CHAPTER 7

Chemistry of Cannabis

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A. Introduction

The aim of this chapter is to present a short summary of cannabinoid [1] chemistry with emphasis on those aspects which have pharmacological relevance. A comprehensive chemical review is beyond the scope of this handbook. Since 1964, when the active principle of cannabis, Δ^1-tetrahydrocannabinol (Δ^1-THC), was identified (GAONI and MECHOULAM, 1964a), nearly 5,000 scientific articles on cannabis, Δ^1-THC and other cannabinoids have appeared; approximately 1,000 of these articles are chemically oriented. For this reason alone the present review will have to be selective.

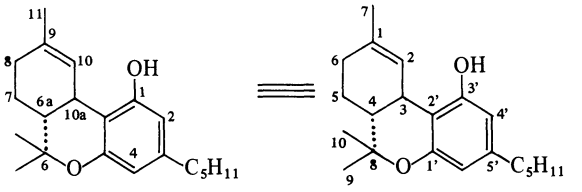
The only natural source of cannabinoids is the dioecious plant *Cannabis sativa*. Both male and female plants produce cannabinoids, in approximately equal concentrations. Botanists recognize numerous "chemotypes" of *C. sativa*, which differ mainly in the ratio of the cannabinoids present in them. Usually chemotypes growing in Mexico, Lebanon, India, Indochina and Africa contain considerable amounts of Δ^1-THC, which in the pure resin (hashish, chagas) may vary between 3% and 10%. The total dried tops (in the Americas called "marihuana") contains ca. 0.5%–1% Δ^1-THC. The chemotypes grown in colder climates generally have low amounts of Δ^1-THC. The differences seem to depend on genetic, climatic and ecological factors. Some chemotypes lack certain constituents. For example, South African *C. sativa*, the source of dagga, does not contain cannabidiol (CBD), which is the major neutral cannabinoid in Lebanese hashish (for a recent review on the pharmacognosy of cannabis, see FAIRBAIRN, 1976).

Two numbering systems for the cannabinoids are in use today. In one of them the formal chemical rules for numbering of pyran type of compounds are used. This system is used by *Chemical Abstracts*. The second nomenclature has a biogenetic basis; the cannabinoids are regarded as substituted monoterpenoids. The latter system is used in the present review.

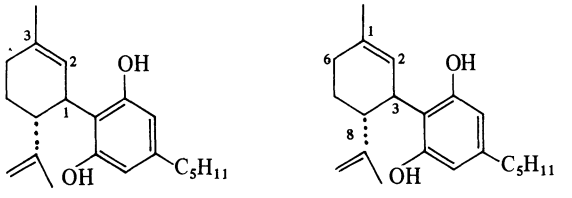
The vast literature on cannabis and cannabinoids has been the object of several books, reviews and annotated bibliographies. The chemistry, pharmacology, metabolism and clinical effects have been reviewed in two books (MECHOULAM, 1973; NAHAS, 1972). In the first of these considerable emphasis is placed on the chemical aspects, including structure–activity relationships; it has since been updated (chemistry: MECHOULAM et al., 1967; pharmacology: PATON, 1975). The chemistry of cannabis has also been reviewed by RAZDAN, 1973. The analytical problems in this field are discuss-

1 The term "cannabinoids" was introduced (MECHOULAM and GAONI, 1967a) to embrace the group of C_{21} compounds characteristically present in *Cannabis sativa*, their carboxylic acids, analogues, homologues and transformation products

F. Hoffmeister et al. (eds.), *Psychotropic Agents*



Δ^9–THC Δ^1–THC



Formal numbering Monoterpenoid numbering (used in this review)

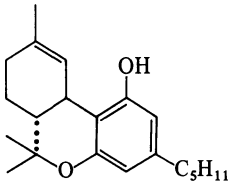
ed in a book published by the U.S. National Institute for Drug Abuse (WILLETTE, 1976). A chapter in the book of LEMBERGER and RUBIN, 1976 and several in those of BRAUDE and SZARA, 1976 and NAHAS, 1976 are devoted to cannabinoid metabolism. The medicinal chemistry aspects of cannabinoids, both natural and synthetic, have been reviewed (COHEN and STILLMAN, 1976; ARCHER, 1974; MECHOULAM and CARLINI, 1978; BHARGAVA, 1978). An annotated bibliography covering the years 1964 to 1974 has been published (WALLER et al., 1976). Work on this valuable bibliographic tool is continuing and further volumes are expected.

B. Naturally Occurring Cannabinoids

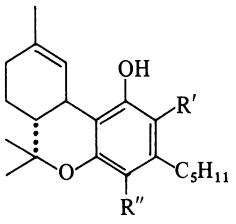
I. Isolation and Structure

The early attempts to isolate the natural cannabinoids was by fractional distillation or crystallization. Both methods failed as cannabinoids generally boil within the same temperature range (ca. 155 °C 0.05 mm) and are mostly oily materials which are difficult to crystallize. The advent of chromatography bypassed cannabinoid chemistry by nearly 30 years and it was only in the 1960s that serious attempts to separate the constituents of marihuana and hashish were recorded. Up till 1964 only two (or possibly three) components had been isolated in pure form. The structure of only one compound, cannabinol (CBN) had been established. The pure constituents isolated did not include compounds with psychotropic activity. An impure mixture apparently containing a high percentage of what was later recognized to be Δ^1-THC was isolated in 1942 (WOLLNER et al., 1942). Work reported by several groups since 1964 has led to the isolation of numerous new cannabinoids which today number 56. The structure of these was determined mainly by the use of physical methods such as mass spectrometry and nuclear magnetic resonance. Figure 1 presents the structures of the predominant natural cannabinoids with references to the original reports of their isolation or structure elucidation.

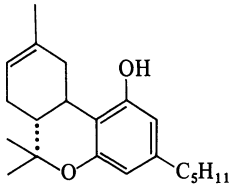
Most natural cannabinoids belong to several basic structural types: THC (including CBN), cannabigerol, CBD, cannabichromene, cannabicyclol and cannabielsoin.



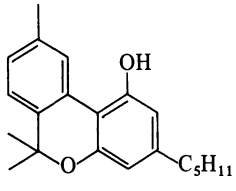
Δ^1–Tetrahydrocannabinol
(Δ^1–THC, also named Δ^9–THC)
(Gaoni and Mechoulam, 1964a)



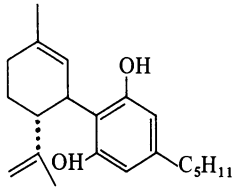
Δ^1–THC acid A
R′ = COOH, R″ = H
(Korte et al., 1965)
Δ^1–THC acid B
R′ = H, R″ = COOH
(Mechoulam et al., 1969)



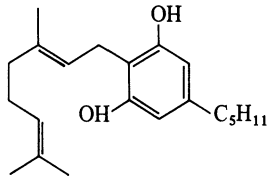
Δ^6–THC
(also named Δ^8–THC)
(Hively et al., 1966)



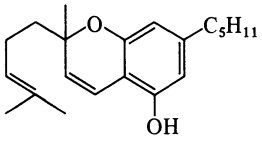
Cannabinol (CBN)
(Adams et al., 1940)



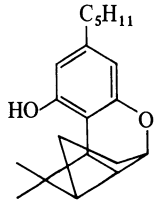
Cannabidiol (CBD)
(Mechoulam and
Shvo, 1963)



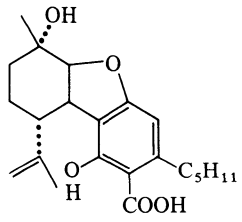
Cannabigerol
(Gaoni and
Mechoulam, 1964b)



Cannabichromene
(Claussen et al., 1966;
Gaoni and Mechoulam, 1966)



Cannabicyclol
(Crombie et al., 1968)



Cannabielsoic acid A
(Shani and Mechoulam, 1974)

Fig. 1. Representative natural cannabinoids

Additional, usually very minor constituents belonging to related structural types have been shown to be present. They include cannabicitran (Bercht et al., 1974), cannabitriol (Chan et al., 1976), cannabichromanons (Grotte and Spiteller, 1978) and a dimeric cannabinoid (Spulak et al., 1968). The variations on the basic types are standard: a carboxyl group on the phenolic ring (e.g. Δ^1-THC acid A, Δ^1-THC acid B); a methyl, propyl or butyl side chain replacing the pentyl one or dehydrogenation of the terpene moiety to an aromatic ring (e.g. CBN).

The cannabinoids in the growing plant are present mostly, or exclusively, as the pharmacologically inactive acids (i.e. Δ^1-THC acids A and B rather than Δ^1-THC). However, during the preparation of the illegal materials – hashish, chagas or even

marihuana – partial decarboxylation takes place leading to the neutral cannabinoids, including the active Δ^1-THC.

Most natural cannabinoids have at least two chiral centres – at C_3 and C_4. The absolute configuration at these centres was determined by MECHOULAM and GAONI, 1967b for Δ^1-THC (3R, 4R) and CBD (3S, 4R) by correlation with a terpene with a known absolute stereochemistry. The structures in Fig. 1 are given with the correct absolute stereochemistry, whenever it has been established.

In addition to cannabinoids, numerous terpenes, phenolic compounds, alkaloids, flavonoids and other natural products have been isolated from *C. sativa* (MECHOULAM, 1973; TURNER et al., 1976; EL-FERALY et al., 1977; SEGELMAN et al., 1978). These non-cannabinoids do not seem to contribute to the typical cannabis-type activity. However, this point needs further substantiation.

Early work on cannabis claimed that the activity was due to a mixture of (unidentified) isomers. With the identification of most major constituents it was conclusively shown (GAONI and MECHOULAM, 1964a) that only one major THC isomer is present, namely Δ^1-THC, with a second one, Δ^6-THC, being a minor constituent. On the basis of a detailed comparison of the activities of several cannabinoids versus a synthetic mixture it was concluded that, in the particular monkey test used, Δ^1-THC was the only pharmacologically active cannabinoid (MECHOULAM et al., 1970). However, later reports have brought evidence that in rodent tests Δ^1-THC cannot always account for all the activity (KARNIOL and CARLINI, 1972). Whatever should be the chemical basis for these observations (synergism or additional active constituents) and its possible relevance to cannabis activity in humans, further research is urgently needed to clarify this important point.

II. Chemical Properties

In this section I propose to discuss only those characteristics of the cannabinoids which seem to be relevant to pharmacology and to reluctantly disregard the fascinating pure chemistry of some of these compounds.

The cannabinoids are lipid soluble compounds which are practically non-soluble in water. The octanol water partition coefficient of Δ^1-THC was reported to be of the order of 6,000 (GILL and JONES, 1972). For administration to animals, therefore, it is always necessary to use a non-aqueous solvent or to add a dispersing agent. The most commonly used vehicles have been olive oil (given intraperitoneally), polyethylene glycol or Tween 80-saline given by any route. Dimethyl formamide, dimethylsulphoxide, gum arabic, serum albumin and polyvinylpyrrolidone have also been employed. The suspensions prepared by dissolving the cannabinoid in a dispersing agent and diluted with water are not stable and should be used shortly after preparation. However, solutions of cannabinoids in ethanol kept at 0 °C in the dark are stable for months or years.

Neither CBD, which has two phenolic groups, nor Δ^1-THC, which has one such group, are soluble in dilute base. The pKa' value of Δ^1-THC has been shown to be 10.6 (GARRETT and HUNT, 1974). This paper also gives detailed information on solubility, partitioning and stability of Δ^1-THC.

Δ^1-THC is very susceptible to oxidation. On exposure to air it slowly converts into CBN. This is due to the lability of the C_3 hydrogen, which is both allylic and benzylic.

Δ^6-THC is considerably more stable and needs very strong oxidation conditions for dehydrogenation to CBN. As Δ^6-THC is active in essentially all animal models used for Δ^1-THC testing it is convenient to employ the Δ^6 isomer for preliminary work.

CBD is easily oxidized, in the presence of base, to coloured quinonic compounds (MECHOULAM et al., 1968). In the crystal form or in ethanolic solution it is, however, quite stable. The same applies for cannabigerol. Little is known about the susceptibility to oxidation of the other cannabinoids. However, in view of the presence of phenolic groups some oxidation on the aromatic rings is to be expected. Allylic oxidation is also possible. Some of the cannabinoids (especially those present in illegal preparations) may in fact be artefacts formed on oxidation. Thus cannabichromene (which has no optical activity, a feature associated with enzymatic synthesis) may be formed by oxidation of cannabigerol followed by cyclization.

Most cannabinoids are stable to heat in the absence of air. Thus the neutral cannabinoids can be distilled at up to 200 °C (at a reduced pressure) or analysed by gas chromatography at 250 °C. However, the cannabinoid acids undergo decarboxylation at ca. 120 °–150 °C. Therefore on smoking (but not on oral consumption), the amount of available neutral cannabinoids including THC is potentially higher than in the crude material. One has, however, to take into account that on smoking, only ca. 20%–25% of the neutral cannabinoids (including those formed on decarboxylation) enter the body; the rest is burned or lost. SPRONG and SALEMINK, 1978 have investigated the reactions taking place on pyrolysis (a smoking model). Most of these involve cleavage of the molecule followed by further modifications leading to non-active molecules. In several cases modifications of the cannabinoid molecule take place. The cleavage and transformation products seem to be inactive, but at present limited pharmacological work on these products has been reported. The quantitative aspects of these transformations are not clear; the impression is that while Δ^1-THC is relatively stable, giving some CBN on smoking, CBD is cleaved or cyclized (possibly partly to Δ^1-THC) or oxidized (to cannabielsoin-type products) with relative ease.

In the presence of acids many cannabinoids undergo transformations (MECHOULAM, 1973). Δ^1-THC with strong acids is easily isomerized into Δ^6-THC. CBD is converted by boron trifluoride into Δ^1-THC, accompanied by Δ^8-iso-THC; with p-toluene sulphonic acid it gives Δ^6-THC in essentially quantitative yield (Fig. 2). Cannabigerol and cannabichromene undergo complicated cyclizations. However, Δ^6-THC and cannabicyclol are relatively stable. In the presence of water or alcohols and mineral acids, additions to the double bonds may occur (MECHOULAM 1973; GARRETT and TSAU, 1974). Are the cannabinoids stable in the acid milieu of the stomach? There is indirect evidence, based on the activity of orally administered Δ^1-THC, that to a large extent no major changes occur. However, one can expect some isomerization to Δ^6-THC, or possibly additions to the double bond. The oral activity of CBD (in anti-epileptic studies) and lack of psychotropic effects indicate that it is not transformed to Δ^1 or Δ^6-THC in the stomach. However, direct experimental evidence is needed.

The cannabinoids are photolabile compounds. CBD can cyclize to Δ^1-THC or iso-cannabinoids (SHANI and MECHOULAM, 1971). This reaction may have biogenetic significance. It has recently been reported that when a growing cannabis plant is exposed the sunlight it contains more Δ^1-THC and less cannabichromene than a non-irradiated plant (VALLE et al., 1978; this observation contradicts previous results, FAIRBAIRN and LIEBMAN, 1974). CBD can also undergo reduction of the Δ^8 double bond

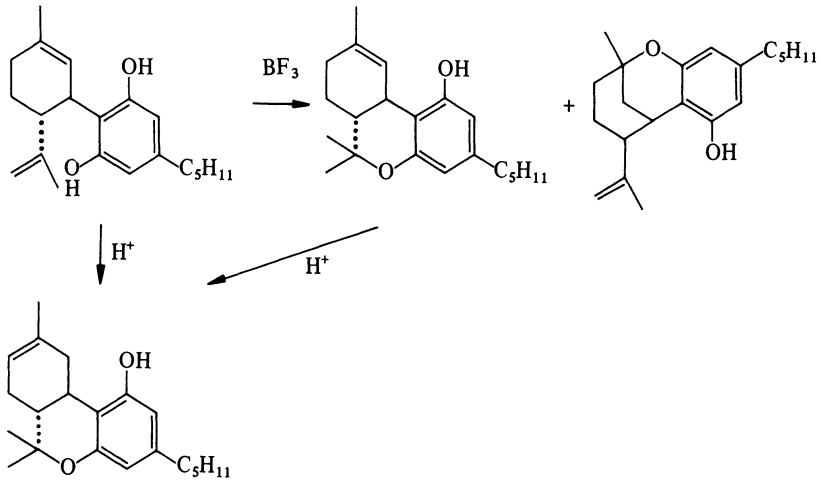


Fig. 2. Some transformations of cannabinoids in acids

or addition of solvent to the aromatic ring. In the presence of oxygen, reactions leading to cannabielsoic-type compounds are observed (SHANI and MECHOULAM, 1974). No detailed work on Δ^1-THC has been reported, but one can expect addition reactions as well as dimerizations through the aromatic ring.

The psychoactive cannabinoids may be classified as partial anaesthetics producing the same perturbation of the membrane structure as that caused by sub-anaesthetic doses of general anaesthetics (LAWRENCE and GILL, 1975). This was determined by estimation of the degree of disorder of the hydrocarbon chain in phospholipid liposomes. Introduction of various cannabinoids altered the order parameters within the hydrophobic core of the liposome, and the change in this factor correlated qualitatively with psychotropic potency.

Cannabinoids bind to serum proteins (WAHLQVIST et al., 1970). Albumin appears to bind Δ^1-THC much less avidly than α-lipoprotein, which in turn shows a slightly reduced avidity compared to β-lipoprotein (MCCALLUM and EASTWOOD, 1978). Δ^1-THC binds to glass or membranes (GARRETT and HUNT, 1974) and the possibility that there is competition by these surfaces for Δ^1-THC during in vitro experiments cannot be ignored.

III. Syntheses

It is beyond the scope of this review to describe all the synthetic routes used to prepare the various natural cannabinoids. These have been reviewed in considerable detail (MECHOULAM, 1973; MECHOULAM et al., 1976). It should be pointed out that facile syntheses for most cannabinoids are available. Δ^1-THC can be prepared in high yield and with high stereospecificty by several methods. The ones generally employed are presented in Fig. 3. They are based on condensation of a suitable monoterpene with olivetol (5-penthylresorcinol) to yield Δ^6-THC which can easily be converted into Δ^1-THC. RAZDAN et al., 1974 have found that the Petrzilka synthesis can be improved to yield directly Δ^1-THC if magnesium sulphate is added to the reaction mixture.

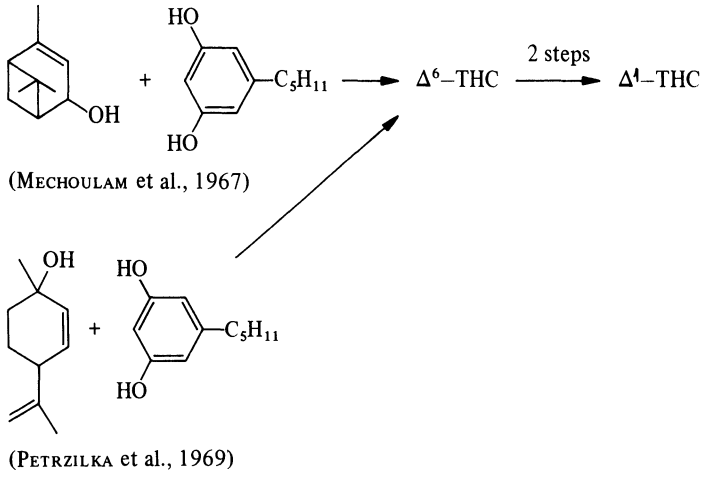


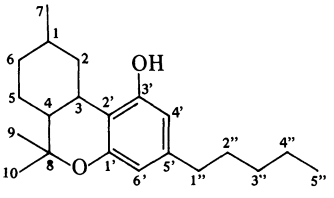
Fig. 3. Some syntheses of Δ^1-THC

(+)-Δ^1-THC can be obtained from the synthesis based on verbenol (MECHOULAM et al., 1972) as the latter compound is obtainable in both (+) and (−) forms. The (+) (unnatural) cannabinoids are of importance as control compounds in pharmacological and biochemical work in order to ascertain that effects observed with natural (−) cannabinoids are specific and are not due to the general liposolubility of this group of compounds.

The above syntheses have been employed for the preparation of labelled material. BURSTEIN, 1973 has presented a list of methods used for this purpose. More recent developments are a detailed report on the syntheses of numerous labelled cannabinoids (PITT et al., 1975), the syntheses of labelled cannabinoid acids (SHOYAMA et al., 1978) and the publication of the method of HOELLINGER et al., 1977 leading to Δ^1-THC with a specific activity of 50 Ci/mmol.

C. Structure-Activity Relationships (SARs)

These relationships, mainly as regards the typical cannabis activity, have been surveyed previously (MECHOULAM, 1973; MECHOULAM et al., 1976). These data, together with newly published results, can be summarized as follows:



1) A tricyclic (preferably 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 loss of activity.

2) The phenolic group has to be free. Blocking of this group as an ether causes complete inactivation while esterfication does not, probably because esters can be hydrolysed in the body.

3) Electronegative groups (such as carboxyl, carbomethoxyl or acetyl) on the aromatic ring eliminate activity. Alkyl groups on the C-4′ aromatic position cause no change in activity, while such a substitution on C-6′ eliminates activity.

4) The minimal C-5′ alkyl side chain seems to be a pentyl one (though little work has been reported on the propyl and butyl homologues). The side chains leading to highest activity apparently are 1,1 or 1,2-dimethyl heptyl or the recently discovered 1-methyl-4-(*p*-flurophenyl)-butyl groups (PARS et al., 1977).

5) Not all the theoretically possible THCs are active. Thus Δ^1- and Δ^6-THC are active in the 3 R, 4 R series only; Δ^5-THC and Δ^7-THC are inactive; Δ^3-THC is active; Δ^1-3,4-*cis*-THC is inactive.

6) Monohydroxylation on the C-7 methyl group, in either Δ^1- or Δ^6-THC, the C-6 position on Δ^1-THC, or on the C-2″, C-3″, C-4″ or C-5″ position of the side chain leads to active compounds; C-1″-hydroxy-Δ^6-THC is, however, inactive. Hydroxylation of the C-9 methyl group in Δ^1-THC also gives an active compound.

7) In the hexahydrocannabinol series the methyl group (or hydroxymethyl group) on C-1 has to be equatorial, i.e. essentially in the same plane as the phenolic hydroxyl. The axial methyl isomer is much less active.

8) The terpenoid and pyran rings may be modified considerably. These modifications do not seem to follow a regular pattern, and even tentative rules cannot yet be put forward.

Detailed SAR studies of synthetic N-containing cannabinoids as regards various pharmaceutically important parameters have been published (PARS et al., 1977; RAZDAN et al., 1976 b).

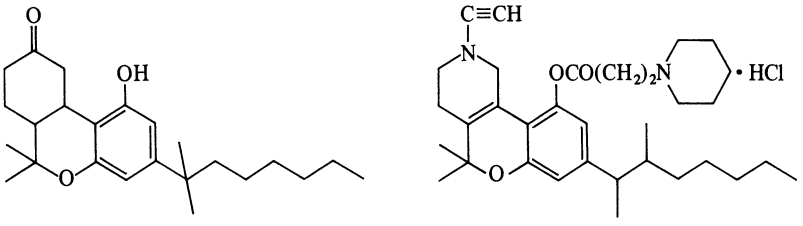
Several cannabinoids have shown considerable clinical promise (for recent reviews see MECHOULAM and CARLINI, 1978; BHARGAVA, 1978). Δ^1-THC in humans exhibits anti-asthma, analgetic, antiglaucoma, antihypertensive and anti-emetic properties. The analgetic, antiglaucoma and antihypertensive effects cannot be exploited due to the CNS side-effects. However, they can serve as synthetic leads. The anti-asthma effect is observed at doses considerably lower than those at which CNS effects are present (HARTLEY et al., 1978). Further clinical work is certainly warranted. The most promising results are in the use of Δ^1-THC as an anti-emetic drug during cancer chemotherapy or irradiation therapy. Repeated vomiting is a serious side-effect of such therapy and it is not always improved by existing anti-emetic drugs during cancer chemotherapy or irradiation therapy. Oral administration of Δ^1-THC, ca. 2 h before the anticancer treatment prevents vomiting in most cases (SALLAN et al., 1975).

In a double-blind study CBD was given (at 200 mg daily doses for 3 months) to epileptics with uncontrolled secondary generalized epilepsy with temporal foci. Very significant improvement was noticed (CUNHA et al., 1980). Further research is indicated. It is of interest that a close spatial structural relationship exists between CBD and the anti-epileptic drug phenytoin. In addition, in each of these compounds the distance between their two electron donating groups is almost the same. It seems possible that the two compounds act on the same, or a similar, receptor (TAMIR et al., 1980).

The synthetic cannabinoid, nabilone, developed by the American firm Ely Lilly, is being clinically tested mainly as an anti-emetic in cancer chemotherapy and as an

anti-anxiety agent (HERMAN et al., 1977; NAKANO et al., 1978). Nabilone is apparently not as good a tranquillizer as diazepam; however, it seems to be a good anti-emetic agent.

Clinical trials with the nitrogen-containing cannabinoid shown below have demonstrated its effectiveness as an analgetic (ca. ten times more active than codeine); however, the side-effects observed make it a poor candidate for further work in man (STAQUET et al., 1978).



Nabilone

D. Cannabinoid Analysis

The identification of crude cannabis is routine in forensic laboratories. It is usually done by a combination of colour tests (Duquenois, Beam etc.) and chromatographic ones [thin layer chromatography (TLC), gas chromatography (GC) etc.]. These have been reviewed in detail elsewhere (MECHOULAM, 1973; MECHOULAM et al., 1976; CROMBIE, 1976). A problem which has not yet found a fully satisfactory solution is the analysis of cannabinoids in body fluids, in particular urine. The main reasons for this difficulty are the low amounts usually consumed by man and the extensive rapid metabolism (VINSON, 1979).

The most widely used method for detecting cannabinoids on TLC is by spraying with a feshly prepared solution of di-*o*-anisidine tetrazolium chloride (fast blue salt B), which offers both excellent sensitivity of detection (to approximately 50 ng) and different colour reactions for different components.

By the fluorescent method of FORREST et al., 1971, in which the cannabinoids are converted to 1-dimethyl-aminoaphthalene sulphonates, cannabinoids may be detected on TLC down to levels of 0.5 ng. VINSON et al., 1977 have developed on alternative facile fluorescent method.

Gas chromatography is the method of choice for rapid qualitative and quantitative identifications. A large variety of stationary phases have been found to provide excellent separations of the cannabinoids on packed columns, and the use of capillary columns has been found to improve separations considerably (NOVOTNY and LEE, 1973; GROTTE and SPITELLER, 1978). Flame ionization detection, normally used with GLC, gives a maximum sensitivity of approximately 50 ng. The formation of trimethylsilyl derivatives increases the maximum sensitivity of detection to about 10 ng.

The use of electron capture detection for suitably derivatized cannabinoids has improved detection sensitivity. SCHOU et al., 1971 report that the use of chloroacetyl derivatives gives maximum sensitivity of approximately 0.04 ng and have applied this method ot urinalysis. GARRETT and HUNT, 1973 demonstrate a maximum sensitivity

of detection of approximately 5 pg for Δ^1-THC pentafluorobenzoate, whereas 1 pg Δ^1-THC heptafluorobutyrate can be detected when a capillary column and low volume coaxial electron capture detector are used (FENIMORE et al., 1973).

To overcome the necessity of purification, MCCALLUM et al., 1978 have developed a method involving GLC with flame ionization detection of cannabinoid phosphate esters. This method has a sensitivity of 0.5 ng/ml of whole blood. The detection is so specific that preliminary clean-up procedures are unnecessary.

High pressure liquid chromatographic (HPLC) methods for the separation of cannabinoids have been developed (SMITH and VAUGHAN, 1976; KNAUS et al., 1976; GARRETT and HUNT, 1977).

Mass spectrometry (MS) is widely employed in cannabis analysis. AGURELL et al., 1973 report that a preliminary purification of the extract from human plasma by chromatography on Sephadex LH-20 provides adequate clean-up for subsequent quantification of the Δ^1-THC by mass fragmentometry. Their method has been found suitable for measuring Δ^1-THC down to levels of 0.3 ng/ml when fragmentograms of the 299 and 314 mass fragments (at 50 eV) are used. Improvements of this method have been reported by ROSENFELD, 1977. A facile GLC–MS method has been described by ROSENTHAL et al., 1978.

A number of laboratories have developed immunoassay methods. TEALE et al., 1975, GROSS and SOARES, 1978 and others (see WILLETTE, 1976) have reported practical procedures. Recently a combined HPLC–radio-immunoassay was described (WILLIAMS et al., 1978) which is capable of quantifying 0.1 ng of a cannabinoid in 1 ml plasma. CAIS et al., 1975 have developed a free radical immunoassay (comparable to the one available for morphine).

E. Cannabinoid Metabolites*

Early in 1970 several groups almost simultaneously identified the major primary route of cannabinoid metabolism – hydroxylation at the allylic C_7 position (BURSTEIN et al., 1970; BEN-ZVI et al., 1970; NILSSON et al., 1970; WALL et al., 1970; FOLTZ et al., 1970). Intensive ongoing work by several groups, mainly in Sweden, United States, Israel and the United Kingdom, has shown that Δ^1-THC, Δ^6-THC, CBD and CBN are hydroxylated (or oxygenated) by many animal species, including man, at most allylic positions as well as on the side chain. The relevant positions are indicated by arrows in Fig. 4.

A further minor primary route (which apparently takes place only very early after administration of the drug) is dehydrogenation of Δ^1-THC and Δ^6-THC to CBN (MCCALLUM et al., 1977). It is usually accompanied by further hydroxylation. Metabolic reduction of the Δ^1 double bond has been recorded (HARVEY et al., 1977a). Epoxidation of this double bond has also been observed.

The monohydroxylated products can undergo further hydroxylations as well as oxidations to the corresponding 7-oic acids. The side chain can also be cleaved and oxidized giving mono- or polycarboxylic acids. Recent publications identifying numerous new metabolites (generally along the above-described pathway) are those by

* Due to the large number of publications on metabolism and metabolites in this area, most of the pre-1976 work is not given in any detail or referenced. The reader should consult the reviews cited in the introduction for full coverage

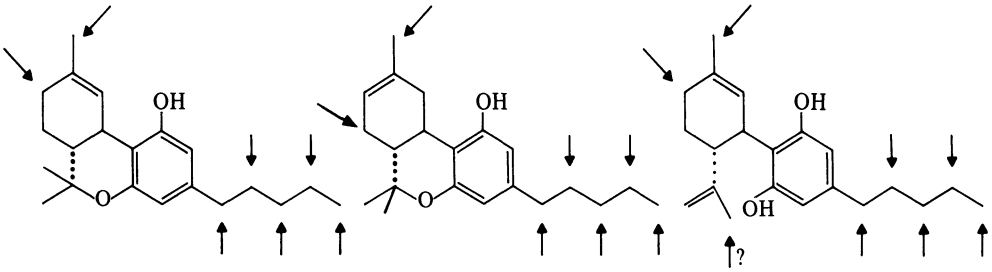


Fig. 4. Positions of phase I oxidations in cannabinoid metabolism

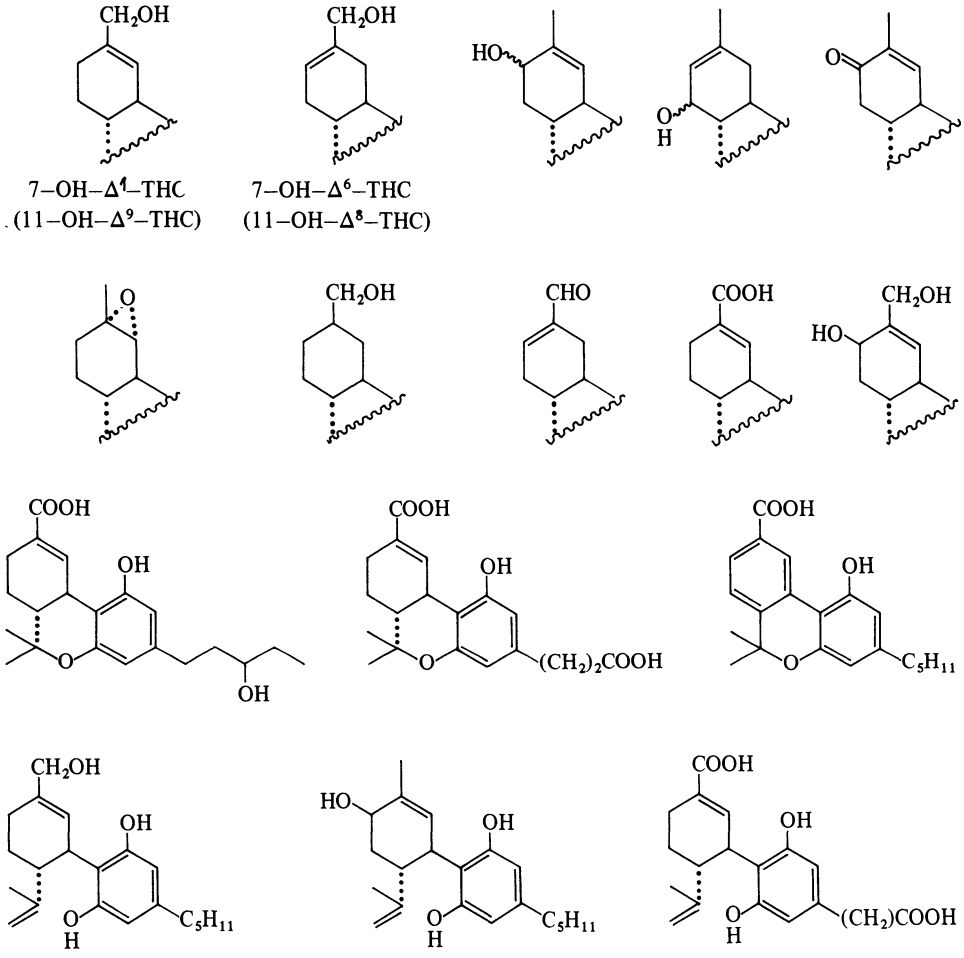


Fig. 5. Examples of phase I cannabinoid metabolites

HARVEY et al., 1977b; MARTIN et al., 1976, and MARTIN et al., 1977. Some cannabinoid metabolites, excluding conjugates, are given in Fig. 5. It should be pointed out that considerable metabolic species specificity exists, although the general pathways apparently are similar.

As already mentioned in Sect. C, most monohydroxylated (or mono-oxygenated) THC metabolites are pharmacologically active. It is still a question of heated dis-

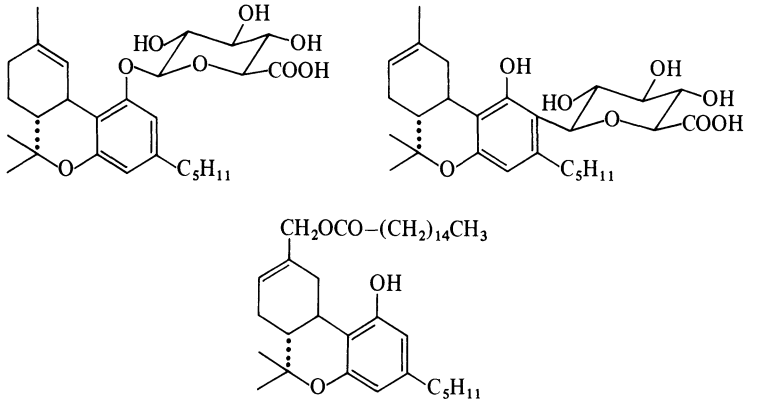


Fig. 6. Examples of phase II cannabinoid metabolites

cussion whether these metabolites (in particular 7-hydroxy-Δ^1-THC) represent the active species in the body or even contribute to the activity observed (see LEMBERGER, 1976; WALL et al., 1976; MARTIN et al., 1978).

Two types of secondary metabolites have been identified. The first are esters of fatty acids with cannabinoids or primary metabolites of cannabinoids (LEIGHTY et al., 1967; YISAK et al., 1978). These compounds are less polar than the natural cannabinoids. A second, much more abundant type of secondary metabolites are the glucuronides of cannabinoids. HARVEY et al., 1977b observed the in vivo formation of 0-glucuronides of CBD and CBN in mice liver. Suprisingly, Δ^6- and Δ^1-THC gave only traces of such metabolites. O-Glucuronides of CBN, CBD, Δ^1-THC and Δ^6-THC as well as of 7-hydroxy-Δ^1-THC and 5′-hydroxy Δ^1-THC have been obtained in vitro by enzymatic catalysis (LYLE et al., 1977; PALLANTE et al., 1978). Under slightly different in vitro conditions the unusual C-glucuronide of Δ^6-THC is formed (YAGEN et al., 1977). This Δ^6-THC C-glucuronide is also formed in vivo in rat liver (LEVY et al., 1978). It is as yet unknown whether the C-glucuronides form a significant portion of the water soluble cannabinoids which represent ca. 75% of the cannabinoid excretion products in urine. It should be pointed out, however, that in man only ca. 10% of the cannabinoid excretion is by this route. The rest is through the faeces (WALL et al., 1976). In Fig. 6 some representatives of metabolic cannabinoid esters and glucuronides are given.

F. Concluding Remarks

In the last 15 years cannabinoid chemistry has reached maturity. Most natural cannabinoids have been isolated and their structures elucidated, syntheses are available and analytical methods have been developed. The basic primary metabolic patterns apparently are known. The secondary metabolism is still, however, partly unexplored territory.

I believe that now the trend is towards development of new drugs based on the cannabinoid nucleus. It has been shown that separation between the various activities is possible. We may look forward to new analgetic, anti-emetic, antiglaucoma, antiasthma and anti-epileptic compounds which cause little or no THC-type effects.

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