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(Vinylaryloxy)acetic Acids. A New Class of Diuretic Agents. 3.[2,3] [(2-Nitro-1-alkenyl)aryloxy]acetic Acids

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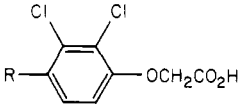
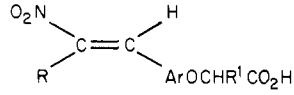
A series of [(2-nitro-1-alkenyl)aryloxy]acetic acids was synthesized and tested in dogs for saluretic and diuretic activity. A number of these compounds exhibit a high order of activity on iv or po administration; representative of these is (*E*)-[2,3-dichloro-4-(2-nitropropenyl)phenoxy]acetic acid (**5**). The most highly active compounds are qualitatively similar in action to [2,3-dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid (ethacrynic acid) in causing a prompt increase in the excretion of water and of sodium and chloride ions in approximately equimolar amounts but are three to five times as potent. Potassium ion excretion is increased but less markedly than sodium excretion.

Earlier papers in this series have demonstrated that the 2-methylenebutyryl group of ethacrynic acid[1] (**1**), [2,3-dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid, can be replaced by diacylvinyl (as in **2**)[2] or acylvinyl (as in **3**)[3] to give potent diuretic–saluretic agents which further resemble **1** in their saluretic and diuretic profile.

This paper describes the synthesis and renotropic properties of a related series of [(2-nitro-1-alkenyl)-phenoxy]acetic acids of general structure I which like the aforementioned compounds incorporate a double bond activated toward nucleophilic attack, in this case by a conjugated nitro group.





I

1, R = C_2H_5CCO- (CH_2)

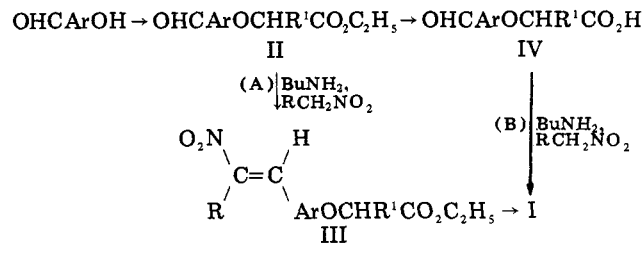
2, R = CH_3CO / CH_3CO >C=CH-

3, R = $CH_3COCH=CH-$

Chemistry. The [(2-nitro-1-alkenyl)aryloxy]acetic acids prepared for this study are listed in Table I. The key step in their preparation was a modified Knoevenagel reaction[4] in which an aromatic aldehyde was made to react with butylamine to produce a Schiff base which then reacted with a nitroalkane, presumably in an addition–elimination sequence, to yield the nitroalkene. In method A-1 (see Scheme I), an ethyl formylaryloxyacetate (II) was condensed with a nitroalkane in this manner to yield an ethyl (2-nitro-1-alkenyl)aryloxyacetate (III) which was isolated, purified, and hydrolyzed in acid to the product I (see Table III). In the "one-pot" method A-2, the isolation and purification of the intermediate III were eliminated. In method B, formylaryloxyacetic acid (IV) was condensed with a nitroalkane in the modified Knoevenagel reaction to yield I.

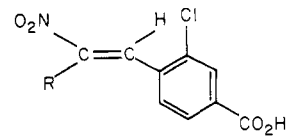
Only one of the two possible geometric isomers of nitroalkenes I and III was isolated in each of the condensation reactions. The disubstituted olefinic products (I, R = H), **10**, **14**, **20**, and **25** may be assigned the trans (*E*) configuration on steric grounds and because of the magnitude of coupling constants (J = 14 Hz) of the vinyl protons of **10** and **25**. Interestingly, the vinyl protons of **14** and **20** are magnetically equivalent giving rise to sharp singlets at δ 8.10 and 8.18, respectively.

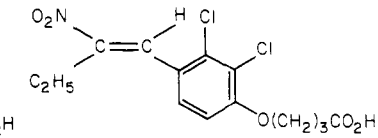
Scheme I



The trisubstituted olefinic products (I, R = alkyl) may tentatively be assigned the *E* configuration (vinyl H cis to NO_2) on the following basis. The chemical shifts of the vinyl protons β to the nitro group in the disubstituted olefins lie in the range δ 7.99–8.18. The shifts of the corresponding protons in the trisubstituted olefins lie in the same downfield range: δ 8.01–8.12. The reasonable assumption is that these protons likewise are located cis to the nitro group.

Two benzoic acid derivatives (**34** and **35**) and a 4-phenoxybutyric acid derivative (**37**) were prepared to determine the effect on biological activity of shortening and lengthening the carboxylic acid chain. Acids **34** and **35** were prepared from 3-chloro-4-formylbenzoic acid (**33**) and **37** from 4-(2,3-dichloro-4-formylphenoxy)butyric acid (**36**) by method B. For the preparation of **33** and **36**, see the Experimental Section.



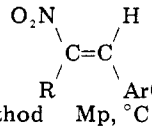


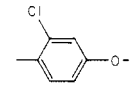
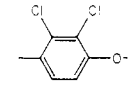
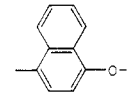
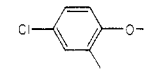
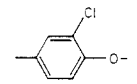
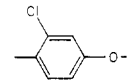
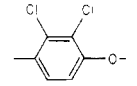
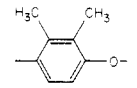
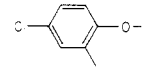
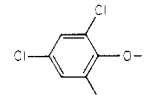
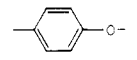
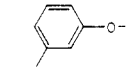
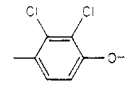
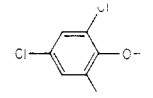
34, R = CH_3
35, R = C_2H_5

37

Saluretic–Diuretic Effects and Structure–Activity Relationships. Compounds **4**–**26**, **34**, **35**, and **37** were

Table I. 2-Nitro-1-alkenylaryloxyacetic Acids (I)

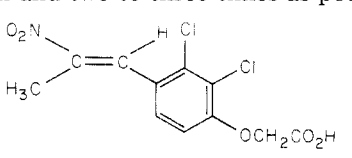


No.	-ArO-	R	R′	Method	Mp, °C	Recrystn solvent	Yield, %	Formula[a]
4		CH_3	H	A-1	145-146	Benzene	56[b]	$C_{11}H_{10}ClNO_5$
5		CH_3	H	A-1	171-173	HOAc-H_2O	73[b]	$C_{11}H_9Cl_2NO_5$
6		C_2H_5	H	A-1	135-136	HOAc-H_2O	51[b]	$C_{12}H_{11}Cl_2NO_5$
7		CH_3	H	A-1	190-191	HOAc	62[b]	$C_{15}H_{13}NO_5$
8		C_2H_5	H	A-1	182-183	HOAc	71[b]	$C_{16}H_{15}NO_5$
9		CH_3	H	A-1	161-163	EtOH-H_2O	67[b]	$C_{11}H_{10}ClNO_5$
10[c]		H	H	A-2	176-177	HOAc-H_2O	19[d]	$C_{10}H_8ClNO_5$
11		CH_3	H	A-2	146-147	Benzene	31[d]	$C_{11}H_{10}ClNO_5$
12		C_2H_5	H	A-2	145-146	HOAc-H_2O	22[d]	$C_{12}H_{12}ClNO_5$
13		C_2H_5	H	A-2	109-110	HOAc-H_2O	15[d]	$C_{12}H_{12}ClNO_5$
14		H	H	A-2	205-206	HOAc-H_2O	31[d]	$C_{10}H_7Cl_2NO_5$
15		C_2H_5	CH_3	A-2	138-139	Hexane-benzene	48[d]	$C_{13}H_{13}Cl_2NO_5$
16		CH_3	CH_3	A-2	144-145	Hexane-benzene	45[d]	$C_{12}H_{11}Cl_2NO_5$
17		C_2H_5	H	A-2	138-139	HOAc-H_2O	65[d]	$C_{14}H_{17}NO_5$[e]
18		C_2H_5	H	A-2	120-121	Benzene	50[d]	$C_{12}H_{12}ClNO_5$
19		C_2H_5	H	A-2	136-137	HOAc-H_2O	5[d]	$C_{12}H_{11}Cl_2NO_5$
20[f]		H	H	B	195-196[g]	EtOH-H_2O	67[h]	$C_{10}H_9NO_5$
21[f]		CH_3	H	B	150-152[i]	EtOH-H_2O	53[h]	$C_{11}H_{11}NO_5$
22		C_2H_5	H	B	114-115	Cyclohexane-benzene	31[h]	$C_{12}H_{13}NO_5$[j]
23		n-C_4H_9	H	B	138-139	Methylcyclohexane	17[h]	$C_{14}H_{15}Cl_2NO_5$
24		n-C_5H_{11}	H	B	132-133	BuCl	10[h]	$C_{15}H_{17}Cl_2NO_5$
25		H	H	B	152-153	EtOH-H_2O	11[h]	$C_{10}H_7Cl_2NO_5$
26		CH_3	H	B	113-114	Hexane-benzene	10[h]	$C_{11}H_9Cl_2NO_5$

[a] All compounds were analyzed for C, H, and N. Except where noted, the results obtained were within 0.4% of the calculated values. [b] Yield from purified nitroalkenyl ester III. [c] NMR δ 4.90 (2 H, s, OCH_2), 7.10 (1 H, d, J = 9 Hz, phenyl H^6), 7.75 (1 H, d of d, J = 9 and 2 Hz, phenyl H^5), 8.01 (1 H, d, J = 2 Hz, phenyl H^3), 7.99 (1 H, d, J = 14 Hz, vinyl H), 8.19 (1 H, d, J = 14 Hz, vinyl H). [d] Overall yield from formyl ester II. [e] C: calcd, 60.20; found, 60.67. [f] Reference 4. [g] Lit. mp 195-196°. [h] Yield from formyl acid IV. [i] Lit. mp 150-152°. [j] C: calcd, 57.37; found, 57.85.

tested in dogs for their saluretic and diuretic properties. Results obtained on iv administration are presented in Table III. Test results obtained on oral administration of selected compounds are given in Table IV.

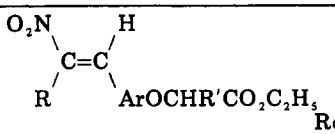
Many of the [(2-nitro-1-alkenyl)aryloxy]acetic acids are potent saluretic and diuretic agents iv and po. The activity of these compounds is qualitatively similar to that of ethacrynic acid (1)[1b] in causing a prompt increase in the excretion of urine and of sodium and chloride ions in approximately equivalent amounts. Potassium ion excretion is also increased but less markedly than sodium excretion. The most highly active compounds (5, 7, 8, 12, and 17) produce peak effects on electrolyte and water excretion that are comparable to those of 1; these compounds are approximately five times as potent as 1 on iv administration and two to three times as potent po.

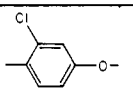
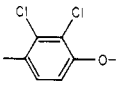
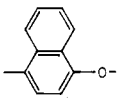
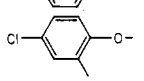


5

Structure–activity relationships in this series roughly parallel those in the previously described series of diacylvinyl-[2] and 3-oxo-1-alkenylaryloxyacetic acids.[3] These relationships can be discerned by examining the effects of structural changes on the iv saluretic action of the highly active compound 5. Activity is highly dependent on the extent and nature of ring substitution; it is retained upon

Table II. Ethyl 2-Nitro-1-alkenylaryloxyacetates (III)



No.	-ArO-	R	R'	Mp, °C	Recrystn solvent	Yield, %	Formula[a]
27		CH_3	H	94-96	EtOH	75	$C_{13}H_{14}ClNO_5$
28		CH_3	H	88-89	EtOH-H_2O	57	$C_{13}H_{13}Cl_2NO_5$
29		C_2H_5	H	109-113	EtOH-H_2O	93	$C_{14}H_{15}Cl_2NO_5$
30		CH_3	H	148-150	EtOH	91	$C_{17}H_{17}NO_5$
31		C_2H_5	H	117-118	EtOH	58	$C_{18}H_{19}NO_5$
32		CH_3	H	66-68	EtOH	85	$C_{13}H_{14}ClNO_5$

[a] All compounds were analyzed for C and H. The results obtained were within 0.4% of the calculated values.

Table III. 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
4	1	6/683	14/92	4/765	3/7
5	1	15/2128	47/104	12/2163	1/11
6	1	29/1174	45/89	70/1295	1/10
7	1	14/1612	14/128	4/1659	3/15
8	1	54/1848	12/179	4/2036	4/13
9	1	3/22	12/17	1/7	2/2
10	10	24/201	32/65	5/146	1/3
11	1	22/734	28/142	8/766	2/8
12	1	43/1618	13/131	7/1727	1/15
13	1	63/1398	31/101	5/1431	1/13
14	1	69/132	6/7	30/47	2/4
15	1	5/490	16/67	0/528	4/7
16	5	26/1191	16/74	11/1228	1/9
17	1	95/1583	41/118	61/1650	2/13
18	5	1/117	12/48	1/75	1/4
19	10	33/71	49/29	3/6	1/3
20	5	25/80	69/35	3/5	2/3
21	1	62/82	6/12	26/61	1/2
	10	66/649	16/70	3/611	2/6
22	10	5/452	7/76	12/639	4/7
23	1	12/322	39/78	5/364	1/4
24	1	30/179	22/56	12/269	3/3
25	5	44/33	49/33	5/3	1/2
26	5	91/80	70/25	65/41	5/3
34	10	22/364	45/45	10/335	4/7
35	10	42/182	63/63	7/146	2/3
37	5	49/62	41/29	7/28	2/3
1	10	48/2989	22/194	64/3324	1/22
	1	32/188	46/52	11/244	4/6
2	1	26/1615	28/104	26/1730	1/11
	0.1	36/984	14/187	14/1096	1/9
3	5	33/911	15/76	7/1078	1/8

[a] The compounds were administered as Na salts in H_2O. [b] The procedure is described in ref 2. 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.

replacement of the chlorine atoms by methyl groups (as in 17) or by a fused benzene ring (7), but it is reduced by removal of either of the chlorine atoms (4, 11) and virtually abolished by removal of both chlorine atoms (21).

Changes in the length of the 1-alkenyl chain are important; lengthening this chain in 5 to 1-butenyl (6) lowers saluretic activity, although this is not the case with differently substituted analogues of 5 (compare 7 with 8, 11 with 12); further chain lengthening to 1-hexenyl (23) and 1-heptenyl (24) strongly reduces activity; chain shortening to vinyl gives a nearly inactive compound (14).

All changes made in the oxyacetic acid chain are detrimental. Substitution with methyl strongly reduces activity (15, 16); shortening the chain to carboxy (34, 35) further weakens activity; lengthening the chain by two methylene units gives a nearly inactive compound (37).

The para relationship between the alkenyl and acid chains appears to be requisite for any substantial saluretic activity; compounds with the ortho and meta disposition of these chains (9, 18, 19, 22, 25, 26) possess only weak activity.

The same structure–activity relationships are indicated

Table IV. Oral Activity in Dogs[a]

Compd	Dose, mg/kg	No. of dogs	mequiv/6 h excreted			Urine vol/6 h
			Na^+	K^+	Cl^-	
4	1	8	16	5	22	402
5	0.4	8	25	7	31	628
6	1	4	26	5	28	465
7	1	4	33	7	39	538
21	5	4	6	2	4	378
24	1	4	10	3	9	413
38	5	4	37	7	47	769
39	2	7	25	8	39	485
1	1	10	21	5	26	560
	3	8	37	7	42	
2	0.4	8	34	6	36	762
	1.0	8	30	7	37	492
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 2, Experimental Section.

by the more limited data from po testing. It should be noted that both the methyl ester (**38**) and the amide (**39**) of **5** possess substantial oral activity.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. The NMR spectra were taken on a Varian T-60 instrument in Me_2SO-d_6. Where analyses are indicated only by symbols of the elements, the analytical results for these elements are within ±0.4% of the theoretical values.

The preparation and properties of the ethyl formylphenoxyacetates have been described in the first paper of this series[2] except for the following compound.

Ethyl (2-Chloro-4-formylphenoxy)acetate. A mixture of 3-chloro-4-hydroxybenzaldehyde[6] (25.0 g, 0.16 mol), ethyl bromoacetate (40.0 g, 0.24 mol), K_2CO_3 (40.0 g, 0.28 mol), and DMF (100 ml) was stirred at 50–55° for 1 h. The mixture was poured into water and the oily product taken up in Et_2O, dried over $MgSO_4$, and distilled in vacuo. There was obtained 18.5 g (48%) of colorless oil, bp 160° (1.5 mm), which crystallized in the receiver: mp 46–48°. Anal. ($C_{11}H_{11}ClO_4$) C, H, Cl.

4-Formylphenoxyacetic acid is commercially available. 3-Formylphenoxyacetic acid[7] and (2,3-dichloro-4-formylphenoxy)acetic acid[2] were prepared by literature procedures.

(2,4-Dichloro-6-formylphenoxy)acetic Acid. A solution of ethyl (2,4-dichloro-6-formylphenoxy)acetate[2] (19.0 g, 0.069 mol) and KOH (4.5 g, 0.08 mol) in methanol (100 ml) and H_2O (10 ml) was heated at reflux for 15 min. The solution was cooled, diluted with H_2O, and acidified with 6 N hydrochloric acid. The precipitated solid was collected and recrystallized from BuCl to yield 12.4 g (72%) of pure product: mp 163–165°. Anal. ($C_9H_6Cl_2O_4$) C, H.

2-Nitro-1-alkenylaryloxyacetic Acids (I, Table I). Method A-1. This method is exemplified by the preparation of (*E*)-[2,3-dichloro-4-(2-nitropropenyl)phenoxy]acetic acid (**5**). A solution of ethyl (2,3-dichloro-4-formylphenoxy)acetate[2] (4.88 g, 0.0176 mol) and butylamine (1.3 g, 0.018 mol) in benzene (25 ml) was refluxed under a water separator until no more water was evolved (1 h). The benzene was distilled at reduced pressure. The residue was mixed with nitroethane (3.73 g, 0.05 mol) and HOAc (10 ml) and the mixture heated to boiling, cooled, and poured into water. The solid that separated was recrystallized from EtOH–H_2O to yield 3.4 g (57%) of **ethyl (*E*)-[2,3-dichloro-4-(2-nitropropenyl)phenoxy]acetate (28).** Data for this and similarly prepared nitroalkenyl esters are collected in Table II. A solution of **28** (3 g, 0.009 mol) in HOAc (16 ml), H_2O (12 ml), and concentrated hydrochloric acid (0.5 ml) was boiled under reflux for 1 h. The product that separated on cooling was recrystallized from HOAc–H_2O to yield 2 g (73%) of pure **5**: NMR δ 2.30 (3 H, s, CH_3), 4.95 (2 H, s, OCH_2), 7.20 (1 H, d, J = 9 Hz, phenyl H^6), 7.54 (1 H, d, J = 9 Hz, phenyl H^5), 8.04 (1 H, s, HC=). Further data for **5** and data for similarly prepared compounds are collected in Table I.

Method A-2 is exemplified by the preparation of (*E*)-**[2-chloro-4-(2-nitropropenyl)phenoxy]acetic acid (11).** A solution of ethyl (2-chloro-4-formylphenoxy)acetate (3.1 g, 0.013 mol) and $BuNH_2$ (1.0 g, 0.014 mol) in benzene (50 ml) was refluxed under a water separator until water evolution was complete (1 h). The benzene was distilled at reduced pressure. The residue was mixed with $C_2H_5NO_2$ (3.7 g, 0.05 mol) and HOAc (10 ml), and the mixture was heated to boiling, cooled, and poured into water. The crude nitroalkenyl ester that separated was extracted into Et_2O. The Et_2O solution was evaporated and the residue dissolved in HOAc (40 ml), H_2O (20 ml), and concentrated hydrochloric acid. The solution was boiled under reflux for 2 h and then poured into 200 ml of water. The precipitated solid was recrystallized from benzene–hexane to yield 1.08 g (31%) of **11**: NMR δ 2.43 (3 H, s, CH_3), 4.95 (2 H, s, OCH_2), 7.20 (1 H, d, J = 8 Hz, phenyl H^6), 7.53 (1 H, d of d, J = 8, 2 Hz, phenyl H^5), 7.78 (1 H, d, J = 2 Hz, phenyl H^3), 8.12 (1 H, s, HC=). Further data on this and on similarly prepared compounds are found in Table I.

Method B is exemplified by the preparation of (*E*)-**[2,3-dichloro-4-(2-nitro-1-hexenyl)phenoxy]acetic acid (23).** A solution of (2,3-dichloro-4-formylphenoxy)acetic acid[2] (5.0 g, 0.02 mol) and $BuNH_2$ (6.4 g, 0.088 mol) in benzene (50 ml) was refluxed under a water separator until water evolution was complete (1 h). Acetic acid (30 ml) was added and the solution concentrated at reduced pressure to about one-third volume. 1-Nitropentane (5.0 g, 0.043 mol) was added, and the solution was heated to boiling, cooled, and poured into water. The precipitated solid was recrystallized from methylcyclohexane to yield 1.2 g (17%) of **23**: NMR δ 0.98 (3 H, t, CH_3), 2.68 (2 H, t, CH_2C=), 4.98 (2 H, s, OCH_2), 7.20 (1 H, d, J = 9 Hz, phenyl H^6), 7.48 (1 H, d, J = 9 Hz, phenyl H^5), 8.04 (1 H, s, HC=). Further data on this and on similarly prepared compounds are listed in Table I.

4-Diacetoxymethyl-3-chlorobenzonitrile. A solution of 3-chloro-*p*-tolunitrile[5] (30.3 g, 0.2 mol) in HOAc (316 ml) and Ac_2O (314 ml) was cooled to 5°, and concentrated H_2SO_4 (47 ml) was added slowly with stirring. Then, CrO_3 (27.8 g, 0.278 mol) was added in portions during 30 min while temperature was kept at 5–10°. The green solution was kept at 25° for 16 h and then poured into ice water. The solid that separated was recrystallized from EtOH to yield 10.0 g (19%) of product: mp 96–97°. Anal. ($C_{12}H_{10}ClNO_4$) C, H.

3-Chloro-4-formylbenzonitrile. A solution of 4-diacetoxymethyl-3-chlorobenzonitrile (5.35 g, 0.02 mol) and H_2SO_4 (1 ml) in 50% aqueous EtOH (20 ml) was boiled under reflux for 45 min. The solid product that separated when the solution was cooled, 2 g (60%), mp 122–123°, was used in the next step. A sample sublimed for analysis had mp 122–123°. Anal. (C_8H_4ClNO) C, H.

3-Chloro-4-formylbenzoic Acid (33). A mixture of 3-chloro-4-formylbenzonitrile (1.0 g, 0.06 mol) and concentrated hydrochloric acid (25 ml) was boiled under reflux for 16 h. The mixture was cooled and the separated solid dissolved in dilute $NaHCO_3$ solution. The solution was extracted with Et_2O and acidified with 6 N hydrochloric acid. The precipitated acid was purified by sublimation. There was obtained 0.86 g (77%) of pure product: mp 214–215°. Anal. ($C_8H_5ClO_3$) C, H.

(*E*)-3-Chloro-4-(2-nitropropenyl)benzoic Acid (34). Compound **33** and nitroethane were condensed using method B to yield **34** (37%): mp 188–189° (from EtOH–H_2O); NMR δ 2.30 (3 H, s, CH_3), 7.70 (1 H, d, J = 9 Hz, phenyl H^6), 7.95–8.08 (2 H, m, phenyl H^2 and H^5), 8.08 (1 H, s, HC=). Anal. ($C_{10}H_8ClNO_4$) C, H, N.

(*E*)-3-Chloro-4-(2-nitro-1-butenyl)benzoic Acid (35). Compound **33** and 1-nitropropane were condensed (method B) to yield **35** (60%): mp 178–179° (from HOAc–H_2O). Anal. ($C_{11}H_{10}ClNO_4$) C, H, N.

4-(2,3-Dichloro-4-formylphenoxy)butyric Acid (36). A mixture of 2,3-dichloro-4-hydroxybenzaldehyde[2] (5.7 g, 0.03 mol), ethyl 4-bromobutyrate (11.7 g, 0.06 mol), K_2CO_3 (8.3 g, 0.06 mol), and DMF (25 ml) was stirred and heated at 50–60° for 1.5 h. Water (50 ml) was added and the separated oil taken up in Et_2O and dried over Na_2SO_4. The Et_2O was evaporated and the residue was treated with a mixture of EtOH (12 ml) and 40% aqueous $NaHSO_3$ solution (48 ml). The precipitated bisulfite addition compound was collected and suspended in water, and the mixture

was heated at 95°. The oily free aldehyde that formed was extracted into Et_2O. The Et_2O was evaporated and the residue was dissolved in a mixture of MeOH (30 ml), H_2O (5 ml), and KOH (2.8 g), and the solution was heated at 80° for 1 h. The solution was cooled and acidified to precipitate the product acid which was recrystallized from benzene to yield 2.9 g (35%) of **36**: mp 147–148°. Anal. ($C_{11}H_{10}Cl_2O_4$) C, H, Cl.

(*E*)-4-[2,3-Dichloro-4-(2-nitro-1-butenyl)phenoxy]butyric Acid (37). Compound **36** and 1-nitropropane were condensed (method B) to yield **37** (38%): mp 155–156.5° (from EtOH); NMR δ 8.02 (1 H, s, HC=). Anal. ($C_{14}H_{15}Cl_2NO_5$) C, H, N.

Methyl (*E*)-[2,3-Dichloro-4-(2-nitropropenyl)phenoxy]-acetate (38). A solution of **5** (1.0 g, 0.0033 mol) and H_2SO_4 (0.5 ml) in MeOH (20 ml) was stirred at 25° for 1 h. The solid that separated was recrystallized from MeOH to yield 0.6 g (57%) of **38**: mp 118–119°. Anal. ($C_{12}H_{11}Cl_2NO_5$) C, H, N.

(*E*)-[2,3-Dichloro-4-(2-nitropropenyl)phenoxy]acetamide (39). A solution of **5** (4.0 g, 0.013 mol) and $SOCl_2$ (4.0 g, 0.033 mol) in benzene (50 ml) was boiled under reflux for 2 h. Solvent and excess $SOCl_2$ were then distilled at reduced pressure. The residue was treated with concentrated NH_4OH (10 ml) to obtain the amide which was recrystallized repeatedly from benzene–hexane to yield 0.58 g (15%) of **39**: mp 161.5–162°. Anal. ($C_{11}H_{10}Cl_2N_2O_4$) C, H, Cl.

Acknowledgment. We wish to thank Mr. K. B. Streeter, Mr. Y. C. Lee, and their staff for elemental analyses and Mrs. J. D. Schneeberg and Dr. D. W. Cochran for NMR spectra.

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Cycloalkanoindoles. 1. Syntheses and Antiinflammatory Actions of Some Acidic Tetrahydrocarbazoles, Cyclopentindoles, and Cycloheptindoles

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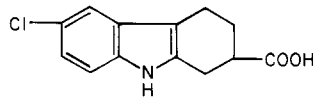
A novel series of acidic cycloalkanoindoles comprising tetrahydrocarbazole-, cyclopentindole-, and cycloheptindole-1-acetic acids has been synthesized via the Fischer indolization between a phenylhydrazine and a 1-alkyl-2-oxocycloalkaneacetic acid ester. These compounds were evaluated, orally, for their capacities to decrease established adjuvant arthritis in rats. The most active compound of the series was 1-ethyl-8-*n*-propyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid (AY-24 873), which had an ED_{50} of 1.1 ± 0.2 mg/kg. AY-24 873 was also studied orally in rats for its effect on the acute inflammatory response in the carrageenin paw edema test. It was found that AY-24 873 was about ten times more active against the chronic than against the acute models of inflammation used.

Several recent reports disclose diverse biological properties for acidic tetrahydrocarbazole derivatives. Antifungal,[1] antifertility,[1] hypocholesteremic,[2] and, particularly, antiinflammatory activity[1,3-6] have been reported in animals. In addition, one of these derivatives, 6-chloro-1,2,3,4-tetrahydrocarbazole-2-carboxylic acid (**1**),[4] has been shown to be clinically active in the treatment of acute gout.[5]



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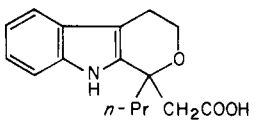

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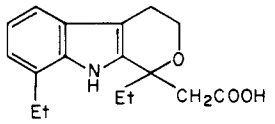

3

We have recently described the antiinflammatory activity of 1-*n*-propyl-1,3,4,9-tetrahydropyrano[3,4-*b*]-indole-1-acetic acid (**2**, prodolic acid, USAN)[7,8] and of the closely related and more potent 1,8-diethyl analogue **3** (etodolic acid, USAN).[9] The tetrahydropyranoindole nucleus of prodolic and etodolic acids may be viewed as an oxygen analogue of a 1,2,3,4-tetrahydrocarbazole. The observation that the antiinflammatory activity of prodolic acid and its congeners is profoundly influenced by the presence of and the nature of alkyl substituents at positions 1 and 8 of the tetrahydropyrano indole-1-acetic acid moiety[7,9] has prompted an investigation of a series of similarly substituted cycloalkanoindoles, comprising tetrahydrocarbazole-, tetrahydrocyclopentindole-, and hexahydrocycloheptindole-1-acetic acid derivatives and related compounds. The results obtained form the basis of this report.

Chemistry. The novel cycloalkanoindole-1-acetic acid derivatives prepared are collected in Table I. They were synthesized via the Fischer indolization between the phenylhydrazines **4–9** and the 1-alkyl-2-oxocycloalkane-acetic acid esters **10–16**. The recently reported synthesis of **24**[10] could not be repeated, and this compound was also obtained via the Fischer condensation of phenylhydrazine and ethyl 2-oxocyclohexaneacetate. The 2-(2-propyl)-, 2-*n*-propyl-, and, 2-*n*-butylphenylhydrazines **6–8** are new compounds and their syntheses are described in the Experimental Section.

The required 1-alkyl-2-oxocyclohexane- and cyclopentaneacetic acid esters were obtained via the ruthenium dioxide–sodium metaperiodate oxidation[11] of the known 2-alkyl-2-allylcyclohexanones **17–19**, and the novel cy-