ing 29.9 g (94.8 mmol) of crude 8 and 250 ml of *tert*-butylamine dissolved in 250 ml of methanol was heated at reflux for 1 hr. After evaporation of the volatile components of the reaction mixture, the oily residue which remained was converted to a crystalline hydrochloride salt: yield 30.2 g (75.3%); mp 174–176°. Recrystallization of the product from toluene gave the analytical sample: mp 181–183°. *Anal.* ($C_{22}H_{29}NO_5$·HCl) C, H, N, Cl.

3-Benzyloxy-5-[3-(*tert*-butylamino)-2-hydroxypropoxy]benzyl Alcohol (10a). To a suspension of 29.1 g (68.5 mmol) of **9a** in 500 ml of THF cooled at 0° was added 5.20 g (137 mmol) of $LiAlH_4$. The resultant mixture was refluxed 18 hr. After the excess $LiAlH_4$ and complex had been destroyed by the addition of water, the reaction mixture was diluted with 500 ml of $CHCl_3$ and the precipitate was removed by filtration. The organic filtrate was washed with water (1 × 500 ml), dried with $MgSO_4$, and evaporated to give the crude solid **10a**: yield 20.7 g (84.0%); mp 99–105°. The analytical sample was obtained from cyclohexane: mp 105–107°. *Anal.* ($C_{21}H_{29}NO_4$) C, H, N.

3-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-5-hydroxybenzyl Alcohol Fumarate (2a). An ethanol solution (250 ml) containing 19.7 g (54.7 mmol) of **10a** was hydrogenated over 8 g of 10% Pd/C catalyst until hydrogen uptake had ceased. The catalyst was removed by filtration through a Celite pad and the filtrate obtained was evaporated to a gummy residue. A crystalline fumerate salt was obtained in analytical purity from MeOH–Et_2O: mp 254–255° dec. *Anal.* ($C_{14}H_{23}NO_4$·0.5$C_4H_4O_4$) C, H, N.

Methyl 3-Benzyloxy-5-[3-(3,4-dimethoxyphenylethylamino)-2-hydroxypropoxy]benzoate (9b). A reaction mixture containing 10.0 g (31.9 mmol) of **8**, 25 g (138 mmol) of 3,4-dimethoxyphenylethylamine, and 100 ml of methanol was heated at reflux for 1 hr. Evaporation of the reaction mixture gave a residual oil which was dissolved in $CHCl_3$ (500 ml), extracted with 1 *N* HCl (2 × 250 ml) and 1 *N* NaOH (500 ml), and dried with anhydrous $MgSO_4$. Evaporation of the $CHCl_3$ gave a residual solid which upon trituration with a Et_2O–hexane mixture gave 14.6 g (92.4%) of crystalline product: mp 75–85°. The analytical material was obtained by recrystallization from toluene: mp 94–95°. *Anal.* ($C_{28}H_{33}NO_7$) C, H, N.

3-[3-(3,4-Dimethoxyphenylethylamino)-2-hydroxypropoxy]-5-hydroxybenzyl Alcohol Fumarate (2b). To a suspension of 3.11 g (82.0 mmol) of $LiAlH_4$ in 250 ml of dry THF was added a THF solution (250 ml) containing 20.3 g (41.0 mmol) of methyl 3-benzyloxy-5-[3-(3,4-dimethoxyphenylethylamino)-2-hydroxypropoxy]benzoate. The resulting reaction mixture was refluxed for 3 hr before the excess $LiAlH_4$ and complex were destroyed by the careful addition of water. The white precipitate which formed was removed by filtration and the filtrate obtained was evaporated *in vacuo* and gave a quantitative yield of the crude **10b** as a straw-colored oil.

An ethanol solution (150 ml) containing 19.6 g (41.2 mmol) of **10b** was hydrogenated over 5.0 g of 10% Pd/C catalyst until hydrogen uptake had ceased. The catalyst was removed by filtration and the filtrate was evaporated to give an oily residue as product. A crystalline fumarate salt was obtained from 1-PrOH: yield 14.1 g; mp 183–186° dec. The analytical sample was obtained by one recrystallization from MeOH–Et_2O: mp 189–191° dec. *Anal.* ($C_{20}H_{27}NO_6$·0.5$C_4H_4O_4$) C, H, N.

2-[3-(3,4-Dimethoxyphenylethylamino)-2-hydroxypropoxy]benzophenone Hydrogen Oxalate (11). A methanolic solution (100 ml) containing 10.0 g (39.3 mmol) of 2-(2,3-epoxypropoxy)-benzophenone[3] and 22.6 g (125 mmol) of 3,4-dimethoxyphenylethylamine was heated at reflux for 2 hr. The reaction mixture was evaporated to remove the volatile components and the residue obtained was dissolved in $CHCl_3$ (500 ml). The $CHCl_3$ solution was washed with 3 *N* HCl (3 × 500 ml), 1 *N* NaOH (1 × 500 ml), and H_2O (1 × 500 ml) before being dried with $MgSO_4$ and evaporated to give 15.8 g (92.2%) of the expected product as an oil. The product was purified as an oxalate salt by recrystallization from 2-PrOH: yield 12.4 g (61.1%); mp 129–130°. *Anal.* ($C_{26}H_{29}NO_5$·$C_2H_2O_4$) C, H, N.

5-[3-(3,4-Dimethoxyphenylethylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone Hydrogen Oxalate (12). A reaction mixture containing 13.4 g (61.6 mmol) of 3,4-dihydro-5-(2,3-epoxypropoxy)-1(2*H*)-naphthalenone,[4] 100 ml of MeOH, and 53.7 g (295 mmol) of 3,4-dimethoxyphenylethylamine was heated at reflux for 1 hr. The mixture was evaporated to an oily residue which was dissolved in $CHCl_3$ (500 ml) and washed with 3 *N* HCl (3 × 500 ml), 20% NaOH (1 × 100 ml), and H_2O (1 × 500 ml). The $CHCl_3$ solution was dried ($MgSO_4$) and evaporated *in vacuo* to give the expected product as a crude oil: yield 13.5 g (54.9%). The product was purified as an oxalate salt by recrystallization from 2-PrOH: mp 152–154°. *Anal.* ($C_{23}H_{29}NO_5$·$C_2H_2O_4$) C, H, N.

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Hashish.[1] Importance of the Phenolic Hydroxyl Group in Tetrahydrocannabinols

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Optically active Δ^9- and Δ^8-tetrahydrocannabinols (THC's), cannabidiol and racemic Δ^9-*cis*-THC, and their corresponding analogs (**1b** → **4b**) in which the positions of the phenolic hydroxyl group and the *n*-C_5 side chain have been interchanged are compared in selected pharmacological tests in mice. The results indicate that the phenolic hydroxyl group in the 1 position in THC's is very important for eliciting activity and that cannabidiol and Δ^9-*cis*-THC possess weak CNS depressant properties.

To date over 30 cannabinoids have been isolated from the plant *Cannabis sativa* and it is generally accepted that the principal compounds of pharmacological interest are Δ^9- and Δ^8-6a,10a-*trans*-tetrahydrocannabinols (THC's). In laboratory animals Δ^9- and Δ^8-THC's cause CNS depression and ataxia. The characteristic effect of THC's, which distinguishes them from all other psychoactive drugs, is a postural arrest phenomenon with relaxed staring associated with hyperexcitability to external stimuli ("popcorn effect").[2] On the basis of behavioral tests in monkeys, Edery, *et al.*,[3] have reported some structure–activity relationships (SAR) in the THC series. However, little is known about the importance of the phenolic hydroxyl group in naturally occurring THC's. In monkeys, the acetates of Δ^9- and Δ^8-THC's have 1/10 to 1/2 the activity of the parent compounds and the methyl ethers are essentially inactive.[3] We have found that the aminoalkyl esters of Δ^9-THC are nearly equiactive with the parent

Table I. Comparison of Selected Pharmacological Properties

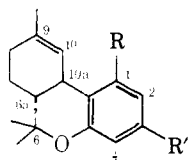
Compound	Approx LD_{50}, mg/kg iv	Ataxia MED, mg/kg iv	"Popcorn" MED, mg/kg iv	Hot-plate ED_{50}, mg/kg ip	Spontaneous act. Dose, mg/kg ip	Spontaneous act. % effect	Antimetrazole act., mg/kg ip	Comment
Δ^9-THC (1a)	>100.0	0.5	0.5	54.0 (25.2–106.5)[b]	10.0	−41.2[d]	NP[f] at 100	Potentiated metrazole
1b	75.0	*a*	None	IA[c] at 100	100.0	−7.1	NP at 100	Essentially inactive
Δ^8-THC (2a)	>100.0	0.5	0.5	34.7 (12.1–89.6)[b]	10.0	−69.3[d]	NP at 100	Potentiated metrazole
2b	75.0	50.0	None	IA at 100	100.0	−11.0	NP at 50	Essentially inactive
CBD (3a)	50.0	25.0	None	IA at 100	100.0	−83.5[d]	NP at 100	Weak depressant
3b	30.0	*a*	None	IA at 100	100.0	−31.0[e]	NP at 50	Essentially inactive
cis-Δ^9-THC (4a)	50.0	10.0	10.0	IA at 100	100.0	−25.1[d]	NP at 100	Weak depressant
4b	100.0	50.0	None	IA at 100	100.0	+4.0	NP at 100	Essentially inactive

[a] At lethal doses only. [b] Numbers in parentheses are 95% confidence limits.[16] [c] IA = inactive. [d] Significantly different from controls $p < 0.005$. [e] The results were erratic and were not statistically significant. [f] NP = no protection.

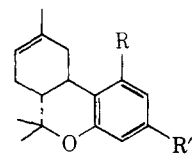
compound on a molar basis in dogs and mice;[4] presumably the activity of these compounds is due to hydrolysis *in vivo* to Δ^9-THC.

A recent study on the synthetic $\Delta^{6a,10a}$-THC's has shown similarly that acetylation of the phenolic group decreases and methylation eliminates activity (rats).[5] Previous work on these compounds indicates that activity is completely lost if the phenolic hydroxyl group is replaced by hydrogen,[6] although surprisingly this is not found to be the case in the series in which the *n*-C_5H_{11} side chain has been replaced by the 1,2-dimethylheptyl group.[5] In addition, the isomers of $\Delta^{6a,10a}$-THC's in which the alkyl is at C-2 and the hydroxyl at C-3 have been reported to have activies varying from low to none.[5,7,8]

As a part of our ongoing program on natural THC's we have prepared (−)-Δ^9-THC (**1a**), (−)-Δ^8-THC (**2a**), (−)-cannabidiol (CBD) (**3a**), and their isomers **1b**, **2b**, and **3b**, in which the positions of the phenolic group and the *n*-C_5 side chain have been interchanged. In addition, we have prepared the racemic Δ^9-6a,10a-*cis*-THC (**4a**) and its isomer **4b** for comparison with **1a** and **1b** in the trans series. The (±)-Δ^9-*cis*-THC (**4a**) has been previously reported to be inactive in monkeys at 1.5 mg/kg.[9] In this paper we report an examination of the activity of these pairs of compounds in selected pharmacological tests and draw conclusions regarding the importance of the position of the phenolic hydroxyl group in THC's.



1a, R = OH; R′ = C_5H_{11} [(−)-Δ^9-THC]
b, R = C_5H_{11}; R′ = OH (levo isomer)



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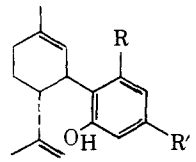
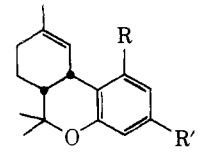


3a, R = OH; R′ = C_5H_{11} [(−)-CBD]
b, R = C_5H_{11}; R′ = OH (levo isomer)



4a, R = OH; R′ = C_5H_{11} [(±)-*cis*-Δ^9-THC]
b, R = C_5H_{11}; R′ = OH (racemic)

Chemistry. All the materials except the *cis*-THC's were prepared from *p*-mentha-2,8-dien-1-ol and olivetol according to our recent syntheses.[1b] The (±)-*cis*-Δ^9-THC (**4a**)[10,11] and a new cis cannabinoid **4b** were synthesized from citral and olivetol in the presence of 0.5 *N* HCl.

Pharmacology. The compounds were tested in selected pharmacological tests in mice as described in the Experimental Section.

Results (Table I). In the trans series, compounds **1b**, **2b**, and **3b** caused lethality at lower doses than the corresponding natural products. This was not the case with the cis compounds since **4a** was more toxic than **4b**. In the pharmacological observations of ataxia and "popcorn," spontaneous activity and antinociceptive activity (hot plate) compounds **1b**, **2b**, and **3b** were essentially inactive. The results also suggest that cannabidiol (**3a**) and *cis*-Δ^9-THC (**4a**) possess weak CNS depressant properties. Cannabidiol is devoid of any "popcorn" effect and our present findings are in agreement with previously reported depressant activity of **3a** in other species.[12] *cis*-Δ^9-THC (**4a**) shows a similar profile to Δ^9-THC but is much less potent. This is consistent with its reported inactivity in monkeys.[9] None of the compounds possessed anticonvulsant activity as indicated by the antimetrazole test. The inactivity of **3a** in this test and potentiation of metrazole by Δ^8- and Δ^9-THC's are in agreement with published data.[12b,13] We conclude from these results that the phenolic hydroxyl group in the 1 position is extremely important for eliciting activity in THC's. Furthermore, since *cis*-Δ^9-THC (**4a**) is much less active than Δ^9-THC, a structural specificity for activity is indicated. However, **4a** is a racemate which may account for its low potency and it would therefore be of interest to test the unknown optically active isomers of **4a**.

Experimental Section†

Chemistry. Olivetol was purchased from Aldrich Chemical Co. and *p*-mentha-2,8-dien-1-ol from Firmenich and Co. (Switzer-

† Nmr, glc, and mass spectra were determined as in ref 1b.

land). Compound **1b** was prepared from **3b** as described by us previously (ref 1b, experiment 3, Tables I and II) and had $[\alpha]_D$ −160° ($CHCl_3$); >97% pure by glc. Compound **2b** was prepared according to a literature procedure.[14] (−)-Cannabidiol (**3a**) and **3b** were prepared by the wet *p*-toluenesulfonic acid method.[1b]

(±)-6aβ,7,8,10aβ-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol (4a) and (±)-6aβ,7,8,10aβ-Tetrahydro-6,6,9-trimethyl-1-pentyl-6*H*-dibenzo[*b,d*]pyran-3-ol (4b). To 1.8 g (0.01 mol) of olivetol and 1.5 g (0.01 mol) of citral in 50 ml of benzene was slowly added 20 ml of 0.5 *N* HCl in ethanol with vigorous stirring. After 1 hr the reaction mixture was neutralized with 1 *N* NaOH. Ether was added to the mixture and the organic phase, after separation, was washed with 1 *N* NaOH, water, and brine. After drying the solution was concentrated to give 3 g of an orange oil. Chromatography on Florisil and gradient elution with ether–petroleum ether (30–40°) mixtures gave 0.3 g (10%) of **4a**[11] and 0.64 g (20%) of **4b** as a resin: nmr (CCl_4) δ 0.90 (3 H, t, ω-CH_3), 1.27 (6 H, s, *gem*-dimethyl), 1.63 (3 H, s, vinylic CH_3), 3.43 [1 H, br, C(10a)-H], 5.60 (1 H, br, vinylic), 5.80 (1 H, br, D_2O exchangeable), 6.17, 6.03 (2 H, 2 d, $J \simeq 2$ Hz, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 314 (100), 299 (90), 271 (75), 258 (55), and 231 (80). *Anal.* ($C_{21}H_{30}O_2$) C, H.

Pharmacology. The compounds were tested in selected neuropharmacological test procedures using male albino CD-1 mice (18–22 g). The drug was administered intravenously (iv) or intraperitoneally (ip) as a solution in 0.06 ml of polyethylene glycol 400 per 25-g mouse. Various doses of the compounds were given iv to at least six mice per dose to determine approximate LD_{50}. Similarly, MED's were determined for ataxia and sensitivity to touch ("popcorn") which are characteristic of THC's.[2] The spontaneous activity and the mouse hot-plate data were obtained (ip route) according to the procedure described previously.[15] The ED_{50} values and 95% confidence limits were determined[16] using data obtained from three groups of six mice each. The anticonvulsant activity of these compounds was determined using the antimetrazole procedure.[17] Mice were premedicated with the drug or the vehicle alone and after 30 min were challenged with a dose of metrazole (33 mg/kg iv). The number of animals which convulsed in each group was counted. The vehicle was inactive in this test.

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A Stereoselective Synthetic Route to (*R*)-Zearalanone

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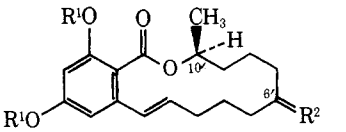
(*R*)-Zearalanone (11) was prepared stereoselectively from the naturally occurring (*S*)-zearalenone. (*R*)-Zearalanone (11) had no mouse uterotropic activity, but it did have a synergistic effect on the activity of (*S*)-zearalanone.

In studying the biological activities of zearalenone and several of its derivatives,[1-3] it became desirable to determine the effect of absolute configuration on uterotropic activity. Since the configuration at C-10′ in naturally occurring zearalenone had been determined as *S* by Kuo, *et al.*,[4] a synthetic sequence was developed to invert this center to the *R* configuration.

Starting with (*S*)-zearalenone (**1**), the phenolic functions and the carbonyl group at C-6′ were protected during the course of inverting the C-10′ position. This was accomplished by converting the phenolic groups into their respective benzyl ethers (**1** → **2**), followed by ketalization of the C-6′ carbonyl function using ethylene glycol to give **3** in high yield.

With the carbonyl group protected in **3**, the 14-membered lactone could then be opened without racemization of the C-10′ position.[5] This was accomplished by treatment of **3** with 40% sodium hydroxide in dimethyl sulfoxide at 120° to give **4**. Hydroxy acid **4** was then converted to its methyl ester **5** with diazomethane.



1, $R^1 = H$; $R^2 = O$
2, $R^1 = PhCH_2$; $R^2 = O$
3, $R^1 = PhCH_2$; $R^2 = OCH_2CH_2O$

Toluenesulfonic ester **6** was prepared from the reaction of hydroxy ester **5** with *p*-toluenesulfonyl chloride in pyridine. Inversion of the C-10′ position was accomplished by reaction of **6** with tetraethylammonium acetate in refluxing methyl ethyl ketone to give **7**. The conversion of **7** to **8**