Total Syntheses of Cannabidiol and Δ^1-Tetrahydrocannabinol Metabolites

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10-Hydroxycannabidiol [2-(10-hydroxy-*p*-mentha-1,8-dien-3-yl)-5-pentylresorcinol] (Va), which has tentatively been identified as a cannabidiol metabolite, as well as 6α- and 6β-hydroxy-cannabidiol [(VIa) and (VIIa)], which are now reported to be metabolites, have been prepared from cannabidiol. Total syntheses of 7-hydroxycannabidiol triacetate (IIIb) and 7-acetoxy-Δ^1-tetrahydrocannabinol (9-acetoxymethyl-6a,7,8,10a-tetrahydro-6,6-dimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol) (IIc) from *p*-mentha-1,8-dien-7-ol are described.

CANNABIDIOL (Ia) is the major neutral cannabinoid in most cannabis products such as hashish and marijuana. It was first isolated [1] in 1940; its structure was fully elucidated in 1963.[2] Unlike Δ^1-tetrahydrocannabinol (Δ^1-THC) (IIa), cannabidiol does not elicit cannabis-type pharmacological effects in either man [3] or monkey.[4] However, it causes prolongation of barbiturate sleeping time, apparently by inhibition of barbiturate metabolism.[5] Cannabidiol also interferes with Δ^1-THC metabolism, causing in mice an increase in brain content of both Δ^1-THC and its pharmacologically active metabolite 7-hydroxy-Δ^1-THC (IIb).[6] Some of the physiological effects caused by Δ^1-THC in animals are

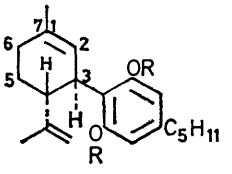
[1] R. Adams, M. Hunt, and J. H. Clark, *J. Amer. Chem. Soc.*, 1940, **62**, 196.
[2] R. Mechoulam and Y. Shvo, *Tetrahedron*, 1963, **19**, 2073.
[3] L. E. Hollister, *Experientia*, 1973, **29**, 825.
[4] R. Mechoulam, A. Shani, H. Edery, and Y. Grunfeld, *Science*, 1970, **169**, 611.
[5] W. D. M. Paton and R. G. Pertwee, *Brit. J. Pharmacol.*, 1972, **44**, 250; A. J. Siemens, H. Kalant, J. M. Khanna, J. Marshman, and G. Ho, *Biochem. Pharmacol.*, 1974, **23**, 477.
[6] G. Jones and R. G. Pertwee, *Brit. J. Pharmacol.*, 1972, **45**, 375.

either enhanced [7,8] or inhibited by cannabidiol.[8] Recently cannabidiol has been shown to possess anticonvulsant activity,[9] to inhibit prostaglandin biosynthesis,[10] and to reduce serotonin uptake.[11] These reports have increased interest in cannabidiol. Nilsson *et al.*[12] have shown that rat liver homogenates metabolize cannabidiol to 7-hydroxycannabidiol (IIIa), 3″-hydroxycannabidiol (IV), and a metabolite tentatively [13] identified as 10-hydroxycannabidiol (Va).

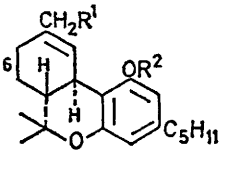
This paper describes the first reported syntheses of 7-hydroxycannabidiol (IIIa), 10-hydroxycannabidiol (Va), and 6α- and 6β-hydroxycannabidiol [(VIa) and (VIIa)]. For practical reasons (IIIa), (Va), and (VIa) were best identified as the acetates (IIIc), (Vb), and (VIb). The preparations of several related oxygenated cannabidiol and Δ^1- and Δ^6-THC derivatives, in particular the important metabolite 7-hydroxy-Δ^1-THC [as its acetate (IIc)] are also reported.[14] By comparison with these synthetic samples it was possible for the first time to identify (VIa) and (VIIa) as cannabidiol metabolites, and to confirm that (IIIa) was a metabolite.

Oxidation of cannabidiol diacetate (Ib) with selenium dioxide in ethanol, followed by acetylation, gave two main products: 10-oxocannabidiol diacetate (VIII) in 33% yield, and 10-hydroxycannabidiol triacetate (Vb) in 12% yield. The structure of (VIII) was determined by spectral measurements and chemical correlations. The i.r. spectrum shows a strong sharp peak at 1 695 cm^{-1} indicative of an unsaturated carbonyl group. The molecular weight (M^+ 412), and the appearance of an aldehydic proton signal (δ 9.40) and the disappearance of one of the olefinic methyl signals in the n.m.r. spectrum [as compared with that of the starting material (Ib)] indicated that one of vinylic methyl groups had been oxidized. The significant downfield shift of the signals due to the two C-9 vinylic protons in (VIII) as compared with those in (Ib) [δ 5.77 and 6.07 in (VIII); 4.4 in (Ib)] suggested that the 10- rather than the 7-methyl group had undergone reaction. This assignment is further supported by the chemical transformations and the unequivocal total synthesis of 7-hydroxycannabidiol triacetate (IIIb) described below.

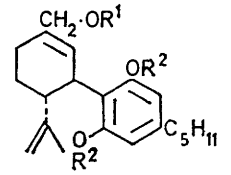
The spectroscopic data of the second product (Vb) are compatible with the proposed structure (see Experimental section) which is corroborated by the conversion of (VIII) into (Vb) by reduction with lithium aluminum hydride followed by acetylation. These reactions constitute a formal total synthesis of the presumed metabolite (Va) [as its acetate (Vb)], as cannabidiol has been synthesized previously.[15,16]



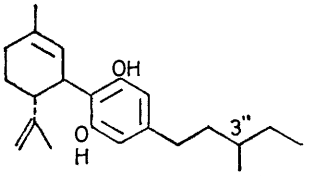
(I) a; R = H
b; R = Ac



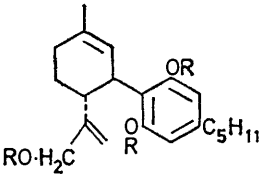
(II) a; $R^1 = R^2 = H$
b; $R^1 = OH, R^2 = H$
c; $R^1 = OAc, R^2 = H$
d; $R^1 = OAc, R^2 = Ac$
e; $R^1 = H, R^2 = Ac$



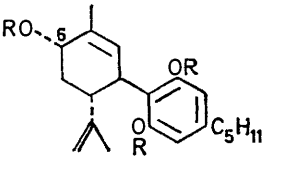
(III) a; $R^1 = R^2 = H$
b; $R^1 = R^2 = Ac$
c; $R^1 = Ac, R^2 = H$



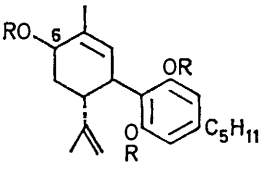
(IV)



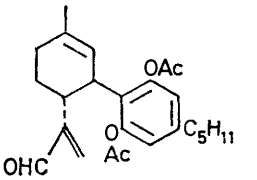
(V) a; R = H
b; R = Ac



(VI) a; R = H
b; R = Ac



(VII) a; R = H
b; R = Ac

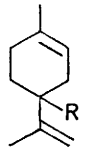


(VIII)

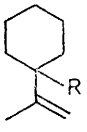
The formation of (VIII) and (Vb) as the major products of oxidation by selenium dioxide is at variance with precedent. Guillemonat [17] has reported that the preference for oxidation of trisubstituted olefins with

[7] M. Fernandez, A. Schabarek, H. Coper, and R. Hill, *Psychopharmacology*, 1974, **38**, 329.
[8] I. G. Karniol and E. A. Carlini, *Psychopharmacology*, 1973, **33**, 53.
[9] I. Izquierdo, A. C. Berardi, and D. A. Orsingher, *Psychopharmacology*, 1973, **28**, 95; E. A. Carlini, J. R. Leite, M. Tannhauser, and A. C. Berardi, *J. Pharm. Pharmacol.*, 1973, **25**, 655; R. Karler, W. Cely, and S. A. Turkanis, *Life Sci.*, 1973, **73**, 1527.
[10] S. Burstein, E. Levin, and C. Varanelli, *Biochem. Pharmacol.*, 1973, **22**, 2905.
[11] S. P. Banerjee, S. H. Snyder, and R. Mechoulam, *J. Pharmacol. Exp. Ther.*, 1975, **194**, 74.
[12] I. M. Nilsson, S. Agurell, K. Leader, J. L. G. Nillson, and M. Widman, *Acta Pharm. Suecica*, 1971, **8**, 701; I. Nillson, S. Agurell, J. L. G. Nilsson, M. Widman, and K. Leander, *J. Pharm. Pharmacol.*, 1973, **25**, 486.
[13] B. Martin, M. Nordqvist, and S. Agurell, unpublished work.
[14] Presented in part at the International Conference on the Pharmacology of Cannabis, Savannah, Georgia, December 1974; to be published in ' The Pharmacology of Marihuana,' eds. M. Braude and S. Szara, Raven Press, New York, 1975.
[15] For recent reviews see (*a*) ' Marijuana. Chemistry, Pharmacology, Metabolism and Clinical Effects,' ed. R. Mechoulam, Academic Press, New York, 1973; (*b*) R. Mechoulam, N. K. McCallum, and S. Burstein, *Chem. Rev.*, 1976, in the press.
[16] B. Cardillo, L. Merlini, and S. Servi, *Gazzetta*, 1973, **103**, 127.
[17] A. Guillemonat, *Ann. Chim. (France)*, 1939, **11**, 143.

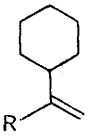
selenium dioxide follows the sequence $CH_2 > CH_3 > CH$. In a disubstituted olefin series, however, Trachtenberg and co-workers [18] have found that the reactivity sequence is $CH > CH_2 > CH_3$. This oxidation order has received additional experimental support. Thomas and Bucher [19] have reported that *p*-mentha-1,8-diene (IX) on oxidation with selenium dioxide in ethanol gives mainly the 4-hydroxy-derivative (X). Bhalerao and Rapoport [20] have investigated the same kind of oxidation with various types of olefin. Their results confirm that for terminal disubstituted unsymmetrical olefins the reactivity sequence is $CH > CH_2 > CH_3$. Thus oxidation of the olefin (XI) gave the products (XII)—(XIV) in the ratio 74 : 18 : 8 (total yield 50%). Prolonged oxidation (6.5 h) however, markedly decreased the amount of (XII). In our case the products (Vb) and (VIII) account for 46% of the starting material. Although any 4-hydroxycannabidiol diacetate (XV)



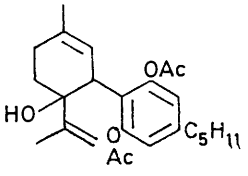
(IX) R = H
(X) R = OH



(XI) R = H
(XII) R = OH



(XIII) R = CH_2OH
(XIV) R = CHO



(XV)

produced could have been destroyed by the prolonged reaction time (7 h), the high total yield (for this type of reaction) of (Vb) and (VIII) indicates that the oxidation preference is $CH < CH_3$ rather than $CH > CH_3$. It has been pointed out [20] that in allylic oxidation of unsymmetrically disubstituted olefins 'it does not appear possible to explain the initial attack of selenium dioxide . . . by any one single pathway.' On the basis of the purely synthetic data presented here it is, in any case, impossible to eliminate any one of the three known mechanisms of selenium dioxide oxidation (oxaselenacyclobutane intermediate, carbocation ion intermediate, or cyclic transition state). It seems plausible however that the bulky aromatic substituent on C-3 sterically inhibits reactions which take place on C-4.

The synthesis of 6α- and 6β-hydroxycannabidiol triacetates [(VIb) and (VIIb)] was accomplished in two steps. Oxidation of cannabidiol diacetate (Ib) with sodium chromate gave 6-oxocannabidiol diacetate (XVIb) in 36% yield. The C-6 position of the ketone group is established by the appearance of an unsaturated carbonyl group peak in the i.r. spectrum (1 670 cm^{-1}) and the presence of two vinylic methyl signals in the n.m.r. spectrum. The C-2 proton in (XVIb) (δ 6.41) is deshielded in comparison with the corresponding proton (δ 5.10) in (Ib). Structure (XVIb) is further supported by conversion into the known [21] 6-oxo-Δ^1-THC acetate (XVII) through hydrolysis to (XVIa), followed by cyclization with boron trifluoride and acetylation of the cyclized product.

Reduction of 6-oxocannabidiol diacetate (XVIb) with lithium aluminium hydride followed by acetylation gave a mixture of (VIb) and (VIIb) in the ratio *ca.* 20 : 1. The stereochemistry at C-6 is tentatively deduced from the n.m.r. spectrum. In (VIb) the C-6 (pseudoaxial) proton is considerably more deshielded than the corresponding (pseudoequatorial) one in (VIIb). In the spectrum of (VIb) the signal is very broad; in that of (VIIb) it is a narrow double doublet. In the case of the corresponding allylic alcohols (VIa) and (VIIa) the signal of the C-6 proton moves upfield. In the spectrum of (VIa) it is apparently in part under the peak of the terminal methylene protons (δ *ca.* 4.4; very broad); in that of (VIIa) it is at δ 4.10 (*J* 4.5 Hz). These data parallel published observations.[22] Thus, in the spectrum of 6α-hydroxy-Δ^1-THC (XVIIIa) the C 6 (pseudoaxial) proton signal is at δ 4.32 (*J* 11 Hz); in that of 6β-hydroxy-Δ^1-THC the corresponding (pseudoequatorial proton) signal is at δ 4.05 (*J* 3 Hz). The above tentative elucidation of the stereochemistry of the reduction of 6-oxocannabidiol diacetate (XVIb) is supported by the observation that 6-oxo-Δ^1-THC acetate (XVII) on reduction with lithium aluminium hydride also gives mainly the 6α-hydroxy-isomer. It may be of some relevance that in the rat liver *in vitro* metabolism of both cannabidiol (Ia) (see below) and Δ^1-THC (IIa) [23] the 6α- is formed in considerably larger amounts than the 6β-hydroxy-epimer.

We tried to correlate the alcohol (VIa) with the known 6α-hydroxy-Δ^1-THC (XVIIIa). Treatment with boron trifluoride caused, however, cyclization at C-2, giving anhydrocannabielsoin (XIXa). Thus, this method represents a new type of entry into the cannabielsoin group.[24] Compound (XIXb) has been prepared pre-

[18] E. N. Trachtenberg and J. R. Carver, *J. Org. Chem.*, 1970, **35**, 1646; E. N. Trachtenberg, C. H. Nelson, and J. R. Carver, *ibid.*, p. 1653, and references therein.

[19] A. F. Thomas and W. Bucher, *Helv. Chim. Acta*, 1970, **53**, 770; see also H. P. Jensen and K. B. Sharpless, *J. Org. Chem.*, 1975, **40**, 264.

[20] U. T. Bhalerao and H. Rapoport, *J. Amer. Chem. Soc.*, 1971, **93**, 4835.

[21] O. Gurny, D. E. Maynard, R. G. Pitcher, and R. W. Kierstead, *J. Amer. Chem. Soc.*, 1972, **94**, 7928; R. Mechoulam, H. Varconi, Z. Ben-Zvi, H. Edery, and Y. Grunfeld, *ibid.*, p. 7930.

[22] Z. Ben-Zvi, R. Mechoulam, and S. Burstein, *J. Amer. Chem. Soc.*, 1970, **92**, 3468; Z. Ben-Zvi, R. Mechoulam, H. Edery, and G. Porath, *Science*, 1971, **174**, 951; C. G. Pitt, F. Hauser, R. L. Hawks, S. Sathe, and M. E. Wall, *J. Amer. Chem. Soc.*, 1972, **94**, 8578.

[23] G. Jones, M. Widman, S. Agurell, and J.-E. Lindgren, *Acta Pharm. Suecica*, 1974, **11**, 283.

[24] (*a*) A. Shani and R. Mechoulam, *Chem. Comm.*, 1970, 273; A. Shani and R. Mechoulam, *Tetrahedron*, 1974, **30**, 2437; (*b*) D. B. Uliss, R. K. Razdan, and H. C. Dalzell, *J. Amer. Chem. Soc.*, 1974, **96**, 7372.

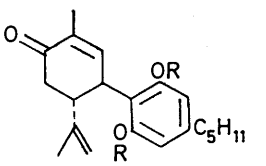
viously [24a] from cannabidiolic acid and from natural cannabielsoic acid; (XIXa) has been reported as a product in a different synthetic sequence.[24b]

The acid-catalysed cyclizations of cannabidiol (Ia) as a route to Δ^1-THC (IIa) and Δ^6-THC (XXa) have been thoroughly investigated.[15] Under mild conditions ring closure is not accompanied by isomerization of the double bond from the 1,2- to the 1,6-position. However, this reaction occurs readily on boiling with toluene-*p*-sulphonic acid. The position of the double bond can be readily determined from the chemical shift of the olefinic proton. That in Δ^1-THC acetate (IIe) (δ 5.92) is considerably more deshielded than the corresponding proton in Δ^6-THC acetate (XXb) (δ 5.43), owing to the influence of the aromatic system. This difference is generally observed in THC-type compounds.

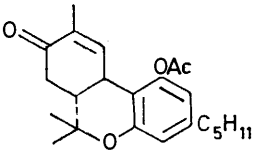
The availability of the oxygenated cannabidiol derivative (Vb) led us to investigate its reactions with acid. Reduction of (Vb) with lithium aluminum hydride gave (Va) which, without further purification, was treated with toluene-*p*-sulphonic acid in benzene. The product was acetylated. The only pure compound isolated was obtained in low yield and its purification was difficult. Its structure (XXI) was established from the disappearance in the n.m.r. spectrum of the signal of the terminal methylene group, and the presence of two acetoxy-groups and of two protons α to an acetoxy-group. The chemical shift of the olefinic proton (δ 5.37) indicated an isomerization of the double bond from the 1,2- to the 1,6-position (see above). Uliss *et al.* have reported [24b] the preparation of the Δ^1-isomer of (XXI) *via* a different reaction sequence. The olefinic proton of this isomer resonated at δ 5.95. The difference in shift of the olefinic protons in the two isomers confirms the positions of the respective double bonds.

The above described oxidations of cannabidiol did not lead to 7-oxygenated cannabidiol derivatives. A full total synthesis was therefore attempted. Our synthetic route is based on the condensation of an appropriately substituted monoterpene with olivetol. However, no monoterpenes were known to us which possessed a reactive centre at C-3 (the point of attachment to the aromatic moiety), an 8,9-double bond, and an oxygen-containing group at C-7. We undertook therefore the preparation of 7-acetoxy-*p*-mentha-1,8-dien-3-ol (XXVIa). The advantage of this starting material is the presence of a chiral centre at C-4 which allows the direct formation of optically active 7-oxygenated cannabinoids. This method follows the routes generally employed in cannabinoid total syntheses, namely condensation of an appropriate monoterpenoid allylic alcohol with olivetol.[15] Merlini and his co-workers [16] have indeed already described the synthesis of cannabidiol from *p*-mentha-1,8-dien-3-ol and olivetol, though under experimental conditions different from those described below.

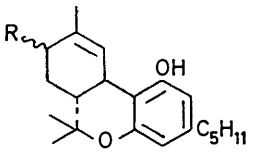
For practical reasons we chose as starting materials the racemic *p*-mentha-1,8-dien-7-ol (XXIIIa), as well



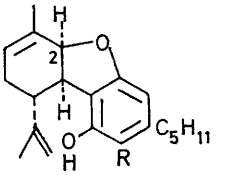
(XVI) a; R = H
b; R = Ac



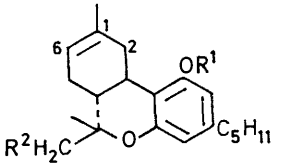
(XVII)



(XVIII) a; R = α-OH
b; R = β-OH



(XIX) a; R = H
b; R = CO_2H



(XX) a; $R^1 = R^2 = H$
b; R^1 = Ac, R^2 = H
(XXI) R^1 = Ac, R^2 = OAc

as the commercially available (−)-(4*S*)-*p*-mentha-1,8-dien-7-al [*cf.* (XXII)] rather than its rarer (4*R*)-enantiomer.[25] For consistency, only the enantiomers leading to the natural (−)-cannabinoids are indicated in the formulae, although the reaction sequences were performed with both the racemic and the (4*S*)-*p*-mentha-1,8-dien-7-ol. The latter, which leads to the unnatural (+)-cannabidiol derivatives was obtained by reduction with lithium aluminum hydride of (4*S*)-*p*-mentha-1,8-dien-7-al.

Oxidation of the acetate (XXIIIb) with chromium trioxide–pyridine complex [26] led to a mixture of the αβ-unsaturated ketones (XXIV) and (XXV) in 10 and 8% yield, respectively. Separation on a column of acid-washed alumina caused isomerization of the terminal double bond in (XXIV), giving the 1,4(8)-dien-3-one (XXVII). However, dry column chromatography on silica gel gave pure (XXIV), which was reduced with lithium hydridotri-t-butoxyaluminate to 7-acetoxy-*p*-mentha-1,8-dien-3-ol (XXVIa), in which the 3-hydroxy-group is presumably mostly α (axial) owing

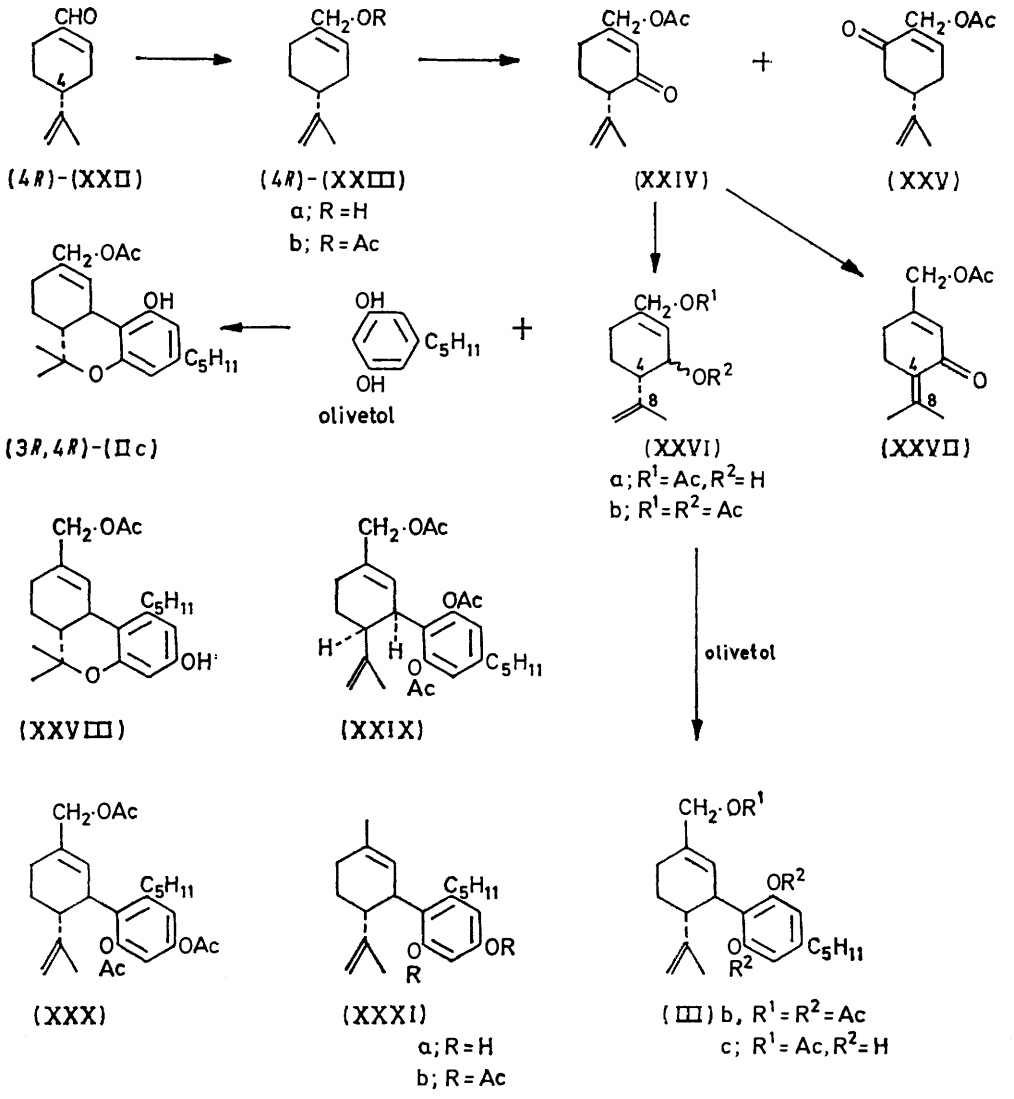
[25] G. Büchi, W. Hofheinz, and J. V. Paukstelis, *J. Amer. Chem. Soc.*, 1969, **91**, 6473; T. R. Keenan, B.Sc. Thesis, Massachusetts Institute of Technology, 1966; we thank Professor G. Büchi for a copy of this Thesis. The use of (+)-(4*R*)-*p*-mentha-1,8-dien-7-al prepared according to the procedures described in these papers should lead to (−)-7-acetoxycannabidiol (IIIc).

[26] W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, 1969, **34**, 3587.

to steric approach control.[27] Indeed in the n.m.r. spectrum of 3,7-diacetoxy-*p*-mentha-1,8-diene (XXVIb), two peaks (in the ratio *ca.* 3 : 1) attributable to the C-2 vinylic proton are observed. Condensation of (XXVIa) with olivetol in methylene chloride in the presence of boron trifluoride–ether complex at −6 °C for 1.5 h gave a mixture from which we were able to isolate 7-acetoxy-Δ^1-THC (IIc) and a compound to which, on the basis of its spectral data and higher polarity on t.l.c., we tentatively assign the isomeric structure (XXVIII). The structure of (IIc) was established by comparison of its physical data with those published for the acetate of the natural product.[28]

The synthetic sequence from (4*S*)-*p*-mentha-1,8-dien-7-al led to (+)-(3*S*,4*S*)-7-acetoxy-Δ^1-THC [*cf.* (IIc)]. This enantiomer of the (3*R*,4*R*)-metabolite of the naturally occurring Δ^1-THC has been observed[29] (as the free alcohol) to be a metabolite, in its own right, of the synthetic[30] (+)-(3*S*,4*S*)-Δ^1-THC.

Condensation of (XXVIa) with olivetol as described above, but for a shorter time (10 min) gave 7-acetoxycannabidiol (IIIc). Acetylation led to 7-hydroxycannabidiol triacetate (IIIb). Several other isomers might be expected to be formed in this reaction: the 3,4-*cis*-isomer (XXIX) and the positional isomers of both (IIIb) and (XXIX) [*cf.* (XXX)]. In (XXX) the two aromatic acetate groups as well as the two aromatic protons are not expected to be equivalent. In order to establish this point we synthesized the corresponding positional isomer (XXXIa) of cannabidiol by a modific-



[27] W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, 1965, **78**, 2579.

[28] I. M. Nilsson, S. Agurell, J. L. G. Nilsson, A. Ohlsson, F. Sandberg, and M. Wahlqvist, *Science*, 1970, **168**, 1228; M. E. Wall, *Ann. New York Acad. Sci.*, 1971, **191**, 23.

[29] G. Jones, R. G. Pertwee, E. W. Gill, W. D. M. Paton, I. M. Nilsson, M. Widman, and S. Agurell, *Biochem. Pharmacol.*, 1974, **23**, 439.

[30] R. Mechoulam, P. Braun, and Y. Gaoni, *J. Amer. Chem. Soc.*, 1972, **94**, 6159.

ation of a published procedure.[31] On acetylation (XXXIb) was obtained. As expected, the acetate methyl groups (δ 2.05 and 2.18) and the aromatic protons (δ 6.7 and 6.5) in (XXXIb) are not equivalent. By contrast in both cannabidiol diacetate (Ib) and 7-hydroxycannabidiol triacetate (IIIb) the two aromatic protons and the two aromatic acetate methyl groups are equivalent. A further difference between the positional isomer (XXXIa) and cannabidiol (Ia) is in the chemical shift of the C-10 protons: δ 1.54 for (XXXIa); δ 1.67 for (Ia). In the synthetic (IIIc), this methyl group resonates at δ 1.65. Furthermore the C-3 proton in (XXXIa) resonates at δ 3.35—3.75, and in (Ia) at 3.65—4.00. In 7-acetoxycannabidiol (IIIc) this signal appears at δ 3.62—4.10.

3,4-*cis*-Cannabidiol has not been observed in any of the condensations, reported so far, between olivetol and various monoterpenoid allylic alcohols.[15] This is probably due to preferred attack by the bulky olivetol on the planar intermediate carbocation from the less hindered side, *trans* to the isopropenyl group. Furthermore if the synthetic (IIIb) was in fact the *cis*-isomer (XXIX) we would have expected considerable differences in the chemical shifts of the various protons in the vicinity of C-3 and C-4 as compared with those in cannabidiol diacetate. No such differences were observed. We conclude that the compound which we identify as 7-acetoxycannabidiol has indeed the relative configuration indicated in (IIIc).

A number of cannabidiol derivatives described above, prepared in Jerusalem, were sent to Uppsala for comparison with cannabidiol metabolites. As cannabinoid acetates are usually more stable than the corresponding free alcohols, only acetylated compounds were sent. These were converted into the free alcohols by reduction with lithium aluminum hydride. The metabolites were obtained by incubation of [^{3}H]cannabidiol (Ia) with 10 000 *g* supernatant from rat liver as previously described by Jones *et al.*[23] After extraction and purification, the metabolites obtained were compared with the synthetic compounds by g.l.c., t.l.c., and g.l.c.–mass spectrometry. The major metabolite was identified as 7-hydroxycannabidiol (IIIa). Both 6-hydroxycannabidiols [(VIa) and (VIIa)] were also shown to be present. The three metabolites (IIIa), (VIa), and (VIb) were present in the ratio 100 : 13 : 0.7. We have been unable, as yet, positively to identify 10-hydroxycannabidiol (Va) as a metabolite although a compound was isolated whose n.m.r. spectrum, mass spectral data (of silylated material), and polarity (on t.l.c.) are similar to those of (Va). However, its g.l.c. retention time is half that of (Va).

In a parallel experiment, metabolic (IIIa) was sent to Jerusalem, where it was acetylated and compared with synthetic (IIIb) by g.l.c. and t.l.c. By both tests the synthetic and natural materials were identical.

Several of the synthetic oxygenated cannabidiol derivatives described above are being tested for anti-epileptic activity by Professor E. A. Carlini of Sao Paulo.

[31] T. Petrzilka, W. Haefliger, and C. Sikemeier, *Helv. Chim. Acta*, 1969, **52**, 1102.

EXPERIMENTAL

Unless otherwise stated, the following apply. Optical rotations were determined for solutions in ethanol. U.v. measurements were made for solutions in ethanol. I.r. spectra were taken for solutions in carbon tetrachloride. ^{1}H N.m.r. data were determined for solutions in deuteriochloroform or carbon tetrachloride with tetramethylsilane as internal standard. T.l.c. was performed on 0.3 mm silica gel plates. Column chromatography was performed on silica gel (Merck Kieselgel 60, 70—230 mesh). Evaporations were carried out under reduced pressure, and drying refers to the use of anhydrous sodium or magnesium sulphate. Analyses, in most cases, are not reported, as the new compounds were oils which partly decomposed on distillation, and were generally purified only by chromatography. ' Worked up in the usual way ' means addition of ether and cold water to the cooled reaction mixture, extraction of the ethereal fraction with N-hydrochloric acid (except in those reactions done in acidic media) and then with saturated aqueous sodium hydrogen carbonate solution, followed by drying and evaporation. Mass spectra were obtained at 70 eV.

Oxidation of Cannabidiol Diacetate with Selenium Dioxide.—Cannabidiol diacetate (Ib) (3.98 g, 0.01 mol) was heated under reflux in ethanol (80 ml) containing selenium dioxide (2.8 g, 0.25 mol) for 7 h. The mixture was cooled and the selenium was filtered off. The solvent was evaporated off. Water (400 ml) was added and the mixture was extracted with ether; the extract was then dried and evaporated. The residual gum was dissolved in pyridine (25 ml) and acetic anhydride (10 ml) and was left at room temperature overnight. The mixture was worked up in the usual way. The residual gum (3.65 g) was chromatographed on silica gel. The first eluted compound [with light petroleum–ether (5 : 1)] was 10-*oxocannabidiol diacetate* (VIII), an oil (1.36 g, 33%), M^+ 412; $[\alpha]_D$ −114°; $\lambda_{max.}$ 220 (ε 34 600), 260 (485), and 270sh nm (300); $\nu_{max.}$ 1 770 (acetate CO) and 1 695 cm^{-1} (aldehyde CO); δ ($CDCl_3$) 0.88, 1.67, and 2.15 (CH_3 groups), 5.20 (s, 2-H), 5.77 and 6.07 (s, 9-H_2), 6.65 (2 H, aromatic), and 9.40 (s, CHO); *m/e* 412 (15%), 384 (13), 370 (17), 369 (13), 353 (54), 352 (57), 328 (27), 327 (27), 310 (60), 246 (48), and 231 (100).

The second eluted compound [with light petroleum–ether (4 : 1)] was 10-*hydroxycannabidiol triacetate* (Vb), an oil (0.54 g, 12%), M^+ 456; $[\alpha]_D$ −108°; $\lambda_{max.}$ 268 (ε 450), 272sh (350), and 281 nm (180); $\nu_{max.}$ 1 770, 1 750 (acetate CO), and 900 cm^{-1} (=CH_2); δ ($CDCl_3$) 0.88 (t), 1.68 (s), 1.97 (s), and 2.15 (s) (Me groups), 3.35—3.80 (m, 3-H), 4.29 (s, 10-H_2), 4.85 and 4.95 (9-H_2), 5.16 (2-H), and 6.69 (aromatic); *m/e* 456 (3%), 414 (3), 396 (12), 354 (20), 337 (41), 336 (25), 288 (37), 231 (100), 229 (50), and 228 (62).

Reduction of 10-*Oxocannabidiol Diacetate.*—10-Oxocannabidiol diacetate (VIII) (412 mg, 0.001 mol) in dry ether (15 ml) was added, during 30 min, to a suspension of lithium aluminum hydride (0.5 g) in ether (20 ml). The mixture was stirred for 2 h at room temperature. The excess of reagent was destroyed with a saturated solution of sodium sulphate, and hydrochloric acid (N), and the mixture was worked up in the usual way. The residual gum was dissolved in pyridine (25 ml) and acetic anhydride (10 ml) and was left at room temperature overnight. The

mixture was again worked up in the usual way (excluding the washing with acid). The oil obtained was purified by preparative layer chromatography (p.l.c.). 10-Hydroxycannabidiol triacetate (Vb) (366 mg, 80%) thus obtained was identical with (Vb) described above (t.l.c., i.r., and n.m.r.).

6-Oxocannabidiol Diacetate (XVIb).—Cannabidiol diacetate (Ib) (5.5 g, 0.0138 mol) was dissolved in acetic acid (18 ml) and acetic anhydride (9 ml). Anhydrous sodium chromate (4.8 g) was added, and the mixture was stirred, at 35 °C, for 96 h. Water (100 ml) and ether (100 ml) were added. The organic layer was washed with 10% sodium hydrogen carbonate solution, and after drying was evaporated to dryness. The residual oil (5 g) was chromatographed on silica gel (250 g). Elution with light petroleum–ether (10 : 2) gave *6-oxocannabidiol diacetate* (XVIb) (2.076 g, 36%), an oil, M^+ 412; $[\alpha]_D$ −126°; $\lambda_{max.}$ 237 nm (ε 12 300); $\nu_{max.}$ 1 770 and 1 670 cm^{-1}; δ (CCl_4) 0.91, 1.59, 1.74, and 2.11 (Me groups), 3.58—4.00 (m, 3-H), 4.52 (9-H_2), 6.41 (2-H), and 6.67 (aromatic); *m/e* 412 (38%), 370 (94), 328 (75), 302 (100), 260 (84), and 231 (65).

6-Oxo-Δ¹-THC Acetate (XVII).—6-Oxocannabidiol diacetate (XVIb) (206 mg, 0.0005 mol) was dissolved in methanolic 5% sodium hydroxide (10 ml), and the solution was boiled for 1 h. The product was diluted with water (100 ml) and extracted with ether. The extract was dried and evaporated. The residual oil (160 mg) without further purification was dissolved in dry methylene chloride (50 ml) containing boron trifluoride–ether complex (1 ml). The solution was kept at ambient temperature for 1 h. After the usual work up, the oil obtained was dissolved in acetic anhydride (2 ml) and pyridine (10 ml) and was left at ambient temperature overnight. The mixture was worked up in the usual way (excluding the washing with acid). The oil obtained was purified by p.l.c. (silica gel; 20% ether–light petroleum). 6-Oxo-Δ¹-THC acetate (XVII) (140 mg, 76%) thus obtained was chromatographically and spectroscopically identical (n.m.r. and i.r.) with an authentic specimen.[21]

6α-Hydroxycannabidiol Triacetate (VIb) *and the 6β-Hydroxy-isomer* (VIIb).—6-Oxocannabidiol diacetate (XVIb) (185 mg, 0.000 45 mol) was reduced and reacetylated as described above for the parallel reaction with 10-oxocannabidiol diacetate (VIII). The oily mixture obtained (150 mg) was separated by p.l.c. (silica gel; 10% ether–light petroleum). Two pure compounds were isolated: (a) *6α-hydroxycannabidiol triacetate* (VIb) (50 mg, 24%), an oil, M^+ 456; $[\alpha]_D$ −130°; $\lambda_{max.}$ 265 (ε 360) and 273sh nm (280); $\nu_{max.}$ 1 770, 1 730, and 900 cm^{-1}; δ ($CDCl_3$) 0.88 (t), 1.54, 1.62, 2.06, and 2.20 (Me groups), 3.35—3.80 (3-H), 4.46 and 4.55 (9-H_2), 5.37 (2-H), 5.4—5.7 (6-H), and 6.67 (aromatic); *m/e* 456 (1.5%), 414 (9), 413 (9), 396 (30), 388 (46), 354 (57), 346 (44), 312 (81), 304 (100), 262 (44), and 231 (29); and (b) *6β-hydroxycannabidiol triacetate* (VIIb) (2.5 mg, 1.2%), an oil, $\nu_{max.}$ 1 775, 1 735, and 900 cm^{-1}; δ ($CDCl_3$) 0.88 (t), 1.52, 1.69, 2.07, and 2.24 (Me groups), 3.20—3.55 (3-H), 4.47br (9-H_2), 5.27 (dd, 6-H, *J* 4 and 1.5 Hz), 5.50 (2-H), and 6.70 (aromatic).

6α- (VIa) and 6β-Hydroxycannabidiol (VIIa).—When, in the above reaction, the reduction product of 6-oxocannabidiol diacetate (XVIb) (106 mg, 0.000 26 mol) was not reacetylated but was separated, after work-up, by p.l.c. (silica gel; 35% ether–light petroleum), two products were isolated. The major, less polar one was *6α-hydroxycannabidiol* (VIa) (35 mg, 41%), an oil, M^+ 330, [α] −173; $\lambda_{max.}$ 275sh (ε 921) and 282 nm (910); $\nu_{max.}$ ($CHCl_3$) 910 cm^{-1}; δ ($CDCl_3$) 0.87 (t), 1.67, and 1.86 (Me groups), 3.92br (3-H), 4.20 to beyond 4.35, underneath 9-H_2 signal (6-H), 4.50 and 4.58 (9-H_2), 5.60 (2-H), and 6.17 (aromatic); *m/e* 330 (5%), 312 (100), 297 (80), 262 (84), 257 (57), and 231 (68). The minor, more polar, product was *6β-hydroxycannabidiol* (VIIa) (2.5 mg, 6%), $\nu_{max.}$ ($CHCl_3$) 890 cm^{-1}; δ ($CDCl_3$) 0.85 (t), 1.65, and 1.84 (Me groups), 3.6—4.0 (3-H), 4.10 (*J* 4.5 Hz, 6-H), 4.56 (9-H), 5.55 (2-H), and 6.22 (aromatic).

Acetylation of (VIa) as described for (XVII) gave the triacetate (VIIb), chromatographically and spectroscopically identical (n.m.r. and i.r.) with an authentic sample.

Reduction of 6-Oxo-Δ¹-THC Acetate (XVII).—6-Oxo-Δ¹-THC acetate (XVII) (107 mg, 0.0003 mol) was reduced with lithium aluminum hydride as described for 10-oxocannabidiol diacetate (VIII). The oily product was separated by p.l.c. The only compound obtained was 6α-hydroxy-Δ¹-THC (XVIIIa) (48 mg, 42%), identical with authentic material [20] (t.l.c., g.l.c., and i.r.). The 6β-isomer was not observed.

Anhydrocannabielsoin (XIXa).—6α-Hydroxycannabidiol triacetate (VIb) (1.85 g, 0.0041 mol) was reduced with lithium aluminum hydride (1.5 g) as described above. The product, without further purification, was dissolved in dry methylene chloride (50 ml). Boron trifluoride–ether complex (0.7 ml) was slowly added. The mixture was stirred for 0.5 h under nitrogen at room temperature. The solution was worked up as usual (without the acidic washing) and the oil obtained (1.1 g) was chromatographed on Florisil (165 g). Elution with 1% ether in light petroleum gave *anhydrocannabielsoin* (XIXa) (0.5 g, 39%) as an oil, M^+ 312; [α] +166°; $\lambda_{max.}$ 271 (ε 942) and 283 nm (873); $\nu_{max.}$ ($CHCl_3$) 900 cm^{-1}; δ ($CDCl_3$) 0.86 (t), 1.80 and 1.91 (Me groups), 3.15 (dd, $J_{2,3}$ 8, $J_{3,4}$ 12 Hz, 3-H), 4.70 (d, $J_{2,3}$ 8 Hz, 2-H), 5.06 (s, 9-H_2), 5.80br (6-H), and 6.23 (s, aromatic); *m/e* 312 (46%), 297 (14), 257 (46), 231 (12), 220 (36), 205 (100), and 193 (36). Anhydrocannabielsoin 3,5-dinitrobenzoate melts at 89—90°.

9-Acetoxy-Δ⁶-THC Acetate (XXI).—10-Oxocannabidiol diacetate (VIII) (217 mg, 0.00053 mol) was reduced with lithium aluminum hydride (250 mg) as described above; however the reduced product was not acetylated but was dissolved in dry benzene (10 ml) containing toluene-*p*-sulphonic acid (50 mg) and was boiled under reflux for 1 h. The mixture was worked up as usual. The oil obtained was dissolved in pyridine (10 ml) and acetic anhydride (2 ml) and left at ambient temperature overnight. After the usual work up the oil obtained was purified by p.l.c. (silica gel; 20% ether–light petroleum). *9-Acetoxy-Δ⁶-THC acetate* (XXI) (21 mg, 9.6%) thus obtained was an oil, M^+ 414; $\nu_{max.}$ (CCl_4) 1 775 and 1 740 cm^{-1}; δ (CCl_4) 0.92 (t), 1.10, 1.70, 2.05, and 2.20 (Me groups), 4.10 (9-H_2), 5.37 (6-H), and 6.31 and 6.51 (aromatic); *m/e* 414 (76%), 372 (100), 355 (5), 354 (5), 316 (57), and 231 (81).

Oxidation of p-*Mentha*-1,8-*dien*-7-*yl Acetate*.—Racemic *p*-mentha-1,8-dien-7-yl acetate (XXIIIb) (4.074 g, 0.02 mol), prepared from the 7-ol, was dissolved in dry methylene chloride (300 ml) freshly distilled over phosphorus pentaoxide. Chromium trioxide–pyridine complex (85 g) was freshly prepared [26] and was dried (reduced pressure) for 30 min. The complex, in methylene chloride (160 ml) was added to the terpene solution, which turned brown. The mixture was stirred at room temperature for 25 h. After the usual work-up an oily mixture (2.64 g) was obtained.

It was separated by p.l.c. (23% ether–light petroleum; two elutions). Three compounds were isolated. One was the starting material (XXIIIb) (863 mg). The minor product was 6-*oxo*-p-*mentha*-1,8-*dien*-7-*yl acetate* (XXV) (358 mg, 8.2%) [Found: *m/e* 165.0926. $C_{10}H_{13}O_2$ (*M* − 43) requires 165.0915]; $\lambda_{max.}$ 229 nm (ε 4 780); $\nu_{max.}$ 1 745, 1 680, and 890 cm^{-1}; δ (CCl_4) 1.75 and 1.97 (Me groups), 2.45 (m, allylic), 4.62 and 4.75 (9- and 7-H_2), and 6.85 (m, 2-H); *m/e* 181 (7%), 169 (10), 166 (21), 165 (30), 148 (100), 133 (21), 106 (52), 105 (42), and 98 (61).

The major oxidation product was 3-*oxo*-p-*mentha*-1,8-*dien*-7-*yl acetate* (XXIV) (441 mg, 10.1%) (Found: M^+, 208.1112. $C_{12}H_{16}O_3$ requires *M*, 208.109 93); $\lambda_{max.}$ 230 nm (ε 12 080); $\nu_{max.}$ 1 750, 1 678, and 897 cm^{-1}; δ (CCl_4) 1.72 and 2.08 (Me groups), 2.32 (m, allylic), 2.88 (t, 4-H), 4.58 (7-H_2), 4.67 and 4.85 (9-H_2), and 5.85 (2-H); *m/e* 208 (7%), 193 (4), 166 (8), 133 (9), and 98 (100).

3-*Oxo*-p-*mentha*-1,4(8)-*dien*-7-*yl Acetate* (XXVII).—3-Oxo-*p*-mentha-1,8-dien-7-yl acetate (XXIV) (208 mg, 0.001 mol) in light petroleum (5 ml) containing 17% ether was filtered through a column of aluminum oxide (Woelm acid-washed; activity IV) (20 g). The filtrate was evaporated to dryness. The 1,4(8)-*diene* (XXVII) was obtained as an oil (200 mg, 96%) (Found: M^+, 208.111 76. $C_{12}H_{16}O_3$ requires *M*, 208.109 93); $\lambda_{max.}$ 232 (ε 8 540) and 278 nm (5 410); $\nu_{max.}$ (CCl_4) 1 750 and 1 670 cm^{-1}; δ (CCl_4) 1.80, 2.05, and 2.07 (Me groups), 4.55 (s, 7-H_2), and 5.85 (2-H); *m/e* 208 (4%), 193 (2), 166 (5), 148 (20), 133 (17), 105 (12), and 98 (100). The diene (XXVII) may contain some starting material.

3-*Hydroxy*-p-*mentha*-1,8-*dien*-7-*yl Acetate* (XXVIa).—3-Oxo-*p*-mentha-1,8-dien-7-yl acetate (XXIV) (66 mg, 0.000 32 mol) in dry tetrahydrofuran (13 ml) was added dropwise to lithium hydridotri-t-butoxyaluminate (0.84 g, 0.0033 mol) in the same solvent (5 ml). The mixture was stirred under nitrogen for 3 h at 0 °C, then for 1 h at room temperature. Acetic acid (0.3 ml) and water (5 ml) were added dropwise. The mixture was stirred for 0.5 h, and was then filtered and washed with chloroform. The chloroform solution was washed with water, dried, and evaporated. The product (60 mg, 89%) showed one spot on t.l.c. However, judging from the multiplicity of bands in the acetate methyl region in (XXVIb) (see below) it seems to be a mixture of isomers. It was further purified by p.l.c. to give 3-hydroxy-*p*-mentha-1,8-dien-7-yl acetate (XXVIa), an oil; $\nu_{max.}$ (CCl_4) 1 740 and 900 cm^{-1}; δ (CCl_4) 1.8 and 2.02 (Me groups), 4.05 (3-H), 4.40 (7-H_2), 4.80 and 4.90 (9-H_2), and 5.70br (2-H); *m/e* 192 (16%), 150 (100), 132 (68), 117 (100), and 100 (88) (no M^+).

Acetylation with acetic anhydride and pyridine led to *p*-mentha-1,8-diene-3,7-diyl diacetate (XXVIb), an oil; $\nu_{max.}$ (CCl_4) 1 740 and 890 cm^{-1}; δ (CCl_4) 1.75br (s), 1.90, 1.95, and 2.02 (Me groups), 4.40br (s, 7-H_2), 4.67br (9-H_2), 5.30 (m, 3-H), and 5.50 and 5.70 (peak ratio 1 : 3) (br, 2-H); *m/e* 210 (2%), 150 (85), 134 (50), 132 (85), 117 (100), 91 (82), and 92 (41) (no M^+).

Condensation of 3-*Hydroxy*-p-*mentha*-1,8-*dien*-7-*yl Acetate* (XXVIa) *with Olivetol.*—(a) 7-*Acetoxycannabidiol* (IIIc). Freshly prepared 3-hydroxy-*p*-mentha-1,8-dien-7-yl acetate (XXVIa) (86 mg, 0.00041 mol) and olivetol (68 mg, 0.00038 mol) were dissolved in methylene chloride (10 ml; distilled over calcium hydride). Boron trifluoride–ether complex (0.5 ml) was added to the solution, which was stirred for 10 min under nitrogen at −5 °C. The mixture was worked up as usual and the product was separated by p.l.c. (20% ether–light petroleum; three elutions). 7-*Acetoxycannabidiol* (IIIc) (9.3 mg, 6.6%) was obtained as an oil, M^+ 372; $\nu_{max.}$ (CCl_4) 1 750 and 900 cm^{-1}; $\lambda_{max.}$ 282 nm (ε 1 900); δ (CCl_4) 0.87 (t), 1.65, and 2.07 (Me groups), 3.72—4.10 (m, 3-H), 4.50 (7-H_2), 5.78br (2-H), and 6.17 (s, aromatic); *m/e* 372 (4%), 312 (65), 297 (17), 284 (21), 269 (21), 244 (100), and 231 (30).

(b) 7-*Hydroxycannabidiol triacetate* (IIIb). When, instead of being isolated directly, the crude product was acetylated with acetic anhydride (0.2 ml) in pyridine (1 ml) and left overnight at room temperature, 7-*hydroxycannabidiol triacetate* (IIIb) (16 mg, 9%) was obtained (by p.l.c.; elution with 15% ether–light petroleum) as an oil M^+ 456; $\nu_{max.}$ (CCl_4) 1 765, 1 740, and 895 cm^{-1}; $\lambda_{max.}$ 265 nm (ε 670); δ (CCl_4) 0.9, 1.50, 1.97, and 2.12 (Me groups), 3.20—3.60 (m, 3-H), 4.42 (7-H_2), 5.42 (2-H), and 6.57 (aromatic); *m/e* 456 (1%), 414 (7), 396 (72), 381 (33), 354 (40), 312 (72), 299 (50), 295 (46), 294 (53), 286 (44), 244 (100), and 231 (54).

(c) 7-*Acetoxy*-Δ^1-*THC* (IIc). Freshly prepared 3-hydroxy-*p*-mentha-1,8-dien-7-yl acetate (XXVIa) (59 mg, 0.000 28 mol) and olivetol (45 mg, 0.000 25 mol) were dissolved in methylene chloride (10 ml; distilled over calcium hydride). The solution was cooled to −6 °C and boron trifluoride–ether complex (0.75 ml) was added. The solution was stirred for 1.5 h under nitrogen while the temperature was kept at −5 to 0 °C. A saturated solution of sodium hydrogen carbonate (10 ml) was added. The mixture was extracted with ether and the extract dried and evaporated. The oil (95 mg) obtained was chromatographed (p.l.c.; 20% ether–light petroleum; 3 runs). In addition to olivetol two compounds were separated. The less polar one was 7-*acetoxy*-Δ^1-*THC* (IIc) (10 mg, 11%), obtained as an oil, M^+ 372; $\nu_{max.}$ (CCl_4) 1 748 cm^{-1} (double peak); $\lambda_{max.}$ 277 (ε 1 710) and 282 nm (1 710); δ (CCl_4) 0.87, 1.05, 1.35, and 2.02 (Me groups), 3.16br (d, *J* 9 Hz) and 4.37 (7-H_2), 5.95 and 6.02 (aromatic), and 6.75 (2-H); *m/e* 372 (23%), 312 (100), 297 (38), 269 (40), 256 (25), and 231 (55).

The more polar compound, 9-*acetoxymethyl*-6a,7,8,10a-*tetrahydro*-6,6-*dimethyl*-1-*pentyl*-6H-*dibenzo*[b,d]*pyran*-3-*ol* (XXVIII) (11 mg, 12%) was an oil, M^+ 372; $\nu_{max.}$ (CCl_4) 1 745 cm^{-1}; $\lambda_{max.}$ 281 (ε 2 046) and 286 nm (2 046); δ (CCl_4) 0.89, 1.02, 1.35, and 2.00 (Me groups), 3.00br (allylic benzylic H), 4.35 (CH_2·OAc), and 5.95 and 6.1 (2 aromatic and 1 vinylic H superimposed); *m/e* 372 (10%), 312 (12), 301 (12), 299 (10), 297 (8), 269 (12), 256 (5), 241 (12), and 231 (100).

(d) 7-*Hydroxy*-Δ^1-*THC diacetate* (IId). The preparation of 7-acetoxy-Δ^1-THC (IIc), as described above, was repeated except that, instead of being purified, the oil obtained (95 mg) was acetylated with acetic anhydride (0.200 ml) in pyridine (1 ml) overnight. 7-*Hydroxy*-Δ^1-*THC diacetate* (IId) (8.3%) was obtained by p.l.c. (15% ether–light petroleum; 4 runs) as an oil, M^+ 414; $\nu_{max.}$ (CCl_4) 1 760 and 1 740 cm^{-1}; $\lambda_{max.}$ 281 nm (ε 2 480); δ (CCl_4) 0.89, 1.07, 1.37, 2.00, and 2.17 (Me groups), 3.20br (d, 3-H), 4.32 (7-H_2), 6.00br (2-H), and 6.2 and 6.4 (aromatic); *m/e* 414 (14%), 399 (1), 372 (6), 354 (51), 343 (16), 312 (100), 301 (24), 299 (22), 297 (20), 269 (29). The n.m.r. spectrum was identical with that of (IId) [obtained from the natural material (IIb)] kindly sent to us by Dr. M. E. Wall, whom we thank.

4-(p-*Mentha*-1,8-*dienyl*)*olivetol Diacetate* (XXXIb).—*p*-Mentha-2,8-dien-1-ol (230 mg, 0.0015 mol) [31] and olivetol

(230 mg, 0.001 28 mol) were dissolved in methylene chloride (20 ml) containing boron trifluoride–ether complex (0.2 ml). The mixture was left at room temperature for 15 min. After the usual work-up the oil obtained was purified by p.l.c. The least polar fraction (90 mg, 22%) was identical with (XXXIa) described by Petrzilka *et al.*[31] (i.r. and n.m.r. data). Acetylation with acetic anhydride (0.2 ml) in pyridine (1 ml) led to 4-(*p*-mentha-1,8-dienyl)-olivetol diacetate (XXXIb) (85 mg), δ (CCl_4) 0.9, 1.49, 1.65, 2.05, and 2.18 (Me groups), 3.25—3.70 (3-H), 4.30 and 4.70 (9-H_2), 5.18 (2-H), and 6.50 and 6.70 (aromatic).

Optical Rotations of Compounds prepared from (4S)-p-*Mentha*-1,8-*dien*-7-*al*.—When the above described series of reactions leading from the aldehyde (XXII) through (XXVI) to various cannabinoids, were undertaken with the (4*S*)-aldehyde (XXII), $[\alpha]_D$ −93° (lit.,[32] −146°) rather than racemic material, the optical rotations of the products were as follows: (4*S*)- (XXIIIb), −52°; (XXIV), −43.9°; (XXVIb), −84.7°; 7-acetoxy-Δ^1-THC (IIc), +51.9°; 7-acetoxy-Δ^1-THC acetate (IId), +92.3°; compound (XXVIII), +74.7°; 7-acetoxycannabidiol (IIIc), +90.9°; 7-hydroxycannabidiol triacetate (IIIb), +105.2°.

In vitro *Metabolism of Cannabidiol* (Ia).—[^{3}H]Cannabidiol (Ia) (125 mg; 0.486 μCi mg^{-1}) was incubated with 10 000 *g* supernatant from rat liver as previously described by Jones *et al.*[23] The incubate was extracted with light petroleum (b.p. 40—60°) followed by diethyl ether. The ethereal extract, which contained the major portion of the metabolites, was chromatographed on a Florisil column. Fractions were rechromatographed on Sephadex LH-20 columns which allowed isolation of the metabolites. Metabolites were identified after comparison with the synthetic references by t.l.c. (precoated silica gel plates; 60% diethyl ether–light petroleum), g.l.c. (6 ft column of 2% SE-30 on GasChrom Q; 250 °C), and g.l.c.–mass spectrometry (70 eV). The major metabolite (5.5 mg) was identified as 7-hydroxycannabidiol (IIIa) by t.l.c. (R_F 0.41), g.l.c. (t_R 10.8 min), and mass spectrometry [*m/e* 330 (7%), 312 (55), 299 (14), 284 (38), 244 (100), 231 (20), 188 (26), and 187 (51)]. The second most abundant metabolite (0.7 mg) was identical with 6α-hydroxycannabidiol (VIa) [R_F 0.49; t_R 8.0 min; *m/e* 330 (4%), 312 (45), 262 (100), 257 (29), 233 (39), 231 (28), and 193 (55)]. Another metabolite (40 μg) was indistinguishable from 6β-hydroxycannabidiol (VIIa) by t.l.c. (R_F 0.58), g.l.c. (t_R 7.8 min), and mass spectrometry [*m/e* 312 (77%), 297 (25), 257 (100), 233 (13), 231 (21), 214 (15), and 193 (85)].

A further unidentified metabolite (0.2 mg) was isolated. The n.m.r. spectrum showed no C-10 protons (δ 1.67) but small peaks at δ 4.16 and 4.08. The C-9 proton signals appeared at δ 5.07 and 5.35.

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[32] J. L. Simonsen and L. N. Owen, 'The Terpenes,' vol. 1, Cambridge University Press, 1947, p. 311.