

Cannabinoids. Structure-Activity Studies Related to 1,2-Dimethylheptyl Derivatives

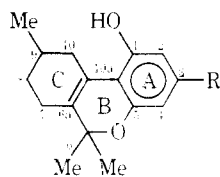
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The effect of structural modifications on the CNS potency of certain cannabinoids has been reexamined in rats. The observed structure-activity correlations differ significantly from those originally reported by Adams, Loewe, and Todd in the dog and rabbit. A variety of new types of cannabinoids are reported including Mannich condensation products, an active deshydroxy compound, reduction products, and cannabinoids with ether and olefinic side chains. Compounds of potencies equal to or greater than that of the 3-(1,2-dimethylheptyl) compound I are described. An isomer (29) in which the 1,2-dimethylheptyl side chain and the hydroxyl groups are in different positions had previously been reported to be inactive; it was now found to have marked CNS activity. The pharmacology of I is described in some detail, and several new types of activities are reported for it including antiinflammatory, gastric antisecretory, and diuretic activities.

Extensive studies of the relationship between basic structural modification of cannabinoids and neurological potency were reported in the 1940's by Adams and Loewe and coworkers^{1,2} and by Todd and coworkers³ who tested the compounds in the dog and rabbit, respectively. More recent chemistry has dealt mostly with the isolation and synthesis of the naturally occurring constituents of marijuana⁴ and their metabolism⁵ and with heteroatom-containing tetrahydrocannabinoids.⁶ Except for some recent studies on certain of the natural materials in monkeys,⁷ there has been comparatively little further work on basic structure-activity studies nor on comparative biological data.

Most of the studies of Adams, *et al.*,^{1,2} and Todd, *et al.*,³ on the effect of basic ring modifications dealt with Δ^6 ,^{10a} compounds having the C₅ (natural) or C₆ side chains (compounds IIa and IIb[†]), compounds which have a relatively low potency for production of overt effects in animals. We wished to examine the effect of structural modifications in the more potent 1,2-dimethylheptyl (DMH)[‡] series,⁸ where effects might be expected to be greater and, hence, more definitive. As our studies progressed and we discovered unexpected relative potencies, these studies were extended to include other side chains.



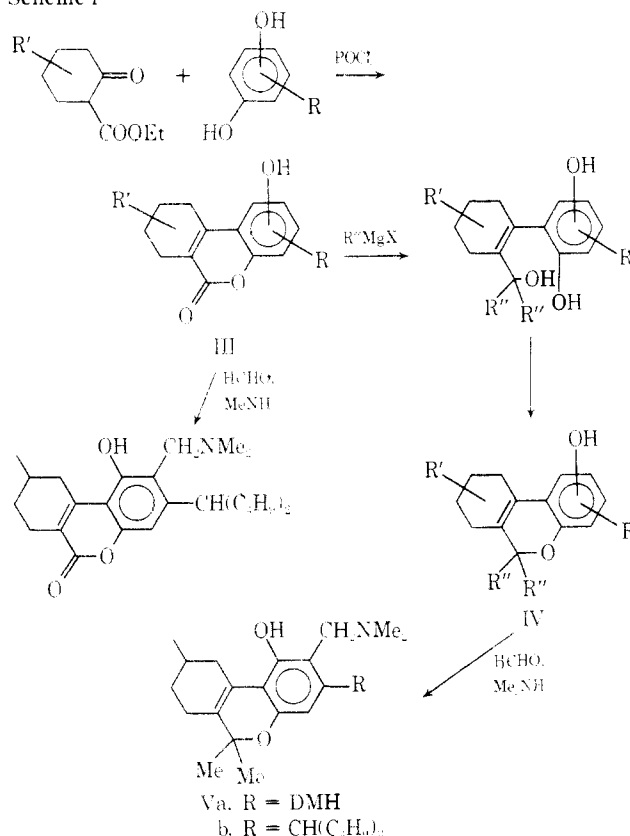
- I. R = CH(CH₂)CH(CH₂)C₂H₅; = DMH
IIa. R = *n*-C₅H₁₁
b. R = *n*-C₆H₁₃

In this paper we present a reexamination of structure-activity relationships among cannabinoids. This was done in the rat since this species, rather than the dog or rabbit, is most frequently used for studies of CNS activities and for many other pharmacological evaluations. The biological activities of one of these compounds, I, previously claimed to be the most potent cannabinoid,⁸ are also described in some detail. We now also report other compounds of equal or greater potency. We also describe a variety of new cannabinoids including Mannich condensation products, an ether, a deoxy compound, reduction products, an ether-containing side chain, and the first example of a cannabinoid with an olefinic side chain. A number of the compounds originally described by Adams,

Todd, and their coworkers have been reprepared in order to complete our structure-activity studies.

Most of the compounds were prepared by the Adams procedure¹ (Scheme I) or modification thereof. In this method, a phenol is condensed with a keto ester to give a coumarin III which is then treated with a Grignard reagent. The resulting product is then cyclized to the tetrahydrodibenzopyran IV. The other compounds were prepared by modified procedures described below.

Scheme I



The 5-(1-alkyl)resorcinol intermediates were prepared by an improved procedure employing lithium 3,5-dimethoxybenzoate. This was treated with methyl- or ethyllithium and the resulting aceto- or propiophenone was then added to the appropriate Grignard reagent giving tertiary alcohols which were transformed to the alkyl resorcinols by standard techniques. The other alkylresorcinols were prepared according to literature procedures.

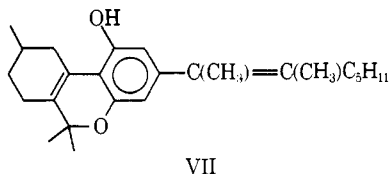
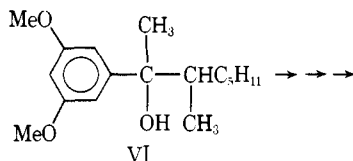
Compounds containing the 1,2-dimethylalkyl side chains possess two asymmetric centers due to this moiety and a third asymmetric center due to the alkyl group on the C ring. I, therefore, is a mixture of eight isomers.

[†] Synhexyl, Pyrahexyl, Parahexyl. Roman numerals refer to compounds in schemes, equations, and general structures; arabic numerals refer to compounds in the tables.

[‡] SKF 5390, DMH-THC.

With the exception of the work of Aaron and Ferguson,⁹ all studies on I and other branched analogs have been on the diastereoisomeric mixtures. In an attempt to minimize this isomer situation, a compound was prepared having a symmetrical dibutyl carbinyl side chain (13, Table I). This side chain was selected because, in addition to being symmetrical, it contains the natural C₅ straight chain, the α branching usually found to enhance CNS activity, and the same total number of side-chain carbon atoms as does I. The appropriate resorcinol intermediate for 13 was prepared from ethyl 3,5-dimethoxybenzoate by reaction with excess butyl Grignard reagent followed by dehydration and reduction.

Cannabinoids containing olefinic side chains have not been previously reported, so olefin-containing analogs of I were prepared. Dehydration of VI, an intermediate in the synthesis of I, gave a mixture of olefins. The ether groups were cleaved using methylmagnesium iodide and the resulting resorcinols were carried through the cannabinoid synthesis as in Scheme I, giving a mixture of the olefinic cannabinoid VII and the exo methylene isomer in a ratio of 5:1. No polymerization difficulties were encountered in the ether cleavage, POCl₃ catalyzed condensation, or subsequent steps.



The synthesis of several 3-*n*-alkoxytetrahydrocannabinols has been described and reported to produce essentially no activity in the corneal reflex test after oral administration to rabbits.¹⁰ Since branching of the alkyl side chain has such a powerful effect on enhancing potency of the 5-alkyltetrahydrocannabinols, we prepared a branched 3-alkoxycannabinoid VIII. In addition to providing structure-activity information, such compounds, if active, would greatly simplify synthetic approaches to cannabinoids of a great variety of new structures.

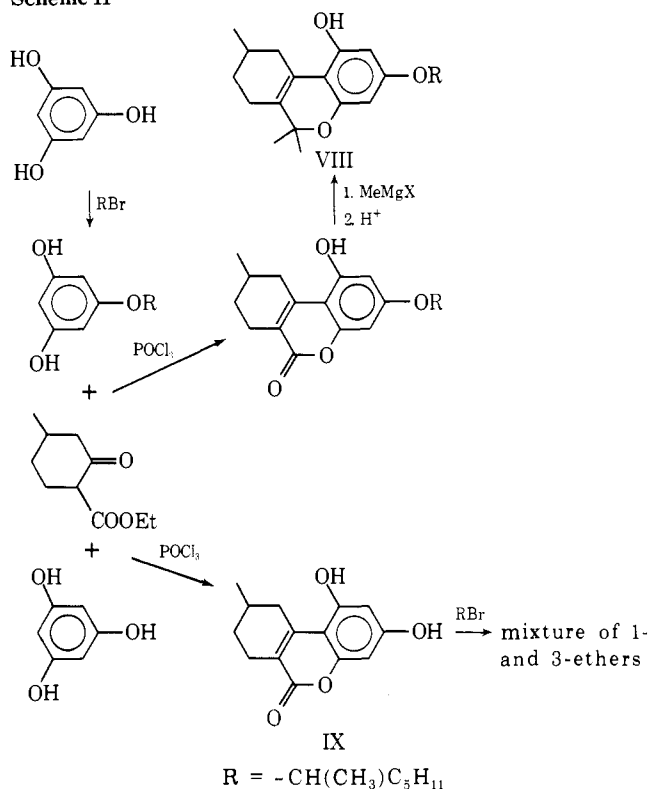
Compound VIII was prepared as shown in Scheme II. The keto ester readily condensed with phloroglucinol to give the coumarin IX. However, alkylation resulted in a mixture of the isomeric monoalkyl ethers which were difficult to separate. Alkylation of phloroglucinol first, gave a readily separable mixture of mono- and dialkyl ethers; the monoether was then carried through the reaction sequence shown giving the single product VIII.

Amine derivatives were desired for structure-activity studies and in attempts to obtain solid, water-soluble salts. Mannich condensation was successfully carried out on certain tetrahydrodibenzopyrans, I and 13 (Table I), to give Va,b and on a coumarin (III, R = CHBu₂). None of these compounds gave water-soluble salts.

The dihydro derivatives of I were prepared: the *cis* by catalytic reduction of I; the *trans*§ by catalytic reduction of the Δ^8 isomer of I.

The methyl ether of I was prepared by reaction of I with methyl sulfate and potassium *tert*-butoxide in dimethyl

Scheme II



sulfoxide. It could not be prepared by the use of diazomethane or methyl iodide in alcoholic alkali.

All but one of the intermediate coumarins were solids. The final products were, in most instances, high-boiling viscous resins. The purity of all compounds was established by tlc (silica gel), nmr, and mass spectral analysis, as well as by the usual elemental analysis; glc (SE-30) was also run on most of the compounds.

Structure-Activity Discussion. Table I lists the oral doses at which significant overt side effects are first observed in the rat and the relative potencies of the cannabinoids. The relative potencies are given with respect to the *n*-hexyl analog 2 (IIb): as standard rather than to the *n*-amyl, 1 (IIa), as done by Adams and Loewe, *et al.*,^{1,2} who tested their compounds in the dog.

Many of the structure-activity results in the rat differ markedly from those reported earlier by Adams and Loewe in the dog and by Todd in the rabbit. Thus, in the *n*-alkyl series where the greatest range of potencies was obtained, we observed *enhancement* of CNS depressant activity with longer chains rather than a marked *decrease* in activity above *n*-hexyl as previously reported.¹¹ Substitution by lower alkyl groups in the 1 position dramatically increased potency, with maximum activity seen with the 1-methylheptyl compound 5, whereas moving the substituent to the 2 position as in 8 was detrimental. The 1-ethyl side-chain compound 7 was as effective as the 1-methyl. Increasing the side-chain substitution to two alkyl groups further enhanced activity, with the maximum being the 1,2-dimethylheptyl (I, 10) as previously observed.⁸ In general, it appears that the length of the side chain from its attachment to the ring is more important than the *total number* of carbon atoms in the side chain in influencing potency.

The most potent cannabinoid tested was the 1,1-dimethylheptyl compound 12, which has a relative potency of 1000 in the rat—twice that of the 1,2-dimethylheptyl analog I (10). This is in sharp contrast with the results of

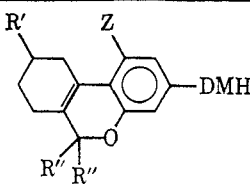
§ Kindly provided by Professor R. Mechoulam, Hebrew University, Jerusalem, Israel.

= Kindly provided by Professor Roger Adams.

Table I. Chemical and Pharmacological Properties

Compd	R	Rel CNS activity ^a		Yield, % ^d	Bp, °C (mm) ^c	Formula ^f
		Rat ^b	Dog ^e			
1 (IIa)	-C ₅ H ₁₁ - <i>n</i>	0.5	0.1	70	164 (0.2) ^g	C ₂₇ H ₃₆ O ₂
2 (IIb)	-C ₆ H ₁₃ - <i>n</i>	1 ^h	1	<i>h</i>		
3	-C ₅ H ₉ - <i>n</i>	4	0.1 ⁱ	75	160-170 (0.02) ^j	C ₂₅ H ₃₄ O ₂
4	-CH(CH ₃)C ₇ H ₁₁	20	9	60	174-178 (0.03) ^k	C ₂₇ H ₄₀ O ₂
5	-CH(CH ₃)C ₆ H ₈	100	18	81	155-180 (0.02) ^l	C ₂₄ H ₃₆ O ₂ ^m
6	-CH(CH ₃)C ₇ H ₇	50	1	75	188-190 (0.03) ⁿ	C ₂₅ H ₃₈ O ₂
7	-CH(C ₂ H ₅)C ₆ H ₁₃	100		77	208-210 (0.005)	C ₂₄ H ₃₆ O ₂
8	-CH ₂ CH(CH ₃)C ₇ H ₁₁	2		83	155-165 (0.01)	C ₂₄ H ₃₆ O ₂
9	-CH(CH ₃)CH(CH ₃)C ₄ H ₉	100	22	67	195-200 (0.3) ^o	C ₂₄ H ₃₆ O ₂
10 (I)	-DMH	500	285, 42, 2 ^p	96	192-194 (0.03) ^q	C ₂₅ H ₃₈ O ₂
11	-CH(CH ₃)CH(CH ₃)C ₆ H ₁₃	100	10	83	205-210 (0.03) ^r	C ₂₆ H ₄₀ O ₂
12	-C(CH ₃) ₂ C ₆ H ₁₃	1000	12	98	190-205 (0.03) ^s	C ₂₅ H ₃₈ O ₂
13	-CH(C ₄ H ₉) ₂	<0.6 ^t		80	212-213 (0.003)	C ₂₇ H ₄₀ O ₂
14 (VII)	-C(CH ₃)=C(CH ₃)C ₅ H ₁₁ ^u	500		72	168-170 (0.03)	C ₂₅ H ₃₆ O ₂
15 (VIII)	-OCH(CH ₃)C ₇ H ₁₁	10		63	224-228 (0.1)	C ₂₅ H ₃₄ O ₂
	R'	Rel CNS activity, ^b rat				
16	H		10	83	185-186 (0.03)	C ₂₄ H ₃₆ O ₂
17	9-Et		20	61	208-210 (0.005)	C ₂₆ H ₄₀ O ₂
18	8-Me		1	74	171-173 (0.02)	C ₂₅ H ₃₈ O ₂
19	7,9-Me ₂		50	53	188-190 (0.01)	C ₂₆ H ₄₀ O ₂ ^r
	R	Olefin				
20	-C ₅ H ₁₁ ^{vc}	Δ ⁸	5	<i>x</i>		
21	-C ₅ H ₁₁ ^v	Δ ⁹	2	<i>x</i>		
22	-DMH	Δ ⁸	100	<i>x</i>		
23	-DMH	Δ ⁹	50	<i>x</i>		
24	-DMH	Δ ^{6a, 10a} - <i>cis</i> -Dihydro	1	73	172-173 (0.03)	C ₂₅ H ₄₀ O ₂
25	-DMH	Δ ^{6a, 10a} - <i>trans</i> -Dihydro	20	<i>x</i>		
	R'	X				
26	3-DMH	1-OAc	>20	75	170-174 (0.03)	C ₂₇ H ₄₀ O ₃
27	3-DMH	1-OMe	<0.4 ^t	49	152-158 (0.03)	C ₂₆ H ₄₀ O ₂
28 (XI)	3-DMH	H	1	58	165-168 (0.03)	C ₂₅ H ₃₈ O
29 (X)	2-DMH	3-OH	10 ^z	72	200-210 (0.004) ^{uu}	C ₂₅ H ₃₈ O ₂
30 (Va)	3-DMH	1-OH, 2-CH ₂ NMe ₂	1	41	<i>bb</i>	C ₂₈ H ₄₁ NO ₂
31 (Vb)	3-CH(C ₄ H ₉) ₂	1-OH, 2-CH ₂ NMe ₂ ·HCl	<0.4 ^t	65	<i>cc</i>	C ₂₈ H ₄₃ NO ₂

Table I (Continued)

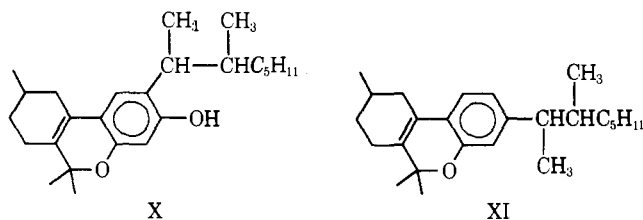
Compd	R'	R''	Z	Rel CNS activity, ^b rat	Yield, % ^d	Bp, °C (mm) ^e	Formula ^f
							
32	H	Me	OAc	>2	66	190–195 (0.005)	C ₂₆ H ₃₀ O ₃
33	Me	Et	OH	2	77	184–187 (0.03)	C ₂₇ H ₄₂ O ₃
34	Me	Et	OAc	0.5	32	200–210 (0.02)	C ₂₅ H ₄₄ O ₃ ^{dd}
35	Me	=O	OH	<0.1 ^c		ee	

^aRelative to compound **2** as standard and compared with respect to minimum dose producing overt side effects. ^bMinimum dose of **2** producing overt side effects is 50 mg/kg po. ^cData of R. Adams and S. Loewe; see corresponding reference for the physical constants. ^dBased on immediate precursor. ^eDistilled in Kugelrohr apparatus. ^fAll compounds analyzed for C and H (and N when present) and analyzed within $\pm 0.4\%$ of calculated values unless otherwise indicated. ^gLit. bp 191–192° (1 mm); R. Adams and B. R. Baker, *J. Amer. Chem. Soc.*, **62**, 2405 (1940). ^hSee footnote #. ⁱPrepared via pulegone route. ^jLit.³¹ bp 190–200° (0.01 mm). ^kLit.³² bp 208–213° (2 mm). ^lLit.³² bp 217–222° (2.5 mm). ^mC: calcd, 80.85; found, 79.45. ⁿLit.³³ bp 220° (1.0 mm). ^oLit.¹ bp 180° (0.05 mm). ^pThree activities were reported for this compound: 512, 75, and 3.6 relative to I² (presumably representing the activities of three different preparations: Professor S. MacKenzie, Jr., private communication). ^qLit.⁸ bp 170–173° (0.04 mm). ^rLit.¹ bp 195–210° (0.7 mm). ^sLit.⁸ bp 176° (0.04 mm). ^tNo activity at highest doses tested. ^uContaining 16% exo methylene isomer; see text. ^vC: calcd, 81.20; found, 80.14. ^w Δ^8 -THC, a minor active constituent of marihuana. ^xSee footnote §. ^y Δ^9 -THC, the major active constituent of marihuana. ^zPreviously reported to be inactive.¹³ ^{aa}Lit.¹³ bp 200–240° (0.05 mm). ^{bb}Mp 103–107° ^{cc}Mp 103–104° ^{dd}C: calcd, 79.04; found, 76.79. ^{ee}Mp 129–134° (lit.⁸ mp 134–136°).

Adams and Loewe who reported that, in the dog, **12** had only $\frac{1}{20}$ th the potency of I.^{1,2,8} The net effect on going from IIa (**1**), the *n*-amyl natural side-chain analog, to **12** is a 2000-fold increase in potency. Compound **12** is 500 times as active as Δ^9 -THC (**21**), the major active constituent of marihuana. Activity appears to be related to the branching pattern since the *n*-nonyl (**3**) and dibutylcarbonyl (**13**) analogs are markedly less active than the dimethylheptyl analogs.

Introduction of unsaturation at the important 1 position did not affect potency; thus, **1** and **14** were equally active. The ether side-chain containing cannabinoid **15** was five times as active as the corresponding methylene compound **8**, although not quite as active as **4**, in which the side chain is directly joined to the ring. The ether **15** is five times as potent as the natural Δ^9 -THC (**21**). This was unexpected in view of the insignificant activities for the *n*-alkyl ethers reported by Todd.¹⁰

Changing the locations of the side chain and phenolic groups gives a molecule having a completely different steric arrangement and a different receptor-site fit, so it might have been expected to decrease or eliminate activity. Indeed, several 2-alkyl-3-hydroxy compounds had previously been reported to have activities ranging from low¹² (approximately equipotent to **2**) to inactive¹³ (the DMH analog X). The total inactivity of X was unexpected, so it was reprepared and tested and was found to be ten times as active as **2** and as potent as the natural tetrahydrocannabinoids in producing CNS effects.



Acetylation of the phenolic group in I (**26**) decreases potency. Methylation (**27**) is much more detrimental, essen-

tially eliminating activity. It was most surprising, therefore, to find that on replacement of the 1-hydroxyl group by hydrogen, as in XI (**28**), significant activity was retained; in the *n*-C₅ series activity is completely lost with this type of modification.^{14a} The Mannich condensation products, **30** and **31**, had relatively weak activity.

In the B ring, modification of the pyran ring substituent at C-6 markedly affects activity. Replacement of the 6,6-dimethyl group in I by a carbonyl (**35**) destroys CNS activity, and replacement of dimethyl by diethyl (**33**) causes a 250-fold decrease in potency in producing CNS depression; the analogous change of IIa from dimethyl to diethyl was reported to decrease potency by only tenfold.^{14b}

Reduction of the $\Delta^{6a,10a}$ double bond between the B and C rings drastically reduces activity. Of the two dihydro compounds, the *trans*-dihydro IIa (**25**) is more active than the *cis* isomer **24**. In the Δ^9 series, the (natural) *trans*- Δ^9 -THC is also more potent than the (synthetic) *cis* analog.

The natural THC double-bond isomers, Δ^8 -THC (**20**) and Δ^9 -THC (**21**), have comparable CNS potency and much greater potencies than the *n*-amyl $\Delta^{6a,10a}$ isomer **1** (IIa). However, in the 1,2-dimethylheptyl series the reverse is true; the $\Delta^{6a,10a}$ isomer **10** (I) is more potent than the "natural" Δ^8 (**22**) and Δ^9 (**23**) isomers.

Changes in the C ring pattern of alkyl substitution generally decrease CNS potency although these compounds are still quite active. Increasing the length of the substituent at C-9 to an ethyl (**17**), addition of a second methyl at C-7 (**19**), shifting the methyl to C-8 (**18**), or total replacement of the 9-methyl with hydrogen (**16**) results in reduction of potency. Comparisons with the earlier reported analogous changes in **1**–**3** show only qualitative agreement. The still considerable activity of the desmethyl compounds **16** and **32** shows that, at least in animals, CNS activity as measured in terms of decreased motor activity does not require the formation of a 9-hydroxymethyl metabolite, since **16** is obviously incapable of forming such a metabolite.

The overt effects produced by most of these compounds are qualitatively similar, varying with respect to potency,

duration of activity, and intensity of individual CNS effects relative to one another.

I was selected for a detailed description of pharmacology as being one of the most potent and well-known† members of the series.

Pharmacology of I. I produces a marked reduction in spontaneous motor activity in rats in open-field testing following oral doses of 0.1-1.0 mg/kg; doses above 2.5 mg/kg produce a complete cessation of motor activity similar to that observed after high doses of neuroleptic agents. Doses above 0.25 mg/kg also produce other effects characteristic of analgesic agents, such as vocalization, hypersensitivity to touch, hypothermia, rigidity of limbs, catalepsy, and analgesia, as well as effects characteristic of neuroleptic agents, *i.e.*, ptosis and low body posture.

Doses above 2.5 mg/kg usually produce inhibition of the corneal, myotactic, myotatic, and placing reflexes. The onset of these effects in rats is usually 1-2 hr following drug administration. The peak drug effects are noted 3-5 hr after treatment and, at the higher doses, are frequently present for as long as 24-36 hr following administration of the drug.

Dogs are particularly sensitive to I. Oral doses as low as 0.5 mg/kg produce hypertonia, limb rigidity, body tremors, decreased motor activity, hypersensitivity, hypothermia, and emesis. At higher doses (1-2 mg/kg) the effects are more severe and mydriasis, loss of pupillary accommodation to light, body jerks, spastic locomotion, somnolence, unresponsiveness to visual stimuli, bradycardia, bradypnea, and difficulty in lying down are also present. As in rats, duration of effects is prolonged, lasting up to 72 hr in dogs that received 2 mg/kg orally.

In cats, only hypothermia is observed following an intraperitoneal dose of 0.1 mg/kg. At 0.25 mg/kg ip decreased motor activity, ataxia, intention tremors, crying, and hypertonia are produced. At doses of 0.5-1.0 mg/kg ip the effects are intensified; also produced are dyspnea, low posture, unsteady stance, somnolence, relaxation of the nictitating membrane, vocalization, tremors, and inability to stand.

I and chlorpromazine were compared in several test systems useful for evaluating neurological properties (Table II). Like chlorpromazine, I produces a graded reduction in motor activity. I is 12 times as potent as chlorpromazine in the confinement motor activity test¹⁵ in rats and three times as potent in decreasing spontaneous motor activity in the mouse.¹⁶ Both compounds produced catalepsy¹⁷ in rats, but I is at least 15 times as potent as chlorpromazine. In mice, I is five times as potent as chlorpromazine in inhibiting foot shock-induced fighting behavior.¹⁸

I has potent analgesic activity in rats as indicated by an ED₅₀ of 0.28 mg/kg in the hot-wire test.¹⁹ It differs from chlorpromazine in exhibiting a more selective effect on the pain-threshold level in rats. Thus, the analgesic ED₅₀ for I occurs at one-half the ED₅₀ dose that reduces motor activity and at the same dose at which catalepsy is first observed, whereas chlorpromazine has an analgesic ED₅₀ well above the ED₅₀ for reduction of motor activity and production of catalepsy.

I also differs from chlorpromazine in having a potent anticonvulsant effect in mice as demonstrated by its ability to prevent convulsions produced after maximal electroshock.²⁰ Chlorpromazine has no anticonvulsive activity in this test. From these data, it is evident that I produces a wide variety of pharmacological effects, some of which mimic CNS depressants and others which mimic the potent analgesic agents.

At a dose of 10 mg/kg po, I elevates the pain-threshold level and reduces the paw temperature without suppress-

Table II. Comparison of Selected Pharmacological Properties of I and Chlorpromazine

Test	Species	ED ₅₀ (po), mg/kg	
		I	Chlorpromazine
Confinement motor activity	Rat	0.52	6.8
		(0.25-0.87) ^a	(4.5-10.4) ^a
Catalepsy	Rat	0.1-0.6 ^b	9.4
			(6.3-14.2)
Analgesia	Rat	0.28	17.2 ^a
		(0.13-0.59)	
Spontaneous motor activity	Mouse	2.1	6.7
		(0.8-4.8)	(3.9-11.2)
Fighting behavior	Mouse	2.0	10.8
		(1.3-3.0)	(7.3-15.8)
Maximal electroshock	Mouse	4.9	Inactive at 50
		(3.1-7.6)	

^aNumbers in parentheses are confidence limits. ^bEstimated value.

ing the paw edema volume in the rat paw yeast-induced edema test.²¹ However, at a dose of 1 mg/kg po, I suppressed both the edema volume and the inflammation in carrageenin-induced abscess formation in rats.²² In confirmation of the antiedema activity, I was found to produce a significant suppression of both primary and secondary lesions of adjuvant-induced arthritic rats²³ at 5 mg/kg po.** It should be noted that, at this dose, significant body weight loss was also observed. No antipyretic activity was demonstrated in the modified yeast-fevered rat procedure.²⁴

I inhibited gastric acid secretion in chronic gastric fistula rats.²⁵ At 0.4 mg/kg po gastric pH was raised about 2 units and acid output was decreased about 80%.**

I showed significant diuretic activity at 2-5 mg/kg po in rats hydrated with 0.9% NaCl²⁶ and produced diuresis in rats treated with antidiuretic hormone.²⁷ It was inactive in the glucose-infused dog²⁸ (at 1 mg/kg po).

Selected pharmacological effects of I in various animal species have been previously described by Hardman, *et al.*²⁹ and Boyd, *et al.*³⁰

Experimental Section††

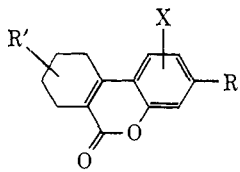
Pharmacology. Rat CNS Effects. Various dosages of the compounds were administered orally to at least three rats (CD Sprague-Dawley strain of rats) and overt effects were recorded over an extended period of time until the animals appeared normal. The drug was administered in solution in polyethylene glycol 400. The animals were observed for at least 6 hr on the day of treatment and at least once daily for 7-10 days after compound administration. The overt effects produced by most of these compounds are qualitatively similar to those described for I, although they vary with respect to potency, duration of activity, and intensity of CNS effects relative to one another.

Phenols and Resorcinols. Olivetol was purchased from Aldrich Chemical Co. The 5-(*n*-nonyl)-,³¹ 5-(1-methylheptyl)-,³² and 5-(1,2-dimethylalkyl)resorcinols^{1,8} were prepared as described in the literature. 5-(1-Methylhexyl)-,³² 5-(1-methyloctyl)-,³³ and 5-(1-ethylheptyl)resorcinols were prepared from the aceto- and propiophenones employing the method of Taylor, Lenard, and Loev.¹³ 5-(2-Methylheptyl)- and 5-(1,1-dimethylheptyl)resorcinols⁸ were synthesized according to the procedures reported for the corresponding pentyl analogs.^{28,33} Following are the boiling points and yields of the new resorcinols: 5-(1-ethylheptyl), bp 130-134° (0.05

**Further details concerning these activities will be described in future publications.

††Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Boiling points and melting points are uncorrected. Elemental analyses were performed by the Analytical Department of Smith Kline and French Laboratories and where analyses are indicated by the symbols of the elements, analytical results for the elements were within ±0.4% of the theoretical values. Mass spectra were obtained on a Hitachi Perkin-Elmer RMN 6E spectrometer. Nmr spectra were obtained on a Varian T-60 instrument (Me₄Si). Ir and nmr spectra of all compounds were consistent with the assigned structures.

Table III. Chemical Properties of New Coumarin Intermediates



Compd	R	R'	X	Yield, ^a %	Mp, °C	Crystn solvent	Formula ^b
36	<i>n</i> -C ₇ H ₁₃	9-Me	1-OH	73	161-162.5	MeNO ₂	C ₂₃ H ₃₂ O ₃
37	-CH(C ₂ H ₅)C ₆ H ₁₃	9-Me	1-OH	69	135-137	MeNO ₂	C ₂₃ H ₃₂ O ₃
38	-CH ₂ CH(CH ₃)C ₃ H ₁₁	9-Me	1-OH	80	199.5-201	MeNO ₂	C ₂₂ H ₃₀ O ₃
39	-CH(<i>n</i> -C ₄ H ₉) ₂	9-Me	1-OH	62	164-166	<i>i</i> -Pr ₂ O-hexane	C ₂₃ H ₃₂ O ₃ ^c
40	-OCH(CH ₃)C ₃ H ₁₁	9-Me	1-OH	58	161-163	MeNO ₂	C ₂₁ H ₂₈ O ₄
41	-CH(CH ₃)CH(CH ₃)C ₃ H ₁₁	H	1-OH	73	149-153	MeNO ₂	C ₂₂ H ₃₀ O ₃
42	-CH(CH ₃)CH(CH ₃)C ₃ H ₁₁	9-Et	1-OH	34	120-121.5	MeCN	C ₂₄ H ₃₄ O ₃
43	-CH(CH ₃)CH(CH ₃)C ₃ H ₁₁	8-Me	1-OH	52	133.5-135.5	MeCN	C ₂₃ H ₃₂ O ₃
44	-CH(CH ₃)CH(CH ₃)C ₃ H ₁₁	7,9-Me ₂	1-OH	46	138-143	MeCN	C ₂₄ H ₃₄ O ₃
45	-CH(CH ₃)CH(CH ₃)C ₃ H ₁₁	9-Me	1-H	25	84-86	Hexane	C ₂₃ H ₃₂ O ₃ ^d
46	-CH(<i>n</i> -C ₄ H ₉) ₂	9-Me	1-OH, 2- CH ₂ N(CH ₃) ₂	54	170-172	<i>i</i> -Pr ₂ O	C ₂₆ H ₄₀ NO ₃ Cl

^aBased on immediate precursor. ^bAll compounds analyzed for C and H (and N when present). ^cC: calcd, 77.49; found, 76.98. ^dC: calcd, 81.13; found, 80.66.

mm) (40% yield); 5-(2-methylheptyl), bp 163-167° (0.35 mm) (32% yield). The other compounds were prepared as described below.

5-(Di-*n*-butylcarbinyl)resorcinol. A solution of methyl 3,5-dimethoxybenzoate (516 g, 2.6 mol) in 3 l. of anhydrous Et₂O was added with stirring over a 1-hr period to a cold (-60°) solution of *n*-BuLi (7.9 mol) in 4.2 l. of hexane under N₂. The mixture was allowed to warm to 25° and was then refluxed for 2.5 hr. This mixture was cooled to 0° and quenched with 250 ml of ice-water. After 45 min, the suspension was filtered, the solid was washed with Et₂O, and the combined filtrates were dried (MgSO₄). The solvent was evaporated and the residue distilled to give 664.5 g (91%) of 5-(3,5-dimethoxyphenyl)-5-nonanol, *n*_D²⁵ 1.5095. This carbinol was dehydrated, reduced, and demethylated by previously described procedures¹³ to give the resorcinol in 69% overall yield, bp 174-198° (0.3 mm). *Anal.* (C₁₅H₂₆O₂) C, H.

5-(1-Methylhexyloxy)resorcinol. To a stirred solution of phloroglucinol (126 g, 1.0 mol) and KOH (19.0 g, 0.34 mol) in DMF was added 2-bromoheptane (186 g, 1.04 mol). After heating the mixture for 16 hr at 100°, 250 ml of AcOH was added and the mixture was filtered. The filtrate was concentrated, dissolved in Et₂O, washed with H₂O, and extracted with 10% aqueous NaOH. The alkaline solution was washed with Et₂O, acidified with dilute HCl, and extracted with Et₂O. The organic phase was dried (MgSO₄), treated with charcoal, and filtered. The solvent was evaporated and the residue distilled to give 16.7 g (22%) of the product as a pale yellow resin, bp 165-170° (0.15 mm). *Anal.* (C₁₃H₂₀O₃) H; C: calcd, 69.61; found, 69.05.

3-(1,2-Dimethylheptyl)phenol. To the Grignard reagent prepared from Mg turnings (13.3 g, 0.56 mol) and 2-bromoheptane (100 g, 0.56 mol) in anhydrous Et₂O, under N₂, was added with stirring a solution of *m*-methoxyacetophenone (41.5 g, 0.28 mol) in 200 ml of anhydrous THF. After refluxing for 12 hr, the mixture was quenched with 300 ml of saturated aqueous NH₄Cl and extracted with Et₂O. The extract was washed with H₂O and dried (MgSO₄), and the solvent was removed to give 2-(3-methoxyphenyl)-3-methyl-2-octanol as an oil. The carbinol was converted to the alkylphenol by previously described procedures¹³ in 16% overall yield, bp 105-110° (0.1 mm).

Coumarins. Typical Procedure. To a stirred solution of the resorcinol (0.05 mol) and the 2-cyclohexanonecarboxylic ester (0.05 mol) in 50 ml of PhH was added POCl₃ (7.7 g, 0.05 mol). After 2 hr, the solution was refluxed for 15 min and allowed to stir at 25° for 24 hr. It was then treated with H₂O and refluxed for 15 min, and EtOAc was added. The organic phase was washed with 5% aqueous NaHCO₃, H₂O, and brine, dried (MgSO₄), and concentrated. The recrystallization solvents, yields, and properties are indicated in Table III.

3-(1,2-Dimethylheptyl)-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyrone (45). The product was prepared from 3-(1,2-dimethylheptyl)phenol (9.0 g, 0.041 mol) and 5-methyl-2-carbethoxycyclohexanone (6.95 g, 0.041 mol) using H₂SO₄ as catalyst¹⁴ and puri-

fied by chromatographing the crude material on a silica gel column with PhH, then distillation [bp 187-190° (0.025 mm)], and recrystallization.

Tetrahydrobenzopyrans. Typical Procedure. A solution of the coumarin (8.8 mmol) in 100 ml of anhydrous THF was added with stirring under N₂ to a solution of methyl or ethyl Grignard reagent (50 mmol) in 25 ml of PhH-THF. After refluxing for 24 hr and stirring at 25° for 72 hr, the solution was poured onto a mixture of dilute HCl-ice and extracted with Et₂O. The organic phase was washed with H₂O, 5% aqueous NaHCO₃, H₂O, and brine and dried (MgSO₄). The solvent was evaporated, the residue (containing the tertiary alcohol) was dissolved in 100 ml of PhH, and 20 ml of Et₂O saturated with HCl was added. After refluxing the solution for 2 hr, the solvent was evaporated and the residue distilled to give the products described in Table I.

1-Hydroxy-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-7,8,9,10,10a-hexahydro-6*H*-dibenzo[*b*,*d*]pyran (24). A mixture of 1 (3.0 g, 8.1 mmol) in 100 ml of absolute EtOH and 10% Pd/C was hydrogenated at 48 psi and 25° until 8 mmol of H₂ was absorbed (1 hr). After addition of some CHCl₃, the mixture was filtered, the solvent evaporated, and the residue was distilled to give the product as a pale yellow resin.

1-Hydroxy-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyrans (14). 5-(1,2-Dimethyl-1-hydroxyheptyl)resorcinol dimethyl ether⁸ (68.6 g, 0.25 mol) was dehydrated by distillation from a few drops of 20% aqueous H₂SO₄ in the usual manner³² to give 52.5 g (82%) of a mixture of 5-(1,2-dimethyl-Δ¹-*cis*- and *trans*-heptyl)- and 5-(1-methylene-2-methylheptyl)resorcinol dimethyl ethers, bp 132-134° (1.0 mm).

A solution of this material (5.4 g, 0.020 mol) in Et₂O was added to the Grignard reagent prepared from Mg turnings (1.96 g, 0.080 mol) and CH₃I (11.4 g, 0.080 mol) in 200 ml of anhydrous Et₂O. The solvent was evaporated under N₂ on a steam bath, and the residue was heated at 150-170° for 25 min. Ice was cautiously added to the cold viscous mixture, followed by Et₂O and dilute HCl. The organic phase was washed with H₂O and dried (MgSO₄), and the solvent evaporated to give 3.3 g (69%) of the olefinic resorcinols as a brown oil.

To a stirred solution of the resorcinols (3.3 g, 0.014 mol) and 5-methyl-2-carbethoxycyclohexanone (2.57 g, 0.014 mol) in 50 ml of PhH was added a solution of POCl₃ (2.17 g, 0.014 mol) in 5 ml of PhH. After 1 hr the solution was refluxed for 5 min and allowed to stir at 25° for 24 hr. It was then treated with H₂O and refluxed for 15 min, and EtOAc was added. The organic phase was washed with 5% aqueous NaHCO₃, dried (MgSO₄), and concentrated. This residue was triturated with a minimum amount of 40% aqueous NaOH. The precipitate which formed was filtered, washed with PhH and 10% aqueous NaOH, and finally reacted with dilute HCl, extracted in PhH, and dried (MgSO₄). Evaporation of the solvent gave 2.7 g (54%) of the coumarin as a brown oil: mass spectrum *m/e* 354 (M⁺), 297, 249 metastable ion.

A solution of the coumarin (2.7 g, 7.6 mmol) in PhH was added to a stirred solution of CH_3MgBr (Arapahoe Chemicals) (50 ml, 100 mmol) in PhH-THF under N_2 . After refluxing for 18 hr, the solution was poured slowly with stirring onto 300 ml of ice- H_2O containing 40 ml of concentrated HCl. The cold mixture was extracted with Et_2O and the organic phase dried (MgSO_4) and concentrated. Distillation of the residue gave the product as an amber resin consisting of a mixture of 1-methylene-2-methylheptane and 1,2-dimethyl- Δ^1 -heptene isomers in a 5.3:1 ratio as indicated by nmr and glc: nmr (CDCl_3) δ 5.28 (m, 0.32 H, methylene H); mass spectrum m/e 368 (M^+), 353.

Acetates. Typical Procedure. A mixture of sodium acetate (2.5 g, 0.031 mol), acetic anhydride (25 ml, 0.26 mol), and the dibenzopyran (8.1 mmol) was refluxed with stirring for 3 hr. The mixture was then concentrated and treated with EtOH , the solvent was evaporated, and then both Et_2O and H_2O were added. The organic phase was washed with 5% NaHCO_3 and H_2O and then dried (MgSO_4), and the solvent was evaporated. The residue was distilled, giving compounds 26, 32, and 34 (Table I).

1-Methoxy-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-7,8,9,10-tetrahydro-6H-dibenzo[b,d]pyran (27). To a stirred solution of 1 (3.0 g, 8.1 mmol) in 75 ml of anhydrous DMSO was added KO-*t*-Bu (1.1 g, 9.6 mmol) and the mixture was heated to 100°. The cooled solution was treated with Me_2SO_4 (2.5 g, 0.020 mol) in portions, heated at 100°, and allowed to stir at 25° for 17 hr. This solution was poured into ice- H_2O , acidified, and extracted with Et_2O . The organic phase was washed with H_2O , dried (MgSO_4), and concentrated. Distillation of the residue gave the product as a pale yellow oil.

1-Hydroxy-2-(N,N-dimethylaminomethyl)-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-7,8,9,10-tetrahydro-6H-dibenzo[b,d]pyran (30). Paraformaldehyde (1.8 g, 0.060 mol), 40% aqueous dimethylamine (7 ml, 0.060 mol), and 10 drops of AcOH were added to a warm solution of 1 (10.1 g, 0.027 mol) in 75 ml of EtOH . The solution was refluxed for 45 min and allowed to stir at 25° for 18 hr. The colorless precipitate was filtered, washed with cold MeOH, and recrystallized from anhydrous MeOH to give the title compound: mass spectrum m/e 427 (M^+); nmr (CDCl_3) δ 10.3 (s, br, 1 H); ir (Nujol) 3.4 μ . The point of attachment of the substituent was assigned on the basis of the presence of a broad OH absorption band in the ir and nmr spectra both indicative of hydrogen bonding of the OH with an ortho substituent. The product was insoluble in dilute HCl and dilute NaOH and did not form a solid salt with ethereal HCl.

1-Hydroxy-2-(N,N-dimethylaminomethyl)-3-(di-*n*-butylcarbonyl)-9-methyl-7,8,9,10-tetrahydro-6H-dibenzo[b,d]pyrone Hydrochloride (46). Paraformaldehyde (95%) (0.90 g, 29 mmol) and 40% aqueous dimethylamine (3.15 g, 28 mmol) were added to a solution of 39 (10 g, 28 mmol) in 80 ml of THF. Additional paraformaldehyde (0.30 g, 9.5 mmol) was added after 48 hr and the solution was refluxed for another 6 hr. A final addition of paraformaldehyde (0.20 g, 6.3 mmol) was made and the solution refluxed for 1.5 hr. After 72 hr the solvent was evaporated, and the residue was dissolved in Et_2O and treated with a saturated solution of HCl in Et_2O . The gummy precipitate was triturated with Et_2O and recrystallized from *i*- Pr_2O to give the title compound.

Compound 31 was prepared from 13 (2.0 g, 5.4 mmol) using the same method.

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