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HASHISH II: REACTION OF SUBSTITUTED RESORCINOLS WITH CITRAL IN THE PRESENCE OF PYRIDINE - A PROPOSED MECHANISM

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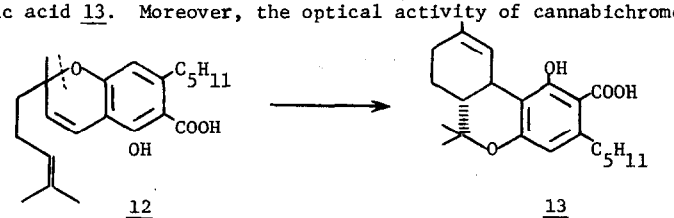
We recently reported a one-step total synthesis of dℓ-cannabicyclol and dℓ-cannabichromene from olivetol and citral in the presence of pyridine.[1] Similar results have also been reported by Crombie and Ponsford.[2] A more recent paper of these authors[3] working with phloroglucinol prompts us to record our new findings at this time. We too have found that phloroglucinol 2 (R = OH) reacts with citral 1 in pyridine (1:1:1) to give a crystalline tetracyclic ether 6 (R = OH), mp 170° in 35% yield. The mass spectrum confirms the molecular composition $C_{16}H_{20}O_3$ (m/e calcd. for $C_{16}H_{20}O_3$ 260.1412. Found: 260.1408).[4] In addition to 6 (R = OH), we have isolated another crystalline compound of the cyclobutane type to which we assign structure 8 or 9,[5] mp 215-217°, in 5% yield. The mass spectrum confirms the molecular composition $C_{26}H_{34}O_3$ (m/e calcd. for $C_{26}H_{34}O_3$ 394.2508. Found: 394.2520). These results confirm our earlier contention[1] that the reaction between substituted resorcinols and citral in pyridine to form tetracyclic ethers of type 6 is a general one and leads to substituted iso-tetrahydrocannabinol (THC) derivatives 7.

The reaction of resorcinol 2 (R = H) with 1 gives a complex mixture from which, by column chromatography on florisil (ether-petroleum ether), we have been able to isolate a bischromene derivative 10. Another fraction contained a mixture of isomeric monochromenes 5 (R = H) and 11, whose structures were suggested by nmr. The mixture could not be separated by glc or thick-plate tlc.

In the olivetol series we found that treatment of cannabichromene 5 (R = C_5H_{11}) with pyridine gave only the tetracyclic ether 6[6a] in contrast to the results of Crombie and Ponsford, who also obtained cannabicyclol 4 (R = C_5H_{11}).[2] The mixture of 5 (R = H) and 11 treated in a

similar manner likewise gave only a tetracyclic ether 6 (R = H) and less than 1% (by glc) of a compound whose identity could not be proven.[6b]

Although Crombie and Ponsford have suggested that cannabichromene appears to be the key compound formed in the pyridine reaction with citral and olivetol, we are more inclined to believe that the triene 3 is first formed. The triene is then converted either to cannabichromene 5 (R = C_5H_{11}) and thus to tetracyclic ether 6 (R = C_5H_{11}) or to cannabicyclol 4.[7] In this connection it is interesting to note that the same products are obtained when 1 and 2 (R = C_5H_{11}) are reacted in the presence of either 1 mole or 3 moles of pyridine.[2,8] The postulation of triene as an intermediate *in vivo* is implied by the recent observation[9] that optically active cannabichromenic acid 12 was found exclusively in the seedling plant almost one week prior to the appearance of tetrahydrocannabinolic acid 13. Moreover, the optical activity of cannabichromene itself (as reported



12 13

by Korte[10]) and now particularly that of 12 strengthens the belief that cannabichromene is, in fact, a natural product and not an artifact.[3]

Crombie and Ponsford[3] proposed a mechanism for the acid-catalyzed (mineral acid/BF_3) reaction of citral and olivetol.[11] We suggest the following alternative mechanism. Mineral acids are known to cyclize citral to 14 and 15. Citronellal, which is considered to have the same geometry as citral, gives isopulegol and neo-isopulegol upon treatment with mineral acids,[12] and citral should give a similar compound in the neo series, although it has not been reported. It is therefore likely that in the presence of mineral acids or BF_3 citral first undergoes a cyclization step, which is followed by the mechanism indicated. We can rationalize the products in this way. In fact, the isolation of 16 by Taylor[11a] lends support to this pathway.

Acknowledgment

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2. L. Crombie and R. Ponsford, Chem. Commun., 894 (1968).

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4. All compounds were characterized by IR, UV, NMR and mass spectra.

5. This possibility is considered because Crombie and Ponsford[2] have suggested an alternative structure for cannabicyclol, which corresponds to 9. Our comments on Crombie's structure for cannabicyclol has been given in Reference 1. Further detail NMR work on this compound 9 is in progress and will be the subject of a future communication.

6. (a) The products of the reaction were determined by glc. A 1/4" x 8' aluminum column packed with 10% SE-31 on 80-100 mesh chromsorb W at 220° was employed in conjunction with a Micro-tek GC 2500 R model gas chromatograph equipped with a flame ionization detector. The flow rate of helium as a gas carrier was about 80 ml/per minute. Pure cannabichromene gave only 40% conversion to the tetracyclic ether at 140° for 7 hours in pyridine (1 mol). After reaction with pyridine at 110° for 7 hr, a mixture of cannabichromene (68.3%), cannabicyclol (11.1%), unknown (6.9%), and tetracyclic ether (13.7%) gave cannabichromene (56.9%), cannabicyclol (12.7%), unknown (9.6%), and tetracyclic ether (19.8%). Glc indicated that the cannabicyclol peak had increased about 1.6%, but such a small difference could lie within the experimental error of measurements of the areas below these peaks.

   (b) The above column was employed at 202°C. When treated with pyridine (1 mole) at 140° for 7 hr, a mixture of pure chromenes (5 and 11) gave the corresponding tetracyclic ether (19%), unidentified compound (0.7%), and chromenes (80.3%). We would like to thank Mr. Rafael Cruz-Alvarez for these measurements.

7. Both the structures (4 and 4a) put forward for cannabicyclol can be arrived at on mechanistic grounds.

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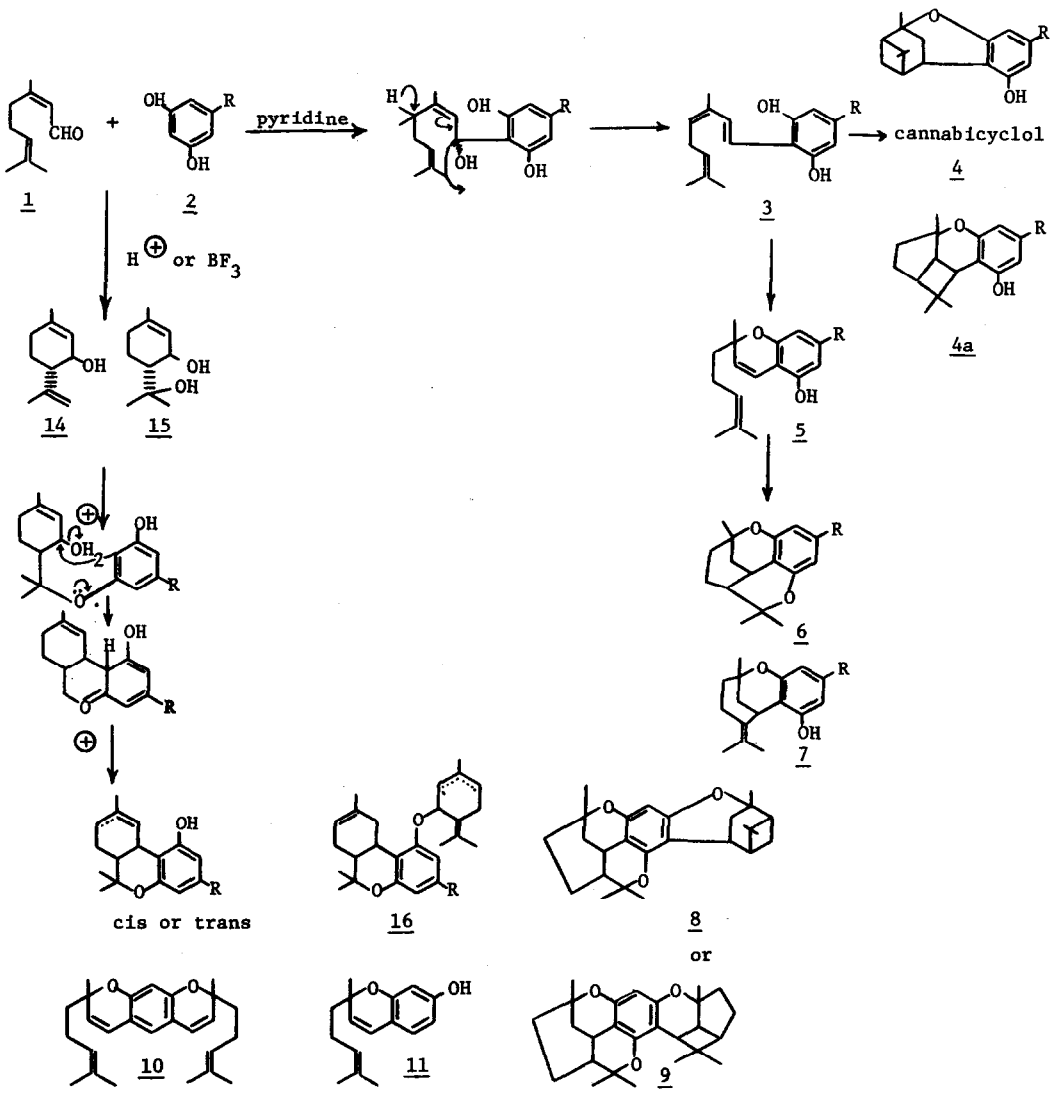
pyridine
cannabicyclol
4
4a
H⊕ or BF3
cis or trans
16
8
or
10
11
9