; Paracetamol derivative; Theophylline

1. Introduction

It is well-known on one hand, the antispasmotic and cardioactive effects of theophylline [1,2] and on the other hand that the isopropyl amino modified paracetamol (paracetamol derivative) acts as β-blocking agent (reduces blood pressure, antihypertensiv and antiaritmic effects).

In order to enhance and combine these properties and also to reduce the serious adverse effects which appears at high doses of theophylline, new xanthine derivatives have been synthesized.

The characterization of these new product implies both the determination of their structure and physico-chemical properties and also carefully testing of the pharmacological activity.

This paper deals with the synthesis and thermal characterization of the 8-substituted (R)-7-[2-hydroxy-3-(4-acetyl-amino)-fenoxy-propyl]-1,3-dimethyl-xanthine derivatives containing various substituents comparatively with starting materials and intermediary products of synthesis namely theophylline, paracetamol and paracetamol derivative, respectively. A short description of their pharmacological activity is also given.

1.1. Synthesis of the xanthine derivatives

The synthesis of 8-substituted-7-[2-hydroxy-3-(4-acetyl-amino)-fenoxy-propyl]-1,3-dimethyl-xanthine derivatives was performed in three steps (Scheme 1). In the first step, the *p*-hydroxy-acetanilide (paracetamol, (I)) was turned into fenoxy form (III) in alkaline medium, that further reacts with epichlorhydrine (IV),

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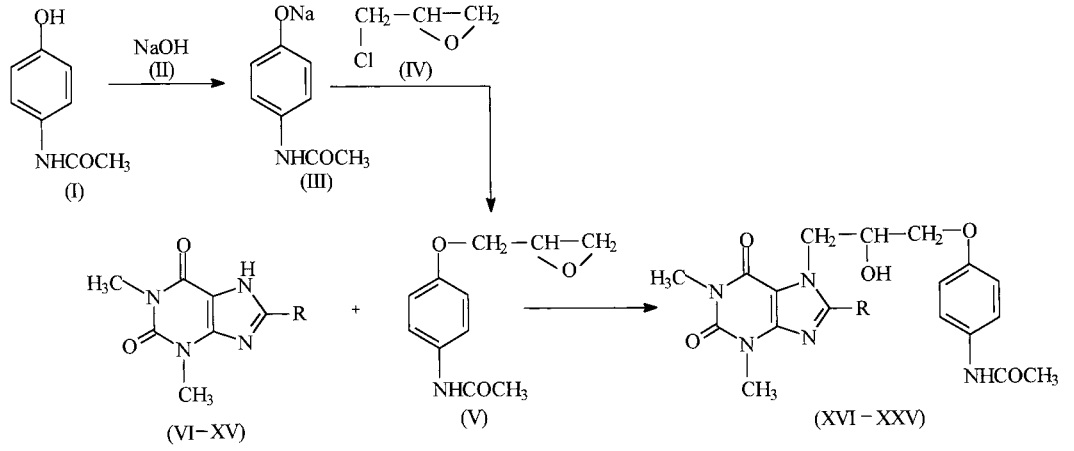
0040-6031/00/$ – see front matter
PII: S0040-6031(99)00342-1



Scheme 1

the second step, in the conditions described in [3] to form 7-(2,3-epoxy-propyl-oxy-acetanilide) (V), (paracetamol derivative). In the third step, the 7-(2,3-epoxy-propyl-oxy-acetanilide) (V) reacts in mild conditions at the boiling temperature of the ethyl alcohol with 8-substituted theophylline giving xanthine derivatives (XVI–XXV).

Nine derivatives with various substituents in 8-position have been obtained. The R-substituent type codes for various 8-R xanthine derivatives are given in Table 1. All reagents used in synthesis were of analytical purity.

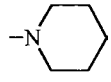
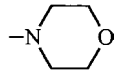
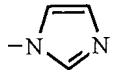
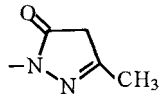
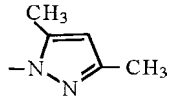
The synthesized xanthine derivatives have been purified by repeated crystallizations from various organic solvents. All compounds are white crystalline solids at room temperature. The control of purity was achieved by melting point determination using Boetius microscope and differential scanning calorimetry (DSC) analysis. Supplementary peaks in DSC curves or large endothermic peaks evidenced the presence of impurities.

1.2. Characterization of the xanthine derivatives

Each compound was characterized by elemental analysis, IR and ^{1}H NMR spectroscopy. IR spectra were recorded with a 577 Perkin Elmer spectrophotometer. ^{1}H NMR spectra were recorded using a JEOL C-60 spectrometer at 60 MHz on DMSO (d_5) or CCl_4 solutions.

The resulting spectra and calculated formula are in good agreement with the expected structures as it appears from selected spectra [4] given in Fig. 1 and elemental analysis results from Table 2.

Table 1
8-R-substituents in xanthine derivatives

R	Compound code
H	XVI
Cl	XVII
Br	XVIII
NO_2	XIX
	XX
	XXI
	XXII
	XXIII
	XXIV
	XXV

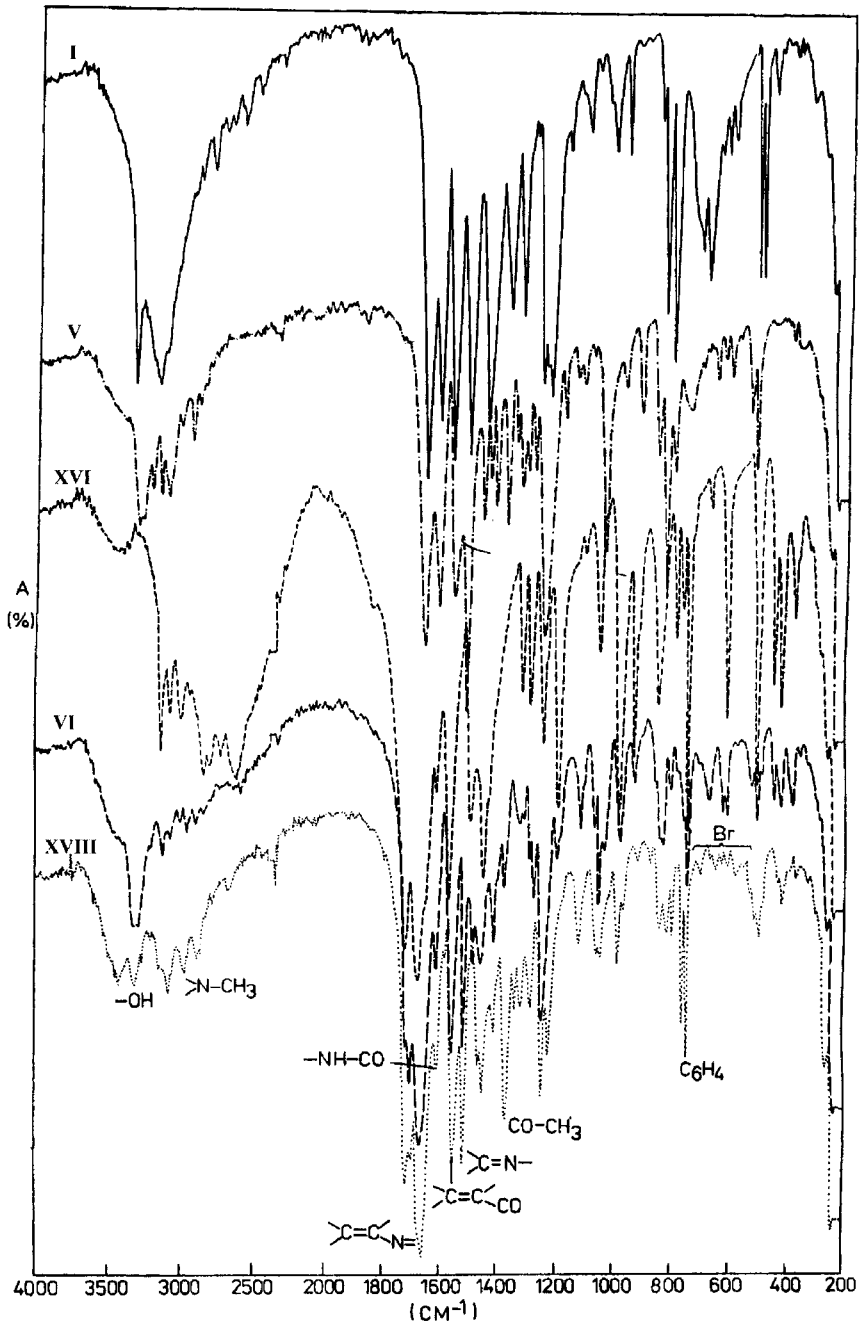


Fig. 1. IR spectra of the paracetamol (I), paracetamol derivative (V), theophylline (VI), xanthine (XVI) and 8-bromo substituted xanthine (XVIII).

Table 2
Elemental analysis results for several xanthine derivatives

Xanthine derivatives	R	Elemental analysis						Calculated formula	Theoretical formula
		C (%)		H (%)		N (%)			
		Calculated	Experimental	Calculated	Experimental	Calculated	Experimental		
XVI	H	55.80	56.24	5.46	5.64	18.08	18.63	$C_{18}H_{21}N_5O_5$	$C_{18}H_{21}N_5O_5$
XVIII	Br	46.36	46.72	4.32	4.98	15.02	15.43	$C_{18}H_{20}N_5O_5Br$	$C_{18}H_{20}N_5O_5Br$
XIX	NO_2	49.99	50.24	4.66	4.93	19.43	19.84	$C_{18}H_{20}N_6O_7$	$C_{18}H_{20}N_6O_7$
XX		57.88	58.12	6.82	7.08	18.41	18.62	$C_{22}H_{28}N_6O_5$	$C_{22}H_{28}N_6O_5$
XXI		58.71	58.97	6.26	6.46	18.41	18.05	$C_{23}H_{30}N_6O_5$	$C_{23}H_{30}N_6O_5$

2. Thermoanalytical methods

In pharmaceutical industry, thermoanalytical methods play an important role either in the development of new products and their characterization or as a simple quality control tool [5–8]. Two methods have been applied for the study of the xanthine derivatives: DSC and thermogravimetry (TG).

DSC curves were recorded by means of a Mettler DSC 12E instrument under the following conditions: heating rate 10°C min^{-1}, nitrogen flow 50 ml min^{-1}, mass of sample 1.2–6 mg; investigated temperature range 20–300°C. Calibration of the calorimeter was performed by determining the heat of fusion of indium, melting point of indium of 156.6°C, $\Delta H_f = 28.43$ J g^{-1} [9]. Each experiment was repeated at least two times. The baseline of DSC curves, for delimitation of the area of melting peak, was obtained by interpolation of initial and final straight line.

The TG and DTG (differential thermogravimetric) curves were recorded on a Paulik-Paulik-Erdey type Derivatograph, MOM - Budapest in the following conditions: heating rate, 12°C min^{-1}, sample mass 50 mg, air flow 30 ml min^{-1}.

In both kinds of thermoanalytical experiments, the sample was in powdered form.

3. Results and discussion

The DSC results are presented in Figs. 2–4 and Table 3. Only the analysis for well-purified compounds are presented.

The starting substances for the synthesis of xanthine derivatives exhibit very different melting temperatures (Fig. 2 and Table 3). The melting point of paracetamol derivative (113°C) is the lowest, while the "melting point" of theophylline is the highest (274°C). As it will be later shown, the theophylline melts with decomposition. The xanthine (XIV) melts at an intermediary temperature of 204°C. The melting heat is also specific for each compound.

Some of the values measured are in accordance with those found in the literature: paracetamol has a mono-

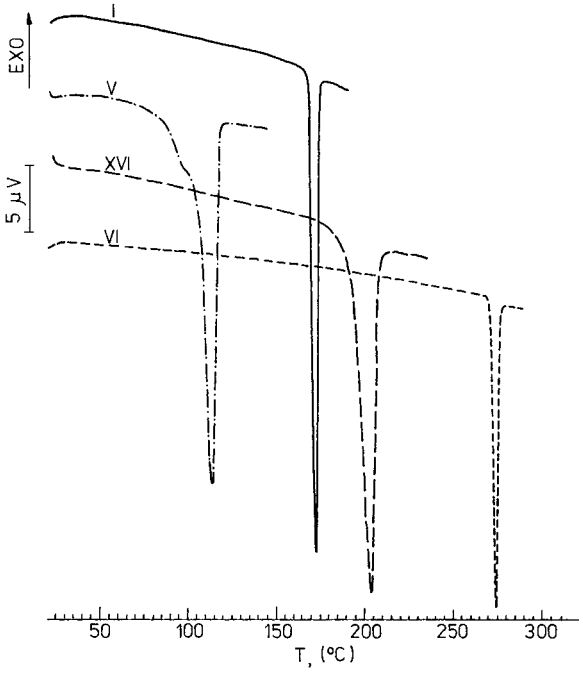


Fig. 2. DSC curves of the paracetamol (I), paracetamol derivative (V), theophylline (VI) and xanthine (XVI).

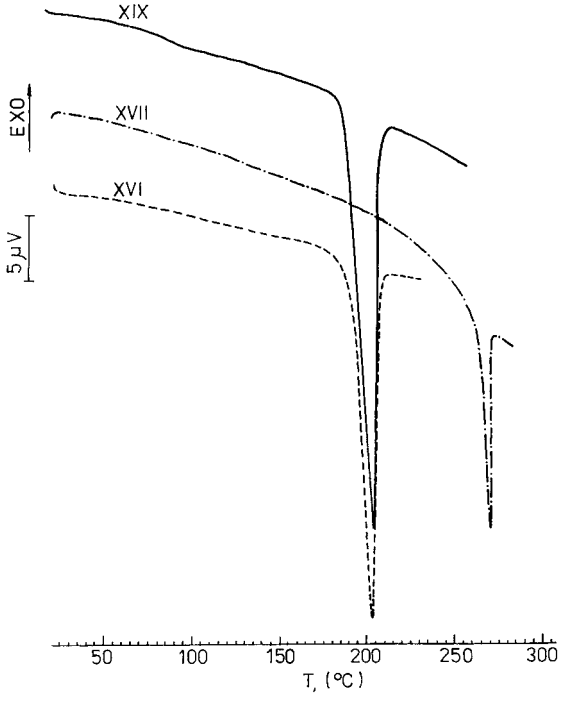


Fig. 3. DSC curves of the xanthine (XVI) and xanthine derivatives: XVII, XIX.

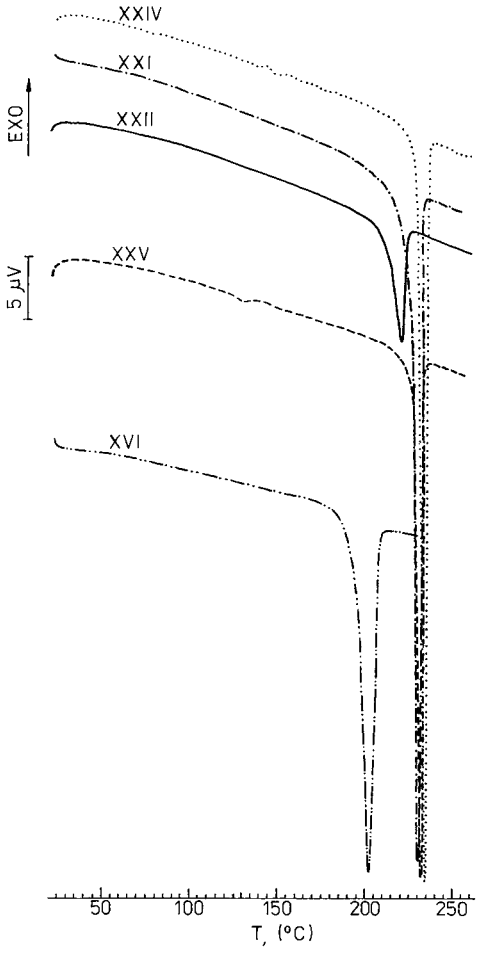


Fig. 4. DSC curves of the xanthine (XVI) and xanthine derivatives: XXI, XXII, XXIV and XXV.

clinic form with melting point of 170°C and a orthorhombic form [10,11] with melting point of 156–157°C [12,13]. The sample of paracetamol studied was in the monoclinic form.

The xanthine derivatives were classified in two groups according to the nature of substituents: derivatives containing non-cyclic or cyclic substituents. The corresponding DSC analysis are shown in Figs. 3 and 4, respectively. Each group have characteristic DSC and TG curves. The 8-bromo (XVIII) and nitro (XIX) xanthine derivatives have melting point of 219°C and 208°C, respectively, and melting heats of 37.8 and 56.8 kJ mol^{-1}, respectively, lower than that of the xanthine derivative (XVI), therefore their structure is less ordered.

Most of the 8-substituted xanthine derivatives with heterocyclic substituents containing only carbon and nitrogen (XXIV, XXV, XXI, XXIII) have melting temperature from 230°C to 234.5°C and high melting heats from 57 to 80 kJ mol^{-1}. The derivative with a heterocyclic substituent containing both carbon, nitrogen and oxygen exhibits low melting point of 220°C and melting heat 24.9 kJ mol^{-1}.

Therefore the DSC curves are particular for each 8-substituted xanthine derivative. The question — is the ''melting point'' >230°C because of the superposition of volatilization/decomposition processes in the chlorine derivative (XVII)? This aspect will be clarified below by comparing DSC results with TG data. The DSC curves of XXIV, XXV, XVIII, XIX, XXIII and XVII derivatives exhibit small endothermic peaks between 130°C and 150°C, Fig. 5, that could be assigned to a crystallographic transition, according to literature results for paracetamol [12,13]. The TG results are given in Figs. 6–8 and Table 4.

Generally, the starting compounds decompose in a single step (Fig. 6) occurring in the 170–470°C temperature range with a weight loss of 58–71 wt.%; xanthine derivative (XVI) exhibits the highest temperature of decomposition, the weight loss being in this temperature interval of 65 wt.% (Table 4). The weight loss at peak temperature from DSC is of 33 wt.%, therefore as it was mentioned above, a decomposition occurs during melting.

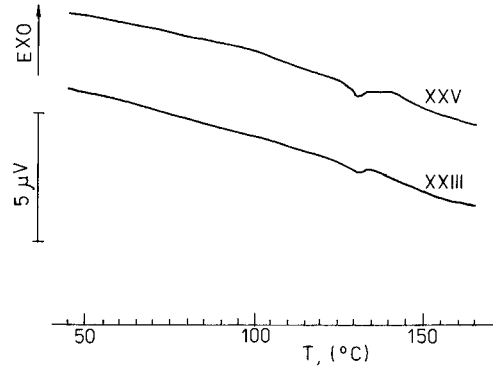


Fig. 5. DSC curves of xanthine derivative XXIII and XXV in the 20–170°C temperature interval.

Table 3
DSC data for the xanthine derivatives and substances employed in their synthesis

No.	Compound	Melting point (T_m) (°C)		ΔH (kJ mol^{-1})	M[a] (g mol^{-1})	Observation
		$T_{Boetius}$	T_{DSC} peak			
1	Theophylline	269–274	274	82.2	180	Melting + decomposition
2	Paracetamol	169–172	173	156.4	151	Melting
3	Paracetamol derivative	116–118	113	29.3	207	Melting
4	XVI	206–208	204	65.9	387	Melting
5	XVII	278–280	270.5	36.1	421.5	Melting + decomposition
6	XVIII	220–222	219	37.8	446	Melting
7	XIX	211–215	208	56.8	432	Melting
8	XXI	227–229	231	57.4	470	Melting
9	XXII	228–230	220	24.9	472	Melting
10	XXIII	266–267	–	–	453	Melting + decomposition
11	XXIV	238–240	234.5	65.9	481	Melting
12	XXV	233–235	233	80.77	483	Melting

[a] M: molecular weight.

Table 4
TG data

No.	Compound	Characteristic temperatures[a] (°C)			Δw (%)	Δw[b] (%)
		T_I	T_M	T_F		
1	Theophylline	221.5	377	421.5	71.3	33.3
2	Paracetamol	171	332	398	63.8	0
3	Paracetamol derivative	193	374	448	58.2	0
			334[c]		15.0[c]	
4	XVI	229	396	469	64.9	0
5	XVII	198	377	446.5	81.7	50
			308[d]		12.5[d]	
6	XVIII	253	346	439	56.5	0
			293[c]		11.7[c]	
7	XIX	210	391	443	62.0	0
8	XXI	250	338	463	57.0	0
			290[c]		7.3[c]	
9	XXII	244	337	473	57.8	0
			300[d]		5.4[d]	
			389.5[d]		45.7[d]	
10	XXIII	250.5	340	467.5	38.59	–
			320[c]		8.77[c]	
11	XXIV	236	335	454	54.89	0
			285[c]		7.27[c]	
12	XXV	234	339	449	54.23	0
			279.5[c]		6.3[c]	
			328[c]		28.1[c]	

[a] T_I, T_M, T_F: onset temperature, temperature corresponding to the maximum rate of weight loss and final temperature, respectively, and Δw is the weight loss.
[b] Weight loss corresponding to T_f (final temperature) of DSC peak.
[c] Inflexion.
[d] Shoulder temperature or weight loss.

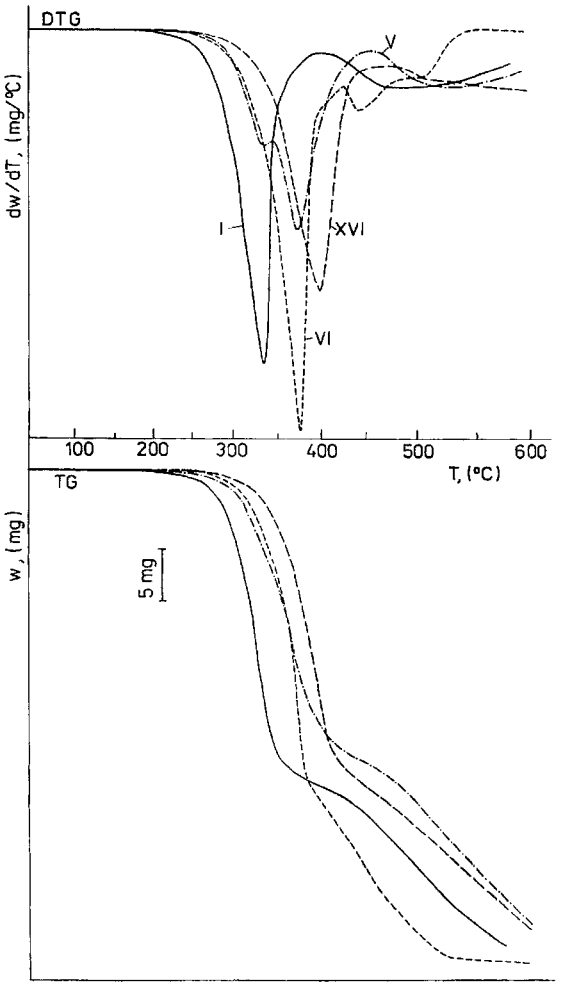


Fig. 6. Derivatograms of paracetamol (I), paracetamol derivative (V), theophylline (VI) and xanthine (XVI).

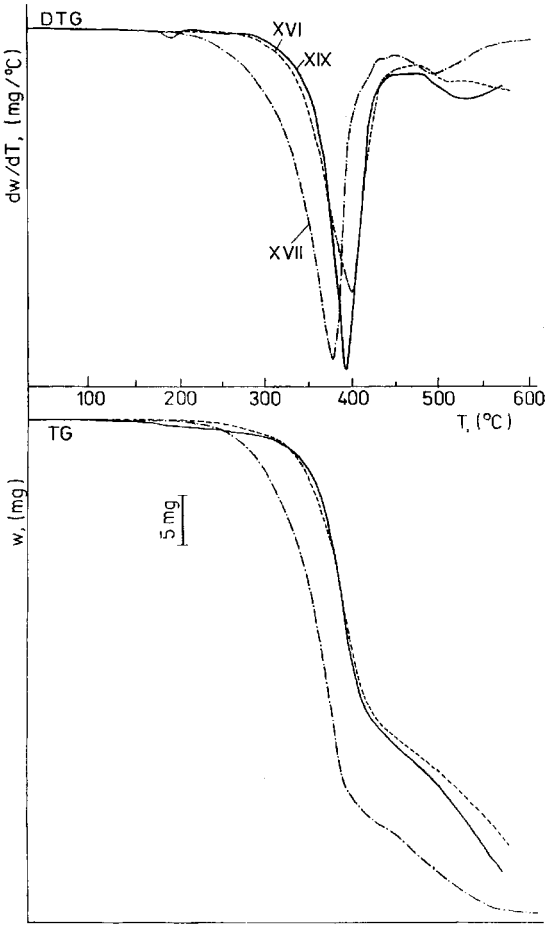


Fig. 7. Derivatograms of the xanthine (XVI) and xanthine derivatives: XVII and XIX.

The onset temperature of the weight loss of the most studied compounds lies above melting temperature (see the last columns of Table 4), therefore the assignment of the peak of melting is correct. The 8-chloro-(XVII) and nitro-(XIX) substituted xanthine derivatives decompose in a single step (Fig. 7), while those containing cyclic substituents decompose in two steps in the 170–470°C temperature interval (Fig. 8). The thermal stability increase with molecular weight, and all 8-substituted xanthine derivatives with cyclic substituents are more stable than XVI xanthine derivative, having higher onset temperature and lower weight losses. At higher temperatures the situation is different. The xanthine derivatives exhibit close thermo-oxidative behaviour, therefore, can suppose be a similar decomposition mechanisms. The decomposition mechanism could involve the breaking of a bond from aliphatic hydroxypropyl segment and the loss in the first step of paracetamol derivative fragment.

3.1. Pharmacological activity test

The effect of the 8-substituted-7-[2-hydroxy-3-(4-acetyl-amino)-fenoxy-propyl]-1,3-dimethyl-xanthine derivatives on the tracheal smooth muscle was studied according to the methods described in [14,15]. The strips of trachea having a weight of 180–200 g

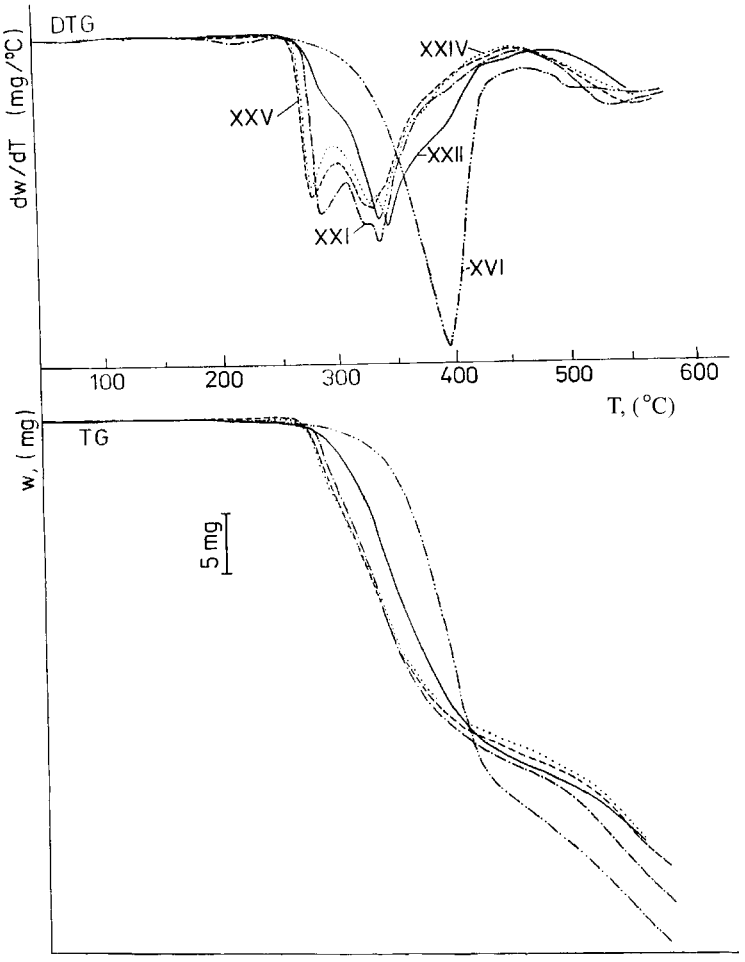


Fig. 8. Derivatograms of the xanthine (XVI) and xanthine derivatives: XXI, XXII, XXIV and XXV.

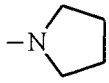
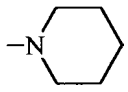
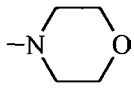
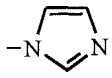
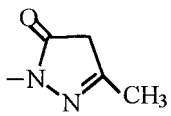
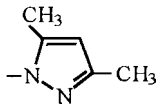
obtained from male adult rats of Wistar specimen have been employed. The control contraction of the tracheal smooth muscle was obtained using either a solution of carbachol 10^{-5} M or a solution of potassium chloride 40 mM. When the control contraction was over, the xanthine derivatives were delivered. The results obtained are given in Table 5.

It can be remarked that all studied compounds had relaxed stronger the tracheal smooth muscle contracted by carbachol than that contracted by potassium chloride.

The activity of the xanthine derivative XVI is 1.2 times higher than the theophylline activity, while the derivatives substituted in 8-position with various radicals intensify or reduce the bronchodilatator property. For example the bromine and imidazolyl radicals (compounds XVIII and XXIII) intensify the bronchodilatator activity. This was 6.5 times and respectively 2.5 times higher than that of theophylline, while the nitro, pirolidin-1-yl, piperidin-1-yl, morpholin-4-yl, 3-methyl-5-oxo-pirazol-1-yl and 3,5-dimethyl-pirazol-1-yl substituents decrease the bronchodilatator activity, this being under the theophylline activity.

The test for the activity on cardiovascular system are in progress and indicated that 8-bromo-substituted xanthine derivative induced an hypotensive effect while 8-morpholine-xanthine derivative induced an hypertensive effect.

Table 5
The effect of the 7-[2-hydroxy-3-(4-acetyl-amino)-fenoxy-propyl]-1,3-dimethyl-xanthine derivatives on the tracheal strips isolated from rats, after contraction with carbachol (10^{-5} M) or potassium chloride (40 mM) solutions

Xanthine derivative	R	Solvent mixture	Dose (mg ml^{-1})	Residual contraction (%)	
				Carbachol (10^{-5} M)	KCl (40 mM)
XVI	H	DMSO:water	10^{-10}–10^{-4}	100	100
		(1:9)	10^{-3}	15.12 ± 4.70	63.11 ± 10.8
XVIII	Br	DMSO:water	10^{-10}–10^{-4}	100	100
		(3:7)	10^{-3}	2.75 ± 1.00	39.82 ± 5.89
XIX	NO_2	DMSO:water	10^{-10}–10^{-4}	100	100
		(1:9)	10^{-3}	41.74 ± 7.3	60.28 ± 8.15
XX		DMSO:water	10^{-10}–10^{-4}	100	100
		(3:2)	10^{-3}	32.30 ± 8.70	64.23 ± 6.85
XXI		DMSO:water	10^{-10}–10^{-4}	100	100
		(3:7)	10^{-3}	35.97 ± 7.50	74.92 ± 8.27
XXII		DMSO:water	10^{-10}–10^{-4}	100	100
		(1:9)	10^{-3}	42.73 ± 9.70	73.15 ± 15.3
XXIII		DMSO:water	10^{-10}–10^{-4}	100	100
		(3:7)	10^{-3}	7.30 ± 2.00	55.17 ± 13.2
XXIV		DMSO:water	10^{-10}–10^{-4}	100	100
		(3:7)	10^{-3}	58.00 ± 11.2	89.97 ± 8.72
XXV		DMSO:water	10^{-10}–10^{-4}	100	100
		(3:7)	10^{-3}	50.00 ± 8.97	71.48 ± 9.84
VI	Theophylline	Water	10^{-10}–10^{-5}	100	100
			10^{-4}	41.00 ± 7.40	57.00 ± 6.40
			10^{-3}	18.00 ± 2.70	35.00 ± 5.30

4. Conclusions

The new synthesized xanthine derivatives exhibit high melting points and decomposition temperatures. Therefore they are stable during thermal treatments used for their processing. By coupling DSC and TG results, the endothermic peak of DSC curves were correctly assigned.

Both DSC and TG curves could be used for the xanthine derivatives identification. This is a very useful information, taking in view their selective activity on bronchodilatator and/or cardiovascular systems.

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