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Drugs Derived from Cannabinoids. 1. Nitrogen Analogs, Benzopyranopyridines and Benzopyranopyrroles

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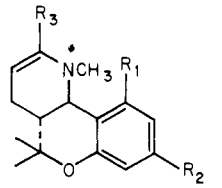
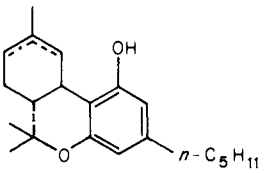
Various nitrogen analogs of $\Delta^{6a,10a}$-tetrahydrocannabinol were synthesized by a general procedure described in an earlier communication. Minimum effective doses (MED_{50}'s) and lethal doses (LD_{50}'s) were determined by a modified Irwin mouse screen after iv administration of compounds in PEG 200. The most potent compounds were the propargyl (**5t**), allyl (**5m**), and chloroallyl (**5o–q**) derivatives. Overt behavioral effects (CNS depression, static ataxia, and hypersensitivity) of 5t and Roger Adams' carbocyclic analog (III) were found to be similar in the mouse, cat, dog, and monkey. Dichloroisoproterenol prevented and reversed many of the depressant effects of both III and 5t but had no effect on the ataxia produced by these compounds. In antinociceptive tests, 5t was active in the phenylquinone and Eddy hot-plate tests but was inactive in the tail-flick test.

The insertion of nitrogen into the carbocyclic nucleus of tetrahydrocannabinol (THC) has long been of interest to chemists and pharmacologists. Francis Bergel has commented that "... it is regrettable that neither hashish nor one of its major constituents has an honest nitrogen from which one could make a soluble salt".[1] Further interest in preparing nitrogen analogs was stimulated by the observation that THC is one of very few drugs which has potent activity on the central nervous system and yet has no nitrogen in its structure. A medicinal chemical basis for orienting the position of nitrogen to obtain a variety of structures and potential activities related to known CNS drugs has been described previously.[2]

The first effort to prepare a pharmacologically active nitrogen analog was reported by Anker and Cook in 1946,[3] but they found no analgetic activity in structures such as **2** (R = CH_3; R' = n-C_5H_{11}). In preliminary communications we reported[4] the successful synthesis of the pharmacologically active analogs **4b** and **4f** (Table IV) having a phenethylamine orientation for the nitrogen. Benzodiazepine and benzopyranopyrimidine analogs have also been synthesized, as have analogs where the pyran oxygen is replaced by NCH_3, but no biological data were reported for the compounds.[5] Recently, Cushman and Castagnoli[6] synthesized the nitrogen-containing structure I having a trans ring fusion similar to that found in the natural product constituents Δ^8- and Δ^9-*trans*-THC (II). The diastereoisomeric mixture obtained on catalytic reduction of Ib was reported by these authors to possess both antidepressant and anticonvulsant activity.[6b] No biological data were given for any of the parent compounds (I).

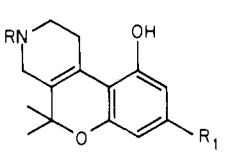


Ia, R_1 = H; R_2 = H; R_3 = H
b, R_1 = OH; R_2 = n-C_5H_{11}; R_3 = CH_3



II

In this paper we present results on the synthesis and comparative activity in mice of a variety of nitrogen analogs **2** (Table II), **5** (Table V), **7** (Table IX; the side chain has been abbreviated to C_9H_{19}), and **11** (Table X).



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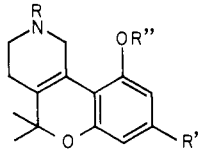

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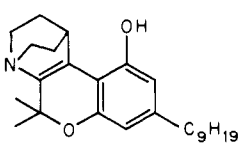

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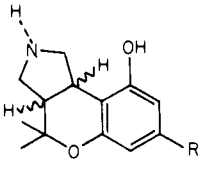

11

The substituents on the nitrogen of **2** and **5** are similar to those found in narcotic analgesics and antagonists and other CNS agents, i.e., where R = allyl, propyl, propargyl, and phenethyl; and the substituents on the aromatic ring

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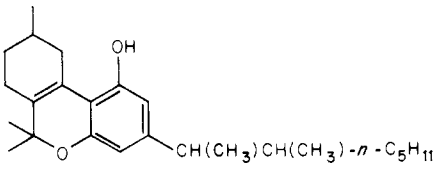
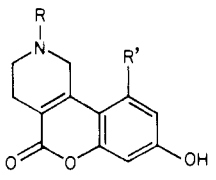
(R') are analogous to those reported by Roger Adams and his collaborators[7] for the carbocyclic cannabinoids. The chemistry and general pharmacological profile of one of the most potent of these nitrogen analogs, **5t** (Table V), will be described in some detail. The latter will be compared with Roger Adams' most active analog, III, dimethylheptylpyran (DMHP), a compound whose chemistry, pharmacology, and clinical effects have been widely studied in recent years.[8]



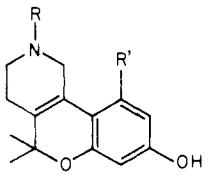
III (DMHP)

Chemistry. The nitrogen analogs were prepared according to general procedures described for the synthesis of benzopyrans from resorcinols.[3,4,7] Compounds of type **5** (Scheme I) were prepared by condensation of an appropriate alkylresorcinol with N-substituted 4-carbethoxy-3-piperidone to yield the pyrone **3** followed by a Grignard reaction to give the corresponding pyrans **4** or **5**. In the case of the *N*-methyl derivatives (**4**, R = CH_3, Table IV) the compounds were isolated at this stage, whereas the *N*-benzylpyran (**5b**, R = CH_2Ph, Table V) was catalytically debenzylated over palladium–charcoal to the key intermediate nor base **5c**. The various N-substituted pyrans (Table V) were then prepared from **5c** by either direct alkylation with an appropriate alkyl halide (method A) or acylation with an acyl halide followed by $LiAlH_4$ reduction (method B). The *N*-propargylpyrone **3h** (Table III) was prepared from the *N*-benzylpyrone **3f** after catalytic debenzylation followed by alkylation with propargyl bromide.

It is of interest to note that in Scheme I when R' is a lower alkyl, the initial condensation to the pyrone generally leads to mixtures of compounds of type **3** and isomeric products of type IV depending on the reaction conditions. For example, in the orcinol series with H_2SO_4 as the condensing agent and at elevated temperatures only the isomer IVa was obtained whereas a mixture of H_2SO_4 and $POCl_3$ gave predominantly the desired product **3** (R = R' = CH_3). With larger branched R' substituents, e.g., R' = $CH(CH_3)CH(CH_3)$-*n*-C_5H_{11}, either reaction condition yields the desired product of type **3**, presumably the steric hindrance resulting at attack at the 2 position rather than the 4 position of the resorcinol. The NMR spectra[4a] of **3** (R = R' = CH_3) and IVa are similar except for the ab-



IV

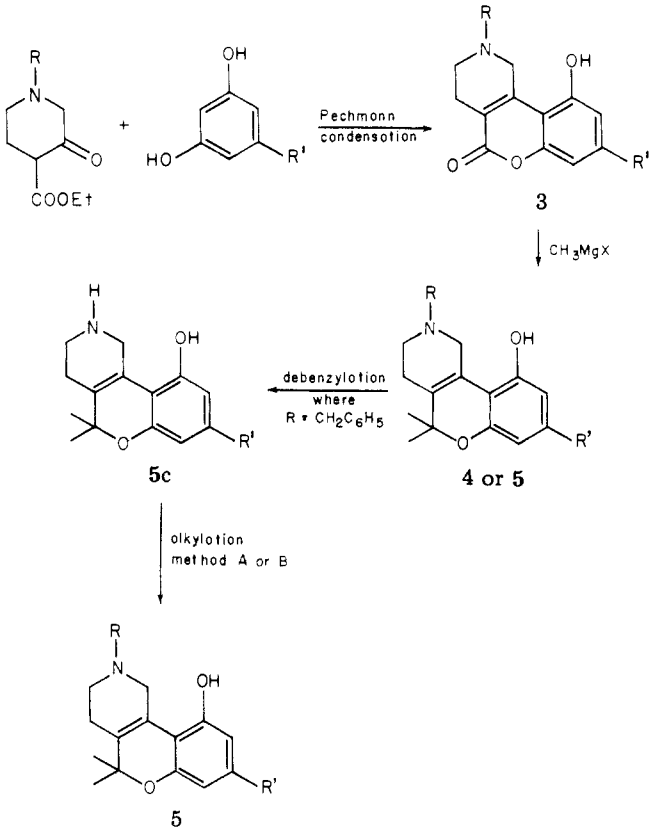


V

a, R = R' = CH_3

sorption positions of the aromatic methyl and aromatic protons. In trifluoroacetic acid the aromatic methyl of **3** (R = R' = CH_3) is at 2.37 ppm and a splitting of the aromatic protons at 6.71 and 6.8 ppm, whereas in IVa, they are at 2.74 and 6.97 ppm, respectively. In addition, the isomeric pyrones IV showed a bathochromic shift in the uv spectra as compared to pyrones **3**. Thus IVa showed λ_{max} 320 nm and **3** (R = R' = CH_3), λ_{max} 305 nm. A similar shift was observed in pyrans V (λ_{max} 305 nm) and compounds **4** and **5** (λ_{max} 278 nm).

Scheme I



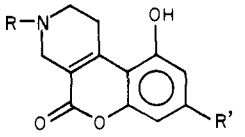
The pyrones shown in Table I and pyrans of type **2** (Table II) were similarly prepared via Scheme I from N-substituted 3-carbethoxy-4-piperidone. The quinuclidinyl analog **7**, listed in Table IX, was prepared by condensation of ethyl 3-quinuclidinone-2-carboxylate and the appropriate 5-alkylresorcinol followed by Grignard reaction.

Compound **8** of Table X was prepared by catalytic reduction of **5c** (Table V). The quaternary salts **9** and **10** were synthesized from **5t** by alkylation with methyl iodide and 3-bromo-1-propyne, respectively. The pyrone **11a** and the pyran **11** (pyrrolo analogs) were prepared via Scheme I from ethyl 1-benzyl-4-pyrrolidone-3-carboxylate.[9] In this series during the debenzylation step the completely reduced hexahydropyrrolopyran, compound **11**, was unexpectly formed.[10] The diastereoisomers of **5t** listed in Table VIII and their intermediates (Table VI and VII) were prepared from the four diastereoisomers of 5-(1,2-dimethylheptyl)resorcinol.[8b]

Pharmacology.[11] **Structure–Activity Results in Mice.** All compounds were evaluated in a general pharmacological screen in mice. Test results are given in Tables I–V and VIII–X. The procedure used was a modification of the Irwin mouse screen.[12] Minimum effective doses or that dose that elicits any effect in 50% of the animals (MED_{50}'s) and lethal doses (LD_{50}'s) were determined. These nitrogen analogs were, like the cannabinoids, insoluble in aqueous media; therefore, they were solubilized in polyethylene glycol 200 and administered intravenously. The overt drug effects seen were qualitatively similar for all compounds tested. The most prominent effects were decreased locomotor activity, increased sensitivity to stimuli, such as sound and touch, general depression, and, at high doses, static and dynamic ataxia.

Adams' most potent carbocyclic compound, III

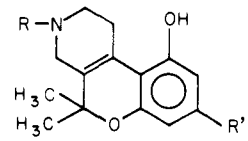
Table I. N-Substituted 5-Oxobenzopyrano[3,4-*c*]pyridines



Compd	R	R'	Mp, °C	Yield, purified, %	Crystn solvent	Formula	Mouse data[b] MED$_{50}$	Mouse data[b] LD$_{50}$
1a	$CH_2C_6H_5$	CH_3	222-224 dec	41	CH_3CN	$C_{20}H_{19}NO_3$	18	18
1b	H	CH_3	250-253 dec	7	C_2H_5OH	$C_{13}H_{13}NO_3$	>10	>10
1c	$CH_2C{\equiv}CH$	CH_3	197-200 dec	17	CH_3CN	$C_{16}H_{15}NO_3$	32	56
1d	CH_3	$CH(CH_3)CH(CH_3)C_5H_{11}$	153-155 dec	62	Aq CH_3OH	$C_{22}H_{31}NO_3$	>10	>10
1e	CH_3	*erythro*-$CH(CH_3)CH(CH_3)C_5H_{11}$	166-169 dec	7[a]	CH_3CN	$C_{22}H_{31}NO_3$	32	>32
1f	$CH_2C_6H_5$	$CH(CH_3)CH(CH_3)C_5H_{11}$	236-240	37	CH_3CN	$C_{28}H_{35}NO_3{\cdot}HCl$	>32	>32
1g	H	$CH(CH_3)CH(CH_3)C_5H_{11}$	177-179	20	CH_3CN	$C_{21}H_{29}NO_3$	5.6	32
1h	$CH_2C{\equiv}CH$	$CH(CH_3)CH(CH_3)C_5H_{11}$	132-135	16	$CH_3COOC_2H_5$	$C_{24}H_{31}NO_3{\cdot}HCl$	>32	>32

[a] Isolated from a mixture of erythro and threo isomers. [b] Values in mg/kg; see also ref 12. For MED$_{50}$ values <1 mg, four animals per dose were used; for >1 mg, two animals per dose.

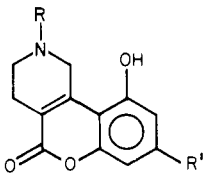
Table II. N-Substituted Benzopyrano[3,4-*c*]pyridines



Compd	R	R'	Mp, °C	Yield purified, %	Crystn solvent	Formula	Mouse data[a] MED$_{50}$	Mouse data[a] LD$_{50}$
2a	$CH_2C_6H_5$	CH_3	206-208	49	CH_3CN	$C_{22}H_{25}NO_2$	18	>32
2b	CH_3	$CH(CH_3)CH(CH_3)$-C_5H_{11}	251-255 dec	40	CH_3CN	$C_{24}H_{37}NO_2{\cdot}HCl$	1.8	>32
2c	CH_3	*threo*-$CH(CH_3)$-$CH(CH_3)C_5H_{11}$	281-283 dec	34[b]	CH_3CN	$C_{24}H_{37}NO_2{\cdot}HCl$	10	>32
2d	H	$CH(CH_3)CH(CH_3)$-C_5H_{11}	168-170	31	C_6H_6	$C_{23}H_{35}NO_2$	>10	>10
2e	$CH_2CH{=}CH_2$	*threo*-$CH(CH_3)$-$CH(CH_3)C_5H_{11}$	208-210 dec	28[b]	Ethyl acetate-petr ether	$C_{26}H_{39}NO_2{\cdot}HCl$	>32	>32
2f	*trans*-CH_2-$CH_2CH{=}CHCl$	*threo*-$CH(CH_3)$-$CH(CH_3)C_5H_{11}$	250-253 dec	15[b]	Ethyl acetate-alcohol	$C_{26}H_{38}ClNO_2{\cdot}HCl$	>32	>32
2g	$CH_2C{\equiv}CH$	$CH(CH_3)CH(CH_3)$-C_5H_{11}	120-125 dec	20		$C_{26}H_{37}NO_2{\cdot}HCl$	18	>32

[a] See footnote *b*, Table I. [b] See footnote *a*, Table I.

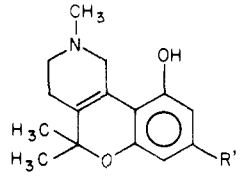
Table III. N-Substituted 5-Oxobenzopyrano[3,4-*d*]pyridines



Compd	R	R'	Mp, °C	Yield purified, %	Crystn solvent	Formula	Mouse data[a] MED$_{50}$	Mouse data[a] LD$_{50}$
3a	CH_3	n-C_5H_{11}	146-147.5	23	Ethyl acetate	$C_{18}H_{23}NO_3$	5.6	56
3b	CH_3	$CH(CH_3)C_5H_{11}$	210-212	15	CH_3CN	$C_{20}H_{27}NO_3{\cdot}HCl$	10	56
3c	CH_3	$CH(CH_3)C_6H_{11}$	200-202 dec	52	Aq CH_3OH	$C_{21}H_{27}NO_3$	>10	>10
3d	CH_3	$CH(CH_3)C_{12}H_{25}$	131-132.5	22	Ethyl acetate	$C_{27}H_{41}NO_3$	3.2	>10
3e	CH_3	$CH(CH_3)CH(CH_3)C_5H_{11}$	179-183	22	CH_3CN	$C_{22}H_{31}NO_3{\cdot}HCl$	10	>32
3f	$CH_2C_6H_5$	$CH(CH_3)CH(CH_3)C_5H_{11}$	137-138	33	CH_3CN	$C_{28}H_{35}NO_3$	>32	>32
3g	H	$CH(CH_3)CH(CH_3)C_5H_{11}$	172-175	50	CH_3CN	$C_{21}H_{29}NO_3$	10	56
3h	$CH_2C{\equiv}CH$	$CH(CH_3)CH(CH_3)C_5H_{11}$	127-131	34		$C_{24}H_{31}NO_3{\cdot}HCl$	1.8	>100

[a] See footnote *b*, Table I.

Table IV. *N*-Methylbenzopyrano[3,4-*d*]pyridine



Compd	R'	Mp, °C	Yield purified, %	Crystn solvent	Formula	Mouse data[a] MED$_{50}$	Mouse data[a] LD$_{50}$
4a	CH_3	219 dec	37	Et_2O	$C_{16}H_{21}NO_2$	5.6	>32
4b	n-C_5H_{11}	187–188	47	CH_3CN	$C_{20}H_{29}NO_2$	18	>32
4c	$CH(CH_3)$-n-C_5H_{11}	183–184	13	CH_3CN	$C_{22}H_{33}NO_2$	>10	>10
4d	$CH(CH_3)C_6H_{11}$	187–189 dec	38	CH_3CN	$C_{23}H_{33}NO_2$	>10	>10
4e	$CH(CH_3)$-n-$C_{12}H_{25}$	222–223	15	CH_3CN	$C_{29}H_{47}NO_2 \cdot HI$	>10	>10
4f	$CH(CH_3)CH(CH_3)$-n-C_5H_{11}	178–179	15	CH_3CN	$C_{24}H_{37}NO_2$	1	22

[a] See footnote *b*, Table I.

(DMHP),[7,8] had an MED$_{50}$ of 0.075 mg/kg in this test. Compound **4f**, the nitrogen analog (isostere) of DMHP, was less potent with an MED$_{50}$ of 1 mg/kg. Altering the side chain (R) of compound **4f** further reduced potency (compounds **4a–e**). Acetylation of the phenolic OH of compound **4f** had little effect on its potency (compound **5a**). The pyrone (5-oxo intermediate) of compound **4f**, compound **3e**, was less potent than compound **4f**. Shifting the ring position of the nitrogen of compound **4f** had no effect on potency (compound **2b**). Different substituents on the nitrogen of compound **4f** resulted in changes in potency (see, for example, compounds **5b,d,f–m,o–q,v**). A propargyl substituent (**5t**) substantially increased potency as did other three-carbon substituents (**5m,o–q**). *N*-Propargyl compounds with long *n*-alkyl side chains were also potent in this test. Compound **5t** was equipotent with DMHP. An examination of the diastereoisomer of **5t** showed the erythro isomers to be more potent than the threo isomers (Table VIII). Compound **5t** and its erythro isomers were the most potent nitrogen analogs tested. Alteration of the structure of compound **5t** in the side chain (R') or acetylation of the phenolic OH slightly reduced potency (**5u**). Shifting the ring position of the nitrogen markedly reduced its potency (compound **2g**). Quaternization of the nitrogen markedly increased toxicity (compounds **9** and **10**).

Pharmacological Profile of 5t Compared to DMHP (III). Adams' most potent carbocyclic compound, DMHP, a stereoisomeric mixture, has been studied extensively in laboratory animals[7,8a,c,e] and in man.[8d,f] The most potent nitrogen analog, compound **5t**, also a stereoisomeric mixture, was compared to DMHP in a variety of tests in different animal species. The results are summarized in Table XI and are described as follows.

In the mouse screen,[12] the MED$_{50}$'s and LD$_{50}$'s for **5t** and DMHP were not statistically different. Effects produced were similar, the most prominent of which were general depression and, at high doses, static and dynamic ataxia. Both compounds also showed similar overt behavior effects in the cat, dog, and in rhesus monkeys: depression, static ataxia, and ataxia. In addition, ptosis was observed in the monkey and relaxation of the nictitating membrane was seen in the cat. Depression in the dog did not resemble that produced by the classical sedative hypnotics or tranquilizers. Although the dog was clearly sedated, it was hyperactive to stimuli (sound and touch). In these three species, **5t** was more potent than DMHP.

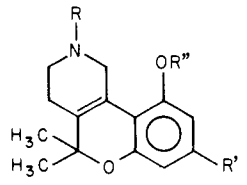
It was shown that β-adrenergic stimulation could account, in part, for the overt behavior effects seen with these compounds. Thus, in the cat, 5 mg/kg iv of the β-blocking agent, dichloroisoproterenol (DCI), both prevented and reversed many of the depressant effects of DMHP and **5t**. This dose of DCI had minimal or no effect on ataxia or on the relaxation of the nictitating membrane which is produced by both compounds.

Compound **5t** and DMHP were also active in other tests for CNS depression (polysynaptic reflex[13] and hexobarbital potentiation[14]) and in a test for neuromuscular effects (inclined screen[15]). These results were consistent with the overt behavior test findings. Both compounds depressed the cat's polysynaptic reflex, with **5t** less potent than DMHP. Both compounds potentiated hexobarbital activity and caused animals to fall from the inclined screen but their potencies were not statistically different in these tests. Neither compound affected conditioned avoidance performance[28] at doses up to 1 mg/kg sc.

In cardiovascular studies in the anesthetized cat, both compounds lowered mean arterial pressure without significantly altering pulse pressure. They were equipotent in their hypotensive activity, with similar minimum effective doses causing comparable decreases in mean blood pressure (**5t**, 19 mmHg; DMHP, 15 mmHg). Both compounds decreased heart rate and respiratory rate. Cardiovascular responses to acetylcholine were not affected by either compound at doses up to 0.1 mg/kg iv. Cardiovascular activity was also tested in the unanesthetized dog. Both compounds decreased mean blood pressure and at their respective MED's **5t** was more potent than DMHP. Each compound was less potent in the unanesthetized dog than in the anesthetized cat. Decreases in heart rate were also noted in the dog but were attributable to the administration vehicle (PEG 200) and were not drug related. No consistent effect on respiration was found. It should be noted that, in the dog, both compounds had overt behavior effects at doses below those which affected blood pressure. This contrasts with results reported in man, where DMHP and its diastereoisomers have been shown to lower blood pressure at doses where no overt CNS effects are observed.[8d,f]

In summary, the pharmacological profiles of **5t** and DMHP were similar. Both compounds exhibited significant CNS depressant activity and hypotensive activity. In overt behavior studies in the mouse, cat, monkey, and dog, general depression (of spontaneous activity, awareness, and, except in the mouse and dog, responses to stimuli) and static and dynamic ataxia were observed. Polysynaptic reflex depression, hexobarbital potentiation, and inclined screen activity were consistent with the observed overt behavior effects. Part of the overt behavior effects of both

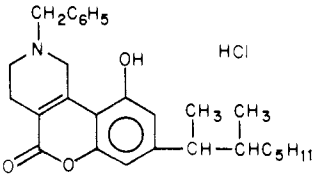
Table V. N-Substituted Benzopyrano[3,4-*d*]pyridines



Compd	R	R'	R''	Mp or bp (mm), °C	Yield purified, %	Crystn solvent	Formula	Mouse data[a] MED50	Mouse data[a] LD50
5a	CH_3	$CH(CH_3)CH(CH_3)$-*n*-C_5H_{11}	$COCH_3$	218–225 (0.5)			$C_{26}H_{37}NO_3$	3.2	32
5b	$CH_2C_6H_5$	$CH(CH_3)CH(CH_3)$-*n*-C_5H_{11}	H	202–205	53	Et_2O and $CH_3COOC_2H_5$	$C_{30}H_{41}NO_2 \cdot HI$	10	>32
5c	H	$CH(CH_3)CH(CH_3)$-*n*-C_5H_{11}	H	114.5–116	95	Petr ether (bp 30–60°)	$C_{23}H_{35}NO_2$	1.8	18
5d	$COCH_3$	$CH(CH_3)CH(CH_3)$-*n*-C_5H_{11}	H	160–161.5	47	C_6H_6	$C_{25}H_{37}NO_3$	5.6	>32
5e	$COCH_3$	$CH(CH_3)CH(CH_3)$-*n*-C_5H_{11}	$COCH_3$	81–82	46	CH_3CN	$C_{27}H_{37}NO_3$	1.8	>32
5f	C_2H_5	$CH(CH_3)CH(CH_3)$-*n*-C_5H_{11}	H	178–180	37	CH_3CN	$C_{25}H_{39}NO_2$	5.6	>10
5g	*n*-C_3H_7	$CH(CH_3)CH(CH_3)C_5H_{11}$	H	178–180	18	CH_3CN	$C_{26}H_{41}NO_2$	0.42	>3.2
5h	CO-c-C_3H_5	$CH(CH_3)CH(CH_3)C_5H_{11}$	H	124.5–126	55	Petr ether	$C_{27}H_{39}NO_3$	10	>32
5i	CH_2-c-C_3H_5	$CH(CH_3)CH(CH_3)C_5H_{11}$	H	173.5–175 dec	36	CH_3CN	$C_{27}H_{41}NO_2$	1.8	>10
5j	*n*-C_5H_{11}	$CH(CH_3)CH(CH_3)C_5H_{11}$	H	159.5–160.5	43	CH_3CN	$C_{28}H_{45}NO_2$	1.8	>10
5k	CH_2-c-C_4H_7	$CH(CH_3)CH(CH_3)C_5H_{11}$	H	182–184.5 dec	17	CH_3CN	$C_{28}H_{43}NO_2$	0.56	25
5l	$CH_2CH_2C_6H_5$	$CH(CH_3)CH(CH_3)C_5H_{11}$	H	176.5–178	23	CH_3CN	$C_{31}H_{43}NO_2$	3.2	>10
5m	$CH_2CH{=}CH_2$	$CH(CH_3)CH(CH_3)C_5H_{11}$	H	174.5–175.5	52	CH_3CN	$C_{26}H_{39}NO_2$	0.75	>10
5n	$CH_2CH{=}CH_2$	$CH(CH_3)CH(CH_3)C_5H_{11}$	$COCH_3$	212 (0.4)	55		$C_{28}H_{41}NO_3$	0.42	32
5o	$CH_2CH{=}CHCl$	$CH(CH_3)CH(CH_3)C_5H_{11}$	H	162–163	50	CH_3CN	$C_{26}H_{38}ClNO_2$	0.42	>32
5p	$CH_2CH{=}CHCl$ (cis)	$CH(CH_3)CH(CH_3)C_5H_{11}$	H	160–162	31	CH_3CN	$C_{26}H_{38}ClNO_2$	0.42	>10
5q	$CH_2CH{=}CHCl$ (trans)	$CH(CH_3)CH(CH_3)C_5H_{11}$	H	171–172	22	CH_3CN	$C_{26}H_{38}ClNO_2$	0.25	>10
5r	$CH_2CH{=}CHC_6H_5$	$CH(CH_3)CH(CH_3)C_5H_{11}$	H	212–213 dec	10	$(CH_3)_2NO_2$	$C_{32}H_{43}NO_2$	>10	>10
5s	$CH_2CH{=}C(CH_3)_2$	$CH(CH_3)CH(CH_3)C_5H_{11}$	H	177–179	16	CH_3CN	$C_{28}H_{43}NO_2$	3.2	>10
5t	$CH_2C{\equiv}CH$	$CH(CH_3)CH(CH_3)C_5H_{11}$	H	141.5–142	26	CH_3CN	$C_{26}H_{37}NO_2$	0.042	40
5u	$CH_2C{\equiv}CH$	$CH(CH_3)CH(CH_3)C_5H_{11}$	$COCH_3$	250 (0.1)	69		$C_{28}H_{39}NO_3$	0.18	>100
5v	$CH_2C{\equiv}CCH_3$	$CH(CH_3)CH(CH_3)C_5H_{11}$	H	236–238	15	CH_3CN	$C_{27}H_{39}NO_2 \cdot HCl$	1	32
5w	$CH_2C{\equiv}CH$	*n*-C_7H_{15}	H	161–164	22	Petr ether	$C_{24}H_{33}NO_2$	0.13	>32
5x	$CH_2C{\equiv}CH$	*n*-C_9H_{19}	H	150–151	2	CH_3CN–EtOH	$C_{26}H_{37}NO_2$	0.32	>20

[a] See footnote *b*, Table I.

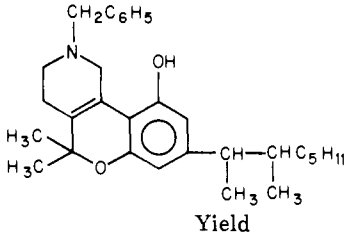
Table VI. Chemical Data for Diastereoisomeric *N*-Benzyl Intermediates (Pyrones) for Compound 5t



Isomer	$[\alpha]^{25}D$,[a] deg	Mp, °C	Yield purified, %	Crystn solvent	Formula
(+)-Erythro	+11.48	253-262 dec	34	CH_3CN	$C_{28}H_{35}NO_3 \cdot HCl$
(−)-Erythro	−10.85	250-262 dec	39	CH_3CN	$C_{28}H_{35}NO_3 \cdot HCl$
(+)-Threo	+29.80	265-271 dec	44	CH_3CN	$C_{28}H_{35}NO_3 \cdot HCl$
(−)-Threo	−30.80	265-267 dec	45	CH_3CN	$C_{28}H_{35}NO_3 \cdot HCl$

[a] Rotations were observed in methanol containing hydrogen chloride (c 1-2), l = 1 dm.

Table VII. Chemical Data for Diastereoisomeric *N*-Benzyl Intermediates (Pyrans) of Compound 5t



Isomer	$[\alpha]^{25}D$,[a] deg	Mp, °C[b]	Yield purified, %	Crystn solvent	Formula
(+)-Erythro	+12.17	211-213	48	CH_3CN	$C_{30}H_{41}NO_2$
(−)-Erythro	−12.28	210-212	36	CH_3CN	$C_{30}H_{41}NO_2$
(+)-Threo	+28.43	175-179	67	CH_3CN	$C_{30}H_{41}NO_2$
(−)-Threo	−29.60	175-180	47	CH_3CN	$C_{30}H_{41}NO_2$

[a] Rotations were observed in methanol containing hydrogen chloride (c 1-2), l = 1 dm. [b] Melting points are for the free base.

compounds appeared to be mediated through β-adrenergic systems since they could be blocked by DCI. 5t was more potent than DMHP for overt behavior effects in the cat, dog, and monkey and hypotensive activity in the unanesthetized dog, less potent for polysynaptic reflex depression, and equipotent with DMHP in other tests performed.

Comparison of 5t with Narcotic and Narcotic-Antagonist Analgesics. The medicinal chemical basis previously described[2] for introducing nitrogen into the carbocyclic nucleus of tetrahydrocannabinols led us to compare the pharmacology of these nitrogen analogs with that of narcotic and narcotic-antagonist analgesics. Table XII summarizes and compares the activities of **5t**, morphine, and pentazocine in various tests for narcotic-agonist properties.

Like both morphine and pentazocine, **5t** exhibited antiwrithing activity in the phenylquinone test.[16] Compound 5t was active in the Eddy hot-plate test[17] and was also equiactive with morphine for inhibition of gastrointestinal propulsion,[18] but differed from morphine and was similar to pentazocine[17c] in the tail-flick test[19] where it was without significant activity. In the morphine-dependent monkey,[20] both withdrawn and nonwithdrawn, **5t** presented a mixed picture of narcotic antagonist-like activity combined with depressant activity,[20a] which is unlike that of morphine or pentazocine.[20b]

Based on the finding that **5t** precipitated abstinence in the morphine-dependent monkey, we reexamined these compounds for narcotic-antagonist activity using the mouse tail-flick test.[21] We have found that **5t** and other compounds in the series have narcotic-antagonist properties characterized by a long onset and duration of activity. Thus **5t** has an onset at 4 h, a peak activity about 24 h, and a duration of nearly 4 days.[22]

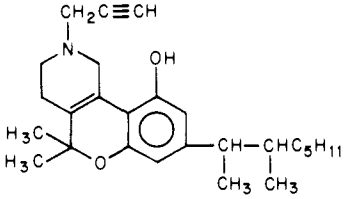
Recently one of us has reported[23] antitumor activity for selective cannabinoids. A number of the benzopyranopyridines reported here also share this property. Details of these data will be published later.

In summary, the pharmacological profiles of these compounds are unique and distinct compared to other CNS drugs. One of these, compound **5t**, is being studied further in animals and in man.

Experimental Section

Melting points were taken on a Fisher-Johns hot-stage apparatus and are uncorrected. Elemental analyses were performed by the late Dr. S. Nagy of M.I.T., Cambridge, Mass., and Spang Microanalytical Laboratory, Ann Arbor, Mich. Where analyses

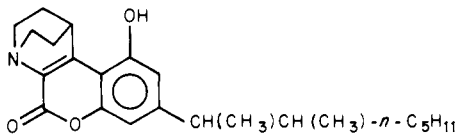
Table VIII. Chemical Data for Diastereoisomers of Compound 5t



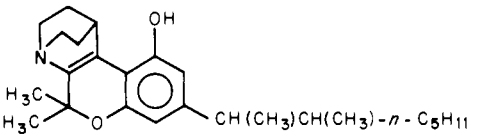
Isomer	Mp, °C	Yield purified, %	Crystn solvent	Formula	Mouse data[c] MED_{50}	Mouse data[c] LD_{50}
(+)-Erythro	113-116	25	CH_3CN	$C_{26}H_{37}NO_2$	0.013	>10
(−)-Erythro	110-112	23	CH_3CN	$C_{26}H_{37}NO_2$	0.056	>10
(+)-Threo	68-70	38	CH_3CN	$C_{26}H_{37}NO_2$[a]	0.13	>10
(−)-Threo	54-59	48	CH_3CN	$C_{26}H_{37}NO_2$[b]	0.13	>10

[a] C: calcd, 78.94; found, 76.53; 76.36. [b] C: calcd, 78.94; found, 77.65; 77.48. [c] See footnote *b*, Table I.

Table IX. Quinuclidinyl Analogs



6

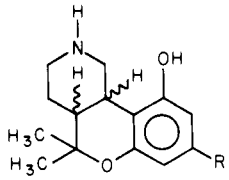


7

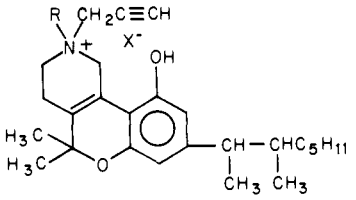
	6	7
Mp, °C	279–282° dec	170.5–171.5
Yield purified, %	15	33
Crystn solvent		CH_3CN
Formula	$C_{23}H_{31}NO_2 \cdot HCl$	$C_{25}H_{37}NO_2$
Mouse data[a]		
MED_{50}	10	0.32
LD_{50}	18	>32

[a] See footnote *b*, Table I.

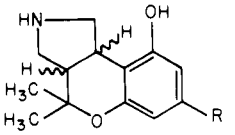
Table X. Dihydro, Quaternary, and Pyrrolo Compounds



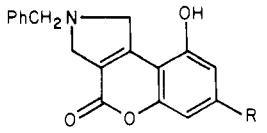
8



9 10



11



11a[a]

	8	9	10	11	11a[a]
R	$-CH(CH_3)CH(CH_3)C_5H_{11}$	$-CH_3$	$-CH_2C{\equiv}CH$	$-CH(CH_3)CH(CH_3)C_5H_{11}$	$-CH(CH_3)CH(CH_3)C_5H_{11}$
X		I	Br		
Mp, °C	78–83	192–194	161–163	131–133	190–193
Yield purified, %	25	65	35	19[b]	
Crystn solvent	Sublimation, 178–185° (0.2 mm)		CH_3CN	Acetone	CH_3CN–ether
Formula	$C_{23}H_{37}NO_2$	$C_{27}H_{40}INO_2$	$C_{29}H_{40}BrNO_2$	$C_{22}H_{35}NO_2$	$C_{27}H_{33}NO_3 \cdot HCl$
Mouse data[c]					
MED_{50}	1.8	5.6	5.6	10	
LD_{50}	18	5.6	18	56	

[a] The crude pyrone was used in the subsequent stage (see Experimental Section) and only a small portion was purified as the hydrochloride. [b] Overall yield. [c] See footnote *b*, Table I.

Table XI. Comparison of the Pharmacological Profiles[a] of 5t and DMHP (III)

	5t, mg/kg	DMHP (III), mg/kg
Primary screen,[b] mouse, iv		
MED_{50}	0.042 (0.018–0.1)[c]	0.075 (0.031–0.18)[c]
LD_{50}	40.0 (32.0–50.0)[c]	63.0 (50.0–79.0)[c]
Overt behavior[d]		
Cat, iv, MED	0.006	0.05
Monkey, iv, MED	0.012	0.05
Dog, iv, MED	0.006	0.05
Synaptic reflexes,[d] cat, iv, MED, intact	↓; 0.006–0.012	↓; 0.0004
Cardiovascular,[d] iv, MED		
Anesthetized cat, BP and respiration	↓0.025	↓0.025
Unanesthetized dog, BP only	↓0.100	↓0.400
Conditioned avoidance, gerbil, sc	>1	>1
Hexobarbital potentiation,[e] mouse, iv, ED_{50}	3.0 ± 1.4	0.72 ± 0.31
Inclined screen,[e] mouse, iv, ED_{50}	0.92 ± 0.22	2.2 ± 0.99

[a] For methodology, see references in text. [b] See footnote *b*, Table I. [c] 95% confidence limits. [d] Two to four animals per dose. [e] Ten animals per dose.

are indicated in the tables, analytical results for the elements were within 0.4% except as noted. All compounds prepared and tested were racemates or mixture of racemates except where otherwise noted. Ir, NMR, and uv spectra were consistent with the assigned structures.

Piperidones of Scheme I. *N*-Methyl-4-carbethoxy-3-piperidone hydrochloride, *N*-methyl-3-carbethoxy-4-piperidone hydrochloride, *N*-benzyl-4-carbethoxy-3-piperidone hydrochloride, and *N*-benzyl-3-carbethoxy-4-piperidone hydrochloride were prepared according to literature methods.[24-27]

Resorcinols. Olivetol (5-*n*-pentylresorcinol) was purchased from the Aldrich Chemical Co. 5-(1,2-Dimethylheptyl)resorcinol and its four stereoisomers were kindly supplied by the Process Chemistry Research Division, Edgewood Arsenal, Md. (see also ref 8b). All other resorcinols were synthesized by the general method of Suter and Weston [27] or by the methods reported by Adams et al. for their alkyl, branched alkyl, and cycloalkylresorcinols.[7]

Pyrones of Tables I and III. Typical Procedure. 2-Benzyl-8-(1,2-dimethylheptyl)-10-hydroxy-5-oxo-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*d*]pyridine (3f, Table III). *N*-Benzyl-4-carbethoxy-3-piperidone hydrochloride (304 g, 1.02 mol) was mixed with 295 g (1.25 mol) of 5-(1,2-dimethylheptyl)resorcinol and 580 ml of concentrated H_2SO_4 was added dropwise with cooling. At the end of the addition (2.5 h), the mixture was stirred until it became clear, and then 175 ml of $POCl_3$ was added during 1.5 h. The mixture was stirred for 60 h longer at room temperature and poured into aqueous $KHCO_3$ (4 lb in 14 l. of ice H_2O) with vigorous mechanical stirring. The brown precipitate was filtered off and stirred with 16 l. of H_2O containing 2 lb of $KHCO_3$. The product was filtered and washed with H_2O until it was neutral. The solid was still largely the HCl salt of **3f**. It was then partially dried in an oven at low temperature. The resulting sticky material was boiled with 2 l. of CH_3CN and

Table XII. Comparison of 5t with Morphine and Pentazocine[a]

	5t	Morphine	Pentazocine
Hot plate, ED_{50}	3.6 (3.0-4.3) mg/kg sc	1.12 (0.9-1.2) mg/kg sc	>200 mg/kg sc
Tail flick, ED_{50} (D'Amour-Smith)	>20 mg/kg iv	4.8 ± 0.6 mg/kg sc	Inactive up to 120 mg/kg sc
Phenylquinone writhing, ED_{50}	0.021 (0.010-0.046) mg/kg iv	0.54 (0.42-0.70) mg/kg sc	2.3 (1.2-4.6) mg/kg sc
Antidiarrheal, % inhibn of gastrointestinal propulsion[b]	50% at 10 mg/kg po, 67% at 100 mg/kg po	52% at 10 mg/kg po	5% at 10 mg/kg po, 29% at 100 mg/kg po
Morphine-dependent monkey			
A. Single dose suppression in withdrawn monkey	Exacerbates abstinence at 1 and 2 mg/kg sc but also produces signs of CNS depression	Suppresses abstinence	No suppression of abstinence
B. Nonwithdrawn monkey	Produces reaction resembling precipitated abstinence at 2, 4, and 8 mg/kg sc but mixed with sedation and accompanied by mydriasis	Produces morphine sedation	Precipitates abstinence

[a] For methodology, see references in text. [b] Diphenoxylate (Lomotil) shows 53% inhibition at 20 mg/kg po. [c] Some nondose related activity between 2.5 and 20 mg/kg iv.

filtered after cooling to give 200 g (48%) of the HCl salt, mp 210–215°. The HCl salt was suspended in aqueous $NaHCO_3$ and the free base was extracted into $CHCl_3$. The $CHCl_3$ extract was dried and evaporated. The residue was recrystallized from CH_3CN to give 150 g of the free base **3f**, mp 134–137°. A small sample was recrystallized again from CH_3CN for elemental analyses: mp 137–138°.

8-(1,2-Dimethylheptyl)-10-hydroxy-5-oxo-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*d*]pyridine (**3g**, Table III). A solution of 2 g (0.0046 mol) of **3f** in 175 ml of absolute EtOH and 10 ml of CH_3CO_2H was shaken under H_2 at 48.5 psi with 0.5 g of 10% Pd/C. Hydrogenolysis was complete after 16 h. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was dissolved in $CHCl_3$ and neutralized with aqueous $KHCO_3$. A precipitate formed during the neutralization reaction. The $CHCl_3$ layer was filtered and evaporated to dryness. The residue was combined with the filtered solid and recrystallized from CH_3CN to give 0.8 g of the nor base **3g**, mp 172–175°.

8-(1,2-Dimethylheptyl)-10-hydroxy-2-(2-propynyl)-5-oxo-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*d*]pyridine Hydrochloride (**3h**, Table III). A mixture of 1.42 g (0.0041 mol) of the nor base **3g**, 0.48 g (0.0040 mol) of 3-bromo-1-propyne, 0.6 g of anhydrous Na_2CO_3, and 20 ml of absolute EtOH was refluxed for 16 h, cooled, and filtered. The filtrate was evaporated to dryness and the residue was extracted with boiling CH_3CN. The extract was cooled in the refrigerator overnight, filtered to remove a small quantity of a dark brown precipitate, and evaporated to dryness to give 0.9 g of a brown solid, mp 74–81°. The crude residue was dissolved in a mixture of hexane and Et_2O and cooled in ice to precipitate a dark gum. The solution was decanted and evaporated to dryness. The residue was dissolved in Et_2O and saturated with anhydrous HCl to yield 0.8 g of **3h** as a light tan crystalline solid, mp 127–131°.

Pyrans of Tables II, IV, and V. Typical Procedure. 2-Benzyl-5,5-dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*d*]pyridine Hydriodide (**5b**, Table V). A solution of 17.2 g (0.039 mol) of the benzopyrone **3f** in 125 ml of dry anisole was added dropwise to a solution of 0.4 mol of MeMgI in 100 ml of anisole. The solution was stirred overnight at 60° and cooled, and the excess Grignard reagent was decomposed with 100 ml of H_2O. The solution was acidified with 400 ml of 4 N H_2SO_4 and the anisole was steam distilled from solution. The mixture was cooled, made basic with solid Na_2CO_3, and filtered. The solid recovered was dried in a desiccator over $CaCl_2$ and then was extracted with CH_3CN. The extracts were filtered and the filtrate was evaporated. The residue was triturated with Et_2O (A) to give 8.2 g of the HI salt, **5b**, mp 197–200°. A small sample recrystallized from a mixture of Et_2O and $CH_3CO_2C_2H_5$ had mp 202–205°: λ_{max} (EtOH) 280 nm (ϵ 12200). The free base of **5b** was obtained by dissolving the salt in $CHCl_3$ and shaking with aqueous $NaHCO_3$. The free base precipitated from solution and remained suspended in the $CHCl_3$ layer. The product was filtered off and washed with H_2O and finally with $CHCl_3$ to yield 5.2 g of the free base of **5b**, mp 194–198°. The $CHCl_3$ layer was evaporated to yield an additional 0.54 g of the free base. More of the base (1.46 g, mp 194–198°) was obtained from the Et_2O filtrate (A) above by evaporating the solution to dryness and treating the residue with $CHCl_3$ and aqueous $NaHCO_3$, as with the main recovery above. The $CHCl_3$ filtrate was also evaporated to dryness and the residue was triturated with CH_3CN to give an additional 2.2 g of base, mp 188–190°. The total yield of **5b** as the free base was 9.32 g (52%): λ_{max} (EtOH) 280 nm (ϵ 7880).

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*d*]pyridine (**5c**, Table V). An attempt to debenzylate **5b** failed, but the free base was easily hydrogenolyzed to the nor base in good yield as follows. A solution of 2 g (0.0044 mol) of the free base of **5b** in 200 ml of absolute EtOH and 4 ml of CH_3CO_2H was shaken under H_2 at 43 psi with 0.5 g of 10% Pd/C. Reduction proceeded smoothly and was complete after 21 h. The mixture was filtered, the filtrate was evaporated, and the residue was dissolved in $CHCl_3$ and neutralized with aqueous $NaHCO_3$. The $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4, and evaporated to give 1.49 g (95%) of the nor base **5c**. A small sample on recrystallization from petroleum ether (bp 30–60°) showed mp 114.5–116°. Thin-layer chromatography gave an R_f value of 0.13 in MeOH and 0.63 in 10% ammoniacal MeOH.

Alkylation. Method A. 5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-2-(2-propynyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*d*]pyridine (**5t**, Table V). A mixture of 1.6 g (0.0044 mol) of the nor base **5c**, 0.52 g (0.0044 mol) of 3-bromo-1-propyne, and 30 ml of absolute EtOH was stirred and refluxed with 0.6 g of anhydrous Na_2CO_3 under N_2. After 16 h, the solution was cooled and filtered, and the filtrate was evaporated to dryness. The residue was triturated with petroleum ether (bp 30–60°) and the insoluble solid was dried. It was recrystallized from CH_3CN with charcoal for decolorizing: mp 141.5–142°; λ_{max} (EtOH) 280 nm (ϵ 14250).

Method B. 2-Cyclopropylmethyl-5,5-dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*d*]pyridine (**5i**, Table V). A solution of 0.46 g (0.0044 mol) of cyclopropanecarbonyl chloride (Aldrich Chemical Co.) in 5 ml of dry C_6H_6 was added dropwise to a solution of 1.6 g (0.0044 mol) of the nor base **5c** in 5 ml of C_6H_6 and 10 ml of pyridine. The mixture was refluxed for 1 h, cooled, and evaporated. The residue was treated with H_2O and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was triturated with boiling petroleum ether and was then filtered ice-cold. The product was washed with cold petroleum ether to yield the amide **5h**: mp 124.5–126°; λ_{max} (EtOH) 280 nm (ϵ 7100).

A solution of 0.82 g (0.002 mol) of the amide **5h** in 100 ml of

dry Et_2O was added dropwise to a mixture of 1.5 g (0.04 mol) of $LiAlH_4$ and 230 ml of dry Et_2O. At the end of the addition, the mixture was refluxed for 20 h. The solution was cooled and the excess $LiAlH_4$ was decomposed with 10 ml of H_2O. The mixture was filtered and the filtrate was washed with 2 × 100 ml of H_2O. The Et_2O solution was dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was recrystallized from CH_3CN to yield colorless crystals: mp 173.5–175°; λ_{max} (EtOH) 280 nm (ϵ 11250).

8-(1,2-Dimethylheptyl)-10-hydroxy-5-oxo-1,2,3,4-tetrahydro-1,4-ethano-5*H*-[1]benzopyrano[3,4-*d*]pyridine Hydrochloride (6, Table IX). Ethyl 3-quinuclidinone-2-carboxylate hydrochloride (Aldrich Chemical Co.) (12 g, 0.051 mol) was added in portions to 12 g (0.050 mol) of 5-(1,2-dimethylheptyl)resorcinol with stirring and 25 ml of concentrated H_2SO_4 was then added dropwise to the mixture at room temperature during 25 min. At the end of this addition, 10 ml of $POCl_3$ was added all at once. The mixture was stirred at room temperature for 16 h. The mixture was neutralized with aqueous $NaHCO_3$ and finally with H_2O. The $CHCl_3$ solution was dried over anhydrous Na_2SO_4 and evaporated to dryness to give 15 g of a dark solid. A solution of 10 g of this crude product in Et_2O was saturated with anhydrous HCl to give 0.5 g of compound 6 as a colorless solid, mp 279–282° dec.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-1,2,3,4-tetrahydro-1,4-ethano-5*H*-[1]benzopyrano[3,4-*d*]pyridine (7, Table IX). The quinuclidinylpyrone hydrochloride 6 (8.5 g) in $CHCl_3$ was shaken with aqueous $KHCO_3$. The solution was washed with H_2O, dried, and evaporated to dryness to give 7.3 g, mp 112–116°, of the free base of 6. A solution of this compound in 70 ml of dry anisole was added dropwise to 0.25 mol of MeMgI in 250 ml of anisole. After the addition was over, the mixture was stirred for 16 h at 35° and cooled. The excess Grignard solution was decomposed with 100 ml of H_2O, the mixture was acidified with 250 ml of 4 N H_2SO_4, and the anisole was removed by steam distillation. The gummy, dark solid that remained was filtered and made crystalline by warming with CH_3CN on a steam bath. The mixture was cooled and filtered, and the solid was washed with cold CH_3CN. The yield was 3.5 g of the HI salt of 7 as a colorless crystalline solid, mp 280° dec. The free base was obtained by shaking a solution of 1 g of the HI salt in $CHCl_3$ with aqueous $KHCO_3$ and then with H_2O. Two recrystallizations of the product from CH_3CN gave 215 mg of 7: mp 170.5–171.5°; λ_{max} (EtOH) 280 nm (ϵ 9700). Thin-layer chromatography gave an R_f value of 0.8 in 75% C_6H_6 and 25% MeOH.

***cis*-5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-5*H*-[1]benzopyrano[3,4-*d*]piperidine** (8, Table X). A solution of 7.8 g (0.021 mol) of **5c** in 200 ml of absolute MeOH was shaken with 3–5 g of W-2 Raney nickel for 16 h under 50 psi of H_2. The solution was filtered and the filtrate was evaporated to dryness, leaving 5.9 g of a green solid. Sublimation of this residue at 178–185° (0.2 mm) gave 1.9 g of 8 as a yellow crystalline sublimate, mp 78–83°. The absorption at 1640 cm^{-1} (C=C conjugated with the aromatic ring) was absent: λ_{max} (EtOH) 280 nm (ϵ 425).

8-(1,2-Dimethylheptyl)-10-hydroxy-2-(2-propynyl)-2,5,5-trimethyl-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*d*]pyridinium Iodide (9, Table X). A solution of 0.4 g (0.001 mol) of the pyran 5t and 4 g of MeI in 20 ml of Et_2O was warmed on the steam bath until precipitation occurred. The mixture was allowed to stand several minutes and then was cooled in an ice bath. The colorless solid was collected, washed with Et_2O, and dried to give 0.35 g of 9: mp 192–194°; λ_{max} (EtOH) 380 nm (ϵ 9370).

5,5-Dimethyl-8-(1,2-dimethylheptyl)-2,2-di(2-propynyl)-10-hydroxy-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*d*]pyridinium Bromide (10, Table X). A solution of 1 g (0.0025 mol) of the pyran 5t and 5 g (0.052 mol) of 3-bromo-1-propyne in 30 ml of Et_2O was gently heated on the steam bath for several minutes and then allowed to stand at room temperature for 64 h. At the end of this time, the precipitated quarternary salt was filtered and dried to give a colorless solid, which was recrystallized from 1:1 CH_3CN–Et_2O to yield 0.63 g of 10 as colorless crystals, mp 161–163°.

2-Benzyl-7-(1,2-dimethylheptyl)-9-hydroxy-4-oxo-1,2,3,4-tetrahydro-[1]benzopyrano[3,4-*c*]pyrrole (11a, Table X). In each of three flasks a stirred and cooled mixture of 10 g (0.04 mol) of ethyl 1-benzyl-4-pyrrolidone-3-carboxylate and 10 g (0.04 mol) of 5-(1,2-dimethylheptyl)resorcinol was dissolved by addition of 25 ml of concentrated H_2SO_4 and 15 ml of $POCl_3$. The mixtures were stirred at room temperature for 4 days, with a subsequent addition of 6 ml of $POCl_3$ to each. Then they were poured over ice with stirring. The resulting granular yellow solid was filtered and taken up in $CHCl_3$. The solution was washed repeatedly with 10% $NaHCO_3$ solution and then with H_2O. Evaporation of the dried (Na_2SO_4) extract yielded 30 g of a clear yellow gum, which was used in the subsequent stage without further purification. A portion of the gum was converted to the HCl salt, which, after several recrystallizations from CH_3CN–Et_2O–ether, gave a solid: mp 190–193°; λ_{max} (EtOH) 316 nm (ϵ 12300).

4,4-Dimethyl-7-(1,2-dimethylheptyl)-9-hydroxy-1,2,3,3a,4,9b-hexahydro-[1]benzopyrano[3,4-*c*]pyrrole (11, Table X). A solution of 4.2 g of the crude pyrone in 50 ml of dry anisole was added dropwise under N_2 to a stirred suspension of 12 g (0.1 mol) of MeMgBr in anisole. The reaction mixture was stirred at 60° for 3 days and then was decomposed with 50 ml of H_2O and 50 ml of 4 N H_2SO_4. Removal of the anisole by steam distillation left the product as a brown gum which was insoluble in H_2O. A solution of the gum in $CHCl_3$ was washed with 10% $NaHCO_3$ and with H_2O and was dried over Na_2SO_4. Evaporation yielded a dark gum, which upon trituration with CH_3CN gave 1.8 g of the *N*-benzylpyran as a colorless solid: mp 175–180°; λ_{max} (EtOH) 290 nm (ϵ 11200).

A solution of 2 g (0.0045 mol) of this *N*-benzylpyran in 200 ml of absolute EtOH and 5 ml of CH_3CO_2H was shaken under H_2 at 55 psi with 0.5 g of 10% Pd/C. Hydrogenolysis was complete after 3 h. The mixture was filtered and evaporated, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was shaken to neutrality with 10% $NaHCO_3$ solution, washed with H_2O, dried over Na_2SO_4, and evaporated. Upon trituration with CH_3CN, the gummy residue gave 1.25 g of the hygroscopic nor base, mp 128–130°. Recrystallization from Me_2CO gave 11 as a colorless solid, mp 131–133°.

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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.
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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-