5α-cholestan-6-one (**3d**) as small, white needles: mp 112.5–114 °C; $[\alpha]_D$ −37°; IR 3610, 3480, 1810, 910, 885 cm^{-1}; UV 286.5 nm (ε 57); NMR 40.5 (s, 3, 18-H), 52 (s, 3, 19-H), 129 (s, 1, OH), 246 (m, $W_{1/2}$ = 8 Hz, 1, C-3 H), 299.5 Hz (s, 1, C-7 H).

Anal. Calcd for $C_{27}H_{44}O_3$ (416.62): C, 77.83; H, 10.65. Found: C, 78.00; H, 10.63.

Evaporation of the first mother liquor gave an additional 69 mg of **3d**, mp 110.5–112.5 °C. Other fractions (686 mg) rich in **3d** were combined and recrystallized twice from 95% ethanol, giving 48 mg of **3d**, mp 110.5–111.5 °C.

The remaining fractions and mother liquor residues were combined and acetylated in the usual manner.[7] The resulting mixture of acetates could not be resolved by thick layer chromatography on silica gel, hence was chromatographed on 120 g of alumina. Elution with benzene gave six homogeneous fractions which were combined and recrystallized from methanol, yielding 239 mg of 3α-acetoxy-5,7α-epoxy-5α-cholestan-6-one (**3e**) as soft, white needles, mp 93–95 °C. Recrystallization from aqueous methanol gave mp 94–95.5 °C; $[\alpha]_D$ −37°; IR 1810, 1738, 918, 885 cm^{-1}; UV 289.5 nm (ε 61); NMR 40.5 (s, 3, 18-H), 53 (s, 3, 19-H), 125 (s, 3, AcO), 296 (s, 1, C-7 H), 304 Hz (m, $W_{1/2}$ = 10 Hz, 1, C-3 H).

Anal. Calcd for $C_{29}H_{46}O_4$ (458.66): C, 75.94; H, 10.11. Found: C, 75.82; H, 10.18.

Total yield of oxetanone (**3d** + **3e**) 22%. All other fractions contained inseparable mixtures.

D. Tosyloxy Ketone 4c. A suspension of 346 mg (0.604 mmol) of **4c** in 16 ml of Me_2SO was treated with 0.50 ml of 1.179 N base for 10 min. The resulting oil was chromatographed on 14 g of silica gel. Elution with 80% benzene–petroleum ether produced 71 mg of a solid that was recrystallized from ether–methanol to give 50 mg (21%) of oxetanone **3a**, mp 95–96 °C. Further fractions contained mixtures of starting material and unidentified products.

3β-Acetoxy-5,7α-epoxy-5α-cholestan-6-one (3c). A sample (138 mg, 0.331 mmol) of oxetanone **3b** was acetylated in the usual manner.[6a] Recrystallization of the product from methanol gave 107 mg (70%) of **3c**: mp 110–110.5 °C; $[\alpha]_D$ −36°; IR 1810, 1740, 910, 885 cm^{-1}; UV 287.5 nm (ε 44); NMR 40.5 (s, 3, 18-H), 54 (s, 3, 19-H), 121.5 (s, 3, AcO), 290 (m, $W_{1/2}$ = 24 Hz, 1, C-3 H), 295 Hz (s, 1, C-7 H) [lit.[6a] mp 108–111 °C; $[\alpha]_D$ −23.3°; IR 1815, 1730 cm^{-1}]. Recrystallization from aqueous ethanol did not alter the melting point.

Registry No.—**2a,** 19043-54-0; **2b,** 60009-78-1; **2c,** 60803-76-1; **2d,** 1258-38-4; **2e,** 50630-98-3; **2f,** 50631-05-5; **2g,** 60803-77-2; **2h,** 60803-78-3; **2i,** 60803-79-4; **3a,** 60803-80-7; **3b,** 50631-08-8; **3c,** 50801-48-4; **3d,** 60803-81-8; **3e,** 60803-82-9; **4a,** 60803-83-0; **4b,** 60803-84-1; **4c,** 60803-85-2; **4d,** 60803-86-3; **4e,** 60803-87-4; PHP, 39416-48-3.

References and Notes

(1) This work was supported, in part, by grants from the Merck Co. Foundation and the Committee on Educational Aid of E. I. du Pont de Nemours and Co. The competent technical assistance of Thomas P. Demuth, Jr., Robert B. Nachbar, Jr., and Scott R. Wilson is gratefully acknowledged.
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(13) In comparison to the relative facility with which **2b** was isomerized to **2c**, the C-5 epimer[3] of bromo ketone **2e** was recovered unchanged after 186 h at room temperature when treated with an equal mass of LiBr in DMF. Further treatment of the same sample with a 2.4-fold excess of LiBr in DMF at room temperature for 92 h gave no reaction. The difficulty encountered in the epimerization in the 5β-hydroxy series may be ascribed to the unfavorable interactions of the C_5–OH, C=O, and C_7–Br dipoles in the resulting 7β-bromo compound.

Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. 47. Cannabinoid Compounds[1]

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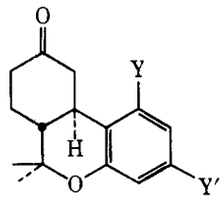
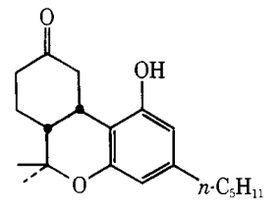
The ^{13}C NMR spectra of (−)-Δ^9-THC, (−)-Δ^8-THC, (±)-Δ^8-*abn*-THC, (±)-*cis*-Δ^9-THC, and four related ketones were recorded and their carbon shifts assigned. A ^{13}C NMR spectral diagnosis of the position of the double bond, location of the aromatic hydroxy and *n*-pentyl groups, and stereochemistry of the bridgeheads in THC derivatives is portrayed. A pyridine-induced shift procedure for the determination of phenol substitution patterns is introduced.

Several years have passed since the appearance of a ^{13}C NMR analysis of Δ^8- and Δ^9-tetrahydrocannabinol (THC) and some of their derivatives.[2,3] The carbon shift assignment had been based preponderantly on the correlation of the δ values among a small group of related compounds. In the light of present, better understanding of the chemical shift parameter as a function of bonding configuration, several shift correlations in the previous study are suspect. As a consequence a reinvestigation of Δ^8- and Δ^9-THC, with the use of additional ^{13}C NMR structure probes, was instituted, the goal of which being not only the proper shift assignment of the tetrahydrocannabinols but also the ^{13}C NMR differentiation of the natural products from their positional and stereochemical isomers. In the course of this work a technique for the recognition of the substitution pattern of phenols also came under study.

The analysis of eight substances—ketones **1a**,[5] **1b**, **1c**, and **2**,[5] (−)-Δ^9-THC (**3**),[6,7] (−)-Δ^8-THC (**4a**),[6,7] (±)-Δ^8-*abn*-THC (**4b**), (±)-*cis*-Δ^9-THC (**5**)[5]—was undertaken. The positional isomer **4b** of Δ^8-THC and its ketone precursor **1c** were prepared in the following fashion. Treatment of the chromanone **6a**, prepared by the acid-induced condensation of olivetol and β-methylcrotonic acid,[5] with benzyl bromide and base and subsequent formylation of the resultant benzyl ether **6b**



1a, Y = OH; Y′ = n-C_5H_{11}
b, Y = OCH_3; Y′ = n-C_5H_{11}
c, Y = n-C_5H_{11}; Y′ = n-OH



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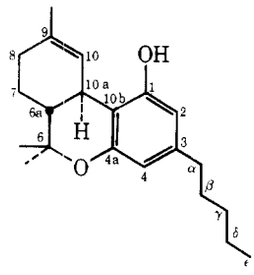

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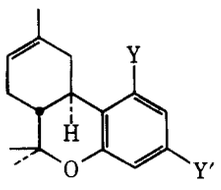
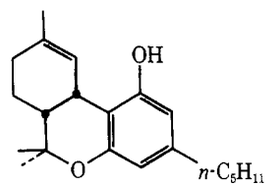


4a, Y = OH; Y′ = n-C_5H_{11}
b, Y = n-C_5H_{11}; Y = OH



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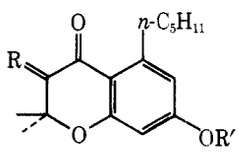
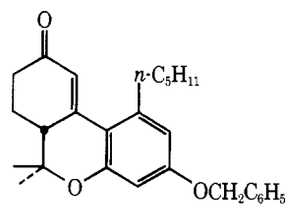


6a, R = H_2; R′ = H
b, R = H_2; R′ = $CH_2C_6H_5$
c, R = CHOH; R′ = $CH_2C_6H_5$



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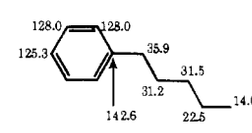
yielded the hydroxymethylene ketone **6c**. Base-catalyzed condensation of the latter with methyl vinyl ketone produced tricycle **7** whose reduction with lithium in ammonia afforded ketone **1c**. Exposure of the latter to methylmagnesium bromide and then to acid yielded Δ^8-*abn*-THC (**4b**), one of various THC isomers obtained by the acid-catalyzed condensation of olivetol with citral.[8]

The ^{13}C NMR analysis of the nonaromatic carbons of ketone **1a** proceeds in the following manner. Nonprotonated C(6) is a unique substitution site both in **1a** and all other cannabinoid compounds to be discussed and is insensitive to stereochemical changes at the nearby bridgehead centers. In view of C(10a) being benzylic the methines C(6a) and C(10a) of **1a** and the other substances can be distinguished by the difference of the magnitude of their residual coupling.[9,10] The methylenes of the n-pentyl side chain are distinguished from the ring methylenes by their shift equivalence with the methylenes of n-pentylbenzene (**8**). The side chain α carbon, a benzylic site, is recognized by its residual coupling, while the δ carbon is represented by a resonance characteristic of the second carbon from the end of a straight, long hydrocarbon chain.[9] The distinction of the β and γ carbons rests on the shift data of n-pentylbenzene (**8**) and its β,β-dideuterio derivative (**9**).[11] Surprisingly, the α and β carbons of the hydroxylated cannabinoid compounds are shielded (by ca. 0.5 ppm) with respect to like sites on n-pentylbenzene (**8**). Since the side chain carbon shifts of both the cannabinoid substances and model **8** are invariant over a 0.05–0.5 M concentration range, the effect cannot be the consequence of some molecular association and appears to be dipolar in nature. The field positions of the ketomethylenes of **1a** distinguish the latter from C(7), while their differentiation from each other is based on the similarity of the C(8) resonance to the ketomethylene shift of 4-*tert*-butylcyclohexanone[12] and the perturbation of the C(10) resonance of **1a** on methylation of the C(1) hydroxy group. In the methyl ether **1b** all tetrahedral carbons possess chemical shifts equivalent to those in **1a** except C(10), which is deshielded by 1.0 ppm. The sensitivity of the C(10) resonance to what is formally ϵ substitution suggests a strong steric compression of the C(1) substituent with H(10α). In the single-frequency off-resonance decoupled (sford) spectra of **1a–c** the C(10) resonance appears as a doublet of doublets revealing strong nonequivalence of the H(10α) and H(10β) resonances[10] whereas C(8) displays a triplet structure. The methyl groups of the dihydropyran ring differ from the side chain methyl unit by their exhibition of sharp quartets in the sford spectra due to the absence of vicinal hydrogens and second-order coupling. Owing to its nonbonded interactions with C(4a) and C(10a) the axial 6α-methyl group resonates ca. 9 ppm upfield of the 6β-methyl signal.



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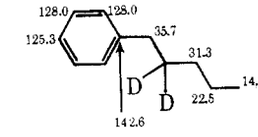

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The aromatic carbon signals of **1a** are composed of a pair of upfield methines, a pair of downfield oxy carbons, and two nonprotonated centers. One occupies a high-field position as a consequence of shielding by two ortho oxygens. The differentiation of the oxy carbons from each other as well as the methines rests on a study of pyridine-induced shifts (vide infra). The large perturbation of the C(1) and C(2) resonances of **1b** by the *O*-methyl group allows the direct assignment of the aromatic carbons of this derivative.

The shift assignment of the nonaromatic carbons of ketone **1c** employs the same arguments as those used for the shift designation of like centers of **1a**. The dissimilarity of disposition of the aromatic methines and nonprotonated aromatic carbons to the oxy substituents permits their individual recognition. The aromatic oxy carbons are distinguished from each other by a pyridine-induced shift study (vide infra). Expectedly, the bridgehead methines and neighboring methylenes of the cis ketone are shielded with respect to like centers in **1a**.[13] Since the carbon–hydrogen coupling behavior of C(10) exhibited in **1a–c** (vide supra) is not duplicated in ketone **2**, the differentiation of the ketomethylenes of **2** relies on the assumed invariance of the C(8) shift despite configurational change of the ketones. The cis ring junction of **2** nullifies the large shift difference of the C(6) methyl groups. The carbon shifts of the four ketones **1a**, **1b**, **1c**, and **2** are listed in Table I.

The dramatic 4–5-ppm deshielding of the carbonyl resonance of **1a** with respect to **1b** and **1c** observed under identical conditions prompted a closer examination of the solvent and concentration dependence of this resonance in the ketone derivatives. The solvent dependence of the carbonyl resonance in aliphatic ketones has been previously characterized and interpreted in terms of dipolar and hydrogen bonding effects.[14,15]

In the presence of aprotic solvents, e.g., cyclohexane, ketonic carbonyl resonances experience increased shielding as the solute concentration is reduced while in protic solvents, e.g., chloroform, decreased shielding accompanies dilution. The former shifts presumably reflect the breakup of solute–solute interactions that are largely dipolar in nature and the down-

Table I. Carbon Shifts of Cannabinoid Compounds[a]

	1a[b]	1b[b,c]	1c[b]	2[b]	3	4a	4b	5
C(1)	155.3	158.1	143.0	155.6	154.4[f]	154.6[f]	143.3	153.4
C(2)	107.7	102.8	109.4	107.9	107.5	107.6	109.3	107.9
C(3)	143.4	143.0	155.2	143.1	142.5	142.4	154.4[f]	142.1
C(4)	108.7	109.9	102.0	108.8	109.8	109.8	102.0	109.5
C(4a)	154.2	153.9	154.3	153.9	154.1[f]	154.4[f]	154.2[f]	154.7
C(10b)	107.7	109.4	114.1	106.6	108.9	110.4	116.5	109.3
C(6)	76.4	76.3	76.1	75.8	77.1	76.3	76.1	76.1
C(6a)	47.3	47.4	48.9	40.0	45.7	44.8	46.4	40.0
C(7)	26.9	26.5	26.5	22.6	25.0	27.8	28.2	20.7
C(8)	40.7	40.7	40.3	41.4	31.1	119.1	119.7	29.7
C(9)	215.2[d]	210.6[e]	211.2	215.9	133.8	134.5	134.2	134.3
C(10)	44.7	45.8	48.4	38.7	123.7	35.9	38.6	122.0
C(10a)	34.7	34.7	35.8	31.1	33.6	31.5	33.2	31.4
6α-Me	18.8	18.6	18.2	24.7[f]	19.2	18.4	18.0	25.2[f]
6β-Me	27.7	27.8	27.5	26.3[f]	27.5	27.5	27.3	25.8[f]
9-Me					23.3	23.4	23.3	23.6
α-C	35.3	36.0	33.1	35.4	35.4	35.4	33.2	35.3
β-C	30.5	30.7	30.6	30.5	30.5	30.5	30.7	30.5
γ-C	31.6	31.6	31.6	31.5	31.4	31.5	31.8	31.5
δ-C	22.5	22.5	22.4	22.5	22.5	22.5	22.4	22.5
ε-C	14.0	13.9	13.9	14.0	14.0	14.0	14.0	14.0

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Solute concentrations in $CDCl_3$ 0.5 M. [c] δ(OMe) 54.8 ppm. [d] This resonance appears at 213.5 ppm in 0.05 M $CDCl_3$ solution. [e] This resonance becomes 210.9 and 205.5 ppm in 0.05 M $CDCl_3$ and 0.5 M cyclohexane solution, respectively. [f] The signals in any vertical column may be reversed.

field shifts in protic solvents are the consequence of increased hydrogen bonding.[16] Dilution effects on ketone resonances are generally less than 2 ppm.

A tenfold reduction in the concentration of **1b** in deuteriochloroform solution (0.5 → 0.05 M) has an insignificant effect on the carbonyl resonance (210.6 → 210.9 ppm) while similar dilution of **1a** results in 1.7-ppm *shielding* of the carbonyl peak (see the legend of Table I). The latter shift, in contrast to that of simple monofunctional ketones,[15] most likely represents the net effect of decreased intermolecular hydrogen bonding between the carbonyl and phenolic hydroxyl functions (a shielding influence) and increased solvent–solute hydrogen bonding (a deshielding effect). The importance of the solvent–solute interaction in the absence of competition from a phenolic hydroxyl group is apparent from comparison of the carbonyl resonance of **1b** in deuteriochloroform (210.6 ppm) and in cyclohexane solution (205.5 ppm) at equal concentrations.

These trends suggest that the carbonyl group of **1a** (and **2**) is involved in a strong solute–solute intermolecular hydrogen bond in 0.5 M deuteriochloroform solution which is eliminated in the methyl ether derivative, **1b**, and strongly inhibited in **1c**, wherein the *n*-pentyl and hydroxyl functions on the aromatic ring are inverted from their natural positions. The carbonyl resonance of the latter two substances, 210.6 and 211.2 ppm, respectively, is similar to that of 4-*tert*-butylcyclohexanone (211.6 ppm) at equal concentration in deuteriochloroform.

The magnitude of the carbonyl shift in **1a** due to solute–solute hydrogen bonding, evaluated from 0.5 M deuteriochloroform solutions of **1a** and **1b**, is 4.6 ppm. In contrast, the carbonyl resonance of 0.5 M deuteriochloroform solution of 4-*tert*-butylcyclohexanone shifts downfield 2.9 ppm in the presence of 1 equiv of phenol. Thus, this system, designed to mimic the solution behavior of **1a**, substantially underestimates the carbonyl shift in the latter.

These correlations suggest that the 4-ppm difference in the carbonyl resonance of **1a** and **1c** is due to contributions from two sources. The five-carbon side chain of **1c** may assume an extended conformation which decreases the stability of solute–solute intermolecular hydrogen bonds. On the other hand, **1a** (and **2**) possesses a geometric configuration in which the carbonyl and hydroxyl functions radiate from the same side of the molecule. This arrangement is sterically compatible with the formation of two equivalent carbonyl–hydroxyl hydrogen bonds in a head-to-tail manner between two solute molecules. The increased stability of this system can account for the larger carbonyl shift contribution from hydroxylic sources in **1a** vs. the 4-*tert*-butylcyclohexanone–phenol mixture.

The analysis of the methylcyclohexenic THC derivatives, **3**, **4**, and **5**, is similar to that of the ketones **1** and **2**. Specific decoupling of the downfield part of the allylic and benzylic hydrogen region sharpens two methylene signals in the sford spectra of Δ^9-THC (**3**), thereby distinguishing C(8) from C(7). The sford spectra of **3** exhibit three distinct multiplet patterns for the methyl groups, sharp quartets for those at C(6), a doublet of quartets for the 9-methyl function, and a complex second-order multiplet for the side chain terminal carbon. Under sford conditions of large olefinic carbon–hydrogen coupling the methyl group of the methylcyclohexene moiety of any of the THC derivatives shows a doublet of quartets which coalesces into a quartet upon direct olefinic hydrogen irradiation.

The allylic methylenes of Δ^8-THC (**4a**) may be differentiated by C(10) revealing a doublet of doublets in the sford spectra. This fact and the expected C(7) shift invariance distinguishes the two methylenes from each other in **4b**. In accord with the ca. 2.5 ppm and ca. 5 ppm shielding of allylic and homoallylic carbons of strain-free cyclohexenes,[17] respectively, by the double bond the difference of the C(7), C(6a), and C(10a) shifts between Δ^9-THC (**3**) and Δ^8-THC (**4a**) is 2.8, −0.9, and −2.1 ppm, respectively, hence close to the ideal 2.5, 0, and −2.5 ppm values. As in the stereochemical change of **1a** → **2** the conversion of Δ^9-THC (**3**) into *cis*-Δ^9-THC (**5**) shields the bridgehead methines and neighboring methylene and decreases dramatically the shift difference between the 6-methyl groups.

Neither chemical shift correlations nor coupling information are sufficient in distinguishing certain sets of aromatic carbon pairs among both the ketones (**1** and **2**) and THC derivatives (**3**, **4**, and **5**). Since all these substances are phenols, it was of interest to develop a ^{13}C NMR procedure of shift diagnosis useful for this class of compounds. In view of the

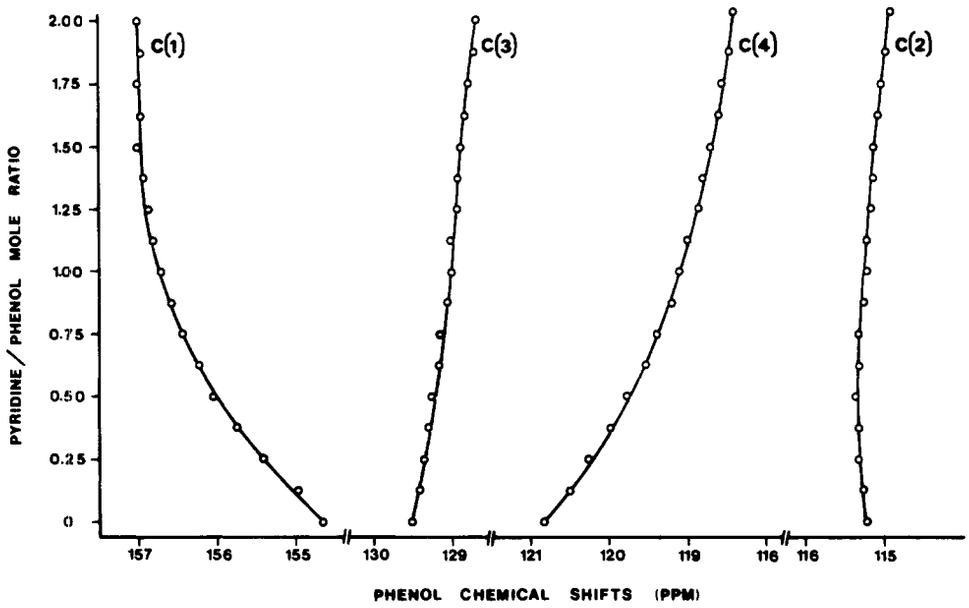


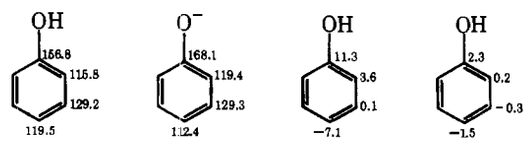
Figure 1.

Table II. Phenol Carbon Shifts and Pyridine-Induced Shift Differences

δ^a	14a	14b	14c^b	14d	15a	15b	16a	16b	17a	17b	18
C(1)	154.6	153.2	153.9	145.1	154.6	156.3	152.5	149.2	151.8	153.6	159.3
C(2)	115.2	123.9	136.0	146.3	115.9	101.5	115.0	115.9	122.9	135.7	113.7
C(3)	129.5	130.8	126.8	110.6	139.6	160.3	129.8	114.8	128.3	124.7	129.2
C(4)	120.8	120.6	120.4	119.9	121.6	106.3	129.2	152.9	120.0	119.5	120.4
C(5)	129.5	126.8	126.8	121.1	129.2	130.0	129.8	114.8	128.3	124.7	129.2
C(6)	115.2	114.8	116.4	114.3	112.2	107.9	115.0	115.9	122.9	135.7	113.7
Me		15.6	29.5	55.5	21.1	55.1	20.2	55.6	15.6	30.3	54.8
$\Delta\delta^c$											
C(1)	2.3	1.9	2.0	1.0	2.0	1.7	1.9	1.6	1.2	−0.1	−0.2
C(2)	0.2	0.7	0.3	0.7	0.3	0.1	0.2	−0.2	0.7	0	−0.1
C(3)	−0.3	−0.1	−0.2	0.4	−0.5	0.3	−0.2	−0.6	−0.2	−0.2	−0.2
C(4)	−1.5	−1.3	−1.1	−0.7	−1.3	−1.4	−0.9	−0.6	−0.5	−0.2	−0.2
C(5)	−0.3	−0.3	−0.2	−0.3	−0.2	−0.4	−0.2	−0.6	−0.2	−0.2	−0.2
C(6)	0.2	0	0.1	0.7	0.3	−0.1	0.2	−0.2	0.7	0	−0.1

^{a} The δ values in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. ^{b} The quaternary carbon is at 34.4 ppm. ^{c} $\Delta\delta_{CDCl_3} = \delta_{CDCl_3}$ (1:1 phenol–pyridine) $- \delta_{CDCl_3}$ (phenol).

diagnostic value of pyridine-induced shifts in the ^{1}H NMR spectroscopy of phenols[18,19] a study of the effect of pyridine on their ^{13}C NMR spectra was undertaken. A simple, nondestructive procedure utilizing the acid properties of phenols is shown in Figure 1. The introduction of pyridine into a deuteriochloroform solution of phenol shields the para carbon and deshields the ipso center. While the complex behavior of the ortho and meta carbon resonances defy simple explanation, their shifts are small in comparison to those of the ipso and para carbons. The shift pattern is similar to the $\Delta\delta$ values depicted in formula **12**, derived from the shifts of phenol (**10**) and potassium phenoxide (**11**) in *tert*-butyl alcohol solution.[20] The $\Delta\delta$ values for 1:1 molar phenol–pyridine mixture in deuteriochloroform are shown on formula **13**. A comparison of the relative magnitude of shift differences (**12** vs. **13**) shows the pyridine-induced shifts to be the consequence of a natural



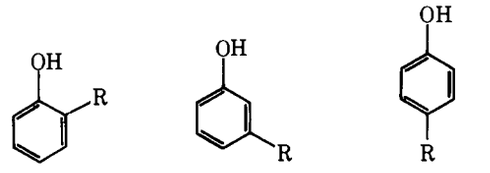
10 **11** **12** **13**

phenol response to base.[21] Since most of the pyridine-created shift is observed already at 1:1 molar ratio of substrate and pyridine and since at this pyridine concentration the aromatic spectral region is affected only minimally, it is convenient to record the pyridine shifts at this phenol–base ratio.

To test the generality of the pyridine-induced shift, the phenols **14–17** and anisole (**18**) were submitted to ^{13}C NMR study. The δ and $\Delta\delta$ values for the phenols are portrayed in Table II. The shift difference data reveal characteristics which are independent of the phenol substitution pattern, i.e., the downfield shift of the ipso carbon is always the largest perturbation. The ipso effect is constant with the notable exceptions of those in **14a, 14d, 17a,** and **17b.** Phenol (**14a**) displays somewhat larger shift differentials indicating that any alkoxy or alkyl ring substitution, independent of position, attenuates this parameter. Analogously, as the data for *p*-cresol (**16a**) and the monomethyl ether of hydroquinone (**16b**) show, the shielding $\Delta\delta$ value of the para carbon resonance, the next largest perturbation, is also subject to attenuation when the para carbon is substituted.

Comparison of the series—phenol (**14a**), 2,6-dimethylphenol (**17a**), and 2,6 di-*tert*-butylphenol (**17b**)—reveals that steric resistance to phenol hydrogen bond formation decreases

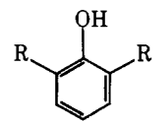
all pyridine-induced shifts of the ring carbons. The minimal shifts of the latter substance are experimentally indistinguishable from those observed in the absence of any ionizing phenolic hydroxy group, e.g., **18**, and indicate a limit to the successful application of this criterion for signal assessment. In the case of the intramolecularly hydrogen-bonded phenol, **14d**, the characteristic ipso and para effects are reduced to one-half of those observed for phenol itself. The shifts are consistent with the notion that guaiacol is stabilized by the intramolecular hydrogen bond and is less prone to complex with pyridine. The nearly superimposable $\Delta\delta$ values of **14d** and **17a** support this idea. The pyridine shift study permits the heretofore difficult shift assignment of the C(4) and C(5) carbon resonances of guaiacol (**14d**).



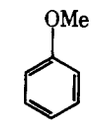
14a, R = H; **b**, R = Me; **c**, R = CMe_3; **d**, R = OMe

15a, R = Me; **b**, R = OMe

16a, R = Me; **b**, R = OMe



17a, R = Me; **b**, R = CMe_3



18

The aromatic methines in the THC derivatives **1a, 2, 3, 4a,** and **5,** containing the natural aromatic substitution pattern, possess similar chemical shifts due to their symmetrical disposition to the aromatic ring substituents. This symmetry also leads to similar δ values for the oxygenated aromatic centers in these substances. The aromatic oxy carbons of **1c** display chemical shifts identical with those in **1a** in spite of the inverted C(1)/C(3) substitution pattern. However, application of the pyridine-induced shift criterion to the ambiguous aromatic signals of these THC derivatives permits their assignment. Thus in Δ^8-THC (**4a**) the 107.6- and 109.8-ppm methine signals show $\Delta\delta$ values of 0 and −0.9 ppm, respectively, for a deuteriochloroform solution of an equimolar **4a**–pyridine mixture, indicating the latter signal to be that of the carbon para to the phenolic hydroxy group. Similarly, the 154.2- and 155.3-ppm oxy carbons of **1a** and the 154.3- and 155.2-ppm oxy carbons of **1c** reveal $\Delta\delta$ values of +0.8 and −0.1 ppm and +1.3 and −0.1 ppm, respectively, allowing the assignment of the high-field resonance of each set to the carbon holding the phenolic hydroxy group.

In summary, the following comments indicate ^{13}C NMR spectroscopy to be useful in the structure analysis of THC derivatives. The determination of the cyclohexene double bond position, e.g., Δ^9-THC (**3**) vs. Δ^8-THC (**4a**), follows from inspection of sford spectra. The double bond isomers differ by their number of allylic methylenes, carbon types easily recognized by their one-bond, residual coupling behavior. In addition, Δ^8 systems which possess a trans ring junction reveal a unique C(10) coupling pattern as a consequence of the large, magnetic nonequivalence of the C(10) hydrogens. Stereochemical isomerism, e.g., **1a** vs. **2** and **3** vs. **5,** is indicated readily by the shift difference of the geminal 6-methyl groups. Positional isomerism, e.g., **1a** vs. **1c** and **4a** vs. **4b,** is reflected by the benzylic methylene shift, 35.4 ppm in its natural state and 33.2 ppm in the *abnormal* series, and by the difference of the aromatic methine shifts.[22]

Experimental Section

The ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode. The compounds in Table II were examined as 3.3 M deuteriochloroform solutions, with eight successive additions of pyridine to reach a 1:1 pyridine–substrate molar ratio. Within these concentrations of pyridine the deuteriochloroform resonance shifts 5 ± 1 Hz downfield. The $\Delta\delta$ values in Table II have been corrected for this drift of the internal reference. The shifts on formulas **8** and **9** are in parts per million downfield from Me_4Si, $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm, while those of **10** and **11** are in parts per million downfield from internal Me_4Si.

7-Benzyloxy-2,2-dimethyl-5-*n*-pentyl-4-chromanone (6b). A mixture of 60.0 g of 2,2-dimethyl-5-*n*-pentyl-7-hydroxy-4-chromanone (**6a**),[5] 47.0 g of benzyl bromide, and 47.5 g of potassium carbonate in 500 ml of acetone was refluxed for 3 h. It then was filtered and the filtrate evaporated under reduced pressure. Chromatography of the residue on 1 kg of silica gel and elution with 10–20:1 hexane–ether yielded 78.1 g (97%) of colorless, oily ketone **6b:** ^1H NMR ($CDCl_3$) δ 0.88 (t, 3, J = 7 Hz, pentyl Me), 1.43 (s, 6, Me_2), 0.7–1.5 (m, 6, methylenes), 2.60 (s, 2, $COCH_2$), 3.00 (t, 2, J = 8 Hz, $ArCH_2$), 5.06 (s, 2, OCH_2), 6.35, 6.45 (d, 1 each, J = 3 Hz, aromatic H), 7.42 (m, 5, aromatic H of $C_6H_5CH_2O$).

Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.38; H, 8.01. Found: C, 78.62; H, 7.80.

7-Benzyloxy-2,2-dimethyl-3-hydroxymethylene-5-*n*-pentyl-4-chromanone (6c). A solution of 33.7 g of ketone **6b** in 77 ml (71.0 g) of ethyl formate was added dropwise onto 23.1 g of sodium hydride. After the initial reaction had subsided, 100 ml of dry ether was added carefully and the mixture refluxed for 2 h. It then was poured onto ice and neutralized with 6 N hydrochloric acid. The aqueous phase was extracted exhaustively with ether and the combined organic phase and extracts were washed with water and saturated brine, dried over anhydrous sodium sulfate, and evaporated. Chromatography of the residue, 39.1 g, over 500 g of silica gel and elution with benzene yielded 13.6 g (37%) of pale yellow, oily ketone **6c;** m/e 380 (M^+); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3, J = 7 Hz, pentyl Me), 1.52 (s, 6, Me_2), 0.7–1.5 (m, 6, methylenes), 3.05 (t, 2, J = 8 Hz, $ArCH_2$), 5.04 (s, 2, OCH_2), 6.31, 6.46 (d, 1 each, J = 3 Hz, aromatic H), 7.36 (m, 5, aromatic H of $C_6H_5CH_2O$), 7.71 (d, 1, J = 8 Hz, OCH) (s after D_2O exchange), 15.6 (d, 1, J = 8 Hz, OH) (exchanges with D_2O).

Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42; O, 16.82. Found: C, 76.06; H, 7.40; O, 17.06.

***trans*-6,6-Dimethyl-6,6a,7,8,10,10a-hexahydro-3-hydroxy-1-*n*-pentyl-9*H*-dibenzo[*b,d*]pyran-9-one (1c).** A solution of 13.6 g of ketone **6c,** 5.0 g of methyl vinyl ketone, and 2 ml of triethylamine in 75 ml of methanol was stirred at room temperature for 18 h. It then was extracted with ether and the extract washed with 10% sodium carbonate solution, water, and saturated brine solution, dried over anhydrous sodium sulfate, and evaporated. A solution of the residual oil, 16.9 g, and 175 ml of 2 N aqueous potassium hydroxide in 175 ml of ethanol was refluxed for 18 h. It was neutralized with 6 N hydrochloric acid and separated. The aqueous phase was extracted with ethyl acetate and the combined organic phase and extracts washed with water, dried over anhydrous sodium sulfate, and evaporated. Chromatography of the residue, 15.6 g, on 500 g of silica gel and elution with 10:1 hexane–ether yielded 6.8 g (47%) of 3-benzyloxy-6,6-dimethyl-1-*n*-pentyl-6,6a,7,8-tetrahydro-9*H*-dibenzo[*b,d*]pyran-9-one (**7**): m/e 404 (M^+); ^1H NMR ($CDCl_3$) δ 0.89 (t, 3, J = 7 Hz, pentyl Me), 1.15 (s, 3, 6α-Me), 1.46 (s, 3, 6β-Me), 0.8–2.7 (m, 13, methylenes and CH), 5.02 (s, 2, OCH_2), 6.40 (d, 1, J = 2 Hz, olefinic H), 6.34, 6.50 (d, 1 each, J = 3 Hz, aromatic H), 7.37 (m, 5, aromatic H of $C_6H_5CH_2O$).

A solution of 6.8 g of ketone **7** in 50 ml of tetrahydrofuran was added dropwise to 400 ml of a blue liquid ammonia solution of lithium at −33 °C. When the color began to fade, more lithium metal was dissolved before further addition of **7.** After complete addition of starting ketone the reaction was stirred for 15 min, solid ammonium chloride then was added, and the ammonia allowed to evaporate. The residue was dissolved in water and extracted with ethyl acetate. The extract was washed with water and saturated brine solution, dried over anhydrous sodium sulfate, and evaporated. Chromatography of the residue, 6.0 g, on 100 g of silica gel and elution with 50:1 benzene–ethyl acetate gave 3.48 g of a viscous oil whose crystallization from ether–petroleum ether yielded plates of ketone **1c:** mp 120–121 °C; m/e 316 (M^+); ^1H NMR ($CDCl_3$) δ 0.87 (t, 3, J = 7 Hz, pentyl Me), 1.06 (s, 3, 6α-Me) 1.44 (s, 3, 6β-Me), 2.53 (t, 2, J = 8 Hz, $ArCH_2$), 0.8–3.5 (m, 14, methylenes, methines), 5.27 (s, 1, OH) (exchanges with D_2O), 6.18, 6.30 (d, 1 each J = 3 Hz, aromatic H).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; O, 15.17. Found: C, 75.91; H, 8.74; O, 15.07.

(±)-*trans*-3-Hydroxy-1-*n*-pentyl-6,6,9-trimethyl-6a,7,10,10a-tetrahydrodibenzo[*b,d*]pyran (4b). A solution of 2.48 g of ketone **1c** in 50 ml of ether was added dropwise to a refluxing solution of 3.2 M methylmagnesium bromide in 50 ml of ether and the heating continued for 18 h. The mixture was poured onto ice and acidified with 0.5 N hydrochloric acid. The aqueous layer was extracted with ether and the combined organic phase and extracts washed with water and saturated brine solution, dried over anhydrous sodium sulfate, and evaporated. Crystallization of the residue from cyclohexane–acetone gave 980 mg of solid alcohol. Chromatography of the mother liquor, 1.6 g, on 40 g of Florisil and elution with 10:1 benzene–ether yielded an additional 380 mg of alcohol. A mixture of 380 mg of the latter and 120 mg of *p*-toluenesulfonic acid in 50 ml of benzene with the presence of a Dean-Stark water separator was refluxed for 2 h. It then was poured into a 5% sodium bicarbonate solution and separated. The aqueous layer was washed with ether and the combined organic solutions dried and evaporated. This gave 200 mg of 10:1 (±)-Δ^8-*abn*-THC (**4b**) and an isomer: *m/e* 314; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3, J = 8 Hz, pentyl Me), 1.04 (s, 3, 6α-Me), 1.34 (s, 3, 6β-Me), 1.66 (s, 3, 9-Me), 0.8–2.0 (m, 12, methylenes, methines), 5.45 (m, 1, olefinic H), 6.14, 6.27 (t, 1, J = 3 Hz, aromatic H); spectra identical with those of **4b** obtained by the condensation of citral with olivetol (vide infra).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.97; H, 9.39.

A solution of 2.80 g of boron trifluoride etherate in 10 ml of dry benzene was added slowly with stirring to a solution of 3.60 g of olivetol (5-*n*-pentylresorcinol) and 3.60 g of citral in 20 ml of benzene and the mixture stirred at room temperature under nitrogen for 18 h. Upon the addition of water it was extracted with ether and the extract washed successively with 2 N sodium hydroxide and with water and dried over anhydrous sodium sulfate. Evaporation of the ether yielded 5.87 g of an orange oil whose GPC analysis revealed ten main peaks including one for unreacted citral. Chromatography of the oil on 250 g of Florisil and elution with 750 ml of hexane, 750 ml of 20:1 hexane–ether, and 1.8 l. of 9:1 hexane–ether led in the middle fractions of the last solvent pair to 480 mg (7% yield) of (±)-Δ^8-*abn*-THC (**4b**) of at least 73% purity (by GPC, the major impurity being (±)-*trans*-Δ^8-THC), spectra and GPC retention time identical with those of **4b** above.

Registry No.—**1a,** 52195-11-6; **1b,** 60761-08-2; **1c,** 60734-16-9; **2,** 60761-09-3; **3,** 1972-08-3; **4a,** 5957-75-5; **4b,** 41408-34-8; **5,** 6087-73-6; **6a,** 16849-52-8; **6b,** 60705-74-0; **6c,** 60705-75-1; **7,** 60705-76-2; **14a,** 108-95-2; **14b,** 95-48-7; **14c,** 88-18-6; **14d,** 90-05-1; **15a,** 108-39-4; **15b,** 150-19-6; **16a,** 106-44-5; **16b,** 150-76-5; **17a,** 576-26-1; **17b,** 128-39-2; **18,** 100-66-3; benzyl bromide, 100-39-0; ethyl formate, 109-94-4; methyl vinyl ketone, 78-94-4.

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(20) The spectrum of the phenoxide ion determined in ethanol/sodium ethoxide solution has been reported previously.[21] The chemical shifts found in the present study show exact agreement for the ipso carbon resonance and minor deviations ($\leq$1 ppm) for the ortho and meta carbon resonances. The para carbon resonance observed here appears 2.5 ppm upfield from that given in the earlier study.
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(±)-Deoxyvernolepin. A Cytotoxic Vernolepin Prototype

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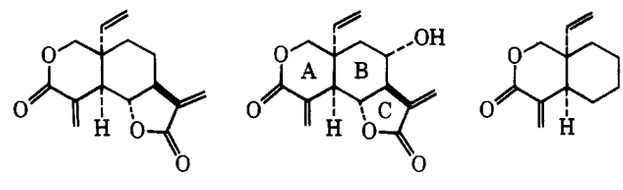
The totally synthetic *trans*-decalone **4** possessing four chiral centers has been converted into (±)-deoxyvernolepin (**1**) via a sequence of transformations involving (a) cleavage of ring A, (b) introduction of the angular vinyl substituent by elimination of the *o*-nitrophenyl selenoxide derived from selenide **28,** and (c) construction of the two α-methylene units via bis-α-hydroxymethylation of bisnordeoxyvernolepin followed by β-elimination. (±)-Deoxyvernolepin was tested as an inhibitor of the growth of CCRF-CEM human lymphoblastic leukemia cells in culture. Deoxyvernolepin was found to be at least an order of magnitude more potent than natural vernolepin.

We wish to disclose the details of the investigation which led to the total synthesis of deoxyvernolepin (**1**)[3] during the course of a program which had as its ultimate goal the total synthesis of vernolepin (**2**).[4] Deoxyvernolepin possesses both the ring A α-methylene-δ-valerolactone unit and the ring C α-methylene-γ-butyrolactone unit of vernolepin while lacking only the C-8 hydroxyl. The synthesis of deoxyvernolepin established the feasibility of bis-α-methylenation, indicating



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