PHARMACOLOGICAL ACTIVITY OF DELTA-9-THC METABOLITES AND ANALOGS OF CBD, DELTA-8-THC AND DELTA-9-THC*

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I. INTRODUCTION

The first systematic study of the structure-activity relationships of cannabinoids was carried out by Adams (1). Since these early investigations in the 1940's, publications from several laboratories (2-5), including our own (6-10), have appeared which describe some of the structural requirements for cannabinoid activity. By and large, the emphasis has been placed on establishing which structural modifications alter behavioral activity rather than the other pharmacological properties of the cannabinoids. One aspect has been the structural changes caused by metabolism, specifically with regard to whether or not metabolic processes activate or inactivate the naturally occurring cannabinoids (11). There is now evidence that shows that delta-9-tetrahydrocannabinol (THC) can exert behavioral effects itself without conversion to 11-hydroxy-delta-9-THC (6) or to other active metabolites (12-13). Of course, it has been confirmed that metabolites are pharmacologically active, but to what extent they contribute to the behavioral actions of THC has not been established (3,4,14-16). A second consideration of the structural requirements for cannabinoid activity (as reviewed by Razdan, this volume) is the implication that behavioral effects are

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mediated through a receptor mechanism (17). However, the search for cannabinoid receptors has been hampered by the lack of an antagonist.

The current interest in cannabinoids as potential therapeutic agents has cast a new direction on studies of structure-activity relationships. With the possibility that cannabinoids may eventually be useful in the treatment of a variety of diseases and/or their symptomatology (18,19), there is a need to develop cannabinoids that are more specific in their effects. In contrast to the early studies in which the interest was on increasing behavioral activity of cannabinoids through structural modifications, there is now a need in many cases to decrease the CNS effects and increase the therapeutic effectiveness of the cannabinoids.

We report here the pharmacological activity of a large number of newly synthesized metabolites and analogs of the cannabinoids in an effort to further characterize the structural requirements for behavioral activity as well as to attempt to separate other pharmacological effects from the behavioral effects. These compounds were evaluated for their ability to alter spontaneous activity and body temperature in mice, to block convulsions in mice and to produce static ataxia in dogs.

II. METHODS

A. Synthesis of Cannabinoids

3'-Hydroxy- and (+/-)-3',11-dihydroxy-delta-9-THC were synthesized as described previously (16). The synthesis of the remaining analogs will be described elsewhere. All drugs were prepared for pharmacological testing by dissolving 100 mg 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).

B. Spontaneous Activity and Body Temperature in Mice

In order to conserve a limited supply of drug, rectal temperature and spontaneous activity were recorded in the same animal. Male ICR mice (22-30 g) were housed in the laboratory for 24 hr before treatment. The ambient temperature of the laboratory, which varied from 21 to 24° from day to day, was recorded at the beginning and end of each experiment. Rectal temperature was determined by a thermistor probe (inserted 25

mm) and a telethermometer (Yellow Springs Instrument Co., Yellow Springs, Ohio) just prior to vehicle or drug administration. Following the initial temperature determinations, mice were injected i.v. with either vehicle or drug (0.1 ml/10 g body weight) and immediately placed individually in photocell activity chambers. After the animals were placed in the chambers, interruptions of the photocell beams were recorded for ten minutes. The results were expressed as percent of control and the ED50's and their confidence limits were determined by the method of Litchfield and Wilcoxon (20). The mice were removed from the activity chambers and rectal temperature measured immediately and at 10 min intervals up to 60 min after drug administration. At least six mice were tested at each dose.

C. Overt Behavior in Dogs

The ability of cannabinoids to produce static ataxia (an effect unique to psychoactive cannabinoids) and other characteristic behavioral effects described by Walton et al. (21) was examined in mongrel dogs of either sex (8-12 kg). Prior to drug administration, the animals were observed for their degree of spontaneous activity, gait, tail-tuck, etc. The animals were then injected i.v. with the drug or vehicle (1 ml per 5 kg body weight) and observed for the occurrence of the signs described in Table I and rated according to the scale. Most of the signs were present for any given score. The animals were rated at 5 min intervals by three observers who were unaware of the drug treatment. The maximum scores (which usually occurred at 30 min) were averaged for each dog. A typical test session consisted of five animals that received either vehicle, 0.2 mg/kg of THC, or one of three other cannabinoid treatments.

D. Anticonvulsant Activity

For anticonvulsant activity against electroshock, mice were treated with vehicle or test drug i.v. 10 min prior to an electrical stimulus (60 Hz, 400 V) administered through ear clips. The number of animals exhibiting the maximal seizure (hind-limb extension) and the number of deaths were recorded for each group (10 mice per group). For protection against pentylenetetrazol-induced seizures, the mice were pretreated with the vehicle or test drug either 10 min (i.v.) or 30 min (i.p.) before i.p. administraton of 75 mg/kg of metrazol (Knoll Pharmaceutical Company, Whippany, N. J.). The number of animals exhibiting clonic and tonic convulsions and the

TABLE I. Quantification of Cannabinoid Behavioral Effects in Dogs

Score	CNS Depression[a]	Static Ataxia[b]	Prancing	Hyperreflexia[c]	Tail-Tucked
0					
1	+	3-5 min	-	-	-
2	+	2-3 min	+/-	+/-	+/-
3	+	1-2 min	+	+	+
4	++	< 1 min	+	++	+
5	++	30 sec	+	++	+
6	+++	Prostrate	N/A	++	+

[a]+slight decrease in spontaneous activity, ++moderate depression, +++severe depression and cannot be aroused.

[b]Animal sways forward and backward and/or side to side after standing in one position for the indicated time.

[c]Exaggerated reflex to an object thrust at their face. -absent, +slight, ++severe.

number of deaths per group were recorded. The results from both tests were expressed as percent of vehicle-treated mice.

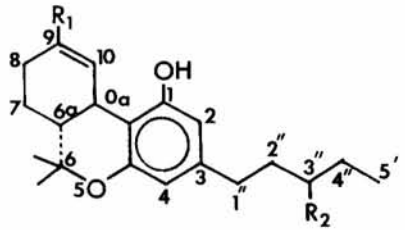
II. RESULTS AND DISCUSSION

A. Metabolites of THC

There has been considerable interest in the side-chain hydroxylated metabolites of delta-8- and delta-9-THC since it has been demonstrated that they are formed in a number of species (5,22,23), including humans (24). The cannabinoids may be hydroxylated only in the side chain or di- and trihydroxylated in the side chain and at positions 11 and/or 8. The monohydroxylated metabolites (side chain) in the delta-8-THC series have been shown to exhibit cannabinoid activity (5,25) but those in the delta-9-THC series have not been investigated. 3'-Hydroxy-delta-9-THC was synthesized and tested for cannabinoid activity. The results in Table II show that this metabolite has a pharmacological profile similar to that of delta-9-THC. The major difference between the two is 3'-OH-delta-9-THC is almost 3 times more potent that delta-9-THC in all three tests. These results are consistent with those reported for the delta-8-THC series (5,15). To our knowledge, the metabolites hydroxylated both in the side chain and at position 11 have not been tested for cannabinoid activity. Indeed, they might be expected to have little activity based upon the relative inactivity of compounds such as 8,11-diOH-delta-9-THC. Therefore, (±)-3',11-diOH-delta-9-THC was synthesized and tested for cannabinoid activity (Table II). The dihydroxylated metabolite had cannabinoid activity in all three tests but was approximately three times less potent that delta-9-THC. Hydroxylation at either position 3' or 11 enhances THC activity 3 or 4 (Table VII) fold, respectively, but hydroxylation at both positions decreases activity. This attenuation in potency may well be due to the increased polarity with a resultant diminuation in brain penetrability.

Clearly, these two metabolites have the potential of contributing to the behavioral pharmacology of THC. The biodisposition studies of cannabinoids carried out thus far have not revealed large quantitites of metabolites in brain so that it would appear that these metabolites play a relatively minor role in the expression of cannabinoid activity. Few, if any, studies have been conducted with the sole intention of measuring 3'-OH- and 3',11-diOH-delta-9-THC in brain during periods of delta-9-THC induced behavioral activity, thereby making it difficult to assess their true contributions. However, our

TABLE II. Pharmacological Activity of Delta-9-THC and Metabolites



COMPOUND	NAME	R1	R2	SPONTANEOUS[A] ACTIVITY	HYPOTHERMIA DOSE	HYPOTHERMIA Δ^0 C	STATIC ATAXIA DOSE	STATIC ATAXIA SCORE	(N)
	Δ^9-THC	CH_3	H	3.2 (1.7 - 6.2)	2.5	3.4	0.1	1	(3)
					5.0	4.4	0.2	3	(4)
					7.5	4.6	0.4	4	(2)
					10.0	5.0			
1	3'-OH-Δ^9-THC	H	OH	0.8 (0.4 - 1.5)	0.1	1.2	0.05	1	(2)
					0.3	2.1	0.1	2	(2)
					1.0	3.6	0.2	5	(2)
					3.0	4.9			
					10.0	8.4			
2	3',11-DiOH-Δ^9-THC	OH	OH	8.7 (3.6 - 20.8)	3.0	1.3	0.2	1	(1)
					6.0	1.1	0.5	3	(2)
					10.0	3.9			
					30.0	5.2			

[A] ED_{50} (C.L.) mg/kg

data suggest that if they do contribute in a significant way, it would be to the overall pharmacological effect rather than to a specific THC action.

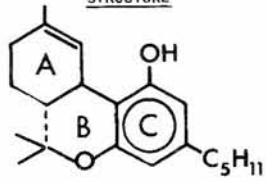
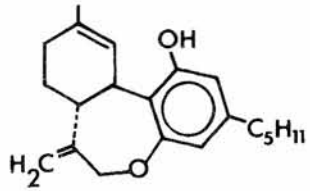
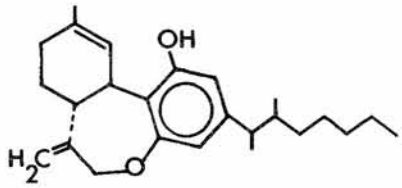
B. Oxepine Derivatives of THC

It has generally been assumed that the intact benzopyran system is necessary for behavioral activity because the opening of the pyran ring (to form CBD, for example) leads to complete loss of behavioral activity. In order to investigate the importance of the B ring (Table III) further, two novel analogs of THC were prepared in which the pyran was expanded to a seven-membered ring with an exo-cyclic methylene rather than gem di-methyls (Table III). These two alterations in the pyran ring essentially elimated cannabinoid activity in all three tests as demonstrated by compound 3. It may be that expansion of the pyran ring results in sufficient realignment of the two remaining rings to cause loss of activity. Interestingly, when the pentyl side chain of 3 was replaced with a 1,2-dimethylheptyl side chain (4), effects on spontaneous activity and body temperature were restored almostcompletely but the compound was at least 5 times less active that THC in the dog static ataxia test. This separation in the composite effects of THC is difficult to attribute to any one of the three structural changes that were made. However, it is well known that branching the side chain enhances cannabinoid activity as first shown by Adams (1). It may be that the structural requirements for altering spontaneous activity and hypothermic effects are less strict than those for the dog static ataxia test which may account for the fact that the dimethylheptyl side chain enhances activity in mice more readily than in the static ataxia test in dogs.

C. Substitution at the 11 Position

The discovery that the 11-hydroxy metabolite of THC exhibited potent cannabinoid activity (25) served to demonstrate the importance of the 11 position. Several structural modifications of this position have been reported previously. Removal of the 11 position for THC does not abolish behavioral activity, but merely reduces it 50-60% (6). On the other hand, when the double bond is delta-9,11 rather than delta-9,10, the behavioral activity is reduced dramatically (26). The addition of a methyl (6) or methoxy (9) group to position 11 also reduces, but does not eliminate, behavioral activity. A series of delta-8-THC analogs were recently synthesized in which aromatic and aliphatic hydrocarbon groups were substi-

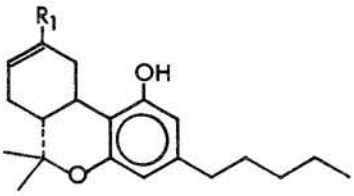
TABLE III. Pharmacological Activity of Delta-9-THC Analogs

COMPOUND	STRUCTURE	SPONTANEOUS[A] ACTIVITY	HYPOTHERMIA DOSE	HYPOTHERMIA Δ°C	STATIC ATAXIA DOSE	STATIC ATAXIA SCORE (N)
Δ^9-THC		3.2 (1.7 - 6.2)	2.5	3.4	0.1	1 (3)
			5.0	4.4	0.2	3 (4)
			7.5	4.6	0.4	4 (2)
			10.0	5.0		
3		41% at 100 mg/kg	30	0	2.0	0 (2)
			100	0	5.0	0 (1)
4		4.2 (1.5 - 11)	5	0.3	0.5	0 (3)
			10	4.5		
			30	5.3		

[A] ED_{50} (C.L.) mg/kg

tuted for the 11 methyl. The effect of these analogs on spontaneous activity and body temperature of mice is depicted in Table IV. All of these compounds were 4-5 times less effective than delta-8-THC in producing hypoactivity with the exception of the phenyl derivative (5) which was almost 10 times less potent. The hypothermic effect was also reduced in all of these compounds, with the exception of the butyl derivative (8). The two exceptions provided by the phenyl and butyl substitutions are probably anomalies rather than unique structural requirements for specific cannabinoid actions. From these data, it appears that optimum activity occurs when a methyl group is at position 9.

TABLE IV. Pharmacological Activity of Delta-8-THC Analogs



COMPOUND	NAME	R_1	SPONTANEOUS[A] ACTIVITY	HYPOTHERMIA[B] DOSE	HYPOTHERMIA[B] Δ°C
	Δ^8-THC	CH_3	7.1 (4.5-11.2)	5	0.2
				10	0.7
				20	2.7
5	9-nor-9-Phenyl-Δ^8-THC	C_6H_5-	67 (44-102)	30	1.3
				100	1.9
6	9-nor-9-Benzyl-Δ^8-THC	$C_6H_5CH_2$-	32 (10-101)	30	0.7
				60	1.2
7	9-nor-9-Isopropyl-Δ^8-THC	$(CH_3)_2CH$-	26 (11-60)	30	0.4
				100	0.9
8	9-nor-9-(n)Butyl-Δ^8-THC	$(CH_3)(CH_2)_3$-	32 (17-61)	30	4.3
				60	5.0
9	9-nor-9-(1-Hydroxy)-propyl-Δ^8-THC	$CH_3CH_2C(OH)H$-	39 (24-61)	30	0
				60	0.9
10	11-N-Methyl-Δ^8-THC	CH_3NCH_2-	11 (6-20)	5	0
				10	0
				20	0.4

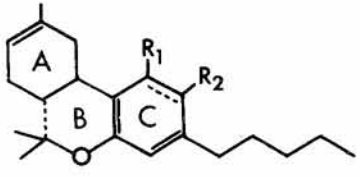
[A] ED50 (C.L.) mg/kg

[B] Dose in mg/kg

D. Substitutions on the C-ring

Alterations in the substituents on the C ring have generally resulted in a marked reduction in behavioral activity. Edery et al. (2) found that addition of methyl, ethyl, carbomethoxy or acetyl groups at positions 2 or 4 attenuated behavioral effects in rhesus monkeys. Also, we have shown that interposing the phenolic hydroxyl with the pentyl side chain eliminated behavioral activity but did not alter the cardiovascular effects (8). An analog of delta-8-THC in which a hydroxyl group was added at position 2 was recently synthesized by Razdan (synthesis to be published elsewhere) and the structure is shown in Table V. 2-Hydroxy-delta-8-THC (12) was almost as active as delta-8-THC in producing hypoactivity but was inactive in decreasing body temperature. In contrast, 11 (the O-methyl derivative of 12) was less effective in producing both hypoactivity and hypothermia. It will be interesting to see if 2-OH-delta-8-THC produces static ataxia in dogs. Hydroxylation at the 2 position may well attenuate cannabinoid behavioral activity without altering its general CNS depres-

TABLE V. Pharmacological Activity of Delta-8-THC Analogs



COMPOUND	NAME	R_1	R_2	SPONTANEOUS[A] ACTIVITY	HYPOTHERMIA[B] DOSE	HYPOTHERMIA[B] $\Delta^{\circ}C$
	Δ^8-THC	OH	H	7.1 (4.5-11.2)	5	0.2
					10	0.7
					20	2.7
11	2-OH-O-METHYL-Δ^8-THC	OCH_3	OH	40 (10-163)	30	0.4
					100	2.4
12	2-OH-Δ^8-THC	OH	OH	10 (3-33)	3	0.4
					10	0.5
					30	0.2
13	Δ^8-THC-1,2-BISQUINONE	=O	=O	12 (5-32)	3	0.4
					10	0.7
					20	1.9
					30	2.2

sant properties. The delta-8-THC-1,2-bisquinone (13) was also synthesized and tested for activity. Suprisingly, the bisquinone was only slightly less potent that delta-8-THC in its effects on spontaneous activity and hypothermia. Edery et al. (2) have reported that delta-8-THC-1,4-bisquinone was at least 100 times less active that delta-8-THC in producing behavioral effects in monkeys. It may be that the 1,2-bisquinone will also be devoid of behavioral effects in the dog.

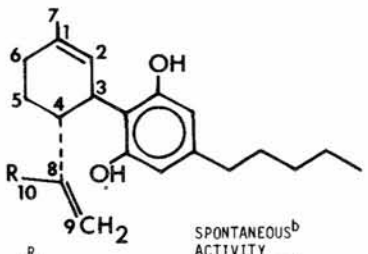
E. Analogs of CBD

The anticonvulsant activity of CBD has been studied extensively and antiseizure activity has been observed, albeit somewhat weak, in a variety of tests (see Karler and Turkanis ref. 27, for additional discussion). Recently, Razdan synthesized a gamma-aminobutyric acid (GABA) derivative of CBD (14, Table VI) in an effort to increase the anticonvulsant activity of CBD (the synthesis will be described elsewhere). In addition, an N-ethylamine derivative (15, Table VI) was also prepared. These analogs were compared to CBD for their ability to alter spontaneous activity, body temperature and produce lethality as well as anticonvulsant activity. The results in Table VI show that CBD is capable of producing hypoactivity and hypothermia at high doses, although it is considerably less potent than delta-9-THC. The addition of a GABA functional group increased the effect on spontaneous activity slightly and body temperature to a somewhat greater degree. The striking difference between CBD and the GABA analog was the greater lethality of the latter. In addition, GABA, a known amino acid inhibitory neurotransmitter, waspractically devoid of any effects in doses up to 400 mg/kg when given i.v. It may be that the analog serves as a vehicle for allowing GABA to penetrate brain much in the same way that chlorination of GABA (to form bacloflen) increases its brain penetrability (28). One might also expect the GABA analog to effect motor coordination, which it did not do in doses up to 30 mg/kg as measured in the inverted-screen test as described previously (29).

When an N-ethylamine group was added at position 10 (15), the effect on spontaneous activity was enhanced 10 fold (compared to CBD) and was nearly equivalent to that produced by THC. In addition, the lethality was much greater than that of CBD. A dose of 6 mg/kg (i.v.) produced 88% lethality within 5 min of the injection. A reliable LD50 could not be determined due to a very steep dose-response curve.

The anticonvulsant activity of compounds 14 and 15 were compared to that of CBD in mice treated with either electroshock or pentylenetetrazol. CBD at doses of 65 mg/kg i.v.

TABLE VI. Pharmacological Activity of Cannabidiol (CBD) Analogs[a]



COMPOUND	NAME	R	SPONTANEOUS[b] ACTIVITY	HYPOTHERMIA[c] DOSE	HYPOTHERMIA[c] Δ^0 C	LETHALITY[d]
	CBD	CH_3-	40 (25 -65)	50 75 100	0.5 2.2 2.6	> 100
14	10-(3-Aminobutyryl-amido)-CBD	$NH_2(CH_2)_3CONHCH_2$-	30 (23 - 38)	25 30 35	1.3 2.0 2.1	41 (37 - 47)
15	10-(N-Ethylamino)-CBD	$CH_3CH_2NHCH_2$-	4 (1.4 - 11.6)	2.5 5.0	0 1.2	<6.0
	Gamma-Aminobutyric acid	---	f	400	1.4	ND[e]

[a]Monoterpenoid numbering system due to lack of a pyran ring in CBD.

[b]ED_{50} (C.L.) mg/kg

[c]Dose of mg/kg

[d]LD_{50} (C.L.) mg/kg

[e]Not determined

[f]13% effect at 400 mg/kg

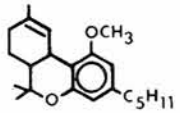
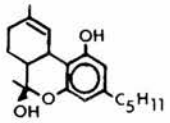
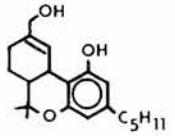
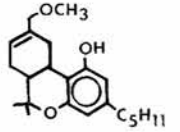
completely blocked tonic seizures and death induced by electroshock. Compounds 14 and 15 were inactive at doses up to 25 and 5 mg/kg, respectively. In the pentylenetetrazol-treated mice, CBD (45 mg/kg, i.v.) did not block clonic seizures but did block tonic seizures (72% of vehicle-treated animals) and lethality (38%). Compound 14 produced a 31 and 21% blockade of tonic seizures and lethality, respectively, at a dose of 25 mg/kg, i.v. Higher doses could not be given due to its lethality. Compound 15 was without effect on either pentylenetetrazol-induced tonic seizures or lethality at a dose of 5 mg/kg, the highest dose permissible without producing death. Compound 15 was also given i.p. at a dose of 25 mg/kg 30 min prior to penylenetetrazol and it only produced a 24% blockade of pentylenetetrazol-induced tonic seizures and did not prevent deaths. The addition of an N-ethyl or a GABA functional group does not appear to impart greater anticonvulsant activity to CBD.

F. Evaluation of Miscellaneous THC and Cannabinol (CBN) Derivatives in the Dog Static Ataxia Test

The behavioral activity of a variety of analogs is presented in Table VII. Methylation of the phenolic hydroxyl group (16) of THC reduced behavioral activity almost 25 fold, whereas methylation of 11-hydroxy-delta-8-THC produced a compound (19) that was about three fold less potent than delta-8-THC. These reductions in activity are consistent with the data presented in Table V in which methylation of the phenolic hydroxyl in 2-OH-delta-8-THC attenuated its effect on spontaneous activity almost 4-fold.

In our earlier discussion of the oxepine derivatives with the exo methylene unit (3), we stressed that possible realignment of the molecule due to expansion of the pyran ring might have resulted in the loss of activity. It may also be that replacement of the gem dimethyls with a methylene unit reduces activity. Loev et al. (30) have shown that a ketone at position 6 reduces cannabinoid activity. When an hydroxyl group was substituted for one of the gem dimethyls, behavioral activity was not altered. Replacement of the dimethyl groups with a carbonyl to form analog 23 resulted in loss of activity. This abolition of activity could have been due to any one of the structural changes in compound 23. However, compound 22 differs from 23 only in that it has the 6,6-dimethyls rather than the ketone and it exhibits weak cannabinoid activity. Therefore, these results, taken together, suggest that both gem dimethyls are not necessary for behavioral activity but certain structural modifications at position 6 can result inaltered behavioral activity. The position of the double

TABLE VII. Evaluation of Other Cannabinoids in the Dog Static Ataxia Test At Least Three Doses of Each Compound was Tested, Usually with Two or More Dogs/Dose

COMPOUND	NAME	STRUCTURE	ACTIVITY RELATIVE TO Δ^9-THC	COMMENTS
	Δ^9-THC		1.0	
	Δ^8-THC		0.4	
16	O-Methyl-Δ^9-THC		0.04	
17	6-nor-6α-OH-Δ^9-THC		1.0	
18	11-OH-Δ^9-THC		4.0	a
19	11-Methoxy-Δ^8-THC		0.1	[a]0.3 compared to Δ^8-THC

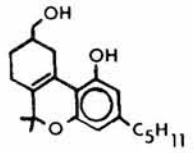
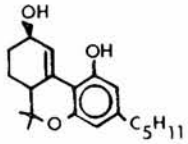
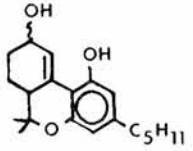
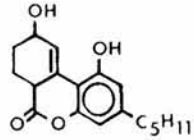
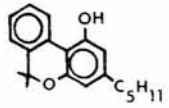
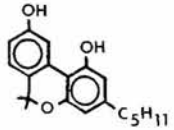
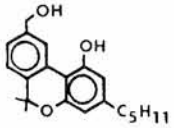
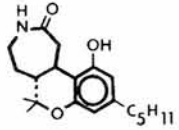
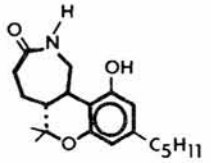
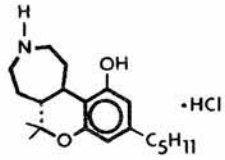
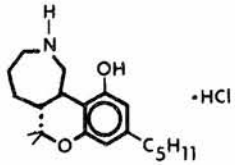
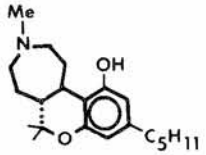
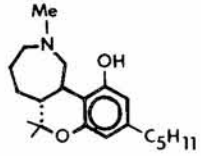
COMPOUND	NAME	STRUCTURE	ACTIVITY RELATIVE TO Δ^9-THC	COMMENTS
20	(±)-11-OH-Δ^{6a-10a}-THC		< 1.0	Difficult to assess due to rapid onset of effects and short duration.
21	9-nor-9β-OH-Δ^{10}-THC		0.4	b
22	9-nor-9-OH-Δ^{10}-THC		0.2	
23	6,6,9-tri-nor-6-oxo-9-OH-Δ^{10}-THC			Causes marked sedation at 2.0 mg/kg, otherwise not cannabinoid.

TABLE VII. (Continued)

COMPOUND	NAME	STRUCTURE	ACTIVITY RELATIVE TO Δ^9-THC	COMMENTS
	CBN		~ 0.2	Severe CNS depression after 5.0 mgkg
24	9-nor-CBN		0.2	
25	9-nor-9-OH-CBN			[b]Not cannabinoid severe CNS depression after 10 mg/kg
26	11-OH-CBN		~ 0.5	Somewhat variable response. All of the typical cannabinc signs were seen after 1.0 mg/kg before the animal became prostrate.
27			0.5	
28				Not cannabinoid up to 8 mg/kg

COMPOUND	NAME	STRUCTURE	ACTIVITY RELATIVE TO Δ^9-THC	COMMENTS
29				Marked CNS depression at 8 mg/kg, few other cannabinoid signs
30				Marked CNS depression at 8 mg/kg, few other cannabinoid signs
31			0.1	
32				Slight CNS depression at 8 mg/kg, few other signs

[a] Reported previously by Wilson-et al. (9)

[b] Reported previously by Wilson et al. (33)

bond in delta-9-THC appears to be of considerable importance since delta-6a,10a-THC is less active than delta-9-THC (2,30). The activity of (+/-)-11-OH-delta-6a,10a-THC (20) was somewhat less than that of delta-9-THC but at least 4 times less than that of 11-OH-delta-9-THC (18). Behavioral activity was also decreased when the double bond was in position 10 as shown in 21 and 22. Analog 23 was inactive but several important changes were made in this structure.

There has also been some interest in CBN since it has been shown to possess weak cannabinoid effects in humans (31). Removal of the 11-methyl (24) did not diminish CBN's behavioral activity (Table VII). Actually, its potency is somewhat comparable to that of 11-nor-delta-9-THC (6). When the11-methyl position was replaced with a hydroxyl group (25), cannabinoid behavioral activity was eliminated completely. This is a contradistinction to11-nor-9-beta-OH-hexahydrocannabinol, which is much more active than THC (7). As in THC, 11-hydroxylation of CBN (26) results in increased behavioral activity (Table VII). 11-Hydroxy-CBN, a known metabolite of CBN (32), is approximately one-half as active as delta-9-THC.

The last group of compounds, synthesized by Drs. Rice and Iorio of the National Institutes of Health, are benzopyrano-azepines, which for the most part are considerably less active that THC. The most active of these derivatives was azepine-10-one (27), which had approximately half the activity of THC. The azepine-9-one (28) and the two unsubstituted azepines (29 and 30) were completely devoid of cannabinoid effects in the dog static ataxia test, with the exception of CNS depression at high doses. The N-methyl azepine derivatives (31 and 32) exhibited little, if any, effects in this test.

III. SUMMARY

The results presented herein demonstrate several structural changes that either attenuate or enhance cannabinoid potency. The 3'-hydroxy metabolite was more potent than THC, whereas dihyroxylation at positions 3' and 11 diminished, but did not eliminate, activity. In addition, 11-hydroxylation of CBN increased cannabinoid behavioral potency almost two and one-half times.

Alterations in the A ring and its substituents also produced dramatic changes in cannabinoid potency. Substitution of bulky hydrocarbon groups at position 9 reduced effects on spontaneous activity and body temperature, in general. The addition of an N-methyl substituent at position 11 did not alter spontaneous activity. Also, changes in the position of the double bond greatly reduced behavioral potency. When the

A ring was changed to a heterocyclic 7-membered ring (benzopyranoazepine), cannabinoid effects were attenuated.

Changes in the pyran (B) ring all served to reduce cannabinoid activity in one way or another. Expansion of the pyran ring to an oxepine, replacement of the gem dimethyl groups with a ketone or methylene resulted in diminution of cannabinoid effects.

Several changes were made in the phenolic ring (C), such as methylation of the phenolic hydorxyl (reduces activity), addition of an hydroxyl group at position 2 (no loss in producing hypoactivity), and formation of a 1,2-bisquinone (no loss in producing hypoactivity).

Selected structural modifications appeared to alter some of the cannabinoid effects more than others. Compounds with increased ability to produce hypoactivity relative to hypothermia included the oxepine with the DMHP side chain (4), 11-N-methylamino-delta-8-THC (10), 2-OH-delta-8-THC (12), and 10-(N-ethylamino)-CBD (15). There was only one compound tested that had a greater effect on body temperature relative to its effects on spontaneous activity and that wasll-nor-9-butyl-delta-8-THC (8). It appears that compounds that are potent in producing both hypoactivity and hypothermia are likely to produce behavioral effects as measured in the dog static ataxia test. Compounds that only diminish spontaneous activity in mice at high doses probably lack cannabinoid behavioral effects, CBD being a prime example. Also, several compounds (Table VII) produced marked sedation in dogs, yet no other signs were present. These data do show that it is possible to get some separation of cannabinoid effects. Certainly the general depressant properties were retained in some of the analogs when the other cannabinoid behavioral effects were lost.

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