Tetrahedron Letters No.56, pp. 4947-4950, 1969 Pergamon Press. Printed in Great Britain.

HASHISH IV[1]: SOME ACID CATALYZED TRANSFORMATIONS IN CANNABINOIDS

Raj K. Razdan and Barbara A. Zitko
Organic and Medicinal Chemistry Laboratories
Arthur D. Little, Inc., Acorn Park, Cambridge, Massachusetts 02140

(Received in USA 8 September 1969; received in UK for publication 5 November 1969)

It is well known that Δ^1-3,4-*trans*-tetrahydrocannabinol (5), the major active constituent of hashish, is completely isomerized to $\Delta^{1(6)}$-3,4-*trans*-THC (7) when refluxed with p-toluenesulfonic acid (p-TSA) in benzene.[2,3,4,5] The acetate of 5 behaves similarly. In contrast Δ^1-3,4-*cis*-THC (1) is converted to $\Delta^{4(8)}$-iso-THC (4) and the acetate of (1) is recovered unchanged under similar conditions. This last experiment led Gaoni and Mechoulam to suggest an apparent concerted reaction for the conversion of 1 to 4. These authors also explained the difference in behavior between the *cis* and the *trans* series on the basis of relief of steric strain in the *trans* series.[6]

In this communication we describe that 1, citrylidene-cannabis (2) and iso-THC's (3 and 4) are interconvertible. On the basis of this equilibrium and other results we wish to propose an interpretation of acid-catalyzed transformations in cannabinoids.

We have found that refluxing 1[7] with p-TSA in benzene, followed by the usual workup and gas chromatographic analysis,[8] gave a product showing peaks for three additional compounds along with unchanged 1. The new compounds were identified[9] as 2 and the isomeric iso-THC's 3 and 4. Similarly we have found that treatment of pure 2[10,11,12] gave mainly 4, with some 3 and 1 along with unchanged 2. A more detailed examination of this reaction of 2 (aliquots taken at different time intervals and analyzed by glc) revealed that initially 3 was formed, which changed mainly to 4 with time. Furthermore, treatment of a pure mixture of iso-THC's[10] 3 and 4 under identical conditions formed 1 and 2 in small amounts.

These results indicate that treatment with p-TSA in refluxing benzene produces an equilibrium[13] among 1, 2, and iso-THC's, which heavily favors the iso-THC's, particularly 4 (scheme a). Ring B of 2 cleaves[11b] preferentially to give 3, which we have shown is mostly converted to 4, the more thermodynamically stable isomer. It therefore follows that the acetate of 1 will be recovered unchanged as observed by Gaoni and Mechoulam,[6] since the formation of 2 is blocked. Our results also explain why a transformation parallel to the *cis* series (to iso-THC's) does not take place in the *trans* series. This is because the tetracyclic 2[10] with a *trans*-3a,4 ring junction cannot be formed. An examination of the Dreiding models clearly confirms this. The conversion of 1 to 4 therefore takes place through 2 which is the key intermediate and has a *cis*-3a,4 ring junction. Had the oxygen ring opened first to give a diol of type 6, some 7 would have been formed[14] (see below).

Furthermore, 1 was allowed to react with boron tribromide in methylene chloride at -20°C for 1.5 hr, and the reaction mixture was quenched in liquid ammonia. A gum was obtained, which after purification by chromatography (60%), was found to be identical to 7 in all respects. This is the first example of an interconversion of *cis* into *trans*-THC. Interestingly, Mechoulam and co-workers[14] have observed that *cis* cannabidiol (6), like *trans* cannabidiol (8), on treatment with p-TSA is changed to 7. The mechanism of conversion of 1 to 7 must therefore involve cleavage of the ether bond to give the *cis* diol 9, followed by inversion to the more thermodynamically stable 10, with the *trans* ring junction, followed by ring closure.

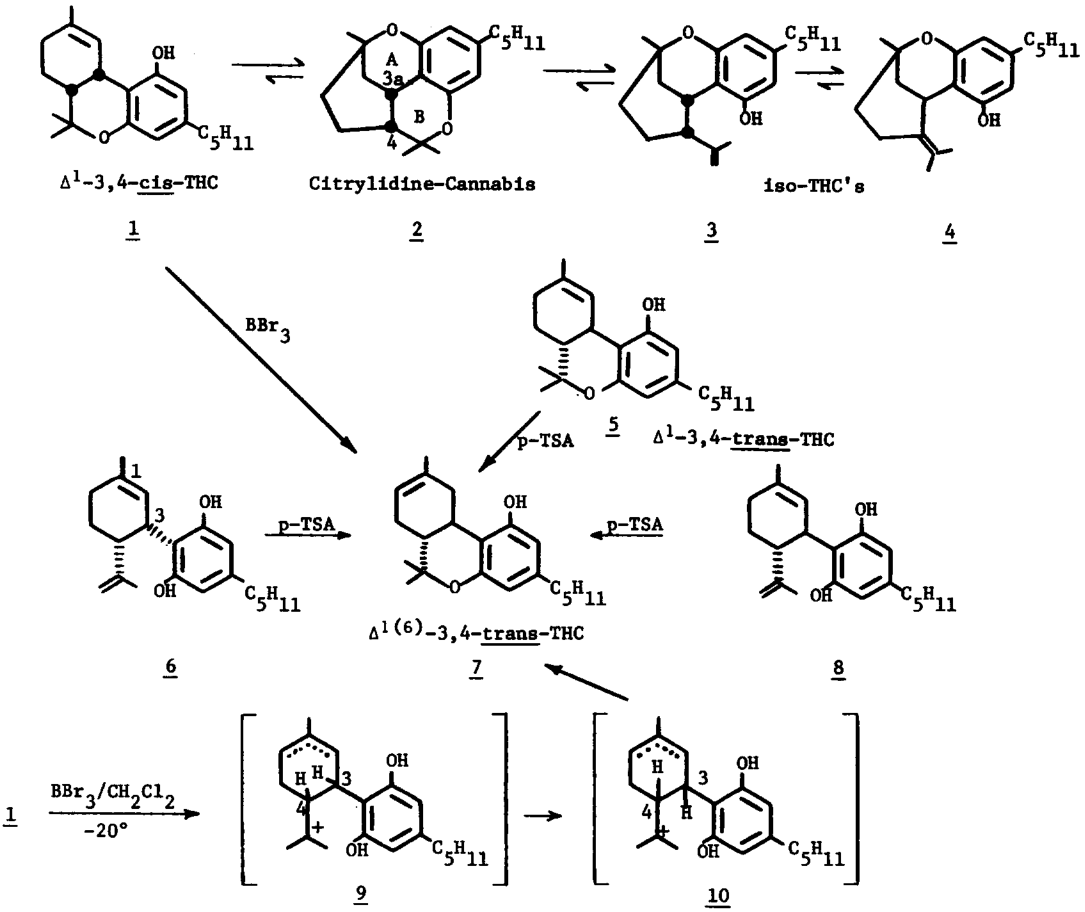
It is also known that another cannabinoid, cannabichromene (11), gives different products with different acid catalysts (scheme b).[10,11b,12,14]

We conclude that in cannabinoids that have one of the oxygens tied up in the form of a pyran ring, acid catalysts like p-TSA, which can protonate a double bond, effect transformations with retention of stereochemistry at the C_3-C_4 ring junction. However, non-protonic acid catalysts like BBr_3, BF_3, effect interconversions with inversion at the C_3-C_4 ring junction to more thermodynamically stable forms.

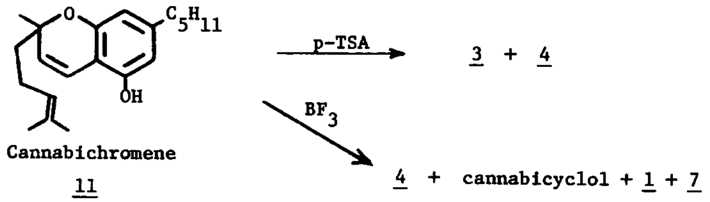
The conversion of both *cis* (6) and *trans* (8) cannabidiols to 7 with p-TSA therefore becomes understandable. The fact that 7 and not the iso-THCs is the major product formed from 6 implies that the rate of inversion should be much faster than oxygen participation at C_1. Similarly the products obtained from cannabichromene (scheme b) can be easily explained. The geometry is fixed[11b] because of the chromene ring in 11, and only iso-THCs 3 and 4 are formed with p-TSA. With BF_3 the cleavage of the chromene is a competitive reaction and thus some *cis* and *trans*-THCs are formed.

Further work along these lines is in progress and will be the subject of future communications.

Scheme a



Scheme b



Acknowledgment: We wish to thank Dr. R. Lyle for helpful discussions.

REFERENCES

1. For Hashish III: see R. K. Razdan and V. V. Kane, J. Am. Chem. Soc., **91**, 5190 (1969).
2. Y. Gaoni and R. Mechoulam, Tetrahedron **22**, 1481 (1966).
3. E. C. Taylor, K. Lenard and Y. Shvo, J. Am. Chem. Soc. **88**, 367 (1966).
4. R. Hively, W. A. Mosher, and F. Hoffmann, ibid. **88**, 1832 (1966).
5. Unpublished results of R. K. Razdan and G. R. Handrick.
6. Y. Gaoni and R. Mechoulam, (a) J. Am. Chem. Soc. **88**, 5673 (1966); (b) Isr. J. Chem. **6**, 679 (1968).
7. Absence of **2** was established by glc.
8. A 1/4" x 6' aluminum column packed with 10% OV-1 on 100-200 mesh Gas Chrom Q at 220° was employed in conjunction with a Micro-tek GC 2500 R model gas chromatograph equipped with a flame ionization detector.
9. The compounds were identified on the basis of relative retention times of authentic samples and by addition of authentic samples to the reaction mixture with subsequent glc. However, in all cases a very minor peak was also observed. It was not **5** or **7** but could not be further characterized.
10. V. V. Kane and R. K. Razdan, J. Am. Chem. Soc. **90**, 6551 (1968).
11. (a) L. Crombie and R. Ponsford, Chem. Commun., 894 (1968).
    (b) Tetrahedron Letters, 4557 (1968).
12. R. Mechoulam, B. Yaganitinsky and Y. Gaoni, J. Am. Chem. Soc. **90**, 2420 (1968).
13. The effect of time on the relative amounts of the components of the system agrees with the postulation in scheme a. Complete details will be published in the full paper.
14. R. Mechoulam, A. Shani, B. Yagnitinsky, Z. Ben-Zvi and R. Braun, Ciba Symposium, April 10, 1969, in London, in press and private communication. They regard the conversion of **6** to **7** as involving an inversion at C_3.