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# Degradation Products of Tiaprofenic Acid

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Tiaprofenic acid is kept under pressure for 12 h and heated in acidic, basic or oxidative medium. Three different products of decomposition of tiaprofenic acid are identified by CPG-SM method.

**Key Words: Tiaprofenic acid, Degradation, CPG-SM.**

## INTRODUCTION

The (RS)-2-(5-benzoyl-2-thienyl) propionic acid, also called tiaprofenic acid (Fig. 1) is the active ingredient of drug SURGAM (Laboratory AVENTIS). This acid use as an analgesic, non-steroid[1] and antiinflammatory drug[2,3] (AINS). It is also used as antiagreggant plate. Its principal mechanism of action is inhibition of cyclooxygenase and the synthesis of prostaglandins[4,5], molecule making it possible to feel the pain during the ignition. According to the International Committee of Harmonization (ICH)[6,7], degradation makes it possible to study the reactivity of the molecule. This study belongs to the strategy of the development of the active ingredients. Its objective is to identify the breakdown products, to know the modes of degradations in each medium as required by the ICH and by comparing the real and theoretical mode of fragmentation of the molecule, to develop methods of proportioning specific to the active ingredient in the presence of its breakdown products. In literature several methods are used in particular HPLC[8-10] and CPG[3].

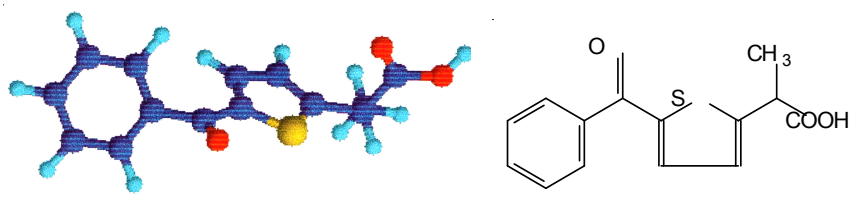


Fig. 1. Chemical structure of tiaprofenic acid

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## EXPERIMENTAL

The CPG -MS are carried out starting from solutions injected with a chromatograph CPG Hewlett Packard series 5890 coupled to a detector with trap door of ions HP 5972. Un injecting automatic HP, an evaporator under nitrogen LIBISCH a vortex HEIDOPH and a centrifugal machine JOUAN CR 412. Tiaprofenic acid comes from Aventis pharma (Tunisia). Methanol, acetonitrile is HPLC grade, from Fisher chemicals (the UK). Hydrogen peroxide, sodium hydroxide and acetic acid from Prolabo (France). Sodium octyl sulphate was procured from National Laboratory of Controls of Drugs, Tunisia.

**Chromatographic conditions:** The parameters of analysis are as follows: Column: HP5, length: 30 m, lower diameter: 0.5 mm, epaissor of the film: 0.25 µm Parameter of the flow Gas vector: helium, Flow of 1.2 mL/min, Pression of 16.7 psi with 180 °C.

**Parameters of injection:** The mode of injection is split, the volume of injection is 0.1 µL, the temperature of injection is 250 °C and the report/ratio of split is of 1/100.

**Program furnace:** The initial temperature is 180 °C and final 280 °C during 1 min, the slope and of 5 °C/min and final time is of 1 min.

**Parameters of the detector of mass:** Mode of ionization: electronic impact with 70 eV, the mode of acquisition: SCAN (50-550 uma), the temperature of interface 280 °C, the multiplier is 1820 emv, temperature of source 280 °C, intern standard is the octacosanoic acid.

**Degradation of tiaprofenic acid:** Quantities of tiaprofenic acid are put in flasks of 50 mL and adjusted by HCl 2 N, NaOH 2 N and $H_2O_2$ 30 v/v, heated under backward flow during 12 h. One neutralizes 1 mL respectively of the solutions with 1 mL of base and of acid then one dilutes until 5 mL with the phase composed by: 1 % acetic acid-acetonitrile (600, 400) with 0.05 mol/L of OSS at pH = 4.5.

**Preparation of the various solutions used:** Four samples into double containing tiaprofenic acid and the three solutions of degradations will undergo an acid and basic extraction and then a derivation by methylation with $CH_3I$.

**Acidic extraction:** From quantities of tiaprofenic acid in methanol, 1 mL of each solution of degradation was taken and then has additions the octadecanoic acid 50 µg/mL, one adjusts the pH 4 to 5 then added diethyl ether, agitates and centrifuges for recovering the organic phase.

**Basic extraction:** To start with aqueous phases of the acid extractions, adjusts pH 9 and then one adds ethyl acetate, agitates and recovers the second respective organic phase. Both organic phases collected for each solution and each product was obtained by evaporation of the solvent.

**Derivatization of the samples:** Dissolve the residue of the two organic phases which have with evaporates dry in acetone then one adds $CH_3I$ and of the $K_2CO_3$ and heats the whole products for 0.5 h. One cooled the whole and evaporates dry and then the residues of each tube is extracted with acetone. These tubes will be analyzed.

## RESULTS AND DISCUSSION

The extracts in the deoxygenated medium of degradation give five products breakdown (Fig. 3), in acid and basic medium, only three products appeared have been isolated (Figs. 4 and 5). The apparent m/z on the basis of mass spectrum of the various peaks as well as the ions corresponding in each medium of degradation are presented in Tables 1-3. Moreover the comparison between real fragmentation and theoretical one (Fig. 2) shows which are not identical in any point. In $H_2O_2$, break downs products number 1, 2 are deduced from the decomposition of tiaprofenic acid but we haven't any explication for the presence of 4 and 5. In the acid medium of degradation the breakdown product 4 contains nitrogen which does not exist in present molecule, one can think that it is under product of synthesis being with it, which was degraded. In basic medium the breakdowns products are identified.

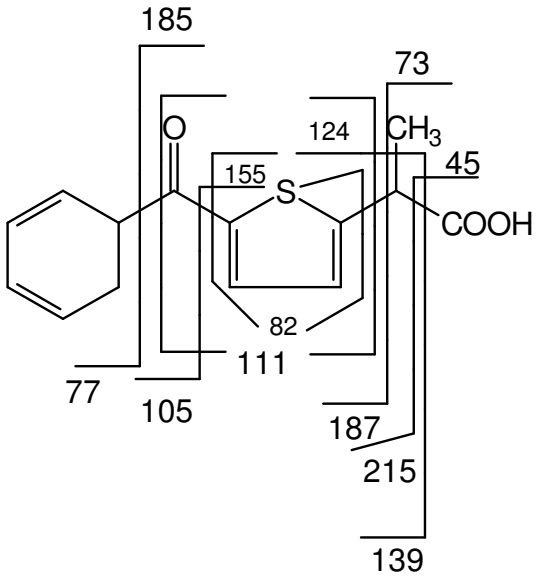


Fig. 2. Theoretical fragmentation of the tiaprofenic acid

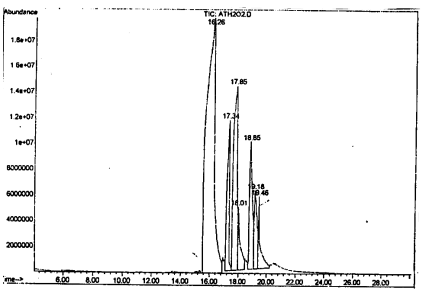

Fig. 3

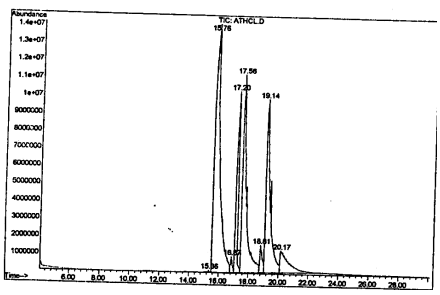

Fig. 4

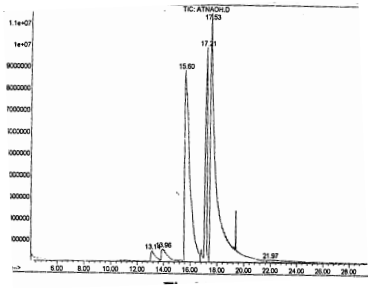

Fig. 5

TABLE-1
IDENTIFICATION OF THE PEAKS EXISTING IN THE MEDIUM OF DEGRADATION $H_2O_2$ m/z THEIR PRINCIPAL IONS

| Number and name of the product | Time of retention | m/z | Allotted ions |
|---|---|---|---|
| **1**: 5-Benzoyl-2-acetylthiophene | 17,85 | 77 | $[Phenyl]^+$ |
| | | 105 | $[Phenyl\text{-}CO]^+$ |
| | | 111 | $[CO\text{-}C_4H_2S]^+$ |
| | | 153 | $[CO_2\text{-}C_4H_2S\text{-}CH_2CH_3]^+\text{-}H_2$ |
| | | 215 | $[Phenyl\text{-}CO\text{-}C_4H_2S\text{-}CH_2CH_2]^+$ |
| **2**: 2-(Methylthio)dibenzothiophene | 18,078 | 215 | $[Phenyl\text{-}CO\text{-}C_4H_2S\text{-}CH_2CH_2]^+$ |
| **3**: 2-Phenyl-4,5,6,7-tetrahydro-benzothiazole | 18,85 | 104 | $[Phenyl\text{-}CO]\ \text{-}H^+$ |
| | | 187 | $[Phenyl\text{-}CO\text{-}C_4H_2S]^+$ |
| | | 215 | $[Phenyl\text{-}CO\text{-}C_4H_2S\text{-}CH_2CH_2]^+$ |
| **4**: 4-Diethylamino-2-ethoxycarbonyl-phenyl-3-azapenta-1,3-diene | 19,18 | 215 | $[Phenyl\text{-}CO\text{-}C_4H_2S\text{-}CH_2CH_2]^+$ |
| **5**: Tiaprofenic methyl ester | 19,462 | 77 | $[Phenyl]^+$ |
| | | 105 | $[Phenyl\text{-}CO]^+$ |
| | | 125 | $[CO\text{-}C_4H_2S\text{-}CH_3]^+$ |
| | | 137 | $[CO\text{-}C_4H_2S\text{-}CH_2CH]^+$ |
| | | 153 | $[CO_2\text{-}C_4H_2S\text{-}CH_2CH_3]^+\text{-}H_2$ |
| | | 171 | $[Phenyl\text{-}CH_2\text{-}C_4H_2S]^+\text{-}H_2$ |
| | | 187 | $[Phenyl\text{-}CO\text{-}C_4H_2S]^+$ |
| | | 215 | $[Phenyl\text{-}CO\text{-}C_4H_2S\text{-}CH_2CH_2]^+$ |

TABLE-2
IDENTIFICATION OF THE PEAKS EXISTING IN THE MEDIUM OF DEGRADATION HCl m/z THEIR PRINCIPAL IONS

| Number and name of the product | Time of retention | m/z | Allotted ions |
|---|---|---|---|
| **1**: 1-[2'-(5,8-dimethoxynaphthalenyl)]-ethanone | 17,56 | 189 | $[Phenyl\text{-}CO\text{-}C_4H_2S]^+\text{+}H_2$ |
| | | 215 | $[Phenyl\text{-}CO\text{-}C_4H_2S\text{-}CH_2CH_2]^+$ |
| **2**: 4-diethylamino-2-ethoxycarbonylphenyl-3-azapenta-1,3-diene | 19,14 | 77 | $[Phenyl]^+$ |
| | | 105 | $[Phenyl\text{-}CO]^+$ |
| | | 187 | $[Phenyl\text{-}CO\text{-}C_4H_2S]^+$ |
| | | 215 | $[Phenyl\text{-}CO\text{-}C_4H_2S\text{-}CH_2CH_2]^+$ |
| **3**: 1-[1-(methylthio)ethylidiene]-4-phenyl-cyclohexane | 20,17 | 216 | $[Phenyl\text{-}CO\text{-}C_4H_2S\text{-}CH_2CH_3]^+$ |

TABLE-3
IDENTIFICATION OF THE PEAKS EXISTING IN THE MEDIUM OF DEGRADATION NaOH m/z THEIR PRINCIPAL IONS

| Number and name of the product | Time of retention | m/z | Allotted ions |
|---|---|---|---|
| **1**: Methanonephenyl-2-thienyl | 13,96 | 77 | $[Phenyl]^+$ |
| | | 111 | $[CO\text{-}C_4H_2S]^+$ |
| | | 171 | $[Phenyl\text{-}CH_2\text{-}C_4H_2S]^+\text{-}H_2$ |
| | | 188 | $[Phenyl\text{-}CO\text{-}C_4H_2S]^+ + H^+$ |
| **2**: 5-Benzoyl-2-ethylthiophene | 15,797 | 77 | $[Phenyl]^+$ |
| | | 105 | $[Phenyl\text{-}CO]^+$ |
| | | 139 | $[CO\text{-}C_4H_2S\text{-}CH_2CH_3]^+$ |
| | | 173 | $[Phenyl\text{-}CH_2\text{-}C_4H_2S]^+$ |
| | | 187 | $[Phenyl\text{-}CO\text{-}C_4H_2S]^+$ |
| | | 201 | $[Phenyl\text{-}CO\text{-}C_4H_2S\text{-}CH_2]^+$ |
| | | 216 | $[Phenyl\text{-}CO\text{-}C_4H_2S\text{-}CH_2CH_3]^+$ |
| **3**: 5-Benzoyl-2-acetylthiophene | 17,53 | 77 | $[Phenyl]^+$ |
| | | 105 | $[Phenyl\text{-}CO]^+$ |
| | | 153 | $[CO_2\text{-}C_4H_2S\text{-}CH_2CH_3]^+\text{-}H_2$ |
| | | 215 | $[Phenyl\text{-}CO\text{-}C_4H_2S\text{-}CH_2CH_2]^+$ |

## Conclusion

According to present results, it is confirmed that the brittleness of the structure of this molecule in the three mediums oxygenated in particular, shows that this reactivity is due to the presence of the sulphur atom which with thirst for oxygen, even of the air.

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