10% NaOH. The aq soln was washed twice with Et_2O and was then neutralized with glacial HOAc. The soln was saturated with solid $NaHCO_3$, and the product was extd with several portions of C_6H_6. Evapn of the dried solvent left 17.7 g (55.5% crude yield) of product of mp 88–95°. Recrystn from 100 ml of *i*-PrOAc gave 13.5 g (42.3% yield) of crystals, mp 88–90°.

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Centrally Acting Emetics. 6. Derivatives of β-Naphthylamine and 2-Indanamine[1,†]

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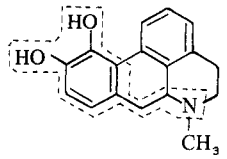
A series of dihydroxy aminotetralins and aminoindans has been prepared as analogs and congeners of fragments of the apomorphine molecule. The high emetic potency observed for certain of these compounds is consistent with current theories of the "dopaminergic" character of apomorphine. Marked differences in potency between the tetralin and the indan series are discussed.

Apomorphine (**1**), which has assumed considerable importance in efforts aimed at understanding the role of *l*-dopa and dopamine in the etiology and therapy of parkinsonism, has structural similarities (as indicated) to dopamine. Apomorphine probably directly activates "dopaminergic" receptors,[2] and McGeer[3] has stated that dopa may cause emesis by stimulation of the *chemoreceptor trigger zone* ("CTZ"), the receptor involved in the emetic action of apomorphine. Ernst and Smilek[4] have shown that dopamine, like apomorphine, is a potent elicitor of the gnawing response in rats.



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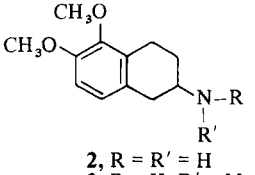

2, R = R′ = H
3, R = H; R′ = Me
4, R = R′ = Me

A prior communication from this laboratory[5] described preparation and emetic effects of a series of 5,6-dimethoxytetrahydronaphthylamines **2–4**. These compounds not only are congeners of a fragment of the apomorphine molecule, but they are also derivatives of a cyclic dopamine structure. Compounds **3** and **4**, while inert as emetics in the dog, were far more active in the pigeon than was apomorphine. Since it has been stated[1,6] that apomorphine must possess free, unetherified phenolic groups in order to exert central emetic effects, it was speculated that perhaps the emetic activity displayed by **3** and **4** in the pigeon reflects an ability of this species (as contrasted with the dog) efficiently to demethylate the phenolic ether systems, and to generate the biologically active catechol moiety. It was further speculated that if this were the case, the free phenol derivatives of **3** and **4** should elicit emesis in the dog as well as in the pigeon. Numerous attempts in this laboratory to cleave the ether links of **2–4** failed;[5] however, success has been realized utilizing a modification of a method of Thrift.[7]

Compounds **2–4** were prepared by the sequence of Sprenger *et al.*;[5] attempts to prepare **6** by the Sprenger method of Neber rearrangement of the oxime tosylate **5** with EtO^- in refluxing EtOH gave erratic results and frequently failed completely. Replacement of the EtOH solvent by benzene permitted consistently successful Neber reactions.

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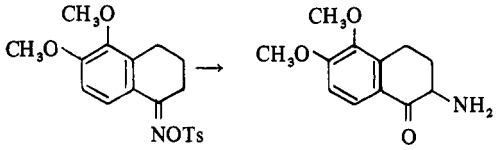
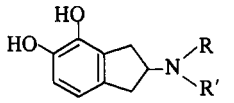


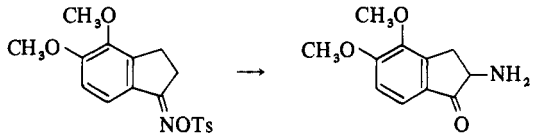
5 **6**

The indanamines **7–9** are cyclic dopamine congeners, closely related to the tetrahydronaphthylamines, and preparation of these was undertaken. Heinzelman, *et al.*,[8,9]



7, R = R′ = H
8, R = H; R′ = Me
9, R = R′ = Me

prepared a series of 1-oxygenated-4,5-dimethoxyindanamines as bronchodilators and hypertensives; however, the ether links were not cleaved, nor were 1-deoxy systems (such as **7–9**) reported. Heinzelman's group[8] prepared 4,5-dimethoxy-2-amino-1-indanone (**11**) by catalytic reduction of 2-isonitroso-4,5-dimethoxy-1-indanone. In the present work, the modification of the Neber rearrangement, described for the tetralin series, was applied to the 1-indanone oxime tosylate **10**. The 1-keto group of **11** was reduced to



10 **11**

CH_2, and this product was subsequently converted to **7–9** by literature procedures. (See Table I.)

Pharmacology. Preparations. HBr salts of the new compds, and apomorphine · HCl were dissolved in appropriate volumes of physiological saline. Solns were prepared immediately before use, or were stored in amber containers in a freezer.

Acute Toxicity in Mice. Graded doses of each compd were administered ip to groups of mice and the animals were observed for 6 hr following injection. Deaths usually occurred within 0.5 hr. Animals given **17** and **18** (which produced no deaths at 1800 μmoles/kg) were observed for 12 hr (see Table II).

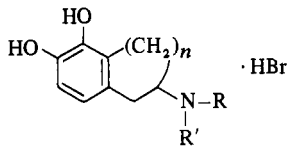
Compulsive Gnawing in Mice. The compulsive gnawing syndrome elicited by low doses of apomorphine in rodents[10] was observed following ip administration of all compds, with the tertiary amines **9** and **19** exhibiting powerful activity, comparable to apomorphine (see Table II).

Compulsive Pecking and Emesis in Pigeons. Pigeons of both sexes, weighing 200–550 g, were injected im. Apomorphine · HCl (1.64 μmoles/kg) induced stereotyped pecking behavior. None of the new compds was active at this level; however, **18** and **19** induced the pecking syndrome at 38 μmoles/kg. All compds except **19** produced vomiting in pigeons at doses of the same order of magnitude as the determined minimum effective dose of apomorphine; several were somewhat more potent than apomorphine. Compd **19** induced no vomiting at 38 μmoles/kg; at this dose level, toxic signs (shivering and prostration) were manifested and higher doses were not given (see Table II).

Emesis in Dogs. Female beagles, weighing 8–12 kg, were injected sc. All compds were active emetics; the secondary and tertiary aminotetralins **18** and **19** were especially potent, with **19** producing violent emesis exceeding that of apomorphine. Emetic effects of all of the agents tested were blocked in dogs by prior administration of chlorpromazine (1 mg/kg) (see Table II).

These data lend support to the proposal†[,2,3] that apomorphine-induced vomiting is a reflection of the dopaminergic character of the drug and further, that the portion of the apomorphine molecule indicated in **1** represents the emetic pharmacophore of the molecule. Potent apomorphine-like

Table I. Dihydroxytetrahydronaphthylamines and Indanamines



Compd. No.	*n*	R	R′	Reaction time, hr.	Yield, %	Mp, °C	Formula[b]
17[c]	2	H	H	6	41	above 300[a]	$C_{10}H_{14}BrNO_2$
18[c]	2	Me	H	3	87	267.5–269.5[d]	$C_{11}H_{16}BrNO_2$
19[c]	2	Me	Me	4.5	80	211–213 dec[d]	$C_{12}H_{18}BrNO_2$
7	1	H	H	1	79	214–219 dec[e]	$C_9H_{12}BrNO_2$
8	1	Me	H	1	83	246.5–249.5 dec[d]	$C_{10}H_{14}BrNO_2$
9	1	Me	Me	1	83	216.5–219.5 dec[d]	$C_{11}H_{16}BrNO_2$

[a]From EtOH–Et_2O. [b]The compds were analyzed for C, H, and N. Analytical results were within ±0.4% of the theoretical value. [c]Dimethyl ether prepd by method of Sprenger, *et al.*[5] [d]From MeOH–Et_2O. [e]From *i*-PrOH–Et_2O.

Table II. Biological Activities of Aminotetralins and Aminoindans

Compd No.	Mouse gnawing, GD_{50}, μmoles/kg[a]	RP[b]	Mouse LD_{50}, μmoles/kg[a]	RP[b]	Pigeon emesis, MED,[c] μmoles/kg[a]	RP[b]	Dog emesis, MED,[c] μmoles/kg[a]	RP[b]
17	13.9	0.57	936	0.63	11.1	5.0	5.5	0.01
18	38.8	0.20	1243	0.48	7.7	7.2	0.31	0.23
19	4.8	2.0	474	1.2			0.03	2.25
7	33.3	0.25	>1800	0.31	109	0.47	10.9	0.006
8	12.6	0.66	>1800	0.31	83.7	0.61	9.4	0.006
9	5.8	1.4	739	0.75	12.9	4.0	8.5	0.008
Apomorphine	8.4	1.0	600	1.0	56.1	1.0	0.07	1.0

[a]In terms of free base. [b]Potency relative to apomorphine. [c]Estimated threshold dose.

emetic activity is thus possible in much simpler chemical structures than apomorphine. Further, these data are consistent with the speculations presented above, with respect to possible O-demethylation mechanisms in the pigeon which seem absent or inoperative in the dog.

The difference in emetic potency in dogs between the indan series **7-9** and the tetralin series **17-19** is striking. Examination of Dreiding models indicates that the tetralin series superimposes almost perfectly, atom for atom, upon the corresponding portion of the apomorphine molecule, if it is assumed that there is a pseudo equatorial disposition of the amino group on the tetralin ring. In contrast, when the benzene ring, the phenolic groups, and the carbons at positions 1 and 2 of the aminoindan systems are superimposed upon apomorphine, the 2-amino moiety of the indan projects out of the plane of the system and does not coincide with the ring N of apomorphine. It is appealing to speculate that the observed difference in biological potency be the aminoindans and the aminotetralins is referrable to the orientation in space of the amino groups with respect to the remainder of the molecules.

Experimental Section‡

3,4-Dihydro-2-amino-5,6-dimethoxy-1-(2*H*)-naphthalenone · HCl (6). To a stirred, freshly prepd soln of 1.64 g (0.041 g-atom) of K in 52 ml of abs EtOH was added a suspension of 16.55 g (0.044 mole) of 3,4-dihydro-5,6-dimethoxy-1(2*H*)-naphthalenone *O*-*p*-toluenesulfonyl oxime (**5**)[5] in 100 ml of anhyd C_6H_6. The resulting yellow suspension was stirred at 0° for 0.25 hr, and was permitted to stand at 4° with occasional agitation for 22 hr. The dark green, viscous mass was filtered through sintered glass and the solid material which collected was washed with 100 ml of anhyd C_6H_6. The combined filtrates were extd with four 100-ml portions of 10% HCl. Evapn of the aqueous exts under reduced pressure at 40° gave a brown solid which was recrystd from Et_2O–EtOH (charcoal) to yield 6.01 g (53%) of a tan solid: mp 227–229.5° (lit.[5] mp 208–210°); ir (KBr) 1675 cm^{-1} (C=O). *Anal.* ($C_{11}H_{16}ClNO_3$) C, H, Cl, N.

4,5-Dimethoxy-1-indanone Oxime (12). A soln of 30 g (0.154 mole) of 4,5-dimethoxy-1-indanone,[11] 17 g (0.123 mole) of K_2CO_3, and 17 g (0.245 mole) of $NH_2OH \cdot HCl$ in 350 ml of MeOH and 30 ml of H_2O was refluxed on a steam bath for 2 hr. Excess cold H_2O was added to the reaction mixt; the solid which sepd was collected and recrystd from MeOH–H_2O (charcoal) to afford 29.76 g (93%) of a white solid: mp 171–173.5° (lit.[12] mp 168°).

4,5-Dimethoxy-1-indanone *O*-*p*-Toluenesulfonyloxime (10). To a stirred soln of 63 g (0.33 mole) of TsCl in 400 ml of pyridine was added 36 g (0.174 mole) of **12**. The reaction mixt was permitted to stand at 4° with occasional agitation for 13 hr, then it was poured over 3 l. of ice H_2O. The tan solid which sepd was collected on a filter and was triturated with several portions of H_2O, then was recrystd from Me_2CO to give 48.8 g (80%) of a white solid: mp 170–174.5°. *Anal.* ($C_{18}H_{19}NO_5S$) C, H, N.

4,5-Dimethoxy-2-amino-1-indanone · HCl (11). The method described for **6** was employed, using 72 g (0.198 mole) of **10**. The crude product was recrystd twice from MeOH–Et_2O (charcoal) to give 27 g (56%) of a white solid: mp 193.5–194.5° dec (lit.[8] mp 185° dec). *Anal.* ($C_{11}H_{14}ClNO_3$) C, H, N.

2-Amino-4,5-dimethoxyindan · HCl (13). A mixt of 3 g (0.013 mole) of **11** and 0.6 g of 10% Pd/C in 100 ml of glacial AcOH was hydrogenated at 38° and a max pressure of 3.16 kg/cm^2. Uptake of 1 equiv of H_2 was complete in 48 hr. The reaction vessel was cooled, 3 ml of $HClO_4$ in 3 ml of glacial AcOH was added, and hydrogenation was contd at 70° for 18 hr at a max pressure of 2.81 kg/cm^2. The catalyst was removed by filtration and the clear yellow filtrate was treated with 6 g of KOAc; $KClO_4$ pptd immediately and was removed by filtration. The filtrate was taken to dryness under reduced pressure (steam bath), and 100 ml of 5% HCl was added to the residue. This aq soln was extd with two 50-ml portions of Et_2O and was made strongly basic with 20% KOH. The resulting mixt was extd with four 75-ml portions of Et_2O. The combined Et_2O exts were washed with 75 ml of H_2O, 75 ml of 10% NaCl, and finally with 75 ml of H_2O, then dried (Na_2SO_4), and filtered. Evapn of the filtrate under reduced pressure (steam bath) gave a yellow oil which was distd through a "short-path" apparatus as a colorless oil: bp 110–119° (0.25 mm). An Et_2O soln of this oil was converted to its HCl salt which was recrystd from MeOH–Et_2O (charcoal) to yield 1.92 g (66%) of white crystals: mp 205–206.5°. *Anal.* ($C_{11}H_{16}ClNO_2$) C, H, N.

2-Formamido-4,5-dimethoxyindan (14). A mixt of 2.8 g (0.0145 mole) of the free base of **13**, 4 ml of 90% HCOOH, and 100 ml of toluene was refluxed using a Dean–Stark trap to collect H_2O. After 19 hr, an addl 10 ml of 90% HCOOH was added and refluxing was contd for another 48 hr. Concn of the yellow soln under reduced pressure (steam bath) left a yellow oily residue which was crystd twice from EtOAc–hexane (charcoal) to give 2.81 g (89%) of product: mp 87–89°. *Anal.* ($C_{12}H_{15}NO_3$) C, H, N.

2-Methylamino-4,5-dimethoxyindan · HCl (15). A mixt of 2.81 g (0.0126 mole) of **14**, 4.78 g (0.126 mole) of LAH, and 600 ml of anhyd Et_2O was refluxed and stirred for 13 hr. After decomp of excess LAH with H_2O, the resulting suspension was filtered and the filtrate was dried ($MgSO_4$) and treated with anhyd HCl to form a light yellow solid. This was triturated with several portions of Et_2O, then was recrystd from MeOH–Et_2O (charcoal) to give 2.12 g (69%) of white plates: mp 117–121°. *Anal.* ($C_{12}H_{18}ClNO_2$) C, H, N.

2-Dimethylamino-4,5-dimethoxyindan · HCl (16). To 1.2 g (0.00621 mole) of the free base of **13** was carefully added, dropwise and with cooling, 2.0 g (0.0039 mole) of 90% HCOOH, followed by 1.5 g (0.017 mole) of 37% HCHO, and the resulting mixt was heated in an oil bath at 100° for 16 hr. Evolution of CO_2 began in 5 min and subsided after approx 1 hr. Concn under reduced pressure (steam bath) gave a brown, oily residue which was dissolved in 100 ml of 10% HCl and extd with two 75-ml portions of Et_2O, then the aq phase was made strongly alk with 20% KOH. The resulting suspension was extd with three 75-ml portions of C_6H_6, then with two 75-ml portions of Et_2O. The combined organic exts were washed with 150 ml of 5% Na_2CO_3, 150 ml of satd NaCl, and finally with 150 ml of H_2O, and were dried ($MgSO_4$). Filtration and concn of the filtrate under reduced pressure (steam bath) gave a light brown oil which was dissolved in anhyd Et_2O and treated with anhyd HCl to form a white solid which was recrystd 3 times from MeOH–Et_2O (charcoal) to give 1.51 g (78%) of product: mp 210.5–214°. *Anal.* ($C_{13}H_{20}ClNO_2$) C, H, N.

Ether Cleavage Reactions. The dimethyl ether (0.5 g) was heated under N_2 with 8 ml of 48% HBr in an oil bath at 110–128°. The reaction mixt assumed a deep color after some min. Removal of the volatiles under reduced pressure (steam bath) left a solid residue which was recrystd (see Table I).

‡Melting points were determined in open glass capillaries on a Thomas-Hoover Uni-Melt apparatus and are corrected. Boiling points are uncorrected. Ir spectra were recorded with Beckman IR-5A and IR-10 instruments, and nmr spectra were measured on a Varian Associates T-60 instrument (Me_4Si). Elemental analyses were performed by the Microanalytical Service, College of Pharmacy, University of Iowa. Where analyses are indicated by symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

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