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Review

Cannabidiol: an overview of some chemical and pharmacological aspects. Part I: chemical aspects

Raphael Mechoulam *, Lumír Hanuš

Department of Medicinal Chemistry and Natural Products, Medical Faculty, Hebrew University of Jerusalem, Ein Kerem Campus, 91120 Jerusalem, Israel

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Abstract

Over the last few years considerable attention has focused on cannabidiol (CBD), a major non-psychotropic constituent of Cannabis. In Part I of this review we present a condensed survey of the chemistry of CBD; in Part II, to be published later, we shall discuss the anti-convulsive, anti-anxiety, anti-psychotic, anti-nausea and anti-rheumatoid arthritic properties of CBD. CBD does not bind to the known cannabinoid receptors and its mechanism of action is yet unknown. In Part II we shall also present evidence that it is conceivable that, in part at least, its effects are due to its recently discovered inhibition of anandamide uptake and hydrolysis and to its anti-oxidative effect.

Keywords: Cannabidiol; Chemical and pharmacological aspects; Cannabis

1. Introduction

Since the isolation and elucidation of the structure of the main active constituent of marijuana, Δ^9-tetrahydrocannabinol (THC; Gaoni and Mechoulam, 1964) an enormous number of published articles have dealt with its chemistry, biochemistry, pharmacology and clinical effects. However, considerable anecdotal evidence has emerged that the effects of marijuana are not due to THC alone (Grinspoon and Bakalar, 1997). At least one constituent, cannabidiol (CBD) was found to cause a plethora of pharmacological effects, some of which may modify the metabolism and effects of THC (see for example Jaeger et al., 1996; Karniol et al., 1974).

In the present overview we shall try to cover some aspects of CBD chemistry and its pharmacological and clinical effects. It is by no means exhaustive. The effects of CBD in numerous systems have been investigated and this short review is not intended to be of encyclopedic nature, but mostly expresses the areas of interest of the authors. The known interactions between THC and CBD are not presented. They require a thorough, separate critical evaluation of the literature, mostly of the 1970's and 1980's, based on

* Corresponding author. Tel.: +972-2-675-8634; fax: +972-2-675-7076
E-mail address: mechou@cc.huji.ac.il (R. Mechoulam).

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the new knowledge of cannabinoid receptors and of CBD effects.

In Part I of this review we present a condensed survey of the chemistry of CBD; in Part II, to be published later, we shall discuss the anti-convulsive, anti-anxiety, anti-psychotic, anti-nausea and anti-rheumatoid arthritic properties of CBD.

2. Isolation, structure and absolute stereochemistry

CBD was first isolated from Mexican marijuana by Roger Adams and from Indian charas by Alexander Todd, both in 1940. For reviews of the early work see Adams (1941), Todd (1946). On the basis of chemical degradation and correlation with cannabinol, a general structure was proposed. However, quite surprisingly, for almost 25 years no further work was reported. In 1963 our group isolated CBD from Lebanese hashish and established its structure and relative stereochemistry, at positions 3 and 4, mostly on the basis of NMR measurements (Fig. 1; Mechoulam and Shvo, 1963). A few years later its absolute stereochemistry was determined by conversion of CBD into menthane carboxylic acid of well established absolute stereochemistry (Mechoulam and Gaoni, 1967; Fig. 1). These early results were of considerable importance for the later elucidation of the structure and stereochemisty of Δ^9-THC, the psychoactive component of Cannabis (Gaoni and Mechoulam, 1964).

The crystal structure of CBD was determined by Jones et al. (1977). Two independent forms of this molecule were noted, which differ mainly in the conformation of the pentyl side chain. The aromatic ring and the terpene ring are almost perpendicular to each other. The two conformers are linked by hydrogen bonding of the hydroxyl moieties.

The chemical nomenclature of CBD differs from that of THC. While the latter has a pyran ring, which determines its numbering (see Fig. 1), CBD has no heterocyclic ring and its numbering stems from that of the terpene ring. This, somewhat unfortunate, technicality leads to the same carbon atom being numbered differently in CBD and THC.

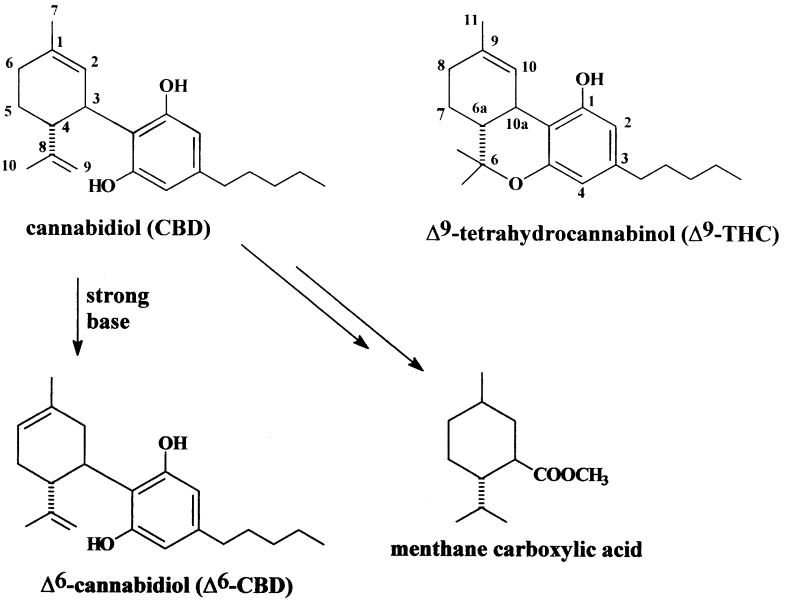


Fig. 1. Conversion of cannabidiol into Δ^6-cannabidiol and degradation to menthane carboxylic acid.

3. Acid cyclizations of CBD

Acid catalyzed cyclizations within the CBD molecule take place leading to Δ^9-THC and to iso-THC (Fig. 2) formed from the respective carbocations on C-8 and C-1 of the CBD skeleton, respectively (Gaoni and Mechoulam, 1966a, 1968). The double bond of THC may further isomerize, leading to Δ^8-THC (Gaoni and Mechoulam, 1966b).

While the THC's, in particular Δ^9-THC, have been thoroughly explored, with thousands of publications appearing since its establishment as the major, or essentially the sole psychoactive Cannabis constituent, the iso-THC's and its derivatives have received almost no attention.

4. Reactions of CBD under basic conditions

The double bond in CBD on heating with *t*-pentyl potassium in toluene-hexamethyl-phosphoric triamide undergoes isomerization to the Δ^6 position, leading to Δ^6-CBD (Srebnik et al., 1984; Fig. 1). Contrary to natural CBD, the Δ^6-isomer showed THC-like activity in rhesus monkeys

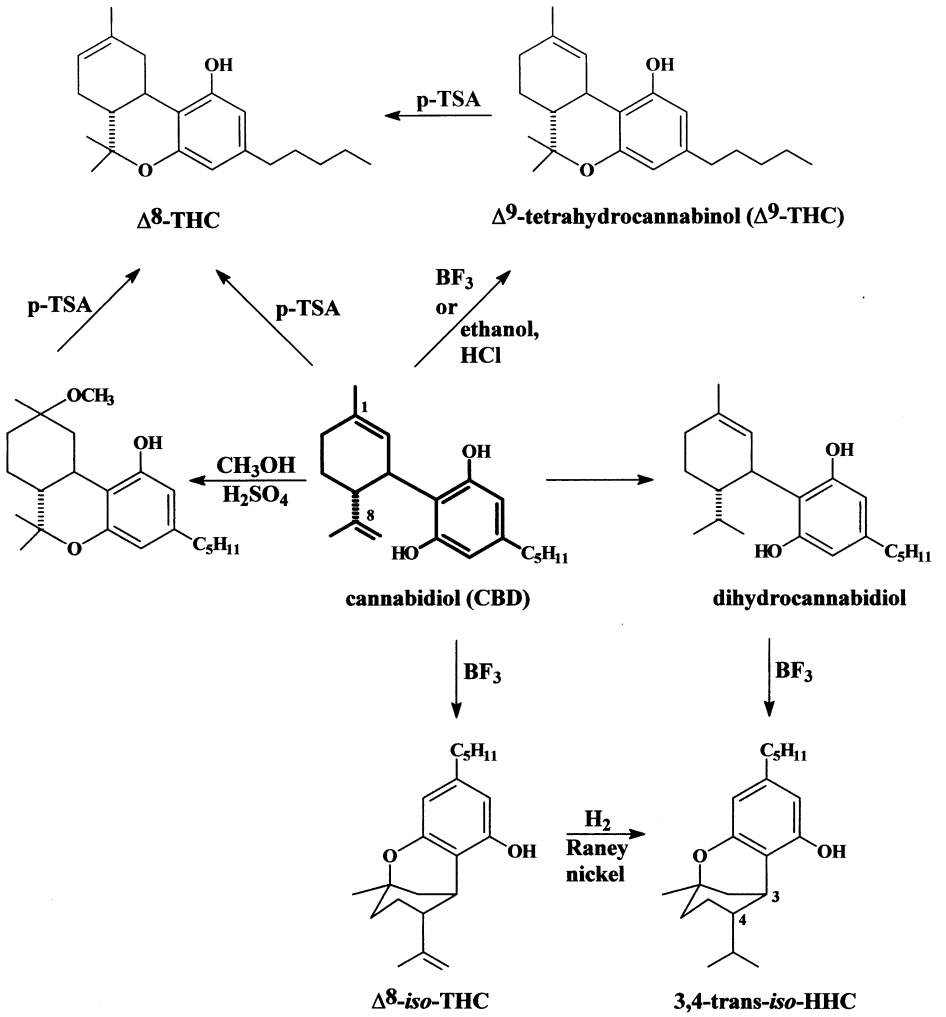


Fig. 2. Cyclizations of CBD and related compounds under acidic conditions.

(unpublished observations). It should be of considerable interest to compare the conformations of the two CBD isomers, in order to establish whether the unexpected difference in activity is due to a steric change. Recently, Wiley et al. (2002) prepared and evaluated the binding and some in vivo effects of a series of bicyclic resorcinols that resemble CBD. Unlike CBD, most of these resorcinol derivatives had good activity in binding to CB_1 and/or CB_2. The lack of activity of CBD remains an enigma.

5. Oxidation of CBD and CBD acid

CBD in base in the presence of oxygen is oxidized to monomeric and dimeric hydroxyquinones (Fig. 3). The anions of the oxidized compounds have a deep violet color (Mechoulam et al., 1968). This is the basis of the Beam reaction used for identification of Cannabis.

Oxidation of CBD diacetate with selenium dioxide leads mainly to the aldehyde on the C-10 position (Fig. 4), with no oxidation of the C-7 position as seen with THC (Lander et al., 1976). However, oxidation with sodium chromate takes place on the C-6 position (Lander et al., 1976).

An alternative entry to substitution at C-10 of CBD was reported (Jorapur et al., 1985), using the 10-bromo-CBD acetate obtained by treatment of CBD diacetate with *N*-bromosuccinimide (Jorapur et al., 1984).

Cannabidiolic acid methyl ester on oxidation with manganese dioxide gave mainly the epimers of the methyl esters of the naturally occurring cannabielsoic acid (Shani and Mechoulam, 1970). This reaction could be significantly improved on bubbling of oxygen, which presumably reactivated the manganese dioxide (Fig. 5).

The same reaction took place without manganese dioxide by oxidative cyclization in the presence of air under irradiation (Fig. 5, Shani and Mechoulam, 1970, 1974).

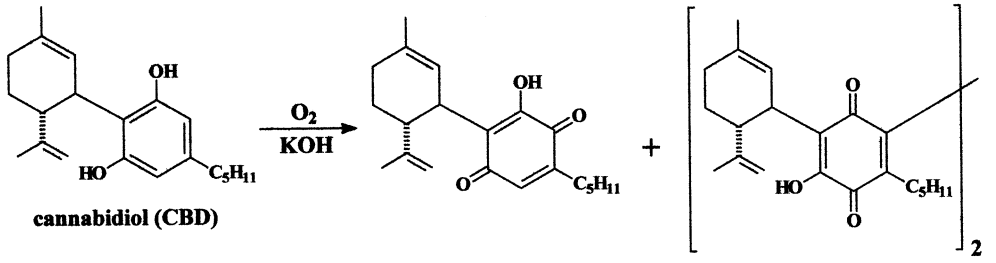
Most of these CBD derivatives were prepared before the biological properties of CBD were discovered and their evaluation may lead to novel therapeutic leads.

6. Photochemical reactions of CBD

In a review of the pharmacological work of his group Loewe mentions that "... unwirksamen Cannabidiol wurde nach Ultraviolet-bestrahlung ein wirkstoffgehalt nachgewiesen ...", but this work was never reported in detail (Loewe, 1950). We have found that irradiation of CBD in methanol with a 450 W lamp in a Corex vessel gave a mixture from which mainly isomeric 1-methoxy dihydro CBD's were obtained (Shani and Mechoulam, 1971). However, irradiation in cyclohexane led to the formation of some THC, in addition to iso-THC, reduced CBD and the addition product of cyclohexane to CBD, giving cyclohexyl CBD (Fig. 6). These reactions indicate that CBD is photoreactive and should be guarded from light when stored.

7. Synthesis of CBD

Several syntheses of CBD have been reported. The most efficient one apparently is the acid condensation of *p*-mentha-2,8-dien-1-ol with oli-



cannabidiol (CBD)

Fig. 3. Quinone formation from CBD.

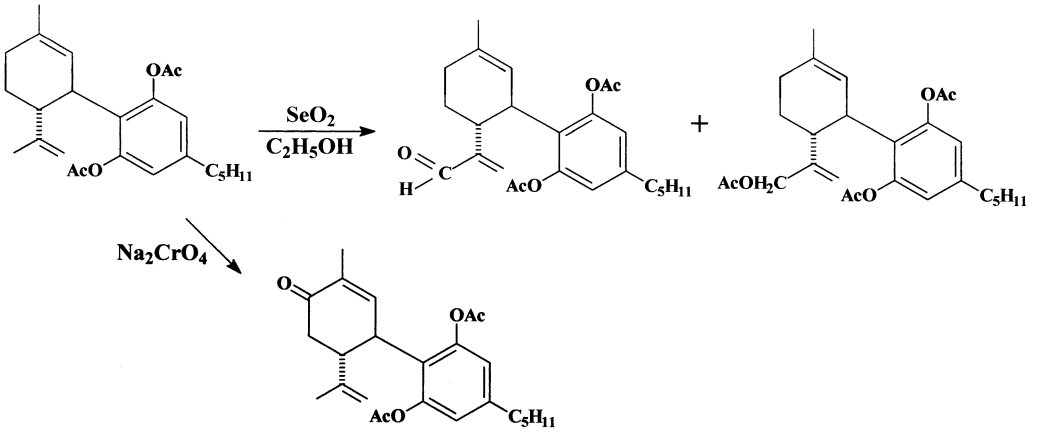


Fig. 4. Oxidations of CBD diacetate.

vetol, as originally proposed by Petrzilka et al. (1967) and later improved by Baek et al., (1985) (Fig. 7). The yield reported (41% of crystalline material) in this one step reaction makes CBD readily available.

8. Metabolism of CBD

The metabolism of CBD is well established. In numerous species, including man, the first step is hydroxylation, mostly on C-7, leading to 7-hydroxy-CBD, followed by further oxidations, leading to CBD-7-oic acid, and numerous hydroxylated derivatives of this acid (Fig. 8, Harvey and Mechoulam, 1990; Harvey et al., 1991). Glucuronides of these oxidized metabolites are also formed (for a review see Agurell et al., 1986).

The syntheses of both 7-hydroxy-CBD (Tchilibon and Mechoulam, 2000) and of CBD-7-oic acid (unpublished) have recently been achieved (Fig. 9).

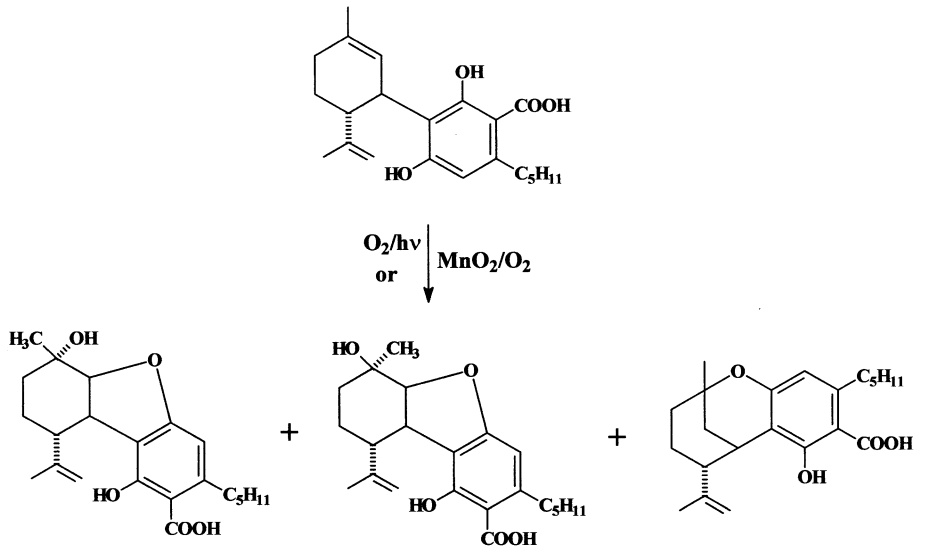


Fig. 5. Formation of cannabelsoic acid-type compounds from CBD.

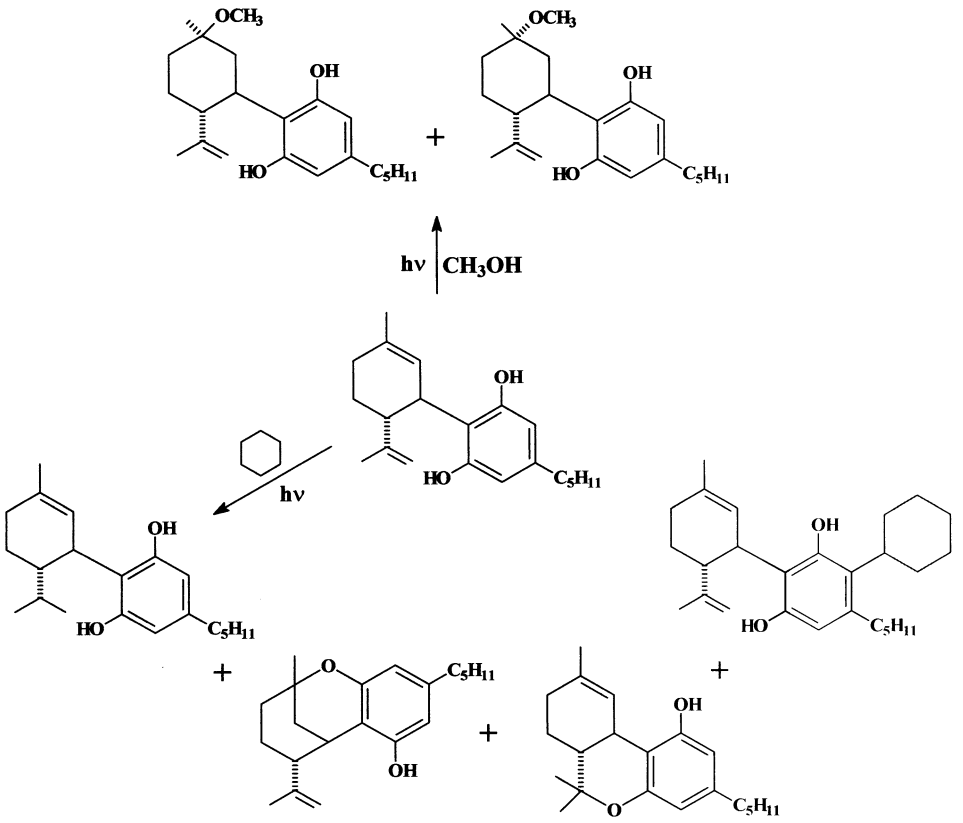


Fig. 6. Photochemical reactions of CBD.

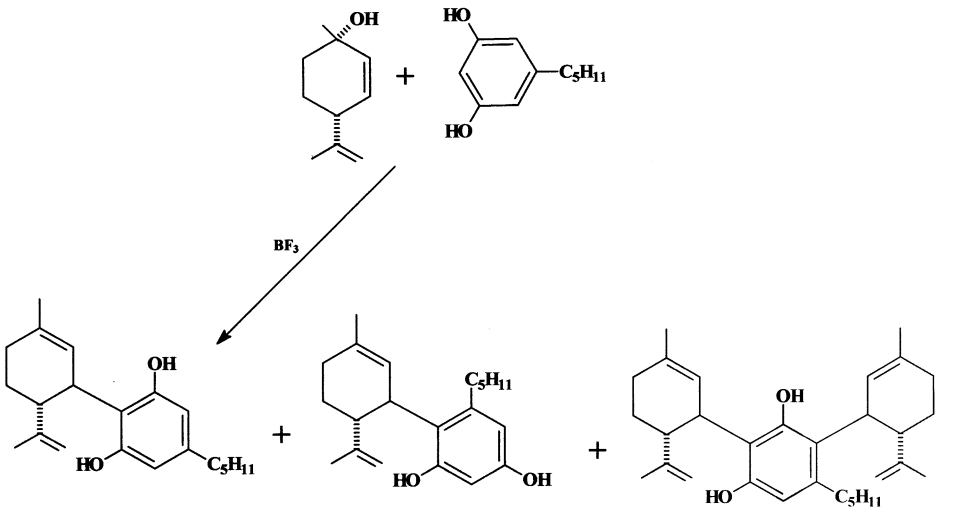


Fig. 7. Synthesis of CBD.

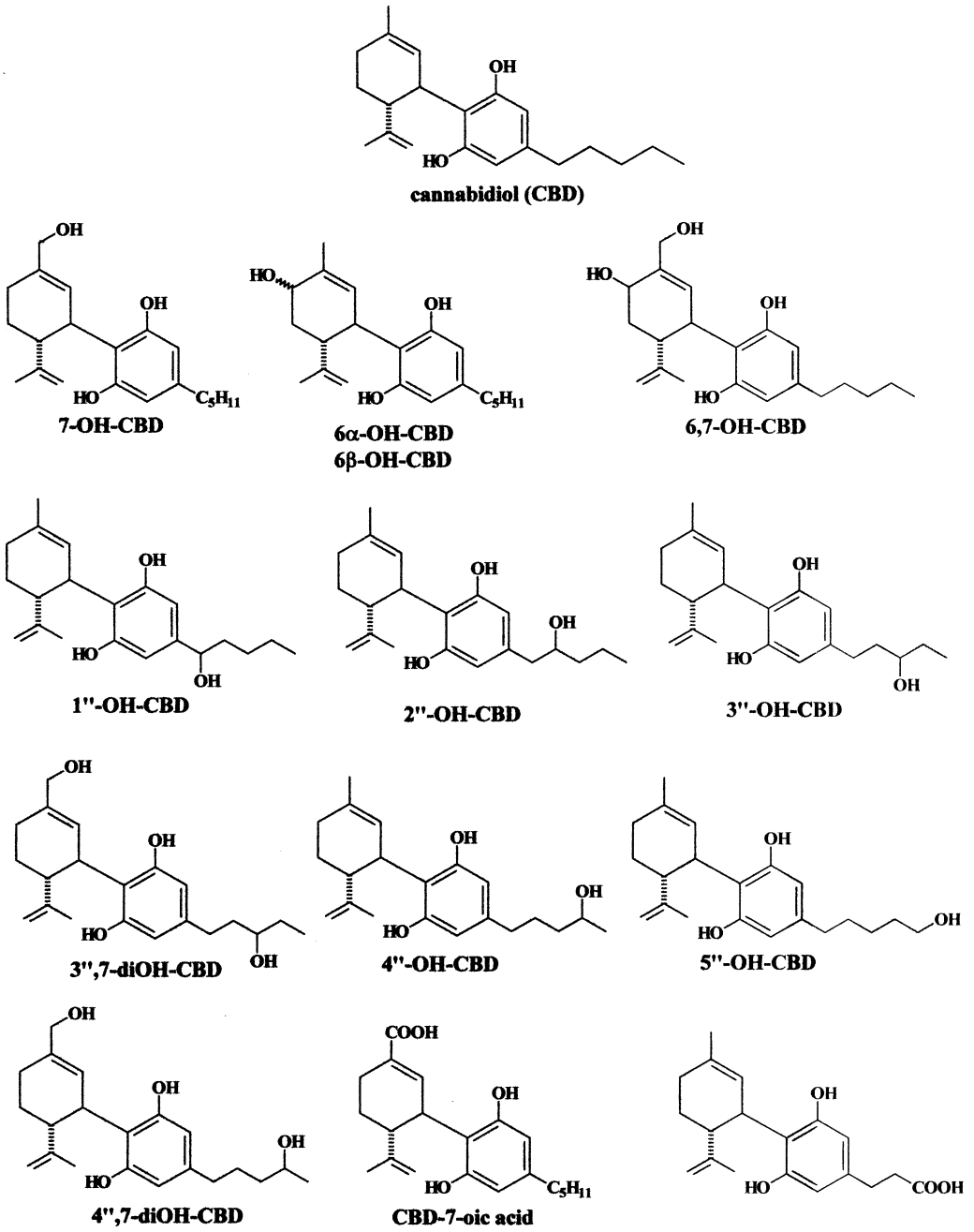


Fig. 8. Metabolites of CBD.

9. CBD chemistry: a summary

The chemistry of CBD has been well explored over the last 35 years. In view of the various, potentially therapeutic, effects caused by CBD, it seems plausible that novel synthetic approaches will be developed in the future to lead to new types of derivatives.

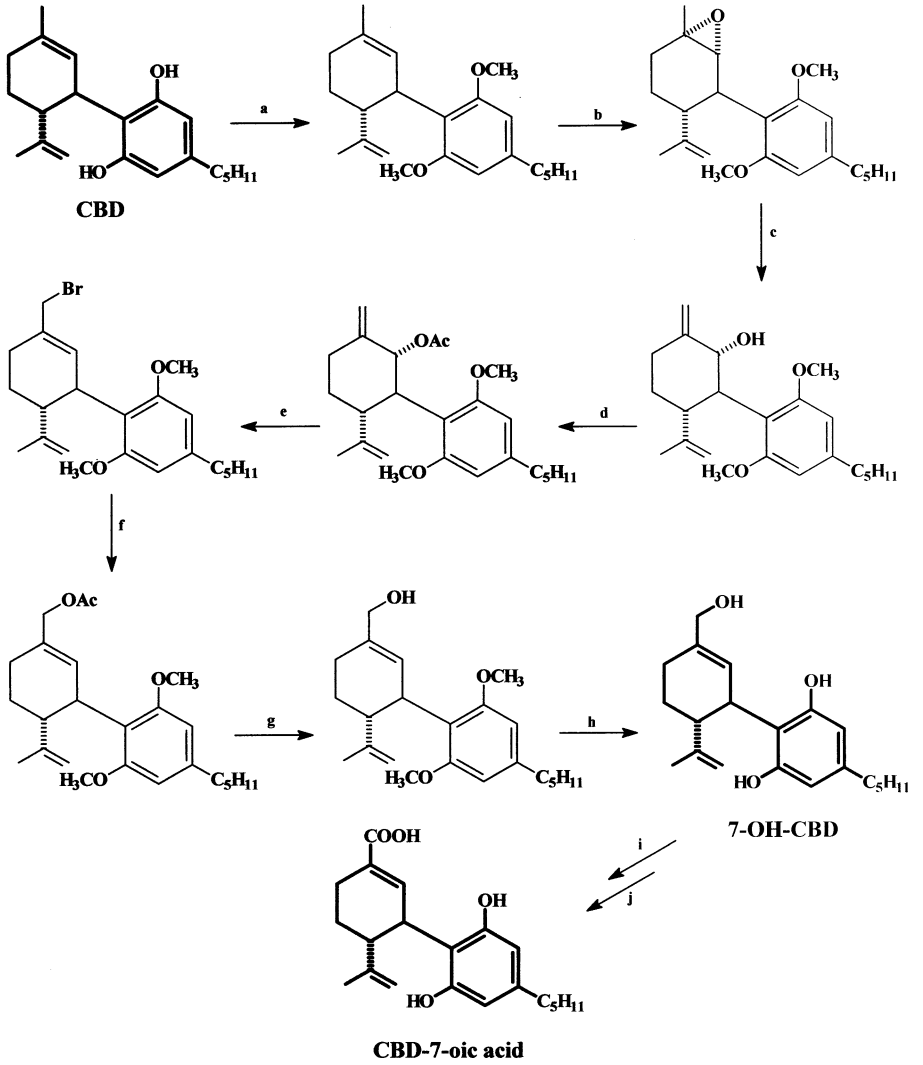


Fig. 9. Synthesis of 7-OH-CBD and CBD-7-oic acid. (a) CH_3I, K_2CO_3 in DMF; (b) 3-chloro-perbenzoic acid in CH_2CK_2; (c) methylmagnesium bromide, N-cyclohexylisopropylamine in toluene; (d) acetic anhydride in pyridine; (e) t-butyl-dimethyl-silyl bromide in CH_2Cl_2; (f) tetrabutylammonium acetate in acetone; (g) NaOH aq; (h) CH_3MgI at 200°C; (i) blocking of phenolic groups; (j) oxidation of allylic alcohol to acid.

References

Adams, R., 1941. Marihuana. Harvey Lect. 37, 168–197.

Agurell, S., Halldin, M., Lindgren, J.E., Ohlsson, A., Widman, M., Gillespie, H., Hollister, L., 1986. Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol. Rev. 38, 21–43.

Baek, S.H., Srebnik, M., Mechoulam, R., 1985. Borontrifluoride on alumina—a modified Lewis acid reagent. An improved synthesis of cannabidiol. Tetrahedron Lett. 26, 1083–1086.

Gaoni, Y., Mechoulam, R., 1964. Isolation, structure and partial synthesis of an active constituent of hashish. J. Am. Chem. Soc. 86, 1646.

Gaoni, Y., Mechoulam, R., 1966a. The isomerization of cannabidiol to tetrahydrocannabinols. Tetrahedron 22, 1481–1488.

Gaoni, Y., Mechoulam, R., 1966b. Concerning the isomerization of Δ^1 to Δ^6-tetrahydrocannabinol. J. Am. Chem. Soc. 88, 5673–5675.

Gaoni, Y., Mechoulam, R., 1968. The iso-tetrahydrocannabinols. Isr. J. Chem. 6, 679–690.

Grinspoon, L., Bakalar, J.B., 1997. Marihuana, the Forbidden Medicine. Yale University Press, New Haven, CT.

Harvey, D.J., Mechoulam, R., 1990. Metabolites of cannabidiol identified in human urine. Xenobiotica 20, 303–320.

Harvey, D.J., Samara, E., Mechoulam, R., 1991. Urinary metabolites of cannabidiol in dog, rat and man and their identification by gas chromatography mass spectrometry. J. Chromatogr. Biomed. Appl. 562, 299–322.

Jaeger, W., Benet, L.Z., Bornheim, L.M., 1996. Inhibition of cyclosporine and tetrahydrocannabinol metabolism by cannabidiol in mouse and human microsomes. Xenobiotica 26, 275–284.

Jones, P.G., Flavello, L., Kennard, O., Sheldrick, G.M., Mechoulam, R., 1977. Cannabidiol. Acta Crystallogr. Sect. B 33, 3211–3214.

Jorapur, V.S., Duffley, R.P., Razdan, R.K., 1984. A procedure for the conversion of cannabidiol into 12-beta-substituted tetrahyrocannabinols (THC's): synthesis of 12-beta-hydroxy-delta-8-THC. Synth. Commun. 14, 655–660.

Jorapur, V.S., Khalil, Z.H., Duffley, R.P., Razdan, R.K., Martin, B.R., Harris, L.S., Dewey, W.L., 1985. Hashish: synthesis and central nervous system activity of some novel analogues of cannabidiol and oxepin derivatives of Δ^9-tetrahydrocannabinol. J. Med. Chem. 28, 783–787.

Karniol, I.G., Shirakawa, I., Kasinski, N., Pfeferman, A., Carlini, E.A., 1974. Cannabidiol interferes with the effects of Δ^9-tetrahydrocannabinol in man. Eur. J. Pharmacol. 28, 172–177.

Lander, N., Ben-Zvi, Z., Mechoulam, R., Martin, B., Nordqvist, M., Agurell, S., 1976. Total syntheses of cannabidiol and Δ^1-THC metabolites. J. Chem. Soc., Perkin I, 8–16.

Loewe, S., 1950. Cannabiswirkstoffe und Pharmakologie der Cannabinole Archiv Exper. Pathol. Pharmakol. 211, 175–193.

Mechoulam, R., Shvo, Y., 1963. The structure of cannabidiol. Tetrahedron 19, 2073–2078.

Mechoulam, R., Gaoni, Y., 1967. The absolute configuration of Δ^1-tetra- hydrocannabinol, the major active constituent of hashish. Tetrahedron Lett., 1109–1111.

Mechoulam, R., Ben-Zvi, Z., Gaoni, Y., 1968. On the nature of the Beam test. Tetrahedron 24, 5615–5624.

Petrzilka, T., Haefliger, W., Sikemeier, C., Ohloff, G., Eschenmoser, A., 1967. Synthese und Chiralitat des (−)-Cannabidiols. Helv. Chim. Acta 50, 719–723.

Shani, A., Mechoulam, R., 1970. A new type of cannabinoids. Syntheses of cannabielsoic acids by a novel photooxidative cyclization. Chem. Commun., 273–274.

Shani, A., Mechoulam, R., 1971. Photochemical reactions of cannabidiol. Cyclization to Δ^1-THC and other transformations. Tetrahedron 27, 601–606.

Shani, A., Mechoulam, R., 1974. Cannabielsoic acids. Isolation and synthesis by a novel oxidative cyclization. Tetrahedron 30, 2437–2446.

Srebnik, M., Lander, N., Breuer, A., Mechoulam, R., 1984. Base catalyzed double bond isomerizations of cannabinoids: structural and stereochemical aspects. J. Chem. Soc., Perkin Trans. I 2881–2886.

Tchilibon, S., Mechoulam, R., 2000. Synthesis of a primary metabolite of cannabidiol. Org. Lett. 2, 3301–3303.

Todd, A.R., 1946. Hashish. Experientia 2, 55–60.

Wiley, J.L., Beletskaya, I.D., Ng, E.W., Dai, Z., Crocker, P.J., Mahadevan, A., Razdan, R.K., Martin, B.R., 2002. Resorcinol derivatives: a novel template for the development of cannabinoid CB_1/CB_2 and CB_2-selective agonists. J. Pharmacol. Exp. Ther. 301, 679–689.