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6,11-Dihydro-11-oxodibenz[*b,e*]oxepinacetic Acids with Potent Antiinflammatory Activity

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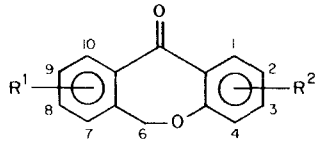
A series of 6,11-dihydro-11-oxodibenz[*b,e*]oxepinacetic acids was synthesized and the antiinflammatory activity determined. Studies on 29 compounds revealed certain structure–activity relationships. In the carrageenan edema test, eight compounds exhibited higher antiinflammatory activities than did indomethacin. Several compounds (**2**, **9**, 14, **22**, **25**) also proved to have activities superior or comparable to indomethacin in suppressing chronic as well as acute inflammation and carrageenan-induced hyperesthesia. Gastric irritation and lethality rates were less frequently observed with these compounds.

Among the various nonsteroidal antiinflammatory drugs, acetic acid derivatives of aromatic and heteroaromatic compounds[1] are reported to be particularly effective in suppressing inflammation. Shen[2] has proposed a most interesting hypothesis concerning the receptor site for 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (indomethacin). Our own research in this field led us to synthesize tricyclic dibenzoxepinacetic acids since these acids in which two benzene rings lack coplanarity were considered to fit the receptor site as is the case with indomethacin. The structure–activity relationships of these derivatives are discussed herein and pharmacological properties of five selected compounds having considerable antiinflammatory activity are described. Recently, analogous studies on dibenzoxepin derivatives have been reported by Hoechst's researchers[3] independently of our work.[4]

Chemistry. Various dibenz[*b,e*]oxepin derivatives (III) were synthesized by the general route outlined in Scheme I and are listed in Table I. Intermediates, 2-carboxybenzyloxyphenylacetic acids (II), were obtained mainly by condensation of phthalides (I) with phenols (method D). Several compounds of type II were also prepared by the reaction of benzyl halides (IV) with phenols, followed by hydrolyses of the resulting benzyloxyphenylacetic acid derivatives (V) (methods F and E). Cyclization of II according to methods A–C described in the Experimental Section gave III. The physical properties of II and V are shown in Table II. Some new compounds were also prepared by the following methods. By esterification, **2**

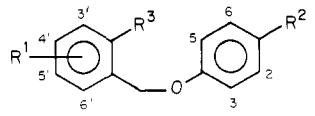
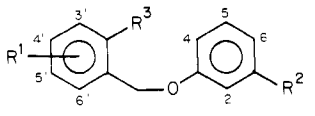
Table I. Physical Properties and Pharmacological Activities of 6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin Derivatives



Compd no.	R^1	R^2	Method	Yield, %	Mp, °C	Recrystn solvent	Formula[a]	Antiinflam act. (carrageenan edema), ID_{50},[i] mg/kg po
1	H	1-CH_2COOH	B	4[b]	145.5–146.5	AcOEt-*n*-C_6H_{14}	$C_{16}H_{12}O_4$	>18
2	H	2-CH_2COOH	A	77	131–132.5	AcOEt	$C_{16}H_{12}O_4$	14.3 (11.5–19.3)
			B	43				
3	H	2-CH_2COOMe	*c*	81	78–79	Et_2O	$C_{17}H_{14}O_4$	15.2 (10.2–31.7)
4	H	2-CH_2COOEt	*c*	91	89–90	C_6H_6-*n*-C_6H_{14}	$C_{18}H_{16}O_4$	17.8 (12.9–29.5)
5	4-NO_2	2-CH_2COOH	*d*	75	182–185	AcOEt-*n*-C_6H_{14}	$C_{16}H_{11}NO_6$	>18
6	8-Cl	2-CH_2COOH	A	32	193–195	$CHCl_3$	$C_{16}H_{11}ClO_4$	41.6 (24.9–103.3)
7	8-OMe	2-CH_2COOH	A	53	165–166	C_6H_6-*n*-C_6H_{14}	$C_{17}H_{14}O_5$	>18
8	9-Cl	2-CH_2COOH	A	8	171–173	$CHCl_3$	$C_{16}H_{11}ClO_4$	>18
9	H	2-CH(Me)COOH (rac)	A	79	Syrup		$C_{17}H_{14}O_4$	2.6 (1.9–4.1)
10	H	2-CH(Me)COOH (*d*)	*e*		Syrup		$C_{17}H_{14}O_4$	1.3 (0.9–1.8)
11	H	2-CH(Me)COOH (*l*)	*e*		Syrup		$C_{17}H_{14}O_4$	7.5 (4.2–28.0)
12	H	2-CH(Me)$COOCa_{0.5}$	*f*	67[f]	180–190		$C_{17}H_{13}O_4Ca_{0.5}$	3.5 (2.8–4.8)
13	8-Cl	2-CH(Me)COOH	A	23	112–114	AcOEt-*n*-C_6H_{14}	$C_{17}H_{13}ClO_4$	7.6 (4.8–20.1)
14	H	3-CH_2COOH	A	38	110.5–111.5	AcOEt	$C_{16}H_{12}O_4$	3.7 (2.9–4.9)
			B	36				
15	H	3-CH_2COOEt	*c*	85	35–35.5	Et_2O-petr ether	$C_{18}H_{16}O_4$	8.6 (5.0–22.9)
16	8-Cl	3-CH_2COOH	A	11	211–213	Me_2CO-*n*-C_6H_{14}	$C_{16}H_{11}ClO_4$	7.6 (4.9–13.5)
17	8-F	3-CH_2COOH	A	35	168–169	C_6H_6-*n*-C_6H_{14}	$C_{16}H_{11}FO_4$	>9
18	8-I	3-CH_2COOH	A	23	237–238	AcOEt-Me_2CO-THF	$C_{16}H_{11}IO_4$	6.7 (5.3–9.4)
19	8-OMe	3-CH_2COOH	A	35	170–171	C_6H_6-*n*-C_6H_{14}	$C_{17}H_{14}O_5$	>9
20	8-Me	3-CH_2COOH	C	33	152–153	Me_2CO-H_2O	$C_{17}H_{14}O_4$	6.6 (4.6–11.9)
21	8-CF_3	3-CH_2COOH	C	41	201–202	C_6H_6	$C_{17}H_{11}F_3O_4$	>9
22	H	3-CH(Me)COOH (rac)	A	51	115.5–117	AcOEt	$C_{17}H_{14}O_4$	0.76 (0.56–1.18)
23	H	3-CH(Me)COOH (*d*)	*g*		102–104	Et_2O-petr ether	$C_{17}H_{14}O_4$	0.43 (0.33–0.62)
24	H	3-CH(Me)COOH (*l*)	*g*		102–104	Et_2O-petr ether	$C_{17}H_{14}O_4$	0.67 (0.53–0.86)
25	8-Cl	3-CH(Me)COOH	A	34	193–194	$CHCl_3$-Et_2O	$C_{17}H_{13}ClO_4$	1.4 (1.1–1.8)
26	8-F	3-CH(Me)COOH	A	34	153–154	IPE-*n*-C_6H_{14}	$C_{17}H_{13}FO_4$	4.0 (3.3–5.0)
27	8-I	3-CH(Me)COOH	A	21	186–187	C_6H_6-*n*-C_6H_{14}	$C_{17}H_{13}IO_4$	4.8 (3.7–6.8)
28	8-CF_3	3-CH(Me)COOH	C	13	173–175	MeOH-H_2O	$C_{18}H_{13}F_3O_4$	>9
29	9-Cl	3-CH(Me)COOH	A	15	132–133	C_6H_6-*n*-C_6H_{14}	$C_{17}H_{13}ClO_4$	11.9 (6.4–42.7)
Indomethacin[h]								8.4 (6.9–10.8)
Phenylbutazone[h]								77.7 (62.2–104.6)
Ketoprofen[h]								12.5 (8.8–21.6)

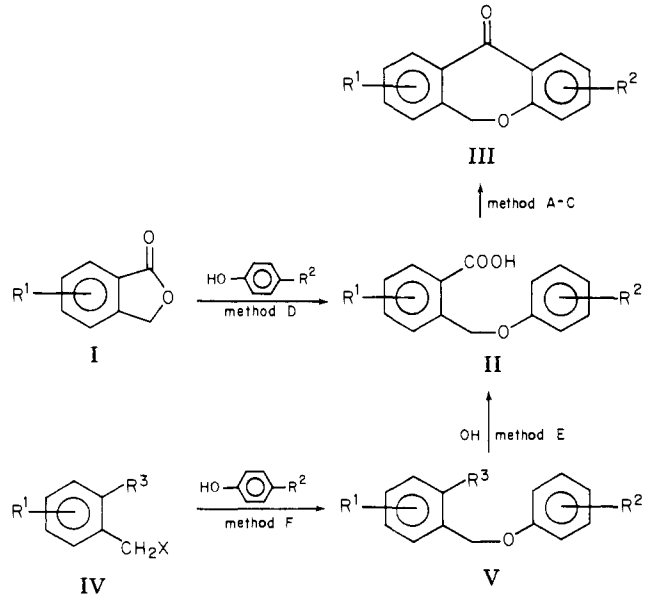
[a] Analyses were obtained for C, H, and, when those elements were present, for N, Cl, I, or Ca. The results obtained for those elements were within ±0.4% of the theoretical values. [b] 1 was separated from the mother liquor of 14 by using a preparative TLC ($CHCl_3$-MeOH-H_2O = 7:3:1, lower phase). [c–g] See the corresponding procedure in the Experimental Section. [h] Indomethacin (mp 157–158°), phenylbutazone (mp 105°), and ketoprofen (mp 94–95°) were synthesized in our Institute for experimental use. [i] ID_{50} values were obtained from the regression line fitted by the least-squares method and their 95% fiducial limits described in parentheses were calculated according to Fieller's equation.[17]

Table II. Intermediates for Table I. 2'-Substituted Benzyloxyphenylacetic Acid Derivatives

Compd no.	R^1	R^2	R^3	Method	Yield, %	Mp, °C	Recrystn solvent	Formula[a]
								
30	H	CH_2COOH	COOH	D	78	181-183	EtOH-H_2O	$C_{16}H_{14}O_5$
31	5'-Cl	CH_2COOH	COOH	D	70	199-201	MeOH-H_2O	$C_{16}H_{13}ClO_5$
32	5'-OMe	CH_2COOH	COOH	D	89	214-215	MeOH-H_2O	$C_{17}H_{16}O_6$
33	4'-Cl	CH_2COOH	COOH	D	31	206-209	MeOH-H_2O	$C_{16}H_{13}ClO_5$
34	H	CH(Me)COOH	COOH	D	64	156-158	EtOH-H_2O	$C_{17}H_{16}O_5$
35	5'-Cl	CH(Me)COOH	COOH	D	69	199-200	MeOH-H_2O	$C_{17}H_{15}ClO_5$
								
36	H	CH_2COOH	COOH	D	59	188-190	EtOH-H_2O	$C_{16}H_{14}O_5$
37	5'-Cl	CH_2COOH	COOH	D	62	210-212	MeOH-H_2O	$C_{16}H_{13}ClO_5$
38	5'-F	CH_2COOH	COOH	D	9[b]	212-214	MeOH-H_2O	$C_{16}H_{13}FO_5$
39	5'-I	CH_2COOH	COOH	E	89	220-222	EtOH-H_2O	$C_{16}H_{13}IO_5$
40	5'-OMe	CH_2COOH	COOH	D	46	198-200	MeOH-H_2O	$C_{17}H_{16}O_6$
41	5'-Me	CH_2COOH	COOH	D	51	198-200	Me_2CO-H_2O	$C_{17}H_{16}O_5$
42	5'-CF_3	CH_2COOH	COOH	E	87	192-193	Me_2CO-n-C_6H_{14}	$C_{17}H_{13}F_3O_5$
43	H	CH(Me)COOH	COOH	E	89	172-174	EtOH-H_2O	$C_{17}H_{16}O_5$
44	5'-Cl	CH(Me)COOH	COOH	D	58	189-191	MeOH-H_2O	$C_{17}H_{15}ClO_5$
45	5'-F	CH(Me)COOH	COOH	D	10[c]	193-194	$CHCl_3$-Et_2O	$C_{17}H_{15}FO_5$
46	5'-I	CH(Me)COOH	COOH	E	53	197-198	EtOH-H_2O	$C_{17}H_{15}IO_5$
47	5'-CF_3	CH(Me)COOH	COOH	E	95	201-202	C_6H_6-Me_2CO	$C_{18}H_{15}F_3O_5$
48	4'-Cl	CH(Me)COOH	COOH	D	66	172-174	MeOH-H_2O	$C_{17}H_{15}ClO_5$
49	5'-I	CH_2COOH	COOEt	F	92	146-147	C_6H_6	$C_{18}H_{17}IO_5$
50	5'-CF_3	CH_2COOH	COOEt	F	49[d]	108-109	C_6H_6-n-C_6H_{14}	$C_{19}H_{17}F_3O_5$
51	H	CH(Me)COOH	CN	F	82	83-85	IPE-n-C_6H_{14}	$C_{17}H_{15}NO_3$
52	5'-I	CH(Me)COOH	COOEt	F	65	99-100	C_6H_6-n-C_6H_{14}	$C_{19}H_{19}IO_5$
53	5'-CF_3	CH(Me)COOH	COOEt	F	43[d]	114-115	n-C_6H_{14}	$C_{20}H_{19}F_3O_5$

[a] All compounds were analyzed for C, H, and, if present, Cl, I, and N; analytical results were within ±0.4% of the theoretical values. [b] 3-(5-Phthalidyloxy)phenylacetic acid (mp 147-148°) was obtained as the main product. Yield, 38%. Anal. Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.99; H, 4.36. [c] 2-[3-(5-Phthalidyloxy)phenyl]propionic acid (mp 153-154°) was obtained as the main product. Yield, 56%. Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.50; H, 4.90. [d] Based on methyl 4-trifluoromethyl-2-methylbenzoate.

Scheme I



and 14 were led to the corresponding Me (3) and Et (4) esters, and to Et ester (15), respectively. Compound 5 was made by nitration of 2. Optical resolutions of 9 and 22 were accomplished with cinchonidine and optically active methylbenzylamine, respectively. Further, one of the starting materials, methyl 2-bromomethyl-4-iodobenzoate (IV), was obtained by reaction of the 2-methyl derivative with NBS. The corresponding 4-trifluoromethyl compound also was prepared by the coupling of methyl 2-methyl-4-iodobenzoate with CF_3I, followed by bromination (NBS).

Pharmacology and Structure-Activity Relationships. The test compounds were first subjected to the carrageenan edema test in male rats according to the method of Winter et al.[5] The compounds, as a suspension in 0.5% CMC, were administered orally to the animals in doses of 1, 3, and 9 mg/kg (13, 14, 17-21, 28), 2, 6, and 18 mg/kg (1-8, 15, 16), and 0.1-4.5 mg/kg (9-12, 22-27, 29). Seven animals were used to test each dose. In Table I, the edema-inhibiting activities are expressed as ID_{50} estimated from dose-response curves of the compounds tested. The compounds more effective than indomethacin were 9, 10, 12, 14, and 22-27. Compound 23 exhibited the highest activity, being 19.5, 180.7, and 29.1 times more active on the weight basis and 15.4, 165.4, and 32.3 times more active on the molar basis as compared with indomethacin, 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione (phenylbutazone), and 2-(3-benzoylphenyl)propionic acid (ketoprofen), respectively. Compounds 11, 13, 15, 16, 18, 20, and 29 revealed activities almost equal to those of indomethacin. In a series of these analogues, 3-acetic acids (14-21) were more active than 2-acetic acids (2-8), while the 1-acetic acid (1) was inactive in a dose of 18 mg/kg or less.

Transformation of acetic acids to esters (**3**, **4**) and Ca salt (**12**) produced little change in the activity. On the other hand, introduction of a methyl group at the α position of the acetic acid led to compounds with remarkably enhanced activity (**9**, **13**, **22**, **25–27**). Of these α-methyl analogues, *d* isomers tended to be more active than *l* isomers (**10** vs. **11**, **23** vs. **24**) although no significant difference was seen in the ID_{50} values between **23** and **24**. As for structural modification in the molecule, 8-substituted derivatives surpassed 9-substituted ones in activity (**6** vs. **8**, **25** vs. **29**). The doses inhibiting the edema by 30% were about 3 mg/kg in **6** and more than 18 mg/kg in **8**. However, substituents such as halogen, Me, OMe, and CF_3 groups in this ring reduced the activity of the parent compound, in general. The reduction in the activity was marked especially in cases of 8-OMe analogues (**7**, **19**) and 8-CF_3 analogues (**21**, **28**). With respect to the relationships between the antiinflammatory activity (carrageenan edema) and the structures of the above compounds, it is evident that the 2- and 3-acetic acids which satisfy the requirements of Shen's receptor model are active and that the 1-acetic acid which does not fit the model is inactive. Of the tricyclic acids in the literature 2-(5*H*-[1]benzopyrano[2,3-*b*]pyridin-7-yl)propionic acid (Y-8004)[6] shows activities comparable to those of indomethacin but 10-methylphenothiazine-2-acetic acid (metiazinic acid)[7] and 2-(9-oxoxanthen-2-yl)propionic acid (Y-5554)[8] exhibit activities which are less potent. These compounds do not fit the model. The other structurally related compounds, 2-(3-phenoxyphenyl)propionic acid (fenoprofen)[9] and ketoprofen,[10] conform to the model, but the former is far less active than the latter. These facts indicate that Shen's model represents one of several receptors and that the effects of the benzene ring and the ethereal and carbonyl groups of the dibenzoxepin series on the activities should be elucidated. In consideration of the chemical structure and efficacy of the compounds in Table I, five compounds (**2**, **9**, **14**, **22**, **25**) were selected for further pharmacological tests. The results obtained are shown in Table III. Measurement was made of the effect on adjuvant-carrageenan-induced inflammation (ACII) described by Mizushima et al.[11] as well as adjuvant arthritis[12] in female rats. In these tests, ten animals were used to test each dose. The experiments showed that **9**, **14**, and **22** were approximately equal to or higher than indomethacin in the activity suppressing ACII, while **2** had a lower activity than indomethacin. The effects of **22** and **25** at 0.25 mg/kg and of **14** at 0.5 mg/kg against adjuvant arthritis were comparable to those of indomethacin at 0.5 mg/kg. **2** (10 mg/kg) showed almost equal activity to 30 mg/kg of phenylbutazone. Compound **9** was weaker than **22** and **25** in the effect. As for analgesic activity measured according to the acetic acid writhing method of Koster et al.[13] in male mice (ten animals at each dose level), **9** and **22** were comparable to indomethacin and **2**, **14**, and **25** to ketoprofen. When tested according to Randall–Selitto's method[14] using male rats (seven animals at each dose level), however, **9**, **14**, **22**, and **25** were about 3.5–8.9 times as potent as indomethacin and ketoprofen. In addition, the induction of gastric lesion was tested according to the method of Jahn and Adrian[15] in male rats (ten animals at each dose level). In this assay, all five analogues tended to be less active than indomethacin and ketoprofen but more active than phenylbutazone. From the statistical viewpoint, however, the compounds significantly less active than indomethacin were **2**, **14**, and **25**. Oral LD_{50} values were determined 7 days after administration of test compounds at each dose level in ten male rats. All compounds except **25** revealed lower acute toxicity as

Table III. Pharmacological Activities (po) of 6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin Derivatives

Compd	ACII,[a] % inhibition (mean ± SE)				Adjuvant arthritis, % inhibition (mean ± SE)		Analgesic activity		Gastric lesion, UD_{50}, mg/kg	LD_{50}, mg/kg
	Acute phase		Prolonged phase		Prophylactic treatment (mg/kg)	Therapeutic treatment (mg/kg)	Acetic acid writhing, ED_{50}, mg/kg	R.S.,[b] $AID_{2.0}$, mg/kg		
	1 mg/kg	2 mg/kg	1 mg/kg	2 mg/kg						
2		28 ± 2.3		55 ± 5.6	77 ± 3.0 (10)	56 ± 1.2 (10)	95 (48–187)[c]	3.18 (2.54–3.79)	63.0 (18.0–221.0)	199.0 (184.8–215.6)
9		57 ± 3.3		82 ± 4.5	36 ± 3.8 (0.25)	12 ± 4.0 (0.25)	14 (9–22)	0.40 (0.25–0.55)	14.1 (6.4–31.0)	130.7 (108.9–156.8)
14		45 ± 4.6		89 ± 4.3	55 ± 4.4 (0.5)	31 ± 1.5 (0.5)	58 (30–109)	0.44 (0.22–0.68)	79.9 (48.4–131.8)	109.6 (84.3–142.5)
22	59 ± 3.7		110 ± 5.5		55 ± 4.9 (0.25)	30 ± 2.1 (0.25)	11 (6–20)	0.18 (0.10–0.27)	11.4 (7.2–18.0)	34.2 (26.7–43.8)
25		NT[d]		NT	50 ± 3.1 (0.25)	26 ± 1.8 (0.25)	36 (24–54)	0.28 (0.18–0.38)	32.3 (19.7–53.0)	12.1 (11.1–13.2)
Indomethacin	48 ± 3.9		85 ± 7.1		48 ± 4.2 (0.5)	26 ± 1.1 (0.5), 58 ± 3.5 (30)	10 (6–17)	1.53 (1.20–1.86)	6.6 (2.2–19.8)	18.9 (14.9–24.0)
Phenylbutazone	NT		NT		71 ± 3.1 (30)		>400	17.22 (13.44–20.99)	96.0 (37.0–248.0)	NT
Ketoprofen	NT		NT		84 ± 2.7 (2)	42 ± 2.0 (1)	71 (35–142)	1.61 (1.40–1.82)	6.80 (2.4–19.0)	101.0 (73.9–138.6)

[a] ACII = adjuvant-carrageenan-induced inflammation. [b] R.S. = Randall–Selitto's method. $AID_{2.0}$ indicates the dose of test compound required to double the pain index of the control group (pain index = pain threshold after carrageenan injection/pain threshold before carrageenan injection). [c] Figures in parentheses indicate 95% fiducial limits. ED_{50}, UD_{50}, LD_{50}, and their fiducial limits were calculated according to Litchfield–Wilcoxon's method[16] and $AID_{2.0}$ and its fiducial limits according to the same method as in case of ID_{50} values in Table I. [d] NT = not tested.

compared with indomethacin. The fact that **25** had the lowest LD_{50} value suggests that introduction of a chlorine atom in the molecule may enhance the toxicity.

From the pharmacological and toxicological points of view, several of the compounds in this series show good potential as antiinflammatory agents. Further studies are in progress and the data will be published in succeeding papers.

Experimental Section

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Ir (KBr) and NMR spectra (in Me_2SO-d_6 or $CDCl_3$ using Me_4Si as an internal standard) were measured on a Hitachi 285 spectrophotometer and a Hitachi R-20B spectrometer (60 MHz), respectively. These spectral data were an accordance with the proposed structures. Where the analyses are indicated only by the symbols of the elements, the analytical results were within ±0.4% of theorectical values.

The following examples are representative of each procedure.

Method A. 2-(6,11-Dihydro-11-oxodibenz[b,e]oxepin-3-yl)propionic Acid (22). A mixture of **43** (40 g, 133 mmol) and PPE prepared from EtOH (87 ml) and P_2O_5 (130 g) was stirred at 120° for 50 min. The reaction mixture was carefully poured into ice water and extracted with Et_2O. The extract was washed with a saturated NaCl solution, dried (Na_2SO_4), and evaporated to give a dark brown oily residue. It was heated with KOH (11.2 g) in 60% EtOH (200 ml) at reflux temperature for 30 min, cooled, and acidified with HCl to give a resulting precipitate which was collected. Recrystallization from AcOEt-n-C_6H_{14} gave colorless crystals of **22** (19.3 g, 51%), mp 115–117°. Anal. ($C_{17}H_{14}O_4$) C, H.

Method B. 6,11-Dihydro-11-oxodibenz[b,e]oxepin-2-acetic Acid (2). A stirred mixture of **30** (15 g, 52 mmol) and PPA prepared from 85% H_3PO_4 (61 g) and P_2O_5 (89 g) was heated at 80° for 50 min, poured into ice water, made basic with 20% NaOH, and washed with Et_2O. The aqueous solution was acidified with HCl and the product was extracted with AcOEt and the washed, dried extract was concentrated in vacuo. The residue was crystallized from AcOEt-n-C_6H_{14} to give colorless crystals of **2** (6.1 g, 43%), mp 131–132.5°. Anal. ($C_{16}H_{12}O_4$) C, H.

Method C. 6,11-Dihydro-8-trifluoromethyl-11-oxodibenz[b,e]oxepin-3-acetic Acid (21). A mixture of **42** (0.80 g, 2.3 mmol) and $SOCl_2$ (2 ml) in dry C_6H_6 (30 ml) was refluxed for 2 h and concentrated to dryness in vacuo. The oily residue was dissolved in dry CH_2Cl_2 (30 ml), and anhydrous $AlCl_3$ (0.55 g, 4.1 mmol) was added to the solution while stirring in an ice bath. After 20 min, the reaction mixture was poured into ice water and extracted with $CHCl_3$ and the washed, dried extract was concentrated. The oily residue was hydrolyzed in 5% NaOH (20 ml) at room temperature for 30 min and the solution was acidified with 5% HCl and extracted with $CHCl_3$. The crude product obtained on evaporation of the solvent was chromatographed on silica gel using $CHCl_3$–MeOH (10:1) and the eluate afforded a white solid which was crystallized from C_6H_6 yielding **21** (0.31 g, 41%), mp 201–202°. Anal. ($C_{17}H_{11}F_3O_4$) C, H.

Method D. 3-(2-Carboxybenzyloxy)phenylacetic Acid (36). A stirred mixture of phthalide (23.5 g, 120 mmol) and disodium 3-hydroxyphenylacetate (23.8 g, 120 mmol) was heated at 180° for 30 min and then at 225° for 30 min, cooled, and dissolved in water. After the solution was acidified with HCl, the resulting precipitate was collected and crystallized from EtOH–H_2O to give colorless crystals of **36** (20.2 g, 59%), mp 188–190°. Anal. ($C_{16}H_{14}O_5$) C, H.

Method E. 2-[3-(2-Carboxy-5-trifluoromethyl)benzyloxyphenyl]propionic Acid (47). A suspension of **53** (1.2 g, 3.0 mmol) in 2.5% NaOH (40 ml) was stirred at room temperature for 1 h, cooled, and acidified with HCl. The resulting precipitate was collected, washed with water, and crystallized from C_6H_6–n-C_6H_{14} to yield colorless crystals of **47** (1.1 g, 95%), mp 201–202°. Anal. ($C_{18}H_{13}F_3O_4$) C, H.

Similarly **43** was also obtained from **51** by treatment with 20% NaOH under reflux for 10 h.

Method F. 3-(2-Ethoxycarbonyl-5-iodobenzyloxy)phenylacetic Acid (49). To a stirred solution of 3-hydroxyphenylacetic acid (0.39 g, 2.6 mmol) and Na (0.12 g, 5.2 mg-atom) in EtOH (24 ml) was added methyl 2-bromomethyl-4-iodobenzoate (0.91 g, 2.6 mmol) and heated under reflux for 8 h. After evaporation of the solvent, the residue was dissolved in water. The solution was acidified with HCl and extracted with $CHCl_3$. Concentration of the extract and crystallization of the residue from C_6H_6 gave colorless crystals of **49** (1.04 g, 92%), mp 146–147°. Anal. ($C_{18}H_{17}IO_5$) C, H, I.

Similarly, **51** was also obtained from 2-cyanobenzyl chloride and 2-(3-hydroxyphenyl)propionic acid.

Esterification. Ethyl 6,11-Dihydro-11-oxodibenz[b,e]oxepin-3-acetate (15). A solution of **14** (10 g, 37 mmol) in EtOH (200 ml) and concentrated H_2SO_4 (5 ml) was refluxed for 3 h and worked up in the usual procedure. The crude product was crystallized from Et_2O–petroleum ether to give colorless crystals of **15** (9.1 g, 82%), mp 35–35.5°. Anal. ($C_{18}H_{16}O_4$) C, H.

Nitration. 4-Nitro-6,11-dihydro-11-oxodibenz[b,e]oxepin-2-acetic Acid (5). To a stirred solution of **2** (2.68 g, 10 mmol) in 80% H_2SO_4 (5 ml), a mixture of 80% H_2SO_4 (5 ml) and fuming HNO_3 (sp gr 1.50) (0.72 g, 11 mmol) was added dropwise over a period of 20 min at a temperature below 6°. The stirring was continued for another 2 h and the mixture was poured into ice water. The resulting precipitate was collected and crystallized from AcOEt-n-C_6H_{14} to yield yellow crystals of **5** (2.36 g, 75%): mp 182–185°; NMR (Me_2SO-d_6) δ 3.67 (s, 2 H, $-CH_2CO-$), 5.34 (s, 2 H, $-CH_2O-$), 7.40–7.65 (m, 3 H, C-7 to C-9 protons), 7.84 (m, 1 H, C-10 proton), 7.89 (d, J = 3 Hz, 1 H, C-3 proton), and 8.28 ppm (d, J = 3 Hz, 1 H, C-1 proton). Anal. ($C_{16}H_{11}NO_6$) C, H, N.

Optical Resolution of 2-(6,11-Dihydro-11-oxodibenz[b,e]oxepin-2-yl)propionic Acid (9). A mixture of **9** (11.3 g, 40 mmol) and cinchonidine (11.8 g, 40 mmol) in C_6H_6 (1500 ml) was warmed to give a clear solution and allowed to stand overnight at room temperature. The resulting precipitate was collected and recrystallized four times from AcOEt and the free acid was liberated from the salt by shaking with a mixture of diluted HCl and $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated. The syrupy residue was purified by adding petroleum ether in its Et_2O solution. The separated syrup was dried in vacuo over P_2O_5 to yield 0.95 g of the l isomer (**11**): $[\alpha]^{25}D$ −38.2° (c 1.1, EtOH). Anal. ($C_{17}H_{14}O_4$) C, H.

The first mother liquor, C_6H_6 solution from the l isomer resolution mentioned above was concentrated to 100 ml. After standing at room temperature, the precipitate was filtered. The filtrate was concentrated to 10 ml and warmed to give a clear solution. The solution was allowed to stand at room temperature and the resulting salt was collected. The free acid was regenerated and purified in the same manner as described above to yield 0.47 g of the d isomer (**10**) as pale yellow syrup: $[\alpha]^{25}D$ +38.2° (c 1.4, EtOH). Anal. ($C_{17}H_{14}O_4$) C, H.

Calcium 2-(6,11-Dihydro-11-oxodibenz[b,e]oxepin-2-yl)propionate (12). In NaOMe solution prepared from Na (0.23 g, 0.01 g-atom) and MeOH (20 ml) was dissolved **9** (2.82 g, 10 mmol). After evaporation of the solvent, water (40 ml) was added to the residue. To the cooled solution was added dropwise a solution of $CaCl_2$ (0.56 g, 5 mmol) in water (10 ml) and the precipitated crystals were collected, washed with water, and dried to give an analytical sample of **12** (2.03 g, 67%), mp 180–190°. Anal. ($C_{17}H_{13}O_4 \cdot 0.5Ca$) C, H, Ca.

Optical Resolution of 2-(6,11-Dihydro-11-oxodibenz[b,e]oxepin-3-yl)propionic Acid (22). A mixture of **22** (10.0 g, 35.4 mmol) and d-α-methylbenzylamine (4.3 g, 35.5 mmol) in AcOEt (600 ml) was warmed to give a clear solution and allowed to stand overnight at room temperature. The precipitated salt was collected and recrystallized four times from AcOEt and the free acid was liberated from the salt by shaking with a mixture of diluted HCl and Et_2O. Evaporation of the Et_2O layer and recrystallization of the residue from Et_2O–petroleum ether gave the d isomer **23** as colorless crystals: mp 102–104°; yield, 0.98 g; $[\alpha]^{26}D$ +38.6° (c 2.0, EtOH). Anal. ($C_{17}H_{14}O_4$) C, H.

A mixture of enriched l-acid (6.7 g, 23.7 mmol), recovered in the usual way from the d isomer resolution mentioned above, and l-α-methylbenzylamine (2.9 g, 23.9 mmol) in AcOEt (500 ml) was warmed to give a clear solution. After standing overnight at room temperature, the precipitated salt was collected and recrystallized four times from AcOEt. The acid was regenerated in the same manner as described above. Recrystallization from Et_2O–pe-

troleum ether gave the *l* isomer **24** as colorless crystals: mp 102–104°; yield, 1 g; $[\alpha]^{26}D$ −39.3° (*c* 2.1, EtOH). Anal. ($C_{17}H_{14}O_4$) C, H.

Methyl 2-Bromomethyl-4-iodobenzoate. A mixture of methyl 4-iodo-2-methylbenzoate (0.83 g, 3 mmol), NBS (0.53 g, 3 mmol), and benzoyl peroxide (0.07 g) in CCl_4 (20 ml) was refluxed with stirring for 19 h and filtered. The filtrate was washed with 2% NaOH and water and dried. After removal of the solvent, the residue was purified by silica gel chromatography using C_6H_6 and crystallized from *n*-C_6H_{14}: yield, 0.85 g (76%); mp 67.5–68.5°. Anal. ($C_9H_8BrIO_2$) C, H.

Methyl 2-Methyl-4-trifluoromethylbenzoate. Methyl 4-iodo-2-methylbenzoate (7.0 g, 25 mmol), active Cu[16] (10 g, dried under vacuum at 100–110° for 5 h), and CF_3I (17 g, 87 mmol) in dry DMF (14 ml) were put into a stainless tube which was chilled at −40 to −50°. The sealed tube was heated at 130–140° for 72 h. After cooling, the reaction mixture was shaken with $CHCl_3$. The washed, dried $CHCl_3$ extract was concentrated and the residue was separated on silica gel chromatography using C_6H_6–petroleum ether (1:1) as an elute. The oily residue was distilled under reduced pressure to yield a colorless oil of 4.3 g (80%): bp 105–107° (30 mm). Anal. ($C_{10}H_9F_3O_2$) C, H.

Methyl 2-Bromomethyl-4-trifluoromethylbenzoate. A mixture of methyl 2-methyl-4-trifluoromethylbenzoate (2.18 g, 10 mmol), NBS (1.78 g, 10 mmol), and benzoyl peroxide (0.5 g) in CCl_4 (40 ml) was refluxed for 8 h and treated in the same manner as described above. The crude colorless oil which showed a methylene proton signal at δ 4.99 (s, 2 H) in the NMR spectrum ($CDCl_3$) was used in the next step without further purification.

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Hypolipidemic Alkoxybenzoic Acids

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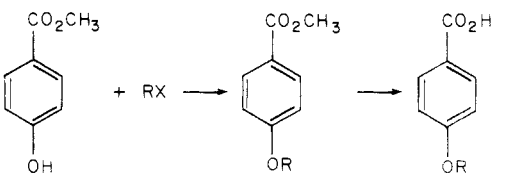
The preparation of a series of *p*-alkoxybenzoic acids bearing aromatic ring substituents or modified alkyl chains is described. The compounds were screened in rats for serum sterol and triglyceride-lowering activity.

The serum sterol and triglyceride-lowering properties of the homologous *p*-(*n*-alkoxy)benzoic acids have been reported.[1] *p*-Hexadecyloxybenzoic acid was selected as the most interesting member of this series; however, administration of this compound to dogs was accompanied by undesirable side effects on the central nervous system. In an effort to find a compound lacking this toxicity, the preparation of a variety of *p*-alkoxybenzoic acid analogues was undertaken. Benzoic acids bearing aromatic ring substituents (**59–63**) or modified alkoxy groups are described here. The latter class includes acids having γ-substituted tetradecyloxy (**64–69**), ω-substituted alkoxy (**70–91**), branched primary alkoxy (**92–94**), *sec*-alkoxy (**95–99**), and *tert*-alkoxy groups (**100–105**). Additionally, olefinic (**106–112**), acetylenic (**113**), polyunsaturated (**114, 115**), and oxygenated (**116–120**) derivatives are reported.

The procedure of greatest utility for the preparation of these analogues involved the alkylation of a phenoxide with the requisite bromide or methanesulfonate (Scheme I). Methyl *p*-hydroxybenzoate (methylparaben) as well as

Scheme I



certain ring-substituted methylparabens and *p*-hydroxybenzoic acids[2] were the phenoxides alkylated in this manner. The ester products were saponified to yield the corresponding acids. Esters and acids prepared by these procedures (methods A and B) are among those shown in Tables I–IV. These include acids having ring substituents, γ-substituted tetradecyloxy, ω-substituted alkoxy, branched primary alkoxy, and *sec*-alkoxy groups, as well as olefinic, acetylenic, polyunsaturated, and oxygenated chains.

The bromides required for these preparations were obtained by the action of phosphorus tribromide or hy-