STEREOSPECIFIC CICLIZATIONS AND ISOMERIZATIONS OF CANNABICHROMENE AND RELATED CANNABINOIDS.

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We have reported the isomerization by p-toluensulphonic acid of \triangle^1 -<u>cis</u>-tetrahydrocannabinol $(\triangle^1$ -<u>cis</u>-THC) (I_a) and cannabichromene (IIa) to $\triangle^{4(8)}$ -<u>iso</u>-THC (III) and related reactions (1,2). Crombie (3) has pointed out that most of the compounds which are obtained from cannabichromene can be formed through cation A. We report now some observations which throw additional light on the subject.

Cannabichromene (IIa) (2) in methylene chloride reacts with excess 10% boron trifluoride etherate in the same solvent at -20° for 5 hr. to give 16% tetracyclic diether (IV) (4), 67% \triangle^8 , 3,4 -<u>cis</u> -<u>iso</u>-THC (V) (3) and 10% starting material. None of them isomeric \triangle^8 -3,4-<u>trans-iso</u> -THC (1) was isolated or detected by vpc. The structure of V was established by hydrogenation to the known dihydrocompound (1). The cyclization apparently takes place with cannabichromene (IIa) in conformation \ll through cation A.

By contrast cannabichromene acetate (IIb) in methylene chloride reacts with excess 5% boron trifluoride etherate in the same solvent at 4° for 40 hr. to give 10% \triangle ¹-<u>cis</u>-THC acetate (Ib) (5), 10% <u>cis</u> tricyclic acetate VIb and ca. 80% polymeric material. The acetate VIb was hydrolysed to the known (6) VIa. The formation of Ib and VIb is unusual. It has been postulated (3) that in this series once ring A is formed at the chromene stage it remains. The isomerization of IIb to Ib which is an exception to this rule, probably proceeds in conformation \propto and by the mechanism indicated through intermediate B.

The formation of VIb involves a stereospecific cyclization and a reduction. Boron trifluoride initiates the ring closure by coordination with the terminal double bond of the diene system, which is probably in conformation β which allows maximal overlap of π orbitals. The <u>cis</u> ring closure is apparently due to the antiparallel nature of the cyclization. The intermediate bensylic cation C then may react with a hydride ion, the origin of which is uncertain (7). In this intermolecular hydride shift the boron trifluoride is essential,^{*} as in the cyclization of cannabichromene acetate IIb with methane sulphonic acid in methylene chloride at 20⁰ for 3 hr. only the expected tricyclic chromene VIIIa and its acetate are formed. Compound VIIIa, which was characterized by analysis and has the

m Boron trifluoride is known to form a complex with phenolic acetate groups. (9a)







RO

с_ц ,5¹11





II (conformation β)







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a, R = H. $b, R = COCH_3$

appropriate i.r., u.v. and n.m.r. spectra, on hydrogenation gives a mixture of the known <u>cis</u> VIa and <u>trans</u> VIIa. (6)

A further type of cyclization is observed when cannabichromene (IIa) reacts with excess 5% boron crifluoride in methylene chloride at 20⁶ for 24 hr. Cannabicyclol (4b,8) (IX) (30%) and $\triangle^{4(8)}$ -<u>iso</u>-THC (III)(56%) are the major products; $\triangle^{1(6)}$ -<u>trans</u>-THC and \triangle^{1} -<u>cis</u>-THC (Ia) are formed in ca. 5% each. When this reaction is stopped after 15 min. \triangle^{1} -<u>trans</u>-THC is likewise isolated (10%). The formation of IX probably proceeds <u>via</u> the hypothetical intermediate D, which involves coordination with both the free phenolic group and the chromene double bond (cf. 9b,10) in conformation β of cannabi-chromene (IIa). (cf. 4b).

In conclusion it should be pointed out that while IX and $\triangle^{1(6)}$ THC are stable to 5% boron trifluoride in methylene chloride at room temperature, $\triangle^{4(8)}$ -iso-THC (III), the tetracyclic diether IV, \triangle^{1} -cis-THC (Ia), \triangle^{8} -cis-iso-THC (V), \triangle^{8} -trans-iso-THC and \triangle^{4} -iso-THC (III) equilabrate (presumably through cation A) to a mixture in which III is the major component (65%).

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^{*} This equilibrium has been independently observed by Dr. R.K. Radzan of A.D. Little, Inc. in Cambridge, Mass. (private communication).

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