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THE ABSOLUTE CONFIGURATION OF Δ^1-TETRAHYDROCANNABINOL, THE MAJOR ACTIVE CONSTITUENT OF HASHISH.[1]

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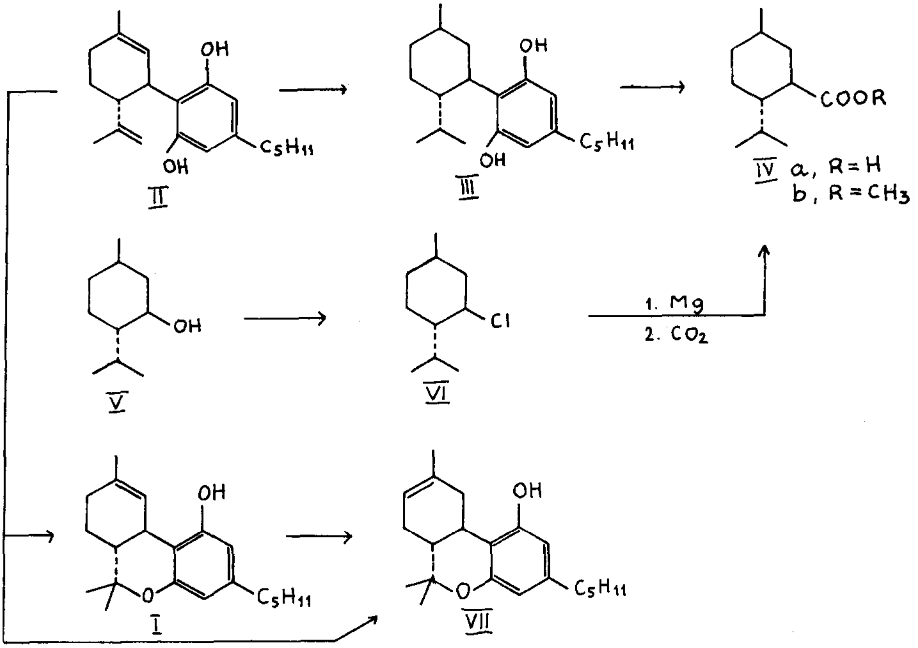
We have recently reported[2,3] the isolation, structure elucidation and partial synthesis of (-)-Δ^1-tetrahydrocannabinol (I), the major active principle in hashish, as well as a total synthesis of the racemate of I. We wish now to present data showing that the absolute configuration of the naturally occuring (-)-I is D, relative to D-(+)-glyceraldehyde.

Adams[4] has reported that tetrahydrocannabidiol (III) obtained by reduction of cannabidiol which has since been shown to possess structure II[5], can be oxidized to menthane carboxylic acid (IVa). The anilide of IVa, thus obtained did not depress the melting point of the anilide of IVa prepared from menthol (V) through the menthyl chloride (VI) followed by carbonation of the Grignard derivative of VI. Unfortunately the rotation of the anilide of IVa prepared by the degradation of the natural product was not reported.

We have now repeated and extended this correlation. Catalytic hydrogenation of (-)-cannabidiol (II) gave a mixture of the two C_1 epimers which could be separated by column chromatography on Florisil. The chromatographically more polar isomer (III) was oxidized with potassium permanganate in acetone. The acidic product obtained was esterified with diazomethane and purified by preparative vapour phase chromatography (0.2% Apiezon L on glass beads at 150°). The pure menthane carboxylic acid methyl ester IVb thus obtained ($[\alpha]_D^{EtOH}$ -40°) was identical in all respects (IR, NMR, TLC, rotation) with IVb prepared from D-(-)-menthol through the acid IVa followed by methylation. Basic hydrolysis of IVb, obtained by degradation of cannabidiol, gave D-(-)-menthane carboxylic acid (IVa) (m.p. 64-5°, $[\alpha]_D$ - 44°) also identical in all respects (IR, NMR, TLC, rotation, mixture m.p.) with IVa prepared from D-(-)-menthol.

D-(-)-Menthol V has been interrelated with D-(+)-glyceraldehyde[6]. This correlation establishes therefore the absolute configuration of cannabidiol (II). As the latter has been converted[2] into Δ^1-tetrahydrocannabinol, the major constituent of hashish and into[7] $\Delta^{1(6)}$-tetrahydrocannabinol (VII) a minor constituent of some marihuana samples[7c], the above correlation establishes the absolute configuration of these natural products. Šantavý[8] has reached similar conclusions, mainly by comparison of optical rotation data from the literature. However, some of the rotations compared were of compounds which were later shown to be mixtures[7b] and hence Šantavý's assignments had to be confirmed.



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