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The Oxidation of Δ^1- and Δ^6-Tetrahydrocannabinol with Selenium Dioxide[1)]

Seiichi Inayama,[2a)] Aiko Sawa and Eikichi Hosoya[2b)]

Pharmaceutical Laboratory,[2a)] and Department of Pharmacology,[2b)] School of Medicine, Keio University

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Δ^1-Tetrahydrocannabinol (Δ^1-THC, Ia) was oxidized with selenium dioxide to yield 7-hydroxy-(VI), 6α-hydroxy-(VIIa), 6β-hydroxy-(VIIIa) and 6-oxo-Δ^1-THC (IX) together with cannabinol (CBN, III), 7-hydroxy-(X), 6-hydroxy-(XI) and 7-oxo-CBN (XII). Δ^6-THC (IIa) was transformed merely to 7-hydroxy-(IVa) and 7-oxo-Δ^6-THC (Va) in a similar manner. Individual products isolated are well defined mainly on the spectroscopic evidences. The oxidation of Ia favors the endocyclic allyl methylene rather than the exocyclic allyl methyl while the reverse is the case with IIa. Such a sharp contrast shown in their reactivities as mentioned above must be interpreted in terms of the steric interference at the reactive center.

In recent years, the habitual and nonmedical consumption of marihuana for a hallucinogenic effect, has been internationally prevalent in juveniles causing social and medical problems. Various studies on its physiologically active constituents of a number of Cannabis preparations have been developed in the field of medical chemistry.[3)] Among the numerous cannabinoids, (−)-Δ^1-3,4-*trans*-tetrahydrocannabinol (Δ^1-THC, Ia), which is considered as a decarboxylative variant of the corresponding acid component in *Cannabis sativa* (hemp), has been isolated, and known to show the psychotomimetic activity in humans.[4)] (−)-Δ^6-3,4-*trans*-Tetrahydrocannabinol (Δ^6-THC, IIa) prepared semisynthetically by facile isomerization of Ia,[5a)] is a minor[5a)] and less[4)] active, but more stable[4)] principle than Ia in marihuana. Several metabolic investigations[5)] have proved that Ia or IIa is converted mainly to 7-hydroxy-Δ^1- or 7-hydroxy-Δ^6-*trans*-tetrahydrocannabinol (7-hydroxy-THC, VI or IVa) *in vivo* or by liver microsomes *in vitro*, the latter of which had been synthesized[6)] by several pathways and found to be more active than the starting tetrahydrocannabinols.[7)] In connection with our pharmacochemical interest in the oxidative derivatives of THCs *in vivo*, these data prompt us to report the difference in the chemical simulation of Ia and IIa using selenium dioxide prior to a study on the biological oxidation.

Many kinds of oxidation products of Ia and IIa, including VI and IVa mentioned above, have been isolated and well characterized as shown later. When 3′-acetyl-Δ^6-THC (IIb) was refluxed in 95% ethanol with selenium dioxide and acetylated, 3′-acetyl-7-acetoxy-

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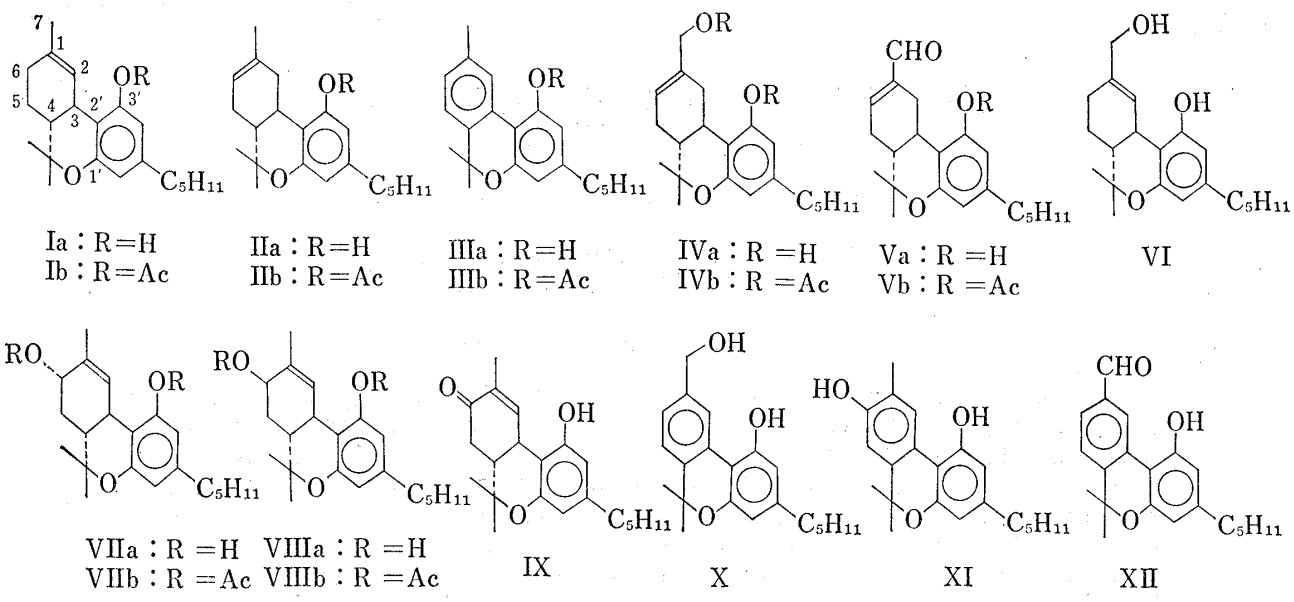

Fig. 1. Structures of Δ^1-, Δ^6-THC and Their Oxidation Products

(IVb, 10%)[6,8,9] and 3′-acetyl-7-oxo-Δ^6-THC (Vb, 21%) were given. The structure of a new compound (Vb), which had not been so far isolated in the similar reaction,[6] was elucidated as follows: 1) The signal of an aldehyde proton appears at δ 9.70 in nuclear magnetic resonance (NMR) spectrum of Vb, while the signal of C-7 methyl (δ 1.65) in the starting compound IIb can not be observed. 2) Infrared (IR) absorption at 1690 and 1646 cm^{-1} corresponds to an α,β-unsaturated aldehyde. 3) $M-C_2H_2O=C_{21}H_{28}O_3$ fragment ion peak is observed at *m/e* 328.2004 (Calcd. 328.2038) in the high resolution mass (Mass) spectrum. 4) The aldehyde (Vb) was further reduced by sodium borohydride in absolute ethanol, and reacetylated to give rise to the same diacetate (IVb) as above, which was easily hydrolysed to the known 7-hydroxy-Δ^6-THC (IVa)[6,8,10] in 14 percent yield from IIb. No other oxidation products except IV and V were identified in the reaction mentioned above.

On the other hand, 3′-acetyl-Δ^1-THC (Ib) was subjected to the similar oxidation at a lowered temperature (40°) under stirring. The reaction mixture was acetylated and chromatographed to isolate 3′-acetylcannabinol (3′-acetyl-CBN, IIIb) in about 12 percent yield. The hydrolysate of the reaction mixture remained after isolation of IIIb was submitted to an extensive chromatography over silicic acid.

7-Hydroxy-CBN (X, 2%),[6] 7-oxo-CBN (XII, 4%) and 6-hydroxy-CBN (XI, 6%) were isolated together with 7-hydroxy-Δ^1-THC (VI, 1%),[5c,d,6,11] 6α-hydroxy-Δ^1-THC (VIIa, 7%),[6,12] 6β-hydroxy-Δ^1-THC (VIIIa, 2%)[12] and 6-oxo-Δ^1-THC (IX, 2%). It should be, however, noted that an expected aldehyde 7-oxo-Δ^1-THC could not be isolated under various conditions of the reaction. Although the reaction condition was almost same as that in Ben-Zui's report,[6] in which the main product was shown to be 7-hydroxy-CBN (X, 18%), the oxidation occurred predominantly at C-6 rather than at C-7 in our hands. Incidentally, almost the identical result was deduced from the oxidation as above except following $NaBH_4$ reduction. It might be assumed that the possible 7-oxo-Δ^1-THC would be so unstable as to be oxidized directly to the biphenyl (XII). The structures of these products were confirmed

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mainly by their NMR spectra (Table I) on comparison with those of Δ^1-(Ia), Δ^6-THC (IIa) and CBN (IIIa) (Table II). With respect to the configuration of the hydroxy group at C-6 in VIIa and VIIIa, the NMR signal of the C-6 proton of VIIa observed at δ 4.40 (bt; J=9 Hz) is deshielded with wider splitting than that of VIIIa appeared at δ 4.20 (d; J=4 Hz). Hence it proves that the configuration of the former proton is axial and the latter is equatorially oriented. These observations were coincident with the data of the authentic material 6α-hydroxy- and 6β-hydroxy-Δ^1-THC, respectively, which had been synthesized in some other ways.[7] The structure of the new compound 6-hydroxy-CBN (XI), that had not been so far prepared, was elucidated as follows: 1) The similar ultraviolet (UV) absorption curve to those of 7-hydroxy-(X) and CBN (III) indicated the formation of an additional aromatic ring conjugated to the olivetol nucleus. 2) In the Mass spectrum, the molecular ion at *m/e* 326 was same as in X and the fragmentation pattern was very resemble to that of X. 3) On comparing the NMR spectrum with that of X, the vinylogous C-7 methyl signal was appeared in XI with loss of one of the aromatic protons at C-5 and C-6 in X. The other two new compounds isolated on the reaction consist of an α,β-unsaturated ketone (IX) and an aromatic aldehyde (XII). The former can be regarded as the intermediate intervening between the corresponding alcohol (VIIa) and biphenyl (XI), and the latter must be a most oxidized product at C-7 derived from the corresponding benzyl alcohol (X) in the reaction. Both are well characterized as follows: In the spectra of IX, 1) IR absorption at 1660 cm^{-1} corresponds to the carbonyl of an α,β-unsaturated ketone. 2) M^+=$C_{21}H_{28}O_3$ ion peak is observed at *m/e* 328. 3) The signal of an aldehyde proton can not be observed in the NMR spectrum, but the signal of C-7 methyl appears at δ 1.74. For the compound XII, 1) IR

Table I. NMR Spectra of Oxidation Products of Δ^1- and Δ^6-THC

Assignments	IVa[6]	Va	VI[5e]	VIIa[6,12]	VIIIa[12]	IX	X[6]	XI	XII
Aldehyde H	—	9.56 (s)[a]	—	—	—	—	—	—	10.13 (s)
Aromatic H	6.26 (d, 1.5)	6.30 (d, 1.5)	6.28	6.35 (d, 1.5)	6.38 (d.1.5)	6.37 (d, 1.5)	6.46 (d, 2)	6.46 (d, 2)	6.52 (d, 2)
	6.12 (d, 1.5)	6.22 (d, 1.5)	6.13	6.24 (d, 1.5)	6.23 (d, 1.5)	6.26 (d, 1.5)	6.31 (d, 2)	6.31 (d, 2)	6.43 (d, 2)
							8.47 (bs)	8.18 (s)	9.09 (d, 2)
							7.27 (s)	6.72 (s)	7.84 (q, 8)
							7.25 (s)		7.45 (d, 8)
Olefinic H	5.73 (b)	7.0 (bm)	6.68 (b)	6.67 (bs)	6.80 (m)	7.9 (b)	—	—	—
$C_{(6)}$–H				4.40 (bt, 9)	4.20 (d, 4)		—	—	—
$C_{(3)}$–H	3.52 (d, 16)	4.02 (bd, 17)	3.3 (b)	3.37 (bd, 11)	3.18 (bm)		—	—	—
Ph–CH_2–			2.45	2.47	2.47 (t)		2.52 (t)	2.53 (t)	2.55 (t)
$C_{(1)}$–CH_2–	4.05 (s)	—	4.04 (s)	—	—	—	4.74 (s)	—	—
$C_{(1)}$–CH_3	—	—	—	1.80 (s)	1.87 (s)	1.74 (m)	—	2.30 (s)	—
gem $(CH_3)_2$	1.34 (s)	1.42 (s)	1.41 (s)	1.42 (s)	1.45 (s)	1.40 (s)	1.60 (s)	1.56 (s)	1.65 (s)
	1.00 (s)	1.14 (s)	1.10 (s)	1.11 (s)	1.11 (s)	1.12 (s)			
ω-CH_3	0.88 (t)	0.88 (t)	0.89 (t)	0.89 (t)	0.89 (t)	0.88 (t)	0.90 (t)	0.90 (t)	0.90 (t)

a) Chemical shifts with coupling constanta in parentheses are given in ppm (Hz) relative to TMS as internal standard in *d*-chloroform solution (s: singlets d: doublet, t: triplet, b: broad, m: multiplet).

Table II. NMR Spectra of Δ^1-, Δ^6-THC and CBN

Assignments	Ia	IIa	IIIa
Aromatic H	6.16(d,2)	6.17(d,2)	6.33(d,2)
	5.99(d,2)	5.93(d,2)	6.13(d,2)
			8.08(b,1)
			7.00(b,2)
Olefinic H	6.31(b)	5.35(b)	—
$C_{(3)}$–H	3.2 (m)	3.3 (b)	—
Ph–CH_2–		2.37(t)	2.45
$C_{(1)}$–CH_3	1.67(b)	1.66(b)	2.35(s)
gem $(CH_3)_2$	1.37(s)	1.32(s)	1.55(s)
	1.05(s)	1.05(s)	
ω-CH_3	0.89(t)	0.88(t)	0.90(t)

absorptions at 1690 and 1660 cm^{-1} correspond to an aromatic aldehyde. 2) $M^+=C_{21}H_{24}O_3$ ion peak is observed at *m/e* 324.[13] 3) The NMR signals are comparable to the corresponding ones of X along with an aldehyde signal at δ 10.13.

It may be assumed that the exocyclic allylic methyl in 3′-acetyl-Δ^6-THC (IIb) would be oxidized prior to the endocyclic allylic methylene. Because C-2 position of IIb is interferred by the phenolic acetyl group, and C-5 position is sterically hindered by *gem*-dimethyl grouping at C-8. In practice, the oxidation occurred exclusively at C-7 exo-allylic position to yield the alcohol (IVb, 10%) and the aldehyde (Vb, 21%) in the ratio of *ca.* 1: 2. On the contrary, the preferred oxidation occurred in the case of 3′-acetyl-Δ^1-THC (Ib), at C-6 endocyclic allylic methylene rather than at C-7 exocyclic methyl resulting in formation of C-6 oxidation products such as VIIa (7%), IX (2%), XI (6%), VIIIa (2%) and IIIb (12%), and of the products oxidized at C-7 such as VI (1%), X (2%) and XII (4%) in the ratio of approximately 4: 1. Another feature of the oxidation in Δ^1-THC, when compared to that in Δ^6-THC, consists apparently in the aromatization of the cyclohexene ring. The ethylenic linkage being formed through dehydrogenation at C-3 and C-4 should be conjugated both to the double bond between C-1 and C-2 and to the olivetol moiety in the molecule. This situation may place easily further dehydrogenation to lead to formation of the biphenyl system in Ib with or without C-6 and C-7 oxygenation. In comparison to the considerable formation of 7-oxo-Δ^6-THC (V), only a few amount of 7-oxo-CBN (XII) was produced instead of the expected 7-oxo-Δ^1-THC. Thus 7-hydroxy-Δ^1-THC (VI) must be transformed into 7-oxo-CBN (XII) probably by such a ready aromatization of the intermediary 7-oxo-Δ^1-THC. It is worthy to note parenthetically that, while 6-hydroxy-CBN (XI) should be derived by the successive dehydrogenation from 6α-hydroxy-Δ^1-THC (VIIa) *via* the 6-oxo intermediate (IX), CBN (III) could be formed secondarily through the hypothetical 3,4-dihydro-CBN being obtained by an easier dehydration of 6β-hydroxy-Δ^1-THC (VIIIa).

Experimental

The IR spectra were recorded on a Hitachi EPI-G3 instrument, the NMR spectra were measured on a Varian A-60 and a JEOL C-60H spectrometer otherweise specified and the UV spectra were determined on a Shimadzu double beam spectrophotometer UV-200. Optical rotations were run on a Jasco DIP-180 automatic polarimeter. The mass spectra were measured on a Hitachi RMS-4 at 80 eV (ion source temperature was 230°).[13] TLC was performed on Silica gel G (Merck) plates with (A) *n*-hexane/ethyl acetate (8: 1), (B) *n*-hexane/ethyl acetate (4: 1) and (C) *n*-hexane/acetone (4: 1) and diazotized benzidine as the coloring agent. Gas chromatography (GLC) was conducted on Shimadzu Model GC-4APF gas chromatograph, using a glass column (2 m×4 mm i.d.) with 1.5% OV-17 on chromsorb W (80—100 mesh), column temperature 240°, and TMS-BA as the silylating agent.

13) A detail of the fragmentations of all the compounds will be reported elsewhere.

Δ^1-Tetrahydrocannabinol (Ia)——The leaves of the domestic hemp in Kumamoto (*Cannabis sativa*, male and female) harvested before blooming, were dried and extracted with *n*-hexane. Δ^1-THC (Ia) was isolated from the chromatographic elution with hexane/ethyl acetate (20: 1) on silica gel in 0.6—1.0 percent of yield on the basis of the dried material. $[\alpha]_D^{20}$ −156° (c=0.34, EtOH).[3] $bp_{0.05}$ 155—157°.[4] TLC (A) Rf=0.40. GLC t_R=5.8. UV λ_{max}^{EtOH} nm (ε): 211 (37000), 230 (9500) (sh), 276 (1500), 283 (1550).[3] Mass Spectrum *m/e*: 314 (M^+).

3′-Acetyl-Δ^1-tetrahydrocannabinol (Ib)——Ia (643 mg) was acetylated with dry pyridine (7 ml) and acetic anhydride (5 ml) overnight at room temperature. After working up as usual, the crude oil remained was chromatographed over silica gel to give rise to a pale yellow syrup, Ib (581 mg, 80%) on elution with hexane/ethyl acetate (20: 1). TLC (A) Rf=0.47. GLC t_R=4.9. UV λ_{max}^{EtOH} nm (ε): 208 (66000), 225 (9200) (sh), 282 (2600). IR ν_{max}^{film} cm^{-1}: 1771 (phenyl acetate). Mass Spectrum *m/e*: 356 (M^+).

Δ^6-Tetrahydrocannabinol (IIa)——The solution of Ia (520 mg) in benzene (52 ml) was refluxed with *p*-toluenesulfonic acid (52 mg) for 30 min on an oil bath. The yellow oil obtained from the reaction mixture was purified by a chromatography on silica gel eluted with benzene to isolate resinous IIa (473 mg, 91%). $[\alpha]_D^{20}$ −226° (c=0.31, EtOH).[4] $bp_{0.1}$ 175—178°. TLC (A) Rf=0.42. GLC t_R=5.3. UV λ_{max}^{EtOH} nm (ε): 211 (47800), 230 (13700) (sh), 276 (2000), 285 (2200).[4] Mass Spectrum *m/e*: 314 (M^+).

3′-Acetyl-Δ^6-tetrahydrocannabinol (IIb)——IIa (294 mg) was acetylated in the same manner as in Ib. The crude acetate gave, on a silica gel chromatography, a syrup, IIb (275 mg, 83%). TLC (A) Rf=0.54. GLC t_R=4.6. UV λ_{max}^{EtOH} nm (ε): 206 (28000), 225 (8900) (sh), 275 (2300). IR ν_{max}^{film} cm^{-1}: 1772 (phenyl acetate). Mass Spectrum *m/e*: 356 (M^+). NMR (CCl_4) δ (ppm): 6.46 (d, J=2 Hz, 1H), 6.28 (d, J=2 Hz, 1H) (arom. H), 5.37 (b, 1H, olefinic $C_{(6)}$–H), 2.17 (s, 3H, $C_{(3')}$–OCOCH_3), 1.65 (s, 3H, $C_{(1)}$–CH_3), 0.88 (t, 3H, ω-CH_3).

3′-Acetyl-7-acetoxy-Δ^6-tetrahydrocannabinol (IVb)——(a) The solution of selenium dioxide (416 mg) in 95% hot ethanol (8.5 ml) was added dropwise to a solution of 3′-acetyl-Δ^6-THC (IIb, 556 mg, containing 2% of IIIb estimated by GLC) in 95% aqueous ethanol (2.5 ml). The mixture was refluxed for 4 hr on an oil bath till the starting material almost disappeared on TLC. The cooled reaction mixture, after filtration of selenium off and removal of the solvent, gave an oil, whose ether solution was washed with sodium bicarbonate and water, dried over magnesium sulfate and evaporated *in vacuo*. The oily residue was acetylated by usual manner. The acetate mixture (680 mg) was subjected to chromatography on silica gel (100 g) eluted with hexane/ethyl acetate (8: 1) and hexane/ethyl acetate (4: 1), successively. The former elution (150 mg) was purified by rechromatography on silica gel eluted with hexane/ethyl acetate (8: 1) to afford IVb (62 mg, 10% of yield from IIb), which was coincident with that obtained on reduction of Vb described below. TLC (B) Rf=0.45. GLC t_R=15.3. UV λ_{max}^{EtOH} nm (ε): 206 (32500), 220 (sh), 276 (3700). IR ν_{max}^{film} cm^{-1}: 1770 (phenyl acetate), 1745 (acetate). Mass Spectrum *m/e*: 414 (M^+). NMR (CCl_4) δ (ppm): 6.44 (d, J=1.5 Hz, 1H), 6.29 (d, J=1.5 Hz, 1H) (arom. H), 5.73 (bm, 1H, olefinic $C_{(6)}$–H), 4.41 (q, J=12 Hz, 2H, $C_{(1)}$–CH_2OCOCH_3), 2.22 (s, 3H, $C_{(3')}$–OCOCH_3), 1.99 (s, 3H, –CH_2OCOCH_3), 1.33 (s, 3H), 1.08 (s, 3H) (*gem* (CH_3)$_2$), 0.88 (t, 3H, ω-CH_3).[8,12] (b) 3′-Acetyl-7-oxo-Δ^6-THC (Vb, 108 mg) in ab. ethanol (1 ml) was added dropwise to a solution of sodium borohydride (35 mg) in ab. ethanol (0.8 ml) under stirring at room temperature. After continuous stirring for additional 2 hr and removal of ethanol *in vacuo*, the residue was acidified (pH 3—4) with acetic acid and extracted with ether, dried over magnesium sulfate, and evaporated *in vacuo*. The crude acetate of the brownish oil (107 mg) obtained as above was purified twice by silica gel chromatographies eluted at first with hexane/ethyl acetate (8: 1) and next with hexane/benzene/methanol (50: 49: 1) to afford a yellow syrup, IVb (53 mg, 44%).

3′-Acetyl-7-oxo-Δ^6-tetrahydrocannabinol (Vb)——The latter elution in the chromatography for isolation of IVb described above (a) gave Vb (118 mg, 21%) as a pale yellow oil on repetition of the same chromatography. $[\alpha]_D^{20}$ −341° (c=0.44, EtOH). TLC (B) Rf=0.20. GLC t_R=10.6. UV λ_{max}^{EtOH} nm (ε): 207 (38300), 224 (19300), 276 (1900) (sh), 282 (2100). IR ν_{max}^{film} cm^{-1}: 1740 (phenyl acetate), 1690, 1646 (α,β-unsaturated aldehyde). Mass Spectrum (high resolution)[14] *m/e*: 328.2004 ($M^+-C_2H_2O$) [328.2038 Calcd. for $C_{21}H_{26}O_3$]. Mass Spectrum *m/e*: 370 (M^+). NMR ($CDCl_3$) δ (ppm): 9.70 (s, 1H, aldehyde H), 6.70 (d, J=1.5 Hz, 1H), 6.58 (d, J=1.5 Hz, 1H) (arom. H), 6.95 (bm, 1H, olefinic $C_{(6)}$–H), 3.48 (bd, J=16 Hz, 1H, $C_{(3)}$–H), 2.57 (t, 2H, Ph–CH_2–), 2.33 (s, 3H, $C_{(3')}$–OCOCH_3), 1.45 (s, 3H), 1.16 (s, 3H) (*gem* (CH_3)$_2$), 0.90 (t, 3H, ω-CH_3).

7-Oxo-Δ^6-tetrahydrocannabinol (Va)——Vb (138 mg) was hydrolyzed in ab. methanol (13 ml) containing sodium methoxide (0.41 mM) with stirring at room temperature for 1 hr. After the ordinary treatment of the reaction, the crude extract was purified by chromatography on silica gel eluted with hexane/ethyl acetate (4: 1) to give a colorless oil, Va (78 mg, 64%). $[\alpha]_D^{17}$ −286° (c=1.96, EtOH). TLC (B) Rf=0.18, (C) Rf=0.35. GLC (TMS-deriv.) t_R=6.1. UV λ_{max}^{EtOH} nm (ε): 209 (27000), 225 (13700) (sh), 276 (1850), 283 (1900). IR ν_{max}^{film} cm^{-1}: 1675, 1645 (α,β-unsaturated aldehyde). Mass Spectrum *m/e*: 328 (M^+).

7-Hydroxy-Δ^6-tetrahydrocannabinol (IVa)——To a solution of IVb (105 mg) in dry ether (30 ml), lithium aluminium hydride (90 mg) was added portionwise and the mixture was stirred at room temperature for 2 hr. After working up as usual a brownish syrup (80 mg) was twice chromatographed on silica gel eluted

14) Determined on a JMS-01SG by courtesy of Mr. K. Sakaguchi of Eisai Co., Ltd. to whom our thanks are due.

with hexane/acetone (4: 1) to give rise to a resinous oil, 7-hydroxy-Δ^6-THC (IVa, 61 mg, 72%). $[\alpha]_D^{17}$ −235° (c=0.20, EtOH).[6,12] TLC (B) Rf=0.06, (C) Rf=0.23. GLC (TMS-deriv.) t_R=4.6. UV λ_{max}^{EtOH} nm (ε): 210 (43500), 230 (11600) (sh), 276 (1400), 283 (1550). Mass Spectrum m/e: 330 (M^+).

Oxidation of 3′-Acetyl-Δ^1-tetrahydrocannabinol (Ib)——Selenium dioxide (470 mg) in 95% hot ethanol (9 ml) was added dropwise to a solution of 3′-acetyl-Δ^1-THC (Ib, 630 mg, containing 5% of IIIb) in 95% ethanol (3 ml). The reaction mixture was warmed at 40° for 3 hr under stirring. After removal of the solvent *in vacuo*, the residue was taken up in ether. The ether solution was washed with aqueous sodium bicarbonate and water, dried, and evaporated to give rise to an oil, which was acetylated as before. The product was chromatographed on silica gel (100 g) and eluted with hexane/ethyl acetate (8: 1) to be divided into two fractions weighing (1) 115 mg and (2) 142 mg, and then with hexane/ethyl acetate (4: 1) to fraction (3) 211 mg. A crystalline compound obtained from the first fraction was shown to be identical with 3′-acetyl-CBN (IIIb) mentioned later in all respects. The overall yield of IIIb from Ib was about 12 percent.[15]

3′-Acetyl-6-acetoxy-Δ^1-tetrahydrocannabinol (VIIb and VIIIb)——The second fraction (142 mg) described above gave, on silica gel chromatography eluted with hexane/ethylacetate (6: 1), an oil (76 mg, 11% of yield from Ib). Even homogeneous on TLC and GLC, it was shown to be a mixture of 6α-acetoxy-(VIIb) and 6β-acetoxy-3′-acetyl-Δ^1-THC (VIIIb) in the ratio *ca.* 4: 1 estimated by NMR. TLC (B) Rf=0.53. GLC t_R=9.8. UV λ_{max}^{EtOH} nm (ε): 207 (43300), 225 (sh), 282 (2600). IR ν_{max}^{film} cm^{-1}: 1772 (phenyl acetate), 1740 (acetate). Mass Spectrum m/e: 414 (M^+). NMR ($CDCl_3$)[16] δ (ppm): 6.55 (t, J=1 Hz, 1H), 6.41 (d, J=1.8 Hz, 1H) (arom. H), 6.37 (b, 0.5H, olefinic $C_{(2)}$–H of VIIIb), 6.26 (b, 0.5H, olefinic $C_{(2)}$–H of VIIb), 5.47 (bt, J=9 Hz, 0.5H, H–$C_{(6)}$–$OCOCH_3$ of VIIb), 5.30 (bd, J=4.5 Hz, 0.5H, H–$C_{(6)}$–$OCOCH_3$ of VIIIb), 3.21 (bd, J=10 Hz, 0.5H, $C_{(3)}$–H of VIIb), 3.0 (bd, J=10 Hz, 0.5H, $C_{(3)}$–H of VIIIb), 2.50 (t, J=7 Hz, Ph–CH_2–), 2.27 (s, 3H, $C_{(3')}$–$OCOCH_3$), 2.09 (s, 1.5H, $C_{(6)}$–$OCOCH_3$ of VIIb), 2.04 (s, 1.5H, $C_{(6)}$–$OCOCH_3$ of VIIIb), 1.67 (m, $C_{(1)}$–CH_3), 1.39 (s), 1.09 (s) (*gem* $(CH_3)_2$ of VIIb), 1.37 (s), 1.07 (s) (*gem* $(CH_3)_2$ of VIIIb), 0.89 (t, ω-CH_3).[6]

6α-Hydroxy-Δ^1-tetrahydrocannabinol (VIIa)——3′-Acetyl-6-acetoxy-Δ^1-THC mixture (VIIb and VIIIb (4: 1), 28 mg) was deacetylated in the same manner as described in IVa, and the reaction mixture was purified by chromatography on silica gel eluted with hexane/acetone (4: 1). The fractions which showed the lower Rf value on TLC yielded resinous VIIa (15 mg, 67%). $[\alpha]_D^{20}$ −176° (c=0.89, EtOH).[6] TLC (C) Rf=0.25. GLC (TMS-deriv.) t_R=3.7. UV λ_{max}^{EtOH} nm (ε): 211 (34400), 230 (sh), 278 (1600), 283 (1700). Mass Spectrum m/e: 330 (M^+).

6β-Hydroxy-Δ^1-tetrahydrocannabinol (VIIIa)——In the above chromatography, all the fractions, which showed the higher Rf value than that of VIIa, gave resinous VIIIa (4 mg, 18%). $[\alpha]_D^{20}$ −122° (c=0.17, EtOH).[12] TLC (C) Rf=0.28. GLC (TMS-deriv.) t_R=3.7. UV λ_{max}^{EtOH} nm (ε): 210 (39000), 230 (sh), 277 (1800), 283 (1900).[12] Mass Spectrum m/e: 330 (M^+).

7-Oxocannabinol (XII)——The third fraction (211 mg) described in the oxidation of Ib containing several products was found to be difficult for separation with each other. This mixture was then deacetylated by sodium methoxide in ab. methanol. When the reaction mixture (185 mg) was subjected to an extensive chromatography on silica gel, XII (20 mg, 4% of yield from Ib), IX (9 mg, 2%), XI (27 mg, 5%), VI (5 mg, 1%) and X (9 mg, 5%) were separated successively on elution with hexane/acetone (4: 1). The characterization of these compounds were as follows. 7-Oxo-CBN (XII): pale yellow syrup. TLC (B) Rf=0.28, (C) Rf=0.55. GLC (TMS-deriv.) t_R=6.6. UV λ_{max}^{EtOH} nm (ε): 210 (15000), 231 (14000), 260 (15000), 288 (8900). IR ν_{max}^{film} cm^{-1}: 1690, 1660 (aromatic aldehyde). Mass Spectrum m/e: 324 (M^+).

6-Oxo-Δ^1-tetrahydrocannabinol (IX)——Pale yellow oil. TLC (B) Rf=0.24, (C) Rf=0.55. GLC (TMS-deriv.) t_R=4.7. UV λ_{max}^{EtOH} nm; 210, 225 (sh), 261, 275. IR ν_{max}^{film} cm^{-1}: 1660 b (α,β-unsaturated ketone). Mass Spectrum m/e: 328 (M^+).

7-Hydroxy-Δ^1-tetrahydrocannabinol (VI)——Colorless glass. $[\alpha]_D^{20}$ −125° (c=0.26, EtOH). TLC (C) Rf=0.23. GLC (TMS-deriv.) t_R=4.4. UV λ_{max}^{EtOH} nm (ε): 211 (38100), 230 (sh) (15000), 276 (4700).[5c,d] Mass Spectrum m/e: 330 (M^+).

6-Hydroxycannabinol (XI)——Colorless glass. TLC (B) Rf=0.18, (C) Rf=0.25. GLC (TMS-deriv.) t_R=5.2. UV λ_{max}^{EtOH} nm (ε): 218 (26600), 230 (18500), 289 (15700), 305 (12200). Mass Spectrum (high resolution) m/e: 326.1817 (M^+) [326.1882 Calcd. for $C_{21}H_{26}O_3$].

7-Hydroxycannabinol (X)——Colorless glass. TLC (C) Rf=0.15. GLC (TMS-deriv.) t_R=6.0. UV λ_{max}^{EtOH} nm (ε): 224 (28000), 286 (15200), 295 (12000) (sh). Mass Spectrum m/e: 326 (M^+).

Cannabinol (IIIa)——Pale yellow oil. TLC (A) Rf=0.36. GLC t_R=7.7. UV λ_{max}^{EtOH} nm (ε): 223 (26400), 283 (15000), 300 (10400) (sh).[4] Mass Spectrum m/e: 310 (M^+).

3′-Acetylcannabinol (IIIb)——CBN (IIIa, 113 mg) was acetylated as usual, and crystallization of the oily acetate from ethanol afforded colorless needles of IIIb (63 mg, 49%). mp 61—64°. TLC (A) Rf=0.43.

15) Subtracted the content of IIIb in the starting material.
16) Measured on a Varian-100 with the sample of VIIb and VIIIb (1: 1) obtained on further oxidation of the above oil (4: 1).

GLC t_R=5.9. UV λ_{max}^{EtOH} nm (ε): 215 (21700), 268 (9400), 276 (9300), 309 (5800). IR ν_{max}^{film} cm^{-1}: 1771 (phenyl acetate). Mass Spectrum *m/e*: 352 (M^+).

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