

Role of Singlet Oxygen Photooxygenation in Supporting the Proposed Pathway for Conversion of Δ^9 -THC to CBN

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Abstract

Singlet oxygen ($^1\text{O}_2$) photooxygenation of Δ^9 -tetrahydrocannabinol (Δ^9 -THC, **1**) afforded products that are intermediates in a proposed pathway for decomposition of **1** to the thermodynamically more stable cannabinol (CBN, **7**). Some of these intermediates have previously been detected by GC-MS or were isolated from cannabis; however, their structures were not fully elucidated. Three key intermediates of the suggested mechanism, namely 9,10-epoxy- $\Delta^{6a(10a)}$ -THC (**4**), (+)-9,10-dihydroxy- $\Delta^{6a(10a)}$ -THC (**5**) and (-)-10-ethoxy-9-hydroxy- $\Delta^{6a(10a)}$ -THC (**6**), and the end product **7** have been purified from the reaction mixture and characterized by spectroscopic analysis (**4** and **5** as their acetates). Compound **8** was later purified and identified as its tosylate.

Keywords: Photooxygenation, (Δ^9 -THC, **1**), GC-MS, tosylate

Introduction

Δ^9 -Tetrahydrocannabinol (Δ^9 -THC, **1**), a natural psychotropic agent isolated from *Cannabis sativa*, has a number of medicinal applications, e.g. control of nausea and vomiting in cancer patients and appetite stimulation for AIDS patients (Galal *et al.*, 2009). Δ^9 -THC (**1**) is subject to decomposition by air oxidation which is accelerated by light (Harvey, 1990; Turner and ElSohly, 1979). Decomposition of an ethanolic Δ^9 -THC (**1**) solution in light and dark is 1% per day and 1% per year respectively (Harvey, 1990). The major degradation product is CBN (**7**) which does not occur naturally in cannabis (Turner and Mahlberg, 1982).

Materials and Methods

Photooxygenation was conducted using irradiation with incandescent light, a photosensitizer, and bubbling oxygen into a double jacketed glass container with a stream of cold water for efficient cooling. At the end of the reaction, the mixture of products was purified by chromatography, and then analyzed with spectroscopic methods.

Results and Discussion

The original aim of this work was to attempt the utilization of singlet oxygen ($^1\text{O}_2$) photooxygenation of Δ^9 -THC (**1**) employing different photosensitizers and reaction conditions to provide sufficient quantities of the minor oxygenated (hydroxy, epoxy and ether) cannabinoids isolated from the plant or as mammalian metabolites for further studies. A number of these products were found to be intermediates in a postulated mechanism for decomposition of Δ^9 -THC (**1**) (Turner and ElSohly, 1979), which was devised to explain the non-equivalent conversion of Δ^9 -THC (**1**) to CBN (**7**). Catalytic antibodies in conjunction with riboflavin as a photosensitizer and $^1\text{O}_2$ has been shown to oxidatively degrade Δ^9 -THC (**1**) with cannabitrinol (CBT, **5**) the main degradation product (Turner and Mahlberg, 1982).

According to the suggested mechanism, the intermediates are formed as follows (**Figure 1**):

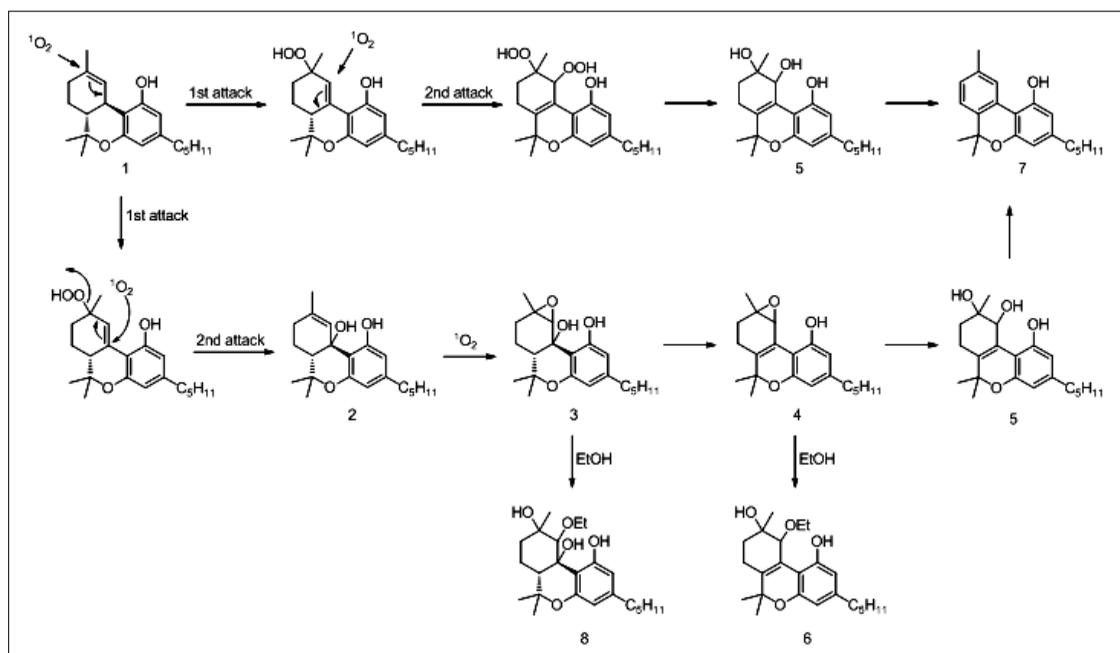


Figure 1: Figure depicts photooxygenation of Δ^9 -THC to CBN

Conclusion

Beside compounds **4**, **5**, and **6**, the characterization of compound **8** as its tosylate supports the possible formation of the intermediates **2** and **3** with benzylic hydroxyl groups. The involvement of light in the process of decomposition has also been previously observed (Harvey, 1990; Brogan *et al.*, 2007). In addition, exposure to atmospheric oxygen accelerates the degradation process. Taking together the light and the oxygen factors lead to the assumption that Δ^9 -THC may play the role of self sensitizer, acting to generate $^1\text{O}_2$ which

needs verification. However, the relative stability of Δ^9 -THC in crude extract of cannabis might be explained by the fact that carotenoids present in the crude mixture of cannabis inhibit the formation of $^1\text{O}_2$ by the powerful photosensitizer, chlorophyll, as carotenoids are known as efficient singlet oxygen quencher (Fairbairn, 1976). Thus it would be concluded that singlet oxygen photooxygenation, using a natural photosensitizer, could therefore be the mechanism for degradation of Δ^9 -THC to CBN via the characterized intermediates.

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