AG 1 × 1 anion exchange resin to remove unreacted acetyl-CoA. After vigorous stirring for 30 sec, each incubation tube was centrifuged for 5 min at 1500 g. Then, 0.5 ml of the supernatant fraction was transferred to 10 ml of scintillation solution (2,5-diphenyloxazole, 7 g; naphthalene, 100 g; dioxane, 1000 ml) and counted in a liquid scintillation counter. The remaining supernatant was transferred to a clean centrifuge tube and 250 mg of Amberlite CG 120 cationic exchange resin was added to trap choline derivatives. After stirring and centrifuging as above, 0.5 ml of the supernatant was again added to 10 ml of scintillation solution for counting. The amount of acetylated product was calculated by subtracting the cpm obtained after both anionic and cationic exchange from the cpm obtained after anionic exchange alone. (10000 cpm is equivalent to 1.04 nmol of acetylated product synthesized/min/mg of acetone powder).

For studies on the reversibility of acryl-DMA, the concentration of ChAc varied from 10 to 30 mg of acetone powder per milliliter. For studies on the inhibition kinetics of acryl-DMA, either the acetyl-CoA concentration varied from 0.016 to 0.065 m*M* while the concentration of choline remained constant at 25 m*M*; or the choline concentration varied from 0.4 to 4.0 m*M* while the acetyl-CoA concentration remained constant at 0.65 m*M*.

Frog Sciatic Nerve–Gastrocnemius Muscle. *Rana pipiens* weighing 20–25 g were stunned, decapitated, and pithed. The muscle with sciatic nerve was removed and suspended in an organ bath in 40 ml of frog Ringer solution at 25°C oxygenated with 95% O_2–5% CO_2. The sciatic nerve was stimulated with a pair of platinum ring electrodes with 7-V voltage, 0.5-msec duration, and 250-Hz frequency administered for 0.1 sec every 10 sec. Muscle contractions were measured with a Narco Bio-Systems myograph-B isometric force transducer and recorded on a Model Four-A Narco Bio-Systems physiograph. Acryl-DMA was added to the bath in volumes of not exceeding 0.8 ml.

Transmurally Stimulated Guinea Pig Ileum. Guinea pigs (common strain), 300–500 g, were stunned with a blow to the head and decapitated. The abdominal cavity was opened to expose the intestine. A terminal portion of the ileum was cut into 20–30 mm sections, tied on either end with silk suture, and suspended in an organ bath of 40-ml capacity. The ileum was mounted on a coaxial electrode such that transmural stimulation could be administered to the nerves. The ileum was bathed with Tyrode solution oxygenated with 95% O_2–5% CO_2 at 37°C. The nerves were stimulated with monophasic square wave pulses administered at a supramaximal voltage of 40 V, frequency of 10 Hz, and 0.5-msec duration for 1 sec every 10 sec. Muscle contractions were recorded as with the frog muscle preparation, and acryl-DMA was added to the bath in volumes not exceeding 0.8 ml.

Statistical Analyses. Standard errors of the mean (SEM) were given for mean figures. Confidence limits at the 95% level were determined for the ED_{50} values according to Litchfield and Wilcoxon.[19]

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Antiinflammatory Activity of Some 2,3-Dihydrobenzofuran-5-acetic Acids and Related Compounds

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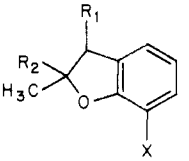
A series of 2,3-dihydrobenzofuran-5-acetic acids and related compounds was prepared as potential antiinflammatory agents. As measured by the carrageenan-induced edema method for the preliminary screening test, introduction of a methyl group α to the acetic acid function enhanced the antiinflammatory activity, and α-(7-chloro-2,2-dimethyl-2,3-dihydrobenzofuran)-α-methyl-5-acetic acid (13a) showed the most potent activity in this series.

Among the reports of compounds exhibiting antiinflammatory activity which have appeared in recent years, a number describe compounds which belong to the aryl- or heteroarylalkanoic acids.[1] Features of typical molecules which are important for the activity include a carboxyl group separated by one or more carbon atoms from the aromatic nucleus, which is further substituted by a relatively large lipophilic group at its meta or para position.

This paper describes the synthesis and antiinflammatory activity of 2,3,7-substituted 2,3-dihydrobenzofuran-5-acetic acids and related compounds (type 1). First of all, in order to investigate the effects of introducing a methyl group at position 2 or 3 in the 2,3-dihydrobenzofuran ring on the activity, 2-methyl-, 2,2-dimethyl-, and 2,3-dimethyl analogs were prepared.

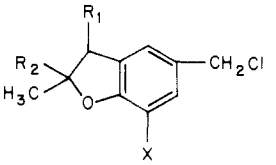
Introduction of a halogen atom at the position meta to the acetic acid residue tends to increase the activity as is known in alclofenac[2] and flurbiprofen;[3] consequently, 7-chloro analogs were synthesized to investigate the effect of chlorine at position 7 in 2,3-dihydrobenzofurans. It is

Table I. 2,3,7-Substituted 2-Methyl-2,3-dihydrobenzofurans



Compd	X	R_1	R_2	Bp, °C (mm)	Yield, %	Formula	Analyses
4a	Cl	H	H	125-129 (17)	79	C_9H_9ClO	C, H
4b	Cl	CH_3	H	128-130 (17)	87	$C_{10}H_{11}ClO$	C, H
4c	Cl	H	CH_3	120-122 (20)	84	$C_{10}H_{11}ClO$	C, H
4d	H	H	CH_3	117-122 (21)	82	$C_{10}H_{12}O$	C, H

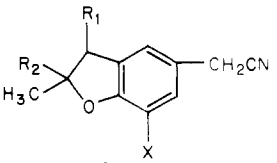
Table II. 2,3,7-Substituted 5-Chloromethyl-2-methyl-2,3-dihydrobenzofurans



Compd	X	R_1	R_2	Bp, °C (mm)	Yield, %	Formula	Analyses
5a	Cl	H	H	134-135 (0.9)	68	$C_{10}H_{10}Cl_2O$	C, H
5b	Cl	CH_3	H	132-135 (1.0)	58	$C_{11}H_{12}Cl_2O$	C, H
5c	Cl	H	CH_3	70-72[a]	65	$C_{11}H_{12}Cl_2O$	C, H
5d	H	H	CH_3	115-119 (0.9)	67	$C_{11}H_{13}ClO$	C, H

[a] Melting point; colorless needles recrystallized from isopropyl ether.

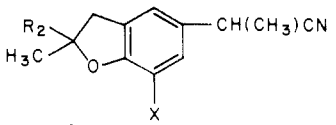
Table III. 2,3,7-Substituted 5-Cyanomethyl-2-methyl-2,3-dihydrobenzofurans



Compd	X	R_1	R_2	Bp, °C (mm)	Yield, %	Formula	Analyses
6a	Cl	H	H	155-159 (0.9)	72	$C_{11}H_{10}ClNO$	C, H, N
6b	Cl	CH_3	H	163-165 (0.8)	73	$C_{12}H_{12}ClNO$	C, H, N
6c	Cl	H	CH_3	70-72[a]	61	$C_{12}H_{12}ClNO$	C, H, N
6d	H	H	CH_3	150-153 (0.8)	67	$C_{12}H_{13}NO$	C, H, N

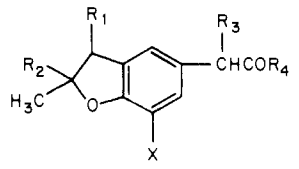
[a] Melting point; colorless needles recrystallized from isopropyl ether–*n*-hexane.

Table IV. 2,7-Substituted 5-(α-Cyanoethyl)-2-methyl-2,3-dihydrobenzofurans



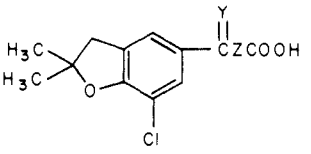
Compd	X	R_2	Bp, °C (mm)	Yield, %	Formula	Analyses
7a	Cl	CH_3	140-144 (1.0)	75	$C_{13}H_{14}ClNO$	C, H, N
7b	Cl	H	165-168 (0.9)	63	$C_{12}H_{12}ClNO$	C, H, N

well known that an introduction of α-alkyl groups on the acetic acid moiety enhances the activity as observed in ibuprofen,[4] fenoprofen,[5] naproxen,[6] etc.; thus α-methyl groups were introduced in these compounds and examined for the effect on the activity. Furthermore, γ-oxocrotonic acid, γ-oxobutyric acid, and butyric acid functions were introduced in place of acetic acid (type 2).



type 1

R_1, R_2, R_3 = H, CH_3
R_4 = OH, NHOH, NH_2
X = H, Cl

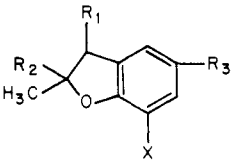


type 2

Y = H_2, O
Z = CH=CH, CH_2CH_2

Chemistry. The compounds of type 1 were obtained as outlined in Scheme I. 2,3-Dihydrobenzofuran analogs (Table I) were prepared from the appropriate 2-(substituted allyl)phenols **3** under acidic conditions using a modified Martini's method.[7] The dihydrobenzofurans **4** were converted to 5-cyanomethyl derivatives **6** (Table III) via 5-chloromethyl analogs **5** (Table II) by a conventional method. Alkaline hydrolysis of **6** afforded 2,3-dihydrobenzofuran-5-acetic acid derivatives **8** (Table V), which were converted into acetohydroxamic acids **9** and acetamides **10** via the appropriate acid chlorides. 2,2-Dimethyl-2,3-dihydrobenzofuran-5-acetic acid (**8d**) was also obtained as follows. 4-Acetyl-2-(2-methylallyl)phenol (**11**) was cyclized with formic acid to 2,2-dimethyl-5-acetyl-2,3-dihydrobenzofuran (**12**) which was converted to **8d** under Willgerodt conditions.[8] The cyanomethyl analogs **6** were treated with sodium hydride followed by methyl iodide to give α-methylacetonitrile analogs **7** (Table IV)

Table V. 2,3,7-Substituted 2,3-Dihydrobenzofuran-5-acetic Acids and Related Compounds



Compd	X	R_1	R_2	R_3	Mp, °C (recrystn solvent[b])	Yield, %	Formula	Analyses
8a	Cl	H	H	CH_2COOH	108-109 (IPE-Hex)	68	$C_{11}H_{11}ClO_3$	C, H
8b	Cl	CH_3	H	CH_2COOH	134-136[a] (IPA)	72	$C_{12}H_{13}ClO_3 \cdot C_6H_{13}N$	C, H, N
8c	Cl	H	CH_3	CH_2COOH	166-167 (IPE)	59	$C_{12}H_{13}ClO_3$	C, H
8d	H	H	CH_3	CH_2COOH	79-81 (C_6H_6-Hex)	67	$C_{12}H_{14}O_3$	C, H
9a	Cl	H	CH_3	$CH_2CONHOH$	163-165 (IPE)	23	$C_{12}H_{14}ClNO$	C, H, N
9b	H	H	CH_3	$CH_2CONHOH$	155-156 (EtOH-Hex)	28	$C_{12}H_{15}NO_3$	C, H, N
10a	Cl	H	CH_3	CH_2CONH_2	137-139 (EtOAc)	83	$C_{12}H_{14}ClNO_2$	C, H, N
10b	H	H	CH_3	CH_2CONH_2	123-124 (C_6H_6-Hex)	85	$C_{12}H_{15}NO_2$	C, H, N
10c	Cl	H	H	CH_2CONH_2	139-140 (IPE)	78	$C_{11}H_{12}ClNO_2$	C, H, N
13a	Cl	H	CH_3	$CH(CH_3)COOH$	116-118 (IPE)	63	$C_{13}H_{15}ClO_3$	C, H
13b	Cl	H	H	$CH(CH_3)COOH$	140-142[a] (IPA)	69	$C_{12}H_{13}ClO_3 \cdot C_6H_{13}N$	C, H, N

[a] Cyclohexylamine ($C_6H_{11}NH_2$) salt. [b] IPE = isopropyl ether, Hex = *n*-hexane, and IPA = 2-propanol.

Table VI. Antiinflammatory Activity (Inhibitory Effect on Carrageenan-Induced Rat Paw Edema) and Gastric Irritation

Compd	Dose,[a] mg/kg po	% inhibn of edema	Gastric irritation[b]
8a	100	27	3
	20	20	
8b	100	30	5
	20	24	
8c	100	37	4
	20	30	
8d	100	32	2
	20	25	
9a	100	13	2
	20	7	
9b	100	9	3
	20	5	
10a	100	31	4
	20	25	
10b	100	20	2
	20	15	
10c	100	17	4
	20	2	
13a	100	58	2
	20	45	
13b	100	57	6
	20	35	
14	100	3	6
	20	9	
15	100	37	5
	20	24	
16	100	32	9
	20	32	
Phenyl-butazone	50	51	3
	10	24	

[a] Four animals were employed for each dose level. [b] Severity for each animal was graded from 0 to 3 according to the overall appearance of the mucosa, and the degree of gastric irritation of the test compounds was indicated by the sum of each score. 0 = no lesions; 1 = slight edema, hyperaemia, or slight erosion; 2 = scattered or limited erosion and pin-point hemorrhage; 3 = intense erosion and linear or broad hemorrhage.

Table VII. Oral ED_{50} and LD_{50} Values of 13a

	mg/kg po	Confidence limits[a] ($p = 0.05$)
ED_{50}	45	34-58
LD_{50}	720	540-960

[a] Calculated by Litchfield-Wilcoxon's method.[12]

which were hydrolyzed to α-methylacetic acid derivatives **13** (Table V).

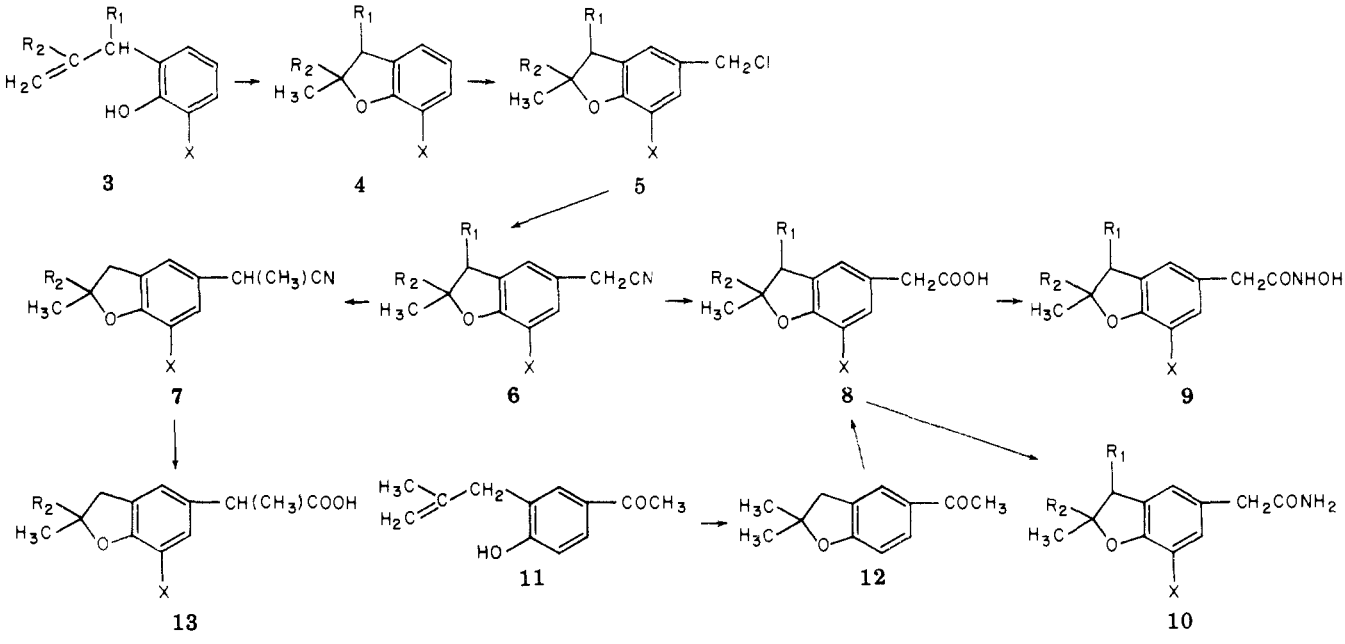
The compounds of type 2 were prepared according to Scheme II. Friedel-Crafts reaction of 2,2-dimethyl-7-chloro-2,3-dihydrobenzofuran (**4c**) with maleic anhydride[9] gave the γ-oxocrotonic acid **14** and with succinic anhydride[10] the γ-oxobutyric acid **15**. Compound **15** was reduced under modified Wolff-Kishner conditions to give the butyric acid **16**.

Antiinflammatory Activity. The carrageenan-induced rat paw edema assay was carried out using a modified Winter's method[11] as a preliminary screening test. The rats (in groups of four animals weighing 140–160 g, young adult male Wistar strain) were starved for 16 hr before the test compound (100 and 20 mg/kg po) was administered. Two hours later, the volume of the right hind paw was measured, and 0.05 ml of a 1% solution of carrageenan in sterile pyrogen-free 0.9% NaCl solution was injected into the paw. Three hours after an injection of carrageenan, the volume of the paw was again measured by Hg displacement. After the final paw volume measurements had been made, the rats were killed, and their stomachs were removed and examined for signs of acute gastric erosions.

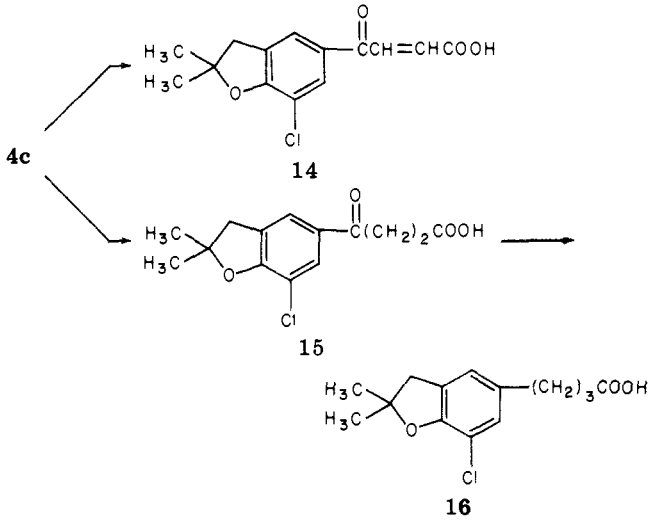
Table VI lists the antiinflammatory activity (percent inhibition of edema) and gastric irritation found for the 14 compounds prepared in this study, along with the activity of the standard compound, phenylbutazone.

The LD_{50} value of the most potent compound **13a** after 72 hr was determined by oral administration to groups of five male mice (dd strain, weighing 16–22 g). The ED_{50}

Scheme I



Scheme II



value was also determined in the carrageenan-induced rat paw edema assay similarly as described above (Table VII).

Results

Most of the compounds prepared in this study exhibited antiinflammatory activity. No significant difference in the activity was observed between the 7-chloro derivatives and the corresponding unsubstituted homologs (**8c**:**8d** and **10a**:**10b**). With respect to the effect of introducing a methyl group in the furan ring (position 2 or 3) on the activity, a significant influence was not found against expectation. It seems, however, that an introduction of methyl group shows a tendency to retain or increase the potency (**8a**:**8b**, **10a**:**10c**, and **13a**:**13b**).

When a methyl group was introduced to the α position of the acetic acid moiety, the potency increased markedly as exemplified by comparing **8c** with **13a** and **8a** with **13b**. As to the acetohydroxamic acids (**9a,b**) and the acetamides (**10a,b**), all the compounds were less active than the corresponding acetic acids (**8c,d**). Thus, replacing OH in the acetic acid moiety with NHOH or NH_2 markedly diminishes the activity.

Lengthening the side chain bearing the carboxylic function in **8c** was attempted. However, change of side chain from CH_2COOH **8c** to $C(=O)CH=CHCOOH$ **14**, $C(=O)CH_2CH_2COOH$ **15**, and $(CH_2)_3COOH$ **16** brought no increase of the activity and resulted in loss of activity in **14**. α-(7-Chloro-2,2-dimethyl-2,3-dihydrobenzofuran)-α-methyl-5-acetic acid (**13a**) showed the most potent activity in this series, which had an ED_{50} of 45 mg/kg and an LD_{50} of 720 mg/kg.

The compounds **8d**, **9a**, **10b**, and **13a** showed low gastric irritation, but **13b**, **14**, and **16** showed high potency. No apparent structure–activity relationship regarding irritation was observed in these compounds. Table VII lists the ED_{50} and LD_{50} values of **13a**.

On the basis of these results, compound **13a** is worth further studying in a variety of antiinflammatory assays, and a detailed presentation and analyses of the biological activities of the compound will be forthcoming from these laboratories.

Experimental Section

Melting points are uncorrected. Ir spectra were recorded as Nujol pastes with a Hitachi 215 spectrophotometer, and NMR spectra were determined on a Hitachi R-25 (60 MHz) spectrometer in $CDCl_3$ (unless otherwise noted) with added Me_4Si. Mass spectra were determined on a JEOL double-focusing mass spectrometer JMS-01 SG and the ionizing energy normally used was 75 eV. Where analogs are represented by elemental symbols, the results of these elements fall within ±0.4% of the calculated values.

2,3,7-Substituted 2-Methyl-2,3-dihydrobenzofurans (4). Compounds **4a–d** (Table I) were prepared from the corresponding substituted allylphenols **3a–d**. A mixture of 0.1 mol of **3a–d** (**3a**, X = Cl, $R_1 = CH_3$, R_2 = H; **3b**,[13a] X = Cl, $R_1 = R_2$ = H; **3c**; X = Cl, R_1 = H, $R_2 = CH_3$; **3d**,[13b] X = H, R_1 = H, $R_2 = CH_3$) and 50 ml of formic acid was heated at reflux while stirring for 3 hr. The reaction mixture was evaporated under reduced pressure and the residue was taken up in Et_2O. The Et_2O solution was washed (5% NaOH and water), dried ($MgSO_4$), and concentrated. The resulting oily residue was distilled in vacuo to give the appropriate 4.

Compounds **3a** [bp 92–95° (1.3 mm), 93%] and **3c** [bp 85–87° (2.0 mm), 82%] were also prepared by refluxing the corresponding allyl phenyl ethers with *N,N*-diethylaniline for 5 hr.

7-Chloro-2-methyl-2,3-dihydrobenzofuran (4a): NMR δ 4.85 (m, 1 H, C_2-H), 2.95 (m, 2 H, C_3-gem-2H), and 1.37 ppm (d, 3 H, C_2-CH_3, J = 7 Hz); mass spectrum m/e 168 (M^+).

7-Chloro-2,3-dimethyl-2,3-dihydrobenzofuran (4b): NMR δ 4.50 (m, 1 H, C_2-H), 3.20 (m, 1 H, C_3-H), and 1.31 ppm (m, 6

H, two CH_3 at C_2 and C_3); mass spectrum m/e 182 (M^+).

7-Chloro-2,2-dimethyl-2,3-dihydrobenzofuran (4c): NMR δ 3.00 (s, 2 H, C_3-gem-2H) and 1.40 ppm (s, 6 H, C_2-gem-2CH_3); mass spectrum m/e 182 (M^+).

2,2-Dimethyl-2,3-dihydrobenzofuran (4d): NMR δ 2.98 (s, 2 H, C_3-gem-2H) and 1.38 ppm (s, 6 H, C_2-gem-2CH_3); mass spectrum m/e 148 (M^+).

2,3,7-Substituted 5-Chloromethyl-2-methyl-2,3-dihydrobenzofurans (5). Compounds **5a–d** (Table II) were prepared by a method similar to that described for **5a** as follows. Hydrogen chloride gas was passed through a stirred mixture of 8.4 g (0.05 mol) of **4a**, 2.0 g of $ZnCl_2$, and 40 ml of 37% formalin while stirring at 0–5°. After the mixture was saturated, the resulting dark solution was allowed to stand overnight. The brown oil separated was extracted with Et_2O, and the extracts were washed (H_2O, aqueous $NaHCO_3$, and H_2O), dried ($MgSO_4$), and evaporated. The residue was distilled to give 7.3 g (68%) of **7-chloro-5-chloromethyl-2-methyl-2,3-dihydrobenzofuran (5a)**: bp 134–135° (0.9 mm); NMR δ 4.75 (m, 1 H, C_2-H), 4.30 (s, 2 H, CH_2Cl), 2.85 (m, 2 H, C_3-gem-2H), and 1.30 ppm (d, 3 H, C_2-CH_3, J = 7 Hz); mass spectrum m/e 216 (M^+).

7-Chloro-5-chloromethyl-2,3-dimethyl-2,3-dihydrobenzofuran (5b): NMR δ 4.75 (m, 1 H, C_2-H), 4.30 (s, 2 H, CH_2Cl), 3.20 (m, 1 H, C_3-H), and 1.30 ppm (m, 6 H, two CH_3 at C_2 and C_3); mass spectrum m/e 230 (M^+).

7-Chloro-5-chloromethyl-2,2-dimethyl-2,3-dihydrobenzofuran (5c): NMR δ 4.35 (s, 2 H, CH_2Cl), 2.95 (s, 2 H, C_3-gem-2H), and 1.40 ppm (s, 6 H, C_2-gem-2CH_3); mass spectrum m/e 230 (M^+).

5-Chloromethyl-2,2-dimethyl-2,3-dihydrobenzofuran (5d): NMR δ 4.35 (s, 2 H, CH_2Cl), 3.00 (s, 2 H, C_3-gem-2H), and 1.40 ppm (s, 6 H, C_2-gem-2CH_3); mass spectrum m/e 196 (M^+).

2,3,7-Substituted 5-Cyanomethyl-2-methyl-2,3-dihydrobenzofurans (6). Compounds **6a–d** (Table III) were prepared by a method similar to that described for **6a** as follows. A suspension of 6.5 g (0.03 mol) of **5a**, 0.04 mol of KCN, a small amount of KI, and 50 ml of acetonitrile was heated to reflux under stirring for 3 hr. The inorganic substance precipitated was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in Et_2O; the ethereal solution was washed, dried ($MgSO_4$), and evaporated. The crude product was distilled to give 4.5 g (72%) of **7-chloro-5-cyanomethyl-2-methyl-2,3-dihydrobenzofuran (6a)**: bp 155–159° (0.9 mm); ir 2250 cm^{-1} (C≡N); NMR (CCl_4) δ 4.80 (m, 1 H, C_2-H), 3.62 (s, 2 H, CH_2CN), 3.05 (m, 2 H, C_3-gem-2H), and 1.45 ppm (d, 3 H, C_2-CH_3, J = 7 Hz); mass spectrum m/e 207 (M^+).

7-Chloro-5-cyanomethyl-2,3-dimethyl-2,3-dihydrobenzofuran (6b): ir 2250 cm^{-1} (C≡N); NMR δ 4.60 (m, 1 H, C_2-H), 3.54 (s, 2 H, CH_2CN), 3.24 (m, 1 H, C_3-H), and 1.32 ppm (m, 6 H, two CH_3 at C_2 and C_3); mass spectrum m/e 221 (M^+).

7-Chloro-5-cyanomethyl-2,2-dimethyl-2,3-dihydrobenzofuran (6c): ir 2260 cm^{-1} (C≡N); NMR δ 3.65 (s, 2 H, CH_2CN), 3.05 (s, 2 H, C_3-gem-2H), and 1.50 ppm (s, 6 H, C_2-gem-2CH_3); mass spectrum m/e 221 (M^+).

5-Cyanomethyl-2,2-dimethyl-2,3-dihydrobenzofuran (6d): ir 2250 cm^{-1} (C≡N); NMR δ 3.60 (s, 2 H, CH_2CN), 3.00 (s, 2 H, C_3-gem-2H), and 1.48 ppm (s, 6 H, C_2-gem-2CH_3); mass spectrum m/e 187 (M^+).

2,7-Substituted 5-(α-Cyanoethyl)-2-methyl-2,3-dihydrobenzofurans (7). Compounds **7a,b** (Table IV) were synthesized by a method similar to that described for **7a** as follows. A suspension of 8.3 g (0.04 mol) of **6a**, 1.8 g (0.045 mol) of sodium amide, and 100 ml of dry benzene was heated gradually to reflux and refluxing was continued for 1 hr under stirring. After the evolution of ammonia ceased, the mixture was cooled to 10°, and 14.2 g (0.1 mol) of CH_3I was added. The mixture was heated to 60° for 3 hr. After being diluted with water, the mixture was extracted with Et_2O and the extracts were washed, dried ($MgSO_4$), and concentrated. The crude **7-chloro-5-(α-cyanoethyl)-2,-2-dimethyl-2,3-dihydrobenzofuran (7a)** was distilled to give 7.2 g (75%) of pure material: bp 140–141° (1.0 mm); ir 2250 cm^{-1} (C≡N); NMR δ 3.75 (q, 1 H, Me-CH-CN, J = 7 Hz), 3.06 (s, 2 H, C_2-gem-2H), 1.55 (d, 3 H, CH_3-CH, J = 7 Hz), and 1.48 ppm (s, 6 H, C_3-gem-2CH_3); mass spectrum m/e 235 (M^+). Anal. ($C_{13}H_{14}ClNO$) C, H.

7-Chloro-5-(α-cyanoethyl)-2-methyl-2,3-dihydrobenzofuran (7b): ir 2245 cm^{-1} (C≡N); NMR (CCl_4) δ 4.96 (q, 1 H, C_2-H, J = 7 Hz), 3.70 (q, 1 H, Me-CH-CN, J = 7 Hz), 3.00 (m, 2 H, C_3-gem-2H), and 1.55, 1.45 ppm (2 d, 6 H, two CH_3 at C_2 and CH_3-CHCN, J = 7 Hz); mass spectrum m/e 221 (M^+).

2,3,7-Substituted 2,3-Dihydrobenzofuran-5-acetic Acids (8). (A) Compounds **8a–d** (Table V) were prepared by a method similar to that described for **8a** as follows. A mixture of **6a** (4.2 g, 0.02 mol), KOH (5.0 g), H_2O (50 ml), and EtOH (50 ml) was refluxed for 3 hr. The reaction mixture was concentrated and the residue was diluted (H_2O) and washed (Et_2O). The aqueous layer was acidified (cold concentrated HCl) and extracted with Et_2O. The extracts were washed (H_2O), dried ($MgSO_4$), and concentrated. The crude product was recrystallized from isopropyl ether–*n*-hexane to give 3.1 g (68%) of **7-chloro-2-methyl-2,3-dihydrobenzofuran-5-acetic acid (8a)**: mp 108–109°; ir 1700 cm^{-1} (COOH); NMR δ 4.90 (m, 1 H, C_2-H), 3.52 (s, 2 H, CH_2COO), 3.05 (m, 2 H, C_3-gem-2H), 1.40 (d, 3 H, C_2-CH_3, J = 7 Hz), and 10.5 ppm (broad s, 1 H, COOH); mass spectrum m/e 226 (M^+). Anal. ($C_{11}H_{11}ClO_3$) C, H.

7-Chloro-2,3-dimethyl-2,3-dihydrobenzofuran-5-acetic acid (8b): ir 1700 cm^{-1} (COOH); NMR (CCl_4) δ 4.65 (m, 1 H, C_2-H), 3.45 (s, 2 H, CH_2COO), 3.26 (m, 1 H, C_3-H), 1.30 (m, 6 H, two CH_3 at C_2 and C_3), and 10.8 ppm (broad s, 1 H, COOH); mass spectrum m/e 240 (M^+). These spectra were determined for free acid.

7-Chloro-2,2-dimethyl-2,3-dihydrobenzofuran-5-acetic acid (8c): ir 1695 cm^{-1} (COOH); NMR δ 3.52 (s, 2 H, CH_2COO), 3.03 (s, 2 H, C_3-gem-2H), 1.50 (s, 6 H, C_2-gem-2CH_3), and 10.4 ppm (broad s, 1 H, COOH); mass spectrum m/e 240 (M^+).

2,2-Dimethyl-2,3-dihydrobenzofuran-5-acetic acid (8d): ir 1700 cm^{-1} (COOH); NMR δ 3.55 (s, 2 H, CH_2COO), 3.00 (s, 2 H, C_3-gem-2H), 1.50 (s, 6 H, C_2-gem-2CH_3), and 10.5 ppm (broad s, 1 H, COOH); mass spectrum m/e 206 (M^+).

(B) Compound **8d** was also prepared as follows. A mixture of 9.5 g (0.05 mol) of **4-acetyl-2-(2-methylallyl)phenol (11)**[14] and 50 ml of formic acid was heated to reflux under stirring for 2 hr. The reaction mixture was evaporated under reduced pressure to dryness and the resulting oily residue was taken up in Et_2O. The Et_2O solution was washed (5% NaOH and H_2O), dried ($MgSO_4$), and evaporated. The solid material obtained was recrystallized from *n*-hexane to give 7.5 g (79%) of **2,2-dimethyl-5-acetyl-2,3-dihydrobenzofuran (12)**: mp 86–87°; ir 1650 cm^{-1} ($COCH_3$); NMR (CCl_4) δ 3.00 (s, 2 H, C_3-gem-2H), 2.40 (s, 3 H, $COCH_3$), and 1.50 ppm (s, 6 H, C_2-gem-2CH_3); mass spectrum m/e 190 (M^+). Anal. ($C_{12}H_{14}O_2$) C, H.

A suspension of 7.5 g (0.04 mol) of **12**, 4 g of sulfur, and 20 ml of morpholine was stirred for 13 hr under reflux. The reaction mixture was poured into ice–water under stirring; the solid material precipitated was filtered and washed (H_2O) thoroughly. The crude thioacetomorpholide was recrystallized from EtOH to give 8.4 g of pure material, mp 118–120°. Anal. ($C_{16}H_{21}NO_2S$) C, H, N. A mixture of 8.2 g of thioacetomorpholide obtained above, 20 ml of EtOH, and 4.0 g of NaOH was refluxed for 9 hr. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in water. After being washed with Et_2O, the solution was acidified with concentrated HCl. Crystals precipitated were filtered, washed (H_2O), air-dried and recrystallized from benzene–*n*-hexane to give 4.8 g (60%) of **8d**, mp 80–81°, undepressed on admixture with a sample prepared by method A. The ir, NMR, and mass spectra of the two substances were identical.

2,3,7-Substituted 2,3-Dihydrobenzofuran-5-acetohydroxamic Acids (9). Compounds **9a,b** (Table V) were prepared by a method similar to that described for **9b** as follows. A solution of 9.2 g (0.045 mol) of **8d** and 12 ml of freshly distilled $SOCl_2$ in 60 ml of dry benzene was refluxed for 2 hr. After removal of excess $SOCl_2$ and benzene under reduced pressure, the residue was distilled to give 6.8 g of the acid chloride of **8d**: bp 120–125° (0.5 mm); ir (liquid film) 1790 cm^{-1} (COCl). A suspension of 6.8 g of the acid chloride and 2.8 g of NH_2OH·HCl in 30 ml of dry pyridine was heated to reflux for 2.5 hr under stirring. The reaction mixture was concentrated to dryness in vacuo; the brown oily residue was dissolved in Et_2O. The Et_2O solution was washed (5% HCl and H_2O), dried ($MgSO_4$), and concentrated to give a crude solid product, which was recrystallized from EtOH–*n*-hexane to give 2.3 g (28%) of **2,2-dimethyl-2,3-dihydrobenzofuran-**

5-acetohydroxamic acid (9b): mp 155–156°; ir 3200 (NHOH), 1630 cm^{-1} (CO); NMR (CCl_4) δ 3.30 (s, 2 H, CH_2CO), 3.20 (broad, 2 H, NHOH), 3.00 (s, 2 H, C_3-gem-2H), and 1.42 ppm (s, 6 H, C_2-gem-$2CH_3$); mass spectrum m/e 221 (M^+). Anal. ($C_{12}H_{15}NO_3$) C, H, N.

7-Chloro-2,2-dimethyl-2,3-dihydrobenzofuran-5-acetohydroxamic acid (9a): ir 3200 (NHOH), 1635 cm^{-1} (CO); NMR δ 3.32 (s, 3 H, CH_2CO), 3.2 (broad, 2 H, NHOH), 2.98 (s, 2 H, C_3-gem-2H), and 1.40 ppm (s, 6 H, C_2-gem-$2CH_3$); mass spectrum m/e 255 (M^+).

2,3,7-Substituted 2,3-Dihydrobenzofuran-5-acetamides (10). Compounds **10a–c** (Table V) were afforded by a method similar to that described for **10a** as follows. A solution of 4.8 g (0.02 mol) of **8c** and 6 ml of freshly distilled $SOCl_2$ in 50 ml of dry benzene was refluxed for 1.5 hr. Solvent and excess $SOCl_2$ were removed in vacuo and the acid chloride was used without purification. Anhydrous NH_3 (gas) was delivered into a cooled (ice bath) well-stirred dry benzene solution of the acid chloride. After 1 hr, H_2O was added and the organic layer was separated, washed (aqueous $NaHCO_3$ and H_2O), dried ($MgSO_4$), and concentrated. The crude solid product was recrystallized from EtOAc to give 4.0 g of **7-chloro-2,2-dimethyl-2,3-dihydrobenzofuran-5-acetamide (10a)**: mp 137–138°; ir 3365, 3150 (NH_2), 1665 cm^{-1} (CO); NMR δ 6.0 (broad, 2 H, $CONH_2$), 3.45 (s, 2 H, CH_2CO), 3.10 (s, 2 H, C_3-gem-2H), and 1.50 ppm (s, 6 H, C_2-gem-$2CH_3$); mass spectrum m/e 239 (M^+). Anal. ($C_{12}H_{14}ClNO_2$) C, H, N.

2,2-Dimethyl-2,3-dihydrobenzofuran-5-acetamide (10b): ir 3360, 3200 (NH_2), 1660 cm^{-1} (CO); NMR δ 7.70 (broad d, 2 H, $CONH_2$), 3.50 (s, 2 H, CH_2CO), 3.00 (s, 2 H, C_3-gem-2H), and 1.40 ppm (s, 6 H, C_2-gem-$2CH_3$); mass spectrum m/e 205 (M^+).

7-Chloro-2-methyl-2,3-dihydrobenzofuran-5-acetamide (10c): ir 3380, 3200 (NH_2), 1650 cm^{-1} (CO); NMR δ 5.8 (broad, 2 H, $CONH_2$), 5.00 (m, 1 H, C_2-H), 3.42 (s, 2 H, CH_2CO), 2.90 (m, 2 H, C_3-gem-2H), and 1.53 ppm (d, 3 H, C_2-CH_3, J = 6 Hz); mass spectrum m/e 225 (M^+).

α-(2,7-Substituted 2,3-dihydrobenzofuran)-α-methyl-5-acetic Acids (13). Compounds **13a,b** (Table V) were prepared by a method similar to that described for **13a** as follows. A solution of 4.7 g (0.02 mol) of **7a** and 1.6 g of NaOH in 100 ml of 50% aqueous EtOH was refluxed for 3 hr. The reaction mixture was concentrated and the residue was diluted with H_2O and washed (Et_2O). The aqueous layer was acidified with HCl and extracted with Et_2O. The ethereal extracts were washed (H_2O), dried ($MgSO_4$), and concentrated. The solid product obtained was recrystallized from isopropyl ether to give 3.2 g (63%) of **α-(7-chloro-2,2-dimethyl-2,3-dihydrobenzofuran)-α-methyl-5-acetic acid (13a)**: mp 116–118°; ir 1700 cm^{-1} (COOH); NMR δ 3.60 (q, 1 H, Me-CH-COO, J = 7 Hz), 2.95 (s, 1 H, C_2-gem-2H), 1.40 (s, 6 H, C_2-gem-$2CH_3$), 1.30 (d, 3 H, CH_3-CHCOO, J = 7 Hz), and 10.8 ppm (broad s, 1 H, COOH); mass spectrum m/e 254 (M^+). Anal. ($C_{13}H_{15}ClO_3$) C, H, N.

α-(7-Chloro-2-methyl-2,3-dihydrobenzofuran)-α-methyl-5-acetic acid (13b): ir 1700 cm^{-1} (COOH); NMR δ 4.95 (m, 1 H, C_2-H), 3.8–2.5 (m, 3 H, Me-CH-COO and C_3-gem-2H), 1.55, 1.45 (2 d, 6 H, CH_3-CHCOO and C_2-CH_3), and 10.9 ppm (s, 1 H, COOH); mass spectrum m/e 240 (M^+). These spectra were determined for the free acid.

γ-(7-Chloro-2,2-dimethyl-2,3-dihydrobenzofuran)-5-γ-oxocrotonic Acid (14). To a stirred suspension of 5.9 g (0.06 mol) of maleic anhydride and 8.1 g (0.06 mol) of $AlCl_3$ (anhydrous) in 70 ml of $Cl_2CHCHCl_2$ was added dropwise a solution of 9.2 g (0.05 mol) of **4c** in 10 ml of $Cl_2CHCHCl_2$ under cooling. After the addition was completed, the mixture was stirred at ordinary temperature for 3 hr. The brown reaction mixture was poured into ice–water, and the separated oil was extracted with Et_2O and washed (H_2O). The Et_2O extracts were extracted with 5% NaOH. The alkaline extracts were made acidic with concentrated HCl and the mixture was extracted with Et_2O. After being dried ($MgSO_4$), the Et_2O extracts were concentrated to give 12.0 g of pasty residue. The residue 14 was converted into the cyclohexylamine salt, and the salt was recrystallized from MeOH to give 14.6 g (76%) of colorless prisms: mp 204° dec; ir 1680 (COOH) and 1625 cm^{-1} [Ar-C(=O)CH=C]. Anal. ($C_{14}H_{13}ClO_4 \cdot C_6H_{13}N$) C, H, N.

γ-(7-Chloro-2,2-dimethyl-2,3-dihydrobenzofuran)-5-γ-oxobutyric Acid (15). To a stirred suspension of 6.0 g (0.06 mol) of succinic anhydride and 8.1 g (0.06 mol) of $AlCl_3$ (anhydrous) in 70 ml of $Cl_2CHCHCl_2$ was added dropwise a solution of 9.2 g (0.05 mol) of **4c** in 10 ml of $Cl_2CHCHCl_2$ at room temperature. The mixture was stirred at 50° for 3 hr and poured into ice–water. The oil separated was extracted with Et_2O and washed (H_2O). The extracts were extracted with 5% NaOH. The alkaline extracts were made acidic with concentrated HCl and the mixture was extracted with Et_2O. After being dried ($MgSO_4$) and concentrated, the crude solid product was recrystallized from $CHCl_3$ to give 10.8 g (76%) of needles: mp 168–170°; ir 1700 and 1695 cm^{-1} (Ar-CO– and COOH); NMR (Me_2SO-d_6) δ 9.1 (broad s, 1 H, COOH), 3.10 [t, 2 H, C(=O)CH_2CH_2, J = 6 Hz], 3.06 (s, 2 H, C_3-gem-2H), 2.63 (t, 2 H, CH_2CH_2COO, J = 7 Hz), and 1.50 ppm (s, 6 H, C_2-gem-$2CH_3$). Anal. ($C_{14}H_{15}ClO_4$) C, H.

γ-(7-Chloro-2,2-dimethyl-2,3-dihydrobenzofuran)-5-butyric Acid (16). A mixture of 2.8 g (0.01 mol) of **15**, 5 ml of 80% $NH_2NH_2 \cdot H_2O$, 2.0 g of KOH, and 30 ml of triethyleneglycol was heated to reflux for 1 hr (bath temperature 120°). The reflux condenser was removed, and low-boiling substances were distilled off. The temperature of the reaction mixture was raised to 220° gradually and kept there for 5 hr. The reaction mixture was cooled and poured into water. After washing with Et_2O, the Et_2O layer was made acidic with concentrated HCl and extracted with Et_2O. The ethereal extracts were washed (H_2O), dried ($MgSO_4$), and concentrated to give 2.2 g of pasty residue. The residue **16** was converted into the cyclohexylamine salt, and the salt was recrystallized from MeOH–EtOAc to give 1.8 g of colorless needles: mp 126–128°; ir 1695 cm^{-1} (COOH). Anal. ($C_{14}H_{17}ClO_3 \cdot C_6H_{13}N$) C, H, N.

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