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(Acylaryloxy)acetic Acid Diuretics. 1. (2-Alkyl- and 2,2-Dialkyl-1-oxo-5-indanyloxy)acetic Acids

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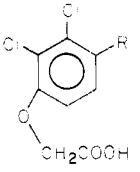
The discovery of the (acryloylaryloxy)acetic acids as a new class of potent diuretics prompted the investigation of related bicyclic compounds. Annelated analogues of the parent series, the (2-alkyl- and 2,2-dialkyl-1-oxo-5-indanyloxy)acetic acids, were the subject of this study. Those compounds, unlike the monocyclic parent compound, lacked the double bond adjacent to the carbonyl group. More importantly, they possessed both saluretic and uricosuric properties. The optimal single 2-substituents for maximal saluretic and uricosuric activity were determined. In general, better activity was observed when a second 2-alkyl substituent (especially methyl) was present in the molecule. Replacement of the carboxy substituent by 5-tetrazolyl generally resulted in a reduction in activity.

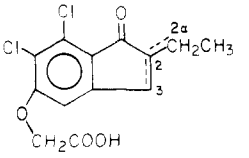
The mercurial phenoxyacetic acid diuretics, merbaphen and mersalyl, served as models for the design, and ultimately led to the discovery, of the potent (acryloylaryloxy)acetic acid diuretics,[1] the best known of these loop diuretics being ethacrynic acid[2] (**1a**). Recently four series of (vinylaryloxy)acetic acids, including those types illustrated by **1b–e**, have been described.[3-6] Each of these types of compounds mimics the mercurials, eliciting marked



1a, R = $-COC(=CH_2)C_2H_5$
b, R = $-CH=C(COCH_3)_2$
c, R = $-CH=C(CH_3)COCH_3$
d, R = $-CH=C(CH_3)NO_2$
e, R = $-CH=CR^1R^2$
f, R = $-COCH(CH_3)C_2H_5$

saluresis in dogs but not in rats. They react with compounds containing sulfhydryl groups in a manner similar to that observed with mercurial diuretics. They differ notably from the mercurials in two respects. Compounds like **1a** show no difference in saluresis under conditions of acidosis or alkalosis, whereas mercurials are ineffective under conditions of alkalosis and are potentiated by acidosis.[7] Mercurials generally produce little change in uric acid excretion while **1a** causes uric acid retention which may result in hyperuricemia.[8,9] In addition, while the compounds of type **1a–e** did react with compounds containing sulfhydryl groups, there was poor correlation between either the rate or extent of this reaction and diuretic activity. Although this lack of correlation may be attributable to the fact that absorption and distribution phenomena as well as metabolic and deactivation reactions are encountered when diuretic activity is measured, it appears that the role of sulfhydryl binding is of secondary importance in the mechanism of action of diuretics of type **1a–e**.

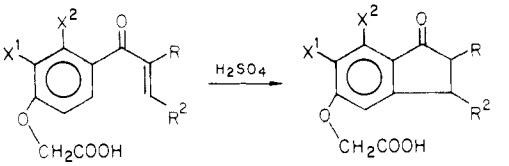
Following the observation that ethacrynic acid underwent intramolecular cyclialkylation to **2a** upon treatment with sulfuric acid, our initial efforts were directed toward the introduction of a double bond in the molecule (**2b,c**).



2a, no double bond
b, 2,3 double bond
c, 2,2α double bond

(The chemistry and biological activity of compounds of type **2b,c** will be reported in a subsequent paper.) It soon became apparent from biological data obtained in chimpanzees that the saturated compounds of type **2a** were also diuretic and had either no effect on serum urate or were frankly uricosuric. It has been shown in our laboratories that dihydroethacrynic acid (**1f**) exhibits weak but significant saluretic and diuretic activity and also is uricosuric in chimpanzees.[10] Thus the mechanism of action of **1f** apparently mimics compounds of type **2a** rather than **1a**.

Chemistry. Most of the (1-oxo-2-monoalkyl-5-indanyloxy)acetic acids (**4**) were prepared by the cyclialkylation of the correspondingly substituted (acryloylphenoxy)acetic acids (**3**)[11] in concentrated H_2SO_4 according to the following reaction and these products are listed in Table I.



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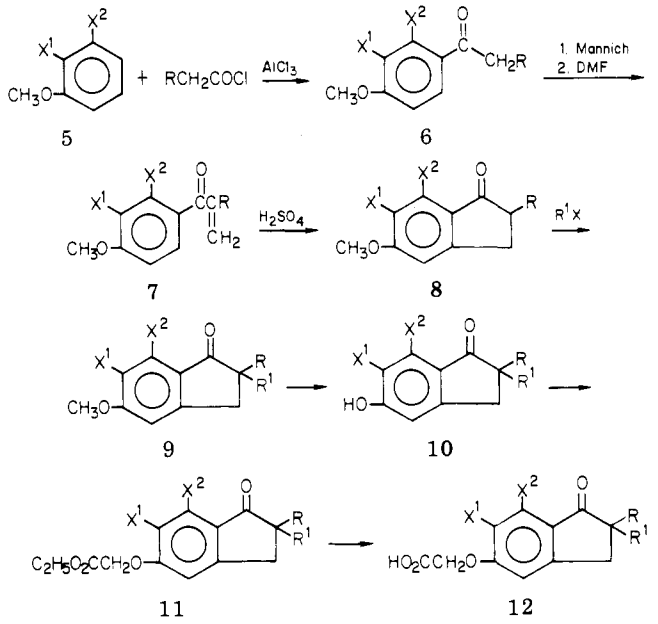
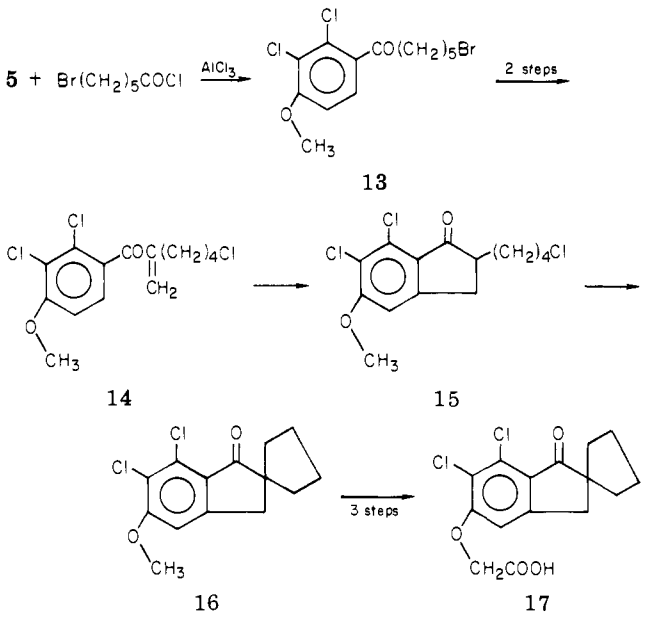
Attempts to prepare the 2,2-dialkyl-substituted compounds **12** by direct alkylation of the methyl esters of the corresponding 2-alkyl-substituted compounds **4** were unsa-

Scheme I



Scheme II

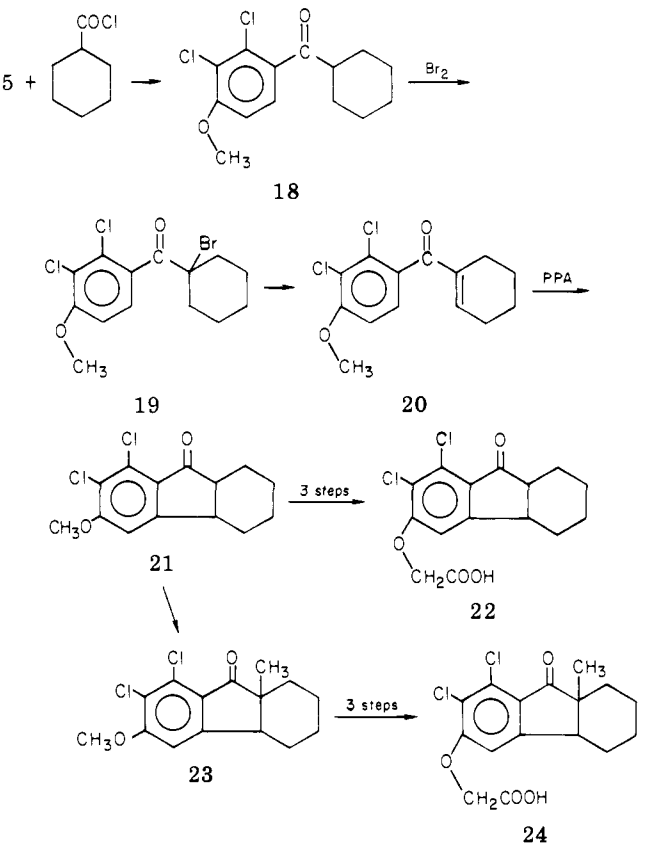


tisfactory; however, 2-alkylation of the corresponding 5-methoxy compounds 8 readily occurred in a variety of solvents after generating the required carbanion with any one of several bases. Subsequent ether cleavage and stepwise carboxymethylation provided the 2,2-dialkyl-substituted compounds 12 which are recorded in Table II. Scheme I shows the complete reaction sequence for the synthesis of these compounds.

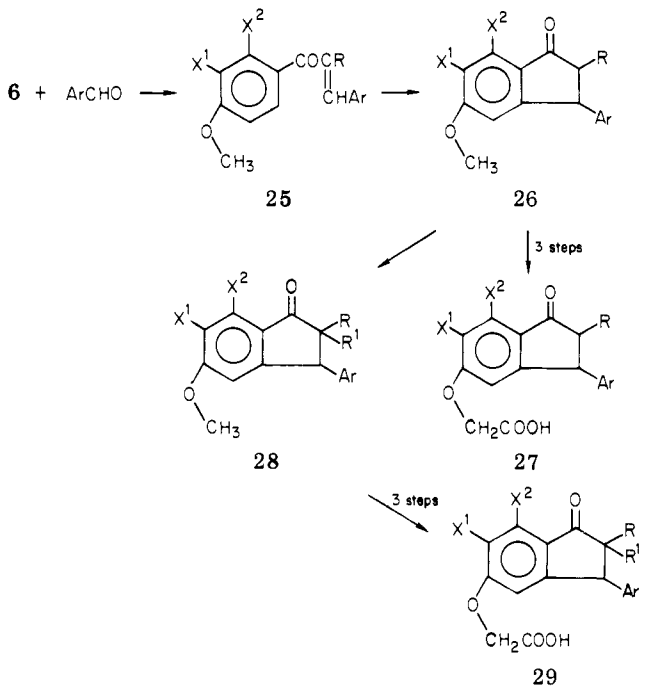
Friedel–Crafts acylation of 5 with 6-bromohexanoyl chloride gave 13 which readily underwent the Mannich reaction to give 14 with concomitant replacement of the terminal bromine atom with chlorine. Cyclialkylation to 15 followed by intramolecular alkylation afforded the 2,2-spirocyclopentyl intermediate 16 which was converted to the corresponding oxyacetic acid 17 by the procedure disclosed earlier (Scheme II).

A modification of the sequence described in Scheme I led to hexahydrofluorenone analogues 22 and 24 as shown in Scheme III. The anisole 5 was acylated with cyclohexanecarbonyl chloride and the product 18 was brominated to form 19 which was dehydrohalogenated using LiCl

Scheme III



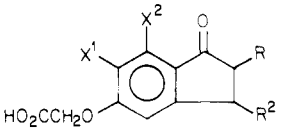
Scheme IV



in DMF to produce 20. Cyclialkylation with polyphosphoric acid formed 21 which was converted to the corresponding oxyacetic acid 22 by the three-step process described earlier. Alternatively, 21 was alkylated to give 23 which was subsequently converted to 24.

The indanyloxyacetic acids bearing a 3-aryl (or 3-pyridyl) substituent were prepared as shown in Scheme IV. The aldol condensation of the appropriate alkanoylanisole 6 with a benzaldehyde or pyridinecarboxaldehyde produced 25 which was cyclialkylated to 26 using

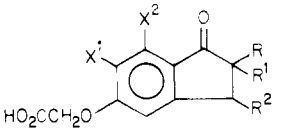
Table I



4

No.	X^1	X^2	R	R^2	% yield	Recrystn solvent	Mp, °C	Emp formula	Analyses
4a	Cl	Cl	Me	H	84	AcOH	202-204	$C_{12}H_{10}Cl_2O_4$	C, H, Cl
4b	Me	Me	H	Me	50	EtOH	223	$C_{14}H_{16}O_4$	C, H
4c	H	Cl	Me	H	43	$MeNO_2$	169-171	$C_{12}H_{11}ClO_4$	C, H, Cl
4d	Cl	Cl	Me	Me	86	$MeNO_2$	175-177	$C_{13}H_{12}Cl_2O_4$	C, H
4e	Cl	Cl	Et	H	26	MeCN	169-171	$C_{13}H_{12}Cl_2O_4$	C, H
4f	Cl	Cl	Et	Me	65	$MeNO_2$	167-168	$C_{14}H_{14}Cl_2O_4$	C, H, Cl
4g	Me	Me	Et	H	95	MeCN	205	$C_{15}H_{18}O_4$	C, H
4h	Cl	H	Et	H	67	C_6H_6	142-144	$C_{13}H_{13}ClO_4$	C, H, Cl
4i	Cl	Cl	*n*-Pr	H	87	AcOH-H_2O	203-205	$C_{14}H_{14}Cl_2O_4$	C, H
4j	Cl	Cl	*i*-Pr	H	78	AcOH-H_2O	167-168	$C_{14}H_{14}Cl_2O_4$	C, H
4k	Me	Cl	*i*-Pr	H	63	AcOH-H_2O	155-156	$C_{15}H_{17}ClO_4$	C, H
4l	Me	Me	*i*-Pr	H	31	AcOH-H_2O	153-154	$C_{16}H_{20}O_4$	C, H
4m	Cl	Cl	*n*-Bu	H	64	EtOH-H_2O	216-219	$C_{15}H_{16}Cl_2O_4$	C, H
4n	Cl	Cl	*s*-Bu	H	30	AcOH-H_2O	132-135	$C_{15}H_{16}Cl_2O_4$	C, H
4o	Cl	Cl	*t*-Bu	H	26	$MeNO_2$	186-188	$C_{15}H_{16}Cl_2O_4$	C, H
4p	Cl	Cl	c-C_5H_9	H	65	AcOH-H_2O	184-185	$C_{16}H_{16}Cl_2O_4$	C, H
(+)-4p	Cl	Cl	c-C_5H_9	H		AcOH	178-180	$C_{16}H_{16}Cl_2O_4$	C, H
(−)-4p	Cl	Cl	c-C_5H_9	H			178-180	$C_{16}H_{16}Cl_2O_4$	C, H
4q	Me	Cl	c-C_5H_9	H	79	AcOH-H_2O	199-201	$C_{17}H_{19}ClO_4$	C, H
4r	Me	Me	c-C_5H_9	H	76	AcOH-H_2O	154-156	$C_{18}H_{22}O_4$	C, H
4s	Cl	Cl	c-C_6H_{11}	H	43	AcOH-H_2O	180-184	$C_{17}H_{18}Cl_2O_4$	C, H
4t	Cl	Cl	CH_2-c-C_5H_9	H	78	AcOH	213	$C_{17}H_{18}Cl_2O_4$	C, H
22	Cl	Cl	——$(CH_2)_4$——		46	AcOH-H_2O	202-206	$C_{15}H_{14}Cl_2O_4$	C, H
27a	Cl	Cl	Me	C_6H_5	71	AcOH-H_2O	220-224	$C_{18}H_{14}Cl_2O_4$	C, H
27b	Cl	Cl	Et	C_6H_5	74	AcOH	203-206	$C_{19}H_{16}Cl_2O_4$	C, H
27c	Cl	Cl	*i*-Pr	C_6H_5	66	AcOH-H_2O	143-145	$C_{20}H_{18}Cl_2O_4$	C, H
27d	Cl	Cl	c-C_5H_9	C_6H_5	61	AcOH-H_2O	171-174	$C_{22}H_{20}Cl_2O_4$	C, H
27e	Cl	Cl	Et	2-C_5H_4N	40	DMF	269-272	$C_{18}H_{15}Cl_2NO_4$	C, H, N
27f	Cl	Cl	Et	3-C_5H_4N	47	MeCN	240-241	$C_{18}H_{15}Cl_2NO_4$	C, H, N

Table II



12

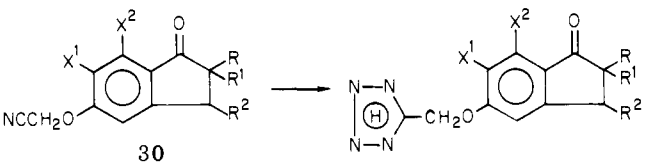
No.	X^1	X^2	R	R^1	R^2	% yield	Recrystn solvent	Mp, °C	Emp formula	Analyses
12a	Cl	Cl	Me	Me	H	85	$MeNO_2$	182	$C_{13}H_{12}Cl_2O_4$	C, H
12b	Cl	Cl	Et	Me	H	45	$MeNO_2$	168	$C_{14}H_{14}Cl_2O_4$	C, H
12c	Cl	Cl	Et	*n*-Pr	H			Oil	$C_{16}H_{18}Cl_2O_4$	C, H
12d	Cl	Cl	*i*-Pr	Me	H	67	$MeNO_2$	156-157	$C_{15}H_{16}Cl_2O_4$	C, H
(+)-12d	Cl	Cl	*i*-Pr	Me	H		AcOH-H_2O	148	$C_{15}H_{16}Cl_2O_4$	C, H
(−)-12d	Cl	Cl	*i*-Pr	Me	H		AcOH-H_2O	145	$C_{15}H_{16}Cl_2O_4$	C, H
12e	Me	Cl	c-C_5H_9	Me	H	59	AcOH-H_2O	115-119	$C_{18}H_{21}ClO_4$	C, H
12f	Cl	Cl	c-C_5H_9	Me	H	75	AcOH	113-114	$C_{17}H_{18}Cl_2O_4$	C, H
(+)-12f	Cl	Cl	c-C_5H_9	Me	H		Hexane	70-74	$C_{17}H_{18}Cl_2O_4$	C, H, Cl
(−)-12f	Cl	Cl	c-C_5H_9	Me	H		BuCl-hexane	70-74	$C_{17}H_{18}Cl_2O_4$	C, H
12g	Cl	Cl	c-C_5H_9	Et	H	60	$MeNO_2$	167	$C_{18}H_{20}Cl_2O_4$	C, H
12h	Cl	Cl	Me	$CH_2C_6H_5$	H	47	AcOH-H_2O	169-170	$C_{19}H_{16}Cl_2O_4$	C, H
12i	Cl	Cl	Me	$CH_2CH{=}CH_2$	H	48		Oil	$C_{15}H_{16}Cl_2O_4$	C, H
17a	Cl	Cl	——$(CH_2)_4$——		H	65	$MeNO_2$	195	$C_{15}H_{14}Cl_2O_4$	C, H
17b	Cl	Cl	——$(CH_2)_5$——		H	73	$MeNO_2$	225	$C_{16}H_{16}Cl_2O_4$	C, H
24	Cl	Cl	Me	——$(CH_2)_4$——		65	AcOH-H_2O	159-161	$C_{16}H_{16}Cl_2O_4$	C, H
29a	Cl	Cl	Me	Me	C_6H_5	42	AcOH	163-164	$C_{19}H_{16}Cl_2O_4 \cdot 0.5H_2O$	C, H
29b	Cl	Cl	Et	Me	C_6H_5	51	AcOH-H_2O	190-192	$C_{20}H_{18}Cl_2O_4$	C, H

PPA or trifluoroacetic acid (which gave fewer by-products than concentrated H_2SO_4). Indanone **26** or its alkylated derivative **28** was converted to the corresponding oxyacetic acids **27** and **29**.

There is considerable evidence that the 5-tetrazolyl moiety serves as a carboxy surrogate in medicinal agents. Therefore, the 5-tetrazolyl analogue of a number of our most active indanyloxyacetic acids was prepared by the reaction sequence shown in Scheme V. The compounds which were prepared are listed in Table III.

The intermediates generated in the various reaction sequences are listed in Tables IV–VII.

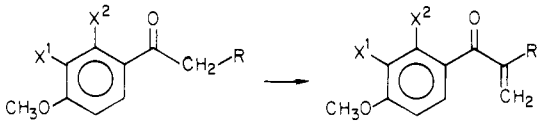
Table III



30 31

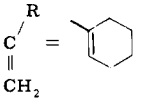
No.	X^1	X^2	R	R^1	R^2	% yield	Recrystn solvent	Mp, °C	Emp formula	Analyses
30a	Cl	Cl	Et	H	H	63	BuCl	138-140	$C_{13}H_{11}Cl_2NO_2$	C, H, N
30b	Cl	Cl	*i*-Pr	H	H	82	Me_2CO-H_2O	112-114	$C_{14}H_{13}Cl_2NO_2$	C, H, N
30c	Cl	Cl	Et	H	C_6H_5	65		Oil	$C_{19}H_{15}Cl_2NO_2$	
30d	Cl	Cl	c-C_5H_9	H	H	80	C_6H_6-C_6H_{12}	124-125	$C_{16}H_{15}Cl_2NO_2$	C, H, N
30e	Me	Cl	c-C_5H_9	H	H	73	C_6H_6-C_6H_{12}	141-142	$C_{17}H_{18}ClNO_2$	C, H, N
30f	Me	Me	c-C_5H_9	H	H	100	Me_2CO-H_2O	83-84	$C_{18}H_{21}NO_2$	C, H, N
30g	Cl	Cl	*i*-Pr	H	C_6H_5	64	C_6H_{12}	120-122	$C_{20}H_{17}Cl_2NO_2$	C, H, N
30h	Cl	Cl	c-C_5H_9	H	C_6H_5	85	C_6H_6-C_6H_{12}	131-133	$C_{22}H_{19}Cl_2NO_2$	C, H, N
30i	Cl	Cl	*i*-Pr	Me	H	66	BuCl	133	$C_{15}H_{15}Cl_2NO_2$	C, H, N
30j	Cl	Cl	—$(CH_2)_5$—		H	51	BuCl	165-167	$C_{16}H_{15}Cl_2NO_2$	C, H, N
30k	Cl	Cl	c-C_5H_9	Me	H	73	C_6H_6-C_6H_{12}	130-131	$C_{17}H_{17}Cl_2NO_2$	C, H, N
30l	Cl	Cl	—$(CH_2)_4$—		H	57	BuCl	153	$C_{15}H_{13}Cl_2NO_2$	C, H, N
31a	Cl	Cl	Et	H	H	85	$MeNO_2$	204-205	$C_{13}H_{12}Cl_2N_4O_2$	C, H, N
31b	Cl	Cl	*i*-Pr	H	H	22	$MeNO_2$	158-160	$C_{14}H_{14}Cl_2N_4O_2$	C, H, N
31c	Cl	Cl	Et	H	C_6H_5	47	$MeNO_2$	205-207	$C_{19}H_{16}Cl_2N_4O_2$	C, H, N
31d	Cl	Cl	c-C_5H_9	H	H	51	MeCN	175-177	$C_{16}H_{16}Cl_2N_4O_2$	C, H, N
31e	Me	Cl	c-C_5H_9	H	H	60	MeCN	185-186	$C_{17}H_{19}ClN_4O_2$	C, H, N
31f	Me	Me	c-C_5H_9	H	H	54	MeCN	173-174	$C_{18}H_{22}N_4O_2$	C, H, N
31g	Cl	Cl	*i*-Pr	H	C_6H_5	61	MeCN	211-213	$C_{20}H_{18}Cl_2N_4O_2$	C, H, N
31h	Cl	Cl	c-C_5H_9	H	C_6H_5	28	EtOH	229-231	$C_{22}H_{20}Cl_2N_4O_2$	C, H, N
31i	Cl	Cl	*i*-Pr	Me	H	60	MeOH-H_2O	173	$C_{15}H_{16}Cl_2N_4O_2$	C, H, N
31j	Cl	Cl	—$(CH_2)_5$—		H	65	EtOH	233	$C_{16}H_{16}Cl_2N_4O_2$	C, H, N
31k	Cl	Cl	c-C_5H_9	Me	H	58	EtOH	218-219	$C_{17}H_{18}Cl_2N_4O_2$	C, H, N
31l	Cl	Cl	—$(CH_2)_5$—		H	58	MeCN	191	$C_{15}H_{14}Cl_2N_4O_2$	C, H, N

Table IV



6 7

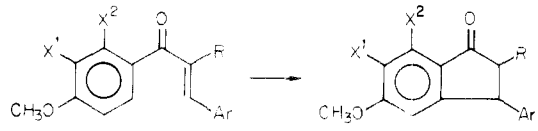
No.	X^1	X^2	R	% yield	Recrystn solvent	Mp or bp (mm), °C	Emp formula	Analyses
6a	Cl	Cl	Et	77	Hexane	43-44	$C_{11}H_{12}Cl_2O_2$	C, H
6b	Cl	Cl	*i*-Pr	72	Hexane	54-55	$C_{12}H_{14}Cl_2O_2$	C, H
6c	Cl	Cl	c-C_5H_9	57	Hexane	60-62	$C_{14}H_{16}Cl_2O_2$	C, H
6d	Me	Cl	c-C_5H_9	80		145-165 (0.6)	$C_{15}H_{19}ClO_2$	C, H
6e	Cl	Cl	CH_2-c-C_5H_9	47		164-166 (0.1)	$C_{15}H_{18}Cl_2O_2$	H; C[a]
13a	Cl	Cl	-$(CH_2)_4$Br	21	BuCl	50	$C_{13}H_{15}BrCl_2O_2$	
13b	Cl	Cl	-$(CH_2)_5$Br	58	C_6H_{12}	57	$C_{14}H_{17}BrCl_2O_2$	C, H
18a	Cl	Cl	*c*	40	Hexane	97-98	$C_{14}H_{16}Cl_2O_2$	C, H
18b	Cl	Cl	*d*	49		120-130 (0.5)	$C_{11}H_{12}Cl_2O_2$	H; C[b]
7a	Cl	Cl	Et		Petr ether	46-48	$C_{12}H_{12}Cl_2O_2$	C, H
7b	Cl	Cl	*i*-Pr	63	Hexane	56-58	$C_{13}H_{14}Cl_2O_2$	C, H
7c	Cl	Cl	c-C_5H_9	67	BuCl	66-67	$C_{15}H_{16}Cl_2O_2$	C, H
7d	Me	Cl	c-C_5H_9	78	Petr ether	45-47	$C_{16}H_{19}ClO_2$	C, H
7e	Cl	Cl	CH_2-c-C_5H_9	85	Hexane	68	$C_{16}H_{18}Cl_2O_2$	C, H
20a	Cl	Cl	*e*	98		126-129	$C_{14}H_{14}Cl_2O_2$	C, H
20b	Cl	Cl	Me	100		59	$C_{11}H_{10}Cl_2O_2$	C, H

[a] C: calcd, 59.81; found, 60.40. [b] C: calcd, 53.46; found, 54.25. [c] CH_2R = -c-C_6H_{11}. [d] CH_2R = $CHMe_2$. [e] $C(R)(=CH_2)$ = 

Structure–Activity Relationships. A. Saluresis–Diuresis. 1. General Discussion. Although the excretion of urine, Na^+, K^+, and Cl^- was measured in the experiments conducted in rats, dogs, and chimpanzees, for the sake of brevity, only the Na^+ excretion is reported here. The other parameters generally paralleled the Na^+, thus any one of these could have been used for the relative potency comparisons among the several classes of compounds. Potassium and chloride as well as sodium excretion data for compounds **4j**, **4p**, **12d**, and **12f** have been reported previously.[10]

a. Rat Data. The oral natriuretic activity of the 2-monosubstituted indanones at four different doses is provided in Table VIII. The activity of the 2-*n*-alkyl

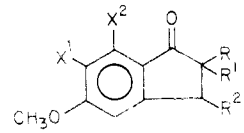
Table V



25 26

No.	X^1	X^2	R	Ar	% yield	Recrystn solvent	Mp, °C	Emp formula	Analyses
25a	Cl	Cl	Me	C_6H_5	95	EtOH	138-139	$C_{17}H_{14}Cl_2O_2$	C, H
25b	Cl	Cl	Et	C_6H_5	91	EtOH	127-130	$C_{18}H_{16}Cl_2O_2$	C, H
25c	Cl	Cl	*i*-Pr	C_6H_5	52	C_6H_6-hexane	113-114	$C_{19}H_{18}Cl_2O_2$	C, H
25d	Cl	Cl	c-C_5H_9	C_6H_5	31		104-106	$C_{21}H_{20}Cl_2O_2$	C, H
25e	Cl	Cl	Et	3-C_5H_4N	87	EtOH	125-126	$C_{17}H_{15}Cl_2NO_2$	C, H, N
25f	Cl	Cl	Et	2-C_5H_4N	79		127-129	$C_{17}H_{15}Cl_2NO_2$	C, H, N
26a	Cl	Cl	Me	C_6H_5	58	C_6H_{12}	155-157	$C_{17}H_{14}Cl_2O_2$	C, H
26b	Cl	Cl	Et	C_6H_5	80	C_6H_6	141-143	$C_{18}H_{16}Cl_2O_2$	C, H
26c	Cl	Cl	*i*-Pr	C_6H_5	95	C_6H_{12}	169-171	$C_{19}H_{18}Cl_2O_2$	C, H
26d	Cl	Cl	c-C_5H_9	C_6H_5	81	C_6H_6-hexane	124-126	$C_{21}H_{20}Cl_2O_2$	C, H
26e	Cl	Cl	Et	3-C_5H_4N	98	EtOH	205-206	$C_{17}H_{15}Cl_2NO_2$	C, H, N
26f	Cl	Cl	Et	2-C_5H_4N	61	EtOH	158-160	$C_{17}H_{15}Cl_2NO_2$	C, H, N

Table VI



8

No.	X^1	X^2	R	R^1	R^2	% yield	Recrystn solvent	Mp, °C	Emp formula	Analyses
8a	Cl	Cl	Et	H	H	74	BuCl	146-147	$C_{12}H_{12}Cl_2O_2$	C, H
8b	Cl	Cl	*i*-Pr	H	H	87	C_6H_6-hexane	118-119	$C_{13}H_{14}Cl_2O_2$	C, H
8c	Cl	Cl	c-C_5H_9	H	H	85	C_6H_6-hexane	114-116	$C_{15}H_{16}Cl_2O_2$	C, H
8d	Me	Cl	c-C_5H_9	H	H	64	Hexane	73-74	$C_{16}H_{19}ClO_2$	C, H
8e	Cl	Cl	CH_2-c-C_5H_9	H	H	68	EtOH-H_2O	118	$C_{16}H_{18}Cl_2O_2$	C, H
15a	Cl	Cl	$(CH_2)_4Cl$	H	H	64	C_6H_{12}	92	$C_{14}H_{15}Cl_3O_2$	C, H, Cl
15b	Cl	Cl	$(CH_2)_5Cl$	H	H	54	C_6H_6-hexane	115	$C_{15}H_{17}Cl_3O_2$	C, H, Cl
21a	Cl	Cl	H	$-(CH_2)_4-$		54	C_6H_6-C_6H_{12}	171-173	$C_{14}H_{14}Cl_2O_2$	C, H
21b	Cl	Cl	Me	H	H	71	EtOH-H_2O	129	$C_{11}H_{10}Cl_2O_2$	C, H
9a	Cl	Cl	Et	Me	H	100	Me-C_6H_{11}	110-115	$C_{13}H_{14}Cl_2O_2$	C, H
9b	Cl	Cl	Et	*n*-Pr	H	40	C_6H_{12}	92	$C_{15}H_{18}Cl_2O_2$	C, H
9c	Cl	Cl	*i*-Pr	Me	H	81	EtOH-H_2O	143	$C_{14}H_{16}Cl_2O_2$	C, H
9d	Cl	Cl	Me	Me	H	54	BuCl	147	$C_{12}H_{12}Cl_2O_2$	C, H
9e	Cl	Cl	Me	$CH_2C_6H_5$	H	89			$C_{18}H_{16}Cl_2O_2$	
9f	Cl	Cl	Me	$CH_2CH=CH_2$	H	64	Me-C_6H_{11}	58	$C_{14}H_{14}Cl_2O_2$	C, H
9g	Cl	Cl	c-C_5H_9	Me	H	83	EtOH	111-113	$C_{16}H_{18}Cl_2O_2$	C, H
9h	Cl	Cl	c-C_5H_9	Et	H	51	BuCl	163	$C_{17}H_{20}Cl_2O_2$	C, H
9i	Cl	Cl	Me	$CH_2=CHCH_2C_6H_5$	H	94			$C_{20}H_{15}Cl_2O_2$	
9j	Me	Cl	c-C_5H_9	Me	H	46			$C_{17}H_{21}ClO_2$	
23	Cl	Cl	Me	$-(CH_2)_4-$		78	EtOH-H_2O	94-95	$C_{15}H_{16}Cl_2O_2$	C, H
28a	Cl	Cl	Et	Me	C_6H_5	71	C_6H_{12}	129-132	$C_{19}H_{18}Cl_2O_2$	C, H
28b	Cl	Cl	Me	Me	C_6H_5	65	C_6H_{12}	146-148	$C_{18}H_{16}Cl_2O_2$	C, H
16a	Cl	Cl	$-(CH_2)_4-$		H	65	EtOH-H_2O	170	$C_{14}H_{14}Cl_2O_2$	C, H
16b	Cl	Cl	$-(CH_2)_5-$		H	98	BuCl	210	$C_{15}H_{16}Cl_2O_2$	C, H

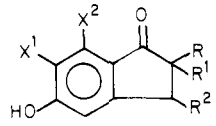
compounds increases as R increases from methyl to ethyl and then rapidly decreases; thus, **4a** < **4e** > **4i** > **4m**. Branching also increases activity, i.e., **4j** > **4i** and **4o** = **4n** >> **4m**. In the 2-cycloalkyl series, the activity of the cyclohexyl (**4s**) > cyclopentyl (**4p**) > cyclopentylmethyl (**4t**) compound. Interestingly, the dextrocyclopentyl enantiomer (+)-**4p** is twice as active as the levo enantiomer (−)-**4p**. As observed with other aryloxyacetic acids **3**–**6**, the activity of the 7-chloro analogues **4c** and **4h** < 6,7-dimethyl compounds **4g**, **4l**, and **4r** < 6-methyl-7-chloro analogues **4k** and **4q** < 6,7-dichloro analogues **4a**, **4e**, **4i**, and **4p**.

The addition of a 3-substituent (R^2) increases the activity when the substituent is small; thus, the activity of **4d** > **4a** and **4f** > **4e** but when R^2 = phenyl or pyridyl, the activity is greatly diminished (**27a**–**f**).

A marked increase in activity was achieved by adding a second small 2-substituent (R^1). Thus the activity of the 2,2-dimethyl compound **12a** > 2-methyl (**4a**) and 2-methyl-2-ethyl (**12b**) > 2-ethyl (**4e**). Likewise **12d** > **4j**, **12f** > **4p**, **12c** > **4i**, and **12g** > **4p**. The 2,2-spirocycloalkyl compounds **17a**,**b** are equipotent to the acyclic analogues of similar molecular weight (**12c**). Resolution of two racemates **12d** and **12f** gave enantiomers with different saluretic activity, (−)-**12d** being more potent than (+)-**12d** while (+)-**12f** was more active than (−)-**12f**. Addition of a large 3-substituent (R^2) **29a**,**b** drastically reduces activity.

It can be seen that many of the indanyloxyacetic acids have a higher natriuretic ceiling than hydrochlorothiazide

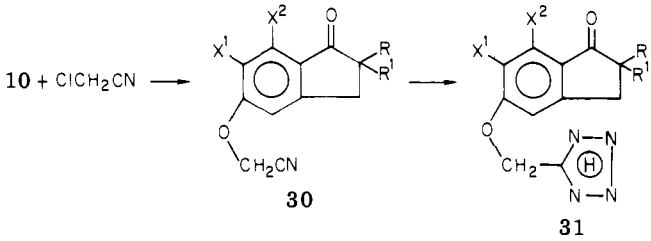
Table VII



10

No.	X^1	X^2	R	R^1	R^2	% yield	Recrystn solvent	Mp, °C	Emp formula	Analyses
10a	Cl	Cl	Et	H	C_6H_5	87	EtOH	220-222	$C_{17}H_{14}Cl_2O_2$	C, H
10b	Cl	Cl	CH_2-c-C_5H_9	H	H	91	EtOH	250	$C_{15}H_{16}Cl_2O_2$	C, H
10c	Cl	Cl	Me	H	C_6H_5	42	EtOH	261-264	$C_{16}H_{12}Cl_2O_2$	C, H
10d	Cl	Cl	*i*-Pr	H	C_6H_5	77	EtOH-H_2O	216-218	$C_{18}H_{16}Cl_2O_2$	C, H
10e	Cl	Cl	c-C_5H_9	H	C_6H_5	78	EtOH-H_2O	195-197	$C_{20}H_{18}Cl_2O_2$	C, H
10f	Cl	Cl	Et	H	3-C_5H_4N	81	EtOH	243-245	$C_{16}H_{13}Cl_2NO_2$	C, H, N
10g	Cl	Cl	Et	H	2-C_5H_4N	69	EtOH-H_2O	205-207	$C_{16}H_{13}Cl_2NO_2$	C, H, N
10h	Cl	Cl	H	$(CH_2)_4$		97	EtOH	215-220	$C_{13}H_{12}Cl_2O_2$	C, H
10i	Cl	Cl	Et	Me	H	71	BuCl	215-217	$C_{12}H_{12}Cl_2O_2$	C, H
10j	Cl	Cl	Et	*n*-Pr	H	86	Me-C_6H_{11}	153	$C_{14}H_{16}Cl_2O_2$	C, H
10k	Cl	Cl	*i*-Pr	Me	H	98	BuCl	215	$C_{13}H_{14}Cl_2O_2$	C, H
10l	Cl	Cl	Me	Me	H	66	$MeNO_2$	273	$C_{11}H_{10}Cl_2O_2$	C, H
10m	Cl	Cl	Me	$CH_2C_6H_5$	H	77	AcOH	220-222	$C_{17}H_{14}Cl_2O_2$	C, H
10n	Cl	Cl	Me	$CH_2CH=CH_2$	H	92	BuCl	180	$C_{13}H_{12}Cl_2O_2$	C, H
10o	Cl	Cl	c-C_5H_9	Me	H	100	EtOH-H_2O	194-196	$C_{15}H_{16}Cl_2O_2$	C, H
10p	Cl	Cl	c-C_5H_9	Et	H	100			$C_{16}H_{18}Cl_2O_2$	
10q	Cl	Cl	$(CH_2)_4$		H	93	$MeNO_2$	236	$C_{13}H_{12}Cl_2O_2$	C, H
10r	Cl	Cl	Me	$CH_2=CHCH_2C_6H_5$	H	70	AcOH	201-203	$C_{19}H_{16}Cl_2O_2$	C, H
10s	Me	Cl	c-C_5H_9	Me	H	64	EtOH-H_2O	175-177	$C_{16}H_{19}ClO_2$	C, H
10t	Cl	Cl	$(CH_2)_5$		H	93	EtOH	273	$C_{14}H_{14}Cl_2O_2$	C, H
10u	Cl	Cl	Me	$(CH_2)_4$		83	EtOH	217-219	$C_{14}H_{14}Cl_2O_2$	C, H
10v	Cl	Cl	Et	Me	C_6H_5	99	EtOH	246-248	$C_{18}H_{16}Cl_2O_2$	C, H
10w	Cl	Cl	Me	Me	C_6H_5	79	EtOH	259-262	$C_{17}H_{14}Cl_2O_2$	C, H

Scheme V



30 31

and equal to that of furosemide. Furthermore, some of them are more potent (i.e., are effective at lower doses) than furosemide. The tetrazole analogues **31a–l** were all considerably less active than their oxyacetic acid counterparts.

In order to demonstrate more precisely the dramatic contribution to saluretic activity of introducing a second 2-substituent into the 2-monosubstituted compounds **4**, a study of a select group of compounds was made in which relative potencies were determined with statistically valid accuracy. The data are recorded in Table IX. For ease of comparison **4a** was arbitrarily set at relative potency of 1.0. Replacement of 2-CH_3 by ethyl, isopropyl, and cyclopentyl increased potency by 2.8-, 3.2-, and 1.8-fold, respectively. Introducing a 2-CH_3 group into each of these 2-monosubstituted compounds produces relative potency increases of 3.9-, 15-, 53-, and 5.4-fold, respectively. The relative toxicity is not a factor; the acute toxicities of all the compounds lie in the same range.

b. Chimpanzee Data (Table VIII). Since these data are generally from single experiments, it is inappropriate to assign relative potency data from this information. However, it can be seen that the structure–activity (S–A) trends are quite comparable to those observed in rats.

c. Dog Data. The compounds that exhibited good saluresis and diuresis in rats and chimpanzees gave a significant oral response in dogs. Thus, **4j**, **4p**, **12b**, **12d**, and **12f** were as active po as furosemide at 5 mg/kg.

The compounds selected for intravenous evaluation in dogs are reported in Table X. In general, the response in this dog protocol was less than that predicted from the other species. The increase in activity produced by the sequential replacement of the nuclear methyl substituents by chloro is again noted, i.e., the activity of **4l < 4k < 4j**. The activity-enhancing effect of introducing a 2-methyl substituent to the 2-cyclopentyl compound is clear, i.e., the activity of **12f >> 4p**.

B. Uricosuria. In contrast to (acryloylaryloxy)acetic acid and (vinylaryloxy)acetic acid diuretics, none of the (indanyloxy)acetic acids were uric acid retaining in chimpanzees; some were more uricosuric than probenecid. It is difficult to make quantitative S–A judgments from single oral experiments, but some general trends can be noted. Structural features which impart uricosuric activity and those that give diuretic–saluretic activity are not identical. For example, compounds which have weak diuretic activity, such as the 6,7-dimethyl compounds **4l** and **4r**, the 3-substituted compounds **27a–d** and **26a**, and most of the tetrazoles **31a**, **31d**, and **31i**, are quite uricosuric. Certain compounds embody optimal activity of both types, i.e., **4i**, **4j**, **4p**, and **4s** and especially **12f** and **24**. Interestingly, one enantiomer proved to be more uricosuric in each of the three examples that were studied; thus the uricosuric activity of (+)-**4p** > (–)-**4p**, (+)-**12d** > (–)**12d**, and (–)-**12f** > (+)-**12f**. The relative saluretic–diuretic activity in chimpanzees and rats did not necessarily parallel the uricosuric effects.

Compounds **4j**, **4p**, and **12f** have been evaluated orally in man and found to be diuretic, saluretic, and uricosuric. Their relative diuretic–saluretic profiles were predictable from animal data, i.e., **12f > 4p > 4j**.[12] Thus it has been possible to design and synthesize a series of compounds in which either saluretic or uricosuric effects predominate or where both effects are optimal.

Table VIII. Oral Activity

Compd	Rat,[a] mequiv of Na^+ × 100/cage				Chimpanzee,[b] 5 mg/kg	
	3 mg/kg	9 mg/kg	27 mg/kg	81 mg/kg	$\Delta\mu$, equiv of Na^+/min	$\Delta C_{urate}/\Delta C_{inulin}$
4a	32	31	43	101	*c*	
4b	13	16	26	50		
4c	10	11	15	33		
4d	18	24	84	132		
4e	24	54	88	124	427	0.09
4f	27	54	80	142		
4g	13	25	34	49		
4h	14	11	7	13		
4i	35	27	55	73	613	0.19
4j	43	46	124	237	649	0.18
4k	48	49	123	111	185	0.07
4l	68	62	83	102	153	0.15
4m	28	24	31	53	126	0.11
4n	41	51	120	240		
4o	33	57	132	228	106	0.00
4p	37	40	67	134	223	0.18
(+)-4p	10	24	105	181	300	0.26
(−)-4p	13	23	52	90	292	0.10
4q	40	35	75	104	141	0.14
4r	52	34	47	78	0	0.43
4s	22	20	79	176	310	0.21
4t	40	35	75	104	105	0.05
22	41	59	80	103	85	0.20
27a	19	20	15	48	64	0.12
27b	30	38	33	36	223	0.28
27c	18	29	44	59	240	0.25
27d	29	26	17	20	22	0.25
27e	21	12	11	27	0	0.08
27f	28	28	30	35	25	0.07
12a	22	54	138	170	535	0.04
12b	61	126	151	237	520	0.07
12c	30	44	86	161	341	0.05
12d	97	125	212	261	506	0.03
(+)-12d	123	128	195	260	1593	0.41
(−)-12d	148	200	237	294	992	0.06
12e	27	66	107	154	86	0.24
12f	65	92	167	223	425	0.20
(+)-12f	67	95	136	258	325	0.10
(−)-12f	64	52	82	143	268	0.17
12g	25	59	115	166	231	0.12
12h	34	32	55	73	251	0.18
12i	22	58	146	169	81	0.01
17a	58	50	109	163	624	0.11
17b	35	46	82	152	489	0.05
24	50	118	131	93	406	0.39
29a	16	21	12	38	22	0.10
29b	25	29	20	35	0	0.00
31a	7	12	19	69	28	0.11
31b	15	19	33	62	42	0.07
31c	21	23	20	23	5	0.06
31d	12	26	28	34	56	0.18
31e	35	50	40	108	*c*	
31f	13	19	32	24		
31g	16	17	14	23		
31h	13	16	12	8		
31i	33	53	66	115	174	0.17
31j	14	13	26	44	0	0.02
31k	19	16	24	46	19	0.07
31l	16	15	19	28	0	0.05
Furosemide		7	125	244	1035	−0.02
Hydrochlorothiazide	123	112	131	128	144	−0.02
Placebo	8					

[a] Female rats (Charles River, 150–170 g) were maintained overnight on a sugar diet with water ad libitum. The test substance was dissolved in pure DMF and subsequently diluted with water (which contained 3 drops of Tween 80 per 100 mL) such that the final vehicle was 4% DMF. At the time of the test, animals were given the vehicle (as placebo) or test substance suspended in a final volume of 5.0 mL po. Rats were housed in groups of three in metabolism cages. Urine was collected for the 0–5-h interval in graduated cylinders and was analyzed for sodium, potassium, and chloride content. Animals that received placebo were run concurrently. Results are reported as milliequivalents × 100 per cage and are the geometric means of three cages per dose level. Standard methodology was used for determination of electrolyte levels. [b] Fasted, male chimpanzees weighing 21–77 kg were immobilized with phencyclidine (which was shown not to affect the results) (1.0–1.5 mg/kg im plus 0.25 mg/kg iv as needed) and were prepared by catheterization for standard renal clearance studies using routine clinical asceptic procedures. Pyrogen-free inulin (iv) was used to measure the glomerular filtration rate (GFR). Clearance of inulin, urate, and the excretion rates of Na^+, K^+, and Cl^- was determined by standard Auto Analyzer techniques. (Inulin and urate in chimpanzee plasma are freely filterable.) Average control clearances were calculated from

Footnotes to Table VIII (*Continued*)

three 20-min consecutive periods. Drug-response values were derived as the average of eight 15–20-min clearance periods after oral administration of an aqueous solution of the compound through an indwelling nasal catheter. All data are reported as the difference between (average) treatment and control values obtained from single experiments. [c] Where no data are recorded, that compound was not evaluated in the chimpanzee.

Table IX[a]

Compd	Acute iv mouse, LD_{50}, mg/kg	Doses, mg/kg	No. of cages at each dose	95% confidence limits		Rel potency
				Lower	Upper	
4a	354	9, 27, 81	9			1.0
4e	245	3, 9, 27, 81	6	2.1	3.7	2.8
4j	505	3, 9, 27, 81	3	2.3	4.9	3.2
4p	222	9, 27, 81	6	1.3	2.5	1.8
4a	354	9, 27, 81	9			1.0
12a	268	3, 9, 27, 81	3	2.8	5.6	3.9
12b	239	0.3, 1, 3, 9	6	10.9	20.5	15
12d	244	0.1, 0.3, 1, 3	6	39.8	72.1	53
12f	213	3, 9, 27, 81	6	4.1	7.3	5.4

[a] The procedure described in Table VIII, footnote *a*, was followed. Results were reported as milliequivalents (or milliliters) per cage and were the average of the indicated number of cages per dose level. In many cases, averaging of multiple tests was required. For statistical analysis, only the 0–5-h values were used and the statistical results were based upon chloride excretion values. The potency values and 95% confidence limits of the seven compounds are presented. For the purpose of stabilizing the variances of the groups considered in each analysis, the response data (here, chloride excretion values) were converted to logs. The dose-response relationship associated with each compound was based on the regression of log response on log dose. The analysis of a variance was based on log response data for a completely randomized design. The salient features of the statistical results are as follows. The test for "lack of parallelism" associated with each analysis was not significant (at $p = 0.05$), indicating fundamental *validity* of the assay. The test for "common regression" associated with each analysis was very highly significant ($p << 0.001$), measuring the steepness of the average slope of the standard and the test based on the regression of log response on log dose. The test for "curvature" associated with each analysis was not significant (at $p = 0.05$), demonstrating linearity of the dose-response curve. The 95% confidence intervals of each relative potency value did not include the value of "one" (the lower confidence limit was greater than one), indicating that the test compound is significantly ($p \leq 0.05$) more potent than the standard.

Table X. Intravenous Dog Diuretic Assay (5 mg/kg stat)[a]

Compd	No. of expt, av	Control/drug treatment results, μ equiv/min			Urine vol, mL/mL
		Na^+	K^+	Cl^-	
4j	5	11/281	7/44	4/330	2/4
4k	2	30/218	8/50	7/204	1/3
4l	2	15/154	3/15	5/100	1/2
4p	2	14/20	30/37	3/5	1/2
12b	2	5/360	10/62	7/450	2/4
12d	2	5/185	5/35	6/218	1/2
12f	3	30/454	14/48	10/478	1/4
12i	1	10/175	6/37	4/171	2/4
17a	2	22/330	15/47	15/254	2/5
Hydrochlorothiazide	3	12/166	15/33	5/156	1/3
Furosemide[b]	2	29/960	18/141	1/1081	1/3

[a] Female animals were starved overnight, anesthetized with phenobarbital, creatinine primed, catherized, and infused with phosphate buffer at a rate of 3 mL/min. The drug was given iv at 5 mg/kg over a period of 5 min, and 15-min collections of urine were taken over a period of 2 h. The data recorded were the average of the two highest consecutive 15-min collections. [b] 1 mg/kg.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained are within 0.4% of the theoretical values. Detailed experimental procedures are given only for selected compounds, which will serve to illustrate the general synthetic methods employed.

[2,3-Dichloro-4-(2-methylbutyryl)phenoxy]acetic Acid (1f). A mixture of **1a** (15.16 g, 0.05 mol), 5% Pd/C catalyst (0.5 g), and *i*-PrOH (150 mL) was shaken in an atmosphere of H_2 for 15 min at an initial pressure of 2.1 kg/cm^2. The pressure drop indicated an absorption of 0.05 mol of H_2. The mixture was filtered and evaporated to dryness to give **1f** which melts at 141.5–142.5 °C after recrystallization from BuCl. Anal. ($C_{13}H_{14}Cl_2O_4$) C, H.

(6,7-Dichloro-2-ethyl-1-oxo-5-indanyloxy)acetic Acid (4e). [2,3-Dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid (100 g) was added with stirring to concentrated H_2SO_4 (95–98%, 500 mL) and heated at 60 °C for 6 h. The reaction mixture was cooled and poured into a mixture of ice and water (4 L) to obtain **4e** which was collected by filtration and purified. Compounds **4a–o** were prepared in a similar manner.

(2-Cyclopentyl-6,7-dichloro-2-methyl-1-oxo-5-indanyloxy)acetic Acid (12f). Step A. (2-Cyclopentyl-2′,3′-dichloro-4′-methoxy)acetophenone (6c). In a 2-L, round-bottom, four-necked flask equipped with stirrer, reflux condenser with drying tube, thermometer, and hopper for $AlCl_3$ were placed 2,3-dichloroanisole (137.3 g, 0.776 mol), cyclopentylacetyl chloride (125 g, 0.854 mol), and CH_2Cl_2 (600 mL). The mixture was stirred and cooled to 5 °C and $AlCl_3$ (114 g, 0.854 mol) was added portionwise over 1 h keeping the temperature at 5 °C. The mixture was allowed to warm to 20–25 °C, kept for 16 h, and then added to 2 L of ice water containing 250 mL of 12 N HCl. The lower organic layer was separated, the aqueous phase was extracted with CH_2Cl_2, and the combined extracts were washed with saturated NaCl solution, 10% NaOH solution, and again with saturated NaCl solution, dried over $MgSO_4$, and evaporated at reduced pressure. The green residual oil was dissolved in hot

hexane (200 mL) and on cooling the solid product separated. Compounds **6a–e** and **18b** were prepared by this procedure.

Step B. 4-(2-Cyclopentylacryloyl)-2,3-dichloroanisole (7c). A viscous mixture of **6c** (140 g, 0.487 mol), paraformaldehyde (36 g, 1.23 mol), $(CH_3)_2NH$·HCl (177 g, 2.17 mol), and AcOH (14 mL) was heated and stirred at 80–85 °C for 25 h; then DMF (600 mL) was added to the semisolid reaction mixture and heating at 80–85 °C was continued for 4 h. The reaction mixture was added with stirring to 1 N HCl (2 L). The slightly gummy solid that separated was collected, washed well with water, and air-dried. Compounds **7a–e** were prepared by this procedure.

Step C. 2-Cyclopentyl-6,7-dichloro-5-methoxy-1-indanone (8c). Finely powdered **7c** (96.8 g, 0.324 mol) was added in portions to cooled 96% H_2SO_4 (350 mL). The reaction mixture was stirred at 25 °C for 1.5 h and then added dropwise to H_2O (2 L). The gum which formed solidified overnight and was collected by filtration. Compounds **8a–c** and **21b** were prepared in this manner.

Step D. 2-Cyclopentyl-6,7-dichloro-5-methoxy-2-methyl-1-indanone (9g). Compound **8c** (81.8 g, 0.274 mol) was dissolved in a mixture of dry *t*-BuOH (0.5 L) and dry C_6H_6 (1.5 L) in an inert atmosphere. The solution was refluxed and KO-*t*-Bu (46.0 g, 0.301 mol) in dry *t*-BuOH (1 L) was added by means of an addition funnel as rapidly as possible. The dark-brown solution was refluxed for 0.5 h, cooled to 20 °C, and treated with CH_3I (195 g, 1.37 mol) in one portion. The reaction mixture was refluxed 10 min, cooled, and treated with H_2O (250 mL). The crude **9g** was washed with H_2O and collected by filtration. Compounds **9a–f** were prepared in a similar manner.

Step E. 2-Cyclopentyl-6,7-dichloro-5-hydroxy-2-methyl-1-indanone (10o). Pyridine hydrochloride (500 g) was heated to fusion in an open flask at 195 °C. **9g** (50 g, 0.167 mol) was added in portions with stirring; the temperature was kept at 195 °C for 0.75 h. The hot reaction mixture was poured into vigorously stirred ice H_2O (2 L) and the crude **10o** collected by filtration and washed well with H_2O. Compounds **10a–l** were prepared similarly.

Step F. (2-Cyclopentyl-6,7-dichloro-2-methyl-1-oxo-5-indanyloxy)acetic Acid (12f). Compound **10o** (12.8 g, 0.0428 mol), K_2CO_3 (6.5 g, 0.0471 mol), and $BrCH_2CO_2Et$ (7.86 g, 0.0471 mol) in DMF (70 mL) were heated at 55–60 °C for 2 h, then treated with H_2O (50 mL) and 10 N NaOH (10 mL), heated on a steam bath for 1 h, poured into ice H_2O, acidified with concentrated HCl, extracted into Et_2O, washed with H_2O and brine, dried ($MgSO_4$), and evaporated at reduced pressure to give the crude **12f**. Compounds in Tables I and II [except **4a–o**, (+)-**4p**, (−)-**4p**, (+)-**12d**, (−)-**12d**, (+)-**12f**, and (−)**12f**] were prepared in this manner. In some cases the crude products separated upon acidification and the ether extraction was unnecessary.

2-(4-Chlorobutyl)-5-methoxy-6,7-dichloro-1-indanone (15a). A stirred mixture of **13a** (10 g, 0.029 mol), dimethylamine hydrochloride (4 g, 0.049 mol), paraformaldehyde (2 g, 0.067 mol), and acetic acid (0.5 mL) was heated on a steam bath for 2 h, treated with DMF (30 mL), and heated an additional 2.5 h. The reaction mixture was poured into H_2O, extracted with Et_2O, washed with water, and dried ($MgSO_4$). Evaporation of the Et_2O gave crude **14** (9 g) which was cyclialkylated to **15a** by treatment with concentrated H_2SO_4.

1-Bromocyclohexyl 2,3-Dichloro-4-methoxyphenyl Ketone (19). Br_2 (22.4 g, 0.14 mol) in AcOH (50 mL) was added dropwise to a stirred solution of **18a** (40 g, 0.14 mol) and 30% HBr (0.5 mL) in AcOH (400 mL) during a 1.5-h period at 25 °C. The mixture was poured into H_2O (1.5 L) and $NaHSO_3$ (10 g). The product which precipitated was crystallized from cyclohexane: yield 47.3 g (95%); mp 94–95 °C. Anal. ($C_{14}H_{15}BrCl_2O_2$) C, H.

1-Cyclohexenyl 2,3-Dichloro-4-methoxyphenyl Ketone (20a). Compound **19** (47.3 g, 0.13 mol), LiCl (16.5 g, 0.39 mol), and DMF (200 mL) were heated at 90 °C for 2 h and then poured into H_2O (1 L) to give **20a**. Compound **20b** was prepared in a similar manner.

1α,1,2,3,4,4α-Hexahydro-6-methoxy-7,8-dichlorofluoren-9-one (21a). A stirred mixture of **20a** (34 g, 0.12 mol) and polyphosphoric acid (340 g) was heated at 90 °C for 17 h in a resin pot. Crushed ice (1 kg) was added to precipitate the product which on crystallization from benzene–cyclohexane (1:1) gave **21a**.

2,3-Dichloro-4-(2-benzylidenebutyryl)anisole (25b). To a mixture of benzaldehyde (19.4 g, 0.183 mol) and **6a** (42.2 g, 0.183 mol) in EtOH (350 mL) a 20% NaOH solution (35.9 mL) was added dropwise with stirring. The mixture was stirred for 22 h. The white solid product that separated was collected and dried.

2-Ethyl-3-phenyl-6,7-dichloro-5-methoxy-1-indanone (26b). Compound **25b** (111.0 g, 0.331 mol) and CF_3COOH (350 mL) were heated at gentle reflux for 70 h. The CF_3COOH was distilled, and the oily residue was triturated with Et_2O to give **26b**.

(6,7-Dichloro-2-isopropyl-2-methyl-1-oxo-5-indanyloxy)acetonitrile (30i). A stirred mixture of **10k** (8.2 g, 0.03 mol), K_2CO_3 (4.15 g, 0.03 mol), $ClCH_2CN$ (2.4 g, 0.032 mol), and KI (0.5 g) in $(CH_3)_2CO$ was refluxed for 18 h. The solvent was evaporated and the residue treated with H_2O (100 mL) affording **30i**.

5-(6,7-Dichloro-2-isopropyl-2-methyl-1-oxo-5-indanyloxymethyl)tetrazole (31i). A stirred solution of **30i** (6.2 g, 0.02 mol), NaN_3 (1.55 g, 0.024 mol), and NH_4Cl (1.24 g, 0.023 mol) in DMF (30 mL) was heated in an inert atmosphere for 1 h, poured into H_2O (200 mL), and acidified with HCl to obtain **31i**.

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