Constituents of *Cannabis sativa* L. An Improved Method for the Synthesis of dl-Cannabichromene

Mahmoud A. ElSohly, Edward G. Boeren, and Carlton E. Turner**

Research Institute of Pharmaceutical Sciences, School of Pharmacy,
University of Mississippi, University, Mississippi 38677

Received January 30, 1978

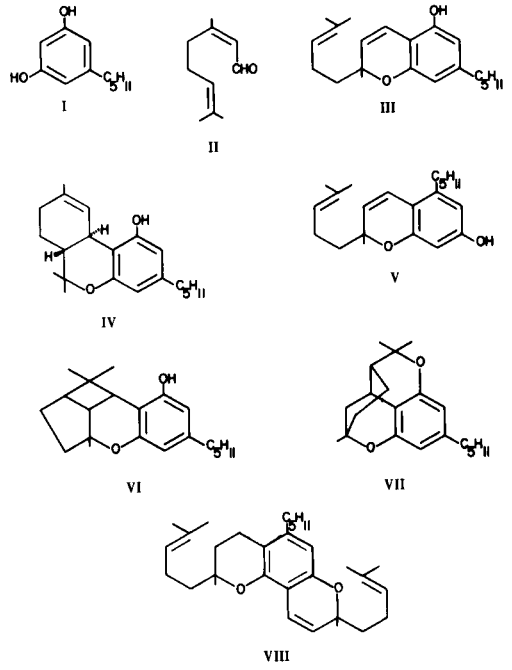
A new procedure was developed for the synthesis of cannabichromene (III) which involves reflux of equimolar amounts of olivetol (I), citral (II) and *t*-butylamine in toluene for 9 hours. The purification of III was best achieved by sodium borohydride reduction of unreacted II followed by column chromatography on 1% sodium hydroxide impregnated silica gel 60-PF. The yield of III (62.0%) was much higher than that reported in the literature.

J. Heterocyclic Chem., 15, 699 (1978)

Sir:

The chemical synthesis of 2-methyl-2(4'-methyl-pent-3'enyl)-5-hydroxy-7-pentylchromene (cannabichromeme), (CBC), (III), a major cannabinoid component of *Cannabis sativa* L. has been the subject of many investigations (1-5). Perhaps the most important method in terms of preparative value includes the condensation of 5-*n*-pentyl-resorcinol (Olivetol), (II), with the monoterpene citral (I) in the presence of pyridine, which results in reported yields of 15% (1,2) and 20% (3) CBC along with other biproducts (Table 1). A mechanism for that reaction was proposed by Kane and Razdan (6). The acid catalyzed condensation of I and II, however, does not give III, but rather a mixture of 3,4-cis and 3,4-trans-Δ^9-THC (IV) along with other side products (7-9).

In our hands, the pyridine catalyzed condensation of I and II yielded 13.7% III when tried under the same conditions (110° for 7 hours) (1,2). In order to study the pharmacology of III and its interaction with other cannabinoids and because of the increasing demand on III by NIDA (National Institute on Drug Abuse) we decided to investigate other reaction conditions that would result in better yields. We found that increasing the molar ratio of II reduces the yield of III and increases that of V and VII. On the other hand, increasing the molar ratio of I significantly decreases the yield of both III and VII and increases that of VI. Also, changing the reaction time did not improve the yield of III. Therefore, we tried other bases for the reaction and we found that *t*-butylamine when used in equimolar amounts with I and II in refluxing toluene (9 hours) resulted in significantly increasing the yield of III (62.0%) while it significantly reduces that of VII (Table 1). We have also noticed that direct chromatography of the reaction product on silica gel faces two problems which make rechromatography a necessity; (a) III and II have almost identical R_f values in different solvent systems. This results in contamination of III with unreacted II, and (b) III and V have close R_f values on silica gel. These two problems were solved in our labs. First, by reduction of the reaciton product with



sodium borohydride in ethanol (1 hour, stirring), II was converted to its corresponding alcohol which is much more polar than III. Analysis of the reaction product before and after reduction showed no effect on the yield of III. Second, column chromatography of the work-up product after the reduction step on 1% sodium hydroxide impregnated silica gel 60-PF[10] resulted in clean separation of III from its isomer V.

This new procedure not only improves on the yield of CBC, but also makes the purification of the reaciton product an easier task.

Acknowledgement.

Supported by the National Institute on Drug Abuse (NIDA), Contract #HSM-42-70-109 and by the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi.

Table 1

Comparison of Literature Procedure with the New Method for the Synthesis of III

	% Yield of Reaction Products				
	III	V	VI	VII	VIII
I + II + Pyridine (110°, 7 hours) (1,2) (1:1:1)	15	3	3	26	6
I + II + *t*-butylamine (reflux in toluene 9 hours) (1:1:1)	62.0	t	t	5.1	t

t = trace

REFERENCES AND NOTES

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

(2) L. Crombie and R. Ponsford, *J. Chem. Soc. (C)*, 541 (1971).

(3) V. V. Kane and R. K. Razdan, *J. Am. Chem. Soc.*, **90**, 6551 (1968).

(4) G. Cardillo, R. Cricchio and L. Merlini, *Tetrahedron*, **24**, 4825 (1968).

(5) R. Mechoulam, B. Yagnitinsky and Y. Gaoni, *J. Am. Chem. Soc.*, **90**, 2418 (1968).

(6) V. V. Kane and R. K. Razdan, *Tetrahedron Letters*, 591 (1969).

(7) E. C. Taylor, K. Lenard and Y. Shvo, *J. Am. Chem. Soc.*, **88**, 367 (1966).

(8) Y. Gaoni and R. Mechoulam, *ibid.*, 5673 (1966).

(9) R. Mechoulam and Y. Gaoni, *Fortshr. Chem. Org. Naturs.*, **25**, 175 (1967).

(10) Sodium hydroxide (1%) impregnated silica gel 60-PF was prepared for column chromatography as followa: A paste was made by adding 1% aqueous sodium hydroxide to silica gel 60-PF for preparative layer chromatography (Brinkmann), (1 ml./1 g.), the paste was dried at 110° and the cake was then passed through a 60 mesh sieve.