chromatographic mobilities similar to one of the major components of the first chloroform extract. Solubility studies showed that both substances contained an acidic function and they could be methylated to give an ester. The reaction conditions also led to concomitant methylation of the phenolic hydroxyl group.

Mass spectroscopic studies of the methyl ester/methyl ether and its d_6 derivative showed that this metabolite contained a hydroxyl and a carboxyl function in addition to the structural features of Δ^1-THC. The fragmentation pattern indicated that the carboxylic group was located on the 7-position: it also exhibited an M−17 fragment. This latter finding is novel for hydroxyl containing cannabinoids suggesting that the hydroxyl is at a hitherto unreported position. This is the first report, to our knowledge, on the chemical nature of a major urinary metabolite of Δ^1-THC in the rabbit.

We have also obtained preliminary data showing that a similar route of metabolism occurs in man. Urine from subjects receiving ^{3}H-Δ^1-THC orally, was processed essentially as above. A mixture of the ^{14}C rabbit metabolite and the ^{3}H human material migrated together in two different thin-layer chromatography systems.

These findings suggest the possibility that an aldehyde may be an intermediate between 7-OH-Δ^1-THC and the acid. The sensitivity of the conjugates to base indicates that they may be either esters or amides.

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E. W. GILL
G. JONES

Department of Pharmacology, Oxford University, South Parks Road, Oxford, England

Distribution and metabolism of tritium labelled tetrahydrocannabinol

Tritium labelled 1-tetrahydrocannabinol (Δ^1-THC) at a specific activity of 600 mCi/mmole was synthesised by a non exchange method. Brain levels of Δ^1-THC and its metabolites were measured in individual mice after intravenous injection and correlated with the degree of catalepsy produced. Δ^1-THC equilibrates rapidly between blood and the C.N.S. and there is no significant blood/brain barrier. Δ^1-THC is oxidised very rapidly

in the liver and 10 min after injection there is a significant amount of 7-hydroxy-THC in the brain. The degree of catalepsy produced correlates equally well with brain levels of Δ^1-THC or 7-hydroxy-THC. SKF 525A (25 mg/kg) inhibits the conjugation of 7-hydroxy-THC completely but only slightly inhibits hydroxylation of THC. Consequently prior treatment with SKF 525A increases brain levels of 7-hydroxy-THC.

It is not yet possible to apportion C.N.S. activity unequivocally between Δ^1-THC and its metabolites.

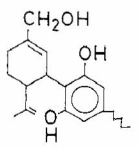
I. M. NILSSON
S. AGURELL
K. LEANDER
J. L. G. NILSSON
M. WIDMAN

Faculty of Pharmacy, University of Uppsala, Box 6804, S-113 86 Stockholm

Cannabidiol: Structure of three metabolites formed in rat liver

Cannabis sativa L. contains three major cannabinoids: Δ^1-tetrahydrocannabinol (Δ^1-THC), cannabinol (CBN) and cannabidiol (CBD). It is assumed that only Δ^1-THC is psychotomimetically active, but its effect is apparently modified by other compounds present in cannabis. It is conceivable that CBD and CBN, which beside Δ^1-THC are the major cannabinoids in the smoke of cannabis preparations could interfere with the pharmacological action of Δ^1-THC.

Metabolic studies on Δ^1-THC and $\Delta^{1(6)}$-THC have been performed by several groups. These investigations have shown that the primary metabolite of THC is 7-hydroxy-THC. 7-Hydroxy-CBN is similarly formed from CBN.



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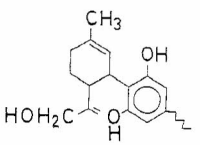

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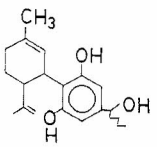

3

We now report on three *in vitro* metabolites of CBN, identified by their mass spectra as 7-hydroxy-CBD (*1*) 10-hydroxy-CBD (*2*) and a metabolite formed by oxidation of the pentyl side chain of CBD (*3*).