Discussion of Naming and Abbreviating Hexahydrocannabinol

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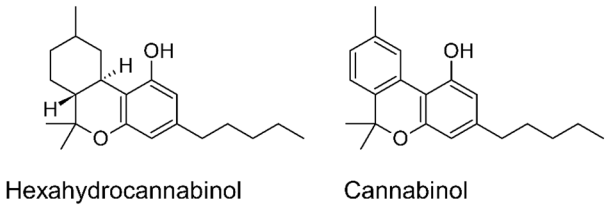
INTRODUCTION

The use of nonstandard abbreviations to refer to various cannabinoids and their synthetic analogues in the cannabis business sector is common and generally accepted. For example, abbreviations such as THC and CBD are widely recognized and used without misunderstandings in scientific communications, product labeling, advertising, and other applications. However, the indiscriminate or unselective use of abbreviations can lead to ambiguity, confusion, and errors of identification if applied to less widely known substances or without verifying that the abbreviation has not been previously used to refer to another substance. Recently, a potential use of the same abbreviation for different, but related cannabinoid derivatives, has come to our attention and will be discussed in the following sections.

HEXAHYDROCANNABINOL AND RELATED SUBSTANCES

Hexahydrocannabinol (HHC) (Figure 1) is named based on its structural relationship to cannabinol (CBN) in which the three double bonds in the ring in the upper left of CBN in the figure have been replaced by saturated bonds in HHC resulting in a hexahydro-derivative with six more hydrogen atoms than CBN. Furthermore, this naming convention also indicates its close chemical relationship to tetrahydrocannabinol. Therefore, the use of HHC as an abbreviation for hexahydrocannabinol is entirely consistent with the use of THC as an abbreviation for tetrahydrocannabinol.

Figure 1. Chemical structures of hexahydrocannabinol (HHC) and cannabinol (CBN)

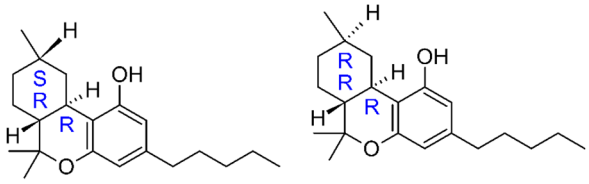


Hexahydrocannabinol Cannabinol

Hexahydrocannabinol has been known since the early 1940s when it was prepared by catalytic hydrogenation of (-)-*trans*-D^9-THC and (-)-*trans*-D^8-THC obtained by acid-catalyzed cyclization of cannabidiol using Adam's catalyst [1; 2]. The synthesis of HHC from THC or its acetate has been repeated by several other groups and results of their findings reported in peer-reviewed scientific publications [3; 4]. Furthermore, the hydrogenation of cannabis oil to produce several derivatives including HHC was described in a patent (US 10,071,127 B2) issued in 2018 [5].

When HHC is prepared from THC by hydrogenation, the stereochemistry at carbon atoms C-6a and C-10a is preserved but a new stereogenic center is created at C-9. Therefore, the HHC resulting from hydrogenation of THC is a mixture of (-)-*trans*-(6a*R*,9*R*,10a*R*)-HHC and (-)-*trans*-(6a*R*,9*S*,10a*R*)-HHC (see Figure 2). These substances are diastereomers that are characterized by different chemical and biological properties.

Figure 2. Diastereomers of HHC produced by catalytic hydrogenation of D^8-THC and D^9-THC



(6aR,9S,10aR)-HHC (6aR,9R,10aR)-HHC

The HHC that is obtained by hydrogenation of THC has been described as the "natural" form of hexahydrocannabinol (*i.e.*, (-)-HHC) because it has the stereochemistry at C-6a and C-10a as the natural materials from which it was prepared. Alternative procedures have been reported for the synthesis of "unnatural" stereoisomers of HHC in efforts to determine the effects of different configurations in the cyclohexane ring of HHC on biological activity [6; 7]. These substances are named as stereoisomeric derivatives of hexahydrocannabinol and are abbreviated accordingly. Since hexahydrocannabinol has three stereogenic carbon atoms, eight stereoisomers and four pairs of enantiomers are possible. The structures of the eight possible stereoisomers of HHC with the configurations at the stereogenic centers indicated by the *R* and *S* nomenclature are shown in Figure 3.

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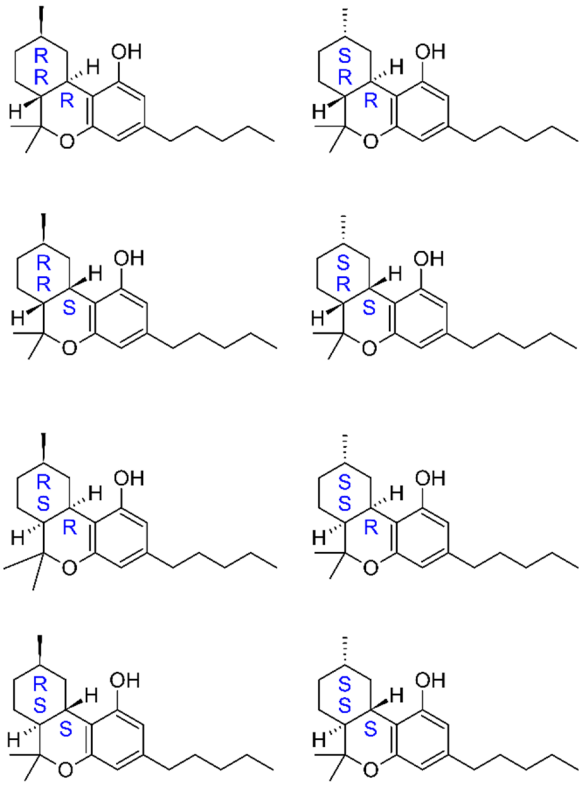
Figure 3. Possible stereoisomers of HHC



Since each of these isomers could be named hexahydrocannabinol and abbreviated HHC, inclusion of a descriptor of the stereochemistry (e.g., (6aR,9S,10aR)-HHC) is necessary to differentiate them.

An alternate route to substituted HHC derivatives involves electrophilic addition of water [8; 9], hydrogen halides [2], or alcohols [10] to the double bond in the cyclohexenyl ring of D^8-THC or D^9-THC or other tetrahydrocannabinoids. For example, HCl was added to the double bond in the cyclohexenyl rings of D^9-THC, D^8-THC, and $D^{9,11}$-THC to form mixtures of the reaction products 9a- and 9b-chlorohexahydrocannabinol which the authors abbreviated as 9a-Cl-HHC and 9b-Cl-HHC [11]. These reaction products were formed in different proportions depending on the THC isomer that was used [11]. Other derivatives of HHC with substituents on the basic scaffold shown in Figure 1 have been reported . These substances are typically named as derivatives of hexahydrocannabinol. For example, addition of water to the double bond in (-)-*trans*-D^9-THC produces a mixture of 9a-OH-HHC and 9b-OH-HHC.

Substituted HHC analogues of D^9-THC have been prepared to investigate the structure activity relationships for cannabimimetic activity [12-19]. One group prepared two pairs of HHC diastereomeric analogues to investigate stereochemical requirements for cannabinoid receptor activity [14; 15]. They identified these pairs of derivatives as (-)-11-OH-b-HHC and (-)-11-OH-a-HHC and 11a-HHC and 11b-HHC, respectively [14; 15]. In addition to investigations of structure activity relationships, studies of the metabolism of HHC derivatives have been reported [20]. In all studies referenced, various substituted hexahydrocannabinols were identified by name and their names were abbreviated as derivatives of HHC in which the substituent groups were identified. In no case, was the abbreviation HHC used to refer to a substituted hexahydrocannabinol.

However, the discovery that 11-OH-Δ^9- THC, a major metabolite of (-)-*trans*-D^9-THC in humans, is more psychoactive than the parent substance [21; 22] led to a search for THC analogues with pharmacologic activity [23]. These studies led to the synthesis of (-)-9-nor-9b-hydroxyhexahydrocannabinol [24; 25] and the discovery that it possesses antinociceptive activity in mice [26] but did not reverse the effects of morphine withdrawal in dependent monkeys [27]. After the first publication in this series [24], this substance was identified as b-HHC [26; 27] or simply HHC [28; 29] in subsequent publications. This use of HHC as an abbreviation for (-)-9-nor-9b-hydroxyhexahydrocannabinol may be problematic because it has the potential to create confusion and uncertainty about the identity and properties of the substance incorporated into products offered for sale to the public unless more specific names and identifications are used. Furthermore, the reference cited above [28] has been cited more than fifty times (as of January 5, 2022) in refereed scientific publications thereby potentially spreading the use of this abbreviation.

CONCLUSIONS AND RECOMMENDATIONS

The use of HHC as an abbreviation for hexahydrocannabinol that is prepared by catalytic hydrogenation of D^9-THC has a long history of use. The use of HHC as an abbreviation for substituted hexahydrocannabinols is much more recent and risks misidentification and uncertainty regarding the intended substance. Therefore, it is recommended that HHC be used as an abbreviation for hexahydrocannabinol and that the stereochemistry and substituents be added to this abbreviation to create an abbreviation that is specific and unambiguous.

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