g, 0.05 mol), 2-butanone (30.2 g, 0.42 mol), 5% NaOH solution (50 ml), and water (100 ml) was stirred at 25° for 30 min. The sodium salt of the starting acid which initially precipitated gradually went into solution. The solution was acidified with 5% hydrochloric acid. The solid product which precipitated was stirred with concentrated $NaHCO_3$ solution to obtain the sparingly soluble Na salt of **3i**. The salt was collected and dissolved in boiling water (200 ml) and the solution acidified to precipitate **3i** which was purified by recrystallization to constant melting point: NMR δ 1.03 (3 H, t, CH_3), 2.73 (2 H, q, CH_3CH_2), 4.94 (2 H, s, OCH_2), 6.86 (1 H, d, J = 16 Hz, COCH=), 7.78 (1 H, d, J = 16 Hz, PhCH=), 7.14 (1 H, d, J = 8 Hz, phenyl H_6), 7.85 (1 H, d, J = 8 Hz, phenyl H_5), 13.1 (1 H, br s, COOH).

(*E*)-[2,3-Dichloro-4-(2-methyl-3-oxo-1-propenyl)phenoxy]acetic Acid (3j). A solution of propionaldehyde (5.2 g, 0.09 mol) in water (150 ml) was added during 30 min to a solution of (2,3-dichloro-4-formylphenoxy)acetic acid[1] (15.0 g, 0.06 mol) and $LiOH \cdot H_2O$ (3.3 g, 0.078 mol) in water (100 ml) at 25° with stirring. After an additional 30 min, the solution was acidified with 6 N hydrochloric acid to precipitate 18.5 g of crude product, mp 122–140°. Five recrystallizations from *i*-PrOH produced pure **3j**: NMR δ 1.87 (3 H, s, CH_3), 4.93 (2 H, s, OCH_2), 7.18 (1 H, d, J = 9 Hz, phenyl H_6), 7.56 (1 H, d, J = 9 Hz, phenyl H_5), 7.58 (1 H, s, PhCH=), 9.70 (1 H, s, HC=O), 13.2 (1 H, br s, COOH). Anal. $C_{12}H_{10}Cl_2O_4$) C, H, Cl.

(*E*)-[2,3-Dichloro-4-(2-oxocyclohexylidenemethyl)phenoxy]acetic Acid (3k). A solution of ethyl (2,3-dichloro-4-formylphenoxy)acetate[1] (5.5 g, 0.02 mol), 4-(1-cyclohexen-1-yl)morpholine[7] (4.0 g, 0.024 mol), and AcOH (1 ml) in toluene (25 ml) was heated at reflux under a constant water separator until output of water ceased (3 h). The mixture was then concentrated to dryness at reduced pressure. The residue was dissolved in a mixture of AcOH (35 ml) and 5% hydrochloric acid (17 ml) and the solution heated at 95° for 0.5 h. The solution was diluted with water to precipitate **3k** as a gum which slowly crystallized. It was purified by recrystallization to constant melting point: NMR δ 7.35 (1 H, s, PhCH=).

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Synthesis and Dopaminergic Activity of (±)-, (+)-, and (−)-2-Dipropylamino-5-hydroxy-1,2,3,4-tetrahydronaphthalene[1]

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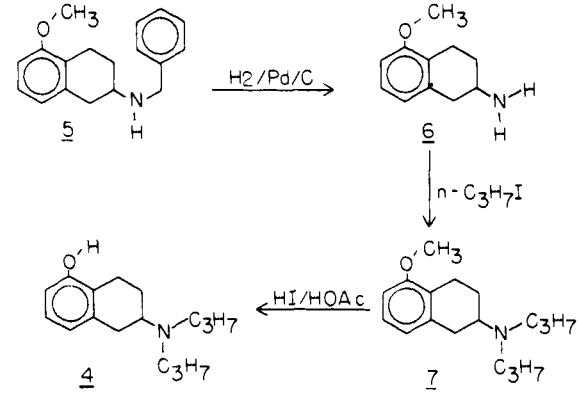
In an effort to identify further the structural requirements for central dopamine receptor agonists, some monohydroxyl analogs of the known agonist 5,6-dihydroxy-2-dipropylamino-1,2,3,4-tetrahydronaphthalene were synthesized. They were examined for production of emesis in dogs and stereotyped behavior in rats. The most potent was 5-hydroxy-2-dipropylamino-1,2,3,4-tetrahydronaphthalene, which was more potent than apomorphine but less so than the dihydroxyl analog. The two enantiomers of the monohydroxyl analog were synthesized by conventional methods from an optically active intermediate, 2-benzylamino-5-methoxy-1,2,3,4-tetrahydronaphthalene. The resolution of this amine was performed with the aid of mandelic acid. Dopaminergic activity was found to be confined to the levo enantiomer. Requirements for both substitution and chirality in the tetralins were found to correspond closely to those known for the dopaminergic aporphines.

In an attempt to elucidate the structural requirements for central dopamine receptor agonists, we recently described the synthesis and pharmacology of a group of 2-amino-1,2,3,4-tetrahydronaphthalenes having substitution at nitrogen and in the aromatic ring.[2] On the basis of results from some compounds lacking a catechol group, we concluded that this functional group is not indispensible for in vivo dopaminergic activity. Other workers have published data on aporphine derivatives from which similar conclusions can be drawn.[3]

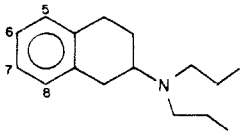
To explore further the significance of the aromatic hydroxyl groups in putative dopaminergic agonists, we have prepared a group of monohydroxytetralins possessing the 2-dipropylamino group, the group which pharmacologically compared favorably with all others. These are racemic compounds **2**–**4** in Table I. These compounds were synthesized from dipropylamine and appropriately substituted β-tetralones using methods previously described.[2]

Scheme I



The reports by Saari and King[4] and by Neumeyer et al.[5] that the dopaminergic properties of apomorphine (APM) reside only in the natural levo enantiomer offered an

Table I. Pharmacological Evaluation[a] of 2-Dipropylaminotetralins



Compd	Substitution	Mp, °C[b] (HCl salt)	E,[c] μg/kg	S,[d] mg/kg
(−)-Apomorphine			26[e]	0.5[e]
(±)-1	5,6-(OH)$_2$	208 dec	0.57[e]	0.03[e]
(±)-2	7-OH	166–168[f]	13	23
(±)-3	6-OH	167–169[f]	36	13
(±)-4	5-OH	201–202	4	0.09
(+)-4	5-OH	228–229	>80[g]	>1.8[g]
(−)-4	5-OH	228–229.5	2	0.05

[a] Test solutions were prepared by dissolving HCl or HI salts in saline. Doses are expressed in terms of free base. See ref 2 for more details of testing protocol and establishment of minimum doses. [b] All new compounds gave satisfactory analyses for C, H, and N. [c] Minimum emetic im dose in the dog. [d] Minimum sc dose required to induce stereotyped behavior for 30–50 min in the rat. [e] These data, reported earlier,[2] are included for comparison. [f] HI salt. [g] Inactive at this level.

opportunity to examine further the similarity of the tetralins to APM. We decided to resolve (±)-4, the most active of the monohydroxytetralins.

We were unsuccessful in obtaining crystalline diastereoisomeric salts from either (±)-4 or its possible precursor, (±)-6 (Scheme I). An attempt to resolve 6 by asymmetric induction, using 5-methoxy-2-tetralone and optically active α-methylbenzylamine,[6] ultimately gave 6 only about 10% optically pure. However, the salt of (±)-5 with mandelic acid yielded readily to fractional crystallization from ether. Hydrogenolysis of the benzyl groups of (+)-5 and (−)-5 gave (+)-6 and (−)-6, respectively. The *n*-propyl groups were substituted onto (+)-6 and (−)-6 with *n*-propyl iodide. Cleavage of the protecting ether groups with hydrogen iodide then yielded (+)-4 and (−)-4, respectively.

Results and Discussion

All compounds were evaluated in two tests in which APM is active at low doses. Details of the test procedures have been published previously.[2] Minimum emetic doses were determined by im injection in three to five dogs. The minimum effective doses for induction of stereotyped behavior were determined in Sprague–Dawley male rats, three animals per dose.

Among the racemic monohydroxytetralins in Table I, the relative importance of the 5-hydroxyl group is evident. This finding coincides structurally and biologically with what Neumeyer et al.[3] have shown recently about the 11-hydroxyl group in the aporphines. The levo enantiomer of 4 displays activity at about half the dose levels of the racemic mixture, while the dextro enantiomer is inactive at doses 20 times as large. Thus, the characteristic effects of this drug appear to be properties of the levo enantiomer only, as in APM. No attempt was made to determine whether (−)-4 and (−)-APM have the same configuration at their chiral centers.

It was determined that pretreatment of animals with (+)-4 does not attenuate the biological effects of either (−)-4 or APM. Thus, the possibility that the potency difference between the racemic mixture and the levo enantiomer might be due in part to dopaminergic antagonist activity in (+)-4 can be ruled out.

The 2-aminotetralins studied here display pharmacology which is qualitatively similar to that of the dopaminergic aporphines to which they are structurally related, with the tetralins being consistently more potent. We interpret these results as supportive of our earlier conclusion[2] that the catechol group in such compounds is not indispensible for in vivo dopamine-like activity. It may also be inferred that the unsubstituted aromatic ring in APM does not play a positive role in promoting this activity.

Experimental Section

Melting points were determined in open capillaries with a Thomas-Hoover oil bath apparatus and are uncorrected. Infrared and proton magnetic resonance spectra were consistent with the proposed structures. Where elemental analyses are indicated, results obtained were within ±0.4% of the theoretical values. Specific rotations were measured in a Perkin-Elmer 141 polarimeter fitted with a 1-dm quartz cell with a water jacket thermostatically controlled to ±0.5 °C.

(±)-2-Benzylamino-5-methoxy-1,2,3,4-tetrahydronaphthalene [(±)-5]. A solution of 3,4-dihydro-5-methoxy-2(1*H*)-naphthalenone (11.3 g, 64 mmol), benzylamine (8.6 g, 81 mmol), and *p*-toluenesulfonic acid monohydrate (0.4 g, 2 mmol) in 100 ml of benzene was refluxed 1.5 h under N_2 with continuous removal of water. The carbonyl absorption was thus removed from the ir spectrum. Most of the benzene was distilled off and replaced by 90 ml of ethanol. The solution was transferred to a Parr reduction bottle, 100 mg of PtO_2 was added, and hydrogenation was performed at 2 atm until uptake was complete (about 1 h). The catalyst was removed, solvent and excess benzylamine were evaporated at reduced pressure, and the crude oily product was converted to the HCl salt. After four recrystallizations from methanol–ethyl acetate 13.8 g (71%) of (±)-5·HCl, mp 246–248° dec, was obtained. Anal. ($C_{18}H_{22}ClNO$) C, H, N.

Resolution of (±)-5. A solution of (±)-5 (4.2 g, 0.016 mol) in 50 ml of ether was added to a stirred solution of (−)-mandelic acid (Aldrich, $[\alpha]^{20}D$ −153°, 2.4 g, 0.016 mol) in 100 ml of ether. The filtrable solid thus obtained was recrystallized six times by dissolving in boiling ether, boiling solvent off until precipitation was extensive, and cooling to room temperature. This treatment was sufficient to produce no further change in the melting point. The yield of (+)-5·(−)-mandelate was 2.3 g (70%), mp 139–141°. The resolved amine was released with $NaCO_3$ solution into ethyl acetate and converted to its HCl salt, which was crystallized from methanol–ethyl acetate: mp 246–247° dec; $[\alpha]^{20}D$ +61° (methanol, *c* 2).

The free amine was isolated from the combined mother liquors from the above crystallization and treated with an equimolar amount of (+)-mandelic acid (Aldrich, $[\alpha]^{20}D$ +154°) in ether. This yielded, after three recrystallizations done as above, 2.8 g (85%) of (−)-5·(+)-mandelate, mp 138–139.5°. The HCl salt obtained from it was (−)-5·HCl: mp 246–247° dec; $[\alpha]^{20}D$ −61° (methanol, *c* 2).

(+)- and (−)-2-Amino-5-methoxy-1,2,3,4-tetrahydronaphthalene [(+)- and (−)-6]. To a solution of 1.5 g (5.6 mmol) of (+)-5 in 50 ml of ethanol was added 1.0 g of palladium hydroxide on charcoal catalyst.[6] Hydrogenolysis was performed at 2 atm. Uptake was complete in 15 min. Removal of catalyst and solvent gave (+)-6 quantitatively as an oil. Conversion to the HCl salt and crystallization from methanol–ethyl acetate gave (+)-6·HCl: mp 260° dec; $[\alpha]^{20}D$ +61° (methanol, *c* 2). Anal. ($C_{11}H_{16}ClNO$) C, H, N.

The optical antipode (−)-6·HCl was prepared in the same way: mp 260° dec; $[\alpha]^{20}D$ −61° (methanol, *c* 2). Anal. ($C_{11}H_{16}ClNO$) C, H, N.

(+)- and (−)-2-Dipropylamino-5-methoxy-1,2,3,4-tetrahydronaphthalene [(+)- and (−)-4]. A solution of *n*-propyl iodide (2.4 g, 14 mmol) and (+)-6·HCl (0.75 g, 3.5 mmol) in 15 ml of benzene was refluxed with 5 ml of a saturated aqueous K_2CO_3 solution for 48 h. By this time TLC aliquots from the benzene layer indicated that most of the primary amine had been consumed, with formation of some secondary amine and a predominant amount of tertiary amine (the most mobile component on silica).

The benzene layer was removed, dried (Na_2SO_4), and evaporated to an oily mixture. Chromatography on silica (20 g) gave 0.40 g (44%) of pure (+)-2-dipropylamino-5-methoxy-1,2,3,4-tetrahydronaphthalene [(+)-7] as an oil by eluting with 10% ethyl acetate–90% benzene. The HCl salt had mp 171–172° dec, $[\alpha]^{20}D$ +65° (methanol, c 2).

To (+)-7 (0.30 g, 1.2 mmol) was added 0.8 g of 47% HI solution at 0 °C with stirring. Acetic anhydride (1.8 g) was then added dropwise. The solution was refluxed gently under N_2 for 1 h, cooled to room temperature, and triturated with 100 ml of ether. The yellow crystalline solid thus obtained was treated with HCl–methanol to exchange the halides.[7] After three recrystallizations from methanol–ethyl acetate, 0.20 g (61%) of (+)-4·HCl was obtained as a colorless crystalline solid: mp 228–229° dec; $[\alpha]^{20}D$ +70° (methanol, c 2). Anal. ($C_{16}H_{26}ClNO$) C, H, N.

By the same procedure (−)-6 was converted to (−)-4·HCl: mp 228–229.5° dec; $[\alpha]^{20}D$ −71° (methanol, c 2). Anal. ($C_{16}H_{26}ClNO$) C, H, N.

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Drugs Derived from Cannabinoids. 3.[1a] Sulfur Analogs,[1b] Thiopyranobenzopyrans and Thienobenzopyrans

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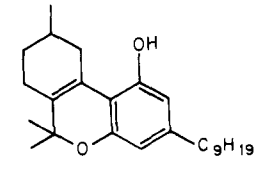
Sulfur analogs of cannabinoids corresponding to DMHP (1) were prepared utilizing the Pechmann condensation between the appropriate keto ester and 5-(1,2-dimethylheptyl)resorcinol, followed by Grignard reaction. Compounds of various structural types (2–6), which had different ring size and position of the sulfur atom substituted in the alicyclic ring, were found to be active CNS agents in pharmacological tests in mice, rats, and dogs. They showed profiles qualitatively similar to those of the nitrogen and carbocyclic analogs. Basic esters of the most interesting parent phenols 2 and 4 were also prepared and tested.

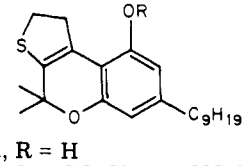
Extending our work on nitrogen and carbocyclic analogs of cannabinoids,[2] we report in this paper the synthesis of sulfur analogs[3] and their biological activity in selected pharmacological tests. In order to define a functional group–activity relationship in this series, we have varied the ring size and the position of the sulfur atom substituted in the alicyclic ring of compound 1[4] and have prepared the structural types **2–6**. These compounds were made with the 1,2-dimethylheptyl substituent on the aromatic ring, because earlier work had shown that this side chain gave the most potent compounds.[2]

As with the nitrogen and carbocyclic analogs[2b] of cannabinoids, the sulfur analogs were water insoluble but very lipid soluble. Hence the water-soluble derivatives (**2b,c** and **4b,c**) of the most potent compounds of the series (**2a** and **4a**) were studied also. These derivatives were prepared by techniques utilized in solubilizing the nitrogen and carbocyclic analogs.[2b]

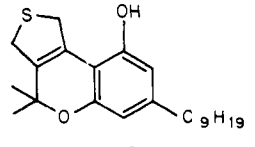
Chemistry. The general synthetic scheme developed in the synthesis of carbocyclic analogs[4,5] was suitable for the preparation of these sulfur analogs (Scheme I). Thus, the appropriate keto esters, which are known in the literature, were prepared and allowed to condense with 5-(1,2-dimethylheptyl)resorcinol under Pechmann conditions[2a,4,5] to give the corresponding pyrones. In the sulfur series, the pyrones were obtained as crystalline compounds and in good yields only when the Pechmann condensation was carried out with anhydrous HCl in methanol or ethanol. The ring-opened triols, which were obtained by a Grignard reaction with the pyrones, ring closed to the corresponding pyrans during an acid work-up.



1 (Roger Adams' DMHP)



2a, R = H
b, R = $CO(CH_2)_3$-c-NC_5H_{10}·HCl
c, $CO(CH_2)_3$-c-$N(CH_2CH_2)_2O$·HCl



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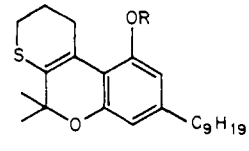
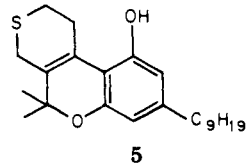


4a, R = H
b, R = $CO(CH_2)_3$-c-NC_5H_{10}·HCl
c, R = $COCH(CH_3)CH_2CH_2$-c-NC_5H_{10}·HCl



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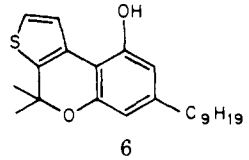

6

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

The water-soluble derivatives were prepared from the pyrans by treatment with the appropriate acid in the presence of dicyclohexylcarbodiimide (DCC) in methylene