

The tissue was challenged every 12 min in all experiments. For the measurement of the antagonist potencies of analogues, the antagonist was given 2 min before ANG II. Antagonist potencies (pA_2) were determined as the negative logarithm of the concentration of antagonist required to reduce the response to an ED50 dose of ANG II to the response to half the ED50 dose. The antagonist effects of some peptides were found not to be reversible within the 12-min time frame between ANG II challenges, and for these peptides each tissue was challenged only once with "pA₂ dose" of the irreversible antagonist. The "pA₂ values" so obtained are considered tentative (see Table I) since these antagonists do not appear to have purely competitive mechanisms of action.⁷

[Sar¹,D-Trp⁴,Ile⁸]angiotensin II: yield 18%; TLC R_f (BPAW) 0.37, R_f (CMAW) 0.41. Amino acid analysis: Arg, 1.10; Val, 1.00; Trp, 0.88; Ile, 2.11; His, 1.08; Pro, 0.92.

[Sar¹,D-Trp⁴]angiotensin II: yield 16%; TLC R_f (BPAW) 0.38, R_f (CMAW) 0.43. Amino acid analysis: Arg, 1.12; Val, 1.00; Trp, 0.87; Ile, 0.89; His, 1.05; Pro, 0.95; Phe, 1.12.

[Sar¹,Tyr(Me)⁴]angiotensin II: yield 16% TLC R_f (BPAW) 0.32, R_f (CMAW) 0.32. Amino acid analysis: Arg, 1.12; Val, 1.00; Tyr(Me)+Tyr, 0.90; Ile, 0.88; His, 1.05; Pro, 0.99; Phe, 1.08. FAB-MS, MH^+ = 1017.

[Sar¹,Tyr(Me)⁴,Ile⁸]angiotensin II: yield 15%; TLC R_f (BPAW) 0.35, R_f (CMAW) 0.38. Amino acid analysis: Arg, 1.08; Val, 1.00; Tyr(Me)+Tyr, 0.92; Ile, 2.04; His, 1.06; Pro, 0.96. FAB-MS, MH^+ = 983.

[Sar¹,D-Trp⁸]angiotensin II: yield 7%; TLC R_f (BPAW) 0.36, R_f (CMAW) 0.40. Amino acid analysis: Arg, 1.10; Val, 1.00; Tyr, 1.05; Ile, 0.89; His, 1.15; Pro, 1.05; Trp, 0.89.

[Sar¹,Tyr(Me)⁴,D-Trp⁸]angiotensin II: yield 10%; TLC R_f (BPAW) 0.39, R_f (CMAW) 0.43. Amino acid analysis: Arg, 1.05;

Val, 1.00; Tyr(Me)+Tyr, 0.95; Ile, 0.96; His, 1.06; Pro, 1.04; Trp, 0.89.

[D-Trp³,Ile⁷]angiotensin III: yield 22%; TLC R_f (BPAW) 0.55, R_f (CMAW) 0.42. Amino acid analysis: Arg, 1.08; Val, 1.00; Trp, 0.92; Ile, 2.08; His, 1.06; Pro, 1.12.

[D-Trp³]angiotensin III: yield 24%; TLC R_f (BPAW) 0.56, R_f (CMAW) 0.40. Amino acid analysis: Arg, 1.12; Val, 1.00; Trp, 0.87; Ile, 0.89; His, 1.05; Pro, 0.95; Phe, 1.12.

[Tyr(Me)³]angiotensin III: yield 14%; TLC R_f (BAPW) 0.53, R_f (CMAW) 0.41. Amino acid analysis: Arg, 1.10; Val, 1.00; Tyr(Me)+Tyr, 0.92; Ile, 0.94; His, 1.06; Pro, 0.93; Phe, 1.07.

[Tyr(Me)³,Ile⁷]angiotensin III: yield 15% TLC R_f (BAPW) 0.52, R_f (CMAW) 0.40. Amino acid analysis: Arg, 1.05; Val, 1.00; Tyr(Me)+Tyr, 0.93; Ile, 1.95; His, 1.08; Pro, 0.90.

[D-Trp⁷]angiotensin III: yield 8%; TLC R_f (BPAW) 0.53, R_f (CMAW) 0.41. Amino acid analysis: Arg, 1.12; Val, 1.00; Tyr, 0.97; Ile, 0.92; His, 1.12; Pro, 0.92; Trp, 0.96.

[Tyr(Me)³,D-Trp⁷]angiotensin III: yield 10%; TLC R_f (BPAW) 0.57, R_f (CMAW) 0.44. Amino acid analysis: Arg, 0.93; Val, 1.00; Tyr(Me)+Tyr, 0.95; Ile, 1.06; His, 1.10; Pro, 0.95; Trp, 0.91.

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Registry No. [Sar¹,D-Trp⁴,Ile⁸]angiotensin II, 95798-24-6; [Sar¹,D-Trp⁴]angiotensin II, 95798-25-7; [Sar¹,Tyr(Me)⁴]angiotensin II, 88874-29-7; [Sar¹,Tyr(Me)⁴,Ile⁸]angiotensin II, 92780-94-4; [Sar¹,D-Trp⁸]angiotensin II, 95841-12-6; [Sar¹,Tyr(Me)⁴,D-Trp⁸]angiotensin II, 95841-13-7; [D-Trp³,Ile⁷]angiotensin III, 95798-26-8; [D-Trp³]angiotensin III, 95798-27-9; [Tyr(Me)³]angiotensin III, 95936-83-7; [Tyr(Me)³,Ile⁷]angiotensin III, 95798-28-0; [D-Trp⁷]angiotensin III, 95798-29-1; [Tyr(Me)³,D-Trp⁷]angiotensin III, 95798-30-4; [Sar¹,Ile⁸]angiotensin II, 37827-06-8.

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Hashish:¹ Synthesis and Central Nervous System Activity of Some Novel Analogues of Cannabidiol and Oxepin Derivatives of Δ^9 -Tetrahydrocannabinol²

Vaman S. Jorapur,[†] Zarif H. Khalil,[†] Richard P. Duffley,[†] Raj K. Razdan,^{*†} Billy R. Martin,^{*†} Louis S. Harris,[†] and William L. Dewey[†]

The SISA Institute for Research, Inc., Cambridge, Massachusetts 02138, and Medical College of Virginia, Richmond, Virginia 23298. Received August 7, 1984

Several C-10 substituted cannabidiol (CBD) derivatives and novel oxepin derivatives of Δ^9 -tetrahydrocannabinol (Δ^9 -THC) were synthesized and evaluated for biological activity in mice and dogs. Treatment of 10-bromocannabidiol diacetate (3) with various amines in Me₂SO gave the corresponding 10-aminocannabidiol derivatives 4-6. Similarly, treatment of 3 with NaN₃ gave the azido compound 7, which with LiAlH₄ afforded the 10-aminocannabidiol 9. However, reduction of 7 with CrCl₂ formed the amide 8, which on further reduction with LiAlH₄ gave the N-ethyl analogue 10. Coupling of 9 with 11 in the presence of dicyclohexylcarbodiimide formed 12, which was then deprotected with HCl to give the analogue 13. The oxepin analogue 14a was synthesized from 3 by treatment with Na₂CO₃ in CH₃OH/H₂O at room temperature. The dimethylheptyl analogue 14b was similarly prepared. Incorporation of N-ethyl (10), N-methyl-N-propargyl (6), and morpholino (4) groups in CBD at position 10 resulted in analogues that were more potent than CBD in producing hypoaesthesia in mice. These analogues had relatively little effect on rectal temperature. Selected substitutions at C-10 also resulted in analogues that were partially effective in blocking Δ^9 -THC antinociceptive activity. This blockade was observed particularly in compound 10, which also showed unusually toxic properties. Incorporation of a seven-membered oxepin in the Δ^9 -THC structure eliminated cannabinoid activity although substitution of the pentyl side chain with a 1,2-dimethylheptyl in the oxepin 14b resulted in CNS depression in mice.

In continuation of our work³ to study structure-activity relationships (SAR) and develop cannabinoids that are more specific in their effects, we directed our efforts toward

cannabidiol derivatives. Interest in cannabidiol (CBD, 1) and related compounds arises from the fact that CBD is

[†] The SISA Institute for Research, Inc.

[†] Medical College of Virginia.

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a naturally occurring constituent of marihuana that has a pharmacological profile different from that of Δ^9 -tetrahydrocannabinol (THC). For example, CBD lacks psychotropic effects in man^{4,5} but shows anticonvulsant properties in man and rodents.⁶ Considerable attention was paid to CBD after it was reported to be an antagonist of Δ^9 -THC.^{7,8} However, subsequent studies failed to produce convincing evidence for antagonistic activity of CBD.⁹

Very few studies have been carried out to delineate the SAR at the isopropenyl group of CBD, primarily because the introduction of substituents at this part of the molecule have not been amenable to synthesis. So far only two C-10 substituted CBD derivatives have been prepared and were reported to be anticonvulsants.¹⁰

We have recently reported^{11,12} a high-yield procedure for the regiospecific bromination of cannabidiol diacetate (2) at C-10 which has resulted in the synthesis of novel C-10 substituted CBD derivatives. During the course of this synthetic work, 10-bromocannabidiol diacetate (3) also provided a novel oxepin 14,¹¹ an analogue of Δ^9 -THC. These compounds were evaluated for their ability to alter spontaneous activity, antinociceptive activity, and body temperature in mice, and in addition, the oxepin derivatives were examined for their effects on the overt behavior in dogs. The results of these studies are presented in this paper.

Chemistry. We had reported^{11,12} earlier that the bromination of cannabidiol diacetate (2) with NBS proceeds regioselectively to give 3 in over 80% isolated yield. Mild alkaline hydrolysis or treatment with NaCN invariably resulted in the formation of a novel oxepin, 14a. However, it was found that treatment of 3 with various amines gave the 10-aminocannabidiol derivatives.

The reaction of 3 with morpholine in Me₂SO furnished 10-morpholinocannabidiol diacetate (4) in 46% yield. Similar treatment of 3 with diisopropylamine and N-methylpropargylamine furnished compounds 5 and 6 in 72% and 71% yield, respectively.

When 3 was stirred with sodium azide in Me₂SO at room temperature, it readily gave 10-azidocannabidiol diacetate

(7) in 87% yield and showed characteristic IR absorption at 2160 cm⁻¹ due to the azide group. The azido compound 7 on reduction with CrCl₂ in aqueous acetone furnished the amide 8 instead of the desired amine 9. The O → N transformation was unexpected but is not unique. On LiAlH₄ reduction, the amide 8 furnished the desired 10-(ethylamino)cannabidiol (10) in 70% yield. Reduction of the azido compound 7 with LiAlH₄ afforded a high yield of the 10-aminocannabidiol (9).

Since γ -aminobutyric acid (GABA) has been implicated in mediating the anticonvulsant effects in several classes of compounds and CBD (1) is known to have anticonvulsant activity, we prepared the GABA derivative 13. It was prepared by the dicyclohexylcarbodiimide coupling of *t*-Boc-GABA (11) with 9 to afford 12, which was then deprotected to give the analogue 13.

The oxepin analogue 14a was prepared from 3 by treatment with Na₂CO₃ in CH₃OH/H₂O at room temperature.^{11,12} The dimethylheptyl analogue 14b was similarly prepared by the bromination of the known corresponding CBD analogue,¹³ followed by treatment with base as in the preparation of 14a.

Pharmacology and Discussion of Results

Several animal test systems were used to evaluate the pharmacological effects of these analogues. This battery of tests allows for a more complete assessment of pharmacological activity than that provided by any one of the individual assays. In this fashion, it can be determined which structural modifications alter each cannabinoid effect.

The results in Table I clearly show that CBD has weak effects on the central nervous system (CNS). The ED₅₀ (95% confidence limits) for producing hypoactivity was 40 (25–65) mg/kg and rectal temperature was not depressed with a dose of 50 mg/kg. In contrast, it has been shown that Δ^9 -THC reduces spontaneous activity by 50% at a dose of 3.2 (1.7–6.2) mg/kg and a dose of 2.5 mg/kg reduces rectal temperature 2.6 °C.¹⁴ These very high doses of CBD are probably producing a nonspecific CNS depression. Addition of either *N*-methyl-*N*-propargyl or morpholino groups (compounds 6 and 4, respectively) increased CBD's ability to depress spontaneous activity but had relatively little effect on CBD's hypothermic activity. The addition of a *N,N*-diisopropyl group (compound 5) did not enhance and, if anything, decreased the CNS depressant effects of CBD. The γ -aminobutyryl group (compound 13) did not significantly alter CBD's effects on spontaneous activity but did increase its effectiveness for producing hypothermia. Incorporation of an *N*-ethyl group (compound 10) at position 10 produced the most dramatic change in the pharmacology of CBD with a 10-fold increase in hypoactivity and hypothermic effects. The 10-*N*-ethyl analogue 10 was equally effective as Δ^9 -THC in depressing spontaneous activity but was much less effective than Δ^9 -THC in altering body temperature. One of the most interesting features of some of these analogues was their toxicity as compared to that of CBD (no deaths after 100 mg/kg). The *N*-ethyl analogue was found to be lethal at intravenous (iv) doses of 6.0, 6.5, and 7.5 mg/kg, producing 84%, 84%, and 100% deaths, respectively. The LD₅₀ (95% confidence limits) for the *N*- γ -aminobutyryl analogue 13 was 41 (37–47) mg/kg. The LD₅₀ was not

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Table I. Effects of CBD and Its 10-Substituted Analogues on Tail-Flick Response, Rectal Temperature, and Spontaneous Activity in Mice

compd	dose, mg/kg	tail-flick		hypothermia, $\Delta^{\circ}\text{C}^c$	spontaneous act. ^d
		% MPE ^a	% antagonism ^b		
vehicle		0	0	0.1 \pm 0.1	
Δ^9 -THC	0.3	27			3.2 ((1.7–6.2))
	1	53			
	2.5	61			
	5			–2.6 \pm 0.2	
	7.5			–3.6 \pm 0.5	
				–3.8 \pm 0.3	
CBD (1)	40	5	0	–0.5 \pm 0.1	40 (25–65)
	50	e		–0.4 \pm 0.1	
	75			–2.1 \pm 0.5	
	100			–2.5 \pm 0.4	
4	10			–0.9 \pm 0.4	16 (10–25)
	20	3	14		
	30			–1.2 \pm 0.2	
	60			–1.3 \pm 0.3	
5	10		0	–1.0 \pm 0.4	NA ^f
	20	0	58		
	30			–0.9 \pm 0.4	
6	10		25	–0.3 \pm 0.3	13 (6–25)
	20	0	63		
	30			–1.0 \pm 0.2	
	60			–1.5 \pm 0.6	
10	1.0		33	–1.0 \pm 0.2	4 (1–12)
	2.5		66	–1.4 \pm 0.4	
	5.0	7	67	–1.0 \pm 0.2	
13	10		14		30 (23–38)
	25	7	43	–1.3 \pm 0.7	
	30			–2.0 \pm 0.6	
	35			–2.1 \pm 0.7	

^a Percent maximum possible effect in tail-flick test. ^b Percent antagonism of Δ^9 -THC (1 mg/kg) in tail-flick test. ^c Difference between preinjection and postinjection (60 min) temperatures, means \pm SEM, $N = 6$. ^d ED₅₀, mg/kg, 95% confidence limits presented in parentheses. ^e Not tested. ^f Not active up to a lethal dose of 60 mg/kg.

determined for the *N,N*-diisopropyl analogue 5, but a dose of 60 mg/kg resulted in 100% deaths. All deaths occurred within 5 min of the injection, apparently from CNS depression. Compounds 10 and 13 were also tested for their anticonvulsant activity, but as reported previously, they did not show any enhancement of anticonvulsant activity over CBD.²

Since we have reported recently that Δ^8 -THC is a potent antinociceptive agent when administered iv,³ CBD and its analogues were also evaluated in the tail-flick procedure. CBD as well as the analogues described in Table I lacked agonist activity in this test even after administration of rather large doses. However, pretreatment with 20 or 25 mg of the *N*-methyl-*N*-propargyl, *N,N*-diisopropyl, or *N*- γ -aminobutyryl analogues resulted in a partial blockade of Δ^9 -THC's antinociceptive activity. CBD and its morpholino derivative were devoid of antagonistic properties at doses of 40 and 20 mg/kg, respectively. On the other hand, the *N*-ethyl analogue 10 of CBD effectively blocked Δ^9 -THC's analgesic effects in a dose-related manner. Higher doses of this analogue could not be examined due to its lethality. While none of these analogues is a potent antagonist of Δ^9 -THC, these data suggest that an appropriate structural modification at the 10-position of CBD may lead to such a compound.

The pharmacology of the two oxepin compounds 14a and 14b, which are analogues of Δ^9 -THC, is described in Table II. Compound 14a was almost completely devoid of CNS activity. It failed to alter rectal temperature in mice and caused only a slight reduction in spontaneous activity at a dose of 100 mg/kg. It also failed to produce behavioral effects in the dog at doses up to 5 mg/kg, whereas Δ^9 -THC is quite active at doses of 0.5 mg/kg.¹⁴ Substitution of the pentyl side chain with a dimethylheptyl side chain resulted in an oxepin analogue (14b) that ef-

Table II. Effects of the Oxepin Derivatives on Spontaneous Activity and Hypothermia in Mice and Overt Behavior in Dogs

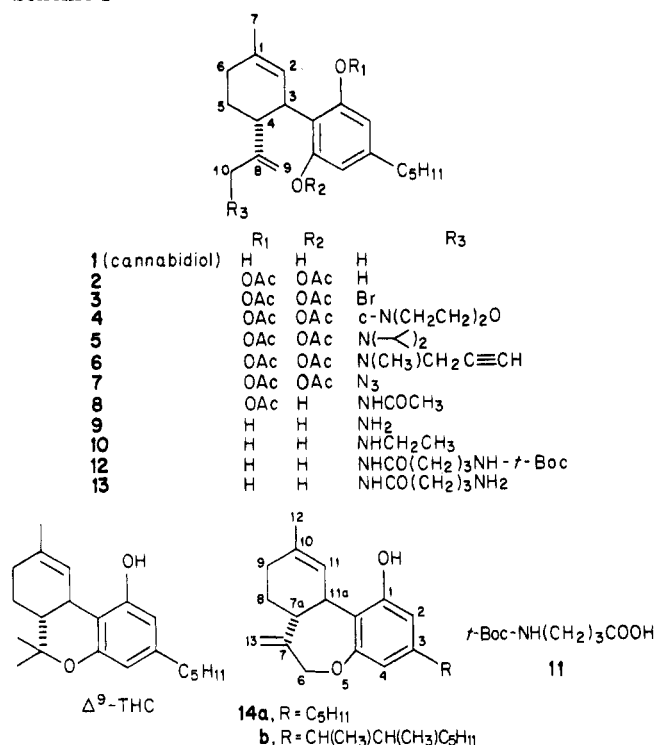
compd	dose, mg/kg	spontaneous activity ^a	hypothermia, $\Delta^{\circ}\text{C}^b$	overt behavior ^c
vehicle			–0.4 \pm 0.2	0 (3)
14a	2			0 (2)
	5			0 (1)
	30	0	0.1 \pm 0.3	
	100	41	0 \pm 0.4	
14b	0.5			0 (3)
	1	10	–0.4 \pm 0.4	
	3	50	–0.6 \pm 0.4	
	10	71	–4.9 \pm 0.8	
	30	58	–5.7 \pm 0.7	
	100	82	–7.8 \pm 0.3	

^a Expressed as percent of vehicle-treated mice. ^b Difference between pre- and postinjection rectal temperatures in mice, mean \pm SEM, $N = 6$. ^c Behavioral rating score in dog static-ataxia test; number of dogs in parentheses.

fectively depressed spontaneous activity (ED₅₀, 95% confidence limits, of 4.2, 1.5–11 mg/kg) as well as rectal temperature. However, this analogue failed to produce behavioral effects in dogs at 0.5 mg/kg, a dose of Δ^9 -THC that is very effective.

In summary, addition of various substituents at position 10 alters CBD's pharmacological profile. Additions of *N*-ethyl, *N*-methyl-*N*-propargyl, and morpholino groups increase the effects of CBD on spontaneous activity more so than those on rectal temperature. On the other hand, the morpholino analogue affected rectal temperature to a greater extent. The highly toxic nature of 10-*N*-ethylcannabidiol (10) has not been observed in other cannabinoids or their analogues. Selected substitutions at position 10 resulted in analogues that were partially effective in blocking Δ^9 -THC antinociceptive activity. In-

Scheme I



corporation of a seven-membered oxepin in the Δ^9 -THC structure eliminated cannabinoid activity although substitution of the pentyl side chain with a 1,2-dimethylheptyl in the oxepin resulted in CNS depression in mice.

Experimental Section

The infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrophotometer and the NMR spectra were measured on a Varian T-60 spectrometer with tetramethylsilane as an internal standard. Elemental analysis was performed by Atlantic Microlab, Inc., Atlanta, GA. Mass spectra were obtained from the Mass Spectrometry Facility, Cornell University, Ithaca, NY. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within $\pm 0.4\%$ of the theoretical values.

10-Morpholinocannabidiol Diacetate (4). To a solution of 10-bromocannabidiol diacetate (3; 384 mg, 0.80 mmol) in 5 mL of Me₂SO was added morpholine (175 mg, 2.0 mmol). The solution was stirred for 16 h at room temperature, after which it was diluted with 150 mL of ether. The solution was washed with water, dried (Na₂SO₄), and evaporated to give a yellow oil. It was purified by column chromatography (silica gel, 50% ether/hexane) to afford 4 as a clear oil (180 mg, 46% yield); NMR (CDCl₃) δ 0.86 (t, 3 H, ω -CH₃), 1.65 (s, 3 H, H-7), 2.18 (s, 6 H, OAc), 2.53 (m, 4 H, N-CH₂), 3.53 (t, 4 H, O-CH₂), 4.90 (m, 2 H, H-9), 5.17 (s, 1 H, H-2), 6.70 (s, 2 H, Ar H); IR ν_{\max} (CDCl₃) 1770 cm⁻¹ (OAc). Anal. (C₂₉H₄₁NO₅) C, H, N.

10-(Diisopropylamino)cannabidiol Diacetate (5). With use of the same procedure as described for 4, treatment of 3 (600 mg, 1.25 mmol) with diisopropylamine (300 mg, 2.96 mmol) followed by purification by column chromatography (50% ether/hexane) gave 5 as a clear oil (450 mg; 72%); NMR (CDCl₃) δ 0.78 and 0.86 (d, J = 7 Hz, 6 H, NCH(CH₃)₂), 1.66 (s, 3 H, H-7), 2.20 (s, 6 H, OAc), 2.70 (m, 6 H), 4.90 (m, 2 H, H-9), 5.20 (s, 1 H, H-2), 6.70 (s, 2 H, Ar H); IR ν_{\max} (CDCl₃) 1775 cm⁻¹ (OAc). Anal. (C₃₁H₄₇NO₄) C, H, N.

10-(Methylpropargylamino)cannabidiol Diacetate (6). With use of the same procedure as described for 4, treatment of 3 (670 mg, 1.4 mmol) with N-methylpropargylamine (400 mg, 5.78 mmol) followed by column chromatography (20% EtOAc/hexane) furnished 6 as a clear oil (460 mg; 71%); NMR (CDCl₃) δ 0.88 (t, 3 H, ω -CH₃), 1.66 (s, 3 H, H-7), 2.06 (s, 3 H, NCH₃), 2.20 (s, 6 H, OAc), 3.06 (d, J = 2.5 Hz, 2 H, NCH₂), 4.86 (m, 2 H, H-9), 5.06 (s, 1 H, H-2), 6.66 (s, 2 H, Ar H); IR ν_{\max} (CDCl₃) 1775 cm⁻¹

(OAc). Anal. (C₂₉H₃₉NO₄) C, H, N.

10-Aminocannabidiol (9). To a solution of 3 (112 mg, 0.235 mmol) in 0.5 mL of Me₂SO was added sodium azide (17 mg, 0.25 mmol) and the mixture was stirred for 3 h at room temperature. It was diluted with ether and the solution was washed with water, dried (Na₂SO₄), and evaporated to give the azide 7 as a colorless oil (90 mg; 87% yield); IR ν_{\max} (CDCl₃) 2140 (azide), 1760 (OAc) cm⁻¹.

Without further purification, the azide 7 was reduced with LiAlH₄. A solution of 7 (1.0 g, 2.275 mmol) in 25 mL of ether was added dropwise to a cold (0 °C) suspension of LiAlH₄ (500 mg, 13.1 mmol) in 50 mL of ether. The mixture was refluxed for 5 h, cooled, and allowed to stand at room temperature for 16 h. After quenching (H₂O), the mixture was filtered, and the solvent was evaporated to give the amine 9 as an oil (0.71 g; 95%), homogeneous by TLC (10% MeOH/CHCl₃ containing 0.1% NH₄OH, R_f 0.32); NMR (CDCl₃) δ 0.86 (t, 3 H, ω -CH₃), 1.76 (s, 3 H, H-7), 3.30 (br s, 2 H, H-10), 3.96 (br d, 1 H, H-3), 4.70 (m, 2 H, H-9), 5.60 (br s, 1 H, H-2), 6.23 (s, 2 H, Ar H), 4.95 (4 H, exchangeable with D₂O); M⁺ calcd for C₂₁H₃₁NO₂ 329.2355, found 329.2341.

10-(Ethylamino)cannabidiol (10). To a stirring solution of CrCl₂ (250 mg, 2.03 mmol) in 12 mL of H₂O/acetone mixture (1:3) was added a solution of the azido compound 7 (300 mg, 0.682 mmol) in 3 mL of acetone. After the mixture was stirred for 0.5 h, it was poured into saturated Na₂CO₃ solution and extracted with ether (3 \times 30 mL). The combined organic extracts were washed with water, dried (Na₂SO₄), and evaporated to give a green, viscous oil. It was filtered through silica gel with 20% methanol in chloroform to yield a colorless oil (230 mg, 81%), homogeneous by TLC (10% MeOH/CHCl₃, R_f 0.6), which was assigned structure 8; NMR (CDCl₃) δ 0.86 (t, 3 H, ω -CH₃), 1.73 (s, 3 H, H-7), 1.83 (s, 3 H, NAc), 2.20 (s, 3 H, OAc), 3.63 (br s, 2 H, H-10), 4.83 (m, 2 H, H-9), 5.90 (s, 1 H, H-2), 6.38 (d, J = 2.5 Hz, 1 H, Ar H), 6.58 (d, J = 2.5 Hz, 1 H, Ar H), 6.73 (s, 1 H, OH); IR ν_{\max} (CDCl₃) 3400 (OH), 1740 (OAc), 1650 (amide) cm⁻¹; M⁺ calcd for C₂₅H₃₅NO₄ 413.2566, found 413.2556.

A solution of the amide 8 (200 mg, 0.48 mmol) in 10 mL of ether was added dropwise to a suspension of LiAlH₄ (120 mg, 3.15 mmol) in 15 mL of ether at 0 °C. After reflux and workup as in the case of 9, a reddish oil was obtained, which was purified by chromatography (silica gel; 10% MeOH/CHCl₃ containing 0.1% NH₄OH). Compound 10 was obtained as a colorless oil (120 mg; 70%), homogeneous by TLC (10% MeOH/CHCl₃ containing 0.1% NH₄OH, R_f 0.32); NMR (CDCl₃) δ 0.86 (t, 3 H, ω -CH₃), 1.76 (s, 3 H, H-7), 3.16 (s, 2 H, H-10), 4.80 (m, 2 H, H-9), 5.16 (s, 2 H, exchangeable with D₂O), 5.60 (s, 1 H, H-2), 6.30 (s, 2 H, Ar H); IR ν_{\max} (CDCl₃) 3450 (OH, NH) cm⁻¹; M⁺ calcd for C₂₅H₃₅NO₂ 357.2668, found 357.2668.

10-[(4-Aminobutyl)amino]cannabidiol (13). A solution of 9 (100 mg, 0.30 mmol) in 5 mL of CH₂Cl₂ was added to a mixture of *t*-Boc-GABA (70 mg, 0.344 mmol) and dicyclohexylcarbodiimide (DCC, 90 mg, 0.437 mmol) in 15 mL of CH₂Cl₂ and the mixture was stirred for 3 h. The excess DCC was decomposed by the addition of 0.5 mL of acetic acid. The urea was filtered off and the filtrate was concentrated. The residue was then diluted with ether, washed with water, dried (Na₂SO₄), and evaporated to give a red oil (142 mg). The oil was dissolved in cold (0 °C) CH₂Cl₂ (30 mL), acidified with gaseous HCl, and stirred for 2 h. The excess HCl was removed by washing with H₂O followed by saturated NaHCO₃ solution; the solution was dried (Na₂SO₄), concentrated, and chromatographed on silica gel with use of 1.5% NH₄OH in MeOH/CHCl₃ (1:6) as eluant to give 13 as an oil (75 mg, 60%), homogeneous by TLC (20% MeOH/CHCl₃ containing 2.0% NH₄OH, R_f 0.27); NMR (CDCl₃) δ 0.91 (t, 3 H, ω -CH₃), 1.70 (s, 3 H, H-7), 3.40 (s, 1 H, H-3), 4.20 (br s, 2 H, H-10), 4.95 (br m, 4 H, H-9, 2 H exchangeable with D₂O), 5.22 (br s, 1 H, H-2), 6.2 and 6.28 (d, J = 2.5 Hz, Ar H); IR ν_{\max} (CDCl₃) 3350 (OH, NH), 1658 (amide) cm⁻¹; M⁺ calcd for C₂₅H₃₈N₂O₃ 414.2892, found 414.2882.

The oxepin 14a was synthesized from 3¹¹ as described earlier.¹² The (dimethylheptyl)oxepin analogue 14b was similarly prepared. The dimethylheptyl analogue of CBD¹³ was acetylated (Ac₂O/pyridine) and brominated as described for 3.¹¹ It was then treated with Na₂CO₃ in methanol/H₂O mixture (10:1) at room temperature for 16 h to give an oil in quantitative yield; NMR (CDCl₃)

δ 0.81 (t, 3 H, ω -CH₃), 1.81 (br s, 3 H, H-12), 3.56 (m, 2 H), 4.55 (br d, $J = 4$ Hz, 2 H, H-6), 4.96 (br s, 2 H, H-13), 5.76 (br s, 1 H, H-11), 5.82 (1 H, D₂O exchangeable), 6.46 (s, 2 H, aromatic). An analytical sample was obtained by chromatography (silica gel; 10% EtOAc/hexane); mass spectra, m/e 368 (100), 270 (97). Anal. (C₂₅H₃₆O₂· $\frac{1}{2}$ H₂O) C, H.

Pharmacology. The cannabinoids (100 mg) were dissolved in 1 mL of a 1:1 mixture of emulphor (GAF Corp., Linden, NJ) and ethanol with the aid of a sonicator. Appropriate dilutions were made with the addition of emulphor/ethanol/saline (1:1:18).

Spontaneous Activity and Body Temperature in Mice. Male ICR mice (22–30 g, obtained from Flow Laboratories, Dublin, VA) were housed in the laboratory for 24 h before treatment. Rectal temperature was determined by a thermistor probe (inserted 25 mm) and a telethermometer (Yellow Springs Instrument Co., Yello Springs, OH) just prior to vehicle or drug administration. The ambient temperature of the laboratory, which varied from 21 to 24 °C from day to day, was recorded at the beginning and end of each experiment. Following the initial temperature determinations, mice were injected iv with either vehicle or drug (0.1 mL/10 g of bodyweight) and immediately placed individually in photocell activity chambers.

Interruptions of the photocell beams were recorded for 10 min. The results were expressed as percent of control (vehicle treated), and the ED₅₀'s and their confidence limits were determined by the method of Litchfield and Wilcoxon.¹⁵ The mice were removed from the activity chambers, and rectal temperatures were measured immediately and at 10-min intervals up to 60 min after drug administration. At least six mice were tested at each dose.

Antinociceptive Activity. The tail-flick procedure (time required for a mouse to flick his tail from a heat source) was carried out as previously described.¹⁶ Control reaction time was determined in each mouse, and then vehicle or drug was administered iv into the tail vein and tested 5 min later. A maximum 10-s test latency was imposed if the animals did not respond. The percent maximum possible effect was calculated as follows:

$$\% \text{ max effect} = \frac{\text{test} - \text{control reaction time}}{\text{cutoff time} - \text{control time}} \times 100$$

A minimum of six mice were tested at each dose. *Antagonistic activity* was evaluated by injecting vehicle or drug iv 10 min prior to an iv injection (opposite tail vein) of Δ^9 -THC or vehicle. Tail-flick activity was measured 5 min after the second injection. Antagonism was calculated as follows:

$$\% \text{ antagonism} = [1 - ((\% \text{ max effect for drug before } \Delta^9 - \text{THC treatment}) / (\% \text{ max effect for vehicle before } \Delta^9 - \text{THC treatment}))] \times 100$$

Overt Behavior in Dogs. Static ataxia (an effect unique to psychoactive cannabinoids) and other characteristic behavioral effects were quantitated in mongrel dogs of either sex (8–12 kg). The animals were observed for their degree of spontaneous activity, gait, tail tuck, etc., prior to drug administration. The animals were then injected iv with the cannabinoid or vehicle (1 mL/5 kg of body weight), and their behavior was rated at 5-min intervals according to the Walton¹⁷ static-ataxia scale as recently modified.¹⁸ A typical test session consisted of five dogs who received either vehicle, 0.2 mg/kg of Δ^9 -THC as a positive control, or one of three other cannabinoid treatments. Behavior was scored by three observers who were blind with regard to treatment.

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