(24) M. J. Waring in ref 23, p 216.
(25) See ref 23, p 243.
(26) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).
(27) J. Hase and H. Oura, *J. Pharm. Bull. Jpn.*, **2**, 368 (1954).
(28) R. Huisgen, H. Oertel, E Rauenbusch, I. Ugi, and V. Vossisus, *Chem. Ber.*, **90**, 1949 (1957).
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(Acylaryloxy)acetic Acid Diuretics. 2. (2-Alkyl-2-aryl-1-oxo-5-indanyloxy)acetic Acids[1a]

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The introduction of an aryl group at the 2 position of the uricosuric diuretics, (1-oxo-2-alkyl-5-indanyloxy)acetic acids, provided compounds with markedly increased potency over their monosubstituted precursors. These compounds were synthesized either by arylation of the corresponding 2-alkyl-5-methoxy-1-indanones with diaryliodonium salts or by alkylation of the 2-aryl-5-methoxy-1-indanones which were cleaved to the corresponding phenols and then converted to the desired oxyacetic acids. Systematic structural variation of the 2-arylindanyloxyacetic acids provided aryl-substituted compounds with varying degrees of uricosuric and diuretic activity.

The discovery that the potent (acryloylaryloxy)acetic acid diuretics could be cyclized intramolecularly to (indanyloxy)acetic acids while still retaining diuretic activity led to a detailed study of these indanyloxy derivatives. The 2-alkyl and 2,2-dialkyl compounds described in paper 1 of this series[1a] exhibited varying degrees of saluretic, diuretic, and uricosuric activity. The series described in this paper retains the 2,2-disubstitution but replaces 2-alkyl by 2-aryl, thus providing new compounds with enhanced diuretic activity as well as significant uricosuric activity as measured in several animal species. The 2-methyl-2-phenyl compound **4a** (MK-196) is currently undergoing clinical evaluation in man.

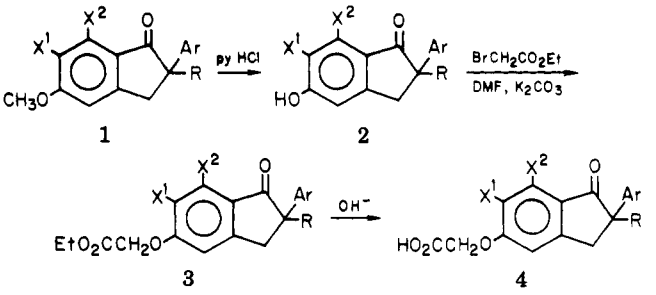
Chemistry. The (2-alkyl-2-arylindanyloxy)acetic acids **4** (Table I) were prepared in several steps (Scheme I) starting with the appropriate anisoles **1** (Tables II and III), following the procedure described in paper 1 of this series.[1a] The 2-alkyl-2-aryl-5-methoxy-1-indanones **1** were synthesized either by arylating 2-alkyl-5-methoxy-1-indanones **5** with a diaryliodonium halide[2] or by alkylating a 2-aryl-5-methoxy-1-indanone **6** (Table II) with an alkyl halide (Scheme II).

A diaryliodonium salt such as diphenyliodonium chloride[3,4] or dithienyliodonium chloride[5] arylated a 2-alkylindanone **5** in *tert*-butyl alcohol–benzene in the presence of potassium *tert*-butoxide to provide the 2-alkyl-2-arylindanone **1**.[6]

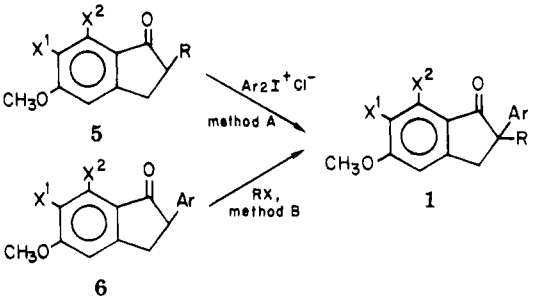
The preparation of the 2-aryl-5-methoxy-1-indanones **6** is illustrated in Scheme III. Preparation of 2-aryl-5-methoxy-1-indanone **6** resulted in complications which were not encountered in the 2-alkyl-5-methoxy-1-indanone synthesis. The Friedel–Crafts acylation of a disubstituted anisole **7** with an arylacetyl chloride in methylene chloride led to poor yields of the aryl benzyl ketone **8**, apparently due to self-acylation by the soluble acid chloride–$AlCl_3$ complex. Use of cyclohexane or carbon disulfide, solvents in which the complex is insoluble, gave excellent yields of clean products, **8** (Table IV).

The standard Mannich reaction with dimethylamine hydrochloride and paraformaldehyde, followed by deamination in DMF to form the α-methylene derivative **9**, was not satisfactory. Treatment of the aryl benzyl ketone **8** with *N,N,N′,N′*-tetramethylmethanediamine and acetic anhydride[7] at temperatures not exceeding 40 °C

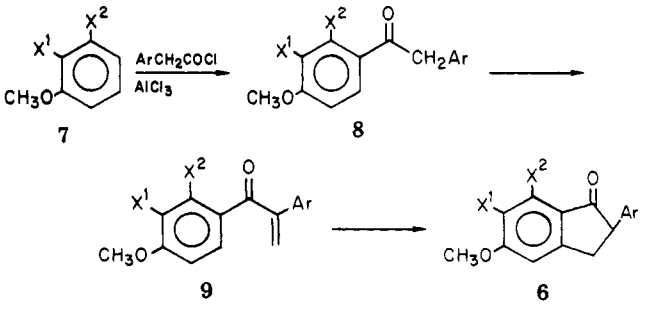
Scheme I



Scheme II



Scheme III



provided the pure α,β-unsaturated ketones **9** in high yields.

The cyclization of **9** in concentrated sulfuric acid led to poor yields of the indanone **6** and highly fluorescent by-products. When the acrylophenone in a dilute solution of methylene chloride was added to concentrated sulfuric

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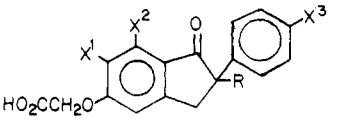
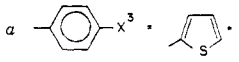
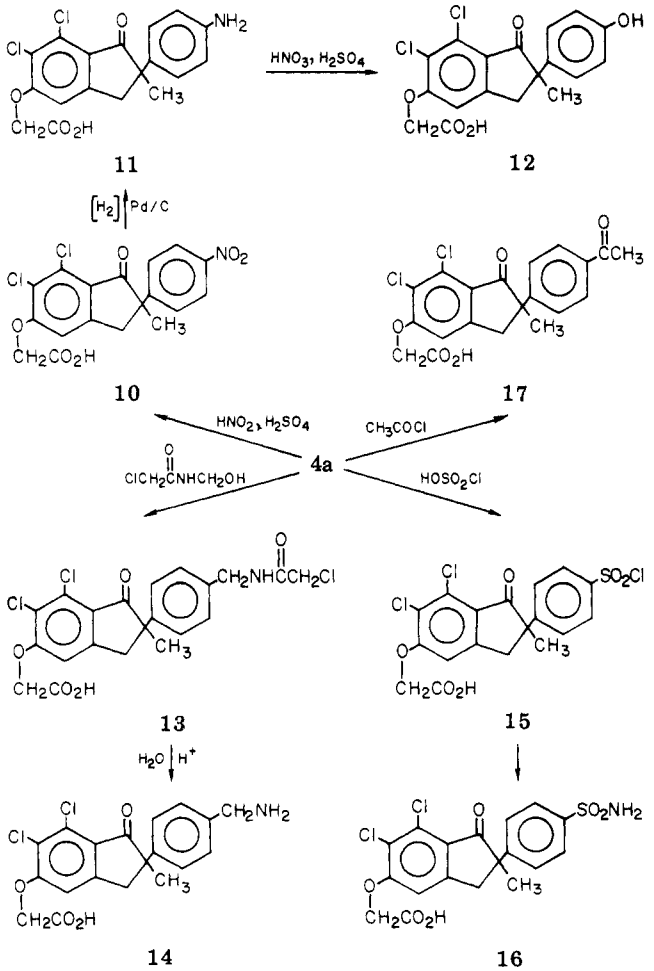
Table I



Compd	X^1	X^2	X^3	R	% yield	Recrystn solvent	Mp, °C	Emp formula	Analyses
4a	Cl	Cl	H	Me	72	AcOH	167-168	$C_{18}H_{14}Cl_2O_4$	C, H
4b	Me	Cl	H	Me	67	AcOH-H_2O	142-144	$C_{19}H_{17}ClO_4$	C, H
4c	Cl	Cl	H	Et	70	$MeNO_2$	187-189	$C_{19}H_{16}Cl_2O_4$	C, H
4d	Cl	Cl	H	c-C_5H_9	53	$MeNO_2$	184-186	$C_{22}H_{20}Cl_2O_4$	C, H
4e	Cl	Cl	H	C_6H_5	63	$MeNO_2$	251-252	$C_{23}H_{16}Cl_2O_4$	C, H
4f	Cl	Cl	H	2,3-c-C_4H_8	76	AcOH-H_2O	194-196	$C_{21}H_{18}Cl_2O_4$	C, H
4g	Cl	Cl	F	Me	38	EtOAc-hexane	165-167	$C_{18}H_{13}Cl_2FO_4$	C, H
4h	Cl	Cl	Cl	Me	51	AcOH-H_2O	141-142	$C_{18}H_{13}Cl_3O_4$	C, H, Cl
4i	Cl	Cl	Br	Me	70	AcOH-H_2O	171-172	$C_{18}H_{13}BrCl_2O_4$	C, H
4j	Cl	Cl	OMe	Me	51	$MeNO_2$	168-171	$C_{19}H_{16}Cl_2O_5$	C, H
4k	Cl	Cl	*a*	Me	48	$MeNO_2$	161-162	$C_{16}H_{12}Cl_2O_4S$	C, H
10	Cl	Cl	NO_2	Me	82	$MeNO_2$	202-205	$C_{18}H_{13}Cl_2NO_6$	C, H, N
11	Cl	Cl	NH_2	Me	19	EtOH-H_2O	235-236	$C_{18}H_{15}Cl_2NO_4$	C, H, N
12	Cl	Cl	OH	Me	76	AcOH	228-230	$C_{18}H_{14}Cl_2O_5$	C, H
14	Cl	Cl	CH_2NH_2	Me	64	EtOH-H_2O	270-271	$C_{19}H_{16}Cl_2NO_4Na$	C, H, N
16	Cl	Cl	SO_2NH_2	Me	98	AcOH	258-260	$C_{18}H_{15}Cl_2NO_6S$	C, H, N
17	Cl	Cl	COMe	Me	17	AcOH	221-224	$C_{20}H_{16}Cl_2O_5$	C, H
20	Cl	Cl	H	Me			164	$C_{18}H_{14}Cl_2O_4$	C, H
21	Cl	Cl	H	Me			164	$C_{18}H_{14}Cl_2O_4$	C, H

a 

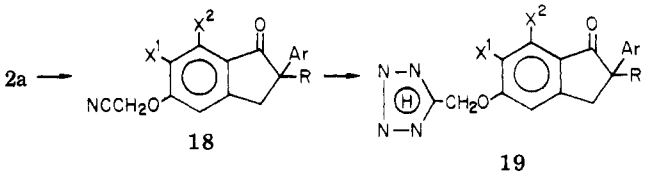
Scheme IV



acid, better yields were obtained with fewer side products.

Alkylation of the 2-arylindanones proceeded rapidly at 0 °C in the presence of sodium methoxide. Optimal results were obtained when the alkyl halide was present in excess before adding base to avoid any indene or dimer formation.

Scheme V



Various substituents were incorporated in the phenyl ring in either the alkylation or arylation procedures by varying the arylacetyl halide (e.g., *p*-fluorophenyl- and *p*-bromophenylacetyl chloride) or the aryliodonium halide [e.g., di(4-methoxyphenyl)- and di(4-chlorophenyl)-iodonium chloride].

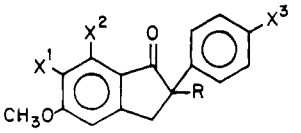
A nitro group was introduced directly in the para position of the 2-phenyl group in **4a** using 1 equiv of nitric acid–sulfuric acid to give **10**. Catalytic reduction of this compound gave the *p*-amino derivative **11**, which was diazotized with sodium nitrite in concentrated sulfuric acid and treated with H_2O–H_2SO_4 to give the *p*-hydroxy derivative **12**, the major metabolite of **4a**, in the chimpanzee,[8a] mouse and man,[8b] and monkey.[8c]

N-Hydroxymethyl-2-chloroacetamide attacked the para position of the 2-phenyl ring of **4a** in the Tserniac–Einhorn reaction[9] to give the amide **13**, which was readily hydrolyzed to the aminomethyl compound **14**. Chlorosulfonic acid similarly afforded the sulfonyl chloride **15**, which was readily converted to the sulfonamide derivative **16** in liquid ammonia. Treatment of **4a** with acetyl chloride gave the *p*-acetyl compound **17** (see Scheme IV).

To study the effect of a carboxy surrogate, the tetrazole **19** was prepared by the reaction sequence shown in Scheme V.

Resolution of **4a** was carried out by recrystallization of the chiral α-methylbenzylamine salts, giving both the (+) (**20**) and (−) (**21**) epimers.

Table II



Compd	X¹	X²	X³	R	Method[a]	% yield	Recrystn solvent	Mp, °C	Emp formula	Analyses
6a	Cl	Cl	H	H		75	C_6H_6-C_6H_{12}	193-195	$C_{16}H_{12}Cl_2O_2$	C, H
6b	Me	Cl	H	H		100	C_6H_6-hexane	160-163	$C_{17}H_{15}ClO_2$	C, H
6c	Cl	Cl	F	H		100	C_6H_6	200-202	$C_{16}H_{11}Cl_2FO_2$	C, H
6d	Cl	Cl	Cl	H		89	C_6H_6	193-195	$C_{16}H_{11}Cl_3O_2$	
6e	Cl	Cl	Br	H		94	C_6H_6-hexane	202-203	$C_{16}H_{11}BrCl_2O_2$	C, H
6f	Cl	Cl	*e*	H		92	C_6H_6-hexane	153-155	$C_{17}H_{14}Cl_2O_2$	C, H
1a	Cl	Cl	H	Me	A, B	86, 69	C_6H_6-C_6H_{12}	161-163	$C_{17}H_{14}Cl_2O_2$	C, H
1b	Me	Cl	H	Me	A	60	C_6H_6-C_6H_{12}	130-132	$C_{18}H_{17}ClO_2$	C, H
1c	Cl	Cl	H	Et	A	64	C_6H_6-hexane	139-141	$C_{18}H_{16}Cl_2O_2$	C, H
1d	Cl	Cl	H	c-C_5H_9	B	38	C_6H_{12}	105-108	$C_{21}H_{20}Cl_2O_2$	C, H
1e	Cl	Cl	H	C_6H_5	B	42	C_6H_{12}	172-174	$C_{22}H_{16}Cl_2O_2$	C, H
1f	Cl	Cl	H	2,3-c-C_4H_8	B	87		136-142	$C_{20}H_{16}Cl_2O_2$	
1g	Cl	Cl	F	Me	A, B	83, 18	C_6H_6-C_6H_{12}	181-183	$C_{17}H_{13}Cl_2FO_2$	C, H
1h	Cl	Cl	Cl	Me	A, B	89, 60	C_6H_6-C_6H_{12}	176-178	$C_{17}H_{13}Cl_3O_2$	H; C[b]
1i	Cl	Cl	Br	Me	A	66		200-203	$C_{17}H_{13}BrCl_2O_2$	C, H
1j	Cl	Cl	OMe[c]	Me	B	31	EtOH	118-121	$C_{24}H_{20}Cl_2O_3$	C, H
1k	Cl	Cl	*d*	Me	B	39	C_6H_6-hexane	145-146	$C_{15}H_{12}Cl_2O_2S$	C, H

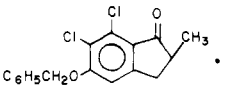
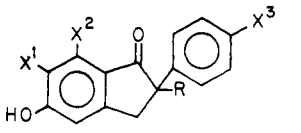
[a] Method A = alkylation; method B = arylation. [b] C: calcd, 57.41; found, 58.33. [c] The iodonium reaction was run on the benzyl ether 6f. See the Experimental Section. [d] See footnote *a*, Table I. [e] Monoalkylindanone,  .

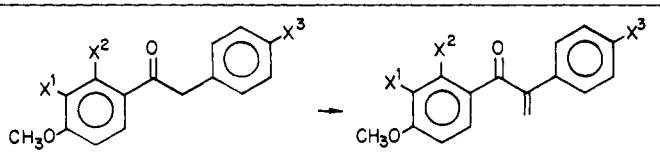
Table III



Compd	X¹	X²	X³	R	% yield	Recrystn solvent	Mp, °C	Emp formula	Analyses
2a	Cl	Cl	H	Me	98	EtOH-H_2O	194-196	$C_{16}H_{12}Cl_2O_2$	C, H
2b	Me	Cl	H	Me	96		183-186	$C_{17}H_{15}ClO_2$	C, H
2c	Cl	Cl	H	Et	92		177-179	$C_{17}H_{14}Cl_2O_2$	C, H
2d	Cl	Cl	H	c-C_5H_9	81	BuCl-$CHCl_3$	161-170	$C_{20}H_{18}Cl_2O_2$	C, H
2e	Cl	Cl	H	C_6H_5	96		207-213	$C_{21}H_{14}Cl_2O_2$	C, H
2f	Cl	Cl	H	2,3-c-C_4H_8	59	EtOH	213-215	$C_{19}H_{16}Cl_2O_2$	C, H
2g	Cl	Cl	F	Me	96	EtOH	204-207	$C_{16}H_{11}Cl_2FO_2$	C, H
2h	Cl	Cl	Cl	Me	76	EtOH-H_2O	211-213	$C_{16}H_{11}Cl_3O_2$	H; C[a]
2i	Cl	Cl	Br	Me	97	EtOH	221-223	$C_{16}H_{11}BrCl_2O_2$	C, H
2j	Cl	Cl	OMe	Me	95		149-156	$C_{17}H_{14}Cl_2O_3$	
2k	Cl	Cl	*b*	Me	96	EtOH-H_2O	224-226	$C_{14}H_{10}Cl_2O_2S$	C, H

[a] C: calcd, 56.25; found, 55.53. [b] See footnote *a*, Table I.

Table IV



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Compd	X¹	X²	X³	% yield	Recrystn solvent	Mp, °C	Emp formula	Analyses
8a	Cl	Cl	H	67	C_6H_6-C_6H_{12}	126-129	$C_{15}H_{12}Cl_2O_2$	C, H
8b	Me	Cl	H	80	C_6H_{12}-hexane	58-60	$C_{16}H_{15}ClO_2$	C, H
8c	Cl	Cl	F	63	C_6H_6-hexane	134-135	$C_{15}H_{11}Cl_2FO_2$	C, H
8d	Cl	Cl	Cl	71		156-157	$C_{15}H_{11}Cl_3O_2$	
8e	Cl	Cl	Br	98	C_6H_6-hexane	163-164	$C_{15}H_{11}BrCl_2O_2$	C, H
9a	Cl	Cl	H	99		87-89	$C_{16}H_{12}Cl_2O_2$	C, H
9b	Me	Cl	H	88		81-85	$C_{17}H_{15}ClO_2$	C, H
9c	Cl	Cl	F	80		102-104	$C_{16}H_{11}Cl_2FO_2$	C, H
9d	Cl	Cl	Cl	95		112-115	$C_{16}H_{11}Cl_3O_2$	
9e	Cl	Cl	Br	97	C_6H_6-hexane	110-116	$C_{16}H_{11}BrCl_2O_2$	C, H

Table V. Oral Activity

Compd	Rat,[a] mequiv of $Na^+ \times 100$/cage				Chimpanzee,[a] 5 mg/kg	
	3 mg/kg	9 mg/kg	27 mg/kg	81 mg/kg	μequiv of Na^+/min	$\Delta C_{urate}/C_{inulin}$
4a	86	97	129	189	409	0.38
4b	135	116	138	162	479	0.31
4c	75	115	119	134	369	0.12
4d	79	40	31	35	47	0.00
4e	40	93	109	95	19	0.03
4f	47	65	86	117	137	0.08
4g	101	86	123	173	310	0.43
4h	21	30	25	37	302	0.25
4i	21	29	27	42	27	0.01
4j	45	76	129	[b]	459	0.01
4k	46	79	141	177	416	0.47
10	89	102	168	198	176	0.03
11	33	53	98	134	244	0.10
12	17	33	35	[b]	151	0.02
14	18	17	27	19	135	0.00
16	32	29	86	[b]	674	0.00
17	49	62	81	163	608	0.08
19	28	17	20	40	44	0.09
20	77	38	71	88	221	0.16
21	101	121	179	271	743	0.28
Furosemide	[b]	7	125	244	1035	−0.02
Hydrochlorothiazide	123	112	131	128	144	−0.02
Probenecid		[b]				0.05
Placebo	8					

[a] For testing methodology, see ref 1a. [b] Where no data were recorded, that compound was not evaluated in the rat at that dose.

Structure–Activity Relationships. A. Saluresis–Diuresis. 1. General Discussion. The excretion of urine, Na^+, K^+, and Cl^- was measured in the experiments conducted in rats, dogs, and chimpanzees, but for brevity, only the Na^+ excretion is reported here. The excretion of Cl^- and urine generally paralleled the Na^+; thus, either of these could have been used for relative potency comparisons.

a. Rat Data. The oral natriuretic activity of the (2-alkyl-2-arylindanyloxy)acetic acids at four different doses is provided in Table V. Using the 2-methyl-2-phenylindanone **4a** as the standard for comparison of all the other aryl-substituted derivatives, some trends are observed. As the 2-alkyl substituent increases in size from methyl (**4a**) to ethyl (**4c**) and then to cyclopentyl (**4d**), the activity drops considerably. The 2,2-diphenyl- (**4e**) and 2-phenylhexahydrofluorenone (**4f**) exhibit only very weak activity. Varying the substituent at the 6 position from Cl (**4a**) to Me (**4b**) does not affect natriuretic activity. The 2-thienyl-2-methyl compound **4k** was equipotent with **4a**. Substituents in the para position of the 2-phenyl ring have a marked effect on the natriuretic response in rats. Although the *p*-F compound **4g** shows good natriuresis, the corresponding *p*-Cl (**4h**) and *p*-Br (**4i**) analogues have only very weak activity. The *p*-OH derivative **12**, the major metabolite of **4a** in primates, exhibits very little natriuresis in the rat. The *p*-methoxy compound **4j** has modest natriuretic activity. The activity increases as the para substituent changes from NH_2 (**11**) < COMe (**17**) < NO_2 (**10**). Resolution of **4a** produced enantiomers with a marked difference in potency, the (−) isomer **21** showing three times more natriuretic activity than the (+) isomer **20**.

It can be seen that many of the (2-alkyl-2-arylindanyloxy)acetic acids have a higher natriuretic ceiling than hydrochlorothiazide. Also, some of the compounds (when studied at a maximal dose of 81 mg/kg) have a ceiling effect as high or higher than furosemide. In addition, many of the compounds are more potent than furosemide (i.e., are effective at lower doses). The tetrazole analogue **19** was considerably less active than its carboxyl counterpart.

b. Chimpanzee Data (Table V). Since these data are generally from single experiments, it is inappropriate to assign relative potency data from this information. Suffice it to say that the S/A relationships correlate well with those observed in rats.

c. Dog Data (Table VI). The compounds that exhibited good saluresis and diuresis in rats and chimpanzees also gave a significant response in dogs after iv administration. Of special interest is the metabolite **12** which gives a marked saluretic response in dogs in contradistinction to rats and chimpanzees where only a moderate response was observed. **4a** is excreted appreciably unchanged by dogs.[8c] Most of the (indanyloxy)acetic acids were more active than hydrochlorothiazide and as active as furosemide at 1 mg/kg.

B. Uricosuria. In contrast to the (acryloylaryloxy)-acetic acid diuretics, none of the indanyloxyacetic acids were uric acid retaining in chimpanzees and some were more uricosuric than probenecid. Quantitative S/A judgments from single oral experiments cannot be made, but some general correlations are observed. Certain para substituents on the 2-phenyl ring such as OMe (**4j**), SO_2NH_2 (**16**), and COMe (**17**) which impart significant saluretic activity are almost devoid of uricosuric activity. **4a** is not only an excellent saluretic agent but also produces a greater uricosuric response than probenecid. Compounds **4b**, **4g**, and **4k**, which exhibit a ceiling saliuretic response comparable to **4a**, also give a significant uricosuric response. The enantiomers of **4a** exhibit relative uricosuric activity roughly parallel to that observed for the saluretic responses, i.e., the (−) isomer **21** is more active than the (+) isomer **20**. Suffice it to say that the S/A relationships for saluretic activity are not the same as that for uricosuric activity. However, some compounds (**4a,b,g,h** and **21**) possess structural features which manifest maximal response in both pharmacodynamic parameters.

An in-depth pharmacological study of **4a** in chimpanzees has been reported by Fanelli et al.[10] This compound has been evaluated orally in man and found to be diuretic.

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

Compd	No. of expt av	Control/drug treatment results: mequiv/min Na^+	K^+	Cl^-	Urine vol, mL/mL
4a	3	107/920	11/62	62/1010	2/8
4b	2	16/226	9/25	9/262	2/4
4c	2	85/431	4/23	6/396	2/4
4d	1	5/11	4/34	1/0.9	0.3/0.8
4e	2	32/44	5/14	2/5	0.7/2
4f	2	10/276	6/18	0.1/211	0.8/4
4g	2	20/352	12/34	8/362	1/3
4h	2	12/305	6/43	4/282	1/6
4i	2	40/96	4/14	12/34	2/3
4j	*b*				
4k	2	28/503	5/33	14/598	2/5
10	2	33/751	4/58	2/810	1/8
11	2	33/1128	8/60	12/1176	1/10
12	2	85/1264	12/64	23/1462	2/10
14	1	82/497	6/24	23/424	2/5
16	*b*				
17	*b*				
19	1	77/279	5/30	12/245	2/3
20	1	5/221	6/41	5/304	2/4
21	1	12/314	5/33	0.4/360	0.8/4
Furosemide[c]	2	29/960	18/141	1/1081	1/3
Hydrochlorothiazide	3	12/166	15/33	5/156	1/3

[a] For testing methodology, see ref 1a. [b] Where no data were recorded, that compound was not evaluated in the dog. [c] 1 mg/kg.

saluretic, uricosuric, and antihypertensive.[11,12]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Where analyses are indicated 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.

(6,7-Dichloro-2-methyl-1-oxo-2-phenyl-5-indanyloxy)acetic Acid (4a). Step A. 2,3-Dichloro-5-phenylacetylanisole (8a). $AlCl_3$ (47 g, 0.35 mol) was added portionwise to a stirred mixture of 2,3-dichloroanisole (62 g, 0.35 mol), phenylacetyl chloride (54 g, 0.35 mol), and CS_2 (250 mL) with cooling at 0–5 °C. The reaction mixture was left to stand at 25 °C for 17 h, the CS_2 removed by distillation, and the residue treated with ice–H_2O and 12 N HCl (50 mL) to give **8a**. Compounds **8b–e** were prepared in a similar manner.

Step B. 2,3-Dichloro-4-(2-phenylacryloyl)anisole (9a). Ac_2O (50 mL) was added dropwise to a stirred suspension of **8a** (29.5 g, 0.01 mol) in *N,N,N',N'*-tetramethylmethanediamine (50 mL) under N_2 with cooling to maintain the reaction mixture temperature below 40 °C. After stirring at 25 °C for 1 h, the solution was added to crushed ice–H_2O (1 L) to precipitate **9a**. Compounds **9b–e** were prepared in a similar manner.

Step C. 6,7-Dichloro-5-methoxy-2-phenyl-1-indanone (6a). **9a** (160 g, 0.52 mol) dissolved in CH_2Cl_2 (4 L) was added dropwise to a mixture of 36 N H_2SO_4 (2 L)–CH_2Cl_2 (2 L) at 5 °C over 3 h. The reaction mixture was stirred for an additional 0.5 h and then added slowly to crushed ice. The organic layer was separated, washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated under reduced pressure to give **6a**. Compounds **6b–e** were prepared in a similar manner.

Step D. 6,7-Dichloro-5-methoxy-2-methyl-2-phenyl-1-indanone (1a). Method A. NaOMe (13.5 g, 0.25 mol) was added portionwise over a 0.75-h period to a stirred solution of **6a** (59.84 g, 0.165 mol) and MeI (103 mL, 1.65 mol) in a mixture of sieve-dried DMF (700 mL)–sieve-dried C_6H_6 (700 mL) under N_2 with cooling at 5–10 °C. After stirring for 0.5 h at 5–10 °C, the mixture was added to H_2O (4 L) and extracted with C_6H_6, and the organic layer was separated, dried ($MgSO_4$), and concentrated to give **1a**. Compounds **1b,c,g–i** were prepared in a similar manner.

Step E. 6,7-Dichloro-5-hydroxy-2-methyl-2-phenyl-1-indanone (2a). **1a** (66.4 g, 0.21 mol) was added to fused pyridine hydrochloride at 175 °C with stirring and heating continued for 1 h. The mixture was added to H_2O (2 L) with vigorous stirring to precipitate **2a**. Compounds **2b–i,k** were prepared in a similar manner.

Step F. (6,7-Dichloro-2-methyl-1-oxo-2-phenyl-5-indanyloxy)acetic Acid (4a). $BrCH_2CO_2Et$ (68.4 g, 0.408 mol) was added to a stirred mixture of **2a** (62.6 g, 0.204 mol), K_2CO_3 (56.5 g, 0.408 mol), and DMF (600 mL) at 55–60 °C. Stirring was continued for 2 h, then H_2O (600 mL)–10 N NaOH (60 mL) was added, and heating at 100 °C was continued for 1 h. The solution was added slowly to crushed ice–H_2O (4 L)–12 N HCl (100 mL) to precipitate **4a**. Compounds **4b–k** were prepared in a similar manner.

6,7-Dichloro-5-methoxy-2-methyl-2-(2-thienyl)-1-indanone (1k). Method B. KO-*t*-Bu (5.06 g, 0.045 mol) dissolved in *t*-BuOH (100 mL) was added to a refluxing solution of 6,7-dichloro-5-methoxy-2-methyl-1-indanone (7.35 g, 0.03 mol) in *t*-BuOH (150 mL)–C_6H_6 (150 mL), refluxing was continued for 3 h under N_2, then the mixture was cooled slightly, and solid dithienyliodonium chloride[6] (16.5 g, 0.05 mol) was added in one portion. Heating at reflux was continued for 2 h, the mixture cooled, H_2O (100 mL) added, and the mixture concentrated to remove the organic solvents. The semisolid residue was extracted with Et_2O, dried ($MgSO_4$), and concentrated in vacuo to give **1k**. Compounds **1a–f,h,i** were prepared in a similar manner.

[6,7-Dichloro-2-(4-methoxyphenyl)-2-methyl-1-oxo-5-indanyloxy]acetic Acid (4j). Step A. 5-Benzyloxy-6,7-dichloro-2-methyl-1-indanone (6f). A stirred mixture of 5-hydroxy-6,7-dichloro-2-methyl-1-indanone (27.6 g, 0.12 mol), K_2CO_3 (24.9 g, 0.18 mol), and benzyl bromide (21.4 mL, 0.18 mol) in DMF (100 mL) was warmed at 55–60 °C for 2 h and then poured into H_2O (1 L) to precipitate **6f**.

Step B. 5-Benzyloxy-6,7-dichloro-2-(4-methoxyphenyl)-2-methyl-1-indanone (1j). KO-*t*-Bu (8.42 g, 0.075 mol) dissolved in *t*-BuOH (450 mL) was added to a refluxing solution of **6f** (16.1 g, 0.05 mol) in *t*-BuOH (150 mL)–C_6H_6 (600 mL), refluxing was continued for 2.5 h, then 4,4'-dimethoxydiphenyliodonium chloride (37.66 g, 0.10 mol) was added, and refluxing was continued for 3 h. The reaction mixture was cooled to 25 °C, 500 mL of H_2O added, and the mixture concentrated in vacuo to give a brown oil which was extracted with Et_2O, dried ($MgSO_4$), and chromatographed on silica gel with $CHCl_3$ to give **1j**.

Step C. 6,7-Dichloro-5-hydroxy-2-(4-methoxyphenyl)-2-methyl-1-indanone (2j). **1j** (3.44 g, 0.008 mol) was catalytically hydrogenated in EtOH (300 mL) with 5% Pd/C (500 mg) in a Parr apparatus at 25 °C for 4 h. The reaction mixture was filtered and concentrated in vacuo to give **2j**.

Step D. [6,7-Dichloro-2-(4-methoxyphenyl)-2-methyl-1-oxo-5-indanyloxy]acetic Acid (4j). A stirred mixture of **2j** (2.6 g, 0.0077 mol), K_2CO_3 (2.14 g, 0.0154 mol), and $BrCH_2CO_2Et$ (2.58 g, 0.0154 mol) in DMF (60 mL) was warmed at 55–60 °C for 2.5 h, then treated with H_2O (60 mL)–10 N NaOH (3 mL, 0.03 mol), and heated at 100 °C for 1 h. The reaction mixture was added slowly to crushed ice–H_2O (600 mL)–12 N HCl (20 mL) to precipitate **4j**.

[6,7-Dichloro-2-(4-hydroxyphenyl)-2-methyl-1-oxo-5-indanyloxy]acetic Acid (12). A stirred mixture of **4j** (1.80 g, 0.0046 mol), 48% HBr (50 mL), and AcOH (50 mL) was heated at reflux for 1 h and then poured into crushed ice–H_2O (800 mL) to precipitate **12**.

[6,7-Dichloro-2-methyl-2-(4-nitrophenyl)-1-oxo-5-indanyloxy]acetic Acid (10). HNO_3 (16 N) (2.6 mL, 0.04 mol) in 36 N H_2SO_4 (4 mL) was added dropwise to a cold solution of **4a** (14.60 g, 0.04 mol) in 36 N H_2SO_4 (60 mL) with stirring in an ice bath. The reaction mixture was stirred in an ice bath for 2 h and then poured into crushed ice–H_2O (800 mL) to precipitate the solvated product which on trituration with hot BuCl (400 mL) gave **10**.

[2-(4-Aminophenyl)-6,7-dichloro-2-methyl-1-oxo-5-indanyloxy]acetic Acid (11). A suspension of **10** (6.11 g, 0.015 mol) in EtOH (250 mL)–36 N H_2SO_4 (2 mL) was hydrogenated in a Parr apparatus with 5% Pd/C for 1 h. The reaction mixture was filtered to remove the catalyst, and the yellow filtrate was concentrated to ~50 mL and added to crushed ice–H_2O (300 mL) with stirring to precipitate the ethyl ester of **11** which was hydrolyzed by refluxing in EtOH (200 mL), 10 N NaOH (4.5 mL, 0.045 mol), and H_2O (100 mL) for 1.5 h. On cooling and concentrating in vacuo to one-third its volume and neutralizing with 6 N HCl, **11** precipitated.

[6,7-Dichloro-2-(4-hydroxyphenyl)-2-methyl-1-oxo-5-indanyloxy]acetic Acid (12). Nitrosylsulfuric acid (1 N), prepared by adding solid $NaNO_2$ (5.83 g, 0.084 mol) portionwise to 36 N H_2SO_4 (85 mL) in an ice bath, was added dropwise to a stirred solution of the ethyl ester of **11** (11.11 g, 0.024 mol) in 36 N H_2SO_4 (60 mL) over 0.5 h. The reaction mixture was stirred at 25 °C for 18 h, poured into crushed ice–H_2O (1 L), and treated with solid urea to remove excess nitronium ion (KI–starch paper indicator). The diazonium solution was added in a slow stream to refluxing 36 N H_2SO_4 (30 mL)–H_2O (30 mL) and Na_2SO_4 (2 g) over 1 h. The mixture was stirred at reflux for 2.5 h and then cooled at 25 °C to precipitate **12**.

[2-(4-Aminomethylphenyl)-6,7-dichloro-2-methyl-1-oxo-5-indanyloxy]acetic Acid Sodium Salt (14). Step A. [4-(2-Chloroacetamidomethyl)phenyl-6,7-dichloro-2-methyl-1-oxo-5-indanyloxy]acetic Acid (13). Well-pulverized *N*-hydroxymethyl-2-chloroacetamide (3.37 g, 0.0274 mol) was added portionwise to **4a** (10.0 g, 0.0274 mol) in 36 N H_2SO_4 (100 mL) and AcOH (100 mL) with stirring at 40–50 °C over 0.5 h. Additional *N*-hydroxymethyl-2-chloroacetamide (1.68 g, 0.014 mol) was added over a 4-h period until no starting material remained. After stirring at 25 °C for 16 h, the reaction mixture was added to crushed ice–H_2O (2 L) to precipitate 11.9 g of **13** which melted at 138–141 °C and was used in the next step without purification.

Step B. [2-(4-Aminomethylphenyl)-6,7-dichloro-2-methyl-1-oxo-5-indanyloxy]acetic Acid Sodium Salt (14). **13** (2.0 g, 0.004 mol), EtOH (20 mL), and 12 N HCl (7 mL) were combined and heated at reflux for 3 h. On cooling to 5 °C, 1.14 g of the ethyl ester of **14** precipitated (mp 211–213 °C) (EtOH). The ester (1.57 g, 0.0034 mol), $NaHCO_3$ (1.15 g, 0.0136 mol), EtOH (50 mL), and H_2O (50 mL) were combined and heated at reflux for 1.5 h, leaving a solution which was filtered and then neutralized with 1 N HCl (10.26 mL, 0.01026 mol) to precipitate **14**.

[6,7-Dichloro-2-methyl-1-oxo-2-(4-sulfamoylphenyl)-5-indanyloxy]acetic Acid (16). Step A. [2-(4-Chlorosulfonylphenyl)-6,7-dichloro-2-methyl-1-oxo-5-indanyloxy]acetic Acid (15). **4a** (0.50 g, 0.0014 mol) was added portionwise with stirring to $ClSO_3H$ (5 mL) in an ice bath. The reaction mixture was stirred at 0 °C for 2 h, left to come to ambient temperature for 2 h, and then slowly added to crushed ice to precipitate 0.51 g of **15**, which melted at 209–210 °C after crystallization from AcOH–H_2O (3:2). Anal ($C_{18}H_{13}Cl_3O_4S$) C, H, Cl.

Step B. [6,7-Dichloro-2-methyl-1-oxo-2-(4-sulfamoylphenyl)-5-indanyloxy]acetic Acid (16). **15** (2.0 g, 0.0043 mol) was added portionwise to liquid NH_3 with stirring. The NH_3 was left to evaporate (3 h). The residue was dissolved in H_2O (400 mL), filtered, and acidified with 12 N HCl to precipitate **16**.

[2-(4-Acetylphenyl)-6,7-dichloro-2-methyl-1-oxo-5-indanyloxy]acetic Acid (17). A mixture of **4a** (10.95 g, 0.03 mol) and CH_3COCl (10.0 mL, 0.15 mol) was treated portionwise with $AlCl_3$ (20.0 g, 0.15 mol) at 25 °C with vigorous bubbling. Additional CH_3COCl (5 mL) was added, and the mixture was heated at 60 °C for 0.5 h at which point the mixture solidified. The solid mass was added to ice–H_2O–HCl to precipitate a gummy solid which on extraction with Et_2O, filtration, and concentration gave **17**.

5-(6,7-Dichloro-2-methyl-1-oxo-2-phenyl-5-indanyloxymethyl)tetrazole (19). Step A. 6,7-Dichloro-2-methyl-1-oxo-2-phenyl-5-indanyloxyacetonitrile (18). **2a** (4.61 g, 0.15 mol), $ClCH_2CN$ (1.13 g, 0.015 mol), K_2CO_3 (2.08 g, 0.015 mol), KI (0.025 g, 0.0015 mol), and acetone (75 mL) were heated at reflux for 23 h. The reaction mixture was cooled to 25 °C and concentrated to dryness in vacuo to give an oily residue which on trituration with H_2O gave 5.12 g of **18**, which melted at 163–165 °C on crystallization from C_6H_{12}–C_6H_6 (5:1). Anal. ($C_{18}H_{13}Cl_2NO_2$) C, H, N.

Step B. 5-(6,7-Dichloro-2-methyl-1-oxo-2-phenyl-5-indanyloxymethyl)tetrazole (19). **18** (4.87 g, 0.014 mol), NaN_3 (1.09 g, 0.0168 mol), NH_4Cl (0.90 g, 0.0168 mol), and DMF (30 mL) were heated at 80 °C for 2.5 h. The reaction mixture was poured into H_2O (500 mL), and the solution was filtered and acidified with 6 N HCl to precipitate **19** from EtOH.

Resolution of the Optical Isomers of 4a. (+) Isomer 20. A mixture of racemic **4a** (26 g, 0.071 mol) and L-(−)-α-methylbenzylamine (8.6 g, 0.071 mol) was dissolved in hot MeCN (250 mL) and aged at 25 °C for 18 h. The MeCN was decanted from the resultant salt (13.2 g) which was thrice recrystallized from a minimum volume of *i*-PrOH, affording 1.9 g of the salt of the pure (+) enantiomer which was converted to the acid by treatment of the salt with dilute HCl–Et_2O. The Et_2O phase was washed with H_2O and dried ($MgSO_4$), and the Et_2O was distilled at reduced pressure. The (+) isomer melted at 164 °C after crystallization from toluene: $[\alpha]^{25}_D$ +90° (*c* 2, acetone); 99 ± 1% optically pure.[13]

(−) Isomer 21. By following substantially the procedure described for the (+) isomer, using as the reactants partially resolved **4a** (15.5 g, 0.042 mol) [obtained from the MeCN mother liquor of the (+) isomer] and D-(+)-α-methylbenzylamine (5.15 g, 0.042 mol), in MeCN (150 mL) and thrice recrystallizing the resultant salt from a minimum volume of *i*-PrOH, there was obtained 2.2 g of the salt of the pure (−) enantiomer. The (−) isomer melts at 164 °C after crystallization from toluene: $[\alpha]^{25}_D$ −90° (*c* 2, acetone); 99 ± 1% optically pure.[13]

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15,15-Ketals of Natural Prostaglandins and Prostaglandin Analogues. Synthesis and Biological Activities[1]

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The synthesis is described of new 15,15-ethylene ketals of natural prostaglandins and prostaglandin analogues. Especially the crystalline trisamine salt of the 15,15-ethylene ketal of 15-dehydro-16-phenoxy-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ is a very active inducer of luteolysis in laboratory animals and cattle.

For the biological activity of natural prostaglandins, the presence of a 15α-hydroxy group is essential, whereas the corresponding 15β-hydroxy compounds, e.g., 15β-hydroxyprostaglandin E_1, show drastically diminished biological activities.[2]

However, in certain analogues, e.g., 15-methyl- or 16-phenoxy-ω-tetranorprostaglandins, the 15β-hydroxy epimers are themselves often biologically active.[3,4]

Since the 15-methyl ether of $PFG_{2\alpha}$ methyl ester shows a two to three times stronger abortifacient activity in the pregnant hamster than $PGF_{2\alpha}$ methyl ester,[5] the presence of a free 15-hydroxy group is apparently not essential for the biological activity in vivo.

It seemed therefore logical to us that the combination of (a) the sometimes considerable biological activity of 15β-hydroxy compounds with (b) the biological activity of 15-methyl ethers would lead to the conclusion that the prostaglandin 15-ketals, e.g., 15,15-ethylenedioxy- or 15,15-dimethoxyprostaglandins, might also possess interesting biological properties. In all conformations of these new analogues, at least one ketal oxygen would always be available for the interaction with the receptor molecules.

It should be noted here that the active form of 15-keto prostaglandins like 15-keto prostaglandin $F_{2\alpha}$, which is formed during metabolism, might act in the hydrated form (15,15-dihydroxyprostaglandins) since they still cause pronounced contractions of the smooth muscles of the guinea-pig ileum as well as of the gerbil colon.[6]

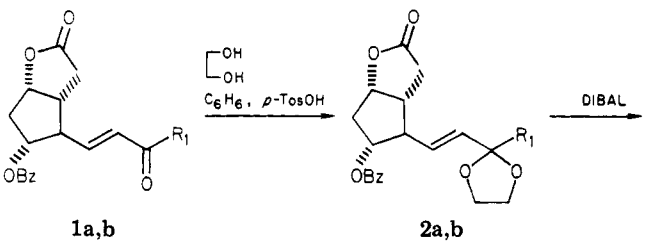
We have therefore synthesized a series of 15-ketals of natural prostaglandins and prostaglandin analogues which are readily available by ketalization of the unsaturated keto lactones (compare Scheme I). The chiral center at C-15 in natural PG's is thereby eliminated, resulting in a simplification of the Corey synthetic scheme[7] (Scheme I).

Chemistry. Starting from unsaturated ketones **1**[8,9] (Scheme I) standard ketalization with ethylene glycol in benzene in the presence of *p*-toluenesulfonic acid gave the ketals **2** in good yields. Reduction of the lactones and simultaneous removal of the benzoate with diisobutylaluminum hydride (DIBAL) afforded the lactols **3** which were transformed by Wittig reaction to the 15-deoxy-15,15-ethylenedioxyprostaglandins **4**. Esterification with diazomethane and butyl bromide–silver oxide yielded the methyl esters **5** and the butyl esters **6**. Treatment of **4** with *p*-phenylphenacyl bromide in the presence of triethylamine afforded the esters **7**.[10]

The free acid **4b** afforded on neutralization with tris(hydroxymethyl)aminomethane the crystalline tris salt **8b**.

In an analogous way, starting from known 15-ketones, other new 15,15-ethylene ketals in Table II, e.g., substituted 16-phenoxy- and 15- or 17-arylprostaglandin analogues, were synthesized, and the structure of the inter-

Scheme I

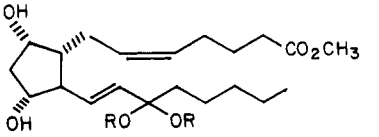


1a,b **2a,b** **3a,b**

4a,b, R_2 = H
5a,b, R_2 = CH_3
6a,b, R_2 = *n*-C_4H_9
7a,b, R_2 = CH_2CO-C_6H_4-C_6H_5
8b, R_2 = $H_3N^+C(CH_2OH)_3$

a, R_1 = *n*-C_5H_{11}
b, R_1 = $-CH_2OC_6H_5$

Chart I



9, R,R = $-CH_2CH_2CH_2-$
10, R,R = $-CH_2C(CH_3)_2CH_2-$
11, R = $-CH_3$

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