

## SYNTHESIS OF CANNABICHROMANONE

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**Abstract** - The synthesis of the cannabis constituent cannabichromanone is reported.

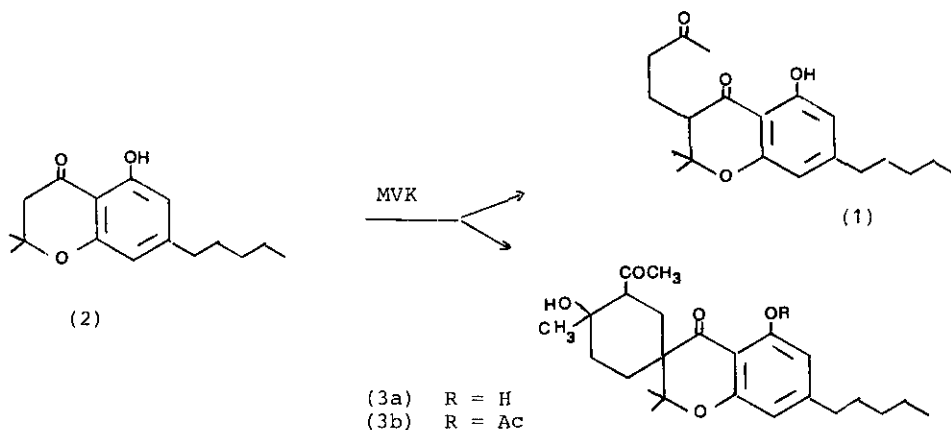
The main constituents of Cannabis extracts are the psychoactive  $\Delta^9$ -tetrahydrocannabinol, cannabidiol and cannabinol. However, a large number of minor components have been found in different materials<sup>1</sup>, some of them in such a low amount, as to prevent their biological activity evaluation.

Among the components of a "green Afghan" sample of hashish Friedrich-Fichtl and Spiteller<sup>2</sup> have recently identified cannabichromanone (1). It was isolated only by preparative gas-chromatography, and its structure assigned on the basis of mass spectral fragmentation. We have now synthesized (1) in sufficient amount to confirm the structure, and to test its biological activity.

An easily envisaged way to prepare (1) is the Michael addition of the anion of the well-known<sup>3</sup> chromanone (2) to methyl vinyl ketone (MVK). Treatment of (2) with equimolar amounts of MVK in benzene in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 1.3 mole/mole) afforded a mixture of two compounds (1 and 3a), which could be separated with great difficulty by repeated thick-layer chromatography. From spectral data (3a) appears to be a product of double attack of MVK on (2), followed by intramolecular aldol condensation. With long reaction times (24 hrs/room temp.) or excess MVK, e.g. when MVK was carried into the reaction vessel by vapor-phase method<sup>4</sup>, almost only (3a) was obtained (71% isolated yield). As we were interested in the preparation of (1), attempts were made to increase the 1/3a ratio, by changing temperature and reagents ratio. Monitoring the reaction with GC showed that a high 1/3a ratio can be obtained only at low (ca 10%) conversion of (2) at 60°C. At room temperature, at 50% conversion, 1:1 ratio of (1) and (3a) was obtained. The benzene solutions were washed with water and HCl, and the extract chromatographed on silica gel Merck plates with benzene:AcOEt 90:5 (2 runs). The reaction on the acetate of (2) gave similar results, due to the hydrolysis of the acetate group in the reaction conditions. Also the enamine method<sup>5</sup> could not be applied, as (2) was reluctant to give the corresponding enamine with pyrrolidine.

Cannabichromanone (1) is obtained as an oil, IR (neat) 1735, 1635  $\text{cm}^{-1}$ , NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  0.88 ( $\epsilon$ - $\text{CH}_3$ ), 1.36 and 1.44 ( $2 \times \text{C}_2$ -Me), 2.12 ( $\text{CH}_3\text{CO}$ ), 2.3-2.7 (Aryl- $\text{CH}_2$ ,  $\text{CH}_2\text{CO}$ , H-3), 6.21 and 6.32 (H-6 and H-8), 11.56 (OH). The mass spectrum of (1) is identical with that reported by Spiteller<sup>2</sup>, the structure thus being confirmed.

The compound (3a), 2,2,4'-trimethyl-5'-acetyl-4',5-dihydroxy-7-pentyl-3,4-dihydro-4-oxo-spiro-2H[1]benzopyran-2,1'-cyclohexan-4-one, is also an oil, IR (neat) 3470, 1730, 1690, 1630  $\text{cm}^{-1}$ , mass ( $\text{M}^+$ , %): 402(40), 384(94), 369(92), 351(34), 341(38), 317(38), 259(58), 207(100),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.90 ( $\epsilon$ - $\text{CH}_3$ ), 1.27, 1.40, 1.47 (3 Me-C-O), 2.27 (Me-C=O), 2.53 (Aryl- $\text{CH}_2$ ), 6.23 and 6.34 (2 arom H), 11.60 (OH);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ) 215.9 (Me-CO), 204.7 (CO-4), 161.7, 158.2, 154.7 (C-5, C-7, C-8a), 108.6, 107.4 (C-6, C-8), 104.3 (C-4a), 84.5 (C-2), 68.8 (C-4'), 53.0 (C-2'), 50.1



(C-3), 36.6 ( $\alpha$ -CH<sub>2</sub>), 34.5 (t), 31.7 ( $\gamma$ -CH<sub>2</sub>), 31.4 (C<sub>4</sub>, -Me), 30.0 (t), 28.8 (q, 2x C<sub>2</sub>-Me), 26.6 (t), 23.8 (t), 23.3, 22.4 (q), 13.9 ( $\xi$ -CH<sub>3</sub>).

The structure shown for (3a) is consistent with these data, and also with those for the monoacetate (3b), prepared with Ac<sub>2</sub>O and pyridine, mass (M<sup>+</sup>, %): 444(6), 402(42), 385(35), 384(96), 370(35), 369(96), 351(35), 341(40), 317(41), 259(60), 207(100), <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  0.88 ( $\xi$ -CH<sub>3</sub>), 1.14 (MeC-O), 2.17 (MeCOO), 2.33 (MeC=O), 2.55 (Aryl-CH<sub>2</sub>), 6.46 and 6.62 (H-6 and H-8); <sup>13</sup>C NMR 216.7 (MeCO), 197.5 (CO-4), 169.7 (MeCOO), 158.9, 151.6, 149.7 (C-5, C-7, C-8a), 115.3, 114.9 (C-6, C-8), 110.2 (C-4a), 84.8 (C-2), 68.9 (C-4'), 52.8 (C-2'), 50.8 (C-3), 36.0 ( $\alpha$ -CH<sub>2</sub>), 35.1, 31.5 ( $\gamma$ -CH<sub>2</sub>), 29.9, 29.7, 28.8, 26.6, 22.9, 22.7, 22.5, 22.2, 21.2, 13.9 ( $\xi$ -CH<sub>3</sub>). The <sup>13</sup>C assignments are based on the analysis of the undecoupled spectrum, and on comparison with models<sup>6</sup> and with the spectrum of 2,2-dimethyl-5-hydroxy-7-pentylchroman-4-one (2),  $\delta$  (CDCl<sub>3</sub>) 197.2 (CO), 161.7, 159.7, 155.0 (C-5, C-7, C-8a), 108.6, 107.8 (C-6 and C-8), 105.5 (C-4a), 78.5 (C-2), 48.0 (C-3), 36.6 (C-1'), 31.4 (C-3'), 30.0 (C-2'), 26.6 (2 Me), 22.5 (C-4'), 13.9 (C-5').

Both compounds (1) and (3a) were tested for activity on central nervous system and found inactive.

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