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Thermal Behaviour of *Auranofin*

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SUMMARY. The thermal behaviour of *Auranofin*, one of the best established gold containing drugs, has been investigated by thermogravimetric and differential thermal analysis under an oxygen flow. A detailed decomposition mechanism could be postulated. Elemental gold is the final pyrolysis product.

RESUMEN. "Comportamiento térmico de la *Auranofina*". El comportamiento térmico de la *Auranofina*, uno de los fármacos a base de oro mejor conocidos, fue investigado por análisis termogravimétrico y térmico-diferencial, en corriente de oxígeno. Fue posible postular un mecanismo detallado para la descomposición. El producto final de la pirólisis es oro elemental.

INTRODUCTION

The empirical use of gold in medicine can be traced back to the Chinese in 2500 B.C. Modern interest in its medicinal use has arisen since the stimulating work by Robert Koch, who puts gold therapy *(chrysotherapy)* on a solid scientific basis [1-3].

In the first decades of this century, gold drugs were used for the treatment of tuberculosis, syphilis and other infectious diseases. Nowadays, gold compounds are almost exclusively used against rheumatoid arthritis and related syndromes [3]. One of these drugs, (2,3,4,6-tetra-O-acetyl-1-thio-β-D-gluco-pyranosato-S)(triethylphosphine) gold(I) *("Auranofin"*, Figure 1) is one of the best established compounds in modern medical practice. It can be orally administered and has a potent action in the treatment of rheumatoid arthritis and also presents some antitumor activity [1-4].

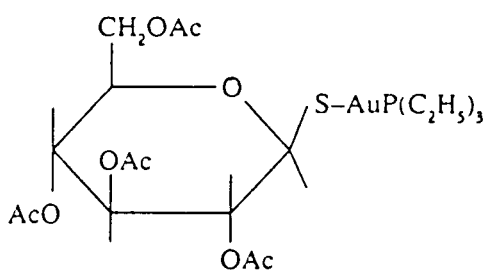

Figure 1. Schematic structure of Auranofin.

As part of a research program devoted to the characterization of new inorganic drugs, we have recently investigated the spectroscopic behaviour of *Auranofin* [5]. To complement this study, and in order to advance in its complete physicochemical characterization, we have now analyzed the thermal behaviour of the drug using TG and DTA techniques.

EXPERIMENTAL

Auranofin was purchased from ICN-Pharmaceuticals and used as supplied. Its purity was checked through its melting point (mean value of three independent determinations was 112 °C, supporting the presence of the so-called A polymorph. The literature value for the melting point of this polymorph is 110-112 °C [6].

Thermogravimetric (TG) measurements and differential thermal analysis (DTA) were made with a Shimadzu thermoanalytical system (models TG-50 and DTA-50, respectively), in a flowing O_2 atmosphere (50 ml/min). Experiments

KEY WORDS: *Auranofin*, Thermal Behaviour, TG and DTA.
PALABRAS CLAVE: Auranofina, Comportamiento Térmico, ATG, ATD.

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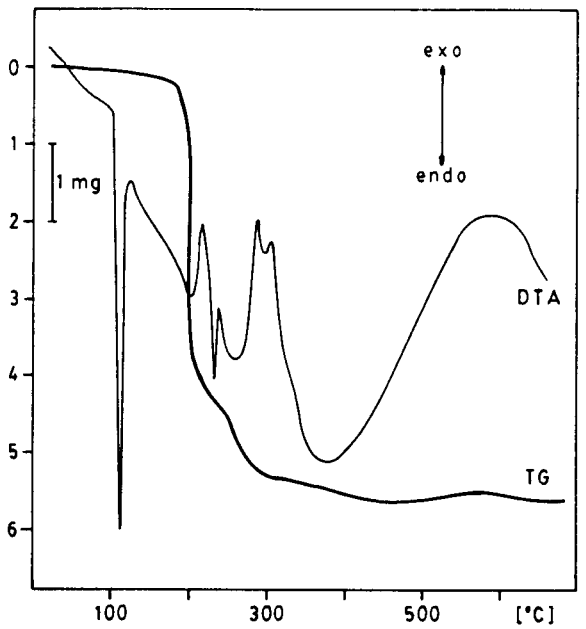

Figure 2. Thermogram of Auranofin. (Sample mass = 8.050 mg).

were carried out in platinum crucibles at a heating rate of 5 °C/min. Sample mass ranged between 6 and 8 mg. Al_2O_3 was used as a DTA standard.

RESULTS AND DISCUSSION

Figure 2 shows the TG and DTA traces of the pyrolysis of *Auranofin* recorded under the experimental conditions described above. The DTA trace shows a strong drift of the base line with increasing temperatures, which could not be corrected or improved, modifying the experimental conditions.

Decomposition starts slowly at temperatures above 80 °C and shows a strong step between 190 and 260 °C in which the greatest mass loss is observed (57.80%). As it can be seen from Figure 2, this process is accompanied by the very strong endothermic DTA signal observed at 112 °C, corresponding to the melting of the drug, and by a medium intensity doublet with peaks at 220 (exothermic) and 229 °C (endothermic).

The observed mass loss is compatible with the following process:

$$C_{14}H_{18}O_9\text{-S-AuP}(C_2H_5)_3 + 18.25\ O_2 \rightarrow 16CO_2 + 11.5H_2O + SO_2 + AuP(C_2H_5)_2 \quad (1)$$

which involves a calculated mass loss of 57.85%, in total agreement with the experimentally found value. The formation of $AuP(C_2H_5)_2$ is exciting but not totally unexpected, as a similar complex is known in the case of phenylphosphine, AuP(phenyl)2, which can be easily obtained and presumably has a polymeric structure with bridging $(phenyl)_2P$ groups, in a similar arrangement than that found in the gold(I) halides [7,8].

A second degradation step occurs between 260 and ca. 340 °C with a weight loss of 8.70%, involving the exothermic DTA-doublet at 285 and 304 °C. This weight loss can be explained by reaction (2), as follows:

$$AuP(C_2H_5)_2 + 6.5\ O_2 \rightarrow AuP + 4\ CO_2 + 5\ H_2O \quad (2)$$

a process for which the expected mass loss is of 8.55%, also in good agreement with the experimental value. The formation of a gold phosphide, under the present experimental conditions, is very interesting. Although the 1/1 stoichiometry is very usual for metal phosphides [9], in the case of gold this species has been scarcely characterized [10,11].

The last pyrolysis step extends between 340 and 650 °C and involves an experimental mass loss of 4.50%, which implies the final degradation of the phosphide according to:

$$4\ AuP + 5\ O_2 \rightarrow 4\ Au + P_4O_{10} \quad (3)$$

with a theoretical weight loss of 4.56%. The last, very strong and broad DTA-signal, centered at about 586 °C, may be related to the formation of the phosphorus (V) oxide which, as known, is a highly exothermic reaction [12]. Very interesting is the small weight increase observed near 600 °C in the TG trace. It may be related to the formation of a superficial oxide deposit, which is given off only at a somewhat higher temperature.

The total observed weight loss, obtained by the summation of the processes represented by the equations **(1)+(2)+(3)**, was of 71.00%, also in excellent agreement with the calculated value of 70.96% for the generation of gold as the final pyrolysis residue.

This final residue was qualitatively characterized as follows: it was dissolved in *aqua regia* and to the resulting solution, previously neutralized with NaOH, a few drops of H_2O_2 were added. Metallic gold is precipitated in the form of a very fine blackish powder [13].

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