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TETRAHYDROCANNABINOLS BY TERPENYLATION OF OLIVETOL WITH (+)-trans-2- and -3-CARENE EPOXIDES

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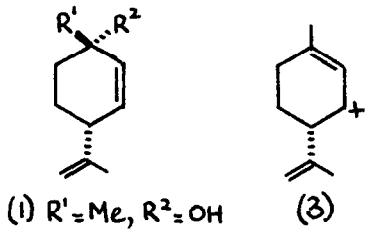
Summary: Re-examination of the acid-catalysed terpenylation of olivetol by (+)-trans-2-carene epoxide shows that cannabidiols, as well as tetrahydrocannabinols, are produced, necessitating a re-evaluation of the mechanism and status of the reaction. The major cannabinogenic intermediate trapped from p-TSA treatment of (+)-trans-3-carene epoxide is phellandrene-8-ol: this explains the formation of tetrahydrocannabinols when olivetol is present.

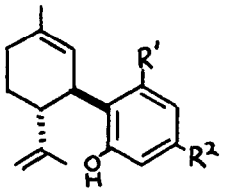
Petrzilka's condensation of (+)-cis- or trans-p-menthadienol (2) or (1) with olivetol under acidic conditions provides a good synthetic route to the sequence (-)-cannabidiol(4), (-)-Δ^1-tetrahydrocannabinol(Δ^1-THC)(6), and its (-)-Δ^6-isomer(7):[1,12] allylic cation(3) is considered to be the terpenylating agent. Condensation of (+)-trans-2-carene epoxide with olivetol, catalysed by p-TSA or BF_3, is claimed by Razdan and Handrick to be a different type of reaction (cf.8).[2] It is reported that although Δ^1- and Δ^6-THC's are formed along with products of the cis-series, no cannabidiol is produced and the results are interpreted as suggesting that trans- and cis-Δ^1-THC's are first formed [(8) → (9) → (6) and cis-(6)] and then partly converted into other products.[2] This mechanism has been widely cited in reviews.[3]

In a re-examination we find that (+)-trans-2-carene epoxide (cf.8)[4] (1.2 mol) and olivetol (1 mol), when treated with p-TSA in benzene at 20°C, do in fact form 'ortho'-(5) and 'para-'(4) cannabidiols[6] along with Δ^1-THC(6) after 2 h (approx. 1:1:2, with traces of Δ^6-THC). Analysis was by gc/ms as trimethylsilyl derivatives using a 50 ft SCOT OV225 column, comparing with synthetic specimens. After 8 h, tlc indicated mixtures of Δ^1- and Δ^6-THC's, along with other products, and glc after 24 h confirmed this and showed no cannabidiols now remained. Reactions of (+)-trans-2-carene epoxide and of (+)-p-menthadienol were closely monitored and compared. Examination (tlc and glc) after 0.5, 1.0 and 2.0 h showed that in both cases 'o-' and 'p-' cannabidiols were formed followed by Δ^1- and then Δ^6-THC. Although the common product profiles were similar, the 2-carene epoxide reaction showed extra peaks not found in the p-menthadienol reaction, and gave lower yields of cannabinoids,

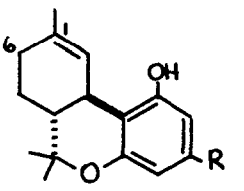


(1) R^1=Me, R^2=OH
(2) R^1=OH, R^2=Me

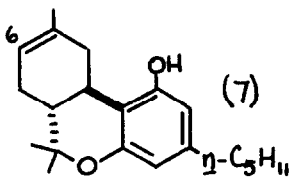
(3)



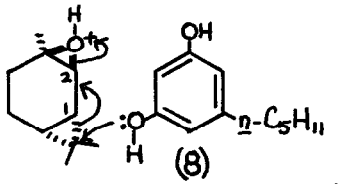
(4) R^1=OH, R^2=$\underline{n}$-C_5H_{11}
(5) R^1=$\underline{n}$-C_5H_{11}, R^2=OH



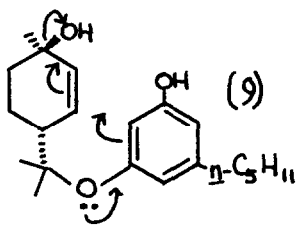
(6) R=$\underline{n}$-C_5H_{11}



(7)



(8)



(9)

indicating competing side reactions.

Treatment of 2-carene epoxide with p-TSA in benzene at 50°C gave (gc/ms) cis-p-menthadienol(2) along with other products, and this is in line with reports that 2-carene epoxide is readily converted into cis-p-menthadienol under acidic conditions.[5,7] Our view of the reaction is that there is no evidence requiring a special mechanism of type (8), (9) and cannabidiol and Δ^1-and Δ^6-THC's arise from the p-menthadienyl cation(3) with 2-carene epoxide acting essentially as a surrogate for (+)-p-menthadienol.

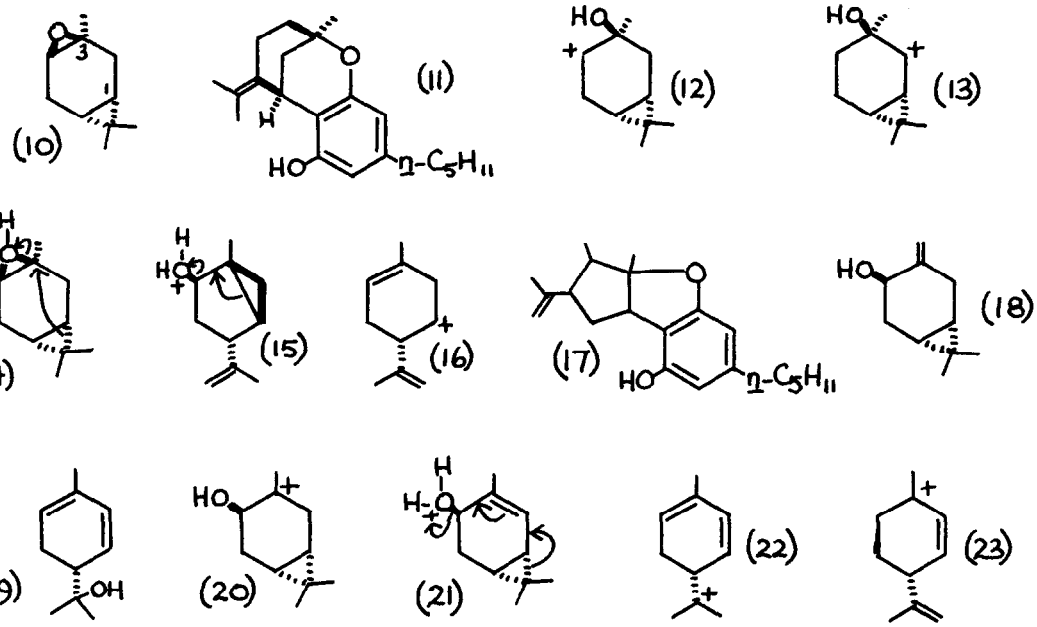
Unexpectedly, Montero and Winternitz[8a] report that terpenylation of olivetol with (+)-trans-3-carene epoxide (10) in the presence of p-TSA in benzene also gives (-)-Δ^6-tetrahydrocannabinol(7)(25%) but no products of the cis-THC series (iso-THC's). Although our yields are poorer (6-10%), and we find that iso-THC's are produced [e.g. $\Delta^{4,8}$-iso-THC(11)], we have confirmed by isolation that the Δ^6-THC does indeed belong to the natural(-)-series ($[\alpha]_D^{25}$-150°). In order to account for the latter chirality it was suggested[8b] that (+)-trans-3-carene epoxide underwent acid catalysed conversion to a secondary carbonium ion(12) followed by a 1,3-hydride shift(13) leading via (2) to (3): there are clearly objections to this scheme.

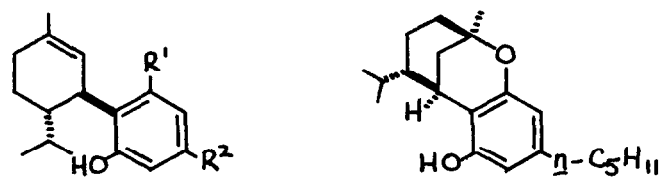
An alternative route to Δ^6-THC would be via a Kropp-type[9] rearrangement leading from (14) to (15) and hence (16), followed by terpenylation of olivetol. In order to test this, we have made the cyclopropylmethanol(15)[9] and treated it with olivetol in the presence of p-TSA in benzene. Among the products,(17) and its isopropylidene isomer were isolated and identified but no THC's were formed (tlc, glc): some other explanation is required.

(+)-trans-3-Carene epoxide was treated with p-TSA in benzene at 60°C for 30 min. At least 33 different compounds were formed and the mixture was separated chromatographically, testing each group of fractions for their

ability to react with olivetol in the presence of p-TSA to give Δ^6-THC. The ability was confined to one fraction from which was separated (18) and (19), and tests showed that the latter was the important precursor. Compound (19), α-phellandrene-8-ol,[10] was identified by uv, ^{1}Hmr and ^{13}Cmr spectra and by comparison with an authentic specimen separated from the many products formed when citral is treated with aqueous acid.[10b] The origins of Δ^6-THC from 3-carene epoxide can thus be explained as initial acid-catalysed reaction of the latter leading via (20) and (21) to carbonium ion (22) which can be trapped as (19) or, via proton elimination and addition, leads to carbonium ion (23) corresponding with (3).

Consistent with these proposals, α-phellandrene and p-TSA react with olivetol at 21°C to give dihydrocannabidiol(24)(45%), together with small amounts of (25). At 80°C the iso-dihydro-THC(26) was obtained (51%). These terpenylations, initiated by proton addition rather than the usual elimination of protonated hydroxyl, were extremely clean reactions. In order to generate the allylic ion (3)⟷(23) from 3-carene epoxide, conditions have to be more





(24) R' = OH, R² = n-C₅H₁₁

(25) R' = n-C₅H₁₁, R² = OH

(26)

severe than, for example, generation from p-menthadienol: consequently Δ^6- rather than Δ^1-THC is obtained. But when phellandrene-8-ol(19) is used as terpenylating agent, conditions can be adjusted so that either Δ^1 or Δ^6-THC predominates: at 50-80° yields of Δ^6-THC were 35%.

The present work raises the question as to whether acid catalysed terpenylations of olivetol with citral,[11] leading amongst other products to (±)-Δ^1- and (±)-Δ^6-THC, involve cyclisation of citral before, or after, attachment to olivetol. Doubtless this will depend on conditions, but our tests using p-TSA in dichloromethane[12] indicate that in that system cyclisation before phenol condensation is a minor pathway.

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