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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]

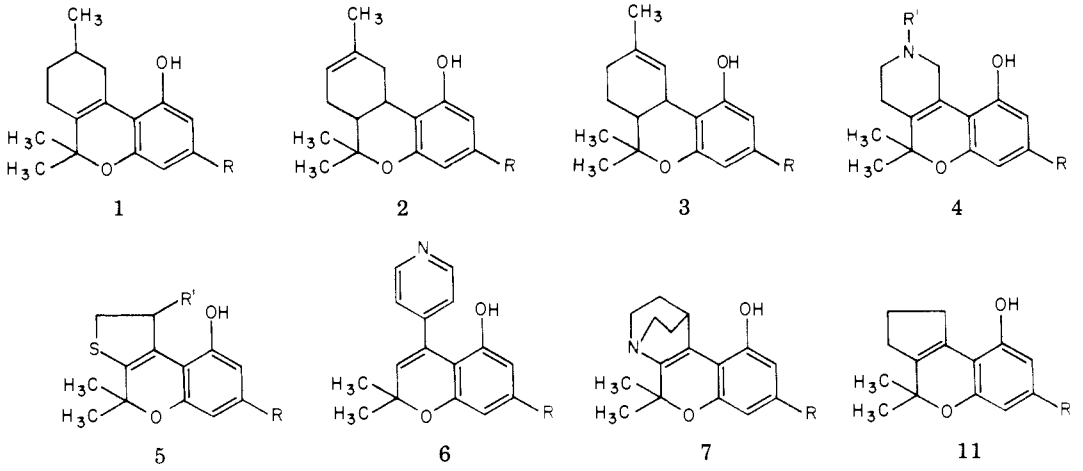
The sulfur analog **5a** (R' = H) was also active.[12,13] In the carbocyclic series, other workers reported that Δ^9-THC was active[16] in the tail-pinch and hot-plate tests and Adams' compound **1a** was found to be a potent analgesic[2] in rats in the hot-wire test. Furthermore, Pars and Razdan synthesized[3] 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**.

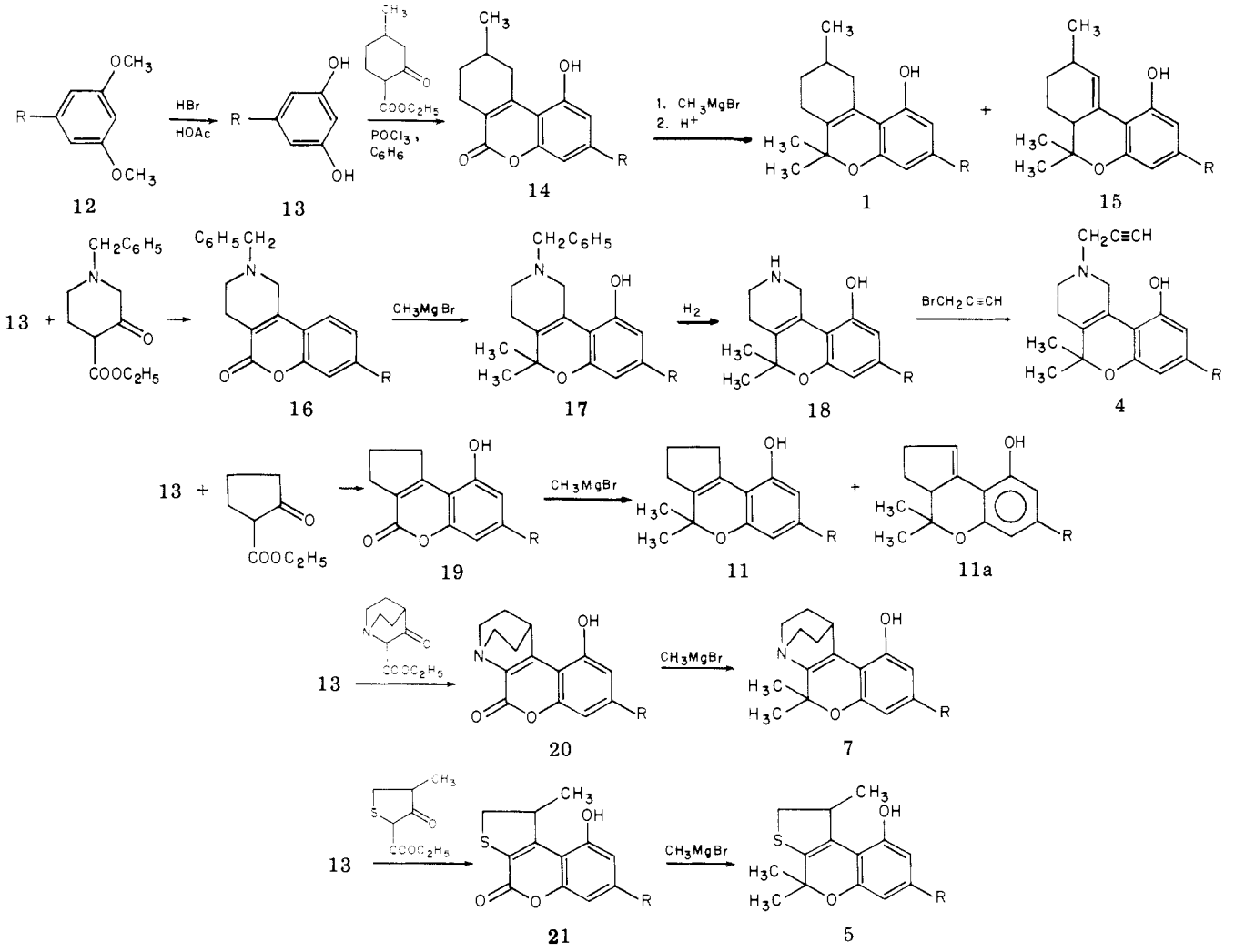
By condensing the 5-substituted resorcinol with *N*-benzyl-4-carbethoxy-3-piperidone hydrochloride in a modification of the method of Pars et al.,[10] the pyridobenzopyrone **16** was obtained. We found that the use of methanesulfonic acid in place of sulfuric acid as solvent gave better and more reproducible 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-

Chart I



a, R = $CH(CH_3)CH(CH_3)C_5H_{11}$
b, R = $C(CH_3)_2C_6H_{13}$
c, R = C_5H_{11}

Scheme 1



ceptors (diisopropylethylamine, 2,6-lutidine, K_2CO_3, etc.) were tried to drive the reaction to completion, but none were successful. The excess starting material **18** could be recovered and recycled with more propargyl bromide.

The resorcinols **13** were prepared using 3,5-dimethoxyacetophenone or 3,5-dimethoxypropiophenone as starting material and following the steps indicated in Scheme II. The 5-[1,2-dimethyl-3-(4-fluorophenyl)-propyl]resorcinol was prepared as outlined in Scheme III. In all cases, the dimethoxyresorcinols (Table I) were demethylated, using HBr–AcOH conditions, and used in the subsequent reaction without further purification. The various intermediate pyrones and final pyrans are shown in Table II.

After completing a number of variations of the side chain in **1** and **4**, the most active side chain [1-methyl-4-(4-fluorophenyl)butyl] was put on three other ring systems, **7**, **11**, and **5** (R' = CH_3) (Scheme I), by condensing 5-

Scheme II

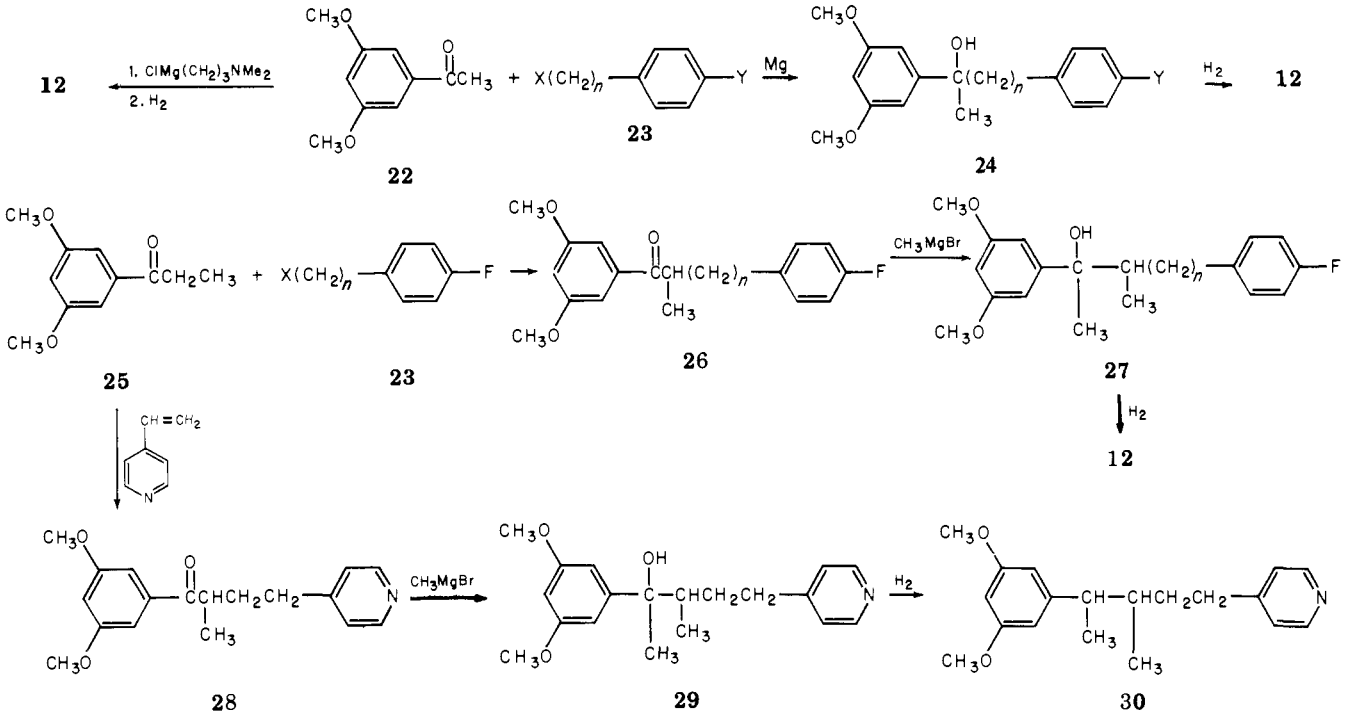
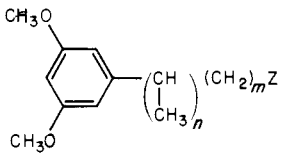
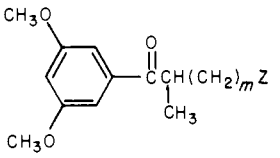


Table I. 5-Substituted Resorcinol Dimethyl Ethers[a]



12d-m, 30



26j,k, 28

No.	*n*	*m*	Z	Formula	Bp (mm), °C	% yield	Synthetic method	Analyses
12d	1	2	4-F-C_6H_4	$C_{18}H_{21}FO_2$	145-155 (0.3)	77	A	C, H
12e	1	3	4-F-C_6H_4	$C_{19}H_{23}FO_2$	145-155 (0.3)	82	A	C, H
12f	1	4	4-F-C_6H_4	$C_{20}H_{25}FO_2$	155-160 (0.3)	72	A	C, H
12g	1	3	C_6H_5	$C_{19}H_{24}O_2$	150-155 (0.3)	70	A	
12h	1	3	4-CH_3-C_6H_4	$C_{20}H_{26}O_2$	170-175 (0.6)	81	A	C, H
12i	2	1	4-F-C_6H_4	$C_{19}H_{23}FO_2$	154-162 (0.1)	35	D	
12j	2	2	4-F-C_6H_4	$C_{20}H_{25}FO_2$	150-155 (0.3)	83	A	C, H
12k	2	3	4-F-C_6H_4	$C_{21}H_{27}FO_2$	170-180 (0.3)	81	A	
12m	0	5	4-F-C_6H_4	$C_{19}H_{23}FO_2$	150-160 (0.5)	67	A	
30	2	2	4-Pyridyl	$C_{19}H_{25}NO_2$	180-185 (0.3)	71	A	C, H
12n	1	3	$N(CH_3)_2$	$C_{15}H_{25}NO_2$	120-125 (0.6)	60	A	C, H, N
26j	0	2	4-F-C_6H_4	$C_{19}H_{21}FO_3$	170-175 (0.3)	69	B	
26k		3	4-F-C_6H_4	$C_{20}H_{23}FO_3$	175-185 (0.3)	51	B	
28		2	4-Pyridyl	$C_{18}H_{21}NO_3$	195-205 (0.3)	91	C	C, H, N

[a] The letter following the structure number always refers to the same side chain in all structures.

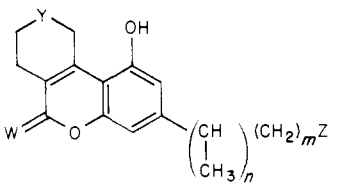
[1-methyl-4-(4-fluorophenyl)butyl]resorcinol with the appropriate keto esters and reacting the resulting pyrones with methylmagnesium bromide using the methods of Razdan and Pars.[10,12,18] The products **5** and **7** showed no evidence of the double bond isomerism seen in **1**; however, in **11** 15–20% of the double bond isomer **11a** was found in the final product.

The most active compounds, **1e** and **4e** (see Table III), were converted into basic esters **35**, **36**, and **32–34** by procedures[11] described earlier in an effort to get water-soluble derivatives for pharmacological testing. The derivatives of **1e** were only slightly water soluble as hydrochlorides, and the basic esters of **4e** were very water soluble as dihydrochlorides but not as monohydrochlorides.

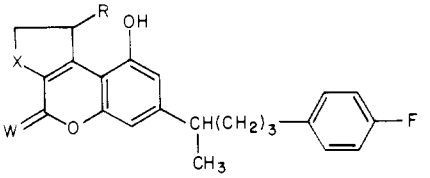
Pharmacology and Structure–Activity Relationships. The final products and some of the intermediates were tested as possible analgesic agents, hypnotics, antidepressants, antipsychotics, tranquilizers, antiulcer agents, antidiarrheal agents, antihypertensives, and anticonvulsants.

Analgesic Activity. These compounds were very potent analgesic agents (more potent than pentazocine) using the writhing method in the mouse and the tail-flick method in the rat. The most potent compounds had the 1-methyl-4-(4-fluorophenyl)butyl (**1e**, **4e**, **5e**, **31–36**), the 1,2-dimethyl-4-(4-fluorophenyl)butyl (**1j** and **4j**), the 1,-2-dimethyl-4-(4-pyridyl)butyl (**8**), as well as the Adams' 1,2-dimethylheptyl (**2a**, **4a**) side chains. Molecular models show that these most active aromatic side chains have the same extended length as Adams' 1,2-dimethylheptyl side chain. The models also show that in the compounds with the most active side chains, the aromatic ring fits easily

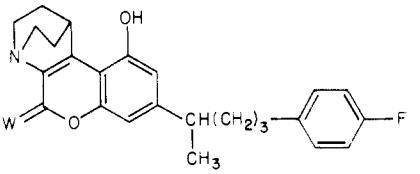
Table II. Tetrahydrocannabinol Analogs with Arylalkyl Side Chains and Intermediate Pyrones. Physical Properties[a]



14d-p, Y = $CHCH_3$, W = O
16c-k, Y = $NCH_2C_6H_5$, W = O
1d-m, 8, 9, Y = $CHCH_3$; W = $(CH_3)_2$
17c-k, Y = $NCH_2C_6H_5$; W = $(CH_3)_2$
18c-k, Y = NH; W = $(CH_3)_2$
4c-k, Y = $NCH_2C{\equiv}CH$; W = $(CH_3)_2$



19, W = O; X = C; R = H
11e, W = $(CH_3)_2$; X = C; R = H
21, W = O; X = S; R = CH_3
5e, W = $(CH_3)_2$; X = S; R = CH_3

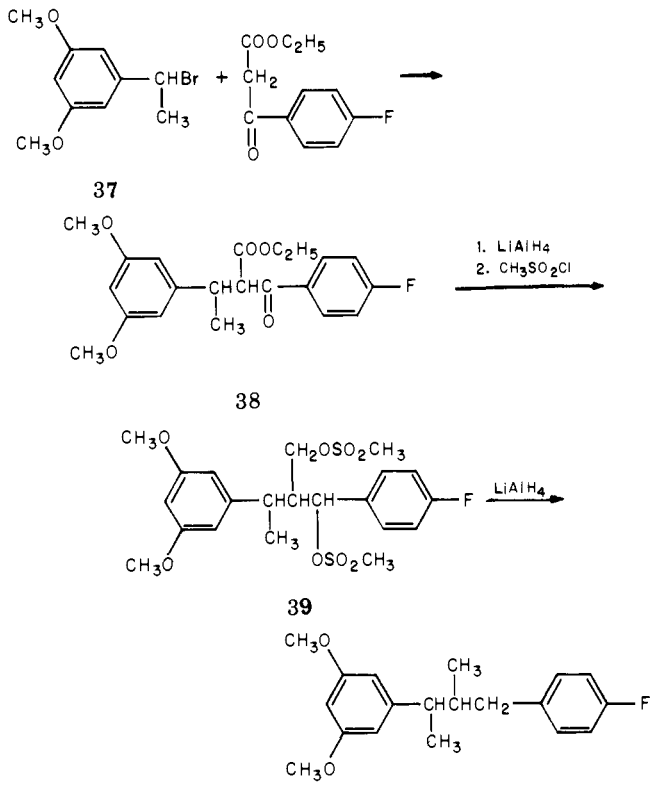


20, W = O
7e, W = $(CH_3)_2$

No.	n	m	Z	Formula	Mp, °C	% yield	Synthetic method	Analyses
14d	1	2	4-F-C_6H_4	$C_{24}H_{25}FO_3$	148-150	70	E	C, H
14e	1	3	4-F-C_6H_4	$C_{25}H_{27}FO_3$	127-129	60	E	C, H
14f	1	4	4-F-C_6H_4	$C_{26}H_{29}FO_3$	146-147	67	E	C, H
14g	1	3	C_6H_5	$C_{25}H_{28}O_3$	129-131	55	E	C, H
14h	1	3	4-CH_3-C_6H_4	$C_{26}H_{30}O_3$	133-135	61	E	C, H
14i	2	1	4-F-C_6H_4	$C_{25}H_{27}FO_3$	Oil	88	E	
14j	2	2	4-F-C_6H_4	$C_{26}H_{29}FO_3$	Oil	89	E	
14k	2	3	4-F-C_6H_4	$C_{27}H_{31}FO_3$	116-117	68	E	C, H
14m	0	5	4-F-C_6H_4	$C_{25}H_{27}FO_3$	132-133	67	E	C, H
14n	2	2	4-Pyridyl	$C_{25}H_{29}NO_2$	163-165	66	I	C, H, N
14p	1	3	$N(CH_3)_2$	$C_{21}H_{29}NO_2$	140-142	76	G	C, H, N
1d	1	2	4-F-C_6H_4	$C_{26}H_{31}FO_2$	Oil	85	F	C, H
1e	1	3	4-F-C_6H_4	$C_{27}H_{33}FO_2$	Oil	83	F	C, H
1f	1	4	4-F-C_6H_4	$C_{28}H_{35}FO_2$	Oil	95	F	C, H
1g	1	3	C_6H_5	$C_{27}H_{34}O_2$	Oil	86	F	C, H
1h	1	3	4-CH_3-C_6H_4	$C_{28}H_{36}O_2$	Oil	73	F	C, H
1i	2	1	4-F-C_6H_4	$C_{27}H_{33}FO_2$	Oil	21	F	C, H
1j	2	2	4-F-C_6H_4	$C_{28}H_{35}FO_2$	Oil	68	F	C, H
1k	2	3	4-F-C_6H_4	$C_{29}H_{37}FO_2$	Oil	80	F	C, H
1m	0	5	4-F-C_6H_4	$C_{27}H_{33}FO_2$	Oil	80	F	C, H
8	2	2	4-Pyridyl	$C_{27}H_{35}NO_2$	Oil	39	J	C, H, N
9	1	3	$N(CH_3)_2$	$C_{23}H_{35}NO_2$	Oil	59	H	C, H, N
16c	0	5	H	$C_{24}H_{27}NO_3 \cdot HCl$	270-273	43	K	C, H, N
16d	1	2	4-F-C_6H_4	$C_{29}H_{28}FNO_3 \cdot HCl$	243-246	58	K	C, H, N
16e	1	3	4-F-C_6H_4	$C_{30}H_{30}FNO_3 \cdot HCl$	254-256	62	K	C, H, N
16f	1	4	4-F-C_6H_4	$C_{31}H_{32}FNO_3 \cdot HCl$	227-228	34	K	C, H, N
16h	1	3	4-CH_3-C_6H_4	$C_{31}H_{33}NO_3 \cdot HCl$	236-240	60	K	C, H, N
16j	2	2	4-F-C_6H_4	$C_{31}H_{32}FNO_3 \cdot HCl$	252-255	53	K	C, H, N
16k	2	3	4-F-C_6H_4	$C_{32}H_{34}FNO_3 \cdot HCl$	217-218	60	K	
17c	0	5	H	$C_{26}H_{33}NO_2$	204-205	42	L	C, H, N
17d	1	2	4-F-C_6H_4	$C_{31}H_{34}FNO_2$	191-193	73	L	C, H, N
17e	1	3	4-F-C_6H_4	$C_{32}H_{36}FNO_2$	188-190	75	L	C, H, N
17f	1	4	4-F-C_6H_4	$C_{33}H_{38}FNO_2 \cdot HCl$	208-210	60	L	C, H, N
17h	1	3	4-CH_3-C_6H_4	$C_{33}H_{39}NO_2 \cdot HCl$	225-226	80	L	C, H, N
17j	2	2	4-F-C_6H_4	$C_{33}H_{38}FNO_2$	201-204	83	L	C, H, N
17k	2	3	4-F-C_6H_4	$C_{34}H_{40}FNO_2 \cdot HCl$	217-218	92	L	C, H, N
18c	0	5	H	$C_{19}H_{27}NO_2 \cdot HCl$	259-261	93	M	C, H, N
18d	1	2	4-F-C_6H_4	$C_{24}H_{28}FNO_2$	Glass	95	M	
18e	1	3	4-F-C_6H_4	$C_{25}H_{30}FNO_2 \cdot HCl$	222-225	96	M	C, H, N
18f	1	4	4-F-C_6H_4	$C_{26}H_{32}FNO_2$	Glass	90	M	C, H, N
18h	1	3	4-CH_3-C_6H_4	$C_{26}H_{33}NO_2$	Glass	93	M	
18j	2	2	4-F-C_6H_4	$C_{26}H_{30}FNO_2$	Glass	97	M	
18k	2	3	4-F-C_6H_4	$C_{27}H_{32}FNO_2$	Glass	91	M	C, H, N
4c	0	5	H	$C_{22}H_{29}NO_2$	186-187	61	N	C, H, N
4d	1	2	4-F-C_6H_4	$C_{27}H_{30}FNO_2$	174-175	41	N	C, H, N
4e	1	3	4-F-C_6H_4	$C_{28}H_{32}FNO_2$	164-166	82	N	C, H, N
4f	1	4	4-F-C_6H_4	$C_{29}H_{34}FNO_2$	146-147	64	N	C, H, N
4h	1	3	4-CH_3-C_6H_4	$C_{29}H_{35}NO_2$	159-160	80	N	C, H, N
4j	2	2	4-F-C_6H_4	$C_{29}H_{34}FNO_2$	174-177	55	N	C, H, N
4k	2	3	4-F-C_6H_4	$C_{30}H_{36}FNO_2$	155-156	76	N	C, H, N
19	1	3	4-F-C_6H_4	$C_{23}H_{23}FO_3$	133-135	54	E	C, H
11e	1	3	4-F-C_6H_4	$C_{25}H_{29}FO_2$	Oil	71	F	C, H
21	1	3	4-F-C_6H_4	$C_{23}H_{23}FO_3S$	Oil	63	Q	
5e	1	3	4-F-C_6H_4	$C_{25}H_{29}FO_2S$	Oil	16	R	C, H
20	1	3	4-F-C_6H_4	$C_{25}H_{26}FNO_3 \cdot HCl$	279-281	48	O	C, H, N, Cl
7e	1	3	4-F-C_6H_4	$C_{27}H_{32}FNO_2 \cdot HBr$	284-286	70	P	C, H, N
31	1	3	4-F-C_6H_4	$C_{30}H_{34}FNO_3$	Oil	85	S	C, H, N
32	1	3	4-F-C_6H_4	$C_{37}H_{47}FN_2O_3 \cdot HCl$	109-110	99	T	C, H, N
33	1	3	4-F-C_6H_4	$C_{36}H_{45}FN_2O_4 \cdot 2HCl$	139-141	82	T	C, H, N, Cl
34	1	3	4-F-C_6H_4	$C_{37}H_{47}FN_2O_4 \cdot 2HCl$	185-187	96	T	C, H, N, Cl
35	1	3	4-F-C_6H_4	$C_{36}H_{48}FNO_3 \cdot HCl$	Glass	98	T	C, H, N, Cl
36	1	3	4-F-C_6H_4	$C_{35}H_{46}FNO_4 \cdot HCl$	144-147	97	T	C, H, N

[a] For 31-36, see Table III for structures.

Scheme III



12d

on top of and parallel to the phenol portion of the ring system, while in the compounds with the shorter (**1d,i**) and longer (**1f,k,l, 4f,k**) distance between aromatic and phenolic rings, the aromatic ring cannot assume a position directly over and parallel to the phenol ring. Thus, one might speculate that compounds in which the phenol portion of the molecule is in a hydrophobic environment are the most active. Similar to our experience in the sulfur analogs with a 1,2-dimethylheptyl side chain,[18] compound **5e**, in which there is a methyl group in close proximity to the phenolic hydroxyl group, is much more active than **11e** in which the OH is relatively exposed. Of all the various compounds prepared and tested by us, the ones with a parafluoro substitution showed the maximum activity (**1e** > **1g** or **1h**, and **4e** > **4h**).

Many of the $\Delta^{6a,10a}$-THC derivatives with aromatic side chains were as potent as Adams' **1a** in the mouse. In the rat **1a** was one of the most active of the $\Delta^{6a,10a}$-THC analogs tested. In the heterocyclic series, the aromatic **4e** was equally potent to the 1,2-dimethylheptyl analog **4a** in the mouse but four times as potent as **4a** in the rat. Putting the natural C_5H_{11} side chain on the heterocyclic system (**4c**) gave a relatively inactive compound.

The compound with a strongly basic side chain (**9**) was inactive as compared to the active but weakly basic pyridyl compound (**8**). All of the intermediates (Table II) were relatively inactive.

Tranquilizer Activity. The tests for tranquilizer or antianxiety activity included the fighting mouse, monkey antiaggression, rat motor activity, and dog ataxia tests (see Experimental Section for details). The structure–activity relationships in these tests for the most part paralleled the analgesic tests.

The most active compounds in the fighting mouse test were **1e** and **5e**, which were also the best analgesics. The nitrogen-containing analog **4** was less potent than the $\Delta^{6a,10a}$-THC analog in the fighting mouse. Surprisingly, **1j**, **8**, **32–34**, and **36**, while highly active as analgesics, were inactive here. While Δ^9-THC was active in our mouse model, Manning[17] found Δ^9-THC to be inactive in a similar fighting rat model.

The $\Delta^{6a,10a}$-THC analog **1e** was active at 0.1 mg/kg in reducing aggressive behavior in monkeys. The nonfluorinated analog **1g** as well as Petrzilka's **2a**, Δ^9-THC, and several esters of **1e** and **4e** were also highly active in this test.

In the dog ataxia test (similar to the one Adams used in his original studies), the most active compound was **1e** and its ester **35**. They were both more active than Adams' **1a**.

Our data show that the most active analgesics **1a,e,j**, **4a,e,j**, and **5e** and esters **31–36** were also the most active in suppression of rat motor activity, an exception being **1f** which was more active in rat motor activity than its analgesic potency would have predicted.

Antipsychotic activity was determined by measuring reduction of methamphetamine (Desocyn) induced hyperactivity in the rat. The carbocyclic THC analogs **1a,e–h,j**, **2a**, **35**, and **36**, the sulfur analog **5e**, and the nitrogen analog **4a** were as active as chlorpromazine in this test. While most of the 1 series showed activity, in the nitrogen analogs only **4a** with the aliphatic side chain was active. Surprisingly, **1f**, although not having optimum chain length, was active. Putting a 2-methyl group on this chain (**1k**), a substitution which usually enhances activity, gave an inactive compound.

Antidepressant Activity. The Dopa potentiation test of Everett[19] was run on most compounds. Δ^9-THC was active in this test at 5 mg/kg (oral dose). This is in contrast to Sofia's[20] findings who reported Δ^9-THC to be inactive as an antidepressant in the tetrabenazine antagonism test. The only other active compounds were the following (minimum dose in parentheses, mg/kg): **1e** (10), **2a** (20), **4a** (2), **7e** (20), and **8** (20).

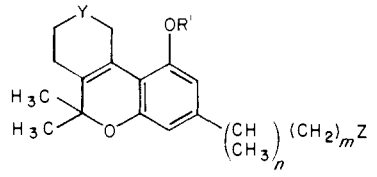
Anticonvulsant activity was determined by measuring the drug's ability to protect specially bred mice against audiogenic seizures. Of the compounds tested, only the following were active in protecting 80% of the mice (oral dose in mg/kg): Δ^9-THC (20), **1a** (10), **1e** (**30**), and **1g** (30). It is difficult to explain the inactivity of **2a** in light of the activity of Δ^9-THC and **1a**. Recently several investigators have shown anticonvulsant activity for Δ^9-THC in animals.[21-24]

Antihypertensive activity was determined in the spontaneous hypertensive (SH) rat for selected compounds. The data are presented in Table III. All of the $\Delta^{6a,10a}$-THC analogs (**1a–m**) were active in the SH rat except **9** which has the strongly basic NMe_2 in the side chain. Compound **8** with the weakly basic pyridine ring in the side chain showed moderate activity. The carbocyclic analog **11e** showed activity with delayed onset of action. Among the nitrogen analogs, **4a** and **4e** were active but compounds with a shorter (**4d**), longer (**4f**), or the C_5H_{11} (**4c**) side chain were inactive. Δ^9-THC was active but less potent than the $\Delta^{6a,10a}$-THC analogs. Thus we see a separation of the analgesic and antihypertensive activity in that **1d,h,i,k,m** had weak analgesic activity but were antihypertensive at a 3 mg/kg oral dose.

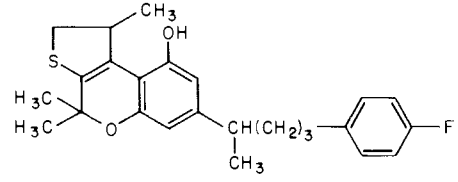
Nahas[25] showed antihypertensive activity and tolerance to Δ^9-THC itself in the SH rat. In normal rats[26] and cats,[27] Δ^9-THC has been reported to show hypotensive activity.

Hypnotic activity was determined in cats implanted with chronic electrodes for continuous measurement of the EEG. The data are present in Table IV. Nitrogen and $\Delta^{6a,10a}$-THC analogs with an aromatic side chain were active in this test whereas the sulfur analog **5e** was inactive.

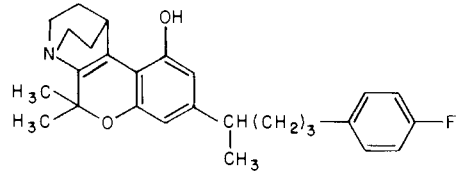
Table III. Pharmacology of Tetrahydrocannabinol Analogs with Arylalkyl Side Chains[a,h]



1d-m, Y = $CHCH_3$; Z = C_6H_4R; R' = H
4d-k, Y = $NCH_2C{\equiv}CH$; Z = C_6H_4R; R' = H
8, Y = $CHCH_3$; Z = C_5H_4N; R' = H
9, Y = $CHCH_3$, Z = NMe_2; R' = H
11, Y = —; Z = C_6H_4R
31, Y = $NCH_2C{\equiv}CH$; R' = $CH_3C{=}O$
32, Y = $NCH_2C{\equiv}CH$; R' = c-$C_5H_{10}N(CH_2)_3C{=}O$
33, Y = $NCH_2C{\equiv}CH$; R' = c-$O(CH_2CH_2)_2N(CH_2)_3C{=}O$
34, Y = $NCH_2C{\equiv}CH$; R' = c-$O(CH_2CH_2)_2NCH_2CH_2CH(CH_3)C{=}O$
35, Y = $CHCH_3$, R' = c-$C_5H_{10}N(CH_2)_3C{=}O$
36, Y = $CHCH_3$; R' = c-$O(CH_2CH_2)_2N(CH_2)_3C{=}O$



5e



7e

No.	n	m	R	Analgesia[b] RTF	Analgesia[b] Wr	Fighting mouse[c]	Rat motor act.[d]	Rat desoxyn antagonism[d]	Monkey anti-aggression[e]	Dog ataxia[f]	Antihypertensive act.[g]
3c	Δ⁹-THC			27.2	43.0	68 (10)	14 (5), 72 (20)	15 (5), 41 (10)	1.0	0.5	39, 21 (25); 6, 8 (10)
2a					7.9	89 (10)	60 (1.25)	52 (2.5), 81 (5)	1.0		
1a				1.4	3.0	58 (5), 92 (10)	96 (5)	48 (2.5), 70 (5)	10.0	1.0	37, 28 (3); 19, 12 (0.3)
1d	1	2	F	70 (40)	27 (10)	+26 (10)	72 (10)	23 (5)			28, 8 (3); 8, 5 (1)
1e	1	3	F	5.9	8.3	60 (1), 92 (5)	90 (5)	30 (0.5), 70 (2)	0.1	0.5	31, 12 (0.3)
1f	1	4	F		20.5	4 (5)	40 (1), 73 (5)	65 (5), 71 (10)			33, 14 (3); 7, 4 (1)
1g	1	3	H		17.0	77 (10)	36 (5)	46 (2), 77 (5)	0.5	1.0	
1h	1	3	CH_3		30 (10)	10 (10)	16 (5)	66 (5), 72 (20)			26, 16 (3); 0, 0 (1)
1i	2	1	F		38 (10)	4 (10)	66 (5)	28 (10), 56 (20)			21, 24 (3); 22, 9 (1)
1j	2	2	F		4.5	0 (5)	66 (5)	58 (0.5), 62 (2), 89 (5)		1.0	27, 12 (1); 13, 10 (0.3)
1k	2	3	F		32 (10)	16 (10)	36 (10), 62 (20)	+23 (5)		10.0	33, 5 (3); 9.0 (1)
1m	0	5	F		41 (10)	36 (5)	16 (5)	39 (5)			27, 17 (3); 6, 9 (1)
8	2	2		58 (10)	4.7	0 (5)	28 (2), 42 (5)	13 (5)			19, 7 (3); 13, 15 (1)
9	1	3			18 (40)	38 (10)	12 (5)	20 (5)	Inact (10)		10, 6 (30); 9, 13 (10)
4a				13.8	4.3	42 (1), 62 (10)	35 (0.5), 71 (1), 75 (10)	52 (5), 74 (10)		1.0	23, 27 (10); 7, 4 (3)
4c					19 (100)	6 (10)	+6 (5)	+47 (5)			0, 9 (30)
4d	1	2	F		10 (10)	0 (10)	+44 (10)	0 (10)			4, 13 (30)
4e	1	3	F	3.7	5.3	47 (10)	60 (1), 77 (4)	8 (10), 34 (20)		1.0	30, 15 (10); 22, 15 (0.3)
4f	1	4	F		48.0	0 (5)	33 (5)	50 (10), 70 (20)			0, 0 (30)
4h	1	3	CH_3		32 (16)	+17 (10)	24 (5)	46 (5)			
4j	2	2	F	8.3	4.4	+30 (5)	59 (5), 73 (10)	23 (1), 53 (5)		10.0	

4k	2	3	F				0 (5)				
11e	1	3	F				58 (5)				
5e	1	3	F				55 (2), 78 (5)	10.0	10.0	3, 30 (10)	
7e	1	3	F				4 (5)	1.0	1.0		
31	1		F	1.0			30 (1), 66 (5)				
32	1	3	F				62 (5)	1.0	0.4		
33	1	3	F	5.0			33 (5)				
34	1	3	F	7.0			24 (5)				
35	1	3	F	1.46			50 (2.5), 75 (5)	1.0	0.2	25, 19 (5)	
36	1	3	F	1.70			86 (2.5), 95 (10)	10.0	10.0		
Pentazocine				60.0			11 (5), 83 (10), 93 (20)				
Chlorpromazine				37 (20)							
Valium				64 (60)			15 (5), 60 (40)	1.0			
Librium							26 (5), 54 (10)				

4k	2	3	F		23 (5)	46 (5)					
11e	1	3	F		47 (10)	41 (5)					
5e	1	3	F		100 (10)	85 (5)					
7e	1	3	F		23 (5)	23 (5), 46 (10)					
31	1		F	1.0		57 (5), 90 (40)					
32	1	3	F		23 (10)	87 (5)					
33	1	3	F	5.0	0 (10)	48 (5)					
34	1	3	F	7.0	26 (10)	71 (5)					
35	1	3	F	1.46	73 (10)	38 (1), 72 (5), 95 (10)					
36	1	3	F	1.70	8 (5)	68 (1), 93 (4)					
Pentazocine				60.0		30 (10), 64 (100)					
Chlorpromazine				37 (20)	79 (5)	76 (10)					
Valium				64 (60)	95 (5)	15 (5), 60 (40)					
Librium					53 (10)	26 (5), 54 (10)					

[a] All doses are oral and in mg/kg. See Experimental Section for interpretation of numbers. All numbers in parentheses refer to given doses. [b] RTF = rat tail flick, ED_{50} or percent increase in pain threshold (dose); Wr = writhing method, ED_{50} or percent decrease in number of writhes (dose). [c] Percent decrease in fighting (dose). [d] Percent decreases (dose). [e] Minimum dose for decreased aggressiveness. [f] Minimum dose producing ataxia. [g] Percent decrease in BP at 3 h, percent decrease at 24 h (dose). Average of two or more spontaneously hypertensive rats. Values of less than 15% are considered inactive. [h] For 1a, 2a, 4a, 4c, and Δ^9-THC(3c), refer to Chart I for structures. For 31-36 $n = 1$, $m = 3$, and Z = 4-F-C_6H_4.

Table IV. Hypnotic Activity. 12-h EEG Study in Cats

No.	Oral dose, mg/kg	Total sleep time, min[a]	Non-REM (slow wave and spindle) sleep time, min
Δ^9-THC	1.0	29	1
	4.0	17	−3
1a	0.5	62	122
1e	0.5	−22	−4
	2.0	126	94
1g	0.5	28	2
5e	0.5	11	8
4a	0.025	−12	25
	0.1	100	62
	0.25	56	21
	0.5	44	28
	1.0	39	43
4c	0.5	28	12
4e	0.25	45	45
	0.5	99	−20
4f	0.5	61	7
4j	0.5	58	60
32	0.5	47	121
35	0.5	50	73
36	0.5	16	39

[a] Increase unless shown by a minus.

Table V. Antisecretory Activity in the 4-h Pylorus Ligated Rat. Percent Decrease from Controls[f]

No.	Dose[a]	Volume	Acidity	Acid output	Pepsin concn	Pepsin output
3e	50	−0.7	7.5	7.3	−8.2	−8.9
1e	50	35.5[d]	7.8	39.6[c]	11.4	43.7[e]
1j	50	45.6[e]	13.4[c]	53.1[d]	20.8[d]	56.4[e]
4a	50	39.3[c]	23.5[d]	49.8[d]		41.9[d]
4c	50	−24.6	14.8	−6.1	8.3	−18.3
4e	50	33.3[c]	12.8[d]	42.9[d]		22.2
32	50	24.9	42.4[d]	56.1[d]	−32.0	1.9
CMN-131[b]	1.0	33.1[c]	3.8	35.5[c]	−29.3[d]	19.0
	2.5	35.8[d]	17.4[c]	47.3[d]	−43.1[e]	8.4[c]
	5.0	64.0[e]	49.8[e]	81.8[e]	−92.6[e]	31.0[c]
	10	76.7[e]	86.3[e]	95.5[e]	−45.8	58.9[c]

[a] mg/kg oral dose. [b] 2-Pyridyl thioacetamide. [c] $p < 0.05$. [d] $p < 0.01$. [e] $p < 0.001$. [f] A minus sign denotes an increase over controls.

In contrast, the sulfur analog with an aliphatic side chain, **5a** ($R^1 = CH_3$), was very active.[18]

Antisecretory Activity. Some of these compounds were evaluated as antisecretory agents using the pylorus ligated rat preparation. The results are shown in Table V. They were active but far less active than CMN-131 (2-pyridyl thioacetamide), a nonanticholinergic potent antisecretory agent.[28] Compounds with the C_5H_{11} side chain, **3c** (Δ^9-THC) and **4c**, were totally inactive.

Antidiarrheal Activity. Most of these compounds were studied in the castor oil induced antidiarrheal test in rats. Some were very potent as shown in Table VI. Compounds **1e** and **1j** have ED_{50}'s in the range of 0.1 mg/kg, which is similar to that of diphenoxylate hydrochloride, a standard potent antidiarrheal drug. However, on repeated dose studies, both **1e** and **1j**, unlike diphenoxylate hydrochloride, demonstrated tolerance effects (Table VII).

Antiulcer Activity. Preliminary studies with **4a** and **4e** were conducted in three experimental models in the rat. They were inactive at 40 mg/kg (oral dose) in the prevention of the stress and reserpine-induced gastric lesions. However, both compounds were active in the Shay rat preparation, examined 18.5 h after intraduodenal dosing of 40 or 50 mg/kg. CMN-131[28] was highly active in all three models (Table VIII).

Acute Toxicity. It is remarkable that these compounds

Table VI. Castor Oil Induced Antidiarrheal Activity in Rats

No.	Dose, mg/kg (oral)	% protected	No.	Dose, mg/kg (oral)	% protected
3c (Δ^9-THC)	0.5	0	4h	0.5	0
1a	0.1	50	4j	0.5	0
	0.2	80	4k	0.5	0
1e	0.05	0	11e	0.5	20
	0.1	50	7e	0.5	10
	0.5	70	32	0.5	40
1f	0.5	80	35	0.1	10
1h	0.5	90		0.4	70
1j	0.05	40		0.8	90
	0.1	60	Diphenoxylate	0.05	46
	0.2	90	hydrochloride	0.1	67
8	0.5	90		0.2	95
4a	0.25	20	Morphine sulfate	0.5	0
	0.5	63		1.0	30
	1.0	100		2.0	50
4e	0.5	53	Pentazocine	0.5	0
4f	0.5	30			

Table VII. Castor Oil Induced Antidiarrheal Activity in Rats. Repeated Oral Dose Studies

No.	Pretest treatment	Test day dose	% protected
1e	0.5 mg/kg for 2 days	0.5	0
	0.5 mg/kg for 2 days	1.0	0
	None	0.5	80
	None	1.0	80
1j	0.5 mg/kg for 2 days	0.5	0
	0.5 mg/kg for 2 days	1.0	0
	None	0.5	80
	None	1.0	80
	0.5 mg/kg for 5 days	0.5	0
	None	0.5	70
Diphenoxylate	0.2 mg/kg for 5 days	0.2	90
	None	0.2	100

which have such great potency in the tests mentioned above have such little toxicity. The appropriate oral LD_{50}'s in mice for the compounds in Table III were greater or equal to 1000 mg/kg except for the following: compounds **1f,g,j** and **32** have $LD_{50} \simeq 750$ mg/kg and compounds **1k** and **5e** have $LD_{50} \simeq 500$ mg/kg.

Experimental Section

All new compounds had NMR and ir spectra consistent with their structure. They were at least 95% pure by TLC or GC. All melting points are uncorrected. Concentrations in vacuo were done on a Buchi rotovac.

1-Bromo-3-(4-fluorophenyl)propane. A solution of 152 g (1.0 mol) of 3-(4-fluorophenyl)-1-propanol[29] in 240 ml of CCl_4 was added dropwise with stirring to a solution of 119 g (0.44 mol) of PBr_3 in 120 ml of CCl_4 at 60°. After refluxing 15 min, the solution was extracted with H_2O, $NaHCO_3$, and H_2O again. Drying ($MgSO_4$) and distillation gave 195 g (90%) of product: bp 97–100° (0.9 mm) [lit.[30] bp 113–115° (12 mm)].

4-(3-Bromopropyl)toluene. This was made above via 4-methylcinnamic acid and 4-(3-hydroxypropyl)toluene: bp 110–112° (8 mm) [lit.[31] bp 75–78° (0.7 mm)].

1-Chloro-4-(4-fluorophenyl)butane. 4-Chloro-4'-fluorobutyrophenone (180 g, 0.90 mol) was hydrogenated at 42 psi over 18 g of 5% Pd/C in 1 l. of EtOH. The catalyst was filtered; the solution was concentrated to 400 ml in vacuo (bath temperature 35°), treated with 1 l. of NaCl solution, and extracted with hexane. The organic layer was dried over $MgSO_4$ and distilled to give 150.1 g (89%) of product: bp 113–116° (13 mm); $n^{25}D$ 1.4994; GC showed it to be 99.2% pure.

Method A. 2-(3,5-Dimethoxyphenyl)-5-(4-fluorophenyl)pentane (12e). 1-Bromo-3-(4-fluorophenyl)propane (195 g, 0.90 mol) in 2.3 l. of ether was added dropwise to 31 g (1.3 mol) of Mg and 150 ml of ether to form the Grignard reagent. 3,5-Dimethoxyacetophenone (138 g, 0.77 mol) was added dropwise and the solution refluxed 1 h and then treated with NH_4Cl in water. The organic phase was dried and concentrated to give the alcohol **24** which was not purified but hydrogenated at 3 atm in 700 ml of AcOH containing 2 ml of H_2SO_4 and 28 g of 5% Pd/C. After uptake of H_2 ceased, the catalyst was filtered and the solution concentrated in vacuo after adding 8 g of sodium acetate, and the residue was partitioned between ether and NaOH solution. The organic layer was dried over $MgSO_4$ and distilled. The fraction, bp 145–155° (0.3 mm), was collected: yield 190 g (82%).

Compounds **12d,f,g,h,n** were prepared in a similar manner (Table I). With compound **12n**, the Grignard reaction was conducted in THF, and 1.1 equiv of acid was used in the hydrogenation to neutralize the basic nitrogen.

Compound **12m** was prepared using 3,5-dimethoxybenzaldehyde and 1-chloro-4-(4-fluorophenyl)butane as starting materials. The product was 85% pure by GC (with two unknowns). This was used as is in the next step.

Compounds **12j,k** and **30** were prepared by reacting methylmagnesium bromide with ketones **26j,k** and **28**, respectively, in a manner similar to that described above. In the case of the pyridyl analog **30**, a grey precipitate formed on addition of the methylmagnesium bromide (2.2 mol), and the reflux period was extended to 3 h. In the hydrogenation of intermediate **29**, 1.1 equiv of H_2SO_4 was used instead of the catalytic amount.

Method B. 2-(3,5-Dimethoxyphenyl)-3-methyl-5-(4-fluorophenyl)pentane. 3,5-Dimethoxypropiophenone[32] (52.0 g, 0.27 mol) was added to a suspension prepared from 13.9 g (0.33 mol) of 57% NaH in mineral oil (which had been freed of mineral oil by washing with toluene) and 130 ml of toluene. The resulting mixture was refluxed 30 min, 51.0 g (0.25 mol) of 2-(4-fluorophenyl)-1-bromoethane[33] was added, and the mixture refluxed 2.5 h. Then dilute HCl was added slowly and the product was isolated by distillation giving 66.4 g (69%) of **26j** (Table I). Compound **26k** was prepared in a similar manner.

Method C. 1-(3,5-Dimethoxyphenyl)-2-methyl-4-(4-pyridyl)-1-butanone. 3,5-Dimethoxypropiophenone[32] (10.0 g, 0.0515 mol), 4-vinylpyridine (5.42 g, 0.0515 mol) and 0.5 ml of a 40% solution of benzyltrimethylammonium hydroxide in methanol were mixed and kept at 75° for 2 h. The solution was treated with cold 10% HCl and extracted with benzene (which was discarded). The aqueous phase was made basic with KOH solution and extracted with ether. The organic phase was distilled yielding 12.0 g (91%) of **28** (Table I).

Ethyl 3,5-Dimethoxy-α-(p-fluorobenzoyl)-β-methylhydrocinnamate (38). To a solution of sodium ethoxide prepared from 6.18 g (0.269 mol) of sodium and 400 ml of ethanol was added over a period of 5 min 49.6 g (0.23 mol) of ethyl *p*-fluoro-

Table VIII. Antiulcer Studies in the Rat

Compd	Stress ulcer: Dose[a]	Stress ulcer: Ulcer score[b] (control)	Reserpine ulcer: Dose	Reserpine ulcer: Ulcer score[b] (control)	Shay ulcer: Dose	Shay ulcer: Ulcer score (control)
4a	10	1.3 ± 0.3 (1.8 ± 0.1)	50	1.8 ± 0.1 (1.6 ± 0.2)	20	4.2 ± 1.1 (7.2 ± 0.6)
	40	1.6 ± 0.2 (1.7 ± 0.2)			40	0.3 ± 0.3* (7.2 ± 0.6)
					50	0.5 ± 0.2* (8.8 ± 0.9)
4e	10	1.7 ± 0.1 (1.8 ± 0.1)	50	1.5 ± 0.3 (1.6 ± 0.2)	50	1.3 ± 0.9* (8.8 ± 0.9)
	40	1.4 ± 0.2 (1.7 ± 0.2)				
CMN-131	5	0.4 ± 0.1* (2.2 ± 0.2)	5	0.1 ± 0.1* (1.7 ± 0.2)	5	3.3 ± 0.8* (7.8 ± 0.8)
	10	0.0* (2.2 ± 0.2)	10	0.0* (1.7 ± 0.2)	10	0.7 ± 0.2* (7.8 ± 0.8)

[a] mg/kg oral. [b] 4–5 rats (see Experimental Section). An asterisk indicates the test score is different from the control mean score ($p < 0.05$) by Duncan's multiple range test.

benzoylacetate (Aldrich). To the above solution was added, over a period of 2 h, a solution of 52.5 g (0.214 mol) of 1-(1-bromoethyl)-3,5-dimethoxybenzene in 100 ml of ether. After stirring at room temperature for 68 h, most (~325 ml) of the solvent was removed by distillation at atmospheric pressure, the mixture was cooled, and 250 ml of ether and ice were added. The layers were separated and the organic layer was washed successively with cold water, dilute HCl, 5% sodium bicarbonate, and water and then dried over anhydrous magnesium sulfate. Filtration and solvent evaporation under vacuum left 84.7 g of oil. This material was used in the next step without purification.

2-[1-(3,5-Dimethoxyphenyl)ethyl]-1-*p*-fluorophenyl-1,3-propanediol. A solution of 35.8 g (0.0955 mol) of ethyl 3,5-dimethoxy-α-(*p*-fluorophenyl)-β-methylhydrocinnamate in 100 ml of ether was added dropwise over a period of 25 min to 4.5 g (0.12 mol) of lithium aluminum hydride in 100 ml of ether. The mixture was stirred overnight and then the excess lithium aluminum hydride was decomposed by the cautious addition of 10 ml of ethyl acetate followed by 10 ml of water. The mixture was acidified with 185 ml of 2.75 N HCl and the layers were separated. The aqueous layer was extracted with one 100-ml and one 50-ml portion of ether. The combined ether solution was washed with two 50-ml portions of water and dried over anhydrous magnesium sulfate. Filtration and solvent evaporation under vacuum left 30.9 g of yellow oil. This material was used without purification in the next step.

2-[1-(3,5-Dimethoxyphenyl)ethyl]-1-*p*-fluorophenyl-1,3-propanediol Dimethanesulfonate (39). A solution of 30.7 g (0.0918 mol) of 2-[1-(3,5-dimethoxyphenyl)ethyl]-1-*p*-fluorophenyl-1,3-propanediol and 38.5 ml (0.275 mol) of triethylamine in 250 ml of methylene chloride was cooled in a bath at −15°C and 18 ml (0.24 mol) of methanesulfonyl chloride was added over a period of 20 min. The mixture was stirred at −10°C for 1 h and then washed with two 50-ml portions of cold water, two 50-ml portions of cold 10% HCl, one 50-ml portion of cold saturated sodium bicarbonate, and one 50-ml portion of cold water. The solution was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed under vacuum to give 42.5 g of yellow oil. This material was free of OH absorption in the ir spectrum and was used without purification in the next step.

Method D. 3-(3,5-Dimethoxyphenyl)-1-(*p*-fluorophenyl)-2-methylbutane (12j). A solution of 42.2 g (0.086 mol) of 2-[1-(3,5-dimethoxyphenyl)ethyl]-1-*p*-fluorophenyl-1,3-propanediol dimethanesulfonate in 15 ml of ether and 150 ml of tetrahydrofuran was added over a period of 30 min to a stirred slurry of 8.40 g (0.221 mol) of lithium aluminum hydride in 75 ml of ether. The mixture was stirred at room temperature for 63 h (over weekend) and 25 ml of ethyl acetate was added slowly to decompose the excess lithium aluminum hydride. Then 8 ml of water, 8 ml of 15% sodium hydroxide, and 16 ml of water were added successively with vigorous stirring. The mixture was then filtered and the solid washed with four 100-ml portions of ether. The combined ether solution was washed with two 10-ml portions of 15% sodium hydroxide solution and three 25-ml portions of water and dried over anhydrous magnesium sulfate. Filtration and solvent evaporation under vacuum left 22.3 g of light yellow oil. This material was vacuum distilled giving 8.96 g [bp 154–162° (0.1 mmHg)]. This material was nearly pure by TLC (5% ether–petroleum ether, bp 30–60°) and the NMR spectrum was in agreement with the proposed structure.

Method E. 3-[4-(Fluorophenyl)-1-methylbutyl]-1-hydroxy-9-methyl-6-oxo-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran (14e). Dimethyl ether **12e** (100 g, 0.33 mol), 1 l. of HOAc, and 400 ml of 48% HBr were mixed and HBr gas was bubbled through until 160 g was absorbed. The mixture was heated to 85° and stirred for 16 h. Most of the solvent was removed in vacuo and the residue treated with ether and $KHCO_3$ solution. The dark organic phase was treated with charcoal and $MgSO_4$, filtered, and concentrated. The resulting crude resorcinol **13** was used directly in the next step. [It could be distilled, bp 180° (0.01 mm), but some decomposition occurs during distillation].

The crude resorcinol, 74 g (0.40 mol) of ethyl 4-methyl-2-cyclohexanone-1-carboxylate, 25 ml of $POCl_3$, and 380 ml of benzene were refluxed 8 h. The solution was neutralized with K_2CO_3 and $KHCO_3$. After adding ether, the solution was dried over $MgSO_4$ and charcoal and concentrated, and the residue was crystallized from acetonitrile to give 78.5 g (60%) of **14e** (Table II).

Ethyl 2-cyclopentanone-1-carboxylate was used to prepare **19** in a similar manner.

Method F. 3-[4-(4-Fluorophenyl)-1-methylbutyl]-1-hydroxy-6,6,9-trimethyl-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran (1e). The above pyrone (compound **14e**, 70.0 g, 0.178 mol) in 350 ml of benzene was added slowly to a solution of 1.5 mol of CH_3MgBr in 900 ml of ether. The solution was refluxed 16 h and then treated with NH_4Cl in water. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and dissolved in 1 l. of benzene containing 0.3 g of Tos OH and refluxed 2 h. The acid was neutralized with $KHCO_3$ solution. The organic layer was dried and concentrated. The residue was chromatographed on a Florisil column 1 m long, 38 mm diameter eluting with 5% ether in hexane giving 62.3 g (83%) of **1e** as a colorless oil. TLC showed one major spot with a minor spot just trailing it. The last fractions off the column were enriched in this minor spot. NMR indicated that this is compound **15** (see text).

Method G. 3-(4-Dimethylamino-1-methylbutyl)-1-hydroxy-9-methyl-6-oxo-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran (14p). Dimethyl ether **12n** (20.6 g, 0.082 mol) in a solution of 180 ml of HOAc, 80 ml of 48% HBr, and 32 g of HBr gas was heated to 90° and stirred 16 h. The solvent was concentrated in vacuo; water was added and the solvent concentrated to dryness again. This resorcinol was used in the next step.

The above resorcinol was dissolved in 40 ml of methanesulfonic acid (cooling) followed by 28 g of $POCl_3$ and 18.0 g (0.098 mol) of ethyl 4-methyl-2-cyclohexanone-1-carboxylate and stirred 5 days. Water was added and the cloudy solution extracted with ether which was discarded. The aqueous solution was neutralized giving an oil which was crystallized from benzene giving 21.5 g (16%) of **14p** (Table II).

Method H. 3-(4-Dimethylamino-1-methylbutyl)-1-hydroxy-6,6,9-trimethyl-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran (9). The above pyrone (**14p**, 6.30 g, 0.0193 mol) was dissolved in 150 ml of THF and treated with 60 ml of 3 M CH_3MgBr in ether and refluxed 17 h. The solution was treated with 250 ml of saturated NH_4Cl solution and extracted with THF. Concentrated NH_3 was added and the mixture extracted with $CHCl_3$ which was concentrated to give a red oil. This was dissolved in C_6H_6, concentrated again (to get rid of THF), and dissolved in $CHCl_3$ (250 ml) and HBr gas was added until acidic. This solution was refluxed 0.5 h to cyclize the triol and then neutralized with $KHCO_3$ in water. The $CHCl_3$ solution was concentrated and the residue chromatographed on a Florisil column eluting with 10% MeOH in $CHCl_3$, yielding 3.70 g (59%) of **9** as a colorless oil (Table II). An HBr salt was prepared for testing, with HBr in $CHCl_3$. It was an amorphous solid.

5-[1,2-Dimethyl-4-(4-pyridyl)]resorcinol. Dimethyl ether **30** (127 g, 0.425 mol) was demethylated by heating for 16 h at 85° in 900 ml of HOAc, 400 ml of 48% HBr, and 145 g of HBr gas. The solvents were concentrated in vacuo and the residue was neutralized with $KHCO_3$ in H_2O to pH 8. The solid which formed was filtered, washed with water and ether, and crystallized from dimethoxyethane and ether yielding 110 g of the desired compound: mp 118–122° (95%). Anal. C, H, N.

Method I. 3-[4-(4-Pyridyl)-1,2-dimethylbutyl]-1-hydroxy-9-methyl-6-oxo-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran (14n). The above resorcinol (9.10 g, 0.0335 mol) was dissolved in 20 ml of CH_3SO_3H and 14 g of $POCl_3$, and 7.70 g (0.0418 mol) of ethyl 4-methyl-2-cyclohexanone-1-carboxylate was added. The solution was stirred 4 days at room temperature. Water and $CHCl_3$ were added and the mixture was neutralized with $KHCO_3$ in H_2O. The $CHCl_3$ solution was concentrated and the residue crystallized from CH_3CN to give 7.72 g (66%) of **14n** (Table II).

Method J. 3-[4-(4-Pyridyl)-1,2-dimethylbutyl]-1-hydroxy-6,6,9-trimethyl-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran (8). The above pyrone **14n** (12.2 g, 0.0375 mol) suspended in 150 ml of THF was treated with 100 ml of 3 M CH_3MgBr in ether. A solid formed. After distilling 50 ml of ether from the flask, the solid dissolved. The solution was refluxed 2 h, diluted with 250 ml of ether, and treated with 400 ml of saturated NH_4Cl solution. The organic phase was concentrated,

benzene was added, and the phase was concentrated again (to get rid of THF) and then dissolved in 250 ml of $CHCl_3$. This solution was made acidic with HBr gas and boiled 15 min (to cyclize). The solution was neutralized with $KHCO_3$, the organic layer was concentrated, and the residue was chromatographed on a Florisil column (90 cm × 32 mm diameter) eluting with graded ether–hexane mixtures. The product came off with 30% ether–70% hexane giving 5.09 g (39%) of a pale yellow gum (Table II).

Method K. 2-Benzyl-8-[4-(4-fluorophenyl)-1-methylbutyl]-10-hydroxy-5-oxo-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine Hydrochloride (16e). Dimethyl ether **12e** (190 g, 0.63 mol) was converted to the resorcinol as described in method E. The crude resorcinol was dissolved in 390 ml of anhydrous CH_3SO_3H; 218 g (0.73 mol) of ethyl *N*-benzyl-3-oxo-4-piperidinecarboxylate hydrochloride (Aldrich Chem. Co.) was added, with cooling, followed by 255 g of $POCl_3$. The dark solution was stirred 5 days at room temperature. Then 1.25 l. of $CHCl_3$ was added followed by 2 l. of cold H_2O. The mixture was stirred 30 min, and the $CHCl_3$ phase was separated and extracted with 2-l. portions of H_2O. The $CHCl_3$ phase was concentrated without drying and the residue crystallized from 800 ml of CH_3CN containing 5 ml of concentrated HCl. There was obtained 198 g (62%) of compound **16e** (Table II).

Method L. 2-Benzyl-5,5-dimethyl-8-[4-(4-fluorophenyl)-1-methylbutyl]-10-hydroxy-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (17e). The above pyrone **16e** (198 g, 0.39 mol) was converted to the base by stirring 40 min with 2 l. of $CHCl_3$ and a saturated solution of 75 g of $KHCO_3$ and H_2O. The $CHCl_3$ layer was dried over $MgSO_4$ and concentrated in vacuo. Benzene was added and the solution concentrated again (to get rid of $CHCl_3$). The residue was dissolved in 750 ml of warm (50°) anisole and added dropwise to a solution of 1.3 l. of 3 M CH_3MgBr in ether plus 750 ml of anisole. The solution was stirred at 60° under N_2 1 h, then at room temperature 16 h, and then at 60° for 30 min. A solution of 1.2 l. of 20% (by volume) H_2SO_4 was added while cooling. The mixture was steam distilled to remove the anisole and the solid which remained was dissolved in $CHCl_3$ and extracted with $KHCO_3$ solution. The $CHCl_3$ layer was concentrated and the residue was crystallized from CH_3CN giving 149 g (75%) of **17e** as a base (Table II).

The hydrochloride of **17e** was prepared by dissolving in 1.5 l. of EtOH containing 30 ml of concentrated HCl, treating with charcoal, filtering, concentrating, and crystallizing from ethyl acetate.

Method M. 5,5-Dimethyl-8-[4-(4-fluorophenyl)-1-methylbutyl]-10-hydroxy-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (18e). The above benzyl compound (149 g, 0.285 mol) as the hydrochloride salt was hydrogenated at 3 atm in 140 ml of EtOH and 7 ml of H_2O over 1.5 g of 5% Pd/C. (Note: the purified hydrochloride of **17e** must be used in this step. Using the base with an equivalent of concentrated HCl gives inferior results.) After the catalyst was filtered, the solution was concentrated to give product **18e** as an HCl salt. For use in the next step, this was converted to the free base by vigorous stirring with a mixture of $KHCO_3$, H_2O, and $CHCl_3$. This base and all others in the series were amorphous solids obtained from $CHCl_3$–hexane: yield 109 g (96%).

Method N. 5,5-Dimethyl-8-[4-(4-fluorophenyl)-1-methylbutyl]-10-hydroxy-2-(2-propynyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (4e). The above NH compound (as the base) (109 g, 0.275 mol) **18e** was dissolved in 420 ml of dry DMF. While cooling, 16.45 g (0.138 mol) of freshly distilled propargyl bromide was added. The solution was stoppered and stirred at room temperature for 20 h. Water (1 l.) was added slowly. The solid which formed was washed with water and crystallized from ether and acetonitrile to give 49.5 g (82% based on propargyl bromide) of **4e** (Table II).

The filtrate above was neutralized with $KHCO_3$ and extracted with $CHCl_3$ to recover the excess **18e**. Traces of **18e** in **4e** were removed by chromatography with Florisil eluting with 3% MeOH in $CHCl_3$.

Method O. 1,4-Ethano-10-hydroxy-8-[4-(4-fluorophenyl)-1-methylbutyl]-5-oxo-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*b*]pyridine Hydrochloride (20). Dimethyl ether **12e** (24 g, 0.08 mol) was converted to the resorcinol as described in method E. The crude resorcinol was dissolved in 37 ml of CH_3SO_3H and 20.0 g (0.10 mol) of ethyl 3-quinuclidinone-2-carboxylate and 24 ml of $POCl_3$ were added and stirred 5 days at room temperature. The addition of 200 ml of $CHCl_3$ and 200 ml of H_2O with stirring gave three layers. The middle layer was separated and acetonitrile added to give 16.4 g (48%) of **20** Table II).

Method P. 1,4-Ethano-10-hydroxy-8-[4-(4-fluorophenyl)-1-methylbutyl]-5,5-dimethyl-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*b*]pyridine Hydrobromide (7e). The above pyrone **20** was allowed to react with CH_3MgBr in a manner described in method L except that the product after steam distillation was not neutralized but crystallized from CH_3CN as the hydrobromide.

Method Q. 1,2-Dihydro-9-hydroxy-7-[4-(4-fluorophenyl)-1-methylbutyl]-1-methyl-4-oxo-4*H*-thieno[2,3-*c*]-[1]benzopyran (21). Dimethyl ether **12e** (25 g, 0.0825 mol) was converted to the resorcinol as described in method E. The crude resorcinol was dissolved in 100 ml of C_6H_6, 16.3 g (0.0935 mol) of methyl 4-methyl-3-oxo-2,3,4,5-tetrahydrothiophene-2-carboxylate[34] and 13.0 g $POCl_3$ were added, and the solution was stirred at 37° for 13 days. The solution was concentrated and partitioned between K_2CO_3–H_2O and ether. The ether was dried ($MgSO_4$) and concentrated and the residue was extracted with pentane to remove unreacted keto ester. The product was chromatographed on Florisil eluting with $CHCl_3$ to get 21.0 g (63%) of an oil. TLC shows some impurities but it was used as is in the next step.

Method R. 1,2-Dihydro-9-hydroxy-7-[4-(4-fluorophenyl)-1-methylbutyl]-1,4,4-trimethyl-4*H*-thieno[2,3-*c*]-[1]benzopyran (5e). The crude pyrone above (**21**) in 200 ml of ether was added to a solution of 0.5 mol of CH_3MgBr in 375 ml of ether. The solution was refluxed 2.5 h, cooled, and treated with 500 ml of NH_4Cl solution. The ether phase was concentrated and the residue was taken up in 250 ml of MeOH containing 0.5 ml of concentrated HCl. After refluxing 10 min, the solution was concentrated and partitioned between ether and $NaHCO_3$–H_2O. The ether was dried ($MgSO_4$) and concentrated and the residue was taken up in hexane leaving behind some insoluble residue. The hexane solution was concentrated and the residue was chromatographed on Florisil eluting with 2% ether in hexane giving 3.30 g (16%) of product **5e**.

Method S. 10-Acetoxy-5,5-dimethyl-8-[4-(4-fluorophenyl)-1-methylbutyl]-2-(2-propynyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (31). The hydroxy compound **4e** (5 g, 0.0115 mol) in 6 ml of pyridine was treated with 1.50 g of acetic anhydride, stirred overnight at room temperature, and heated on the steambath 1 h. The solvents were removed in vacuo, cyclohexane was added, the solution was extracted with diluted $KHCO_3$ and dried over $MgSO_4$, and the cyclohexane was removed in vacuo to get 4.313 g (85%) colorless oil. There was no trace of starting materials and only one spot on TLC analysis.

Method T. 3-[4-(4-fluorophenyl)-1-methylbutyl]-1-(4-morpholinobutyryloxy)-6,6,9-trimethyl-7,8,9,10-tetrahydro-6*H*-dibeno[*b*,*d*]pyran Hydrochloride (36). Hydroxy compound **1e** (7.11 g, 0.0174 mol), dicyclohexylcarbodiimide (3.58 g, 0.0172 mol), and 4-morpholinobutyric acid hydrochloride[35] (3.54 g, 0.0169 mol) were added to 125 ml of CH_2Cl_2 and stirred overnight at room temperature. The dicyclohexylurea was removed by filtration. The CH_2Cl_2 was concentrated and the residue crystallized from CH_2Cl_2–Et_2O to give 8.65 g (97%) of **36** (Table II).

In preparing **33** and **34** which are dihydrochlorides, HCl gas was added to the CH_2Cl_2 solution before concentrating.

Compound **34** required 2-methyl-4-morpholinobutyric acid hydrochloride as a starting material. It was prepared from ethyl 4-bromo-2-methylbutyrate[36] by the method of Cruickshank and Sheehan[35] and had mp 146–148°. Anal. C, H, N.

Pharmacology. The acetic acid writhing, rat tail-flick, fighting mouse, rat motor activity, desoxyn antagonism (antipsychotic activity), antidepressant activity, anticonvulsant (audiogenic seizure), sedative–hypnotic activity, dog ataxia, and monkey antiaggression tests were carried out according to procedures described earlier.[11]

Antihypertensive Activity. The blood pressure in conscious restrained, genetically hypertensive rats was measured directly

via a cannulated caudal artery and/or indirectly using an occluding cuff on the tail. The data are presented in Table III.

Antisecretory Activity. Male Sprague–Dawley rats weighing 170–190 g were fasted for 24 h. Water was allowed ad libitum. All groups were comprised of six rats. Thirty minutes prior to ligation, the test compound was administered at an oral dose of 50 mg/kg. Water was withheld after drug administration. Ligation of the pyrloric sphincter was performed under ether anesthesia, and 4 h after ligation the animals were sacrificed with CO_2. The stomach was dissected out and the contents were expelled into a graduated centrifuge tube. The samples were centrifuged and the volume, less debris, was measured. Sample aliquots were titrated with 0.05 N NaOH to determine acid concentration. Pepsin activity was determined on an auto analyzer using hemoglobin as the substrate by the method of Anson.[37]

Group means for volume, acid and pepsin concentrations, and pepsin outputs were compared for statistically significant differences from control means by Student's t test. The results are expressed in Table V.

Antidiarrheal Activity. Male Charles River rats, weighing 150–200 g, fasted overnight with water given ad libitum were used to study the inhibition of castor oil induced diarrhea. The compound was suspended in polyethylene glycol 300 and administered intragastrically to groups of ten rats. Controls were given PEG 300 alone. One hour after compound administration, 1 ml of castor oil was given to each rat intragastrically. The rats were observed for presence or absence of diarrhea 1 h after administration of the castor oil. The values in Table VI are the percent of rats protected for each group calculated by using a formula which compensates for the percent of control rats that did not get diarrhea.

Antiulcer Activity. Three experimental ulcer models in the rat were used in the preliminary examination of two of the compounds, namely **4a** and **4e**. Albino male rats (Sprague–Dawley) of 180–190 g were used. For the stress ulcer model the rats were fasted 16 h prior to restraining in the stress box[38] in the cold room (10 ± 1°C) for 4 h. The rats were then sacrificed by the use of CO_2 and the stomachs were examined for the hemorrhagic lesions over the corpus. The test compounds were given orally 30 min prior to the stress. Reserpine ulcer was induced in the rat by injecting reserpine (0.5% solution in acidified 10% alcohol) 5 mg/kg intraperitoneally after 40 h of fasting. The test compound was given orally 30 min prior to the reserpine injection. All rats were sacrificed 6 h after the reserpine. In these two ulcer models the gastric lesions over the corpus were examined and similarly graded arbitrarily (0–5). In the Shay ulcer model the rats were fasted 48 h before pyloric ligation under ether anesthesia. Test compounds were administered intraduodenally after the pyloric ligation. The rats were sacrificed 18.5 h later. The ulcerations over the rumen and those over the esophagus were separately scored for severity, 0–5 (5 = perforation). The total score was used for comparison. In all ulcer models the test compounds were suspended in an aqueous solution of 0.5% methylcellulose at a concentration to give the appropriate dose in 2 ml/kg. The suspending vehicle was given 2 ml/kg by the same route as the treated group. A randomized schedule was adopted in all experiments.

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