

A Possible Decomposition Pathway of  $\Delta^9$ -Tetrahydrocannabinol to Cannabinol

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A pathway is proposed for the decomposition of  $\Delta^9$ -tetrahydrocannabinol (I) and its  $\Delta^8$ -isomer (IX) with the eventual formation of cannabinol (II) through epoxy and hydroxylated intermediates.

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Sir:

$\Delta^9$ -Tetrahydrocannabinol ( $\Delta^9$ -THC) (I) is the main psychomimetically active component of *Cannabis sativa* L. (marihuana).

It has been shown that  $\Delta^9$ -THC, synthetic or in plant material, decomposes upon storage to the less psychoactive compound cannabinol (CBN) (1,2,3) (II). Cannabinol has been shown to potentiate  $\Delta^9$ -THC-like activity (4). Although II is the major observed decomposition product, it could not account for the decrease in the concentration of I over a period of time when the latter is kept under conditions suitable for decomposition (5). A decomposition pathway from I to II has been suggested by Turner, *et al.*, (2) and Garrett and Tsau (6).

During our work with *Cannabis* plant material we have isolated many polyoxygenated cannabinoids as minor components. These include 9,10-dihydroxy- $\Delta^6$ a(10a)-THC (VI) (two compounds, each of which is a racemic mixture), 10-ethoxy-9-hydroxy- $\Delta^6$ a(10a)-THC (VII), and 8,9-dihydroxy  $\Delta^6$ a(10a)-THC (VIII) (racemic mixture) (7,8). The fact that all these compounds were racemic mixtures, or partially racemic, indicated that they might

be artifacts derived either from I or  $\Delta^8$ -THC (IX). The latter is also believed to be an artifact in *Cannabis* (9) through migration of the double bond of I to the 8,9 position to provide the more thermodynamically stable isomer.

We found that all these hydroxylated cannabinoids could only be detected by GC as their TMS derivatives. Direct injection into the GC of any of these compounds underivatized resulted in CBN (II). Also, these compounds were easily converted to CBN by reflux with trace amounts of acid in methanol. These observations indicated that these compounds were susceptible to acid or heat and in all cases the final product was CBN.

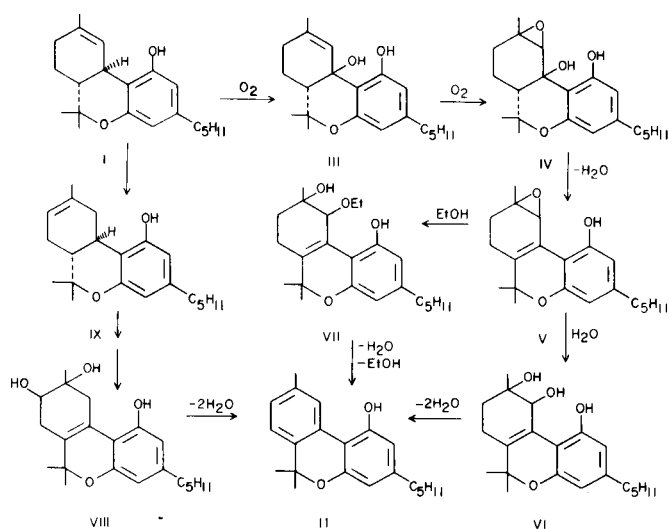
Thus, our data suggest that the conversion of  $\Delta^9$ -THC to CBN in the plant material should proceed, at least in part, through hydroxylated intermediates. A mechanism for such conversion is herein suggested as shown in Scheme I.

Compound III and IV are the only compounds that have not been isolated or detected in *Cannabis* while compound V has previously been detected (7). We propose III and IV as intermediates in the formation of V. In the same study, compounds VI and VII were isolated from an old ethanol extract of *Cannabis*. This adds supportive evidence to the existence of compound V, since VI and VII would be the logical products formed by solvolysis of V with water and ethanol respectively. Treatment of VI or VII with acid provided II. Also direct gc of either compound gave II.

In another study on Indian *Cannabis sativa* L. plant material, stereo isomers of VI and VIII were isolated (8). Formation of VIII is best explained through IX following the same general mechanism as shown for VI. As in the case of VI and VII, compound VIII was smoothly converted to II.

Razdan (10) proposed the epoxide V as an intermediate in the biosynthesis of cannabidiolic acid-tetrahydrocannabinol ester which was isolated by Van Spulak, *et al.*, (11).

The decomposition of I to II occurs in stored *Cannabis*. Previously it was shown that II was not present in freshly



Scheme I — Proposed pathway for decomposition of  $\Delta^9$ -THC (I) to CBN (II).

harvested plant material (12); moreover, the biosynthetic pathway proposed in 1970 by Nishioka's group (13) and validated by his group in 1975 (14) shows no cannabinol. Therefore, it would seem that our proposed mechanism is for the decomposition of I to II rather than a biosynthetic pathway. Further support for this decomposition is indicated by the fact that all four stereo isomers of VI have been isolated (7,8). Work is in progress to ascertain if pure  $\Delta^9$ -THC would undergo decomposition to CBN through the same intermediates (15).

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