

SPECIALIA

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A new one-step synthesis of hexahydrocannabinoid analogs

S. Y. Dike, Meera Kamath and J. R. Merchant¹

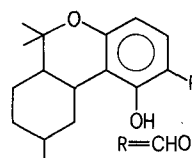
Department of Organic Chemistry, Institute of Science, 15, Madame Cama Road, Bombay-400032 (India),
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Summary. A one-step synthesis of hexahydrocannabinoid analogs (HHC) is described making use of the condensation of phenolic ketones and aldehydes with citronellal in the presence of pyridine.

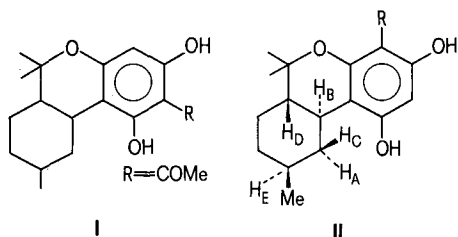
During the last few years, a number of syntheses have been developed for obtaining tetrahydrocannabinoids (THC) and their derivatives²⁻⁴. Some of the earlier syntheses of THC derivatives involved the condensation of citral with the lithium derivative of olivetol dimethyl ether, giving an overall yield of 2% of the final product⁵. A minor modification of this synthetic procedure giving about 20% yield of Δ^1 THC utilizes the reaction of citral with olivetol in the presence of acid reagents, giving different compounds depending upon the reagents used⁶. Crombie and co-workers⁷ have published a number of papers on the reaction of citral with different phenolic compounds in the presence of pyridine, when the reaction proceeds in a different manner and yields compounds having structures different from THC. In the course of our work on the synthesis of naturally occurring chromene derivatives⁸, we studied the reaction of phloroacetophenone with citronellal in the presence of pyridine. Citronellal has only 1 double bond and it was of interest to see what course the reaction followed under basic conditions. Equimolecular amounts of the reactants were heated at 145–150°C for 8 h. The resinous reaction product after chromatography over silica-gel afforded [from the fraction with benzene-chloroform (80:20)] a colourless crystalline compound, m.p. 233–235°C in 7% yield. TLC showed it to be a single compound, and the mass spectrum indicated its mol.wt to be 304. On mechanistic grounds as well as analytical and spectral evidence, the compound could have either the structure **I** or **II**.

on C₁. It is coupled to H_C, which appears at unusually high field, for the same reason, at δ 0.2 as a quartet ($J = 12$ Hz). Thus H_C has 2 other large couplings, namely to H_B and H_E which are diaxial to it, and therefore both H_B and H_E are axial, while CH₃ at C₉ is equatorial. H_E produces a very broad signal at δ 1.62 and H_B gives a double triplet at δ 2.37 ($J = 12.12$ and 4.5 Hz) since this hydrogen has 2 large couplings, it too is axial and therefore the ring junction is trans. This defines the relative stereochemistry of all 3 chiral centres as shown in **II**. The remaining signals are: δ 0.94 (3H, d, $J = 12$ Hz, C₉-CH₃), δ 1.07 (3H, s, gem-dimethyl), δ 1.37 (3H, s, gemdimethyl). The latter signal is shifted downfield due to the influence of the neighbouring heterocyclic oxygen, δ 1.75 (8H, m, 4-CH₂).

The reaction of β -resorcyraldehyde with citronellal in the presence of pyridine gave a similar type of compound as an oil. Its NMR (CDCl₃) showed an AB pattern for 2 aromatic protons, in addition to other signals confirming structure **III**.



III



Structure **I** was ruled out on the basis of the NMR (60 Mc)-spectrum (CDCl₃ + deuterated (DMSO), the aromatic proton was observed at δ 5.85 and the hydrogen bonded OH at δ 14.8, whereas the other hydroxyl proton appeared at δ 9.8. These data are consistent with structure **II**, since for **I** the 2 hydroxyl protons would have given a signal around δ 11.62⁹. The 270 Mc spectrum (CDCl₃) further confirmed structure **II** and also its stereochemistry. The proton H_A appears at unusually low field¹⁰ at δ 3.15 as a broadened doublet ($J = 12.5$ Hz), presumably because of steric crowding with the OH group

- 1 Grateful thanks are accorded to Drs L. Chopard and S. Selvayayakam for spectral measurements and Dr I. Fleming for useful discussion.
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