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THERMAL ANALYSIS OF PHARMACEUTICAL COMPOUNDS

II. THERMAL ANALYSIS OF SOME ANTIALLERGIC AGENTS

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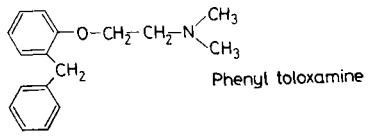
The thermal behaviour of some antiallergic drugs belonging to different groups of antihistaminics, such as phenyltoloxamine, chlorpromazine, clemizole and meclozine was examined. Thermogravimetry, derivative thermogravimetry and differential thermal analysis curves were used for the elucidation of the mechanisms of thermal decomposition. The melting temperatures of the compounds and their thermal stabilities were determined. The stability was found to decrease in the order: clemizole > chlorpromazine > meclozine > phenyltoloxamine.

The kinetic parameters of the thermal reactions were calculated and their values are in accordance with the results obtained, especially those of the stability.

Infrared spectroscopic analysis of the compounds together with their thermal decomposition products was performed in order to establish the possible sites of decomposition.

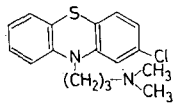
Research on antihistaminic drugs was initiated by Fourneau and Bovet [1].

Phenyltoloxamine, B-dimethylaminoethyl o-benzylphenyl ether, is an isomer of diphenhydramine that belongs to a most active class of dialkylaminoalkyl ethers of o-benzylphenol [2].



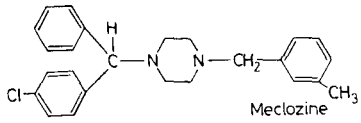
Phenyl toloxamine

Chlorpromazine, 2-chloro-10-(3-dimethylaminopropyl)phenothiazine, besides being antihistaminic, also has antipsychotic activity [3].



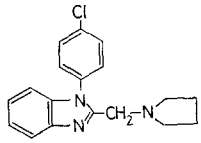
Chlorpromazine

Meclozine contains a piperazine ring system: 1-(4-chlorobenzhydryl)-4-(3-methylbenzyl)piperazine [4]. It is characterized by a slow onset and a prolonged duration of activity, and is among the most potent antihistaminics [5].



Meclozine

Clemizole (allercur), 1-p-chlorobenzyl-2-(1-pyrrolidinylmethyl)benzimidazole, is a benzimidazole derivative containing the ethylenediamine system [6].



Clemizole

Many methods have been investigated for the analysis of these antiallergic compounds: chromatographic methods, including gas chromatography [7–10] and thin-layer chromatography [11–14].

Zone electrophoresis has also used for the analysis and separation of chlorpromazine [15].

Further, antihistaminics have been determined colorimetrically [16, 17], fluorimetrically [18, 19], spectrophotometrically [20–22] and by NMR spectroscopy [23].

The reaction of chlorpromazine with metavanadates has been made the basis for conductometric, turbidimetric and gravimetric procedures for its determination [24]. A simple and sensitive radioreceptor assay has also been proposed [25].

In the present work, which is a continuation of the series of thermal analysis of pharmaceutical compounds started by the author for the thermal analysis of antibiotics [26] – the thermal analysis of some antiallergic drugs is carried out.

Phenyltoloxamine, chlorpromazine, clemizole and meclozine, which belong to different groups of antihistaminics, were chosen for study.

The thermal decomposition reactions, thermal stabilities and the possibility of the identification of these compounds through differences in their TG (thermogravimetry), DTG (derivative thermogravimetry) and DTA (differential thermal analysis) curves were studied.

The following kinetic parameters were calculated: activation energy (E), additive constant (A) and hypothetical reaction rate constant extrapolated to $T = \alpha(K_0)$.

Analysis of the studied drugs and their thermal decomposition products was performed by infrared spectroscopy and their decomposition pathways during thermal analysis were assumed accordingly.

Experimental

Materials

Antihistamine samples:

1-Phenyltoloxamine dihydrogen citrate: $C_{17}H_{21}NO \cdot C_6H_8O_7$
Dott Bonapeca. Mol. wt. 447.5

2-Chlorpromazine hydrochloride: $C_{17}H_{19}ClN_2S \cdot HCl$
R. P., Pharmachim. Mol. wt. 355.33

3-Clemizole (allercur hydrochloride): $C_{19}H_{20}ClN_3 \cdot HCl$
Schering. Mol. wt. 362.31
4-Meclozine hydrochloride: $C_{25}H_{27}ClN_2 \cdot 2\,HCl$
Siegford. Mol. wt. 463.88
Aluminium oxide: May and Baker, heated at 1200° for 2 hours.

Apparatus and procedure

A Paulik–Paulik–Erdey MOM derivatograph [27] was used.

100 mg of each of the different antihistaminics was accurately weighed. The samples were examined with the derivatograph, using aluminium oxide as reference material.

The experiments were carried out with a heating rate of 5°/min.

The curves were plotted by the instrument as a function of time and were then converted into temperature functions.

Mathematical methods

Assuming a first-order reaction, the rate of thermal decomposition can be calculated *via* the formula [28, 29]:

$$K = \frac{\frac{dw}{dt}}{W - W_e}$$

where W = weight at any time
W_e = weight at the end of the reaction
t = time
K = reaction rate constant, dependent on the temperature and calculated from the equation

$$\log K = \frac{B}{T} + A$$

where T = temperature in Kelvin degrees (K)
B = constant (slope of $\log K$ *vs.* $1/T$)
A = additive constant, which is related to the hypothetical reaction rate constant extrapolated to $T = \alpha$ °C (K_0)

Some adjacent points were chosen from the DTG curves of the antihistaminics examined and $\log K$ plotted against $1/T$. A linear function was obtained, indicating that the thermal decomposition reactions of the examined antihistaminics are first-order reactions. The slope of this linear function, B, is related to the activation energy E;

$$E = 2.303\ B.R$$

where R = universal gas constant.

Results and discussion

Figures 1 – 4 illustrate the thermal curves of phenyltoloxamine, chlorpromazine, clemizole and meclozine.

Table 1 indicates the thermal reactions of the studied antihistaminics; the temperatures at which the reactions begin and end are given and also the weight losses in the reactions.

The temperatures of endothermic and exothermic peaks, together with the melting temperatures of the compounds, are given in Table 2.

From the kinetic studies, linear relation were found between the reaction rate constants and the absolute temperature (log K and $1/T$, respectively). This indicates that the thermal decomposition reactions of the studied antihistaminics are first-order reactions.

Table 3 presents the calculated kinetic parameters, namely the activation energy (E), the additive constant (A) and the hypothetical reaction rate constant extrapolated to $T = \alpha(K_0)$ for the thermal reactions of these antihistaminics.

Table 1

The main thermal reactions of the antihistaminics

Samples	First reaction			Second reaction		
	Temperature, °C		Weight loss, %	Temperature, °C		Weight loss, %
	Start	End		Start	End	
Phenyltoloxamine	133	214	35	204	357	88.3 (total) 53.3 (specific)
Chlorpromazine	211	370	62.1			
Clemizole	226	396	61.6			
Meclozine	164	359	70.7			

Table 2

Temperatures (°C) of DTA peaks and melting of the antihistaminics

Samples	Melting temperature*	Temperatures of DTA peaks	
		endothermic	exothermic
Phenyltoloxamine	138–140	137, 176	293
Chlorpromazine	192–195	190, 300	337
Clemizole	230–245	238, 392	353, 442, 475
Meclozine	206–216	207	

* As reported in the literature [30].

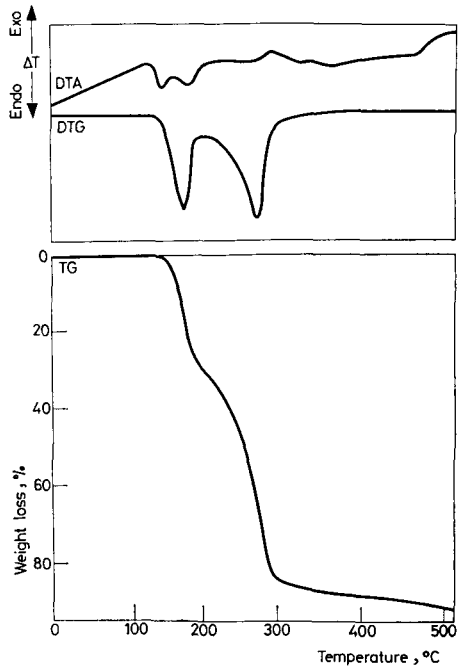


Fig. 1 Thermal curves of phenyltoloxamine

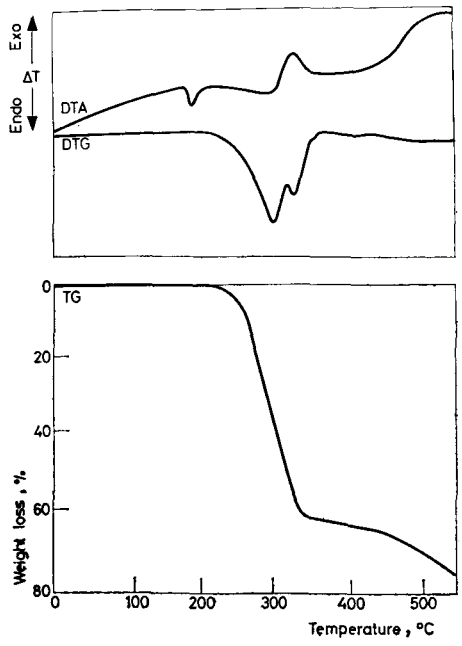


Fig. 2. Thermal curves of chlorpromazine

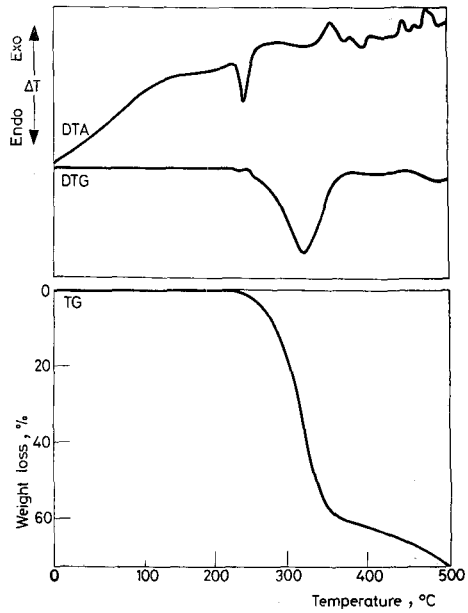


Fig. 3. Thermal curves of clemizole

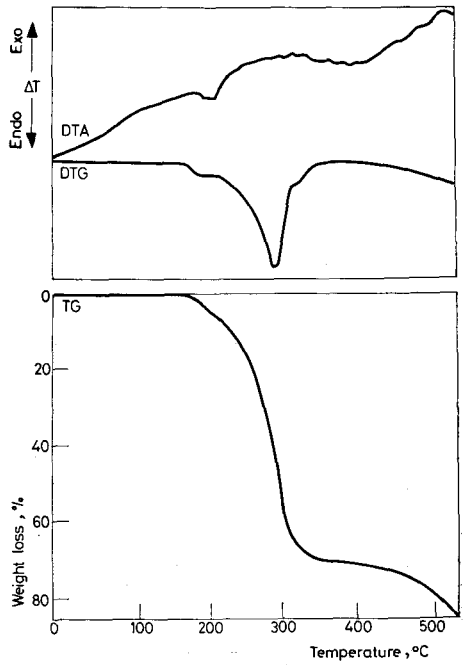


Fig. 4. Thermal curves of meclozine

Table 3

Calculated kinetic parameters for the thermal reactions of the antihistaminics

Samples	Activation energy E, KJ/mol	Additive constant, A	Hypothetical reaction rate constant extrapolated to $T \rightarrow \infty$ (K_0)
Phenyltoloxamine			
First reaction	70.23	16.99	$10^{7.38}$
Second reaction	154.33	34.88	$10^{15.16}$
Chlorpromazine	115.85	27.17	$10^{11.8}$
Clemizole	129.44	27.84	$10^{12.09}$
Meclozine	107.42	24.61	$10^{10.69}$

Phenyltoloxamine undergoes two thermal decomposition reactions on thermal treatment. The first reaction is endothermic, while the second is exothermic, showing a somewhat flattened peak.

From a consideration of the weight loss, the first reaction is probably due to decomposition of the diphenylmethane moiety, the loss of which will cause a weight loss of 37%, as calculated theoretically [31].

For the other examined compounds one main reaction occurs in the temperature range of interest, during thermal analysis. In the case of chlorpromazine this reaction is found to consist of two stages; the first of them is endothermic, ending at 322° with a weight loss of 46.1%, while the second stage starts at 322°, ends at 370° and is exothermic in nature.

The reactions of the pyrrolidine and piperazine derivatives, clemizole and meclozine are exothermic. In addition to the peaks indicated in Table 2, clemizole gives a small exothermic peak at 459°.

The DTA curve of meclozine has a small shoulder (inflection) at the beginning of the endothermic reaction at 190°; this may be attributed to the partial melting and recrystallization of the compound above 160° and before melting [30]. The exothermic peaks of meclozine are flattened and indistinguishable in its DTA curve.

The DTG curves of clemizole and meclozine show an inflection near the beginning, indicating a very small reaction stage. These stages end at 246 and 213°, with a weight loss of 2.5 and 7.1%, respectively.

The thermal analysis of the examined antihistaminics aids in the determination of their melting temperatures, since the peak temperature of the first endothermic reaction is comparable with the melting temperatures of the compounds as stated in the literature [30]. This endothermic peak is not accompanied by a weight loss as in the case of chlorpromazine. For the other studied compounds, the endothermic peak corresponding to melting occurs at the very beginning of its thermal decomposition reaction, i.e. the compound melts and starts to decompose at the same time.

As regards the stabilities of these antihistaminics during their thermal analysis, clemizole is found to be the most stable (it starts to decompose at the highest temperature, 226°), while phenyltoloxamine is the least stable (it starts to decompose at 133°). Chlorpromazine and meclozine start to decompose at 211 and 164°, respectively (Table 1). That is, the thermal stabilities of the compounds decrease in the following order:

Clemizole > Chlorpromazine > Meclozine > Phenyltoloxamine

This conclusion is in accordance with the calculated activation energy (E) values for the thermal reactions of the compounds (Table 3). The first reaction of phenyltoloxamine needs the lowest activation energy and hence the compound is the least stable and starts to decompose first.

The stability increases with the increase in the activation energy needed for the thermal decomposition reactions of the compounds, this being 70.23, 107.42, 115.85 and 129.44 kJ/mol for phenyltoloxamine, meclozine, chlorpromazine and clemizole, respectively.

In order to establish the possible sites of decomposition on thermal treatment, the infrared spectra of the parent compounds in KBr were compared with the spectra of the decomposition products (residues remaining when heating was stopped at the end of the reactions of interest) using a Perkin–Elmer IR 683 spectrophotometer.

For phenyltoloxamine, the IR data on the decomposition product (at the end of the first reaction) showed the disappearance of the C–O–C asymmetric stretching band in the region 1000–1230 cm^{-1} characteristic of the ether linkage. This indicates cleavage of the parent compound at the ether linkage. The decomposition product showed a C–H band at 2925 cm^{-1} due to symmetric and asymmetric in-plane deformation vibrations, and at 1465 cm^{-1} due to scissoring and rocking vibrations for the CH_2 group.

As regards chlorpromazine, the presence of the CH_3 asymmetric bending deformation at 1460 cm^{-1} and also the symmetric deformation band at 1410 cm^{-1} indicate the presence of the N–CH_3 group; together with the C–H stretch at 2930 cm^{-1}, this indicates the presence of an alkylamine side-chain. Thus, the decomposition may occur at the N–C attachment to the phenothiazine ring.

In a comparison of the IR spectra of clemizole and its decomposition product, the overtone peaks characteristic of ortho-disubstituted benzene in the region 2000–1667 cm^{-1} are seen to disappear, indicating cleavage of the benzimidazole ring. Disappearance of the absorption bands of the CH_2 group is also noticed, probably due to cleavage of the pyrrolidine ring.

As for meclozine, the disappearance of the CH_3 asymmetric bending deformation band at 1450 cm^{-1} in the spectrum of the decomposition product (as compared with that of the parent compound) indicates the possible cleavage of the meta-disubstituted benzene ring.

To summarize, for the identification of the examined antihistaminics: Phenyltoloxamine undergoes two thermal reactions, with two distinct peaks in the DTG

curve. Its DTA curve exhibits two endothermic peaks before 200°. It starts to decompose at the lowest temperature, with the lowest activation energy.

Chlorpromazine displays one main thermal reaction consisting of two stages (DTG curve); its DTA curve shows an endothermic peak before 200°.

Clemizole and meclozine both have one main thermal decomposition reaction (their DTG curves exhibit a distinct peak with an inflection at its beginning). Their DTA curves show no distinct peaks before 200°.

Clemizole is distinguished from meclozine by its exothermic DTA peak at 353° and by being the most stable (starting to decompose at the highest temperature, with the highest activation energy).

From the IR spectroscopic study, the possible sites for the decomposition on thermal treatment are: the ether linkage for phenyltoloxamine, the N–C attachment to the phenothiazine ring for chlorpromazine, the benzimidazole and pyrrolidine rings for clemizole, and the 3-methylbenzyl ring for meclozine.

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RÉSUMÉ — On a étudié le comportement thermique de quelques médicaments antiallergiques appartenant aux différents groupes des antihistaminiques, comme la phényltoloxamine, la chlorpromazine, la clémizole et la méclozine. On s'est servi des courbes thermogravimétriques, de leurs dérivées ainsi que des courbes d'analyse thermique différentielle pour élucider le mécanisme de la décomposition thermique. On a déterminé les températures de fusion et la stabilité thermique des composés. On a trouvé que la stabilité diminue dans l'ordre suivant: clémizole > chlorpromazine > méclozine > phényltoloxamine.

On a calculé les paramètres cinétiques des réactions thermiques; leurs valeurs, en particulier celles de la stabilité, sont en accord avec les résultats obtenus.

Les composés de départ et leurs produits de décomposition thermique ont été examinés par spectroscopie infrarouge afin de trouver les sites possibles de décomposition.

ZUSAMMENFASSUNG — Das thermische Verhalten einiger, verschiedener Antihistaminika angehörender antiallergetischer Arzneimittel, wie Phenyltoloxamin, Chlorpromazin, Clemizol und Meclozin wurde untersucht. Die Methoden der Thermogravimetrie, derivativen Thermogravimetrie und Differentialthermoanalyse wurden zur Klärung des Mechanismus der thermischen Zersetzung eingesetzt. Die Schmelztemperaturen der Verbindungen und ihre Thermostabilität wurden bestimmt. Es zeigte sich, dass die Stabilität in der Reihenfolge Clemizol > Chlorpromazin > Meclozin > Phenyltoloxamin abnimmt.

Die kinetischen Parameter der thermischen Reaktionen wurden berechnet und ihre Werte, besonders die der Stabilität, sind in Übereinstimmung mit den erhaltenen Ergebnissen.

Die infrarotspektroskopische Analyse der Verbindungen erfolgte zusammen mit der ihrer thermischen Zersetzungsprodukte um die möglichen Zerfallsbereiche zu ermitteln.

Резюме — Исследовано термическое поведение некоторых антиаллергических препаратов, относящихся к различным группам антигистаминных препаратов: фенилтолоксамин, хлорпромазин, клемизол и меклозин. Для установления механизма термического разложения были использованы методы ТГ, ДТГ и ДТА. Определены температуры плавления и термическая устойчивость этих соединений. Найдено, что термическая устойчивость уменьшается в ряду клемизол > хлорпромазин > маклозин > фенилтолоксамин. Вычислены кинетические параметры термических реакций, значения которых согласуются с результатами полученными при изучении стабильности этих соединений. С целью установления возможных стадий разложения, проведено ИК спектроскопическое исследование как исходных соединений, так и продуктов их термического разложения.