The biomedical marihuana research program has been supported by the NIMH through a dual system of grants and contracts. There are at present 57 active grants and 16 contracts dealing exclusively with marihuana research. They cover a wide variety of preclinical and clinical studies, ranging from chemical, analytical and preclinical pharmacologic studies to clinical studies of the physiologic, pharmacologic, behavioral and social effects of the cannabinoids.

The emphasis has been to elucidate the effects of the compounds responsible for the psychoactive effects of marihuana *in man*, to quantify these compounds or metabolites in biological fluids, to determine their toxicity and side effects and to correlate these data with "street use" of marihuana.

It is hoped that these studies will help in evaluating the effects of marihuana on health and contribute to a better understanding of the causes leading to the widespread use of marihuana.

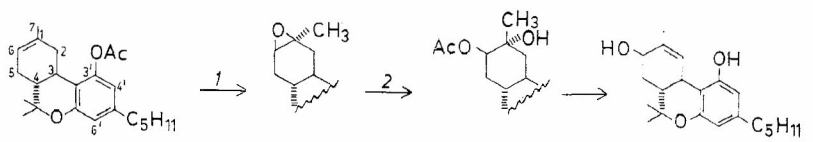
R. MECHOULAM

Laboratory of Natural Products, Hebrew University, Pharmacy School, Jerusalem, Israel

Recent advances in cannabinoid chemistry

The major pathway of THC metabolism so far identified is hydroxylation of the 7-methyl group. Both 7-hydroxy-Δ^6-THC and 7-hydroxy-Δ^1-THC show high THC-type activity in animals.

Recently 6β-hydroxy-Δ^1-THC has been shown to be a minor metabolite of Δ^1-THC *in vitro*. We have now synthesized this compound by the following route:



Reagents: 1) *m*-chloroperbenzoic acid. 2) perchloric acid; acetylation. 3) thionyl chloride; lithium aluminum hydride.

6β-Hydroxy-Δ^1-THC thus prepared has been found to be active in monkeys by Professor H. Edery. This finding may complicate still further the quest towards the understanding of the molecular basis of cannabis

activity in humans. It is possible that the non-identical effects of cannabis on different individuals are due, in part, to different ratios of Δ^1-THC and metabolites (or only metabolites) at the receptor site. This should be taken into account if THC and the metabolites are not identical in activity in the human.

While few cannabinoids have so far been tested in the human, the structural requirements for activity in the rhesus monkey are gradually being unraveled. We have synthesized numerous THC isomers, analogs and homologs, which have been tested by Professor H. Edery. The following conclusions can so far be drawn:

1. A benzopyran-type structure with a hydroxyl group at the 3′ aromatic position and an alkyl group on the 5′ aromatic position seems to be a requirement. Opening of the pyran ring leads to complete loss of activity.

2. The aromatic hydroxyl group has to be free, or esterified. Blocking of the hydroxyl group as an ether inactivates the molecule.

3. Substitution on the phenolic ring with alkyl groups at $C_{4'}$, retains activity. Substitution at $C_{6'}$, eliminates activity. Electronegative groups such as carboxyl, carbomethoxyl and acetyl at either $C_{4'}$, or $C_{6'}$, eliminate activity.

4. A certain length of the aromatic side chain is a requirement for activity. Branching of the side chain may lead to considerable increase in potency. The 1,2-dimethyl-heptyl side chain seems to be optimal.

5. The terpenoid ring may apparently be amended considerably. It seems that substituents on C_1 and C_2 have to be in the plane of the ring (i.e. equatorial) in order that high activity be retained. A double bond in the terpenoid ring is not a requirement. While Δ^1 and Δ^6-THC's (in the 3R, 4R series only) are active, Δ^5-THC is inactive; Δ^3-THC is active; Δ^1-THC (3,4-*cis*) is inactive.

J. LARS G. NILSSON
STIG AGURELL
INGER M. NILSSON

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

Synthesis of cannabinoid metabolites

We have synthesized 7-hydroxy-Δ^6-THC (*3*) from Δ^6-THC (*1*) by a route involving photochemical isomerization of Δ^6-THC to Δ^7-THC (*2*) and subsequent hydroxylation to (*3*) as shown in the Scheme.