responding results from Δ^1-THC. Less than a few per cent of 7-hydroxy-$\Delta^{1(6)}$-THC is eliminated unchanged in urine although some is excreted as a conjugate (sulphate or glucuronide). A major urine metabolite appears, just as for Δ^1-THC, to be a carboxylic acid.

Beside the psychotomimetically active Δ^1-THC, cannabis preparations contain varying but considerable amounts of CBN and CBD. Metabolic studies of CBN will be reported separately (Inger Nilsson *et al.*).

Cannabinol-^{14}C prepared from Δ^1-THC-^{14}C by sulphur dehydrogenation according to Petrzilka, was metabolized *in vitro* using a 10 000 xg rabbit liver supernatant as described previously. (*Science* **168**, 1228 (1970)). Beside some more polar compounds, a major phenolic metabolite was isolated by repeated thin layer chromatography. The NMR-spectrum of this metabolite was largely in agreement with that of CBN, the major discrepancy being the lack of the C-1 methyl signal ($\delta = 2.38$; $CDCl_3$). Instead a two proton signal at $\delta = 4.75$ appeared indicating two benzylic protons. A hydroxylation of the C-1 methyl group was also in agreement with results obtained by gas chromatography-mass spectrometry. The spectrometric evidence is thus consistent with the formulation of the metabolite of CBN as 7-hydroxycannabinol — a metabolic conversion to that of Δ^1-THC and $\Delta^{1(6)}$-THC.

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The isolation and characterization of a major metabolite of Δ^1-THC

The purpose of the experiments reported here is the identification of the urinary metabolites of Δ^1-tetrahydrocannabinol (THC). These results are a continuation of this project in our laboratory, some of which have been previously reported [1—3].

The general procedures used were as follows. Carbon-14 labelled Δ^1-THC was injected into rabbits by either an i.v. or s.c. route. Urine was collected for a suitable period and pooled for extraction. An initial treatment with XAD-2 resin, after acidification to pH 3.5, allowed the radioactivity to be obtained in a concentrated methanolic solution essentially free of inorganic salts. The methanol was then evaporated and the residue dissolved in water. Exhaustive extraction with chloroform removed about 30 % of the radioactivity. The aqueous phase was brought to pH 7.0 and evaporated on high vacuum. Various chromatographic techniques were used to separate and purify the components of each extract.

Careful hydrolysis with dilute alkali was found to liberate more chloroform soluble material from the aqueous phase. This material showed

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.

1. S. H. Burstein, F. Menezes, E. Williamson and R. Mechoulam. *Nature* **225**, 87 (1970)
2. Z. Ben-Zvi, R. Mechoulam, S. Burstein. *J. Amer. Chem. Soc.* **92**, 3468 (1970)
3. S. Burstein and D. Kupfer. *Ann. N. Y. Acid Sci.* In press

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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