Potential Hypolipidemic Agents. 7.† Synthesis and Lipid-Lowering Properties of 2-(Dibenzofuranyloxy)-2-methylpropionates and Related Compounds

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Ethyl 2-(4-dibenzofuranyloxy)-2-methylpropionate (8) was found to be one of the most potent compounds of a series of 2-(dibenzofuranyloxy)-2-methylpropionates and some closely related compounds which have been synthesized and evaluated as potential hypolipidemic agents. Compound 8 reduces cholesterol and triglyceride levels in mice and rats to a considerable extent. In rats this reduction occurs at dose levels which are lower than those of clofibrate in comparative experiments. The 2 and 3 isomers (4 and 6) decrease the blood levels of triglycerides significantly in mice while the levels of cholesterol are unaffected. 2-(1-Dibenzofuranyloxy)-2-methylpropionate (2) is completely inactive in mice. Substitution with chlorine in the 1 and 3 positions of 2-(4-dibenzofuranyloxy)-2-methylpropionate is favorable for activity and this is also the case with substitution in the 6 position by a methoxyl group. The hypolipidemic properties of the compounds, which are most active in mice, have been confirmed in spontaneously hyperlipidemic old rats.

Several studies in man have shown that an intimate correlation exists between the occurrence of atherosclerotic diseases and elevated levels of cholesterol and/or triglycerides in blood plasma. Consequently a rational approach to the treatment and the prevention of atherosclerotic diseases would be to decrease high levels of lipids in plasma by pharmacological means. A number of compounds with lipid-lowering properties have been investigated during recent years. Special attention has been focused on aryloxyacetic acid derivatives, and one of these, ethyl 2-(4-chlorophenoxy)-2-methylpropionate (clofibrate), is the agent most commonly used for the treatment of hyperlipidemia. Clofibrate is effective in the treatment of hyperlipoproteinemia of types IIB, III, and IV,[2] *i.e.*, elevated levels of triglycerides, while the effect on hyperlipoproteinemia of type IIA, *i.e.*, high levels of cholesterol only, is less pronounced.[3]

The aim of the present investigation has been to find compounds more potent than clofibrate. In this paper we wish to report the synthesis and lipid-lowering properties of a series of dibenzofuranyloxyacetic acid derivatives listed in Table I.

Chemistry. The compounds were prepared from various hydroxydibenzofurans by reaction with 1,1,1-trichloro-*tert*-butyl alcohol under alkaline conditions, followed by esterification with ethanol. In some cases, sodium salts of the hydroxydibenzofurans were allowed to react with the appropriate bromo esters.

The hydroxydibenzofurans used as starting materials were prepared according to known procedures. However, some results of interest were obtained which are reported. The synthesis of 1-chloro-4-hydroxydibenzofuran was performed by chlorination of 4-hydroxydibenzofuran with sulfuryl chloride in chloroform.[4] It was found that an extension of the reaction time from 1.5 to 24 hr increases the yield considerably. In addition, a small amount of 3-chloro-4-hydroxydibenzofuran was isolated from the reaction mixture. A practical route to 8-chloro-3-hydroxydibenzofuran started with the treatment of 3-nitrodibenzofuran with sulfuryl chloride. The resulting 8-chloro-3-nitrodibenzofuran was reduced with hydrazine and Raney nickel catalyst to 3-amino-8-chlorodibenzofuran, which was converted to the corresponding phenol *via* diazotization (*cf.* ref 5 and 6). The preparations of 3-hydroxy-4-methoxydibenzofuran and 4-hydroxy-6-methoxydibenzofuran have been described by Gilman, *et al.*,[7] who lithiated 4-methoxydibenzofuran and obtained a mixture of the two phenols after oxidation of the lithiated products. The phenols were then separated utilizing the different solubilities of their sodium salts. However, tlc revealed that this separation was insufficient and we had to purify the two isomers further by column chromatography. It was also found to be more practical to convert the mixture of lithiated products to the corresponding phenols by treatment with tributyl borate, followed by oxidation with hydrogen peroxide. This method also gives a superior yield.

Structure–Activity Relationships. All the esters listed in Table I were tested for hypolipidemic effects in male mice of the NMRI strain with a body weight of 20–22 g. Some of the most potent compounds were subjected to further tests on spontaneously hyperlipidemic old male rats of the Sprague–Dawley strain with a body weight of 550–650 g, and an age of 1–1.5 years.[8] The compounds were supplemented to the diet, usually 0.3%, and the levels of cholesterol and triglycerides in plasma were determined after 6 days of treatment. Clofibrate was used as the reference drug. The results are given in Tables II (mouse) and III (rat).

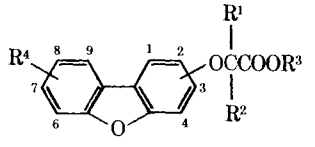
Four unsubstituted dibenzofuranyloxy-2-methylpropionates (2, 4, 6, and 8) have been tested in the mouse model. It was found that the compound with the side chain in the 1 position (2) lacked effect on both cholesterol and triglyceride levels in plasma. The 2 and 3 isomers (4 and 6) showed appreciable triglyceride-lowering properties, decreasing the blood levels by 35 and 45%, respectively. The plasma cholesterol levels were not affected. The hypolipidemic effect of the two compounds 4 and 6 is very similar to that of clofibrate, which in our tests gives a 45% reduction of the triglyceride level while the cholesterol level increases with 11%. Ethyl 2-(4-dibenzofuranyloxy)-2-methylpropionate (8) showed a considerable cholesterol-lowering effect, decreasing the cholesterol concentration by 11%. The triglyceride level was reduced by 32%.

The cholesterol-lowering effect of compound 8 was considered to be so interesting that the hypolipidemic properties of some closely related derivatives were investigated. Two derivatives of compound 8 with less branching in the side chain have been studied. Ethyl 2-(4-dibenzofuranyloxy)propionate (10) gave a significant decrease in plasma cholesterol but showed no effect on the triglyceride level. The corresponding acetate 12 lacked effect on both cholesterol and triglyceride levels. These observations led us to focus our interest on 2-(4-dibenzofuranyloxy)-2-methylpropionates.

† For part 6, see ref 1.

‡ This paper is dedicated to my former professor, Alfred Burger.

Table I. Dibenzofuranyloxyacetic Acid Derivatives



Compd no.	Side chain in position	R^1	R^2	R^3	Ring substituent R^4	Bp (mm), °C	Mp, °C	Recrystn solvent	Yield purified, %	Formula[a]
1	1	Me	Me	H			138–140	EtOH–H_2O	72	$C_{16}H_{14}O_4$[b]
2	1	Me	Me	Et		156–158 (0.06)	74–77[c]		58	$C_{18}H_{18}O_4$
3	2	Me	Me	H			113.5–115	EtOH–H_2O	92	$C_{16}H_{14}O_4$
4	2	Me	Me	Et		168–174 (0.1)			63	$C_{18}H_{18}O_4$
5	3	Me	Me	H			104–106.5	EtOH–H_2O	65	$C_{16}H_{14}O_4$
6	3	Me	Me	Et		183–185 (0.1)	45–46	MeOH–H_2O	80	$C_{18}H_{18}O_4$
7	4	Me	Me	H			125.5–126.5	EtOH–H_2O	80	$C_{16}H_{14}O_4$
8	4	Me	Me	Et		150–155 (0.02)	62–63, 49–50[d]	MeOH–H_2O	80	$C_{18}H_{18}O_4$
9	4	H	Me	H			177–178	EtOH–H_2O	*e*	$C_{15}H_{12}O_4$
10	4	H	Me	Et		170–173 (0.2)	38.5–40		43	$C_{17}H_{16}O_4$
11	4	H	H	H			153.5–155	EtOH–H_2O	*e*	$C_{14}H_{10}O_4$
12	4	H	H	Et		238–241 (1.0)	50–51.5		39	$C_{16}H_{14}O_4$
13	4	Me	Me	H	1-Cl		112–113.5	Pet. ether[f]	97	$C_{16}H_{13}ClO_4$
14	4	Me	Me	Et	1-Cl		56.5–57.5	MeOH–H_2O	78	$C_{18}H_{17}ClO_4$
15	4	Me	Me	H	3-Cl		131–135	Pet. ether[f]	72	$C_{16}H_{13}ClO_4$
16	4	Me	Me	Et	3-Cl	155–160 (0.01)			91[g]	$C_{18}H_{17}ClO_4$
17	4	Me	Me	H	1,3-Cl_2		185.5–188.5	Pet. ether[f]–C_6H_6	85	$C_{16}H_{12}Cl_2O_4$
18	4	Me	Me	Et	1,3-Cl_2		64.5–65	MeOH–H_2O	79	$C_{18}H_{16}Cl_2O_4$
19	4	Me	Me	H	6-OMe		164.5–167	Pet. ether[f]–C_6H_6	89	$C_{17}H_{16}O_5$
20	4	Me	Me	Et	6-OMe	172–178 (0.01)	76–77	EtOH–H_2O	76	$C_{19}H_{20}O_5$
21	3	Me	Me	H	4-OMe		107–111	Pet. ether[f]–EtOAc	91	$C_{17}H_{16}O_5$
22	3	Me	Me	Et	4-OMe	150–160 (0.1)			75	$C_{19}H_{20}O_5$
23	3	Me	Me	H	8-Cl		153.5–155	Pet ether[f]–$CHCl_3$	94	$C_{16}H_{13}ClO_4$
24	3	Me	Me	Et	8-Cl	168–173 (0.01)			79	$C_{18}H_{17}ClO_4$

[a]All compounds were analyzed for the elements C, H, O, and, where present, Cl; unless otherwise indicated, microanalytical results were within ±0.4% of the theoretical values. [b]O: calcd, 23.68; found, 24.3. [c]Crystallized after additional chromatography on SiO_2. [d]Two crystal forms have been observed. [e]Prepared only for analytical purpose. [f]Petroleum ether with bp 95–110°. [g]Refers to crude yield.

Table II. Hypolipidemic Activity in Mice

Compd no.[a]	Body wt change, g per mouse[b]	Plasma cholesterol[i] % reduction vs. control	Plasma cholesterol[i] Significance	Plasma triglycerides[j] % reduction vs. control	Plasma triglycerides[j] Significance
2	+3	0	NS[c]	2	NS
4	+1	−6[d]	NS	35	$p < 0.05$
6	±0	6	NS	45	$p < 0.01$
8	+2	11[e]	$p < 0.001$	32[f]	$p < 0.001$
10	±0	12	$p < 0.05$	14	NS
12	±0	3	NS	15	NS
14	±0	18	$p < 0.001$	49	$p < 0.001$
16	+1	6	NS	52	$p < 0.001$
18	−1	13	$p < 0.001$	47	$p < 0.001$
20	−2	31	$p < 0.001$	59	$p < 0.001$
22	+4	−5[d]	NS	0	NS
24	+2	39	$p < 0.001$	−18[d]	NS
Clofibrate	+2	−11[d,g]	$p < 0.001$	45[h]	$p < 0.001$

[a]The compounds were supplemented to the diet at a level of 0.3%. [b]For control mice the average body weight gain is 2 g. [c]NS: not significant, $p > 0.05$. [d]Negative figure indicates an increase. [e]Mean of 46 determinations vs. 65 control determinations. [f]Mean of 46 determinations vs. 77 control determinations. [g]Mean of 42 determinations vs. 65 control determinations. [h]Mean of 42 determinations vs. 77 control determinations. [i]Control values averaged 160 mg/100 ml of plasma. [j]Control values averaged 1.2 μmol/ml of plasma.

Table III. Hypolipidemic Activity in Rats

Compd no.	% compn in diet	Daily food intake, g per rat	Plasma cholesterol[j] Individual reduction in %	Plasma cholesterol[j] Significance vs. 0 day[a]	Plasma cholesterol[j] Significance vs. control[b]	Plasma triglycerides[k] Individual reduction in %	Plasma triglycerides[k] Significance vs. 0 day[a]	Plasma triglycerides[k] Significance vs. control[b]
8	0.1	18	28[d]	$p < 0.001$	$p < 0.001$[i]	45[d]	$p < 0.001$	$p < 0.001$[i]
8	0.3	17	38[e]	$p < 0.001$	$p < 0.001$[i]	60[e]	$p < 0.001$	$p < 0.001$[i]
14	0.1	17	20	$p < 0.01$	$p < 0.01$	50	$p < 0.001$	$p < 0.01$
14	0.3	12	46	$p < 0.001$	$p < 0.001$	63	$p < 0.001$	$p < 0.001$
18	0.1	18	31	$p < 0.001$	$p < 0.001$	57	$p < 0.001$	$p < 0.001$
18	0.3	12	40	$p < 0.001$	$p < 0.001$	51	$p < 0.01$	$p < 0.05$
20	0.3	19	33	$p < 0.05$	NS[c]	50	$p < 0.01$	$p < 0.05$
Clofibrate	0.1	19	11[f]	$p < 0.001$	NS[i]	2[f]	NS	NS[i]
Clofibrate	0.3	18	30[g]	$p < 0.001$	$p < 0.001$[i]	48[g]	$p < 0.001$	$p < 0.001$[i]
Control		21	6[h]	$p < 0.001$		7[h]	$p < 0.05$	

[a]Significance of the individual reductions was calculated by the t test. [b]Significance of the difference between the value of the treated group and the control group in the same experiment. [c]NS: not significant, $p > 0.05$. [d]Mean of four experiments with a total of 35 rats. [e]Mean of five experiments with a total of 34 rats. [f]Mean of three experiments with a total of 24 rats. [g]Mean of six experiments with a total of 46 rats. [h]Mean of nine experiments with a total of 70 rats. [i]Calculated vs. nine control groups with a total of 70 rats. [j]The 0-day values averaged 310 mg/100 ml of plasma. [k]The 0-day values averaged 3.7 μmol/ml of plasma.

Some derivatives of compound 8 with substituents in the ring system were tested. Chlorine substitution in the 1 position (**14**) does not change the hypolipidemic activity compared with 8. Substitution in the 3 position (**16**) seems to abolish the cholesterol-lowering effect while the hypotriglyceridemic effect increases. The 1,3-dichloro-substituted derivative 18 lowers the cholesterol level to the same extent as compound 8 and is even more active regarding effect on triglycerides. Substitution in the 6 position by a methoxyl group (**20**) increases significantly ($p < 0.001$) the effect on triglyceride levels, and the effect on cholesterol levels also becomes more pronounced. However, a decrease in body weight is observed with compound **20**.

Two derivatives of 2-(3-dibenzofuranyloxy)-2-methylpropionate, namely those containing 4-methoxyl and 8-chloro substituents (**22** and **24**, respectively), have been tested. Compound **22** was found to be inactive and compound **24** showed cholesterol-lowering properties.

It was now considered to be of interest to investigate the lipid-lowering properties of our compounds in a species which has a lipoprotein pattern more similar to that of man. We have found that the spontaneously hyperlipidemic rat can be suitable in this respect. Four of the most active esters were evaluated in this animal model. Compound 8 was found to possess appreciable cholesterol and triglyceride-lowering properties. At the 0.1% level compound 8 is significantly ($p < 0.05$) more active than clofibrate regarding effects on both cholesterol and triglyceride levels. The reductions are of the same magnitude as those obtained with clofibrate at the 0.3% level. The chloro-substituted compounds 14 and 18 and the methoxy derivative **20** all show approximately the same potency as compound 8. Compounds 14 and 18 are also significantly superior to clofibrate when tested at the 0.1% level.

It may be concluded that ethyl 2-(4-dibenzofuranyloxy)-2-methylpropionate and its derivatives are active in both animal models and constitute a new class of potent hypolipidemic agents. Compound 8 is presently being subjected to more extensive investigations.

Experimental Section

Biological Methods. Hypolipidemic Effect in Mice. Male mice of the NMRI strain (AB Anticimex, Stockholm, Sweden) weighing 20–22 g at the start of the experiments were used. The animals were housed in mesh-bottomed cages in groups of 12 and kept in air-conditioned rooms with alternate 12-hr periods of light and dark. The animals had free access to food and water. The

compounds to be tested were mixed with ground commercial mouse chow (AB Astra Ewos, Södertälje, Sweden) at the 0.3% level. A control group, usually 24 animals, received ground chow without addition of test compound. The body weights were measured at the start and the end of the experiment. After 6 days the animals were sacrificed by decapitation under ether anaesthesia (*ca.* 8.00–9.30 a.m.) and the blood was collected. There was no period of fasting prior to the blood sampling. In order to obtain sufficient plasma volumes for the lipid analyses, usually blood samples from two mice had to be pooled. Total cholesterol[9] and triglycerides[10] in plasma were determined by semiautomated procedures.

The values for plasma cholesterol and triglyceride concentrations in the treated animals were compared with the values obtained for the untreated control mice run simultaneously. Significance of the difference between the values was calculated by Student's t test. The data are expressed as the percentage reduction compared to control levels.

Hypolipidemic Effect in Rats. Male rats of the Sprague–Dawley strain (AB Anticimex, Stockholm, Sweden) weighing 550–650 g and having an age of 1–1.5 years were used. In a pretest the cholesterol concentrations in plasma were determined and rats with values exceeding 200 mg/100 ml were selected. These animals were divided into groups of six in such a way that the mean cholesterol values of the different groups were similar and that the standard deviations were of approximately the same magnitude. The animals were housed in mesh-bottomed cages and kept in air-conditioned rooms with alternate 12-hr periods of light and dark. The rats had free access to food and water. The compounds to be tested were mixed in ground commercial rat chow (AB Astra Ewos, Södertälje, Sweden) at levels of 0.1 or 0.3%. Food consumption was recorded daily. A control group received pure rat chow. There were no fasting periods prior to the blood samplings. For determination of plasma lipids blood was taken from the ophthalmic venous complex under ether anaesthesia both at the start and the end of the experiments (*ca.* 8.00–9.30 a.m.). In this way the rats served as their own individual controls. The data are expressed as the percentage reduction of individual 0-day values. Significance of the decrease was calculated by Student's t test. Furthermore, the significance of the difference between the values for the treated group and the control group was t tested.

Chemistry. Melting points were determined on a Büchi-Tottoli capillary apparatus and are uncorrected. Boiling points are expressed as vapor temperature determined by distillation. Ir spectra were run on a Perkin-Elmer 157 spectrophotometer. Nmr spectra were recorded on a Varian T-60 spectrometer (TMS) and chemical shifts are reported in δ (ppm) units (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet) and J values in hertz. The spectra of all new compounds were consistent with the proposed structures. Tlc were run on precoated plates (Merck, Silica Gel F_{254}). Spots were detected by visual examination under uv light and/or potassium iodoplatinate spray reagent for compounds containing an amino group.

4-Hydroxydibenzofuran was obtained by a modification of the procedure described by Gilman, *et al.*[7] Dibenzofuran (101 g, 0.6 mol) was dissolved in 1500 ml of Na-dried Et_2O, and a mixture of 0.7 mol of BuLi and 1 mol of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) in 500 ml of hexane was added. The mixture was stirred for 24 hr at the internal temperature of +1°. The suspension of lithiodibenzofuran and 1 mol of *n*-butylmagnesium bromide in Et_2O were then added simultaneously to 1000 ml of Et_2O saturated with oxygen by a continuous flow at −70°. The mixture was stirred overnight at room temperature still with oxygen bubbling through. The reaction mixture was acidified with concentrated HCl; the organic layer was separated and extracted with 3% NaOH. The alkaline extract was acidified and extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$) and the solvent was evaporated to give 65.9 g of crude product. This solid was triturated with boiling *n*-hexane, from which 52.7 g (48%) of 4-hydroxydibenzofuran crystallized: mp 98.5–99.5° (lit.[7] 101–102°); nmr ($CDCl_3$) δ 5.7 (s, 1, OH), 6.9–7.6 (m, 6, arom protons), 7.9 (m, 1, H-9).

1-Chloro-4-hydroxydibenzofuran and 3-Chloro-4-hydroxydibenzofuran. 4-Hydroxydibenzofuran was chlorinated in $CHCl_3$ with 1 equiv of SO_2Cl_2, essentially according to Gilman and Esmay.[4] The reflux period was extended to 24 hr instead of 1.5 hr. Recrystallization three times from CCl_4 gave white needles of 1-chloro-4-hydroxydibenzofuran: mp 150–151° in 23% yield (lit.[4] 154–155°, 12%); nmr (Me_2CO-d_6) δ 7.0 (br, 1, OH), 7.0–7.7 (m, 5, arom protons), 8.4 (m, 1, H-9). On standing, faint red crystals with mp 113–115.5° precipitated from the mother liquor from the second recrystallization. After repeated recrystallizations from petroleum ether (bp 95–110°) white crystals of 3-chloro-4-hydroxydibenzofuran were obtained in 6% yield; mp 117–118° (lit.[11] 121°); nmr (Me_2CO-d_6) δ 7.1–7.7 (m, 5, arom protons), 8.0 (m, 1, H-9), 9.2 (br, 1, OH).

1,3-Dichloro-4-hydroxydibenzofuran was prepared according to Gilman and Esmay,[4] with the exception that the reflux period was increased from 1.5 to 8 hr. The product was obtained in 47% yield after recrystallization from CCl_4: mp 158.5–159.5° (lit.[4] 160–161°, 36%); nmr (Me_2CO-d_6) δ 7.3 (s, 1, H-2), 7.2–7.7 (m, 3, arom protons), 8.2 (m, 1, H-9).

4-Hydroxy-6-methoxydibenzofuran and 3-Hydroxy-4-methoxydibenzofuran. A. The compounds were prepared essentially according to Gilman, *et al.*[7] The same modifications as described above for the preparation of 4-hydroxydibenzofuran were used. After hydrolysis, the two isomeric phenols were separated according to Gilman, *et al.*,[7] but 3-hydroxy-4-methoxydibenzofuran had to be purified further by column chromatography. The crude product (6.3 g) was chromatographed on a column of 250 g of neutral Al_2O_3, activity grade III, constructed in benzene. Elution was performed with a gradient of benzene–$CHCl_3$–MeOH. Evaporation of the fractions containing the first compound eluted gave 5.7 g of 3-hydroxy-4-methoxydibenzofuran: mp 109–110° (lit.[7] 109–110°) after recrystallization from petroleum ether (bp 95–110°)–benzene; nmr ($CDCl_3$) δ 4.2 (s, 3, OMe), 6.0 (s, 1, OH), 6.9 (d, 1, J = 9, H-2), 7.1–7.6 (m, 4, arom protons), 7.8 (m, 1, H-9). 4-Hydroxy-6-methoxydibenzofuran was recrystallized from petroleum ether (bp 95–110°)–benzene: mp 109–110° (lit.[7] 111–112°); nmr ($CDCl_3$) δ 4.0 (s, 3, OMe), 5.9 (br, 1, OH), 6.8–7.7 (m, 6, arom protons). The mixture melting point of the isomers was 80–95°.

B. A solution of 4-methoxydibenzofuran[12] (1.4 g, 7.0 mmol) and TMEDA (1.2 ml, 8 mmol) in 15 ml of dry Et_2O was cooled with CCl_4–Dry Ice to −15° under a nitrogen atmosphere. BuLi (8 mmol) in hexane was added slowly to the stirred solution, and the reaction mixture was kept at −15° for 2 hr. Butyl borate (2.4 ml, 9 mmol) in 10 ml of dry Et_2O was then added to the reddish brown solution and the color became fainter. The mixture was stirred for 2 hr at −15°. Crystalline NH_4Cl (0.8 g, 15 mmol) was then added, followed by 30% H_2O_2 (1.7 ml, 15 mmol). A beige precipitate developed. The suspension was stirred overnight and was allowed to warm to room temperature. HCl (2 *M*) and additional Et_2O were added and the layers were separated. The aqueous phase was extracted with Et_2O. The combined organic phases were washed with $FeSO_4$ in 2 *M* HCl. The two isomeric phenols in the organic phase were separated according to Gilman, *et al.*,[7] yielding 0.51 g (34%) of 3-hydroxy-4-methoxydibenzofuran and 0.26 g (17%) of 4-hydroxy-6-methoxydibenzofuran. Both isomers were further purified by chromatography on SiO_2 columns (activity grade 2–3, wt ratio 1:50, 0.2–0.5 mm) with $CHCl_3$ as eluent. Recrystallization from petroleum ether (bp 95–110°)–benzene yielded products with the same melting points as in A.

8-Chloro-3-nitrodibenzofuran. 3-Nitrodibenzofuran[13] (42.7 g, 0.2 mol) was dissolved in 400 ml of $PhNO_2$ at 120° and SO_2Cl_2 (24.4 ml, 0.3 mol) was then added during 20 min. The mixture was kept at 120° for 42 hr while being stirred (a later experiment showed that the reaction was complete after 18 hr). $PhNO_2$ (300 ml) was then removed by distillation and aqueous EtOH was added to the remaining slurry. The precipitate was collected by filtration and recrystallized from AcOH yielding 32 g (65%), mp 202–217°. After two recrystallizations from AcOH the melting point was 226–228.5° (lit.[5] 226°).

3-Amino-8-chlorodibenzofuran. 8-Chloro-3-nitrodibenzofuran (2.48 g, 10 mmol) was suspended in 50 ml of EtOH at 40° and hydrazine monohydrate (1.5 ml, 30 mmol) and Raney nickel were added. After 1 hr additional hydrazine and Raney nickel were added. The mixture was then refluxed for 1 hr to destroy the excess of hydrazine. Tlc (SiO_2 plate, $PhCH_3$–MeOH–Et_2NH 19:1:1) showed that the reduction was complete. An additional 150 ml of EtOH was added and the hot suspension was filtered. The filtrate was treated with charcoal and concentrated to 75 ml *in vacuo*. Water was added and the amine precipitated on cooling. The white product (1.5 g, 69%) melted at 146.5–147.5° (lit.[6] 147–148°).

8-Chloro-3-hydroxydibenzofuran. The hydrochloride (9.25 g, 36.3 mmol) of 3-amino-8-chlorodibenzofuran was suspended in 50 ml of H_2O and 40 ml of 2 *M* HCl. The mixture was diazotized with $NaNO_2$ (2.68 g, 39 mmol) in 15 ml of H_2O at +6° during 2 hr. A yellow solution was first obtained and at the end of the reaction a precipitate was formed. The cold suspension was added (during 0.5 hr) to a refluxing solution of 500 ml of 2 *M* HCl and

1500 ml of H_2O. The mixture was refluxed for an additional 3 hr and after cooling extracted with Et_2O. The Et_2O phases were treated with 5 *M* NaOH and the red phenolate precipitated. It was collected and then dissolved in Et_2O saturated with HCl. The Et_2O solution was dried ($MgSO_4$) and the solvent evaporated to afford 5.7 g of a solid product. Recrystallization from aqueous EtOH gave 5.25 g (66%) of yellowish phenol: mp 175.5–177° (lit.[6] 177–178.5°); nmr (Me_2CO-d_6) δ 6.9–7.6 (m, 4, arom protons), 7.9 (m, 2, H-1 and H-9), 8.9 (s, 1, OH).

2-(4-Methoxy-3-dibenzofuranyloxy)-2-methylpropionic Acid (21). A solution of 4-methoxy-3-hydroxydibenzofuran (6.5 g, 30 mmol) in 100 ml of dry Me_2CO was stirred at room temperature with 10.1 g (180 mmol) of solid KOH. After 15 min the reaction mixture was cooled in an ice bath, and a solution of 1,1,1-trichloro-2-methyl-2-propanol (8.4 g, 45 mmol), prepared according to Fishburn and Watson,[14] in 50 ml of dry Me_2CO was added dropwise during 45 min. The suspension was kept in the ice bath for 45 min. The reaction mixture was stirred at room temperature for 1 hr, refluxed for 4 hr, and finally stirred overnight at room temperature. The mixture was dissolved in H_2O and the Me_2CO was evaporated. The aqueous solution was acidified with HCl and extracted with Et_2O. The Et_2O solution was treated with saturated $NaHCO_3$ solution and the aqueous solution was acidified and extracted with Et_2O. After drying ($MgSO_4$) and evaporation of the solvent 8.3 g (91%) of a yellow oil was obtained. The oil crystallized upon standing. Recrystallization from petroleum ether (bp 95–110°)–EtOAc gave crystals with mp 107–111°.

The acids **1**, **3**, **5**, **7**, **13**, **15**, **17**, **19**, and **23** were similarly prepared (Table I). However, in the preparations of **1**, **3**, **5**, and **7** equimolar amounts of 1,1,1-trichloro-2-methyl-2-propanol were used. 1-Hydroxydibenzofuran and 3-hydroxydibenzofuran used as starting materials in the syntheses of the acids **1** and **5** were prepared according to Stjernström[15] and Erdtman, *et al.*,[16] respectively.

Ethyl 2-(1-Dibenzofuranyloxy)-2-methylpropionate (2). 2-(1-Dibenzofuranyloxy)-2-methylpropionic acid (**1**, 6.7 g, 25 mmol) was dissolved in 250 ml of EtOH saturated with HCl gas and the mixture was refluxed for 4 hr. The solvent was evaporated and the dark oil was dissolved in Et_2O. The Et_2O solution was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated to yield 6.6 g (88%) of a dark oil. The oil was distilled *in vacuo* to give 5.4 g (72%) of a slightly yellow oil, bp 156–158° (0.06 mm). After chromatography on a column of 300 g of SiO_2 (Merck, activity grade 2–3, 0.2–0.5 mm) with benzene as eluent, 4.3 g (58%) of a crystalline product was obtained: mp 74–77°; nmr ($CDCl_3$) δ 1.2 (t, 3, J = 7, OCH_2CH_3), 1.8 [s, 6, $C(CH_3)_2$], 4.25 (q, 2, J = 7, OCH_2CH_3), 6.6 (m, 1, H-2), 7.1–7.6 (m, 5, arom protons), 8.2 (m, 1, H-9).

The esters **4**, **6**, **8**, **14**, **16**, **18**, **20**, **22**, and **24** were similarly prepared; however, chromatography was unnecessary in these preparations (Table I).

Ethyl 4-Dibenzofuranyloxyacetate (12). Sodium (0.58 g, 25 mmol) was added to 200 ml of super-dry EtOH. When the reaction had ceased 4.6 g (25 mmol) of 4-hydroxydibenzofuran and 5.0 g (30 mmol) of ethyl bromoacetate were added. The reaction mixture was refluxed for 16 hr. The solvent was then evaporated and the remaining solid was dissolved in 150 ml of H_2O and 150 ml of Et_2O. The ethereal layer was washed with NaOH solution, dried ($MgSO_4$), and evaporated to give 3.3 g of crude product. Distillation gave 2.65 g (39%) of a colorless oil, bp 238–241° (1.0 mm). The oil crystallized upon cooling, mp 50–51.5°.

Ethyl 2-(4-dibenzofuranyloxy)propionate (10) was prepared from 4-hydroxydibenzofuran and ethyl 2-bromopropionate in analogy with **12**. The product was distilled to give a colorless oil in 43% yield, bp 170–173° (0.2 mm), which crystallized upon cooling, mp 38.5–40°.

2-(4-Dibenzofuranyloxy)propionic acid (9) and **4-dibenzofuranyloxyacetic acid (11)** were obtained by alkaline hydrolysis of **10** and **12**, respectively.

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Synthesis of Phosphonic Acid Isosteres of 2-Phospho-, 3-Phospho-, and 2,3-Diphosphoglyceric Acid

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Phosphonic acid isosteres of 2-phosphoglyceric acid, 3-phosphoglyceric acid, and 2,3-diphosphoglyceric acid were prepared using the Arbuzov reaction and the Michaelis–Becker modification, followed by vigorous acid or base hydrolysis of the precursor esters. The small, highly charged molecules were tested *in vitro* on human red cell suspensions in physiological buffer for their effects on the oxygen-dissociation curve. None of the compounds exhibited a right or left curve shift in this assay when compared to controls.

Recent reports have shown that the affinity of oxygen for hemoglobin can be altered by 2,3-diphosphoglyceric acid,[1,2] the predominant organic phosphate in the red blood cell. Our interest in improving performance of oxygen transport mechanisms *via* the 2,3-diphosphoglyceric acid–hemoglobin interaction has encouraged investigations directed at the utilization of drug-induced shifts[3] in the hemoglobin–oxygen dissociation curve. The ultimate objective was a compound which would alter the dissociation pressure and shift the curve to the right by *ca.* 3–5 mm at 50% saturation.[4] If a compound can induce a right shift of this magnitude, it will impart a greater "unload-

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