water and administered ip. Three to five dose levels were used for each LD_{50} value, and there were ten animals at each dose level. Control animals received vehicle at a dose volume comparable to the highest dose volume of test compound. The LD_{50} values and 95% confidence limits were calculated by the minimum logit χ^2 method.[19]

Acknowledgment. The authors wish to thank Mrs. M. P. Hogan for analyzing the testing data and Drs. E. Meymaris, W. McKenzie, and E. Byrnes for helpful discussions.

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Notes

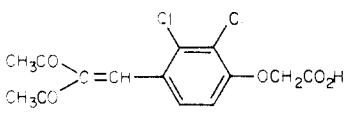
(Vinylaryloxy)acetic Acids. A New Class of Diuretic Agents. 2.[1] [4-(3-Oxo-1-alkenyl)phenoxy]acetic Acids

John B. Bicking,* Charles M. Robb, L. Sherman Watson, and Edward J. Cragoe, Jr.

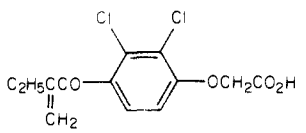
Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486. *Received August 27, 1975*

A series of (*E*)-[4-(3-oxo-1-alkenyl)phenoxy]acetic acids was synthesized and tested in dogs for saluretic and diuretic properties. Several compounds exhibited noteworthy activity, e.g., (*E*)-[2,3-dichloro-4-(3-oxo-1-butenyl)phenoxy]acetic acid (**3a**). While possessing only half of the dose potency of ethacrynic acid (**2**), the active compounds act similarly to this diuretic in causing a prompt increase in the excretion of water and in the excretion of sodium and chloride ions in approximately equimolar amounts. Potassium ion excretion is increased but less markedly than sodium excretion.

The initial paper in this series described the saluretic and diuretic properties of [(diacylvinyl)aryloxy]acetic acids[1] including the highly active diacetylvinyl compound **1**. The presence of the double bond activated toward nucleophilic attack is critical to the high potency of these compounds. In this regard and in general structure, they are related to the prototypical ethacrynic acid[2] (**2**) which they also resemble in profile of action on electrolyte and water excretion.

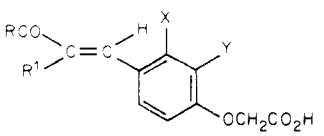


1



2

This report discloses synthesis and renotropic properties of a series of [4-(3-oxo-1-alkenyl)phenoxy]acetic acids of general structure **3** which, like ethacrynic acid, incorporate a double bond activated by a single conjugated carbonyl group (Table I).



3

Chemistry. Three synthetic routes to the compounds **3** have been followed; all involve aldol condensations between substituted benzaldehydes and aliphatic or alicyclic ketones or aldehydes.

In the first route (Scheme I), a 4-hydroxybenzaldehyde (**4**) is condensed with a ketone to yield a 4-(3-oxo-1-alkenyl)phenol (**5**). Strongly basic Claisen-Schmidt conditions were employed in condensations with acetone, cyclobutanone, and cyclopentanone. The use of acid catalysis in reactions with 2-butanone typically[3] effected condensation at the methylene group of this ketone, as is clearly shown by the NMR spectra of **5e** and **5f**. Phenols **5** were alkylated with ethyl bromoacetate and the resulting crude esters hydrolyzed in acid to yield products **3a-f**.

In a second route (Scheme II), hydroxybenzaldehydes (**4**) are alkylated with ethyl bromoacetate and the resulting esters hydrolyzed to yield the formylphenoxyacetic acids **6**, which then are condensed in dilute NaOH solutions with the appropriate ketones or propionaldehyde to give the products **3g-j**. Under these conditions, condensation with 2-butanone occurs at the 1-methyl group (yielding **3i**).

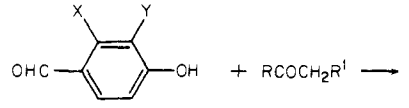
Cyclohexanone failed to give isolable 1:1 condensation products with hydroxybenzaldehydes or formylphenoxyacetic acids according to Schemes I or II. However, the morpholine enamine of cyclohexanone did react satisfactorily with ethyl (2,3-dichloro-4-formylphenoxy)acetate (**7**) according to the procedure of Birkofer, Kim, and

Table I. (*E*)-[4-(3-Oxo-1-alkenyl)phenoxy]acetic Acids (3)

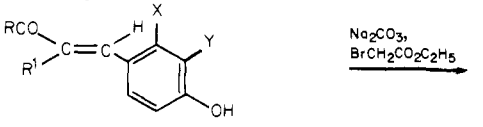
Compd	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses
3a	204-205	*i*-PrOH	83[a]	$C_{12}H_{10}Cl_2O_4$	C, H, Cl
3b	147-148	*i*-PrOH	28[a]	$C_{13}H_{14}O_5$	C, H
3c	218-219	AcOH	74[a]	$C_{13}H_{10}Cl_2O_4$	C, H, Cl
3d	226-227	AcOH	72[a]	$C_{14}H_{12}Cl_2O_4$	C, H, Cl
3e	173.5-174.5	CH_3NO_2	74[a]	$C_{13}H_{12}Cl_2O_4$	C, H, Cl
3f	157-158	CH_3NO_2	85[a]	$C_{14}H_{14}Cl_2O_4$	C, H, Cl
3g	169.5-172.5	*i*-PrOH	47[b]	$C_{12}H_{11}ClO_4$	C, H
3h[c]	178-181.5[c]	*i*-PrOH	51[b]	$C_{12}H_{12}O_4$	
3i	193.5-194.5	*i*-PrOH	10[b]	$C_{13}H_{12}Cl_2O_4$	C, H, Cl
3j	153-155	*i*-PrOH	23[b]	$C_{12}H_{10}Cl_2O_4$	C, H, Cl
3k	161-162	CH_3CN	28[d]	$C_{15}H_{14}Cl_2O_4$	C, H, Cl

[a] Overall yield from appropriate 3-oxo-1-alkenylphenol (5) according to Scheme I (see General Method, Experimental Section). [b] Yield from ketone or aldehyde and formylphenoxyacetic acid (6) (Scheme II). [c] T. Elkan, *Chem. Ber.*, **19**, 3041 (1886); lit. mp 177-178°. [d] Overall yield from 4-(1-cyclohexenyl)morpholine and 7 (see Experimental Section).

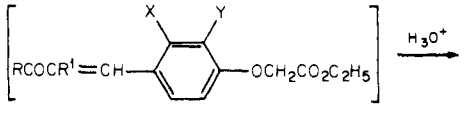
Scheme I



4a, X = Y = Cl
b, X = H; Y = OCH_3



5a, R = CH_3; R' = H; X = Y = Cl
b, R = CH_3; R' = H; X = H; Y = OCH_3
c, R-R' = CH_2CH_2; X = Y = Cl
d, R-R' = $CH_2CH_2CH_2$; X = Y = Cl
e, R = R' = CH_3; X = Y = Cl
f, R = C_2H_5; R' = CH_3; X = Y = Cl

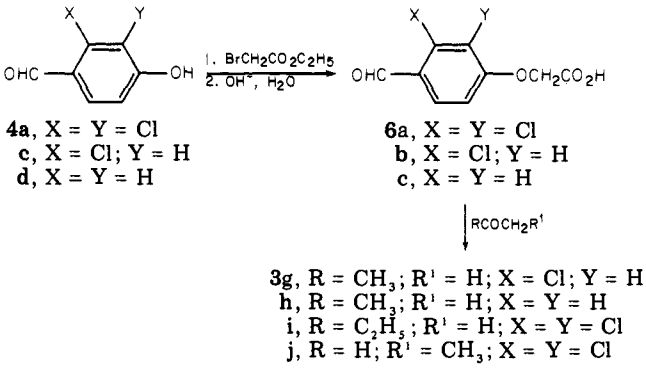


3a, R = CH_3; R' = H; X = Y = Cl
b, R = CH_3; R' = H; X = H; Y = OCH_3
c, R-R' = CH_2CH_2; X = Y = Cl
d, R-R' = $CH_2CH_2CH_2$; X = Y = Cl
e, R = R' = CH_3; X = Y = Cl
f, R = C_2H_5; R' = CH_3; X = Y = Cl

Engels[4] to give, after hydrolysis of the intermediate iminium ester, [2,3-dichloro-4-(2-oxocyclohexylidenemethyl)phenoxy]acetic acid (**3k**) in 28% yield.

Only one of the two possible geometric isomers was isolated from each condensation reaction. The trans (E) configuration (vinyl proton cis to carbonyl group) can be assigned to the condensation products on the basis of their NMR spectra. The trans arrangement of the vinyl protons in the disubstituted olefinic compounds, **5a,b** and **3a,b,g,h,i**, is indicated by the magnitude of the coupling constant (J = 16 Hz). The signals of the vinyl protons adjacent to phenyl in these same compounds are seen at

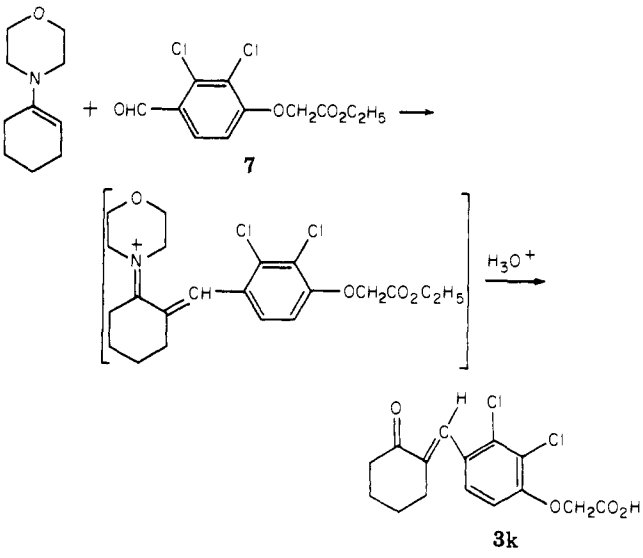
Scheme II



4a, X = Y = Cl
c, X = Cl; Y = H
d, X = Y = H

6a, X = Y = Cl
b, X = Cl; Y = H
c, X = Y = H

3g, R = CH_3; R' = H; X = Cl; Y = H
h, R = CH_3; R' = H; X = Y = H
i, R = C_2H_5; R' = H; X = Y = Cl
j, R = H; R' = CH_3; X = Y = Cl



7

3k

δ 7.70-7.80 being shifted downfield by the deshielding effect of the cis carbonyl groups.[5] The corresponding vinyl protons of the remaining trisubstituted olefinic compounds are similarly downfield (δ 7.35-7.60, except δ 7.16 for the cyclobutanone **3c**) indicating their position cis to carbonyl.

Saluretic-Diuretic Activity and Structure-Activity Relationships. Compounds **3a-k** were tested for saluretic and diuretic effects in dogs by iv administration. Results are presented in Table II along with comparable data for ethacrynic acid (**2**) and the closely related diacylvinyl diuretic **1**.

Certain of the compounds **3** show substantial saluretic and diuretic activity, most notably **3a,c,e,i,k**. Their activity is qualitatively similar to that of **2**[2b] and **1**[1] involving a prompt increase in the excretion of water and of sodium and chloride ions to an approximately equal degree. Potassium ion excretion is also increased but less markedly than sodium excretion. However, the most highly active of the present compounds are substantially less potent than **2** and only $^1/_{20}$-$^1/_{10}$ as potent as **1**.

Some structure-activity relationships can be discerned by examining the effects of structural changes on the saluretic action of active **3a**. As in the related, previously published series,[1] activity is highly dependent on the extent and nature of ring substitution: removal of the 2-Cl atom (to give **3g**) reduces activity considerably; removal of both Cl atoms greatly reduces activity (**3h**); the 2-OMe analog (**3b**) is inactive. Some minor changes in the alkenyl chain produce major changes in potency: thus, lengthening this chain to 3-oxo-1-pentenyl (**3i**) reduces potency; chain branching by addition of a 2-Me group (**3e**) does not significantly affect activity; combined lengthening and branching (**3f**) markedly reduces activity as does short-

Table II. Iv Activity in Dogs

Compd	Dose,[a] mg/kg	μequiv/min excreted[b] (control period/drug period) Na+	K+	Cl-	Urine vol,[b] ml/min, control/drug
3a	5	33/911	15/76	7/1078	1/8
3b	5	5/13	29/36	11/27	1/1
3c	10	40/833	37/93	12/822	1/8
	0.1	73/393	35/89	48/408	3/9
3d	1	58/298	37/74	10/330	3/4
3e	5	99/1096	26/132	15/1140	1/10
3f	10	54/79	31/42	15/67	1/2
3g	10	20/265	28/79	8/258	1/3
3h	10	13/91	16/50	4/55	2/5
3i	10	16/973	28/118	14/1089	1/8
3j	5	68/140	40/51	13/130	2/3
	25	42/449	42/86	6/542	5/5
3k	5	22/1306	55/119	8/1340	2/12
2	10	48/2989	22/194	64/3324	1/22
	1	32/188	46/52	11/244	4/6
1	1	26/1615	28/104	26/1730	1/11
	0.1	36/984	14/87	14/1096	1/9

[a] The compounds were administered as Na salts in H_2O. [b] The procedure is described in ref 1. Control values are averages of data from two 15-min clearance periods prior to dosage. Response values are averages of data from two consecutive 15-min periods during which Na^+ excretion was maximal; these periods usually occurred between 15 and 45 min after dosage. The data are from single representative experiments.

Table III. Oral Activity in Dogs[a]

Compd	Dose, mg/kg	No. of dogs	Av mequiv/6 h excreted Na+	K+	Cl-	Av urine vol, ml/6 hr
3e	2	4	16	3	21	506
	1	6	9	5	9	422
2	1	10	21	5	26	560
Furosemide	1	10	19	4	18	624
Placebo		35	2	1	2	180

[a] Oral tests were carried out in trained female mongrel dogs weighing 8–10 kg. Compounds were given in gelatin capsules. The procedure has been reported in ref 1, Experimental Section.

ening the chain to 2-methyl-3-oxo-1-propenyl (**3j**). The three analogs of **3a** with 2-oxocycloalkylidenemethyl chains (**3c,d,k**) are active, the cyclohexanone-derived **3k** being significantly more potent than **3a**.

That compounds of this series can be effective when administered orally is shown in Table III. One of the more active compounds, **3e**, gives a saluretic response at 2 mg/kg po which is comparable to that produced by 1 mg/kg po of either ethacrynic acid or furosemide.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. The NMR spectra were taken on a Varian T-60 instrument in Me_2SO-d_6. Analyses are indicated by symbols of the elements; analytical results for these elements are within 0.4% of the theoretical values.

(3-Chloro-4-formylphenoxy)acetic Acid (6b). A mixture of ethyl (3-chloro-4-formylphenoxy)acetate[1] (23.4 g, 0.096 mol), EtOH (40 ml), and 10% aqueous NaOH solution (100 ml) was heated 10 min at 95°. The resulting solution was then acidified with 6 N hydrochloric acid to precipitate the product. Recrystallization from AcOH–H_2O gave 15.5 g (75%) of **6b**, mp 174–176.5°. Anal. ($C_9H_7ClO_4$) C, H.

(*E*)-2,3-Dichloro-4-(3-oxo-1-butenyl)phenol (5a). A solution of 2,3-dichloro-4-hydroxybenzaldehyde[1] (**4a**) (3.8 g, 0.02 mol) in acetone (7.2 g, 0.125 mol) and 12% aqueous NaOH solution (7 ml, 0.021 mol) was allowed to stand at 25° for 48 h. The solution was then diluted with H_2O (25 ml) and acidified with 6 N hydrochloric acid to precipitate the solid product. Recrystallization from CH_3CN gave 3.5 g (76%) of **5a** as yellow prisms: mp 188.5–189.5°; NMR δ 2.32 (3 H, s, CH_3CO), 6.98 (1 H, d, J = 8 Hz, phenyl H_6), 7.70 (1 H, d, J = 8 Hz, phenyl H_5), 6.70 (1 H, d, J = 16 Hz, COCH=), 7.74 (1 H, d, J = 16 Hz, PhCH=), 10.1 (1 H, br s, OH). Anal. ($C_{10}H_8Cl_2O_2$) C, H, Cl.

(*E*)-2-Methoxy-4-(3-oxo-1-butenyl)phenol (5b). This compound was prepared similarly from vanillin and acetone in 67% yield: mp 127–128° (from *i*-PrOH) (lit.[6] mp 129°).

(*E*)-2,3-Dichloro-4-(2-oxocyclobutylidenemethyl)phenol (5c). A mixture of **4a** (7.6 g, 0.04 mol), cyclobutanone (5.6 g, 0.08 mol), and 12% aqueous NaOH solution (26.7 ml, 0.08 mol) was stirred at 25° for 24 h. The solid present was collected and dissolved in hot water and the solution acidified with 6 N hydrochloric acid to precipitate the product. Recrystallization from CH_3CN gave 5.4 g (55%) of **5c** as yellow prisms: mp 210.5–211.5°; NMR δ 7.16 (1 H, s, PhCH=). Anal. ($C_{11}H_8Cl_2O_2$) C, H, Cl.

(*E*)-2,3-Dichloro-4-(2-oxocyclopentylidenemethyl)phenol (5d). This compound was prepared similarly from **4a** and cyclopentanone in 23% yield: mp 185–187° (from CH_3CN); NMR δ 7.44 (1 H, s, PhCH=).

(*E*)-2,3-Dichloro-4-(2-methyl-3-oxo-1-butenyl)phenol (5e). A finely ground suspension of **4a** (3.8 g, 0.02 mol) in 2-butanone (11.2 g, 0.16 mol) was chilled in an ice bath and treated with anhydrous HCl for 45 min. The resulting solution was allowed to stand at 25° for 65 h. The volatile materials were then removed at reduced pressure. The residue was dissolved in Et_2O, washed with H_2O, and dried over $MgSO_4$. Evaporation of the solvent left the product as a solid. Recrystallization from BuCl gave 1.9 g (38%) of **5e**: mp 157–159°; NMR δ 1.87 (3 H, d, J = 1 Hz, CH_3C=), 2.42 (3 H, s, CH_3CO), 7.04 (1 H, d, J = 8 Hz, phenyl H_6), 7.30 (1 H, d, J = 8 Hz, phenyl H_5), 7.56 (1 H, broad s, PhCH=). Anal. ($C_{11}H_{10}Cl_2O_2$) C, H, Cl.

(*E*)-2,3-Dichloro-4-(2-methyl-3-oxo-1-pentenyl)phenol (5f). This compound was prepared similarly from **4a** and 3-pentanone in 39% yield: mp 112–113°; NMR δ 7.60 (1 H, s, PhCH=). Anal. ($C_{12}H_{12}Cl_2O_2$) C, H, Cl.

(*E*)-[4-(3-Oxo-1-alkenyl)phenoxy]acetic Acids 3a–f (Table I). A mixture of 3-oxo-1-alkenylphenol (0.02 mol), ethyl bromoacetate (0.04 mol), Na_2CO_3 (0.04 mol), and DMF (20 ml) was stirred and heated at 55–60° for 1.5 h. The reaction mixture was then treated with 100 ml of water and the precipitated solid ester collected on a filter. A solution of the ester in AcOH (40 ml) and 5% hydrochloric acid (20 ml) was heated at 95° for 0.5 h. The solution was diluted with water, and the precipitated acid was collected and recrystallized to constant melting point.

Also presented in Table I are data for the following products **3g**–i.

(*E*)-[3-Chloro-4-(3-oxo-1-butenyl)phenoxy]acetic Acid (3g). A solution of (3-chloro-4-formylphenoxy)acetic acid (4.3 g, 0.02 mol) in acetone (40 ml) and 5% NaOH solution (12 ml) was allowed to stand at 25° for 30 min. It was then diluted with water (30 ml) and acidified with 5% hydrochloric acid. The precipitated solid product was recrystallized to constant melting point.

(*E*)-[2,3-Dichloro-4-(3-oxo-1-pentenyl)phenoxy]acetic Acid (3i). A mixture of (2,3-dichloro-4-formylphenoxy)acetic acid[1] (12.5

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=).

Acknowledgments. The authors are indebted to T. P. Strobaugh for the preparation of **3b** and to S. F. Kwong for the preparation of **3h**. We are also indebted to K. B. Streeter, Y. C. Lee, and their staff for elemental analyses and to W. R. McGaughran for NMR spectra.

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

John D. McDermed,* Gerald M. McKenzie, and Harold S. Freeman

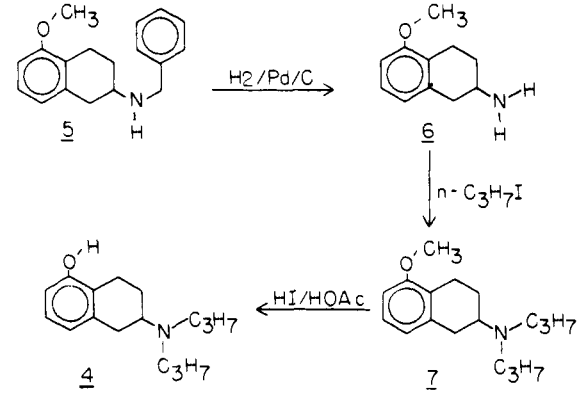
Departments of Chemistry and Pharmacology, Wellcome Research Laboratories, Research Triangle Park, North Carolina 27709. *Received August 6, 1975*

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