Hashish:[1] Factors Influencing Double-Bond Stability in Cannabinoids[1]

Haldean C. Dalzell, David B. Uliss, G. Richard Handrick, and Raj K. Razdan*

Sisa† Institute for Research, Inc., Cambridge, Massachusetts 02138

Received October 3, 1980

It is shown that Bucourts methods for estimating torsion strain can be successfully applied to the THC ring system to give a surprisingly good quantitative estimate of the relative stability of various THC double bond isomers (Table II). *trans*-C_1-Deoxy-THC's **2a** and **2b** are synthesized from the corresponding THC's by conversion to their phenyl ethers followed by cleavage with Na/NH_3. The C_6-demethyl-THC's in the trans (**3a** and **3b**) and cis (**5a** and **5b**) series are synthesized from the pyrone (**6**) as shown in Scheme I.

A problem of long standing in the cannabinoid field has been the lack of knowledge of the factors which control the relative thermodynamic stabilities of the Δ^9 and Δ^8 double bond isomers in tetrahydrocannabinols (THC's).[2] A thorough understanding of these factors is desirable because the main physiologically active constituent of marijuana (*Cannabis sativa* L), Δ^9-6a,10a-*trans*-THC (Table I, **1b**), and its major metabolites in man and laboratory animals possess the thermodynamically less stable Δ^9-unsaturation.

It is well-known that treatment of Δ^9- or Δ^8-6a,10a-*trans*-THC (Table I; **1b** and **1a**) with acid results in an equilibrium mixture containing approximately 3% of the Δ^9 and 97% of the Δ^8 isomer. The same isomer ratio was observed when the corresponding acetates were similarly treated. On the other hand, we have recently shown that in the *cis*-THC's (as their acetates)[3] equilibration with acid gives 77% of the Δ^9 and 23% of the Δ^8 isomer (Table I; **4b** and **4a**).[4]

Previous attempts to rationalize these findings were based on steric arguments. In the preferred conformation of Δ^9-6a,10a-*trans*-THC (Figure 1; derived from Westheimer calculations and nuclear Overhauser effects) substantial steric interactions exist between the C10 proton and the phenolic oxygen ($r_{H_{10}-O_1}$ = 2.30 Å), and the C10a proton and the C6α-methyl group ($r_{H_{10a}-C_{12}}$ = 2.89 Å).[5] It was suggested[4,6] that these interactions are relieved by isomerization to the Δ^8 isomer, thus accounting for the preponderance of this isomer in the equilibrium mixture. Presumably these steric effects are absent in the cis isomers. To verify the validity of these arguments, we synthesized the C_1-deoxy (**2**) and C_6-didemethyl (**3** and **5**) THC's to minimize the nonbonded interactions. In light of the equilibrium data obtained for these cannabinoids (Table I), it is evident that the steric arguments are no longer tenable. Thus, acid treatment of Δ^8- and Δ^9-*trans*-deoxy-THC's (**2a** and **2b**) and Δ^8- and Δ^9-*trans*-didemethyl THC's (**3a** and **3b**) does not significantly alter the equilibrium ratios when compared with their more hindered counterparts.

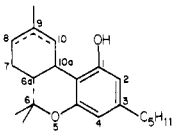
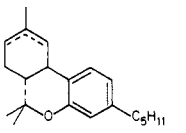
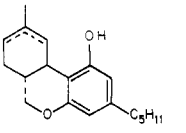
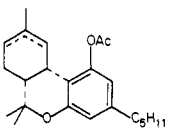
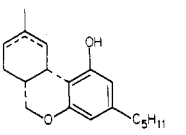
We have noted that the double-bond equilibria in the 6a,10a-*cis*- and *trans*-THC's are qualitatively similar to those in the corresponding octalins.[4] It appears, then, that the methods pioneered by Barton and Corey and later expanded by Bucourt and Robinson[7] to analyze conformational deformations and predict the relative stability of double-bond isomers in octalins, hexahydronaphthalenes, and other polycyclic molecules can be extended to the THC's. These considerations satisfactorily explain the results obtained to date in cannabinoids and are presented in this paper.

Discussion

As a result of work on triterpenoid ketones, Barton[7b] postulated that conformational deformations brought about by the introduction of unsaturated substituents were

Table I. Amounts of Various Cannabinoids under Equilibrium Conditions

a b

	% a	% b
 1	97	3
1 acetate	97	3
 2	97	3
 3	97	3
 4	23	77
 5	42	58

(1) Part 26. For part 25, see: Duffley, R. P.; Handrick, G. R.; Uliss, D. B.; Lambert, G.; Dalzell, H. C.; Razdan, R. K. *Synthesis* **1980**, 733. Presented in part at the John C. Sheehan Symposium held at Hoboken, NJ, on Mar 20, 1980.

(2) Reviews: (a) Razdan, R. K. *Prog. Org. Chem.* **1973**, *8*, 78–101; (b) Mechoulam, R., Ed. "Marijuana, Chemistry, Pharmacology, Metabolism and Clinical Effects"; Academic Press: New York, 1973; pp 2–100. (c) Mechoulam, R.; McCallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 75.

(3) This equilibrium study was carried out on the acetates of *cis*-THC's since it is known that on acid treatment, *cis*-THC's undergo rearrangement to iso-THC's.[2]

(4) Uliss, D. B.; Razdan, R. K.; Dalzell, H. C.; Handrick, G. R. *Tetrahedron Lett.* **1975**, 4369; *Tetrahedron* **1977**, *33*, 2055.

(5) Archer, R. A.; Boyd, D. B.; Demarco, R. V.; Tyminski, I. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1970**, *92*, 5200.

(6) Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1966**, *88*, 5673.

(7) (a) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1955**, *77*, 2505. (b) Barton, D. H. R.; Head, A. J.; May, P. J. *J. Chem. Soc.* **1957**, 935. (c) Bucourt, R. *Top. Sterochem.* **1974**, *8*, 159–224 and references therein. (d) Robinson, M. J. T.; Whalley, W. B. *Tetrahedron* **1963**, *19*, 2123.

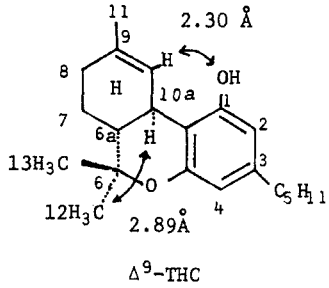
† Formerly Sheehan.

0022-3263/81/1946-0949$01.00/0

Table II. Observed and Calculated Equilibrium Amounts[a]

compd	θ,[b] deg	ϕ_{AO},[b] deg	obsd amt Δ^9	obsd amt Δ^8	calcd amt Δ^9	calcd amt Δ^8	ΔE, kcal/mol
trans-THC (1)			3	97			−2.4
trans-1-deoxy-THC (2,			3	97			−2.4
trans-6,6-didemethyl-THC (3)			3	97			−2.4
	110	45			6.0	94.0	−1.92
	113	45			3.1	96.9	−2.40
cis-THC (4)			77	23			0.84
cis-6,6-didemethyl-THC (5)			58	42			0.23
		45			81.3	18.7	1.02
		46.4			77.1	22.9	0.85

[a] ϕ_{BO} taken as 45° and 61° for Δ^9 and Δ^8 type fusion, respectively. [b] Angles used in calculating equilibrium amounts, using eq 1 and 2.



Δ^9-THC

Figure 1.

transmitted through the molecule by "flexing valency angles". This concept, known as conformational transmission, has since been interpreted in terms of the distortion of torsion (dihedral) angles[8] at ring junctions from strain-free values. A semiquantitative method for estimating torsion strain has been developed by Bucourt[7c] and successfully used to predict the relative stabilities of double-bond isomers in a variet of carbocyclic systems including octalins and hexahydronaphthalenes. Because we have shown that reducing selected intramolecular interactions in the THC's has little or no effect on the equilibrium ratio of the Δ^8 and Δ^9 double bond isomers, it may be that torsion strain about the 6a,10a fusion is the determining factor.

The use of torsion angles for estimating conformational energetics in the THC's is illustrated in Figure 2. The THC system can be considered as a fusion of a cyclohexene molecule and a benzopyran system as shown in Figure 2. The unfused torsion angle for the benzopyran system is approximated as 45°, the value for cyclohexene. This assumes that the substitution of carbon by oxygen in the benzopyran system has minimal effect on the torsion angle.

The amount of change in the torsion angles at the ring junction introduced in making the fusion is a measure of the torsional strain of the fused system. The geometry of fusion requires that for a trans fusion the sum of the absolute value of the two torsion angles at the junction equals a constant (approximately 110° when the substituents at a trans junction are hydrogen) while for a cis fusion the two torsion angles are equal. Thus, in the trans series the Δ^9- and Δ^8-THC analogues have torsion strains of 20° [110 − (45 + 45)] and 4° [110 − (45 + 61)], respectively. In the cis series the Δ^9 and Δ^8 analogues have torsion strains of 0° (45 − 45) and 16° (61 − 45), respectively. The above torsional considerations agree qualitatively with the observed stabilities of THC isomers. Namely, that *trans*-Δ^8-THC is more stable than *trans*-Δ^9-THC and *cis*-Δ^9-THC is more stable than *cis*-Δ^8-THC.

In addition to the above qualitative conclusions, we have found that very straightforward torsion angle energy considerations give a surprisingly good quantitative estimate of the relative stability of THC double-bond isomers. An estimate of the energy increase introded in a cyclohexane ring by a change ($\Delta\phi$) in a torsion angle from its equilibrium value has been given by Bucourt as $(\Delta\phi)^2/100$ for an opening and $^2/_3(\Delta\phi)^2/100$ for a closing (energy in kilocalories and $\Delta\phi$ in degrees) of the torsion angle. When these functions are summed for the two rings involved in a fusion and then minimized, eq 1 and 2 are obtained,

$$\Delta H_{Kcal} = \frac{1}{100}\left(\frac{f_A f_B}{f_A + f_B}\right)[\theta - (\phi_{AO} + \phi_{BO})]^2 \text{ for trans fusion} \quad (1)$$

$$\Delta H_{Kcal} = \frac{1}{100}\left(\frac{f_A f_B}{f_A + f_B}\right)(\phi_{BO} - \phi_{AO})^2 \text{ for cis fusion} \quad (2)$$

representing the torsion strain introduced in trans and cis ring fusions, respectively. (ϕ_{AO} and ϕ_{BO} are the equilibrium torsion angles at the junction in degrees for rings A and B before fusion; f_A (and f_B) equals 1 if fusion requires an angle opening in that ring and $^2/_3$ if a closing; θ is approximately 110°.)

The torsion strain and calculated equilibrium values obtained by using these equations are compared with experimental values in Table II. Also shown in Table II are values of θ and ϕ_{AO} that would lead to agreement between calculated and observed equilibrium constants for *trans*-THC's and *cis*-THS's. These values (ϕ of 113° and ϕ_{AO} of 46.4°) are not at all unreasonable as starting parameters.

The agreement of calculated and experimental equilibrium values is remarkable considering the simplicity of the energy calculations. Implicit in these calculations is the assumption that the relative energy of the THC double-bond isomers can be approximated by torsion strain at the ring junction, using a torsion energy function for cyclohexane. It is further assumed that no change in entropy occurs during the isomerizations. While this assumption may be reasonalbe for *trans*-THC's, being quite rigid with a single conformer highly favored, it may not be so for *cis*-THC's, which appear more flexible. We speculate that entropy effects may, in fact, be responsible for the different equilibrium values found for *cis*-THC and *cis*-6,6-didemethyl-THC. The lack of the gem-dimethyl groups in the latter may allow the population of additional conformations.

The results reported here are a further example of the value of simple ring-junction torsion angle considerations in the evaluation of energetics of multiring systems.

(8) Defined as the angle subtended by the planes of two vicinal bonds when viewed along the connecting bond in the Newman projection. An ortho ring fusion contains two such angles. See: Klyne, W.; Prelog, V. *Experientia* **1960**, *16*, 521.

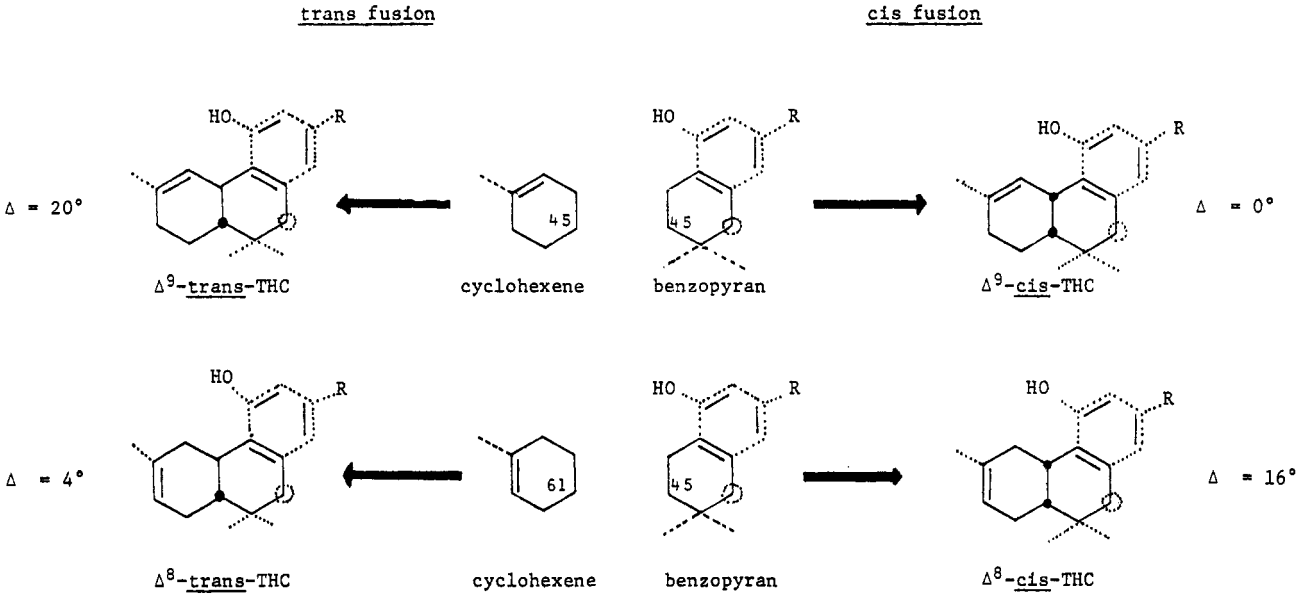
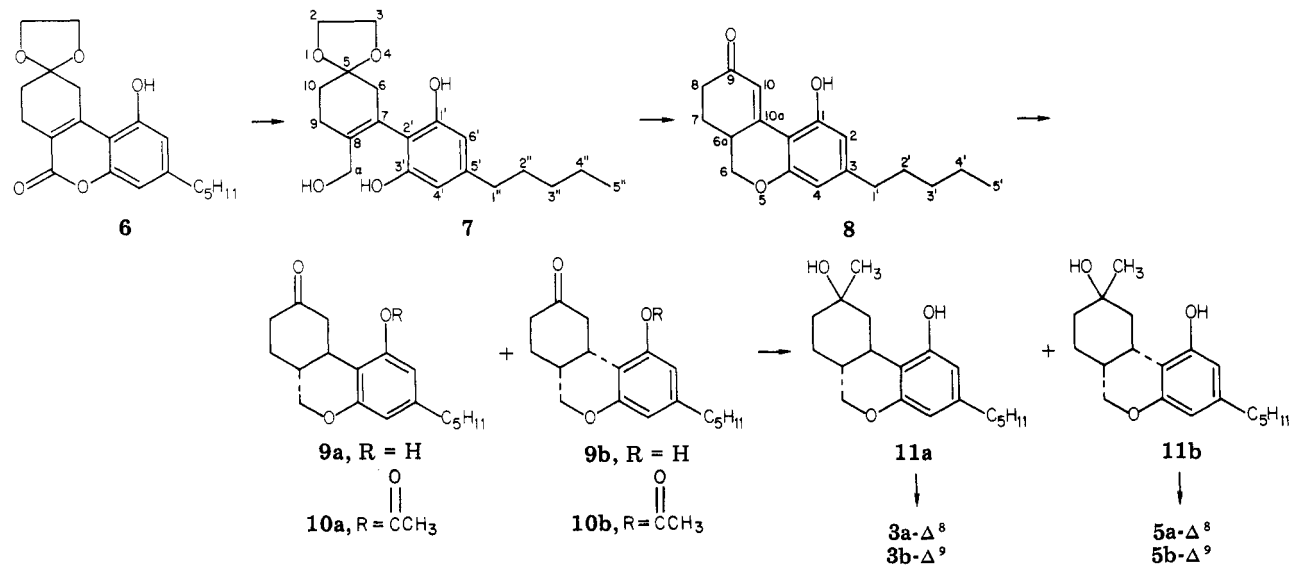


Figure 2.

Scheme I



Synthesis

The C_1-deoxy THC's in the trans series (**2a** and **2b**) were synthesized from the corresponding THC's by conversion to their phenyl ethers followed by cleavage of the phenyl ether with sodium and liquid ammonia. In the Δ^8 series, compound **2a** was formed in good yield and was identical with the compound prepared by Kraatz and Korte[9] by a different route. However, in the Δ^9 series, the Na/NH_3 reaction gave a complex mixture from which **2b** was isolated in poor yield. It was only ~60% pure by GLC and could not be purified further despite the repeated use of high-pressure liquid chromatography (LC). The structure was confirmed by comparison of its NMR spectra with those of **2a**. The vinylic proton in **2b** was observed at δ 5.93 compared to δ 5.38 in **2a**. The major product formed during this reduction has been tentatively identified as 1-deoxyhexahydrocannabinol (see Experimental Section).

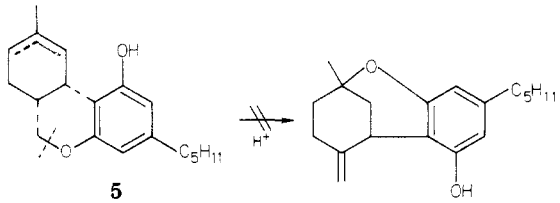
The C_6-didemethyl THC's in the trans (**3a** and **3b**) and cis (**5a** and **5b**) series were synthesized from the known pyrone **6**[10] following the sequence as shown in Scheme I. The pyrone **6** with $LiAlH_4$ in ether formed the triol **7** which on treatment with thionyl chloride/triethylamine in CH_2Cl_2 followed by hydrolysis of the ketal with 6 N HCl furnished **8**. Reduction with Li/liquid NH_3 converted **8** into a mixture of cis and trans ketones **9b** and **9a** respectively, which were separated as their acetates **10b** and **10a** by using high-pressure LC. Pure **9a** and **9b** were obtained by saponification of the corresponding acetates **10a** and **10b**. Grignard addition to **10a** and **10b** gave **11a** and **11b**, respectively, which were dehydrated with thionyl chloride in pyridine to yield a mixture of Δ^8- and Δ^9-THC's. Thus **11a** gave a mixture of **3a** and **3b** whereas **11b** gave a mixture of **5a** and **5b**. The trans and cis ring junctures of **3** and **5** were assigned on the basis of the position of the olefinic protons at C10 and C8 in the NMR.[4,10] In the trans series (**3b** and **3a**) they were observed at δ 6.37 and 5.38, respectively, compared to δ 5.53 and 5.30 in the cis series (**5b** and **5a**).

It is interesting to note that *cis*-didemethyl-THC's (**5**), unlike *cis*-THC's, do not undergo rearrangement to iso-

(9) Kraatz, U.; Korte, F.; *Tetrahedron Lett.* **1976**, 1977.

(10) Fahrenholtz, K. E.; Lurie, M.; Kierstead, R. W. *J. Am. Chem. Soc.* **1967**, *89*, 5938.

THC's in the presence of acids. This is not surprising because the necessary cleavage of the C–O bond requires formation of the unfavorable primary carbonium ion in the former as opposed to a tertiary carbonium ion in the latter.



5 iso-THC

Experimental Section

All compounds are (±) racemic mixtures. Melting points were determined in a Thomas-Hoover melting-point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer Model 700 instrument and the NMR spectra were measured on a Varian T-60 spectrometer. The high-pressure liquid chromatographic separations were made with a Waters Associates ALC-202 chromatograph equipped with a Model 6000 solvent delivery system. Preparative separations were made on a 7 ft × 0.375 in. i.d. column packed with Porasil C. Analytical separations were made on a 1 ft × 0.25 in. o.d. column packed with μPorasil. The analyses by gas chromatography were made on a Varian Aerograph Model 1440, equipped with a 6 ft × 0.125 in. i.d. stainless-steel column packed with 2% OV-17 on 100/200-mesh Supelcoport and a flame-ionization detector. Compounds **4a** and **4b** were prepared according to the procedure described by us earlier.[4]

Preparation of 6a,10a-*trans*-3-Pentyl-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran (2a). Refluxing **1a** (0.51 g, 1.62 mmol) with 1 mL of bromobenzene in 12 mL of pyridine containing 117 mg of copper powder and 268 mg of anhydrous potassium carbonate, according to a procedure of Sawa,[11a] gave the phenyl ether of **1a** in 65% yield. The analytical sample was obtained as a colorless oil after passage through a short Florisil column with petroleum ether; NMR (CCl_4) δ 0.87 (t, 3, 5′-CH_3), 1.07, 1.33 (2 s, 6, 6-$C(CH_3)_2$), 1.60 (s, 3, 9C-CH_3), 2.42 (t, 2, 1′-CH_2), 2.97 (dd, 1, J = 4, 17 Hz, 10-CH_a), 5.30 (br, 1, 8-CH), 6.18, 6.37 (2 d, J = 2 Hz, 2-CH, 4-CH), 6.8–7.4 (m, 5, OC_6H_5). Anal. Calcd for $C_{27}H_{34}O_2$: C, 83.03; H, 8.77. Found: C, 83.11; H, 9.04.

Cleavage of the phenyl ether (0.50 g, 1.28 mmol) with Na/NH_3[11b] gave **2a** in 63% yield as a colorless oil which was pure by GLC (retention time 2.75 min; column temperature 240 °C); NMR (CCl_4) δ 0.88 (t, 3, 5′-CH_3), 1.13, 1.37 (2 s, 6, 6-$C(CH_3)_2$), 1.70 (s, 3, 9C-CH_3), 2.47 (t, 2, 1′-CH_2), 2.63 (d, J = 4 Hz, 10a-CH), 5.38 (br s, 1, 8-CH), 6.50 (d, $J_{2,4}$ = 1 Hz, 1, 4-CH), 6.60 (dd, $J_{1,2}$ = 8, $J_{2,4}$ = 1 Hz, 1, 2-CH), 6.97 (d, $J_{1,2}$ = 8 Hz, 1, 1-CH). Anal. Calcd for $C_{21}H_{30}O$: C, 84.50; H, 10.13. Found: C, 84.24; H, 10.27.

These data agree with those of **2a** prepared by Kraatz and Korte[9] by a reductive cleavage of a phosphate ester of (−)-Δ^8-THC by Li/NH_3.

Preparation of 6a,10a-*trans*-3-Pentyl-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran (2b). The phenyl ether of **1b** was prepared in 70% yield in the manner described for the Δ^6 isomer. Chromatography on Florisil using 1:1 benzene–petroleum ether as eluant gave the analytical sample; NMR (CCl_4) δ 0.87 (t, 5′-CH_3), 1.03, 1.37 (2 s, 6, 6-$C(CH_3)_2$), 2,43 (t, 2, 1′-CH_3), 3.00 (br d, J = 9 Hz, 1, 10a-CH), 6.2 (br, 1, 10-CH), 6.27, 6.40 (2 d, J = 2 Hz, 2-CH, 4-CH), 6.7–7.4 (m, 5, C_6H_5). Anal. Calcd for $C_{27}H_{34}O_2 \cdot H_2O$: C, 79.37; H, 8.88. Found: C, 79.39; H, 8.71.

Cleavage of the ether as described above and separation of products by preparative thick-layer chromatography gave **2b** (9%, 60% pure by GLC) and two other compounds tentatively identified as 1-deoxycannabinol (5%) and 1-deoxyhexahydrocannabinol (48%). Compound **2b** could not be purified further despite repeated high-pressure liquid chromatography: NMR (CCl_4) δ 0.88 (t, 3, 5′-CH_3), 1.13, 1.37 (2 s, 6, 6-$C(CH_3)_2$), 1.70 (s, 3, 9C-CH_3), 2.47 (t, 2, 1′-CH_2), 3.27 (br d, 1, J = 24 Hz, 10a-CH), 5.93 (br s, 1, 10-CH), 6.53 (d, $J_{2,4}$ = 1 Hz, 1, 4-CH), 6.58 (dd, $J_{1,2}$ = 8, $J_{2,4}$ = 1 Hz, 1, 2-CH), 7.10 (d, $J_{1,2}$ = 8 Hz, 1, 1-CH); GLC retention time 2.99 min (column temperature 240 °C).

Preparation of 7-(5′-Pentyl-2′-resorcinyl)-1,4-dioxaspiro-[4,5]dec-7-ene-8-methanol (7). A solution of **6**[10] (6.88 g, 0.02 mol) in 70 mL of benzene and 10 mL of ether was added dropwise to a slurry of lithium aluminum hydride (3.20 g, 0.08 mol) in 250 mL of ether at room temperature. The mixture was brought to reflux for 45 min and cooled to 0 °C, and excess hydride was destroyed by addition of 10 mL of ethyl acetate in 6 mL of ether followed by 40 mL of saturated aqueous ammonium chloride. The organic layer was decanted and the residue was dissolved by addition of ammonium chloride and water. The aqueous layer was washed with ether, and the combined organic layer was washed with water and saturated sodium chloride solution, dried, and concentrated. The residue crystallized when a solution in ether was mixed with excess petroleum ether. The yield of triol **7** was 6.23 g (89%). The analytical sample, mp 111.5–112 °C, was obtained by recrystallization from ether: IR ($CDCl_3$) ν 1040, 1440, 1570, 1625, 3450 (OH) cm^{-1}; NMR ($CDCl_3$) δ 0.87 (t, 3, 5″-CH_3), 1.38 (m, 6), 1.92 (m, 2, 10-CH_2), 2.2–2.8 (m, 6, 1″-CH_2, 6-CH_2, 9-CH_2), 3.90 (s, 2, α-CH_2), 4.02 (s, 4, 2-CH_2, 3-CH_2), 6.35 (s, 2, 4′-CH, 6′-CH), exchangeable OH at δ 3.1, 6.3. Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.89; H, 8.09.

Preparation of 9-Oxo-3-pentyl-6a,7,8,9-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-1-ol (8). A solution of thionyl chloride (1.90 mL, 0.026 mol) in 23 mL of methylene chloride was added over 1.5 h to a solution of **7** (6.00 g, 0.017 mol) and triethylamine (24 mL, 0.17 mol) in 90 mL of methylene chloride cooled to −20 °C under nitrogen. The reaction mixture was allowed to warm to 5 °C and then poured onto 200 mL of ice and water. The organic layer was washed with water, dilute HCl, dilute sodium bicarbonate, and water. Drying over Na_2SO_4 and removal of solvent gave an oil which solidified on standing. A solution of the solid in dioxane (50 mL) was mixed with 20 mL of 6 N HCl and the two-phase mixture was heated to 80 °C for 75 min. The reaction mixture was then diluted with an equal volume of water and the dioxane removed in a rotary evaporator. Crude ketone **8** (4.62 g) was collected by filtration and purified by extraction from tar with hot CCl_4. Addition of ether to the CCl_4 extract precipitated **8** in 56% yield: mp 172–175 °C; IR ($CDCl_3$) ν 1610 (C=O, conjugated ketone), 3150 (OH, strongly hydrogen bonded) cm^{-1}; NMR ($CDCl_3$) δ 0.88 (t, 3, 5′-CH_3), 3.73, 4.30 (m, 2 H, 6-CH_2), 6.32, 6.60 (2 d, 2, 2-CH, 4-CH), 7.95 (d, 1, J = 2 Hz, 10-CH).[10] Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.17; H, 7.48.

Preparation of 6a,10a-*trans*- and -*cis*-6a,7,8,9,10,10a-Hexahydro-9-oxo-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol Acetates (10a and 10b). Lithium wire was added to 200 mL of liquid ammonia until a permanent blue color was obtained. Compound **8** (2.70 g, 0.0094 mol) in 30 mL of tetrahydrofuran was added over 1 h. During the addition a further 0.74 g (0.01 mol) of lithium was added to maintain the blue color. Excess ammonium chloride was added and the ammonia allowed to evaporate. Water and ether were added, the organic layer was washed with water, dilute HCl, dilute $NaHCO_3$ solution, and brine and dried over Na_2SO_4 and solvent was removed. The residue was 3.10 g of a solid, which was passed through a short column of Florisil with methylene chloride and crystallized from ether–petroleum ether to give a mixture of **9a** and **9b** (2.0 g, 76%).

A mixture of the corresponding acetates (**10a** and **10b**) was prepared in 75–85% yield by reaction with acetic anhydride in pyridine. Separation was effected by high-pressure liquid chromatography using a Porasil column and 1:2 ether–isooctane as eluant; k' was 2.00 and 2.47 for **10a** and **10a**, respectively. Analytical samples were obtained from the concentrated eluants by trituration with petroleum ether (**10a**, mp 101–103 °C; **10b**, mp 59–61 °C). **10a**: NMR ($CDCl_3$) δ 0.87 (t, 3, 5′-CH_3), 2.32 (s, 3, CO_2CH_3), 3.70 (dd, 1, J = 10, 10 Hz, 6α-CH), 4.25 (dd, 1, J = 10, 4 Hz, 6β-CH), 6.43, 6.62 (2 d, 2, J = 2 Hz, C2-H, C4-H). The NMR spectrum of **10b** was very similar to that of **10a** except that 6α-CH and 6β-CH appeared as a multiplet at δ 4.20. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found for **10a**: C, 72.72; H. 7.95. Found for **10b**: C, 72.72; H, 7.94.

Preparation of 6a,10a-*trans*- and -*cis*-6a,7,8,9,10,10a-Hexahydro-9-oxo-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ols (9a

(11) (a) Sawa, Y. K.; Tsuji, N.; Maeda, S. *Tetrahedron* **1964**, *20*, 2255; (b) *Ibid.* **1961**, *15*, 144, 154.

Table III. Equilibration Studies with Tetrahydrocannabinols[c]

compd	time, min	% Δ^8	% Δ^9
1a	0	100	
	4-1350	97	3
1a acetate	0	100	
	4-1350	97	3
1b	0	0	100
	4	93	7
	30	97	3
1b acetate	0	0	97
	4	32	68
	10	78	22
	30	97	3
2a	0-1080	100	0
	0	0	100[a]
	5	97	3
	10	97	3
	35	97	3
3	0	83	17
	20	97	3
4a acetate	0	93	7
	30	87	13
	60	80	20
	120	77	23
	222[b]	80	20
	300	28	72
	336	23	77
4b acetate	0	0	100
	30	13	87
	60	23	77
5	0	56	44
	20	53	47
	180	45	55
	390	42	58

[a] Material could not be purified >60% (GLC). It did not contain any Δ^8 isomer. [b] More *p*-TSA added at 270 min. [c] Refluxing dilute solutions in benzene with *p*-TSA.

and 9b). Pure **9a** and **9b** were obtained by saponification of the corresponding acetates (**10a** and **10b**) with 5% KOH in methanol at room temperature for 15 min. Analytical samples were recrystallized from ether–petroleum ether (**9a**, mp 173 °C; **9b**, mp 161 °C); **9a**: IR ($CDCl_3$) ν 1685 (C=O), 3270 (OH) cm^{-1}. **9b**: 1700 (C=O), 3320 (OH) cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found for **9a**: C, 74.77; H, 8.45. Found for **9b**: C, 74.83; H, 8.40.

Preparation of 6a,10a-*trans*- and -*cis*-6a,7,8,9,10,10a-Hexahydro-9-methyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1,9-diols (11a and 11b). A solution of **10a** (0.55 g, 0.0016 mol) in 6 mL of ether and 2 mL of benzene was added over 10 min under nitrogen to a solution of methylmagnesium iodide, prepared from 0.40 g (0.016 mol) of magnesium turnings and 1.2 mL (2.36 g, 0.0166 mol) of iodomethane, in 9 mL of ether. After 60 min the cooled reaction mixture was quenched by successive addition of ethyl acetate and methanol in ether and saturated ammonium chloride. The organic layer was washed with dilute sodium chloride, dried, and concentrated to give **11a** (88%) as a resin (mixture of isomers at C_9 which was not separated). The analytical sample was obtained by addition of petroleum ether to an ethereal solution off **11a**: mp 141–142 °C; NMR ($CDCl_3$) δ 0.87 (t, 3, 5'-CH_3), 1.37 (s, 3, 9-CH_3), 2.42 (t, J = 6 Hz, 2), 3.2–4.2 (m, 3), 6.10, 6.25 (2 d, J = 2 Hz, 2, 2-CH, 4-CH), 2.01, 6.82 (br, 2, exchangeable OH); IR ($CDCl_3$) ν 3330 (OH) cm^{-1}. Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.05; H, 9.29.

In a similar fashion, **11b** was obtained from **10b** in 97% yield (mp 131–133 °C): NMR ($CDCl_3$) δ 0.87 (t, 3, 5'-CH_3), 1.38 (s, 3, 9-CH_3), 4.0 (d, J = 4 Hz, 1), 4.25 (t, J = 10 Hz, 1), 4.70 (m, 1), 6.15, 6.28 (2 d, J = 2 Hz, 2, 2-CH, 4-CH), 1.8, 5.9 (br, 2, exchangeable OH); IR ($CDCl_3$) ν 3350 (OH) cm^{-1}. Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.85; H, 9.29.

Preparation of 6a,10a-*trans*-9-Methyl-3-pentyl-6a,7,10,10a- and -6a,7,8,10a-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-1-ols (3a and 3b). To an ice-cold solution of **11a** (0.100 g, 0.320 mol) in a mixture of 1 mL of methylene chloride and 2 mL of pyridine was added a solution of thionyl chloride (0.16 g, 0.001 37 mol) in 1 mL of methylene chloride. After 1 h, 10 mL of ether and 6 mL of water were added. The organic layer was washed with water, dilute HCl, dilute $NaHCO_3$ solution, water, and saturated sodium chloride solution. Drying and removal of solvent left 91 mg of a compound tentatively identified as a cyclic sulfite ester. This material was hydrolyzed with 5% KOH in methanol and enough ether was added for homogeneity. After 1 h at room temperature ether was added. The ether layer was washed with water, dilute HCl, dilute $NaHCO_3$, and brine. Drying and evaporation of solvent left 92 mg of resin which was purified by column chromatography (Florisil, 2% ether–petroleum ether). A fraction was obtained which consisted of 83% **3a** and 17% **3b** (GLC); NMR (CCl_4) δ 0.88 (t, 3, 5'-CH_3), 1.68 (s, 3, 9-CH_3), 5.38 (br, olefinic, 8-CH), 5.98, 6.18 (2 d, J = 2 Hz, 2, 2-CH, 4-CH), 6.37 (br, olefinic, 10-CH), 5.03 (s, 1, exchangeable OH). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.67; H, 9.15. Found: C, 79.47; H. 9.25.

By a similar series of reactions, 100 mg of **11b** was converted to a mixture of 53% **5a** and 47% **5b** (GLC) in 62% yield; NMR (CCl_4) δ 0.90 (t, 3, 5'-CH_3), 1.63 (s, 3, 9-CH_3), 5.30 (br, olefinic, 8-CH), 5.53 (br, olefinic 10-CH), 6.00, 6.17 (2 d, 2, 2-CH, 4-CH), 4.83 (s, 1, exchangeable OH). Anal. Calcd for $C_{19}H_{26}O_2 \cdot 0.5H_2O$: C, 77.25; H, 9.21. Found: C, 77.58; H, 8.98.

Equilibration of Tetrahydrocannabinols. The general procedure was to reflux under nitrogen a stirred solution of the THC's (approximately 0.01 mol) in dry benzene containing *p*-toluenesulfonic acid monohydrate as the acid catalyst. Samples for GLC analysis, taken at regular intervals, were treated with solid $Na_2CO_3 \cdot H_2O$ before injection. The reaction was stopped when it appeared to reach equilibrium, and solid $Na_2CO_3 \cdot H_2O$ was added to neutralize the acid catalyst. The products were identified by comparison with authentic specimens from other sources, both unsilylated and silylated analyses being required in the GLC because of overlapping retention times.

Treatment of a mixture containing 53% **5a** and 47% **5b** (GLC) with excess *p*-TSA in refluxing benzene for 6.5 h showed that no other product had formed during the reaction (NMR, GLC) and only the ratio of **5a** and **5b** had changed to 42% and 58%, respectively.

Equilibration studies showing composition vs. time for various THC's are shown in Table III.

Acknowledgment. This work was carried out with the support of National Institutes of Drug Abuse (NIDA) (Grant No. DA-00574-05).

Registry No. (±)-**1a**, 6087-61-2; (±)-**1a** acetate, 76248-17-4; (±)-**1a** phenyl ether, 76207-25-5; (±)-**1b**, 3556-79-4; (±)-**1b** acetate, 76248-18-5; (±)-**1b** phenyl ether, 76207-26-6; (±)-**2a**, 76248-19-6; (±)-**2a**, 76207-27-7; (±)-**3a**, 76207-28-8; (±)-**3b**, 76207-29-9; (±)-**4a**, 6216-87-1; (±)-**4a** acetate, 58769-87-2; (±)-**4b**, 6087-73-6; (±)-**4b** acetate, 23050-53-5; (±)-**5a**, 76207-30-2; (±)-**5b**, 76207-31-3; (±)-**6**, 6469-57-4; (±)-**7**, 76207-32-4; (±)-**8**, 76207-33-5; (±)-**9a**, 76207-34-6; (±)-**9b**, 76207-35-7; (±)-**10a**, 76207-36-8; (±)-**10b**, 76207-37-9; **11a**, 76207-38-0; 1-deoxyhexahydrocannabinol, 76207-39-1; 1-deoxycannabinol, 76207-40-4; methyl iodide, 74-88-4.