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(11) In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals", as promulgated by the Committee of Revision of the "Guide for Laboratory Animals, Facilities and Care" of the Institute of Laboratory Animal Resources, National Research Council.
(12) Consists of a battery of approximately 50 primary screening tests in mice as described by S. Irwin in "Animal and Clinical Pharmacologic Techniques in Drug Evaluation", J. A. Nodine and P. E. Siegler, Ed., Year Book Medical Publishers, Chicago, Ill., 1964, pp 36–54; additionally elaborated by Vane in "Evaluation of Drug Activities: Pharmacometrics", Vol. 1, D. R. Laurence and A. J. Bacharach, Ed., Academic Press, London and New York, 1964, pp 23–41; see also R. A. Turner in "Screening Methods in Pharmacology", Academic Press, London and New York, 1965, pp 26–34; and S. Irwin, Psychopharmacologia, 13, 222 (1968).
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Drugs Derived from Cannabinoids. 2.[1a] Basic Esters of Nitrogen and Carbocyclic Analogs

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Various basic esters of nitrogen (**2**) and carbocyclic (**3** and **4**) analogs of cannabinoids were synthesized using dicyclohexylcarbodiimide in methylene chloride. The compounds in the three series were studied in selected pharmacological tests in mice, rats, dogs, and cats. It was shown that making the basic ester from the phenol retains biological activity and can lead to a greater selectivity of action, particularly the antinociceptive activity. The most interesting esters were **5**, **6**, **10**, and **14** in the nitrogen analogs series and **19** and **20** in the carbocyclic series. Compound **5** was more potent than codeine in the writhing, hot-plate, and tail-flick tests and is at present undergoing clinical testing. Compound **20** was very potent in the mouse audiogenic seizure test and is of interest as an anticonvulsant agent.

We have recently reported[1] the synthesis and pharmacological profile of various nitrogen analogs of tetrahydrocannabinols (THC's) and shown that the most interesting and active compounds are analogs of type **1**, which have a phenethylamine orientation for the nitrogen. Like the THC's these nitrogen analogs cause CNS depression and ataxia in various laboratory animals. In particular, mice and dogs show the characteristic cannabinoid-like hypersensitivity to external stimuli ("popcorn effect").[2,3] At low doses, ptosis and relaxation of the nictitating membrane are observed in the monkey (rhesus monkey unless otherwise noted) and the cat, respectively, and at higher doses ataxia follows in both species.[1a]

The most potent compound of this series, **2**, had a basic profile generally similar to Roger Adams' DMHP (**3**) in mice but was found to be more active in overt behavior tests in the cat, the monkey, and the dog. In addition, **2** like morphine showed good dose-related antinociceptive properties and antidiarrheal effects in mice. Furthermore, interaction of **2** with morphine in rodents and monkeys showed narcotic–antagonist like effects.[1]

The solubility characteristics of these nitrogen analogs are similar to the cannabinoids in that they are very lipid soluble and insoluble in water. Furthermore, the acid addition salts of the nitrogen compounds are also insoluble in aqueous media. However, the presence of the phenolic hydroxyl group in these compounds led us to prepare various basic esters in the hope of achieving some selectivity of pharmacological action by (a) synthesizing dif-

Scheme I

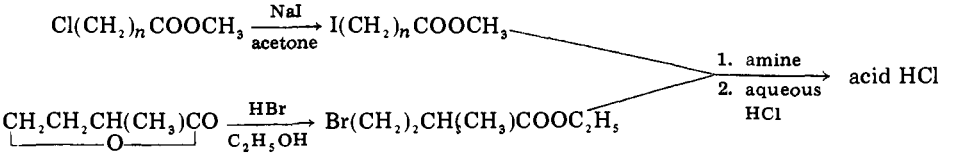
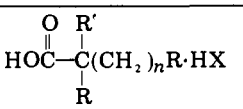
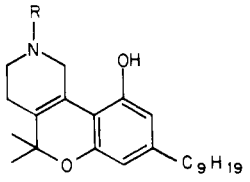


Table I. Carboxylic Acids

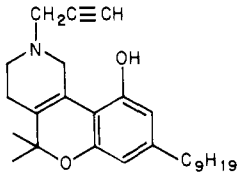


R	R′	R′	*n*	Recrystn solvent[a]	Mp, °C	Yield,[b] %	Mol formula[c]
Piperidine	CH_3	H	2	A	165-166.5	71	$C_{10}H_{19}NO_2 \cdot HCl$
Piperidine	CH_3	CH_3	2	B	232-234	24	$C_{11}H_{21}NO_2 \cdot HCl$
Piperidine	H	H	3	B	202-204	75	$C_{10}H_{19}NO_2 \cdot HCl$
2-Methylpiperidine	H	H	2	B	180-182	40	$C_{10}H_{19}NO_2 \cdot HCl$
2-Methylpiperidine	CH_3	H	2	C	126-127	41	$C_{11}H_{21}NO_2 \cdot HCl$
Morpholine	H	H	2	D	151-152.5	95	$C_8H_{15}NO_3 \cdot HBr$
Morpholine	CH_3	H	2	B	155-157	85	$C_9H_{17}NO_3 \cdot HCl$
Pyrrolidine	H	H	2	A	127-128	33	$C_8H_{15}NO_2 \cdot HCl$
Homopiperidine	H	H	2	A	178-179	71	$C_{10}H_{19}NO_2 \cdot HCl$
Thiomorpholine	H	H	2	B	242-245	45	$C_8H_{15}NO_2S \cdot HCl$

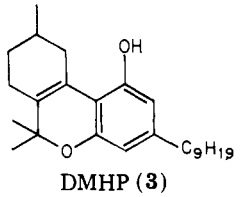
[a] A = acetic acid–acetone mixture; B = recrystallization not required; C = acetone; D = acetic acid. [b] Yields have not been optimized and are given for the cumulative alkylation and hydrolysis steps. [c] C, H, N, and, in the case of thiomorpholino acid, S analyses were within ± 0.4% of theoretical values.



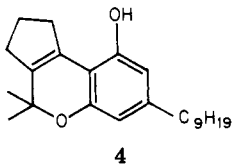
1



2



DMHP (3)



4

C_9H_{19} = $CH(CH_3)CH(CH_3)$-*n*-C_5H_{11}

ferently hindered esters and (b) increasing their hydrophilicity. The latter would make these derivatives "water soluble", a property which would facilitate pharmacological study of these compounds and allow their evaluation in self-administration monkey studies.[4] Our earlier work had shown that Δ^9-THC can be converted to a basic ester which was "water soluble"[5] and retained biological activity.

In this paper we report the syntheses and an examination of the activity in selected pharmacological tests of various basic esters of compound **2**. The chemistry and pharmacological profile of one of these esters which is at present undergoing clinical trials are described in some detail. Since we had previously noted[1a] that compound **2** was more potent than DMHP (**3**), it was considered of interest to prepare and compare the esters of **3** with those of **2**. In addition, we report the comparative activity of these compounds with the basic esters of another potent carbocyclic analog **4**, previously reported by us.[6a] Some structure–activity relationships (SAR) in the three series are discussed.

Compound **4** differs from DMHP in that the cyclohexane ring in **3** is replaced by a cyclopentane ring. In our previous studies[6b] we had found that **4** exhibits a pharmacological profile similar to DMHP (**3**) but was less active. It is interesting to note that the *n*-C_5H_{11} homolog of **4** (i.e., where the 1,2-dimethylheptyl side chain is replaced by the *n*-C_5H_{11} group) was described by Todd and co-workers[7] in 1941 and was reported to be relatively inactive.

Chemistry. Syntheses of compounds **2** and **4** have been previously described.[1a,6a] The basic esters of these and DMHP (**3**) were prepared by allowing them to react with the appropriate acid (as the hydrochloride or the hydrobromide salt) in the presence of dicyclohexylcarbodiimide (DCC) in methylene chloride according to our procedure for the preparation of water-soluble derivatives of Δ^9-THC.[5]

The straight-chain carboxylic acids were prepared according to the procedure described by Blicke et al.[8] (Scheme I) for the preparation of 4-diethylaminobutyric acid hydrochloride from methyl 4-chlorobutyrate and later utilized by Cruickshank and Sheehan[9] for the preparation of 4-morpholino- and 4-piperidinobutyric acid hydrochlorides. The 2-methyl acids were prepared from 2-methyl-4-butyrolactone[10] by treatment with C_2H_5OH–HBr to form the 4-bromo esters[11] which were subsequently treated with the appropriate amine and hydrolyzed as described above. In the case of the 2,2-dimethyl acid, 4-butyrolactone was first alkylated[12] with CH_3I–NaH to give the 2,2-dimethyl-4-butyrolactone which was converted to the acid following the same sequence of reactions used in the preparation of 2-methyl acids. Thiomorpholine was prepared according to a literature[13] procedure. The various acids thus prepared are listed in Table I.

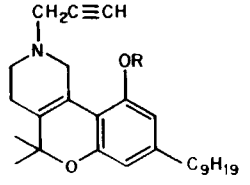
The method of choice for the preparation of compound **11** was via the acrylic ester with subsequent Michael addition of piperidine.

The basic esters of **2**, **3**, and **4** are listed in Tables II–IV.

Pharmacology. The compounds were studied in selected pharmacological tests (Tables II–IV) in mice, rats, dogs, and cats as described in the Experimental Section. All compounds showed a very high therapeutic index as in no case was the approximate LD_{50} (po) in mice <0.5 g/kg.

We have previously[1a] described the overt behavioral and neurological effects of this class of compounds (type **1**),

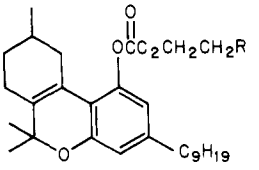
Table II. Basic Esters of Compound 2



Compd	R	Chemical properties[a] Yield,[c] %	Mp, °C	Crystn solvent[d]	Pharmacological properties[b] Dopa, 5 mg/kg	Mouse fighting, 10 mg/kg	Motor act., 10 mg/kg	Analgesia, ED_{50}, mg/kg	Dog ataxia	Sedative–hypnotic, mg/kg (TST)
2	H				+++	1 (++), 5 (++)	1 (+++)	W (4.3), RTF (13.8), HP (7.7)	1 (++)	0.1 (+100), 0.25 (+56), 0.5 (+44)
5	C(=O)$CH_2CH_2CH_2$-c-NC_5H_{10}·HCl	94	108-111	A	+	1 (+), 5 (++)	1 (++)	W (12.0), RTF (12.5), HP (4.2)	1 (++)	0.1 (+38), 0.25 (+33), 0.5 (+48)
6	C(=O)$CH(CH_3)CH_2CH_2$-c-NC_5H_{10}·2HCl	88	173-176	A	+	IA	++	W (12.21), RTF (9.8)	1 (+)	0.25 (+58), 0.5 (+45)
7	C(=O)$C(CH_3)_2CH_2CH_2$-c-NC_5H_{10}·2HCl	70	143-150	A	+	IA	++	W (17.5), RTF (>20)		0.5 (+15)
8	C(=O)$CH_2CH_2CH_2$-c-NC_4H_8·2HCl·H_2O	16	168-171	A	+	+	++	IA	1 (+)	
9	C(=O)$CH_2CH_2CH_2$-c-NC_5H_9-o-CH_3·HCl	61	Foam		+	+	+	W (26.8)	1 (++)	0.5 (+92)
10	C(=O)$CH(CH_3)CH_2CH_2$-c-NC_5H_9-o-CH_3·2HCl	62	190-194	A	+	IA	+	W (7.3), RTF (10.7)		0.5 (+38), 1.0 (+104)
11	C(=O)CH_2CH_2-c-NC_5H_{10}·2HCl	67	196-201	B	+	++	+	W (12.3), HP (22.3)		0.5 (+69)
12	C(=O)$CH_2CH_2CH_2CH_2$-c-NC_5H_{10}·HCl	71	140-144	A	+	++	++	W (>10)	1 (+)	
13[e]	C(=O)$CH_2CH_2CH_2$-c-NC_5H_{10}·HCl·$0.5H_2O$	22	90-110	A	+	5 (+)	+	IA		
14	C(=O)$CH_2CH_2CH_2$-c-$N(CH_2CH_2)_2O$·2HCl	67	158-163	A	+	5 (++)	+	W (9.5), RTF (14.4)	1 (++)	1.0 (+30)
15	C(=O)$CH(CH_3)CH_2CH_2$-c-$N(CH_2CH_2)_2O$·2HCl	52	188-192	A	+	+	++	W (>10)		0.5 (+36)
16	C(=O)$CH_2CH_2CH_2N(C_2H_5)_2$·HCl·$0.5H_2O$	70	Foam		+	++		W (>40)	10 (++)	
17	Bisquarternary salt 14·$2CH_3I$	97	154-159	C	+	++	+	IA	10 (+)	

[a] C, H, and N analyses for all compounds were within ±0.4% of the theoretical value except in the case of compound 17: C: calcd, 51.80; found, 50.90. [b] All doses are in mg/kg po; in the Dopa potentiation test, results have been graded as + (slight), ++ (moderate), and +++ (marked) increases. In the mouse fighting and motor activity tests, + corresponds to 1-33%, ++ (33-66%), and +++ (66-100%) reduction. In the dog ataxia test, + corresponds to decreased activity only and ++ to decreased activity and ataxia; W = writhing; RTF = rat tail flick; HP = hot plate; TST = change in total sleep time; IA = inactive. [c] Yields have not been optimized. [d] A = CH_2Cl_2-ether; B = CH_2Cl_2; C = $CHCl_3$-ether. [e] C_9H_{19} side chain replaced by C_5H_{11}.

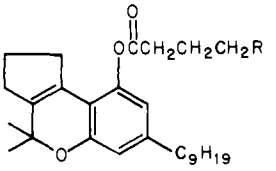
Table III. Basic Esters of DMHP (3)



Compd	R	Chemical properties[a] Yield,[c] %	Mp, °C	Crystn solvent	Pharmacological properties[b] Dopa, 5 mg/kg	Audiogenic seizure, ED_{50}, mg/kg	Mouse fighting, 10 mg/kg	Motor act., mg/kg	Analgesia, ED_{50}, mg/kg	Dog ataxia, mg/kg
3	H				+	2.9	+++	5 (+++)	W (19.6), HP (12.4)	1 (++)
18	-c-NC_5H_{10}·HCl	74	Foam		+	2.8	++	5 (++)	W (25.9)	1 (++)
19	-c-$N(CH_2CH_2)_2O$·HBr	26	123-126	Benzene-ether	++	2.4	++	5 (+++)	W (2.34), RTF (4.2), HP (0.5)	0.05 (+), 1 (++)
20	-c-NC_6H_{12}	40	Gum		+	1.1	5 (++)	1 (++)		1 (++)
21	-c-$N(CH_2CH_2)_2S$	17	Gum		+	>100.0		2 (++)		

[a] C, H, and N analyses for all compounds were within ±0.4% of theoretical values except in the case of compound **18**: C: calcd, 72.89; found, 72.36. [b] For explanation of the table, see footnote *b* in Table II. In the audiogenic seizure (anticonvulsant) test, ED_{50}'s are given in mg/kg po after 4 h. [c] Yields have not been optimized.

Table IV. Basic Esters of Compound 4



Compd	R	Chemical properties[a] Yield,[c] %	Mp, °C	Crystn solvent[d]	Pharmacological properties[b] Dopa, 5 mg/kg	Audiogenic seizure, ED_{50}, mg/kg	Mouse fighting, 10 mg/kg	Motor act., mg/kg	Analgesia, ED_{50}, mg/kg	Dog ataxia, mg/kg
4	H				++	35.3	5 (++), ++	5 (+++)	W (25.3), HP (45.1)	10 (++)
22	-c-NC_5H_{10}·HCl	55	183-185	A	+	182.7	5 (++), ++	5 (IA)	W (46.8), HP (30.2)	1 (+) 10 (++)
23	-c-NC_4H_8·HCl	72	138-141	A	++	50.7	+	5 (+)	W (>40)	1 (+) 10 (++)
24[e]	-c-NC_4H_8·HCl	65	137-141	A	++	100 (IA)	5 (IA)	5 (IA)	W (>20)	
25	-c-NC_6H_{12}·HCl	78	150-152.5	A	+	30 (IA)	+	5 (+)	W (17.9), RTF (25.3)	1 (+) 10(++)
26[e]	-c-NC_6H_{12}·HCl	71	187-188	B	+	100 (IA)	5 (+)	5 (+)	W (>20)	
27	-c-$N(CH_2CH_2)_2O$·HCl	35	151-153	A	+	~60.0	++		W (13.4), HP (16.0)	1 (++)
28[e]	-c-$N(CH_2CH_2)_2O$·HCl	65	181-183	C	+++	50.0	+	5 (IA)	W (>40)	
29	-c-$N(CH_2CH_2)_2S$·HCl	35	175-178	D	+++	55.4	5 (+)	5 (IA)		

[a] C, H, and N analyses for all compounds were within ±0.4% of the theoretical value. [b] For explanation of the table, see footnote *b* in Table II. In the audiogenic seizure test, ED_{50}'s are given in mg/kg po after 1 h. [c] Yields have not been optimized. [d] A = benzene-ether; B = CH_2Cl_2-ether; C = CH_2Cl_2-cyclohexane; D = $CHCl_3$-ether. [e] C_9H_{19} side chain replaced by C_5H_{11}.

when administered intravenously to mice, cats, dogs, and monkeys. The same qualitative profile is observed when these compounds are administered orally to the same species.

SAR Results. Formation of the basic esters of **2** (Table II) reduces the activity in the Dopa test and the rat motor activity of the parent phenol. A similar effect is also observed in their tranquilizing activity (mouse fighting) with the reduction being more pronounced in the case of hindered esters like α-methyl or α,α-dimethyl derivatives (the Greek letters used in names of derivatives with substituents on the alkyl chain of the acid indicate the point of substitution relative to the carbonyl group) (compare **6** or **7** with **5**; **10** with **9**; **15** with **14**). The effect on analgesia varies with the nature of the substituent R. Thus ω-piperidino and morpholino groups retain analgetic activity; α-methyl substitution in both cases has little or no effect; α,α-dimethyl substitution decreases activity. Methyl substitution in the 2 position of the piperidine ring (**9** and **10**) retains activity and varying the length of the

Table V. Analgetic Activity

Compd	Mouse writing test, ED_{50}, mg/kg po[a]	Mouse hot-plate test, ED_{50}, mg/kg po[a]	Rat tail-flick test, ED_{50}, mg/kg po[a]
2	4.3 (3.2-5.9)	7.7 (4.1-12.7)	13.8 (4.5-23.9)
5	12.0 (9.3-16.9)	4.2 (2.0-6.8)	12.5 (9.4-15.7)
Codeine phosphate	15.2 (8.2-24.1)	27.0 (5.2-57.7)	105.9 (19.1-240.9)
d-Propoxyphene	31.8 (26.6-37.3)	57.7 (17.2-86.7)	52.7 (16.9-96.5)
Anileridine hydrochloride	15.6 (11.5-21.1)	10.6 (8.6-13.6)	5.6 (2.8-8.6)

[a] 95% confidence limits are shown in parentheses.

chain also has little effect. Replacement of piperidine or morpholine by pyrrolidine eliminates and diethylamine reduces analgetic activity. Similarly, quarternization of the basic nitrogen (**17**) or replacement of the C_9H_{19} side chain in the aromatic ring by *n*-C_5H_{11} (**13**) eliminates activity. The limited sedative–hypnotic studies show that this activity can be retained but is somewhat decreased by making a very hindered (α,α-dimethyl) ester. An interesting fact which emerges from these studies is the selectivity of action (analgesia and sedative–hypnotic) in the ester derivatives compared to the parent phenol (compare **2** with **5**, **6**, and **10**). Compound **5** is at present undergoing clinical evaluation.

In the case of DMHP (**3**) derivatives (Table III) the selectivity of action is even more pronounced since the parent phenol is moderately active as an analgesic whereas the γ-morpholinobutyrate ester (**19**) is extremely active and is more potent than codeine. All the compounds except the thiomorpholino derivative **21** show potent anticonvulsant activity (audiogenic seizure). One of these derivatives **20** is of particular interest as an anticonvulsant since it is active in a variety of anticonvulsant tests (supramaximal electroshock, metrazol and psychomotor electroshock) and has the potency of Dilantin (ED_{50} 2.7 mg/kg, audiogenic seizure test).

The derivatives of the carbocyclic analog **4** (Table IV) show that masking of the phenol as a basic ester markedly reduces or eliminates the effects on rat motor activity. The analgetic activity is slightly enhanced only in the morpholine (**27**) and homopiperidino (**25**) derivatives. Like the SAR in esters of compound **2** the analgetic activity decreases in the pyrrolidino derivatives or where the C_9H_{19} side chain is replaced by *n*-C_5H_{11} (**24**, **26**). The tranquilizer activity is decreased except in the piperidino and morpholino compounds. In contrast to the DMHP derivatives these compounds have much less anticonvulsant activity and, surprisingly, the homopiperidino analog is inactive (compare **20** with **25**).

We conclude from the SAR of these compounds that (a) basic ester formation of the parent phenol retains biological activity, (b) formation of the ester can lead to a greater selectivity of action, particularly the analgetic activity, and (c) SAR cannot be carried over from one series to another.

As stated above compound **5** is at present undergoing clinical trials. This compound and its parent phenol **2**, which is also being studied in man, are of interest and further pharmacological data relating to their analgetic, cardiovascular, and sedative–hypnotic properties are described below.

Analgetic Activity of Compounds 2 and 5. A comparison of compounds **2** and **5** with codeine and other analgetics is given in Table V. It appears that both compounds **2** and **5** are more potent than codeine.

Table VI. EEG Sleep Studies (Cat)

Compd	Dose, mg/kg po	Δ total sleep time, min[a]	No. of animals
2	0.1	+100 (32-139)	3
	0.5	+44 (43-44)	2
	1.0	+39 (22-59)	3
5	0.1	+38 (22-54)	2
	0.5	+48 (17-84)	5
	1.0	+49 (15-102)	3

[a] Mean values; 95% confidence limits are shown in parentheses.

Table VII. Comparison in Other Pharmacological Tests[a]

Compd	Monkey aggression, MED, mg/kg	Rat desoxyn antagonism, ED_{50}, mg/kg	Acute toxicity, LD_{50}, g/kg	
			Mouse	Rat
2	0.2	3.7 (2.1-7.1)[b]	2.5	0.9
5	<1.0	6.3 (3.5-32.3)[b]	0.57	0.13

[a] Route of administration was po. [b] 95% confidence limits in parentheses.

Cardiovascular Activity of Compounds 2 and 5. Cardiovascular studies of compound **2** showed it to have potent hypotensive effects[1a] in anesthetized intact cats. This activity was confirmed in spontaneous hypertensive rats where 10 mg/kg po caused a significant reduction in BP (up to 32%) lasting 24 h. In three out of five neurogenic hypertensive dogs, 1 mg/kg po produced a moderate decrease (>20%) in arterial BP beginning approximately 40–60 min after drug administration. In four out of five dogs this dose also produced a moderate decrease in heart rate beginning at 10–60 min after administration. When given at 10 mg/kg po, compound **2** produced hypotension (21.4%) and decrease in heart rate of long duration (24–48 h). On the other hand, compound **5** produced inconclusive results in spontaneous hypertensive rats at 10 mg/kg po, since on one occasion blood pressure was reduced but this could not be confirmed. In the neurogenic hypertensive dogs intravenous injection of **5** produced a dose-dependent (0.1, 0.3, 1 mg/kg) decrease in BP and caused a heart rate decrease (3.8, 33.2, and 11.4% with 0.1, 0.3, and 1 mg/kg, respectively) both lasting about 3 h. Significant behavioral effects which lasted for about 4 h were seen only at the high dose of 1 mg/kg.

Both compounds produced inconsistent changes in BP and heart rate in normotensive dogs and are considered inactive at doses as high as 10 mg/kg po.

Sedative–Hypnotic Activity of Compounds 2 and 5. The sedative–hypnotic activity of **2** and **5** was demonstrated in EEG sleep studies using cats with chronic indwelling electrodes. Based on EEG sleep-pattern analysis, both compounds were shown to increase the amount of total sleep time when compared to paired placebo control experiments. The predominant effect on the EEG stages of sleep was an increase in slow wave sleep without affecting REM sleep and a decrease in spindle sleep. A comparison of changes in total sleep time in cats at various doses shows (Table VI) that with compound **2** there is a reverse dose–response relationship to total sleep time. Although this phenomenon was not examined further, it can be explained on the basis of mixed depressant–stimulant activity of this compound which has been observed in other species.

A further comparison in other tests (po) between compounds **2** and **5** is shown in Table VII. In acute toxicity studies in mice, death occurred from 3 to 72 h after drug administration and side effects of decreased activity,

dyspnea, ataxia, jerks, tremors, and clonic convulsions were observed. Compound 2 was approximately three times and compound 5 four times as toxic in rats as in mice. In rats lethality was observed from 18 to 72 h with the same side effects as in mice. In addition, limb abduction, ptosis, and vocalization were noted.

In physical dependence studies[14] both 5 and 2 did not suppress the manifestations of abstinence in morphine-dependent monkeys. Furthermore, compound 5, unlike 2, did not precipitate abstinence. This difference was also shown in narcotic-antagonist studies in mice[1b] where 2 showed long acting (2 days) antagonism to morphine but 5 showed little or no antagonism.

DMHP (3) is a potent cardiovascular agent[1a,15] and has been shown to lower blood pressure in man at doses where no other overt CNS effects are observed.[16,17] It was therefore of interest to determine if the cardiovascular activity was effected by preparing a basic ester. We compared DMHP with compound 19 which is the most potent derivative in the series and found in preliminary experiments that the cardiovascular activity was not changed in spontaneous hypertensive rats. Both compounds reduced BP (38–40%) at 10 mg/kg po for 24 h. Compared to DMHP (3) the other carbocyclic analog 4 was much less active and decreased BP 23% at 4 h and only 11% at 24 h at 10 mg/kg po.

Experimental Section

Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. Elemental analyses were carried out by Spang Microanalytical Laboratories, Ann Arbor, Mich. NMR spectra were determined on a Varian T-60 instrument. Ir and NMR spectra of all compounds were consistent with the assigned structures. TLC used silica gel (Adsorbosil-2) on microscope slides developed in 5–20% CH_3OH–$CHCl_3$ and visualized in iodine. For GLC analysis a Varian Model 1440 instrument was used (column packing, 2% OV-17). All compounds prepared and tested were racemates or mixtures of racemates.

Carboxylic Acids. A typical procedure used for the alkylation and hydrolysis to the acid is illustrated by the following preparation. All materials used in the preparation of these acids were obtained from Aldrich Chemical Co.

α-Methyl-1-piperidinebutyric Acid Hydrochloride. A mixture of 11.3 g (0.054 mol) of ethyl 2-methyl-4-bromobutyrate,[11] 18.5 g (0.218 mol) of piperidine, and 100 ml of PhH was heated at 60° for 4 h and allowed to stand at room temperature for 18 h. The precipitate of piperidine hydrobromide was removed by filtration. The filtrate was concentrated and the product distilled as 9.5 g (83% yield) of colorless liquid, bp 55–58° (0.05 mm). A GLC analysis indicated the material to be free of starting bromo compound with a purity >99%.

A mixture of 9.5 g of the above piperidino compound and 100 ml of aqueous 18% HCl was heated together at reflux temperature for 18 h. The excess acid was removed under reduced pressure to give a residue which crystallized upon trituration with ether. Recrystallization from HOAc–acetone gave 8.35 g (85% yield) of colorless crystals, mp 165–166.5°.

Basic Esters. These were prepared by using the general procedure as described in the preparation of compound 6. In the case of basic esters which were isolated as monohydrochloride salts the material was isolated and crystallized directly after removal of the insoluble material (dicyclohexylurea). The experimental conditions are included for the only example (compound 20) in which the basic ester was isolated as the free base after purification by chromatography. In addition, the preparation of compound 11 via the acrylate ester route and the procedure for the formation of the quarternary salt 17 are described.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-(α-methyl-1-piperidinebutyryloxy)-2-(2-propynyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*d*]pyridine Dihydrochloride (6). Compound 2 (3.0 g, 0.0076 mol) was combined with 1.68 g (0.0076 mol) of α-methyl-1-piperidinebutyric acid hydrochloride, 1.67 g (0.0081 mol) of dicyclohexylcarbodiimide, and 140 ml of CH_2Cl_2 and stirred at room temperature for 18 h. The reaction mixture was cooled and filtered and the filtrate concentrated to give a semisolid residue which was dissolved in 10 ml of CH_2Cl_2–50 ml of cyclohexane. After cooling for 18 h, a small amount of insoluble material (additional dicyclohexylurea) was removed by filtration. The solvents were evaporated, and the ester was converted to the dihydrochloride salt by dissolving in ether and the addition of ethereal HCl. Crystallization from 25 ml of CH_2Cl_2–40 ml of Et_2O in two crops gave 3.90 g (81% yield) of colorless crystals, mp 173–178°.

3-(1,2-Dimethylheptyl)-1-(1-homopiperidinebutyryloxy)-7,8,9,10-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran (20). A mixture of 3.1 g (0.0084 mol) of DMHP (3), 1.86 g (0.0084 mol) of 1-homopiperidinebutyric acid hydrochloride, 1.85 g (0.090 mol) of dicyclohexylcarbodiimide, and 150 ml of CH_2Cl_2 was stirred at room temperature for 16 h. The reaction mixture was cooled and filtered and the filtrate concentrated to a residue which was purified by column chromatography using Florisil and graded CH_3OH–$CHCl_3$ mixtures. Those fractions eluted with 5% CH_3OH–$CHCl_3$ were combined, evaporated, and dried in vacuo to give 1.78 g (40% yield) of the basic ester 20 as a yellow gum.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-(1-piperidinepropionyloxy)-2-(2-propynyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*d*]pyridine Dihydrochloride (11). A mixture of 6.0 g (0.015 mol) of compound 2, 2.24 ml (0.016 mol) of $(C_2H_5)_3N$, 1.26 ml (0.016 mol) of acryloyl chloride, and 80 ml of CH_2Cl_2 was stirred at room temperature for 18 h. Following removal of the precipitated amine hydrochloride by filtration, the filtrate was washed with 1 N HCl, 5% $NaHCO_3$, and water. The solution was dried (Na_2SO_4) and evaporated to give 6.50 g (95% yield) of the acrylate as a brown resin. Anal. ($C_{29}H_{39}NO_3$) C, H, N.

To 2.35 g (0.0052 mol) of the acrylate in 50 ml of CH_2Cl_2 was added slowly, with stirring, a solution of 0.45 g (0.0052 mol) of piperidine in 15 ml of CH_2Cl_2. After stirring overnight at room temperature, the solvent was evaporated under reduced pressure. The addition of ethereal HCl to an ether solution of the residue gave the dihydrochloride salt which crystallized from CH_2Cl_2 as colorless crystals: 2.14 g (67% yield); mp 196–201° dec.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-(1-morpholinebutyryloxy)-2-(2-propynyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*d*]pyridine Dimethiodide (17). To 2.08 g (0.0033 mol) of compound 14 in 60 ml of CH_2Cl_2 was added 0.7 g (0.0066 mol) of $(C_2H_5)_3N$. After stirring for 0.25 h, the solvent was evaporated on a rotary evaporator and excess dry ether was added. The precipitated solid was removed by filtration and the filtrate was evaporated in vacuo to leave a gum which was dissolved in CH_2Cl_2. Excess CH_3I was added and the solution was refluxed for 6 h and left at room temperature for 48 h. After removal of the solvent in vacuo, the residue was dissolved in a small quantity of $CHCl_3$ and precipitated by the addition of a large quantity of dry ether. This procedure was repeated to give a colorless powder: 2.67 g (97% yield); mp 154–159°.

Pharmacology. All compounds were administered orally. The basic esters were dissolved in water prior to administration whereas compounds 2 (powder), 3 (gum), and 4 (gum) were given as a suspension in olive oil and 0.5% methylcellulose and, in some cases, as powder in a gelatin capsule (dogs, cardiovascular studies) or mixed with food (cats, sedative–hypnotic studies).

Acute Toxicity Studies. A dose–response curve was obtained for acute oral toxicity of compounds 2 and 5 in mice and rats. Various doses of the drug prepared as a 5% solution in 0.5% methylcellulose solution were given to groups of ten female Swiss–Webster mice, 16–24-g weight, and to groups of six male Rolfsmeyer (Sprague–Dawley "derived") rats, 50–100-g weight. The groups were observed for 7 days and a LD_{50} with 95% confidence limits was calculated by the Litchfield and Wilcoxon[18] method.

Neuropharmacological Studies. The *spontaneous motor activity studies* were carried out in male Long–Evans rats in chambers equipped with photocells (Lehigh Valley, Model 1497, 24 in. diameter). The animals were medicated 2 h prior to placement in test chambers. Three animals were placed in each chamber and a total of nine animals used per test dose. Motor activity was recorded as counts from the photocells over a 2-hr

period and the drug-induced effects were reported as a percent change from the vehicle control values.

The compounds were tested in the (±)-*Dopa potentiation test*[19] to detect potential antidepressant activity. This test consisted of determining the potentiation of motor responses to mice to a challenge dose of (±)-Dopa (200 mg/kg ip) following pretreatment with the monoamine oxidase inhibitor pargyline (40 mg/kg po) and the test compound. The test drug was given to four animals and the Dopa challenge was administered 4 h after the test drug. The mice were then observed and graded. The mice showed a maximal behavioral response consisting of a marked increase in motor activity, jumping, squeaking, and fighting (+++ response) if the test compound is an active antidepressant agent such as imipramine or amitriptyline.

The *mouse fighting test* (footshock-induced fighting behavior in mice) was carried out for potential tranquilizer activity using a modified Tedeschi procedure.[20] Male, albino BALB/cJ mice (Jackson Labs), weighing 12–22 g, were paired on an equal weight basis and each pair was trained to fight in response to footshock. The paired mice were placed on the grid floor of an open-top plexiglass chamber (Lehigh Valley fighting mouse apparatus) and confined under an 800-ml glass beaker. When electroshock was delivered to the grids, the mice responded with distinct and easily recognized aggressive and/or escape responses. The duration of footshock for each test session was limited to 1 min. After training, the animals were tested before (control) and at 30 and 90 min after drug administration. The number of aggressive responses obtained in each test session after drug administration was converted to a percentage of the predrug control values. The data recorded in the tables correspond to readings taken after 90 min.

The *antinociceptive properties* of these compounds were studied by determining ED_{50} values in various procedures. A modification of Whittles[21] procedure for the acetic acid writhing test was used. The test drug was given orally 30 min prior to injection (ip) of acetic acid and the number of writhes per group of five mice was counted for a 20-min period beginning 5 min after the injection of the acid. Analgetic potency was calculated from the difference between the test groups and their controls. For the *tail-flick test* a modification of the method of D'Amour and Smith[22] was used. A light source was focused on the ink-blackened tails of male rats (150–210 g, Sprague–Dawley) in groups of ten and the time was recorded until an escape response occurs. The intensity of the stimulus was moderated through a Variac adjustment so that the normal response time averages approximately 7 sec as reported by Gray et al.[23] Two normal pain thresholds were recorded for each rat at least 30 min apart. The test compound was then administered orally (0.025–2.5% suspensions in 0.5% methylcellulose) at various dose levels and response readings were taken at 15, 30, 45, 60, and 90 min. The results were expressed as graded responses, calculated from percent increase over normal pain threshold values. The ED_{50} values were calculated from the linear regression curve using the greatest analgetic activity obtained at any test period. The mouse *hot-plate test* was used according to the procedure of Woolfe and Macdonald.[24]

Dog ataxia studies were carried out on adult beagle-like dogs. In this test dogs were given a single dose of the drug and observed for 24 h at regular intervals starting with 15 min after the administration of the test drug. The compound was rated as showing "decreased activity" if the dog showed reduced reactivity to the observer when he entered the test room. Unmedicated dogs generally responded to the observer's entry by barking, jumping, and pacing back and forth in their cages.

Potential anticonvulsant activity was determined by the *audiogenic seizure test*.[25] Groups of five mice, specially bred for susceptibility to audiogenic seizures, were employed and the drug was administered 1 and 4 h before testing in an auditory stress chamber.

The *sedative–hypnotic studies* were carried out in adult male cats which were prepared surgically with chronic indwelling electrodes to monitor cortical EEG potentials, eye movements (EOG), and neck muscle potentials (EMG). The animals were acclimated to dimly lit, sound attenuated experimental chambers with white noise provided to mask unwanted external sounds and with a plexiglass door to allow observation of gross behavior on closed circuit television.

All experimental sessions began at approximately 5:00 p.m. and had a duration of at least 14 h. The animals were routinely fed at the start of each session and polygraph recordings were made continuously thereafter throughout the night. To administer the drug substances orally to the cat, the drug was mixed in cat food which was presented at the usual feeding time. The food was generally consumed within 15–20 min.

For compounds **2** and **5** the MED and ED_{50} values were determined in the *monkey aggression* and the *rat desoxyn tests*, respectively. In the former, six rhesus monkeys were preselected for high scores in responsiveness to pole prodding. The response of the hostile aggressive monkey to pole prodding includes biting, pushing, vocalizing (screeching), attacking, jumping and riding on the pole, alternating with running and evasion of the pole, etc. The animals were tested before and at hourly intervals after drug administration; reduction or absence (abolition) of any of these responses was considered to be a drug effect. In the rat desoxyn test, the antagonism or potentiation of methamphetamine-induced hyperactivity in rats is evaluated in motor activity chambers equipped with photocells (Lehigh Valley, Model No. 1497). Groups of rats are premedicated with the test compound and then administered methamphetamine (1 mg/kg ip). One rat is placed in each chamber and three rats are used per test dose. Changes in motor activity are recorded as counts from the photocells and compared to methamphetamine-treated controls.

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Drugs Derived from Cannabinoids. 5. $\Delta^{6a,10a}$-Tetrahydrocannabinol and Heterocyclic Analogs Containing Aromatic Side Chains

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Ten new $\Delta^{6a,10a}$-THC analogs with arylalkyl side chains, one with a dimethylaminoalkyl side chain, and six heterocyclic $\Delta^{6a,10a}$-THC analogs [8-substituted 5,5-dimethyl-10-hydroxy-2-(2-propynyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-c]pyridines] were prepared. They showed pharmacological activity as analgesics, tranquilizers, antihypertensives, and hypnotics and as antisecretory, antiulcer, and antidiarrheal agents. The most potent compounds had either a 1-methyl-4-(4-fluorophenyl)butyl or a 1,2-dimethyl-4-(4-fluorophenyl)butyl side chain.

Adams and co-workers, in the 1940's, found that changes in the side chain had a profound influence on the pharmacological activity of $\Delta^{6a,10a}$-THC (**1c**). They made a series of analogs with branched and linear aliphatic hydrocarbon chains in place of the natural *n*-C_5H_{11} group and discovered that $\Delta^{6a,10a}$-THC with the 1,2-dimethylheptyl side chain (**1a**) was the most potent in producing ataxia in the dog.[1] More recently Loev and co-workers[2] also varied the side chain in $\Delta^{6a,10a}$-THC and found that the compound with the 1,1-dimethylheptyl side chain (**1b**) is twice as active as **1a** in producing overt symptoms in the rat. (Adams reported **1b** to be much less active than **1a** in the dog.) Other variations in the side chain studied by Loev were (1) unsaturation in the 1 position of the side chain of **1a** (activity equal to **1a**); (2) an ether linkage OCHMe-*n*-C_5H_{11} (much less active); (3) $CH(n\text{-}C_4H_9)_2$ (inactive). Both Adams and Loev found that the *n*-C_5H_{11} side chain in the unnatural $\Delta^{6a,10a}$-THC series gives a compound with little, if any, activity in their tests. Compound 1 (R = O-*n*-C_6H_{13}) showed no activity in the corneal reflex test in rabbits.[4]

Other workers have studied variations of the side chain in the natural series, Δ^8-THC (**2**) and Δ^9-THC (**3**). Even in these systems, the dimethylheptyl analogs (**2a** and **3a**) are much more potent than the natural compounds themselves in producing behavioral changes (stupor, ataxia, ptosis, crouched posture) in the rhesus monkey.[5] Petrzilka has synthesized compounds **2a** and **3a**[6] as well as **2** with R = $NMe(CH_2)_3NMe_2$[7] and a 3-(1-methyl-3-propyl-3-pyrrolidinyl)[8] side chain. No biological activity was reported. Fahrenholtz synthesized Δ^8-THC with a 1-hydroxypentyl and a 3-hydroxypentyl side chain as metabolites of Δ^8-THC.[9]

In the preceding papers[10-12,18] and earlier communications,[13,14] Pars and Razdan have incorporated the 1,2-dimethylheptyl side chain into various heterocyclic (**4a**, **5a**, **6a**, **7a**) and carbocyclic analogs (11) of $\Delta^{6a,10a}$-THC and reported their biological activity in various CNS tests.

They found that the nitrogen analog **4a** (R' = $CH_2C{\equiv}CH$) had analgesic activity ranging between that of codeine and morphine with no physical dependence liability.[10,15]

The sulfur analog **5a** (R' = H) was also active.[12,13] In the carbocyclic series, other workers reported that Δ^9-THC was active[16] in the tail-pinch and hot-plate tests and Adams' compound **1a** was found to be a potent analgesic[2] in rats in the hot-wire test. Furthermore, Pars and Razdan synthesized[3] the $\Delta^{6a,10a}$-THC analog 1 [R = $CH_2CH_2N(CH_3)_2$] with a basic side chain and reported it to produce "significant CNS effects when given intravenously to dogs".

In this paper we report on the synthesis and pharmacological activity of various $\Delta^{6a,10a}$-THC's and their nitrogen, sulfur, and carbocyclic analogs with an arylalkyl side chain (Chart I).

Chemistry. The $\Delta^{6a,10a}$-THC derivatives were prepared using Adams' procedure of condensing a 5-substituted resorcinol with ethyl 3-methylcyclohexanone-5-carboxylate to give the dibenzopyrones **14** (see Scheme I). These were treated with methylmagnesium bromide to give the final products. These products consisted of about 95% $\Delta^{6a,10a}$-THC (**1**) and about 5% of the double bond isomer **15**. The presence of this isomer was revealed in the NMR. There was an olefinic proton at 400 Hz (doublet) (the downfield shift due to the proximity to the hydroxyl oxygen) and an OH peak different from **1**. The isomer **15** could be partially separated by column chromatography from the main product **1**.

By condensing the 5-substituted resorcinol with *N*-benzyl-4-carbethoxy-3-piperidone hydrochloride in a modification of the method of Pars et al.,[10] the pyridobenzopyrone **16** was obtained. We found that the use of methanesulfonic acid in place of sulfuric acid as solvent gave better and more reproducible yields. The pyrones **16** were treated with methylmagnesium bromide to give **17**. In this series there was no evidence of double bond isomerism. The benzyl group was removed by hydrogenation and the propargyl compound prepared by alkylation with propargyl bromide. In this last step, it was necessary to use 2 mol of base **18** to one of propargyl bromide to get good yields. Many different proton ac-