5(4aS,10bR)·HCl, 93711-34-3; 6(4aR,10bR), 93601-82-2; 6-(4aR,10bR)·HCl, 93711-35-4; 6(4a5,10bS), 93601-83-3; 6-(4aS,10bS)·HCl, 93711-36-5; 7, 93601-84-4; 8(R), 93601-85-5; 8(S), 93601-86-6; 9(R), 93503-08-3; 9(S), 93503-09-4; 10(4aR,10bS), 93601-87-7; 10(4aS,10bR), 93601-88-8; 11(4aR,10bS), 93601-89-9; 11(4aS,10bR), 93601-90-2; 12(4aR,10bR), 93601-91-3; 12(4aS,10bS), 93601-92-4; 16, 93503-11-8; 16·HBr, 93503-10-7; 2-oxo-2-phenylethyl acetate, 2243-35-8; α-chloroacetophenone, 532-27-4; triethyl phosphonoacetate, 867-13-0; (E)-4-acetoxy-3-phenyl-2-butenoic acid ethyl ester, 72335-13-8; (Z)-4-acetoxy-3-phenyl-2-butenoic acid ethyl ester, 72335-15-0; 4-acetoxy-3-phenylbutanoic acid ethyl ester, 93503-12-9; (R)-O-methylmandelic acid, 3966-32-3; (±)-7-methoxy-2-(propylamino)tetralin hydrochloride, 93601-93-5; (S)-7-methoxy-2-(propylamine)tetralin (R)-O-methylmandelamide, 93503-13-0; (R)-7-methoxy-2-(propylamine)tetralin (R)-O-methylmandelamide, 93503-14-1; (S)-N-propionyl-7-methoxy-2-(propylamine)tetralin, 93503-15-2; (S)-7-methoxy-2-dipropylamino)tetralin, 93601-94-6; *cis*-7-methoxyoctahydrobenzoquinoline hydrochloride, 93503-16-3; (4aR,10bS)-7-methoxyoctahydrobenzo[f]quinoline (R)-O-mandelamide, 93503-17-4; (4aS,10bR)-7-methoxyoctahydrobenzo[f]quinoline (R)-O-mandelamide, 93601-95-7; *trans*-7-methoxyoctalhydrobenzo[f]-quinoline hydrochloride, 93503-18-5; (4aR,10bR)-7-methoxy-octahydrobenzo[f]quinoline (R)-O-mandelamide, 93601-96-8.

Substituted 5*H*-Dibenz[*b*,*g*]-1,4-oxazocines and Related Amino Acids with Antiinflammatory Activity

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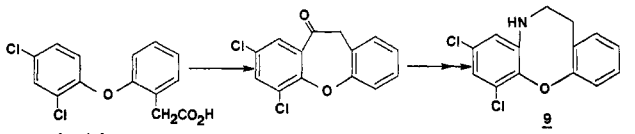
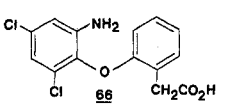
During an investigation of the antiinflammatory properties of a number of tetracyclic derivatives of 6,8-dichlorodibenz[b,f]oxepin-10(11*H*)-one, the ring-expanded 1,3-dichloro-5*H*-dibenz[b,g]-1,4-oxazocine (**9**) was prepared and found to be of considerable pharmacological interest. It was subsequently found that the corresponding ring-opened amino acid **66**, a close analogue of the antiinflammatory agent fenclofenac, also possessed significant antiinflammatory activity, superior both to the dibenzoxazocine and to fenclofenac. These findings prompted extensive synthetic programs in both areas, and a number of derivatives in the amino acid series showed potencies considerably in excess of the standard compound. These phenylacetic acids, however, were significantly more ulcerogenic than fenclofenac whereas the corresponding dibenzoxazocines showed few signs of ulcerogenicity at doses up to 1 g/kg.

In our continuing search for compounds of greater potency than fenclofenac,[1] [2-(2,4-dichlorophenoxy)phenylacetic acid], derivatives of the ring-closed compound 6,8-dichlorodibenz[b,f]oxepin-10(11*H*)-one were prepared. One of these, 1,3-dichloro-6,7-dihydro-5*H*-dibenz[b,g]-1,4-oxazocine (**9**) was found not only to be twice as potent



as fenclofenac in the adjuvant arthritis test but also to have no measurable ulcerogenic potential at doses up to 1 g/kg. This was considered to be a lead of considerable importance particularly as it was one of the few nonacidic compounds which showed activity in the adjuvant arthritis test. It was soon realized however that a metabolic breakdown to the corresponding 2-(6-amino-2,4-dichlorophenoxy)-phenylacetic acid (**66**) was possible and this was subse-

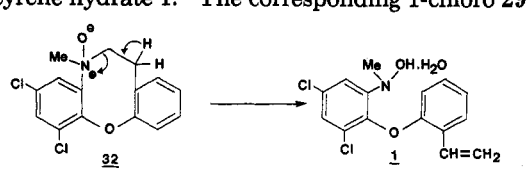


quently confirmed in metabolic studies in rats.[2] The amino acid **66** showed enhanced potency over the corresponding oxazocine **9** in the adjuvant arthritis test, and extensive synthetic programs in both the amino acid and oxazocine series were initiated. This paper describes the synthesis and testing results for these compounds.

Chemistry. The route used to prepare all the NH-substituted oxazocines was that described in Scheme I. Cyclization of the readily available phenoxyphenylacetic acids[1] using polyphosphoric acid gave the corresponding oxepinones which were then treated with sodium azide in sulfuric acid to give the highly insoluble oxazocinones. Without further purification these were reduced with lithium aluminum hydride to give the oxazocines, the majority of which were purified by crystallization of their hydrochloride salts. An alternative scheme involving the Beckman rearrangement of the oximes derived from the oxepinones failed to give satisfactory results.

N-Methyl derivatives of the oxazocines were normally prepared by simple methylation as described in Scheme I, although in one case (compound **28**), formylation and reduction was used. A potentially useful method involving the lithium aluminum hydride reduction of the corresponding *N*-methyloxazocinone gave complex mixtures of products. Other *N*-alkyl, *N*-alkenyl, *N*-acyl, and *N*-benzyl derivatives of the oxazocines were prepared by standard procedures and representative examples are described in the Experimental Section.

Oxidation of the *N*-alkyl compounds **28**, **31**, and **33** with peracid gave the corresponding *N*-oxides **29**, **32**, and **34**. After storage at room temperature for 1 month, compound **32** showed some signs of decomposition and further investigations revealed that heating the free base in ethyl acetate for 10 min resulted in complete decomposition to the styrene hydrate **1**. The corresponding 1-chloro **29** and



N-propyl **34** compounds appeared to be considerably more stable although even in these cases some degre of decomposition was noted after storage for several months.

(1) Atkinson, D. C.; Godfrey, K. E.; Meek, B.; Saville, J. F.; Stillings, M. R. *J. Med. Chem.* **1983**, *26*, 1353.
(2) Rance, M. J., unpublished results.

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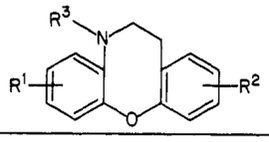
Table I. 6,7-Dihydro-5*H*-dibenz[*b*,*g*]-1,4-oxazocines



no.	R^1	R^2	R^3	mp, °C	formula	anal.	adjuvant arthritis test: primary[a] (mg/kg)	adjuvant arthritis test: rel to fenclofenac[b]
3	H	H	H	205–208	$C_{14}H_{13}NO\cdot HCl$	C, H, N	6 (50)	
4	1-Cl	H	H	207–210	$C_{14}H_{12}ClNO\cdot HCl$	C, H, N	33 (100)	0.2
5	2-Cl	H	H	198–200	$C_{14}H_{12}ClNO\cdot HCl$	C, H, N	0 (50)	
6	3-Cl	H	H	201–207	$C_{14}H_{12}ClNO\cdot HCl$	C, H, N	0 (50)	
7	1-F	H	H	204–206	$C_{14}H_{12}FNO\cdot HCl$	C, H, N	0 (50)	
8	3-Me	H	H	157–160	$C_{15}H_{15}NO\cdot HCl$	C, H, N	0 (50)	
9	1,3-Cl_2	H	H	170–172	$C_{14}H_{11}ClNO\cdot HCl$	C, H, N	41 (25)	2.1
10	1-Cl, 3-Me	H	H	126–128	$C_{15}H_{14}ClNO\cdot HCl$	C, H, N	23 (25)	
11	1-Cl, 3-OMe	H	H	208–210	$C_{15}H_{14}ClNO_2\cdot HCl$	C, H, N	18 (50)	
12	1-Me, 3-Cl	H	H	173–176	$C_{15}H_{14}ClNO\cdot HCl$	C, H, N	32 (50)	0.9
13	1,3-Cl_2, 2,4-Me_2	H	H	105–106	$C_{16}H_{15}Cl_2NO$	C, H, N	6 (50)	
14	1-Cl	9-Me	H	220–222	$C_{15}H_{14}ClNO\cdot HCl$	C, H, N	22 (50)	
15	1,3-Cl_2	9-Me	H	149–151	$C_{15}H_{13}Cl_2NO\cdot HCl$	C, H, N	17 (50)	
16	2,3-Cl_2	9-Me	H	167–168	$C_{15}H_{13}Cl_2NO\cdot HCl$	C, H, N[c]	8 (50)	
17	1-Cl, 3-Me	9-Me	H	175–180	$C_{16}H_{16}ClNO\cdot HCl$	C, H, N	19 (40)	
18	1-Cl, 3-Et	9-Me	H	156–158	$C_{17}H_{18}ClNO\cdot HCl$	C, H, N	13 (100)	
19	1-Cl, 3-*sec*-Bu	9-Me	H	186–188	$C_{19}H_{22}ClNO\cdot HCl$	NMR	14 (50)	
20	1-F, 3-Et	9-Me	H	143–145	$C_{17}H_{18}FNO\cdot HCl$	C, H, N	NT	
21	1-OMe, 3-Cl	9-Me	H	218–220	$C_{16}H_{16}ClNO_2\cdot HCl$	C, H, N	1 (75)	
22	1-Cl	9-Cl	H	196–198	$C_{14}H_{11}ClNO$	C, H, N	16 (50)	
23	1,3-Cl_2	9-Cl	H	148–150	$C_{14}H_{10}Cl_3NO\cdot HCl$	C, H, N	25 (50)	0.8
24	1,4-Cl_2	9-Cl	H	152–153	$C_{14}H_{10}Cl_3NO$	C, H, N	14 (50)	
25	1-Cl, 3-Me	9-Cl	H	118–122	$C_{15}H_{13}Cl_2NO\cdot HCl$	C, H, N	21 (100)	0.5
26	1,3-Cl_2	9-OH	H	165–167	$C_{14}H_{11}Cl_2NO_2\cdot HCl$	C, H, N	2 (10)	
27	1-Cl	10-Cl	H	218–220	$C_{14}H_{11}ClNO\cdot HCl$	C, H, N	10 (50)	
28	1-Cl	H	Me	173–176	$C_{15}H_{14}ClNO\cdot HCl$	C, H, N	31 (50)	1.4
29	1-Cl	H		135–140	$C_{15}H_{14}ClNO_2$	C, H, N	23 (25)	0.7
30	1-Cl	H	CHO		$C_{15}H_{12}ClNO_2$	C, H, N	33 (100)	
31	1,3-Cl_2	H	Me	119	$C_{15}H_{13}Cl_2NO$	C, H, N	35 (50)	2.4
32	1,3-Cl_2	H		147–149	$C_{15}H_{13}Cl_2NO_2HCl$	C, H, N	42 (50)	2.2
33	1,3-Cl_2	H	Pr^n	56–58	$C_{17}H_{17}Cl_2NO$	C, H	39 (50)	0.6
34	1,3-Cl_2	H		110–115	$C_{17}H_{17}Cl_2NO_2\cdot HCl$	C, H, N	36 (50)	
35	1,3-Cl_2	H	$CH_2CH{=}CH_2$	74	$C_{17}H_{15}Cl_2NO$	C, H, N	18 (50)	
36	1,3-Cl_2	H	$CH_2CH{=}CHCH_3$	115–116	$C_{18}H_{17}Cl_2NO$	C, H, N	21 (50)	
37	1,3-Cl_2	H	COCl	98–100	$C_{15}H_{10}Cl_3NO_2$	Cl	7 (50)	
38	1,3-Cl_2	H	$COCH_3$	110	$C_{16}H_{13}Cl_2NO_2$	C, H, N	10 (75)	
39	1,3-Cl_2	H	$COPr^n$	100–102	$C_{18}H_{17}Cl_2NO_2$	C, H, N	8 (100)	
40	1,3-Cl_2	H	*p*-COC_6H_4Cl	163–164	$C_{21}H_{14}Cl_3NO_2$	C, H, N	0 (50)	
41	1,3-Cl_2	H	*N*-$CH_2C_6H_5$	131	$C_{21}H_{17}Cl_2NO$	C, H, N	2 (10)	
42	1,3-Cl_2	H	*p*-$CH_2C_6H_4Cl$	133–135	$C_{21}H_{16}Cl_3NO$	C, H, N	10 (50)	
43	1,3-Cl_2	H	CO_2Et	79–81	$C_{17}H_{15}Cl_2NO_3$	C, H, N	21 (10)	0.5
44	1,3-Cl_2	H	CONHMe	170–172	$C_{16}H_{14}Cl_2N_2O_2$	C, H, N	4 (10)	
45	1,3-Cl_2	H	$CONHNH_2$	174–176	$C_{15}H_{13}Cl_2N_3O_2$	C, H, N	32 (25)	0.6
46	1,3-Cl_2	H	$CONHNHCOCH_3$		$C_{17}H_{15}Cl_2N_3O_3$	C, H, N	18 (100)	
47	1-Cl	9-Me	Me	102–103	$C_{16}H_{16}ClNO$	C, H, N	+15 (50)	
48	1-Cl	9-Cl	Me	169–171	$C_{15}H_{13}Cl_2NO\cdot HCl$	C, H, N	13 (50)	

[a] In rat, percentage reduction in swelling of the injected left hind paw vs. controls; fenclofenac gave a 35% reduction at 100 mg/kg, po, in this test. [b] A three-dose level relative potency assay vs. fenclofenac using a standard parallel line assay method. [c] C; calcd, 53.11; found, 54.68. NT not tested.

A dibenzoxazocine not listed in Table I, 1-chloro-6-methyl-6,7-dihydro-5*H*-dibenz[*b*,*g*]-1,4-oxazocine (**2**) was prepared by the reductive cyclization of a nitro ketone derived from the osmium tetraoxide/sodium periodate oxidation of the corresponding allyl derivative as described in Scheme II. Several attempts to adapt this method to the synthesis of more conventional oxazocines via the reductive cyclization of nitro aldehydes consistently afforded mixtures of products.

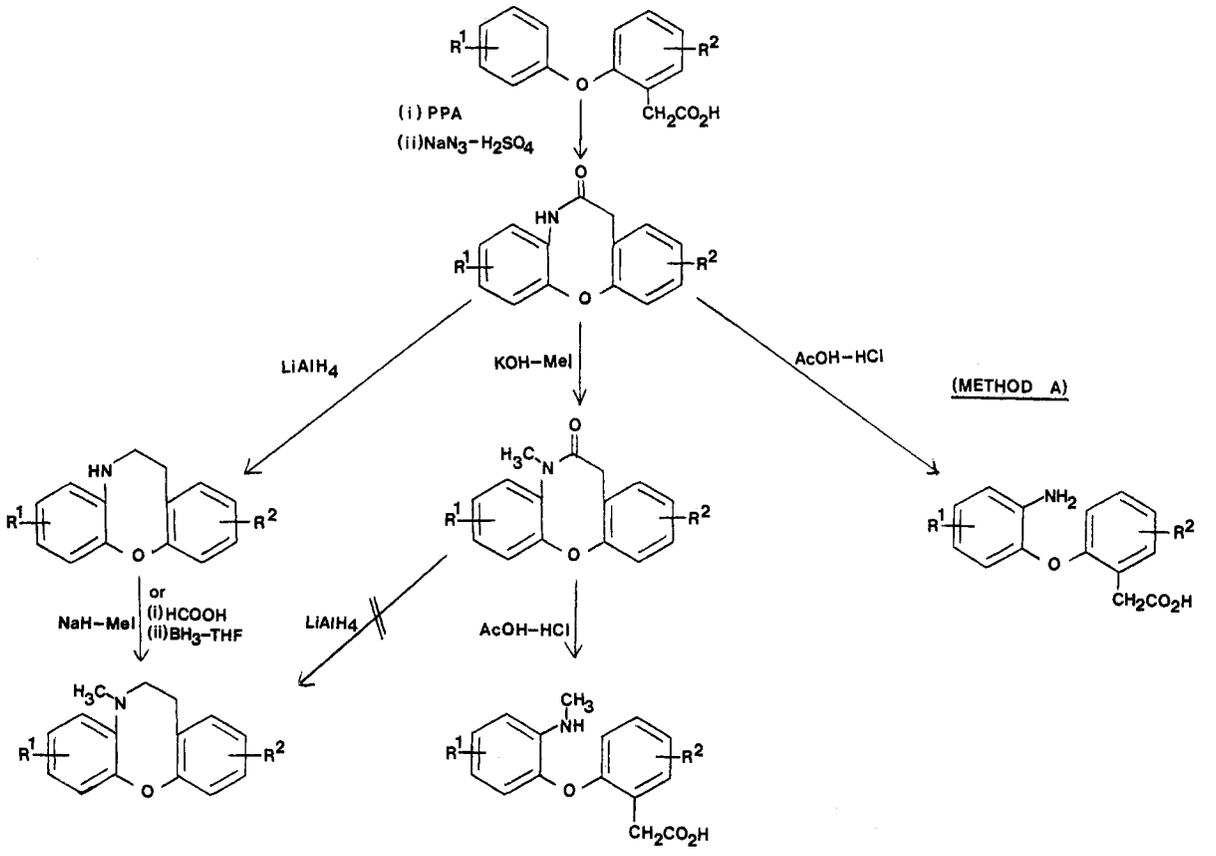
Two routes were used in the preparation of the primary amino acids. The first (method A, Scheme I) involved the acid hydrolysis of an oxazinone; the second involved the simple three-stage procedure described in Scheme II (method B). *N*-Methyl compounds were produced either by hydrolysis of the corresponding *N*-methyl oxazocinone or by the multistep route described in Scheme II. *N*,*N*-Dimethyl compounds were prepared by reductive methylation of the secondary amino acid.

Results and Discussion

The pharmacological results presented in Tables I–III are derived from the adjuvant arthritis test in rats and a measure of the minimum ulcerogenic dose (MUD) in the same species. Details of these tests are described in the Experimental Section.

The possibility that at least part of the activity of the dibenzoxazocines was the result of metabolic breakdown to the corresponding amino acid was recognized early in

Scheme I



Scheme II

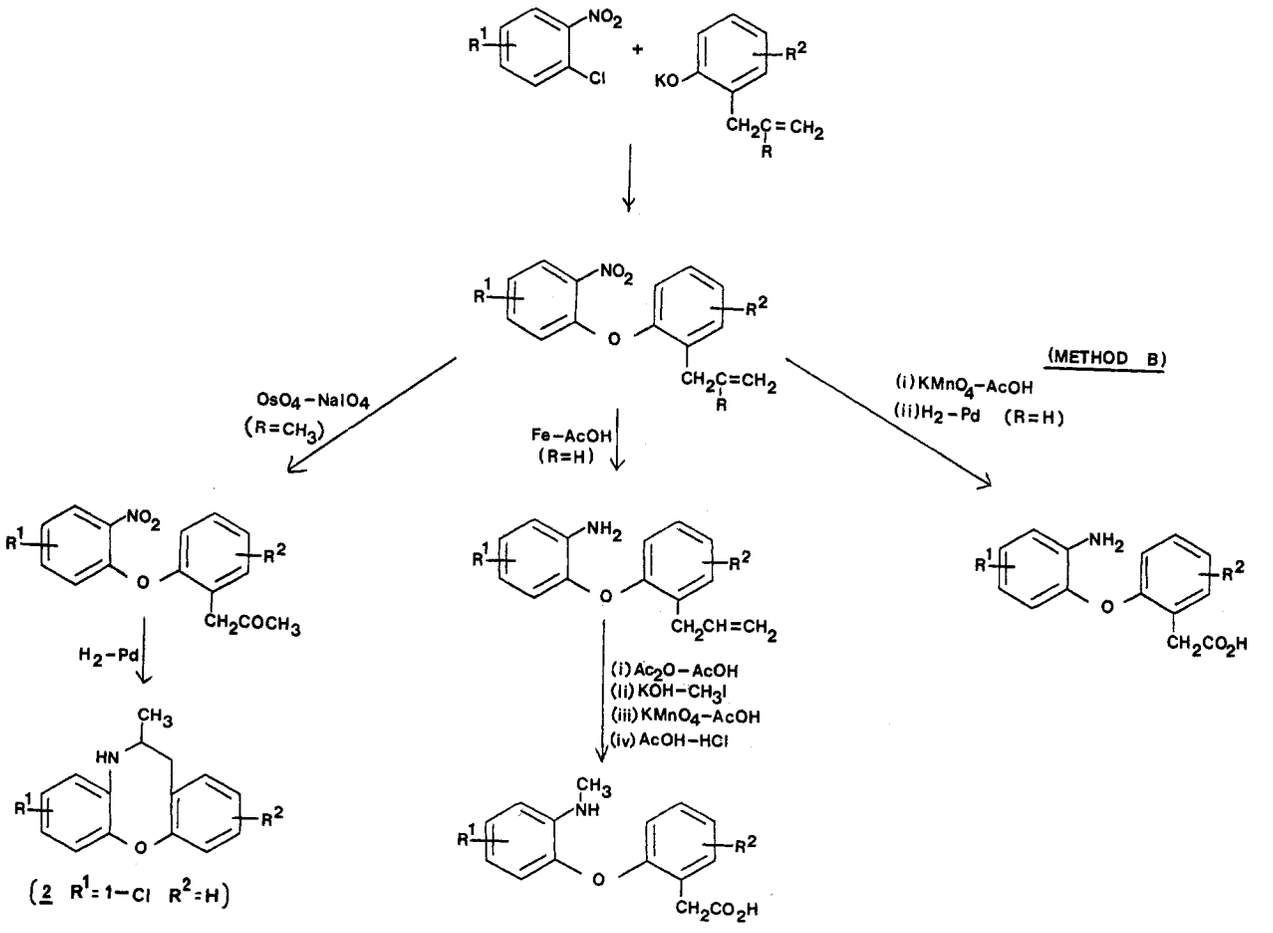
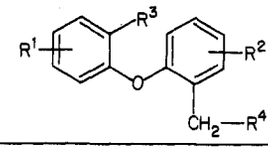


Table II. Substituted 2-(6-Aminophenoxy)phenylacetic Acids and Derivatives[a]

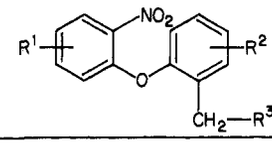


no.	R^1	R^2	R^3	R^4	*b*	mp, °C	formula	anal.	pharmacological screening results: adjuvant arthritis test: primary[c] (mg/kg, po)	rel to fenclofenac[d]	MUD, mg/kg[e] po (24 h)
49	H	H	NH_2	CO_2H	A	168–170	$C_{14}H_{16}NO_3 \cdot HCl$	C, H, N	2 (35)		
50	2-Cl	H	NH_2	CO_2H	A	198–200	$C_{14}H_{12}ClNO_3 \cdot HCl$	C, H, N	36 (25)	3.5	25–50
51	2-Cl	H	NH_2	CO_2Me	A	117–118	$C_{15}H_{14}ClNO_3$	C, H, N	35 (25)		
52	2-Cl	H	NH_2	CO_2Pt[f]	A	136–138	$C_{22}H_{16}ClNO_5$	C, H, N	36 (100)		
53	2-Cl	H	NH_2	$CONH_2$	A	196–197	$C_{14}H_{13}ClN_2O_2$	C, H, N	14 (50)		
54	2-Cl	H	NH_2	$CONEt_2$	A	139–141	$C_{18}H_{21}ClN_2O_2$	C, H, N	6 (50)		
55	2-Cl	H	NHMe	CO_2H	B	158–161	$C_{15}H_{14}ClNO_3$	C, H, N	toxic at 25 mg/kg	15.0	<12.5
56	3-Cl	H	NH_2	CO_2H	A	128–130	$C_{14}H_{12}ClNO_3$	C, H, N	12 (25)		
57	4-Cl	H	NH_2	CO_2H	B	163–165	$C_{14}H_{12}ClNO_3$	C, H, N	+4 (100)		
58	2-F	H	NH_2	CO_2H	A	172–174	$C_{14}H_{12}FNO_3$	C, H, N	27 (25)		
59	2-Me	H	NH_2	CO_2H	B	186–188	$C_{15}H_{15}NO_3$	C, H, N	32 (25)	1.9	400–800
60	2-Me	H	NHMe	CO_2H	B	144–145	$C_{16}H_{17}NO_3$	C, H, N	46 (25)	6.5	25–50
61	2-Me	H	NMe_2	CO_2H	B	120–121	$C_{17}H_{19}NO_3$	C, H, N	38 (20)	2.1	100–200
62	$2\text{-}NH_2$	H	NH_2	CO_2H	B	201–203	$C_{14}H_{14}N_2O_3$	C, H, N	5 (25)		
63	$4\text{-}CF_3$	H	NH_2	CO_2H	B	138–139	$C_{15}H_{12}F_3NO_3$	C, H, N	36 (100)	2.1	400–800
64	$2,3\text{-}Cl_2$	H	NH_2	CO_2H	A	198–202	$C_{14}H_{11}Cl_2NO_3$	C, H, N	33 (25)		
65	$3,5\text{-}Cl_2$	H	NH_2	CO_2H	B	164–166	$C_{14}H_{11}Cl_2NO_3$	C, H, N	37 (10)	6.6	
66	$2,4\text{-}Cl_2$	H	NH_2	CO_2H	A	177–180	$C_{14}H_{11}Cl_2NO_3$	C, H, N	41 (10)	6.8	12.5–25
67	$2,4\text{-}Cl_2$	H	NH_2	CO_2Me	A	92–93	$C_{15}H_{13}Cl_2NO_3$	C, H	38 (25)	7.5	50–80
68	$2,4\text{-}Cl_2$	H	NHMe	CO_2H	A	181–182	$C_{15}H_{13}Cl_2NO_3$	C, H, N	22 (2)	13.0	toxic at 25 mg/kg, 5/5 animals dead
69	$2,4\text{-}Cl_2$	H	NHMe	CO_2Me	A	109–110	$C_{16}H_{15}Cl_2NO_3$	C, H, N	36 (50)	2.5	50–100
70	$2,4\text{-}Cl_2$	H	NMe_2	CO_2Me	A	91–92	$C_{17}H_{17}Cl_2NO_3$	C, H, N	33 (10)	2.7	
71	$2,4\text{-}Cl_2$	H	NHAc	CO_2H	A	221	$C_{16}H_{13}Cl_2NO_4$	C, H, N	NT		
72	$2,4\text{-}Cl_2$	H	NHAc	CO_2Me	A	141–142	$C_{17}H_{15}Cl_2NO_4$	NMR	18 (25)		
73	$2,4\text{-}Br_2$	H	NH_2	CO_2H	A	166–173	$C_{14}H_{11}Br_2NO_3$	C, H, N	50 (25)	8.6	25–50
74	2-Cl, 4-Me	H	NH_2	CO_2H	A	188–190	$C_{15}H_{14}ClNO_3$	C, H, N	20 (25)		
75	2-Cl, 4-OMe	H	NH_2	CO_2H	A	178–179	$C_{15}H_{14}ClNO_4$	C, H, N	24 (25)		
76	$2,4\text{-}Cl_2$, $3,5\text{-}Me_2$	H	NH_2	CO_2H	A	229–231	$C_{16}H_{15}Cl_2NO_3$	C, H, N	4 (25)		60–120
77	$2,3,4\text{-}Cl_3$	H	NH_2	CO_2H	B	217–219	$C_{14}H_{10}Cl_3NO_3$	C, H, N	33 (10)	8.2	
78	$2,4,5\text{-}Cl_3$	H	NH_2	CO_2H	B	204–206	$C_{14}H_{10}Cl_3NO_3$	C, H, N	37 (10)	11.6	50–100
79	2-Me, 3-Cl	H	NH_2	CO_2H	B	202–204	$C_{15}H_{14}ClNO_3 \cdot HCl$	C, H, N	34 (25)	4.1	100–200
80	2-Me, 4-Cl	H	NH_2	CO_2H	A	221–223	$C_{15}H_{14}ClNO_3 \cdot HCl$	C, H, N	34 (10)	5.6	25–50
81	2-Me, 4-Cl	H	NHMe	CO_2H	A	174–175	$C_{16}H_{16}ClNO_3$	C, H, N	28 (10)	2.8	
82	2-Et, 4-Cl	H	NH_2	CO_2H	A	192–193	$C_{16}H_{17}Cl_2NO_3$	C, H, N	25 (10)	2.8	
83	$3,4\text{-}Cl_2$	5-Me	NH_2	CO_2H	A	122	$C_{15}H_{13}Cl_2NO_3$	C, H, N[g]	+10 (25)		
84	2-Cl, 4-Me	5-Me	NH_2	CO_2H	A	181–183	$C_{16}H_{16}ClNO_3$	C, H, N	+3 (25)		
85	2-Cl, 4-Et	5-Me	NH_2	CO_2H	A	152–153	$C_{17}H_{18}ClNO_3$	C, H, N	34 (25)	1.0	
86	2-Cl, 4-*sec*-Bu	5-Me	NH_2	CO_2H	A	146–148	$C_{19}H_{22}ClNO_3$	C, H, N	10 (10)		
87	2-F, 4-Et	5-Me	NH_2	CO_2H	A	122–123	$C_{17}H_{18}FNO_3$	C, H, N	+1 (25)		100–200
88	2-Cl	4-Cl	NH_2	CO_2H	A	164–166	$C_{14}H_{11}Cl_2NO_3$	C, H, N	1 (25)		
89	2-Cl, 4-Me	5-Cl	NH_2	CO_2H	A	199–201	$C_{15}H_{13}Cl_2NO_3$	C, H, N	32 (25)	1.4	
90	2-Cl	H	NHMe	CH_2OH	B	83	$C_{15}H_{16}ClNO_2$	C, H, N	36 (10)	5.0	100–200

[a] For convenience and clarity, all amino functions are numbered in the 6-position in the table and discussion; in the Experimental Section, IUPAC rules are observed. [b] Method of preparation. [c] See footnote *a*, Table I. [d] See footnote *b*, Table I. [e] Minimum ulcerogenic dose, in this test, fenclofenac had an MUD of 400–800 mg/kg. [f] 3-Phthalidyl ester. [g] C: calcd, 55.23; found, 56.19. NT not tested.

the program. Subsequent metabolic studies[2] confirmed that the amino acid **66** was present in the plasma of rats dosed with the dibenzoxazocine **9**. As the obvious point of enzymic attack was the 6-position, compound **2** with a methyl group in that position was synthesized (Scheme II) and found to be totally inactive at 100 mg/kg, po, whereas the corresponding 6-H derivative **4** showed a 33% reduction in paw swelling at the same dose level. It seemed to us therefore that although it was possible that the dibenzoxazocines themselves possessed some inherent antiinflammatory activity, two other factors might be important in defining the overall activity of these compounds. These were the predisposition of the dibenzoxazocines for metabolism to an amino acid and the subsequent activity of that amino acid. It is reasonable to assume that the only compounds whose rate of metabolism to the amino acid might be reduced are those possessing an N-substituent which could provide some steric constraint to oxidation at C-6. However the necessary comparative data to assess the contribution of steric factors to overall activity is scarce. Only in the case of *N*-methyl compounds can valid comparisons be made and these derivatives (**28** vs. **55** and **31** vs. **68**) (Tables I and II) do show a good interseries correlation of activities. It is questionable however whether the relatively small size of the methyl group would have a significant effect on metabolism at C-6 and hence the

Table III. Substituted 2-(6-Nitrophenoxy)phenylacetic Acids and Derivatives



no.	R^1	R^2	R^3	mp, °C	formula	anal.	pharmacological screening results: adjuvant arthritis test: primary[a] (dose mg/kg, po)	pharmacological screening results: adjuvant arthritis test: rel to fenclofenac[b]	MUD, mg/kg,[c] po (24 h)
91	H	H	CO_2H	156–157	$C_{14}H_{11}NO_5$	C, H, N	1 (50)		
92	2-Cl	H	CO_2H	153–154	$C_{14}H_{10}ClNO_5$	C, H, N	45 (75)	2.0	100–200
93	2-Cl	H	CO_2Me	94–95	$C_{15}H_{12}ClNO_5$	C, H, N	31 (25)		
94	2-Cl	H	CO_2Bu^t	94–95	$C_{18}H_{18}ClNO_5$	C, H, N	21 (50)		
95	2-Cl	H	CO_2Pt[d]	138–139	$C_{22}H_{14}ClNO_7$	C, H, N	30 (50)	0.7	>800
96	2-Cl	H	$CONH_2$	163–165	$C_{14}H_{11}ClN_2O_4$	C, H, N	36 (50)	1.1	>800
97	2-Cl	H	CONHOH	150–153	$C_{14}H_{11}ClN_2O_5$	C, H, N	36 (50)		
98	2-Cl	H	CH_2OH	71–72	$C_{14}H_{12}ClNO_4$	C, H, N	37 (100)		50–100
99	2-Me	H	CO_2H	145–146	$C_{15}H_{13}NO_5$	C, H, N	26 (10)		
100	4-CF_3	H	CO_2H	104–105	$C_{15}H_{10}F_3NO_5$	C, H, N	29 (100)		
101	2,3-Cl_2	H	CO_2H	162–163	$C_{14}H_9Cl_2NO_5$	C, H, N	25 (25)		
102	2,4-Cl_2	H	CO_2H	173	$C_{14}H_9Cl_2NO_2$	C, H, N	36 (25)		
103	3,5-Cl_2	H	CO_2H	155–157	$C_{14}H_9Cl_2NO_2$	C, H, N	34 (10)	2.9	
104	2-Me, 4-Cl	H	CO_2H	193–194	$C_{15}H_{12}ClNO_2$	C, H, N	34 (25)	3.3	
105	2,3,4-Cl_3	H	CO_2H	185–187	$C_{14}H_8Cl_3NO_5$	C, H, N	17 (10)	0.6	
106	2,4,5-Cl_3	H	CO_2H	164–165	$C_{14}H_8Cl_3NO_5$	C, H, N	30 (10)		
107	2-Cl	3-Cl	CO_2H	129–130	$C_{14}H_9Cl_2NO_5$	C, H, N	1 (25)		
108	2-Cl	3-Me	CO_2H	165–166	$C_{15}H_{12}ClNO_5$	C, H, N	0 (25)		

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. [c] See footnote *e*, Table II. [d] See footnote *f*, Table II. [e] C: calcd, 62.71; found, 62.04.

modest activities shown by the compounds **33**, **35**, **36**, **41**, and **42** (Table I) in which the N-substituent is considerably more bulky might reflect either the poor activity of their corresponding amino acids, for which data are not available, or steric constraint to metabolism. A further factor limiting the activity of the oxazocines is insolubility and this probably contributes significantly to the poor results obtained for compounds **38–40** and **43–46**, all of which were highly insoluble. Furthermore, insolubility almost certainly plays a major role in the very low ulcerogenic potential of the oxazocines, none of which had a minimum ulcerogenic dose of less than 800 mg/kg.

It is clear from the pharmacological results of the amino acids presented in Table II that substitution in the amino-containing ring is essential for good activity. In the monosubstituted primary amino series (**50–54**, **56–59**, and **62**, **63**), while not all substituents conferred significant activity, the 2-chloro **50**, 2-methyl **59**, and 4-trifluoromethyl **63** compounds were all substantially more potent than the unsubstituted compound **49**, which was devoid of antiinflammatory activity. The importance of the 2- and 4-positions was highlighted in the disubstituted series where the introduction of a 4-chloro group in both the 2-chloro and 2-methyl series gave compounds with enhanced potencies over their monosubstituted analogues (**66** vs. **50** and **80** vs. **59**). Introduction of groups other than chloro in the 4-position of the 2-chloro compound appeared to cause a decrease in potency however (**74** and **75**). The 2,4-dibromo analogue **73** showed a surprising degree of activity and was relatively less ulcerogenic than its 2,4-dichloro counterpart.

Substituting the primary amino function with a methyl group in general gave compounds of increased potency (**55** vs. **50**, **60** vs. **59**, and **68** vs. **66**). In all cases where data are available, however, toxicity and/or ulcerogenicity was also considerably increased. Adding a further methyl group proved deleterious in the one case where valid comparisons are available (**61** vs. **60**).

Only three tri- and tetrasubstituted amino acids were synthesised (**76–78**), but of these, the two trichloro compounds **77** and **78** showed good potency and in the case of **78** a relatively low ulcerogenicity. This result is interesting as it reflects the apparently distinctive properties of tetrasubstitution in this ring system also shown by tetrachloro compounds described elsewhere.[3]

In the small series of compounds **83–89** with substituents in the phenylacetic ring, only two (compounds **85** and **89**) showed significant activity.

The effects of esterification were variable; in some cases potency was retained (**50** vs. **51**, **66** vs. **67**) and in others a sharp decrease occurred (**68** vs. **69**); as expected ulcerogenicity and/or toxicity was generally lower than for the corresponding acids.

A small number of 6-nitro compounds used as intermediates in the synthesis of the amino acids were also tested for antiinflammatory activity and several proved to be surprisingly potent (Table III). In particular the 2-methyl, 4-chloro compound **104** was found to be 3 times more potent than fenclofenac in a relative potency determination. However the small number of compounds synthesised precluded any meaningful structure–activity study, and further synthesis in this area was abandoned after the discouraging results from the oxazocine and amino acid series.

In conclusion, although the therapeutic ratios of a number of oxazocines are superior to that of the standard drug fenclofenac, the very poor solubility characteristics prevented further progression of these compounds. A number of *N*-oxides of the oxazocines were prepared as a means of enhancing solubility and hence absorption, but their inherent instability precluded further study. Sufficient evidence has been presented to suggest that antiinflammatory activity of the oxazocines in rats is due, at least in part, to their metabolic breakdown to the corresponding amino acids. Unfortunately, despite the high potencies associated with these compounds, their corre-

(3) Atkinson, D. C.; Godfrey, K. E.; Myers, P. L.; Phillips, N. C.; Stillings, M. R.; Welbourn, A. P. *J. Med. Chem.* **1983**, *26*, 1361.

spondingly high ulcerogenic potential gave therapeutic ratios which were inferior to fenclofenac, and consequently work was terminated in this area.

Experimental Section

Chemistry. Melting points were determined on a Buchi apparatus in glass capillary tubes and are uncorrected. IR and NMR spectra were recorded on Perkin-Elmer 700 and Varian Associates T60 instruments, respectively, and were consistent with the assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.

1. Dibenzoxazocines (Scheme I). 1,3-Dichloro-6,7-dihydro-5*H*-dibenz[*b*,*g*]-1,4-oxazocine Hydrochloride (9). 2-(2,4-Dichlorophenoxy)phenylacetic acid[1] (5.0 g, 0.017 mol) was added to a stirred slurry of polyphosphoric acid (80 g) and the mixture was stirred at 80–90 °C for 0.5 h. The mixture was then cooled and poured into water, and the resulting precipitate was filtered off and dried to give 6,8-dichlorodibenz[*b*,*f*]oxepin-10(11*H*)-one; yield 3.5 g (74%); mp 91–92 °C; IR($CHBr_3$) ν max 1695, 1440 cm^{-1}.

Sodium azide (8.45 g, 0.13 mol) was added over 0.5 h to a stirred solution of the oxepinone (30 g, 0.11 mol) in concentrated H_2SO_4 (109 mL) and chloroform (500 mL) at 0 °C. After the addition, cooling was removed and the mixture was stirred for 3 h at room temperature. The chloroform layer was then discarded and the aqueous layer was poured onto ice, and the fine suspension which was produced was filtered off, washed with ethanol, and crystallized from dimethylformamide to give 1,3-dichloro-5*H*-dibenz[*b*,*g*]-1,4-oxazocine-6-one: yield 19.9 g (62%); mp > 300 °C; satisfactory analyses could not be obtained for any of the dibenzoxacines due to their extreme insolubility and high melting points.

The oxazocinone (5.7 g, 0.019 mol) was added portionwise over 0.5 h to a stirred suspension of lithium aluminum hydride ($LiAlH_4$, 1.7 g, 0.045 mol) in dry tetrahydrofuran (THF, 50 mL) at room temperature in an atmosphere of dry nitrogen. The stirred mixture was then heated under reflux for 4 h and cooled, and water was added dropwise with ice cooling. A saturated solution of sodium potassium tartrate was then added, and the resulting two layers were separated. The aqueous layer was extracted with ether, and the combined organic layers were washed with water, dried ($MgSO_4$), and evaporated. The resulting yellow solid was crystallized to give 1,3-dichloro-6,7-dihydro-5*H*-dibenz[*b*,*g*]-1,4-oxazocine: yield 3.1 g (58%); mp 159–160 °C. The free base was subsequently converted in quantitative yield to the hydrochloride salt **9** with use of ethereal HCl: mp 170–172 °C. Anal. ($C_{14}H_{11}ClNO\cdot HCl$) C, H, N.

1,3-Dichloro-6,7-dihydro-5-methyl-5*H*-dibenz[*b*,*g*]-1,4-oxazocine (31). Sodium hydride (70%, 1.0 g, 0.029 mol) was added to dry dimethyl sulfoxide (Me_2SO, 40 mL) and the mixture was stirred under nitrogen at 70 °C until evolution of hydrogen had ceased. After the mixture was cooled to room temperature, the free base of the oxazocine hydrochloride **9** (4.1 g, 0.015 mol) was added and stirring was continued for 5 min, after which methyl iodide (6.2 g, 0.044 mol) was added dropwise with stirring. After 0.5 h at room temperature the mixture was poured into water and the resulting suspension was extracted with ether, and the organic layer was washed with water, dried ($MgSO_4$), and evaporated to give a yellow oil. This was dissolved in boiling ethanol, which was then allowed to cool to room temperature. The solid which crystallized was filtered off and dried to give **31**: yield 0.9 g (20%); mp 119 °C. Anal. ($C_{15}H_{13}Cl_2NO$) C, H, N.

1,3-Dichloro-6,7-dihydro-5-methyl-5*H*-dibenz[*b*,*g*]-1,4-oxazocine *N*-Oxide Hydrochloride (32). *m*-Chloroperbenzoic acid (2.6 g, 0.015 mol) was added portionwise to a stirred solution of the *N*-methyloxazocine **31** (1.5 g, 0.005 mol) in dichloromethane (30 mL) at 0 °C. The mixture was stirred for a further 3 h at 0 °C and then allowed to stand at room temperature overnight. A mixture of sodium sulfite solution (10% w/v, 22.5 mL), sodium carbonate solution (10% w/v, 22.5 mL), and dichloromethane (20 mL) was added to the reaction mixture, which was then stirred for 2 h. The dichloromethane layer was separated, washed with water, dried ($MgSO_4$), and evaporated to give a yellow solid, which was dissolved in methanol. Ethereal HCl was added and the precipitated hydrochloride salt was filtered off and crystallized from ethanol/ether to give **32**: yield 0.7 g (44%); mp 147–149 °C. Anal. ($C_{15}H_{13}Cl_2NO_2\cdot HCl$) C, H, N.

2-[2,4-Dichloro-6-(*N*-hydroxy-*N*-methylamino)phenoxy]styrene (1). A solution of the free base of the *N*-oxide **32** (1.0 g, 0.0032 mol) was heated under reflux for 10 min in ethyl acetate (50 mL). The solution was evaporated and the resulting colourless oil was chromatographed on silica gel (70–230-mesh ASTM), eluting with ether/40–60 °C petroleum. The recovered solid was crystallized from aqueous ethanol to give **1** as a monohydrate: yield 0.41 g (39%); mp 79–80 °C. Anal. ($C_{15}H_{13}Cl_2NO_2\cdot H_2O$) C, H, N.

1-Chloro-6,7-dihydro-5-methyl-5*H*-dibenz[*b*,*g*]-1,4-oxazocine Hydrochloride (28). A mixture of the oxazocine hydrochloride **4** (20.0 g, 0.071 mol), anhydrous sodium formate (9.65 g, 0.14 mol), and formic acid (65.22 g, 1.2 mol) was heated at reflux for 4 h and then allowed to stand at room temperature overnight. The mixture was then poured into ice/water and extracted with ethyl acetate. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to give a yellow solid which was crystallized from ethyl acetate/40–60 °C petroleum to give **30**: yield 12.5 g (59%). Anal. ($C_{15}H_{12}ClNO_2$) C, H, N.

A solution of the *N*-formyl compound **30** (15.0 g, 0.058 mol) in dry THF (100 mL) was added dropwise to a stirred solution of borane/THF complex (1 M, 137 mL, 0.137 mol) at 0 °C under nitrogen. The mixture was stirred at this temperature for 0.5 h and then stirred for a further 6 h at room temperature, after which 6 N HCl (200 mL) was added. The resulting mixture was washed with ethyl acetate and the aqueous layer was then made basic with 880 aqueous ammonia solution followed by extraction with ether. The ether layer was washed with water, dried ($MgSO_4$), and evaporated to give a white solid, which was dissolved in the minimum quantity of dry ethanol. Addition of ethereal HCl precipitated the hydrochloride salt which was crystallized from ethanol/ether to give **28**: yield 9.2 g (61%); mp 173–176 °C. Anal. ($C_{15}H_{14}ClNO\cdot HCl$) C, H, N.

1,3-Dichloro-6,7-dihydro-5-*n*-propyl-5*H*-dibenz[*b*,*g*]-1,4-oxazocine (33). A mixture of the free base of the oxazocine hydrochloride **9** (15.0 g, 0.054 mol), propionaldehyde (52.5 mL, 0.73 mol), 10% palladium on charcoal (3.8 g), and ethanol (750 mL) was shaken vigorously under 3 atm of hydrogen at room temperature for 60 h. The catalyst was then filtered off and the ethanol was evaporated to give a brown oil. This was chromatographed on silica gel (70–230-mesh ASTM), eluting with 10% ether/40–60 °C petroleum. The required fractions (as judged by TLC) were combined to give **33**: yield 12.9 g (74%); mp 56–58 °C. Anal. ($C_{17}H_{17}Cl_2NO$) C, H, N.

5-Allyl-1,3-dichloro-6,7-dihydro-5*H*-dibenz[*b*,*g*]-1,4-oxazocine (35). A solution of the free base of the oxazocine hydrochloride **9** (5.0 g, 0.018 mol) in dry dioxane (75 mL) was cooled and stirred at 0 °C during the addition of a solution of methyllithium (1.9 M in ether, 11.5 mL, 0.022 mol). The solution was then stirred at 0 °C for 0.5 h after which a solution of allyl bromide (2.6 g, 0.022 mol) in ether (25 mL) was added dropwise at 0 °C. After a further 0.5 h at this temperature the mixture was allowed to warm to room temperature and stirred for 48 h. The mixture was then evaporated and the residue partitioned between ether and water. The organic layer was dried ($MgSO_4$) and evaporated to give a solid which was chromatographed on silica gel (70–230-mesh ASTM), eluting with 40–60 °C petroleum. The white solid which was eluted was crystallized from 40–60 °C petroleum to give **35**: yield 3.8 g (66%); mp 74 °C. Anal. ($C_{17}H_{15}Cl_2NO$) C, H, N.

1,3-Dichloro-6,7-dihydro-5*H*-dibenz[*b*,*g*]-1,4-oxazocine-5-carbonyl Chloride (37). A solution of phosgene (12.5% w/w in toluene, 46 mL, 0.058 mol) in dry ether (125 mL) was stirred and cooled at 5–7 °C during the dropwise addition of a solution of the free base of the oxazocine hydrochloride **9** (7.0 g, 0.025 mol) in ether (130 mL) and triethylamine (2.5 g, 0.025 mol). The mixture was stirred at this temperature for 6 h and then for 24 h at room temperature. The precipitated solid was filtered off and washed with ether, and the combined organic layers were evaporated. The resulting yellow solid was crystallized from 40–60 °C petroleum to give **37**: yield 5.0 g (59%); mp 98–100 °C. Anal. ($C_{15}H_{10}Cl_3NO_2$) Cl.

Ethyl 1,3-Dichloro-6,7-dihydro-5*H*-dibenz[*b*,*g*]-1,4-oxazocine-5-carboxylate (43). Sodium ethoxide (2.07 g, 0.03 mol)

was added to a solution of the *N*-carbonyl chloride **37** (1.0 g, 0.0029 mol) in ethanol (10 mL) at room temperature. After 0.5 h the mixture was evaporated, water was added, and the pH was adjusted to 7.0 with 2 N HCl. The aqueous mixture was extracted with ether, which was dried ($MgSO_4$) and evaporated. The solid residue was crystallized from 40–60 °C petroleum to give **43**: yield 0.33 g (32%); mp 79–81 °C. Anal. ($C_{17}H_{15}Cl_2NO_3$) C, H, N.

***N*-Methyl-1,3-dichloro-6,7-dihydro-5*H*-dibenz[*b*,*g*]-1,4-oxazocine-5-carboxamide (44).** A solution of the *N*-carbonyl chloride **37** (1.0 g, 0.0029 mol) in ether (10 mL) was added to a solution of methylamine (33% w/w in ethanol, 1.4 g, 0.015 mol) at room temperature. The mixture was allowed to stand for 0.5 h and then evaporated to dryness. Water was added and the resulting precipitate was filtered off and crystallized from ethanol to give **44**: yield 0.18 g (19%); mp 170–172 °C. Anal. ($C_{16}H_{14}Cl_2N_2O_2$) C, H, N.

1,3-Dichloro-6,7-dihydro-5*H*-dibenz[*b*,*g*]-1,4-oxazocine-5-carbohydrazide (45). A solution of the *N*-carbonyl chloride **37** (1.0 g, 0.0029 mol) in ethanol (105 mL) was added to a stirred solution of hydrazine hydrate (0.4 g, 0.0087 mol) in ethanol (5 mL) at 10 °C. The mixture was stirred at room temperature for 18 h and then evaporated. Water was added and the resulting precipitate was filtered off and crystallized from ethanol to give **45**: 0.42 g (43%); mp 174–176 °C. Anal. ($C_{15}H_{13}Cl_2N_3O_2$) C, H, N.

***N*-Acetyl-1,3-dichloro-6,7-dihydro-5*H*-dibenz[*b*,*g*]-1,4-oxazocine-5-carbohydrazide (46).** The carbohydrazide **45** (0.4 g, 0.0012 mol) was acetylated with acetyl chloride (0.10 g, 0.0013 mol) in benzene (20 mL) containing triethylamine (0.2 g, 0.002 mol) by using standard procedures. The crude product was crystallized from ether/40–60 °C petroleum to give **46**: yield 0.33 g (72%). Anal. ($C_{17}H_{15}Cl_2N_3O_3$) C, H, N.

5-(*p*-Chlorobenzyl)-1,3-dichloro-6,7-dihydro-5*H*-dibenz[*b*,*g*]-1,4-oxazocine (42). A solution of the free base of the oxazocine hydrochloride **9** (3.0 g, 0.011 mol) in benzene (100 mL) containing triethylamine (5.4 g, 0.053 mol) was stirred and cooled at 0 °C during the dropwise addition of *p*-chlorobenzoyl chloride (9.4 g, 0.053 mol). After the mixture was stirred for 3 h at 0 °C, further quantities of triethylamine (3.5 g, 0.035 mol) and *p*-chlorobenzoyl chloride (6.1 g, 0.035 mol) were added, and the mixture was allowed to stir at room temperature for 24 h. The resulting precipitate was filtered off and the organic layer was washed successively with 2 N HCl, 2 N NaOH, and water, dried ($MgSO_4$), and evaporated. The solid residue was chromatographed on neutral alumina (activity I), eluting with ether/ethyl acetate, giving a pure sample of 5-(*p*-chlorobenzoyl)-1,3-dichloro-6,7-dihydro-5*H*-dibenz[*b*,*g*]-1,4-oxazocine (**40**): yield 1.7 g (37%); mp 163–164 °C. Anal. ($C_{21}H_{14}Cl_3NO_2$) C, H, N.

A solution of the amide **40** (2.2 g, 0.0053 mol) in THF (20 mL) was reduced with borane/THF (1 M, 13.0 mL, 0.013 mol) by using the procedure described for the reduction of the *N*-formyl compound **30**. The crude product was chromatographed on neutral alumina (activity I), eluting with ether/40–60 °C petroleum, to give **42**: yield 1.3 g (61%); mp 133–135 °C. Anal. ($C_{21}H_{16}Cl_3NO$) C, H, N.

1-Chloro-6,7-dihydro-6-methyl-5*H*-dibenz[*b*,*g*]-1,4-oxazocine (2) (Scheme II). The potassium salt of 3-(2-hydroxyphenyl)-2-methylprop-1-ene (15.0 g, 0.08 mol) was added to a mixture of the corresponding phenol (17.0 g, 0.12 mol) and 2,3-dichloronitrobenzene (18.0 g, 0.094 mol) and the mixture was stirred and heated at 115 °C under nitrogen for 4.5 h. After cooling, the mixture was partitioned between ether and water. The ether layer was washed with 2 N NaOH solution and water, then dried, and evaporated to give crude 3-[2-(2-chloro-6-nitrophenoxy)phenyl]-2-methylprop-1-ene as a brown oil: yield 24.0 g (100%); IR (thin film) ν max 1540, 1450 cm^{-1}.

The crude diphenyl ether (24 g, 0.08 mol) in a mixture of osmium tetraoxide (catalytic quantity) and aqueous dioxane (3:1, 360 mL) was stirred at room temperature during the addition of sodium periodate (36.0 g, 0.17 mol) for 0.5 h. After stirring for 5 h, the mixture was evaporated and the residue partioned between ether and water. The aqueous layer was extracted with ethyl acetate, and the organic layers were combined, dried ($MgSO_4$), and evaporated to give an oil. This was chromatographed on silica gel (70–230-mesh ASTM), eluting with chloroform, to give a white solid which was triturated with 40–60 °C petroleum giving 1-[2-(2-chloro-6-nitrophenoxy)phenyl]propan-2-one: yield 10.6 g (43%); mp 82–83 °C; IR (Nujol) ν max 1720, 1535, 1450 cm^{-1}.

A mixture of the nitro ketone (4.0 g, 0.013 mol) and 10% palladium on carbon (0.2 g) in ethanol (200 mL) was hydrogenated at atmospheric pressure until the theoretical quantity of hydrogen had been absorbed. The catalyst was then filtered off and the filtrate was evaporated. The solid residue was chromatographed on silica gel (70–230-mesh ASTM), eluting with chloroform, and the resulting white solid was crystallized from aqueous ethanol to give **2**: yield 1.4 g (42%); mp 133–137 °C. Anal. ($C_{15}H_{14}ClNO$) C, H, N.

2. Amino Acids. Method A (Scheme I). 2-(2-Amino-4-chloro-6-methylphenoxy)phenylacetic Acid Hydrochloride (80). A solution of 3-chloro-1-methyl-5*H*-dibenz[*b*,*g*]-1,4-oxazocine-6-one (**80**) (prepared as previously described for the 1,3-dichloro compound **9**, 4.0 g, 0.015 mol) in acetic acid (120 mL) and concentrated HCl (40 mL) was heated under reflux for 50 min. The mixture was then cooled and evaporated, water was added to the residue, and the mixture was adjusted to pH 6 with 880 aqueous ammonia solution. The aqueous layer was extracted with ethyl acetate, which was then dried ($MgSO_4$) and evaporated. The resulting black solid was chromatographed on silica gel (70–230 mesh ASTM), eluting with ethyl acetate/40–60 °C petroleum, giving the free base of the amino acid as a yellow solid. This was converted to the hydrochloride salt with use of ethereal HCl to give **80**: yield 1.6 g (37%); mp 221–223 °C. Anal. ($C_{15}H_{14}ClNO_3$) C, H, N.

2-[4-Chloro-2-methyl-6-(methylamino)phenoxy]phenylacetic Acid (81). A suspension of 3-chloro-1-methyl-5*H*-dibenz[*b*,*g*]-1,4-oxazocine-6-one (prepared as previously described, 19.0 g, 0.069 mol) in dry Me_2SO (290 mL) was stirred at room temperature during the addition of powdered potassium hydroxide (15.6 g, 0.28 mol) and the mixture was stirred for 5 min. The mixture was then cooled (cold water bath) during the dropwise addition of methyl iodide (19.7 g, 0.14 mol) and stirring was continued for 2 h. The mixture was poured into water and extracted with ether, and the organic layer was washed with water, dried ($MgSO_4$), and evaporated to give 3-chloro-1,5-dimethyl-5*H*-dibenz[*b*,*g*]-1,4-oxazocin-6-one: yield 17.5 g (88%); IR ($CHBr_3$) ν max 1660, 1470 cm^{-1}.

The *N*-methyloxazocinone (16.0 g, 0.056 mol) was hydrolyzed by using the procedure described in method A. The crude product was chromatographed on silica gel (70–230-mesh ASTM), eluting with ethyl acetate/40–60 °C petroleum followed by crystallization from aqueous ethanol to give **81**: yield 2.4 g (14%); mp 174–175 °C. Anal. ($C_{16}H_{16}ClNO_3$) C, H, N.

Method B (Scheme II). 2-(2-Amino-6-methylphenoxy)-phenylacetic Acid (59). The preparation of 3-[2-(2-methyl-6-nitrophenoxy)phenyl]prop-1-ene was carried out in essentially the same manner as that of 3-[2-(2-chloro-6-nitrophenoxy)-phenyl]-2-methylprop-1-ene described earlier, using the potassium salt of 2-allylphenol (215 g, 1.25 mol), 2-allylphenol (168 g, 1.25 mol), and 2-chloro-3-nitrotoluene (66.7 g, 0.39 mol). The crude product was distilled under reduced pressure to give pure material: yield 83.6 g (79%); bp 166–168 °C (0.8 mm); IR (thin film) ν max 1640, 1540, 1380 cm^{-1}.

The 2-allyl diphenyl ether (17.0 g, 0.063 mol) was dissolved in a mixture of acetic acid (120 mL) and water (20 mL), and potassium permanganate (44 g, 0.28 mol) was added portionwise over 1.5 h at 0–10 °C. The mixture was stirred for a further 4 h at room temperature. Sodium metabisulfite solution was added and the colorless aqueous mixture was extracted with ethyl acetate. The organic layer was washed with 2 N NaOH solution which was acidified and extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give a crude sample of the nitro acid **99**: yield 13.0 g (72%). A small sample was further purified by chromatography using silica gel (70–230-mesh ASTM) eluting with ethyl acetate, followed by crystallization from aqueous ethanol to give **99**: mp 145–146 °C. Anal. ($C_{15}H_{13}NO_5$) C, H, N.

A solution of the nitro acid **99** (2.0 g, 0.0069 mol) in ethanol (150 mL) was hydrogenated at 3 atm over 10% palladium on carbon (0.4 g) for 16 h at room temperature. The mixture was then filtered and evaporated. The residue was crystallized from aqueous dioxane to give **59**: yield 1.0 g (56%); mp 186–188 °C. Anal. ($C_{15}H_{15}NO_3$) C, H, N.

2-[2-Methyl-6-(methylamino)phenoxy]phenylacetic Acid (60). A mixture of 3-[2-(2-methyl-6-nitrophenoxy)phenyl]prop-1-ene described above (22.7 g, 0.084 mol), iron filings (19.1 g, 0.34 mol), and acetic acid (100 mL) was stirred and heated under nitrogen at 95–100 °C for 2 h. After cooling, the mixture was filtered and the filtrate was evaporated to dryness. The resulting oil was dissolved in ethereal HCl and the precipitated hydrochloride salt was filtered off, washed with ether, and then added to aqueous ammonia solution. The aqueous layer was extracted with ether, which was separated, washed with water, dried ($MgSO_4$), and evaporated to give crude 3-[2-(2-amino-6-methylphenoxy)phenyl]prop-1-ene as an oil: yield 14.5 g (73%); IR (thin film) V_{max} 3400, 1620, 1490 cm^{-1}.

A mixture of the amine (10.6 g, 0.044 mol), acetic anhydride (19.5 g, 0.19 mol), and acetic acid (180 mL) was heated at reflux for 0.5 h before pouring into iced water. The resulting precipitate was filtered off, washed with water, and dried to give crude 3-[2-(2-acetamido-6-methylphenoxy)phenyl]prop-1-ene: yield 11.5 g (93%); IR ($CHBr_3$) ν max 3420, 1685 cm^{-1}.

The acetamidopropene (11.0 g, 0.039 mol) was methylated in Me_2SO (150 mL) containing potassium hydroxide (2.7 g, 0.048 mol) with methyl iodide (26.6 g, 0.19 mol) by using the procedure described in method A to give 3-[2-[2-*N*-methylacetamido)-6-methylphenoxy]phenyl]prop-1-ene: yield 11.0 g (96%); IR (thin film) ν max 1670, 1490, 1230 cm^{-1}.

A solution of the *N*-methylacetamido compound (11.0 g, 0.037 mol) in acetic acid (240 mL) and water (80 mL) was oxidized with potassium permanganate (31.6 g, 0.2 mol) by using the procedure described in the preparation of the nitro acid **99**. The crude product was chromatographed on silica gel (70–230-mesh ASTM), eluting with chloroform, to give 2-[2-methyl-5-(*N*-methylacetamido)phenoxy]phenylacetic acid: yield 6.9 g (60%); IR ($CHBr_3$) ν max 1720, 1640, 1240 cm^{-1}.

A solution of the *N*-methylacetamido acetic acid (6.9 g, 0.022 mol) in a mixture of acetic acid (125 mL) and 2 N HCl (125 mL) was heated under reflux for 12 h. The mixture was then evaporated to dryness and the residue was chromatographed on silica gel (70–230-mesh ASTM), eluting with chloroform. The eluted product was crystallized from aqueous ethanol to give **60**: yield 1.1 g (19%): mp 144–145 °C. Anal. ($C_{16}H_{17}NO_3$) C, H, N.

2-[2-(Dimethylamino)-6-methylphenoxy]phenylacetic Acid (61). A suspension of the amino acid **60** (4.0 g, 0.016 mol), formaldehyde solution (40% w/v in water, 8.0 mL, 0.11 mol), and 10% palladium on carbon (0.4 g) in ethanol (100 mL) was hydrogenated at 3 atm at 50–60 °C for 48 h. The mixture was then filtered and evaporated and the residue was partitioned between ether and water. The ether layer was washed with water, dried ($MgSO_4$), and evaporated. The resulting colorless oil was chromatographed on silica gel (70–230-mesh ASTM), eluting with ether/40–60 °C petroleum, and the eluted solid was crystallized from ether/hexane to give **62**: yield 3.2 g (70%); mp 120–121 °C. Anal. ($C_{17}H_{19}NO_3$) C, H, N.

Pharmacology. Established Adjuvant-Induced Arthritis. The method used was based on procedures described previously.[4-6] On day 0 of the test, 0.05 mL of liquid paraffin containing 5 mg/mL of dead *Mycobacterium tuberculosis* (derived from human strains PN, DT, and C, , grown for 8 weeks, steam killed and dried) was injected into the plantar surface of the left hind paws of male rats (ca. 160–220 g). On day 21, the animals were weighed, and the arthritis was assessed by measurement of the volume of the injected paw with an electronic volume differential meter (the paw volumes measured were linearly related, but not directly proportional, to absolute values). Those animals in which the arthritis was least developed were rejected; in the present investigations, animals with an estimated absolute paw volume of <4 mL were not included. The remaining animals were divided into experimental groups (unless otherwise stated, the drug-treated groups consisted of a maximum of seven rats, the control group 21) such that the mean left hind paw volume reading for each group was approximately equal. The rats were then dosed orally once daily with the drugs on test on days 21–27 inclusive. The left hind paw volumes were redetermined either daily on days 22–28 inclusive or, as in some experiments (relative potency determinations), only on day 28 (ca. 24 h after the final dose). Changes in paw volume were expressed as a percentage of their respective measured initial values, those occurring in drug-treated groups being considered in relation to similar changes occurring in control animals.

Gastric Ulcerogenic Activity. The gastric ulcerogenic activity was assessed by using a modification of the method described by Martindale et al.[7] Groups of 10 female rats (80–120 g) were dosed with the drugs on test over a suitable range of doses. Either 3 or 24 h after dosing, the rats were killed by neck dislocation and the stomachs were removed, washed out with 0.9% w/v saline, and inflated with 70% v/v alcohol. The stomachs were then numbered randomly and stored in 70% v/v alcohol. An operator working "blind" then scored the glandular region of the stomachs for damage using transmitted light for examination. Scoring was on a 0–4 scale of increasing severity. The mean score for each group was calculated and the level of significance of the difference between the control and treatment groups was determined by using the Wilcoxon rank sum test for nonparametric data.[8] The ulcerogenic potential of each drug was expressed as the minimum ulcerogenic dose (MUD), i.e., the range of doses within which falls the lowest dose producing a statistically significant ($p < 0.05$) degree of gastric damage when compared with the controls.

Statistical Methods. Unless otherwise stated, the statistical significance of difference between experimental groups was calculated by using the two-tailed Student's *t* test. Differences were considered significant if $p < 0.05$. In cases where the control and test variances were not homogeneous, the procedure described by Welch[9,10] was employed. Potency ratios were determined by using a standard parallel-line assay method.[11]

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Registry No. **1**, 93565-38-9; **2**, 93565-39-0; **3**·HCl, 93565-40-3; **4**·HCl, 93604-20-7; **5**·HCl, 93565-41-4; **6**·HCl, 93565-42-5; **7**·HCl, 93565-43-6; **8**·HCl, 93565-44-7; **9**, 93566-42-8; **9**·HCl, 93565-45-8; **9**-one, 93566-41-7; **10**·HCl, 93565-46-9; **11**·HCl, 93565-47-0; **12**·HCl, 93565-48-1; **12**-one, 93566-48-4; **12**-one (R^3 = Me), 93566-49-5; **13**, 93565-49-2; **14**·HCl, 93565-50-5; **15**·HCl, 93565-51-6; **16**·HCl, 93565-52-7; **17**·HCl, 93565-53-8; **18**·HCl, 93565-54-9; **19**·HCl, 93565-55-0; **20**·HCl, 93565-56-1; **21**·HCl, 93565-57-2; **22**, 93565-58-3; **23**·HCl, 93565-59-4; **24**, 93565-60-7; **25**·HCl, 93565-61-8; **26**·HCl, 93565-62-9; **27**·HCl, 93565-63-0; **28**, 93566-44-0; **28**·HCl, 93565-64-1; **29**, 93565-65-2; **30**, 93565-66-3; **31**, 93565-67-4; **32**, 93566-43-9; **32**·HCl, 93565-68-5; **33**, 93565-69-6; **34**·HCl, 93604-21-8; **35**, 93565-70-9; **36**, 93565-71-0; **37**, 93565-72-1; **38**, 93565-73-2; **39**, 93565-74-3; **40**, 93565-75-4; **41**, 93565-76-5; **42**, 93565-77-6; **43**, 93565-78-7; **44**, 93565-79-8; **45**, 93565-80-1; **46**, 93565-81-2; **47**, 93565-82-3; **48**·HCl, 93565-83-4; **49**·HCl, 93565-84-5; **50**·HCl, 93565-85-6; **51**, 93565-86-7; **52**, 93565-87-8; **53**, 93565-88-9; **54**, 93565-89-0; **55**, 93565-90-3; **56**, 93565-91-4; **57**, 86308-38-5; **58**, 93565-92-5; **59**, 93565-93-6; **60**, 93565-94-7; **60** (R^3 = NMeAc), 93566-54-2; **61**, 93565-95-8; **62**, 93565-96-9; **63**, 93565-97-0; **64**, 86335-27-5; **65**, 93565-98-1; **66**, 93565-99-2; **67**, 93566-00-8; **68**, 93566-01-9; **69**, 93566-02-0; **70**, 93566-03-1; **71**, 93566-04-2; **72**, 93566-05-3; **73**, 93566-06-4; **74**, 93566-07-5; **75**, 93566-08-6; **76**, 93566-09-7; **77**, 93566-10-0; **78**, 93604-22-9; **79**·HCl, 93566-11-1; **80**, 93566-47-3; **80**·HCl, 93566-12-2; **81**, 93566-13-3; **82**, 93566-14-4; **83**, 93566-15-5; **84**, 93566-16-6; **85**, 93566-17-7; **86**, 93566-18-8; **87**, 93566-19-9; **88**, 93566-20-2; **89**, 93566-21-3; **90**, 93566-22-4; **91**, 93566-23-5; **92**, 93566-24-6; **93**, 93566-25-7; **94**, 93566-26-8; **95**, 93566-27-9; **96**, 93566-28-0; **97**, 93566-29-1; **98**, 93566-30-4; **99**, 93566-31-5; **100**, 93566-32-6; **101**, 86350-18-7; **102**, 93566-33-7; **103**, 93566-34-8; **104**, 93566-35-9; **105**, 93566-36-0; **106**, 93566-37-1; **107**,

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93566-38-2; **10B**, 93566-39-3; EtCHO, 123-38-6; $BrCH_2CH{=}CH_2$, 106-95-6; p-$ClCOC_6H_4Cl$, 122-01-0; 2,3-$Cl_2C_6H_3NO_2$, 3209-22-1; 2-$CH_2{=}C(CH_3)CH_2C_6H_4OH$, 20944-88-1; 2-$CH_2{=}C(CH_3)$-$CH_2C_6H_4OK$, 93566-55-3; 2-Cl,6-$O_2NC_6H_3OC_6H_4$-2-$CH_2C(CH_3)$-$=CH_2$, 93566-45-1; 2-Cl,6-$O_2NC_6H_3OC_6H_4$-2-$CH_2COCH_3$, 93566-46-2; 2-$CH_2{=}CHCH_2C_6H_4OH$, 1745-81-9; 2-$CH_2{=}$ $CHCH_2C_6H_4OK$, 79015-70-6; 2-Cl,3-$O_2NC_6H_3CH_3$, 3970-40-9; 2-CH_3,6-$O_2NC_6H_3OC_6H_4$-2-$CH_2CH{=}CH_2$, 93566-50-8; 2-H_2N,6-$CH_3C_6H_3OC_6H_4$-2-$CH_2CH{=}CH_2$, 93566-51-9; 2-AcNH,6-$CH_3C_6H_3OC_6H_4$-2-$CH_2CH{=}CH_2$, 93566-52-0; 2-AcNMe,6-$CH_3C_6H_3OC_6H_4$-2-$CH_2CH{=}CH_2$, 93566-53-1; fenclofenac, 34645-84-6; 6,8-dichlorodibenz[*b,f*]oxepin-10(11*H*)-one, 93566-40-6.

Mineralocorticoid Properties of Potential Metabolites of 18-Hydroxydeoxycorticosterone and 18-Hydroxyprogesterone

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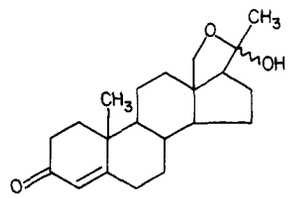
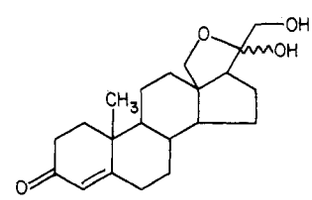
The high secretion rate of 18-hydroxydeoxycorticosterone in hypertensives and the steroids implication as a mineralocorticoid has led to the synthesis of potential di-, tetra-, and hexahydro metabolites of it and 18-hydroxyprogesterone. These potential metabolites have been synthesized by reduction of the double bond and the 3- and 20-ketones, singly or in combination. They have been evaluated for pro- and antimineralocorticoid activity and their affinity for the renal aldosterone receptor. All except one of the potential metabolites either lack or have reduced mineralocorticoid activity and aldosterone receptor binding affinity. The exception is the 3-ketopregn-4-ene-18,20-diol which has high receptor affinity but functions as an aldosterone antagonist.

The physiological role of 18-hydroxydeoxycorticosterone (**4G**) (18-OH-DOC) has been a controversial issue for a number of years. It has mineralocorticoid activity both in vivo[1] and in vitro[2] and, unlike the classical mineralocorticoids, is produced primarily in the zona fasciculata of the adrenal cortex[3] and is ACTH dependent.[4] However its presence in high concentration makes it a mineralocorticoid of potentially great significance.[5] Although the significance of 18-OH-DOC in human essential hypertension is debatable,[6] the parent compound or a metabolite may play a role in sensitizing the kidney to other hypertensinogenic hormones.[7]



4E

(18-hydroxyprogesterone)



4G

(18-hydroxydeoxycorticosterone)

Both oxidized and reduced metabolites of 18-OH-DOC have been isolated. Melby[8] isolated 16,18-dihydroxydeoxycorticosterone from human adrenal incubations.[9] Although inactive as a mineralocorticoid, this metabolite appeared to potentiate the action of aldosterone,[10] although this activity has not been confirmed.[11] Reduced metabolites of 18-OH-DOC have been observed after incubation with the adrenals and liver of adult rats. These metabolites are all tetrahydro derivatives derived from reduction of the A-ring enone, primarily the 3β-hydroxy-5α-pregnane and 3α-hydroxy-5β-pregnane derivatives, although the 3α-hydroxy-5α-pregnane has been tentatively identified.[12] This reduction pattern indicates that the metabolism of 18-OH-DOC is similar to that of progesterone[13] and would be expected to proceed through the saturated 3-ketones. Additionally, the reported isolation of the reduced 20-ketone metabolite of aldosterone indicates that this group is potentially capable of reduction in the 18-OH-DOC series.[14] At the inception of this work, none of the potential dihydro, tetrahydro, and hexahydrometabolites had been adequately characterized. During the course of this study, the 3α-hydroxy-5β-pregnane (**2G**) was described[15a] and, after its completion, the preparation from 18-OH-DOC of a variety of AB-ring potential metabolites was published.[15b] To the best of our knowledge, no published report exists on the biological activity of the metabolites of 18-OH-DOC. As part of our continuing interest in 18-oxygenated steroids,[16] we have prepared a series of di-, tetra-, and hexahydro derivatives of both 18-hydroxyprogesterone (18-OH-PROG, **4E**) and 18-OH-DOC and evaluated them for

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