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Note

Thermal properties of diftalone and compounds related to its metabolism

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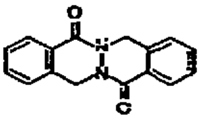
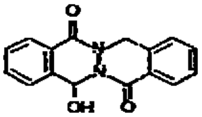
The chemical and physical properties of diftalone* (phthalazino [2,3 b]-phthalazine-5,12 (7H, 14H) dione) (I), a synthetic antiinflammatory drug[1–3], and of its main metabolites have been investigated in the last few years[4–6]. The present paper deals with the study of the thermal properties of the drug and of its metabolites 7-hydroxy-(II) and 7,14-dihydroxy-diftalone (III).


(I)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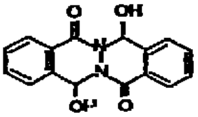
(III)

EXPERIMENTAL

The compounds used were of pure analytical grade.

Thermal analysis was performed with a DuPont 990 instrument equipped with a differential scanning calorimetric cell (DSC) and a thermogravimetric analyser (TG) coupled to a gas chromatograph. The working conditions were: gas flow N_2 25 ml min^{-1}; scan speed 10°C min^{-1}; reference empty aluminum pan. The melting temperatures were corrected for the non-linear temperature response of the thermocouple employed[7]. The areas of the peaks were measured with a planimeter and the melting heat was calculated after calibrating the instrument with a phenanthrene standard (99,99 mole %) having a molecular melting heat of 4.33 kcal mol^{-1}.

Thermomicroscopy was performed with a Köfler hot stage instrument.

RESULTS AND DISCUSSION

The heating curve of a sample of diftalone [99,975% molar, as determined

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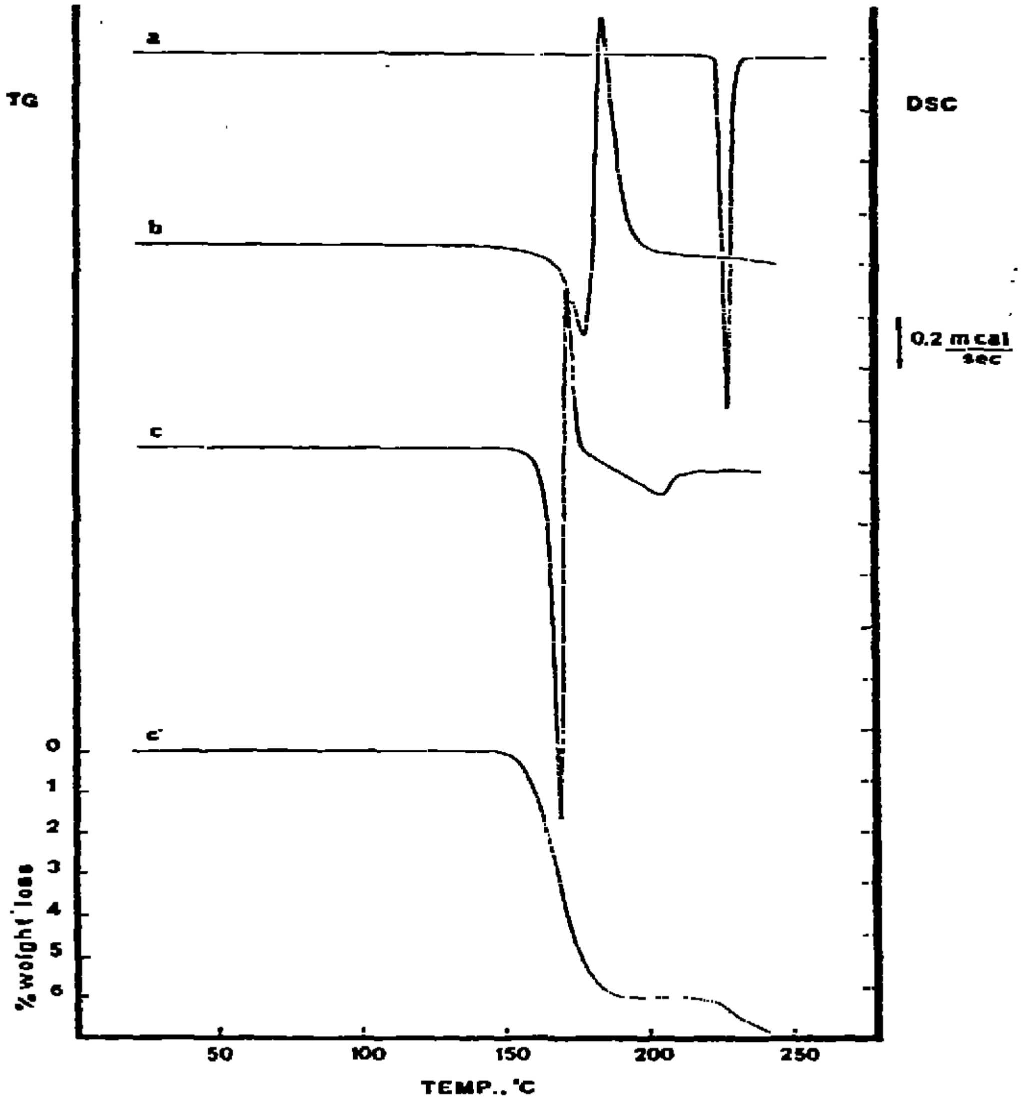


Fig. 1. Heating curves: (a) DSC of I; (b) DSC of II; (c) DSC of III; (c') TGA of III.

by the Plato and Glasgow method[8]] is reported in Fig. 1a. Thermal properties were calculated as average value of five runs: m.p. = 223.5°C; ΔH = 7.7 kcal mol^{-1}; ΔS = 15.5 cal mol^{-1} K^{-1}. The crystals of diftalone show a noticeable vapor tension and tend to sublimate at about 180°C as can be observed by thermomicroscopy; consequently, the sample to be analyzed by DSC must be prepared in such a way to avoid a drift in the baseline. The crystals are very stable: no change has been evidentiated either on grinding or on exposition to moisture saturated air. Moreover, until now no other crystalline modifications have been obtained by crystallization from different solvents. The lack of polymorphism in diftalone might be due to the symmetry of the molecular structure leading to only one possible arrangement of the molecules in the solid state, determined by Van der Waals forces.

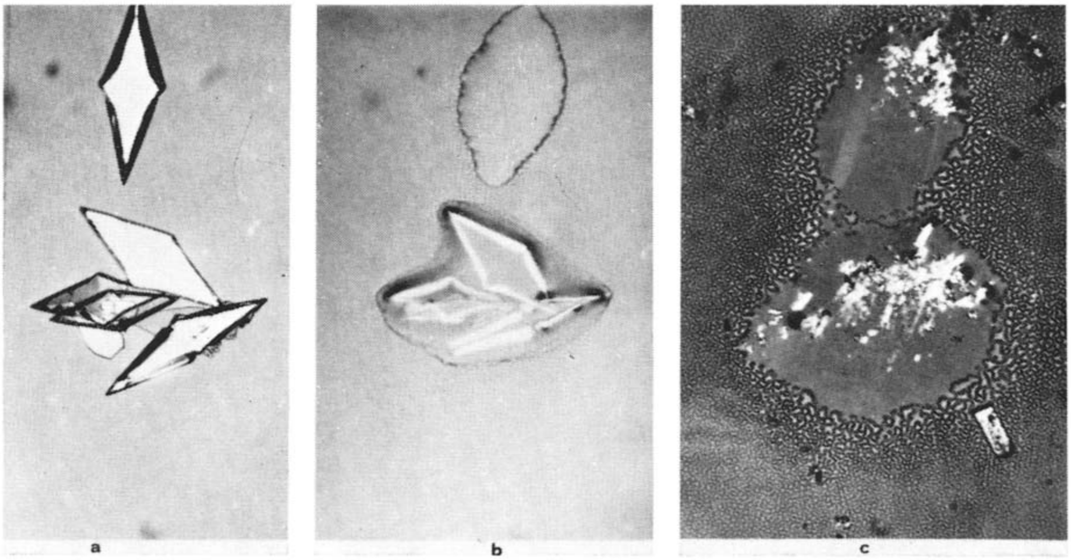
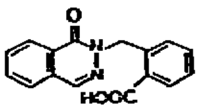


Fig. 2. Rearrangement of II into IV by thermomicroscopy: (a) room temperature; (b) 172°C; (c) 200°C.

The two metabolites of diftalone, II and III, are unstable in the liquid state in that both of them rearrange after melting, giving rise to different compounds. In fact, the heating curve of II shows an endo–exothermic process, that occurs without weight modification at 172–183°C (Fig. 1b). By thermomicroscopy the melting is observable in this range of temperature, while crystals appear after a certain time at about 200°C, which in turn melt at 225°C (Fig. 2). As the compound obtained at 200°C appeared different from II by TLC, a sufficient amount was prepared by DSC to determine its chemical structure. On the basis of IR, MS and NMR spectra the structure of 2-[1(2H)-oxo-2-phthalazinyl]methyl benzoic acid (IV), a substance previously described[9], was assigned to the rearranged product. In the heating curve the endotherm corresponds to the melting of II and the exotherm to the transformation into IV, which at that scanning rate does not crystallize. The instability of II at its melting temperature accounts for different mass spectra at different DIS temperatures[10]. Compound IV shows polymorphism, which will be described elsewhere[11].



(IV)

The heating curve of compound III shows an endo–exothermic process at 165–170°C (Fig. 1c) with a loss of weight of 6.0% as determined by TG (Fig. 1c'). The weight loss corresponds to elimination of one molecule of water, evidentiated by gas chromatography of the effluent vapor. By thermomicroscopy new crystals can be seen forming from the melt at about 167°C, which in turn melt at 210°C (Fig. 3).

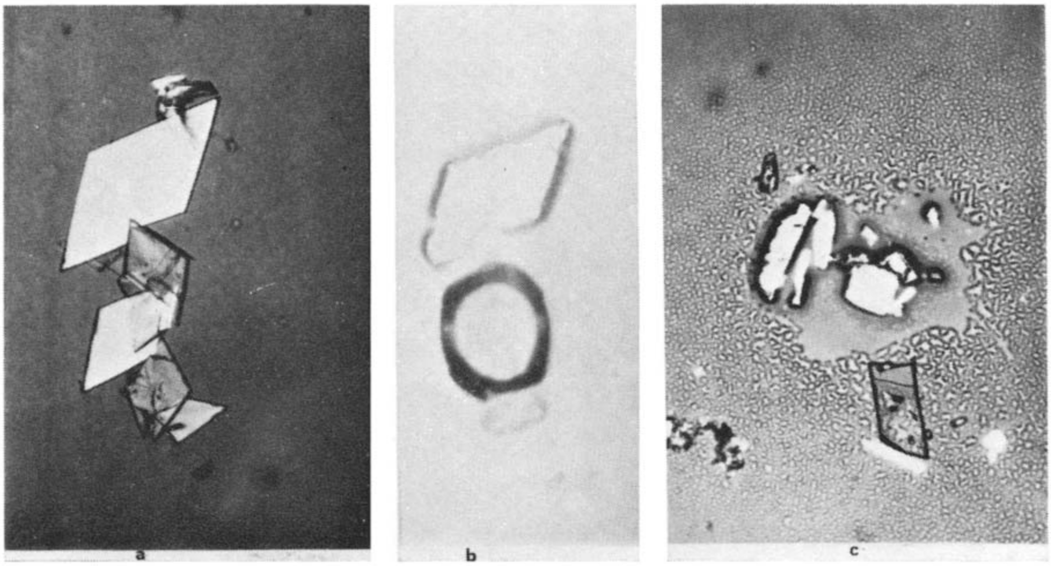


Fig. 3. Transformation of III into V: (a) room temperature; (b) 165°C; (c) 167°C.

On the basis of IR and NMR spectroscopy the transformation product was confirmed to be compound V previously described[6].

(V)

Thus the endo–exothermic process is the result of four close events, requiring or yielding heat: melting, chemical reaction, water evaporation and crystallization, and no area can be associated to any of them. The transformation of III into V by heating is observed also under the conditions to obtain the mass spectrum[10].

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