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Synthesis of 2,3-Dihydro-1,4-benzodioxin Derivatives. II.¹⁾ 5(or 6)-Acyl 2,3-Dihydro-1,4-benzodioxin Derivatives: New Phenoxyacetic Acid Diuretics

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5(and 6)-Acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2-carboxylic acids (VI) and related compounds were synthesized and tested for diuretic and antihypertensive properties. These compounds (VI) were prepared by the reaction of 3,4-dichloro-1,2-dihydroxybenzene (**2**) with epibromohydrin (EBH) in the presence of a base and the Friedel-Crafts acylation, or by acylation of **2** and reaction with EBH, followed by oxidation. Acylation of 7,8-dichlorodihydrobenzodioxin-2-ylmethanol (**15a**) gave the corresponding 5- and 6-acyl compounds, (**17** and **10**). Diuretic activity was generally observed when a 5-acyl substituent was present in the molecule. Compound **20e** showed strong diuretic and antihypertensive activities, like indacrinone (**II**).

Keywords—diuretic; thiazide; phenoxyacetic acid; 5(or 6)-acyl-2,3-dihydro-1,4-benzodioxin; antihypertensive; uricosuric

Diuretic thiazides^{2a)} which show moderate antihypertensive activity on oral administration have been used for many years as first-choice drugs. However, a severe problem is that they generally cause uric acid retention and may result in hyperuricemia. In trying to overcome this problem, studies have been conducted on phenoxyacetic acid diuretics such as tienilic acid (**I**),^{2b)} indacrinone (**II**)^{2c)} and other related compounds (**III**,^{2d)} **IV**,^{2e)} and **V**^{2f)}), but few drugs have been marketed. As we are interested in the biological activity of these new

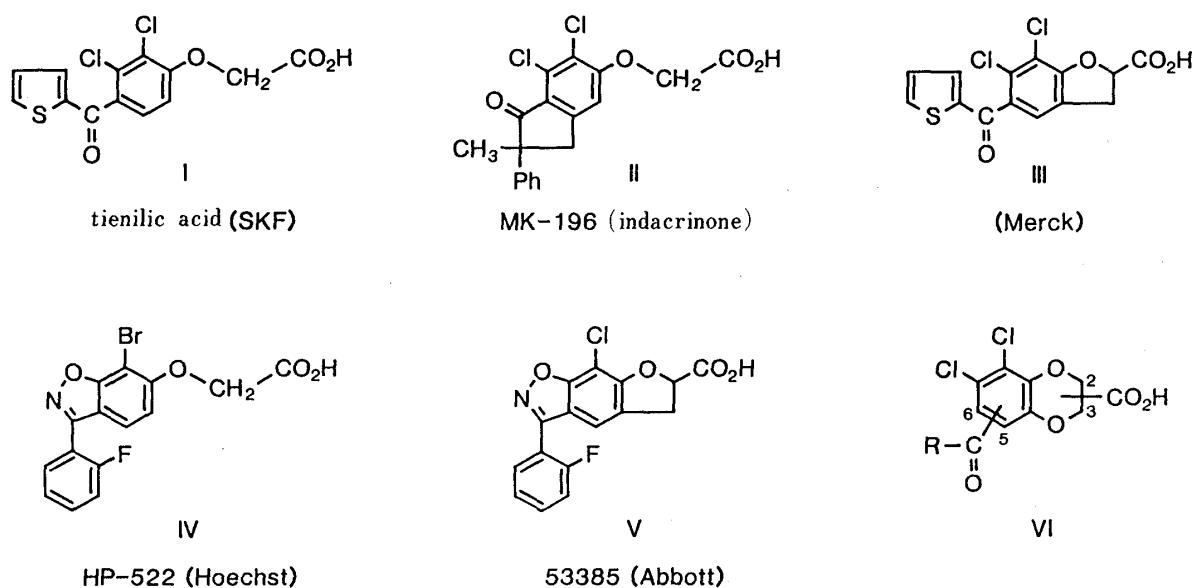


Fig. 1. The Phenoxyacetic Acid Family

phenoxyacetic acid diuretics, we synthesized a series of novel 6(or 5)-acyl-7,8-dichloro-1,2-dihydro-1,4-benzodioxin-2(or 3)-carboxylic acids (VI), as shown in Fig. 1.

Chemistry

We tried to synthesize 6-aroil-2,3-dihydrobenzodioxins from 5-aroil-3,4-dichloro-1,2-dihydroxybenzenes (**3**). As shown in Chart 1, 5-aroil-1,2-dihydroxybenzenes (**3a**, **b**, and **c**) were obtained in good yield (75–83%) by Friedel–Crafts acylation of 3,4-dichloro-1,2-dihydroxybenzene (**2**), which was prepared in 90% yield from 3,4-dichloro-2-hydroxyacetophenone on treatment with hydrogen peroxide in aqueous sodium hydroxide (Dakin oxidation^{3a)}), with aroil chloride in the presence of aluminum chloride,^{2d)} followed by hydrolysis of the esters with 2N sodium hydroxide. Next, regioselective construction of the dihydrobenzodioxin ring was done as described in the previous paper.¹⁾ On treatment of 3,4-dichloro-5-(2-fluorobenzoyl)-1,2-dihydroxybenzene (**3c**) with benzyl bromide (1.1 eq) in the presence of sodium hydride (2.0 eq) in *N,N*-dimethylformamide (DMF) at room temperature for 10 min, the 1-benzyl ether (**5c**) was obtained in 71.4% yield along with the dibenzyl ether (**5d**) in 7% yield. On the other hand, **3c** was heated at 100 °C for 2 h in DMF with benzyl bromide (1.1 eq) in the presence of sodium hydride (1.2 eq) to give the 2-benzyl ether (**4c**) in 52% yield together with **5d** in 14.4% yield. Other aroil regioisomers (**4a**, **5a** and **4b**, **5b**) were obtained by the same method. The structures of **5a** and **5c** were determined unequivocally by X-ray crystal analysis.⁴⁾

The reason for this regioselective reaction may be that the phenoxy anion derived from a less acidic hydroxy group is more reactive than the corresponding one from a more acidic hydroxy group. Under the former conditions, both the more acidic 2-hydroxy group and the less acidic 1-hydroxy group of **3c** react with sodium hydride to form the disodium salt. Therefore, the 1-benzyl ether (**5c**) is obtained almost exclusively. When one equivalent of sodium hydride is used as in the latter case, the more acidic 2-hydroxy group tend to form the sodium salt, which gives the 2-benzyl ether (**4c**).

Chart 2 depicts how the dihydrobenzodioxin ring is constructed from both monobenzyl ethers (**4** and **5**) by the conventional method.⁵⁾ The 2-benzyl ether (**4**) was alkylated with EBH

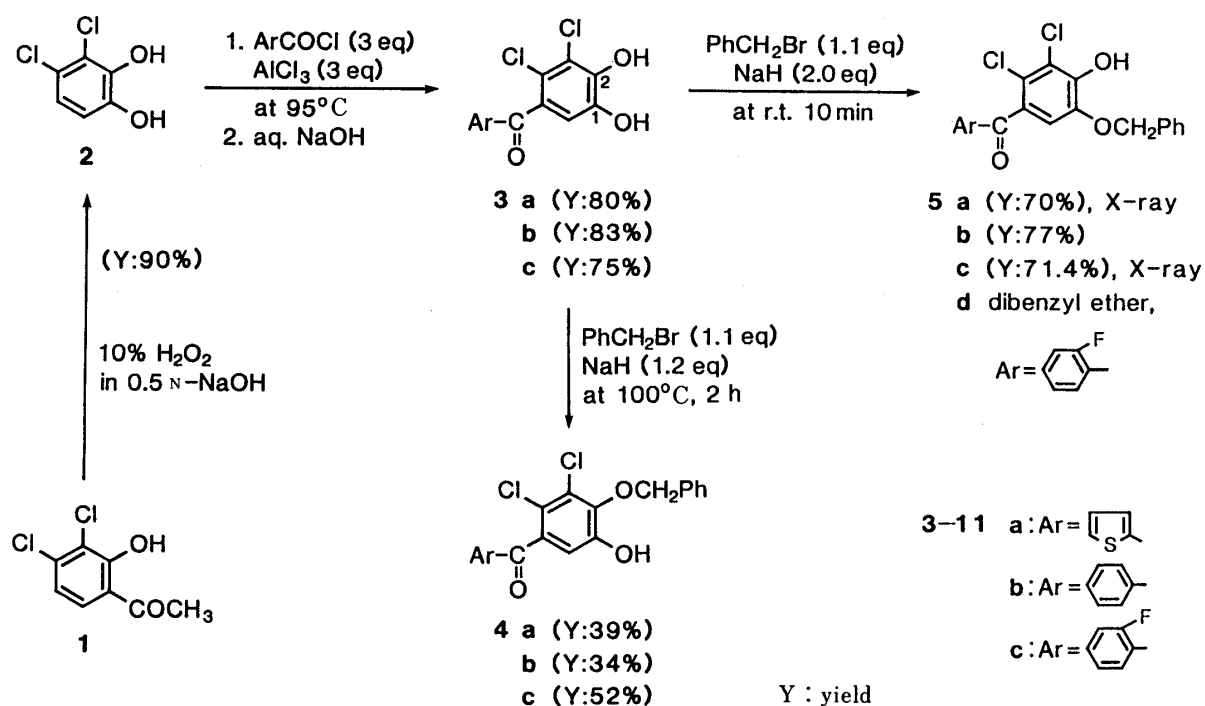


Chart 1

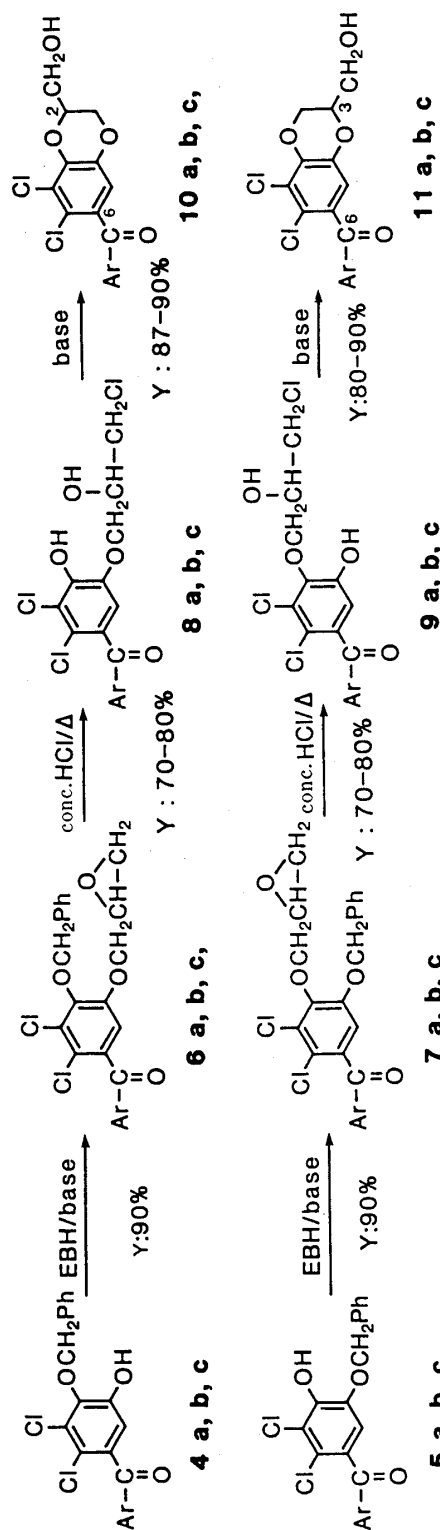


Chart 2

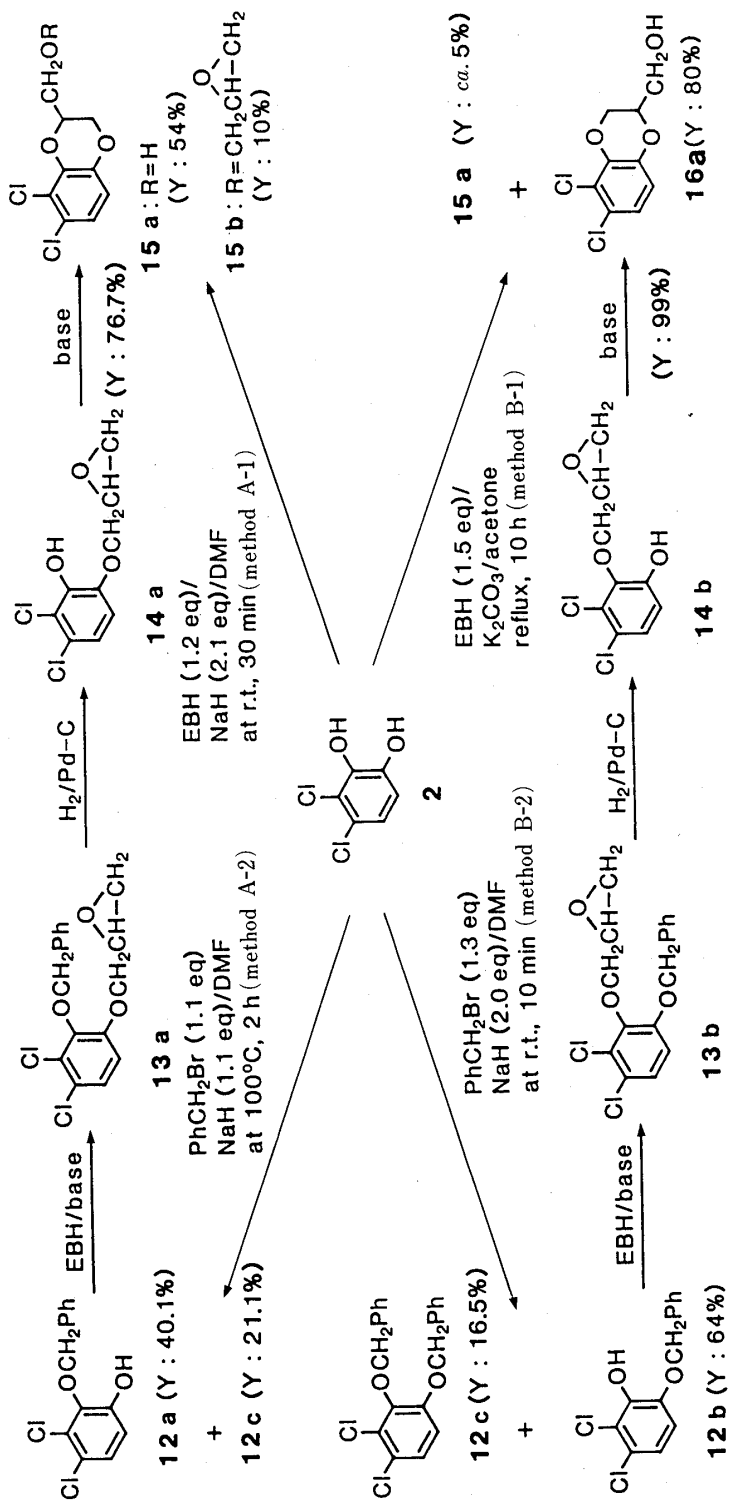


Chart 3

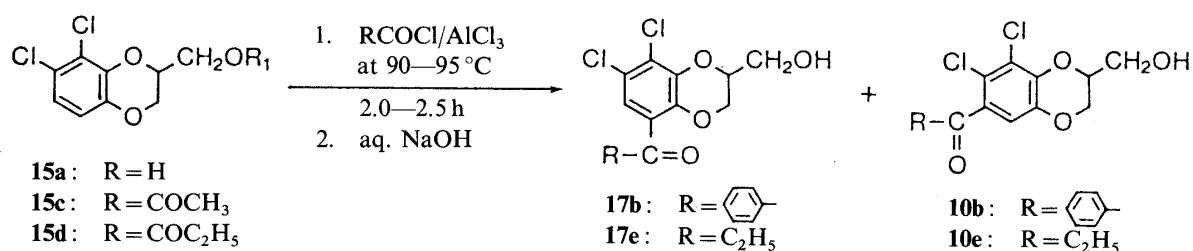
in the presence of a base, the benzyl ether (**6**) was then cleaved by acid, and finally, ring closure was effected with a base to afford 6-aryl-7,8-dichloro-2,3-dihydrobenzodioxin-2-ylmethanol (**10**) in 60–70% overall yield. The 1-benzyl ether (**5**) was converted into the 3-hydroxymethyl analogue (**11**) by the same method.

For the preparation of various acyl dihydrobenzodioxins, acylation of dihydrobenzodioxin is apparently effective and simple. 2-Benzyloxy-3,4-dimethylacetophenone was subjected to Baeyer–Villiger oxidation^{3b)} using peracetic acid to give 2-benzyloxy-3,4-dimethyl-1-hydroxybenzene in good yield. However, the reaction of 2-benzyloxy-3,4-dichloroacetophenone with peracetic acid gives 2-benzyloxy-3,4-dichloro-1-hydroxybenzene (**12a**) in a poor yield of only 8.7%.

Therefore, 3,4-dichloro-1,2-dihydroxybenzene (**2**) was treated with benzyl bromide (1.3 eq) and sodium hydride (2.0 eq) in DMF at room temperature similarly to 5-aryl-3,4-dichloro-1,2-dihydroxybenzenes (**3**), giving the 1-benzyl ether (**12b**) in 64% yield along with the dibenzyl ether (**12c**) in 16.5% yield, whereas **2** was heated with benzyl bromide (1.1 eq) and sodium hydride (1.1 eq) in DMF at 100 °C for 2 h to afford the 2-benzyl ether (**12a**) in 40.1% yield along with the dibenzyl ether (**12c**) in 21.1% yield. These monobenzyl ethers (**12a** and **12b**) were converted into the corresponding dihydrobenzodioxin-2(or 3)-ylmethanols (**15a** and **16a**) in the same way as described above for the preparation of **10** and **11**. 3,4-Dichloro-1,2-dihydroxybenzene (**2**) was directly treated with EBH (1.2 eq) in the presence of sodium hydride (2.1 eq) in DMF at room temperature for 30 min, giving the 2-hydroxymethyl compound (**15a**) in 54% yield along with **15b** in 10% yield. When **2** was refluxed with EBH (1.5 eq) in the presence of potassium carbonate in acetone for 10 h, the 3-hydroxymethyl compound (**16a**) was obtained in 80% yield along with a small amount of the 2-hydroxymethyl compound (**15a**) (ca. 5%) as shown in Chart 3.

7,8-Dichloro-2,3-dihydrobenzodioxin-2-ylmethanol (**15a**), when treated with benzoyl

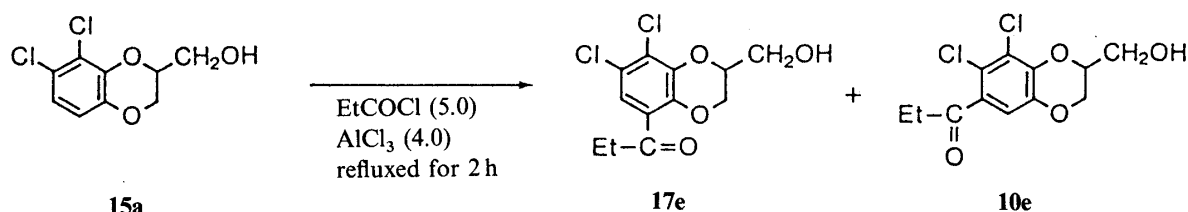
TABLE I. Friedel–Crafts Acylation: Proportions of Reagents



No.	Compound	Reagent (Ratio, eq)		Product (Yield %) ^{a)}	
		PhCOCl	AlCl ₃	17b	10b
1	15a	2.5	3.0	< 5	72.5
2	15a	4.0	3.0	45.0	43.0
3	15a	5.0	4.0	45.0	43.0
4	15a	10.0	4.0	45.0	45.0
		C ₂ H ₅ COCl	AlCl ₃	17e	10e
5	15a	2.5	3.0	(25)	(75)
6	15a	4.0	3.0	57.0	31.0
7	15a	5.0	5.0	(29)	(60)
8	15c	4.0	4.0	(56)	(44)
9	15d	4.0	4.0	52.0 (60)	34.0 (40)
10	15d	6.0	5.0	51.3	31.2

^{a)} The product ratio in parentheses was determined from the ¹H-NMR spectrum (Ar-H, δ, **17e** 7.34, **10e** 7.07).

TABLE II. Solvent Effect in Friedel-Crafts Acylation



Run	Solvent (Temp. °C)	Yield (%) ^{a)}		
		17e	10e	15a (Recovered)
1	CH ₂ Cl ₂ (40—50)	41	36	23
2	CH ₂ Cl ₂ (80—90)	60	40	—
3	CCl ₄ (76)	50	50	—
4	Cyclohexane (81)	41	49	—
5	(CH ₂ Cl) ₂ (81)	6	—	94
6	CH ₃ NO ₂ (101)	40	60	—

a) The products ratio was determined from the ¹H-NMR spectrum.

chloride or propionyl chloride (2.5 eq) and aluminum chloride (3.0 eq) in dichloromethane at 95 °C, gave the 6-acyl compound (**10b** or **10e**) as the major product and a small amount of the 5-acyl compound (**17b** or **17e**). As 5-acyldihydrobenzodioxins showed stronger diuretic effects than 6-acyl compounds, we investigated the optimal conditions of acylation in order to prepare more 5-acyl compounds. Tables I and II show the results under various reaction conditions, the proportions of benzoyl chloride (or propionyl chloride) and aluminum chloride employed (Table I), and the solvent effect (Table II) in the Friedel-Crafts acylation of **15a**. The ratio of the 6-acyl compound increased when the proportion of aluminum chloride employed was more than that of acyl chloride.

In general, **15a** was treated with acyl chloride/aluminum chloride (4:3 eq) or (5:4 eq) in dichloromethane at 90—95 °C for 2 h.

The results of Friedel-Crafts acylation of **15a** are summarized in Table III. Formylation was carried out by treatment of **15a** with dichloromethyl methyl ether⁶⁾ (in place of acyl chloride) and aluminum chloride.

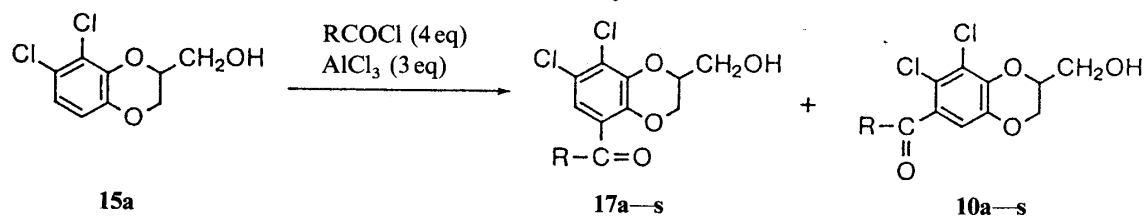
The structures of the 5-aroyle compounds (**17a**, **b** and **c**) were easily confirmed by comparison with the corresponding 6-aroyle compounds (**10a**, **b** and **c**) shown in Chart 2. Moreover, the structures of acyl regioisomers (**10e** and **17e**) were determined from the proton and carbon-13 nuclear magnetic resonance (¹H- and ¹³C-NMR) spectra as shown in Table IV. The C-6 proton signal of 5-acyl compounds (**17**) was shifted to lower field than that of the C-5 proton of 6-acyl compounds (**10**). In the case of acyl compounds (**10d**, **17d** and **10e**, **17e**), moreover, the signal of carbon-13 carrying the acyl group is moved to lower field.

On acylation of the 3-hydroxymethyl compound (**16**), the 5-acyl compound (**18**) was obtained as a minor product and the 6-acyl compound (**11**) as the major one, as shown in Table V.

In place of the 2-hydroxymethyl compound (**15a**), the 2-carboxyl ester (**19b**), which was obtained by oxidation of **15a** followed by esterification, was found to be unreactive for acylation. However, this was formylated with dichloromethyl methyl ether in the presence of a Lewis acid such as aluminum chloride or titanium(IV) chloride⁶⁾ and gave a mixture of the 5-formyl and 6-formyl compounds (**24e** and **25e**) as shown in Table VI.

These acyl-2(or 3)-hydroxymethyl compounds (**17**, **10**, **18** and **11**) were easily oxidized with Jones reagent to give the corresponding carboxylic acids (**20—23**) in good yields as

TABLE III. Friedel-Crafts Acylation of 7,8-Dichloro-2,3-dihydro-1,4-benzodioxin-2-ylmethanol



R	Reagent (Ratio) RCOCl : AlCl ₃	Method	Yield (%)	
			17	10
a	4:3	B	45.7	45.0
b	4:3	B	45.0	43.0
c	4:3	B	49.4	33.2
d CH ₃	4:3	A	39.6	58.6
e C ₂ H ₅	4:3	B	57.0	31.0
f n-C ₃ H ₇	4:3	A	50.7	38.2
g iso-C ₃ H ₇	4:3	B	36.8	—
h n-C ₄ H ₉	4:3	B	17.1	22.1
i	4:3	B	8.3	—
j	4:3	B	—	27.5
k PhCH ₂ —	4:3	In CS ₂ r.t. 12 h	21.0	5.6
l o-Cl-C ₆ H ₄ —	4:3	B	51.4	40.3
m m-Cl-C ₆ H ₄ —	4:3	B	21.0	30.6
n p-Cl-C ₆ H ₄ —	4:3	B	46.6	42.4
o o-CH ₃ -C ₆ H ₄ —	4:3	B	38.0	43.8
p m-CH ₃ -C ₆ H ₄ —	4:3	B	40.9	38.9
q p-CH ₃ -C ₆ H ₄ —	4:3	B	23.1	27.8
r	4:3	B	47.0	48.0
s H	3 (Cl ₂ CHOCH ₃) : 3 (AlCl ₃)	r.t.	33.3	22.3
s H	3 (Cl ₂ CHOCH ₃) : 3 (TiCl ₄)	r.t.	20.0	42.3

A: In CH₂Cl₂, reflux for 2—3 h. B: At 90—95 °C for 2—3 h.

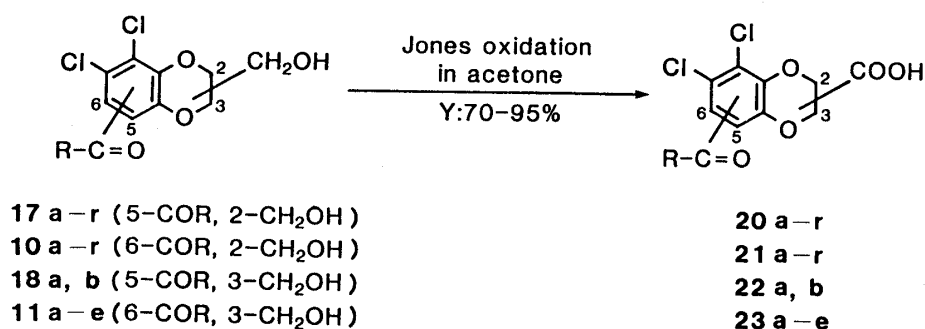
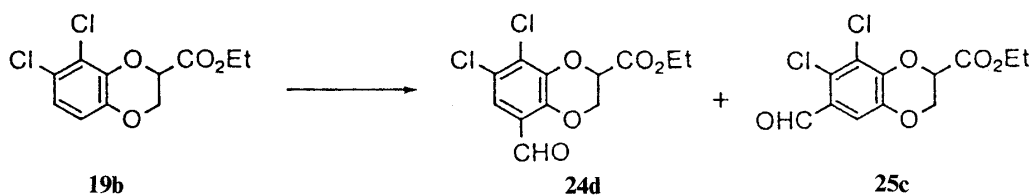


Chart 4

shown in Chart 4.

According to the method reported by Coudert *et al.*,⁷⁾ 5(or 6)-aroyl-7,8-dichloro-1,4-benzodioxin-2(or 3)-carboxylic acids (30—32) were synthesized from the corresponding

TABLE VI. Formylation of Ethyl 7,8-Dichloro-2,3-dihydro-1,4-benzodioxin-2-carboxylate



Reagent	Reaction conditions	Yield (%)	
		24d	25c
$\text{Cl}_2\text{CHOCH}_3/\text{AlCl}_3$	At 0°C —r.t. 3 h	48	47
$\text{Cl}_2\text{CHOCH}_3/\text{TiCl}_4$	At 0°C —r.t. 3 h	19	39

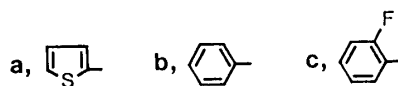
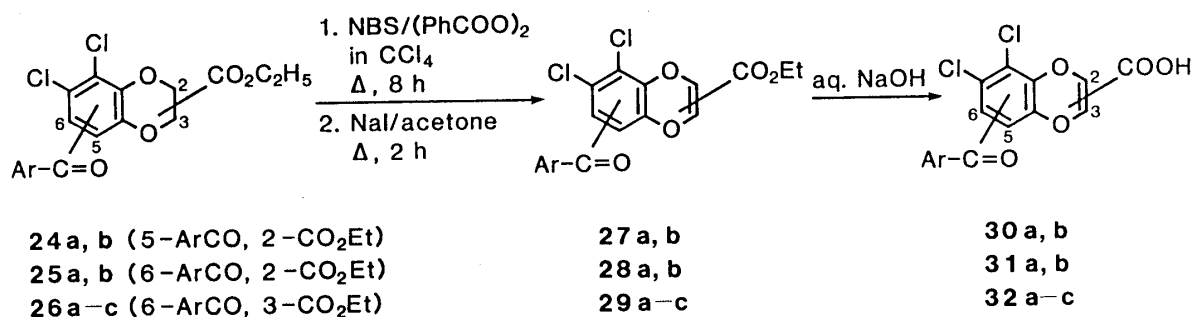


Chart 5

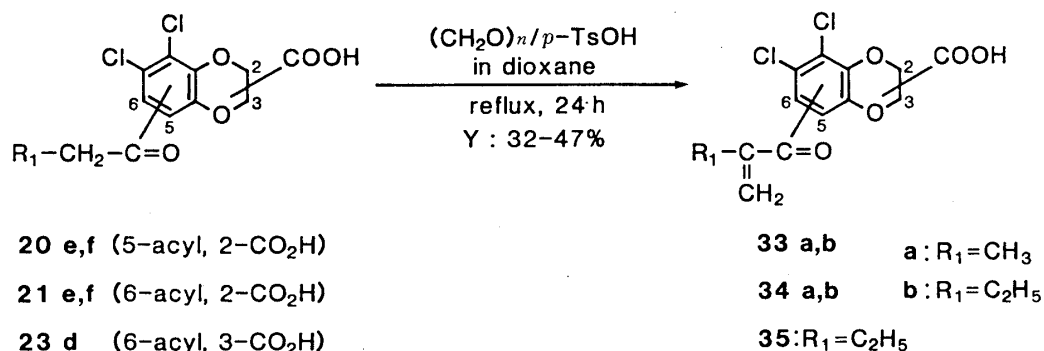


Chart 6

dihydrobenzodioxin-2(or 3)-carboxylates (**24**—**26**) as shown in Chart 5. Compounds **24** were heated with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide in carbon tetrachloride followed by sodium iodide in acetone to obtain the ethyl esters (**27**). Hydrolysis of **27** with base afforded the corresponding benzodioxin (**30**) in good yield.

As ethacrynic acid has strong diuretic activity like indacrinone, 2-alkylacryloyl compound (**33**—**35**) were synthesized by treatment of 5(or 6)-acyl-2,3-dihydrobenzodioxin carboxylic acids (**20**, **21** and **23**) with paraformaldehyde and *p*-toluenesulfonic acid in dioxane according to the reported method⁸⁾ as shown in Chart 6.

As racemic 7,8-dichloro-5-propionyl-2,3-dihydrobenzodioxin-2-carboxylic acid (**20e**)

showed strong diuretic activity, resolution of **20e** was carried out as follows; namely treatment of the acid chloride of **20e** with D-(–)-phenylglycinol gave amide diastereoisomers (**36a** and **36b**), which were separated on a Lobar column, followed by hydrolysis of each diastereoisomer with aqueous sulfuric acid to yield one (+) enantiomer (**37a**) $[\alpha]_D^{23.0} + 83.8^\circ$ and another (–) enantiomer (**37b**) $[\alpha]_D^{23.0} - 83.5^\circ$ according to Obase *et al.*⁹⁾ (Chart 7).

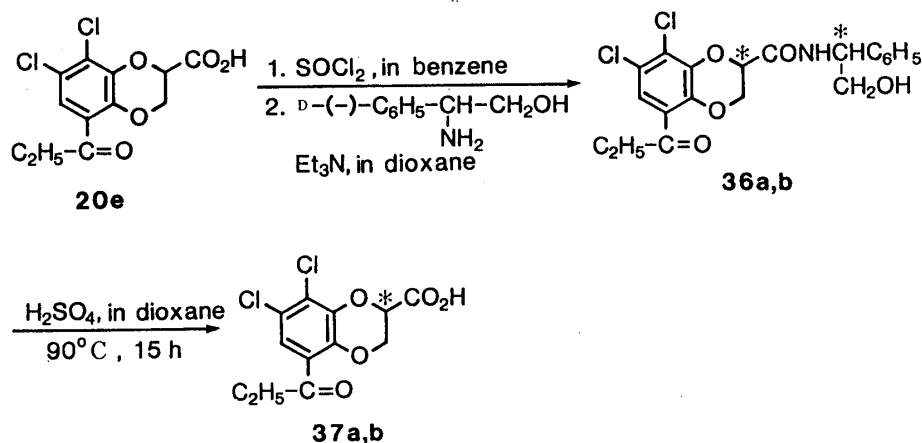


TABLE VII. Diuretic Activity of 5-Acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2(or 3)-carboxylic Acids in Rat and Mouse

Compound No.	CO ₂ H	Diuretic activity ^{a)}	
		Rat	Mouse
20a	2	2.04 ^{b)} /0.45	4.63 ^{b)} /0.85
20b	2	1.36 ^{b)} /0.46	4.56 ^{b)} /0.93
20c	2	1.02 ^{b)} /0.46	3.36 ^{b)} /0.93
20d	2	2.08 ^{b)} /0.92	1.98 ^{b)} /0.85
20e (racemic)	2	3.04 ^{b)} /0.71	5.68 ^{b)} /0.78
37a (–)	2	4.11 ^{b)} /0.69	4.62 ^{b)} /0.96
37b (+)	2	1.20 ^{b)} /0.69	1.93 ^{b)} /0.96
20f	2	2.20 ^{b)} /0.75	4.31 ^{b)} /0.64
20g	2	3.54 ^{b)} /0.75	5.78 ^{b)} /0.82
20h	2	1.83 ^{b)} /0.75	1.67 ^{b)} /0.82
20i	2	3.90 ^{b)} /0.59	1.67 ^{b)} /0.82
20k	2	2.95 ^{b)} /0.59	7.43 ^{b)} /0.74
20l	2	0.96 ^{b)} /0.49	3.15 ^{b)} /0.92
20m	2	0.97 ^{b)} /0.49	1.73 ^{b)} /0.92
20n	2	0.69 /0.49	1.48 /0.92
20o	2	1.42 ^{b)} /0.50	3.58 ^{b)} /0.54
20p	2	1.49 ^{b)} /0.50	4.10 ^{b)} /0.54
20q	2	1.67 ^{b)} /0.50	1.48 ^{b)} /0.54
20r	2	1.61 ^{b)} /0.64	2.10 ^{b)} /0.82
33a	2	0.85 /0.75	8.87 ^{b)} /0.64
33b	2	1.06 /0.50	7.31 ^{b)} /0.85
30a (benzodioxin)	2	1.98 ^{b)} /0.51	2.56 ^{b)} /0.69
30b (benzodioxin)	2	0.91 ^{b)} /0.51	2.03 ^{b)} /0.69
22a	3	0.64 /0.56	1.02 /0.69
22b	3	1.28 ^{b)} /0.59	1.16 /0.99
Indacrinone (reference)		1.26 ^{b)} /0.55	6.44 ^{b)} /0.77

a) Na meq/kg body weight; treated/control. b) Statistically significant. Dose: rat, 50 mg/kg; mouse, 30 mg/kg, *p.o.*

TABLE VIII. Diuretic Activity of 6-Acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2(or 3)-carboxylic Acids in Rat and Mouse

Compound No.	CO ₂ H	Diuretic activity ^{a)}	
		Rat	Mouse
21a	2	0.60 /0.63	—
21b	2	0.84 /1.03	—
21c	2	0.95 /0.61	0.77 /0.65
21d	2	0.82 /0.94	0.68 /0.62
21e	2	0.93 /0.54	0.37 /0.81
21f	2	0.62 /0.69	—
21r	2	0.61 /0.64	0.87 /0.69
21s	2	1.01 /0.94	0.58 /0.85
23a	3	0.59 /0.57	—
23b	3	1.53 ^{b)} /0.55	1.12 /0.69
23c	3	1.72 ^{b)} /0.61	0.74 /0.69
23d	3	0.77 /0.76	0.55 /0.30
34a	2	0.54 /0.76	2.51 ^{b)} /0.64
34b	2	0.82 /0.54	0.71 /0.78
35	3	0.78 /0.52	0.38 /0.30
31a (benzodioxin)	2	1.05 ^{b)} /0.43	1.18 ^{b)} /0.69
31b (benzodioxin)	2	1.35 ^{b)} /0.65	0.83 /0.60
32a (benzodioxin)	3	1.54 /1.02	—
32b (benzodioxin)	3	1.35 ^{b)} /0.65	0.83 /0.60
32c (benzodioxin)	3	1.11 ^{b)} /0.65	0.94 /0.60

a) Na meq/kg body weight; treated/control. b) Statistically significant.

Biological Activities

5-Acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxine-2-carboxylic acids (**20**) showed strong diuretic activity in rat and mouse and antihypertensive activity in rat,¹⁰⁾ whereas the corresponding 3-carboxylic acids (**22**) were less diuretic than the 2-carboxylic acids, as summarized in Table VII.

6-Acyl-2(and 3)-carboxylic acids (**21** and **23**) displayed little or no diuretic activity as can be seen from Table VIII.

The excretion of urine, Na⁺, and K⁺ were measured in experiments conducted with rats and mice. For brevity, only the data on Na⁺ excretion are reported here. The excretion of urine and K⁺ generally paralleled that of Na⁺, and any of these parameters could be used for relative potency comparisons.

Experimental

Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected. Infrared (IR) spectra were recorded in Nujol with a Hitachi 260-10 IRS spectrophotometer, unless otherwise noted. Wave numbers are expressed in reciprocal centimeters. ¹H-NMR spectra were taken in CDCl₃ solution on a Varian EM-390 or T-60 spectrophotometer, unless otherwise noted. Chemical shifts are expressed as δ values (ppm) from tetramethylsilane. Column chromatography was conducted using silica gel (E. Merck, 70—230 mesh ASTM) or a Lobar column (E. Merck). The general procedure for isolating products by solvent extraction consisted of extracting the aqueous layer with two or three portions of the indicated solvent, washing the organic layer with saturated NaCl-H₂O or H₂O, drying it over Na₂SO₄ or MgSO₄, and evaporating the solvent *in vacuo*.

2-Benzyloxy-3,4-dichloro-1-hydroxybenzene (12a)—A mixture of 2-benzyloxy-3,4-dichloroacetophenone (1.0 g), and 40% peracetic acid (1 ml) in AcOH (2 ml) was heated at 50 °C for 23 h. The cooled reaction mixture was mixed with water and extracted with CH₂Cl₂. The residue obtained from the extract was recrystallized from petroleum ether (PE), giving 3,4-dichloro-2-hydroxyacetophenone (**1**) (276 mg, mp 113—114 °C, yield 39.7%) and a crystalline residue (361 mg). A mixture of the crystalline residue and Na₂CO₃ (100 mg) in EtOH (2 ml) was refluxed for 10 min and allowed to stand for 1 h at room temperature. The mixture was acidified with aqueous HCl and

extracted with CH_2Cl_2 . The residue (320 mg) was separated by chromatography on a Lobar column with benzene as the eluent. The first fraction gave **1** (81 mg) and the second fraction gave 2-benzyloxy-3,4-dichloro-1-hydroxybenzene (**12a**) (79 mg, mp 61 °C, from pentane, yield 8.7%). *Anal.* Calcd for $\text{C}_{13}\text{H}_{10}\text{Cl}_2\text{O}_2$ (M_r 269.135): C, 58.02; H, 3.75; Cl, 26.35. Found: C, 57.38; H, 3.82; Cl, 26.35. IR cm^{-1} : 3400, 1590, 1570. $^1\text{H-NMR}$ δ : 7.40 (5H, m), 7.12, 6.72 (each 1H, d, $J=9$ Hz), 5.41 (1H, s, OH), 5.05 (2H, s, CH_2Ph).

Preparation of 5-Aroyl-3,4-dichloro-1,2-dihydroxybenzene (3a, b and c)

General Procedure—A mixture of 3,4-dichloro-1,2-dihydroxybenzene (**2**) (0.01 mol), ArCOCl (0.03–0.04 mol) and AlCl_3 (0.025–0.03 mol) in dry 1,2-dichloroethane (350 ml) was refluxed for 20–24 h. The cooled reaction mixture was poured into ice water/concentrated HCl, and then the reaction mixture was extracted with ether or EtOAc. The extract was concentrated and the residue was mixed with 2N NaOH (250 ml) and EtOH (200 ml), then the mixture was refluxed for 30 min, followed by conventional work-up to give the 5-aryl-3,4-dichloro-1,2-dihydroxybenzene (**3a, b or c**) in 75–83% yield.

3,4-Dichloro-1,2-dihydroxy-5-thenoylbenzene (**3a**): mp 202–204 °C (from acetone–ether, yield 80%). *Anal.* Calcd for $\text{C}_{11}\text{H}_6\text{Cl}_2\text{O}_3\text{S}$ (M_r 289.140): C, 45.69; H, 2.09; Cl, 24.53; S, 11.09. Found: C, 45.48; H, 2.38; Cl, 24.60; S, 11.09. IR cm^{-1} : 3360, 1720, 1710. $^1\text{H-NMR}$ (acetone- d_6) δ : 8.97 (2H, br), 7.97 (1H, dd, $J=5$, 1 Hz), 7.53 (1H, dd, $J=5$, 1 Hz), 7.17 (1H, t, $J=5$ Hz), 6.97 (1H, s).

5-Benzoyl-3,4-dichloro-1,2-dihydroxybenzene (**3b**): mp 178–180 °C (from CH_2Cl_2 –PE, yield 83%). *Anal.* Calcd for $\text{C}_{13}\text{H}_8\text{Cl}_2\text{O}_3$ (M_r 283.118): C, 55.15; H, 2.85; Cl, 25.05. Found: C, 55.05; H, 2.98; Cl, 25.30. IR cm^{-1} : 3425, 3100, 1655, 1595, 1580. $^1\text{H-NMR}$ (acetone- d_6) δ : 6.95 (1H, s), 7.93–7.50 (5H, m).

3,4-Dichloro-5-(2-fluorobenzoyl)-1,2-dihydroxybenzene (**3c**): mp 164–165 °C (from benzene, yield 75%). *Anal.* Calcd for $\text{C}_{13}\text{H}_7\text{Cl}_2\text{FO}_3$ (M_r 301.108): C, 51.86; H, 2.34; Cl, 23.55; F, 6.31. Found: C, 51.88; H, 2.47; Cl, 23.49; F, 6.28. IR cm^{-1} : 3400, 3170, 1665, 1655, 1610. $^1\text{H-NMR}$ δ : 9.50–8.40 (2H, br), 7.78–7.10 (4H, m), 7.03 (1H, s).

Preparation of 7,8-Dichloro-6-(2-fluorobenzoyl)-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (10c)

1) 2-Benzyloxy-3,4-dichloro-5-(2-fluorobenzoyl)-1-hydroxybenzene (4c)—A mixture of **3c** (3.217 g), NaH (282 mg, 1.1 eq) and PhCH_2Br (1.919 g, 1.05 eq) in dry DMF (100 ml) was heated at 100 °C under stirring for 2 h. The cooled reaction mixture was poured into ice water and acidified with aqueous HCl. The reaction mixture was extracted with ether. The residue (4.124 g) was chromatographed on SiO_2 (100 g) with CH_2Cl_2 to afford the dibenzyl ether (**5d**) from the first fraction and the 2-benzyl ether (**4c**) (2.257 g) from the later fraction. The former was recrystallized from hexane, giving the dibenzyl ether (**5d**) (766 mg, mp 84–85 °C, yield 14.4%), and the latter gave the 2-benzyl ether (**4c**) (2.189 g, mp 109–110 °C, from cyclohexane, yield 52%). *Anal.* Calcd for $\text{C}_{20}\text{H}_{13}\text{Cl}_2\text{FO}_3$ (M_r 391.233): C, 61.40; H, 3.35; Cl, 18.13; F, 4.86. Found: C, 61.41; H, 3.50; Cl, 18.34; F, 4.81. IR cm^{-1} : 3210, 1670, 1610. $^1\text{H-NMR}$ δ : 7.86–7.00 (4H, m), 7.45 (5H, m), 6.93 (1H, s), 5.64 (1H, s), 5.14 (2H, s).

The Dibenzyl Ether (**5d**): *Anal.* Calcd for $\text{C}_{27}\text{H}_{19}\text{Cl}_2\text{FO}_3$ (M_r 481.358): C, 67.37; H, 3.98; Cl, 14.73; F, 3.95. Found: C, 67.28; H, 3.95; Cl, 14.61; F, 3.90. IR cm^{-1} : 1645, 1605. $^1\text{H-NMR}$ δ : 7.83–6.99 (4H, m), 7.39 (1H, br, OH), 7.04 (1H, s), 5.13 (2H, s), 5.10 (2H, s).

2-Benzyloxy-3,4-dichloro-1-hydroxy-5-thenoylbenzene (**4a**): mp 159–160 °C (from ether–PE, yield 39%). *Anal.* Calcd for $\text{C}_{18}\text{H}_{12}\text{Cl}_2\text{O}_3\text{S}$ (M_r 379.265): C, 57.00; H, 3.19; Cl, 18.70; S, 8.45. Found: C, 56.74; H, 3.26; Cl, 18.71; S, 8.46. IR cm^{-1} : 3300, 1640, 1581. $^1\text{H-NMR}$ δ : 7.78 (1H, dd, $J=5$, 1 Hz), 7.43 (5H, s), 7.42 (1H, dd, $J=5$, 1 Hz), 7.18 (1H, t, $J=5$ Hz), 6.93 (1H, s), 5.68 (1H, s), 5.15 (2H, s).

5-Benzoyl-2-benzyloxy-3,4-dichloro-1-hydroxybenzene (**4b**): mp 111–112 °C (from ether–PE, yield 34%). *Anal.* Calcd for $\text{C}_{20}\text{H}_{14}\text{Cl}_2\text{O}_3$ (M_r 373.243): C, 64.36; H, 3.78; Cl, 19.00. Found: C, 64.34; H, 4.00; Cl, 18.79. IR cm^{-1} : 3350, 1665, 1597, 1580. $^1\text{H-NMR}$ δ : 7.93–7.45 (5H, m), 7.45 (5H, s), 6.87 (1H, s), 5.73 (1H, br, OH).

2) 2-Benzyloxy-3,4-dichloro-1-(2,3-epoxypropoxy)-5-(2-fluorobenzoyl)benzene (6c)—A mixture of the 2-benzyl ether (**4c**) (2.60 g), NaH (192 mg, 1.2 eq) and EBH (1.16 g, 1.23 eq) in dry DMF (60 ml) was heated at 80 °C with stirring for 5 h. The cooled reaction mixture was poured into ice water and extracted with benzene. Treatment of the organic layer in a conventional manner gave a residue (3.46 g), which was purified by chromatography on SiO_2 with CH_2Cl_2 to afford **6c** (2.68 g, oil, yield 90.1%). IR (CHCl_3) cm^{-1} : 1665, 1610. $^1\text{H-NMR}$ δ : 7.84–7.08 (9H, m), 6.99 (1H, s), 5.26 (2H, s), 4.38–3.85 (2H, m), 3.35 (1H, br), 2.93–2.67 (2H, m).

3) 3,4-Dichloro-1-(3-chloro-2-hydroxypropoxy)-5-(2-fluorobenzoyl)-2-hydroxybenzene (8c)—A solution of **6c** (2.68 g) in concentrated HCl (100 ml) was refluxed for 6 h. The reaction mixture was cooled and the resultant precipitate (2.484 g) was collected by filtration. Recrystallization from benzene gave the 2-hydroxy compound (**8c**) (1.626 g, mp 144–146 °C, yield 69%). *Anal.* Calcd for $\text{C}_{16}\text{H}_{12}\text{Cl}_3\text{FO}_4$ (M_r 393.637): C, 48.82; H, 3.07; Cl, 27.02; F, 4.83. Found: C, 48.46; H, 3.16; Cl, 26.80; F, 4.86. IR cm^{-1} : 3470, 3230, 1630, 1603. $^1\text{H-NMR}$ (acetone- d_6) δ : 7.81–7.11 (4H, m), 7.23 (1H, s), 7.5–6.2 (2H, br), 4.33–4.14 (1H, m), 4.24 (2H, m), 3.81 (2H).

4) A solution of **8c** (2.30 g) in 2N NaOH (23.5 ml) and EtOH (47 ml) was refluxed for 10 min. The cooled reaction mixture was neutralized with aqueous HCl, concentrated *in vacuo* and extracted with CH_2Cl_2 . The residue (2.16 g) obtained from the extract was passed through an SiO_2 column with CH_2Cl_2 /acetone (95:5) to afford 7,8-dichloro-6-(2-fluorobenzoyl)-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (**10c**) (1.829 g, yield 87.6%). Recrystallization from isopropyl ether gave a pure substance (mp 109–110 °C). *Anal.* Calcd for $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{FO}_4$ (M_r 357.172): C, 53.80; H, 3.10; Cl, 19.85; F, 5.32. Found: C, 53.87; H, 3.18; Cl, 19.86; F, 5.10. IR cm^{-1} : 3420, 1665, 1610. $^1\text{H-NMR}$

δ : 7.80—7.08 (4H, m), 6.99 (1H, s), 4.46—4.11 (1H, m), 4.33 (2H, m), 3.95 (2H, m), 2.20 (1H, t, $J=6$ Hz).

Preparation of 7,8-Dichloro-6-(2-fluorobenzoyl)-2,3-dihydro-1,4-benzodioxin-3-ylmethanol (11c)

1) **1-Benzylloxy-3,4-dichloro-5-(2-fluorobenzoyl)-2-hydroxybenzene (5c)**—A mixture of **3c** (3.01 g), NaH (480 mg, 2 eq), and PhCH₂Br (1.88 g, 1.1 eq) in dry DMF (50 ml) was stirred at room temperature for 15 min. The reaction mixture was poured into water, acidified with aqueous HCl, and then extracted with ether. The residue (4.227 g) was passed through a column of SiO₂ with CH₂Cl₂, and the eluted fraction (2.99 g) was recrystallized from benzene, affording **5c** (2.791 g, mp 156—157 °C, yield 71.4%). *Anal.* Calcd for C₂₀H₁₃Cl₂FO₃ (M_r 391.233): C, 61.40; H, 3.35; Cl, 18.13; F, 4.86. Found: C, 61.41; H, 3.40; Cl, 18.24; F, 4.73. IR cm⁻¹: 3200, 1655, 1615. ¹H-NMR δ : 7.78—6.98 (4H, m), 7.41 (5H, m), 7.07 (1H, s), 6.34 (1H, s), 5.12 (2H, s). The structure of **5c** was unequivocally determined by X-ray crystal analysis.

1-Benzylloxy-3,4-dichloro-2-hydroxy-5-thenoylbenzene (5a): mp 146—148 °C (from ether-PE, yield 70%). *Anal.* Calcd for C₁₈H₁₂Cl₂O₃S (M_r 379.265): C, 57.00; H, 3.19; Cl, 18.70; S, 8.45. Found: C, 56.87; H, 3.30; Cl, 18.56; S, 8.44. IR cm⁻¹: 3450, 1648, 1600. ¹H-NMR δ : 7.73 (1H, dd, $J=5$, 1 Hz), 7.32 (1H, dd, $J=5$, 1 Hz), 7.08 (1H, t, $J=5$ Hz), 7.38 (5H, s), 6.95 (1H, s), 6.40 (1H, br), 5.13 (2H, s). The structure of **5a** was determined by X-ray crystal analysis.

5-Benzoyl-1-benzylloxy-3,4-dichloro-2-hydroxybenzene (5b): mp 171—173 °C (from CH₂Cl₂-ether, yield 77%). *Anal.* Calcd for C₂₀H₁₄Cl₂O₃ (M_r 373.243): C, 64.36; H, 3.78; Cl, 19.00. Found: C, 64.31; H, 3.77; Cl, 19.05. IR cm⁻¹: 3455, 1668, 1598, 1573. ¹H-NMR δ : 7.90—7.40 (5H, m), 7.40 (5H, s), 6.97 (1H, s).

2) **1-Benzylloxy-3,4-dichloro-2-(2,3-epoxypropoxy)-5-(2-fluorobenzoyl)benzene (7c)**—A mixture of **5c** (2.789 g), NaH (205 mg, 1.2 eq) and EBH (1.20 g, 1.23 eq) in dry DMF (60 ml) was heated at 80 °C with stirring for 23 h. The reaction mixture was diluted with water and extracted with ether. Passing the residue (3.0 g) obtained from the extract through SiO₂ with CH₂Cl₂ gave **7c** (2.931 g, yield 91.9%). This was recrystallized from cyclohexane to afford a pure substance (mp 81—82 °C). *Anal.* Calcd for C₂₃H₁₇Cl₂FO₄ (M_r 447.297): C, 61.76; H, 3.83; Cl, 15.85; F, 4.25. Found: C, 61.64; H, 4.01; Cl, 15.79; F, 4.15. IR (CHCl₃) cm⁻¹: 1665, 1607. ¹H-NMR δ : 7.83—7.07 (4H, m), 7.38 (5H, m), 7.03 (1H, s), 5.09 (2H, s), 4.38—4.03 (2H, m), 3.45—3.27 (1H, m), 2.86—2.59 (2H, m).

3) **3,4-Dichloro-2-(3-chloro-2-hydroxypropoxy)-5-(2-fluorobenzoyl)-1-hydroxybenzene (9c)**—A mixture of **7c** (2.80 g) in concentrated HCl (100 ml) was refluxed for 6 h. The cooled reaction mixture was extracted with CH₂Cl₂. Passing the residue (3.0 g) obtained from the extract through SiO₂ with benzene/AcOEt (9:1) gave the 1-hydroxy compound (**9c**) (1668 mg, yield 67.8%). IR (CHCl₃) cm⁻¹: 3600—2700 (br), 1675, 1610. ¹H-NMR δ : 7.83—7.08 (4H, m), 6.96 (1H, s), 6.5—4.8 (2H, br), 4.31—4.01 (3H, m), *ca.* 3.73 (2H, br).

4) A mixture of **9c** (1668 mg) and NaOH (600 mg) in EtOH (50 ml) was refluxed for 15 min under an atmosphere of nitrogen. The cooled reaction mixture was mixed with water and acidified with aqueous HCl, and then extracted with CH₂Cl₂. Passing the residue (1738 mg) obtained from the extract through an SiO₂ column with CH₂Cl₂ gave **11c** (1478 mg, oil, yield 97.5%).

Preparation of 7,8-Dichloro-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (15a)

Method A-1—A suspension of NaH (60% in oil, 4.25 g, 2.1 eq) was added to a solution of 3,4-dichloro-1,2-dihydroxybenzene (**2**) (9.04 g) in dry DMF (190 ml) under cooling on an ice bath and under nitrogen gas flow. The temperature of the mixture was raised to room temperature, then a solution of EBH (8.30 g, 1.2 eq) in dry DMF (10 ml) was added. After stirring at room temperature for 1 h, the reaction mixture was poured into ice water and extracted with ether. Chromatography of the residue on a Lobar column with CH₂Cl₂ afforded an oily material (1.60 g) (oil from NaH) as the first fraction, 7,8-dichloro-2-(2,3-epoxypropoxymethyl)-2,3-dihydro-1,4-benzodioxin (**15b**) (1.22 g, yield 10%) as the second fraction, and compound **15a** (6.41 g, mp 53—54 °C, from hexane-ether, yield 54%) as the last fraction. *Anal.* Calcd for C₉H₈Cl₂O₃ (M_r 235.074): C, 45.99; H, 3.43; Cl, 30.16. Found: C, 46.07; H, 3.53; Cl, 29.53. IR (CHCl₃) cm⁻¹: 3580, 3400, 1590, 1570. ¹H-NMR δ : 6.94, 6.72 (each 1H, d, $J=9$ Hz), 4.38—4.03 (3H, m), 3.96—3.83 (2H, m), 2.13 (1H, t, $J=6$ Hz, OH).

15b: Oil. ¹H-NMR (CDCl₃) δ : 6.91, 6.70 (each 1H, d, $J=10$ Hz), 4.50—3.70 (6H, m), 3.54—3.28 (1H, m), 3.23—3.03 (1H, m), 2.77 (1H, t, $J=4$ Hz), 2.53—2.63 (1H, m).

Method A-2. 1) **2-Benzylloxy-3,4-dichloro-1-hydroxybenzene (12a)**—A solution of PhCH₂Br (9.4 g, 1.1 eq) in dry DMF (30 ml) was added to a suspension of **2** (8.95 g) and NaH (60% in oil, 2.2 g, 1.1 eq) in dry DMF (300 ml). The mixture was stirred at 100 °C for 2 h, then poured into ice water and extracted with ether. The ether layer was washed with aqueous 2N NaOH, water, dried and then evaporated. The residue (5.9 g) was recrystallized from hexane, affording the dibenzyl ether **12c** (3.79 g, mp 74—75.5 °C, yield 21.1%). The above alkaline layer was acidified with concentrated HCl and extracted with ether. The residue (8.37 g) obtained from the extract was passed through a column of SiO₂ with benzene as an eluent. Recrystallization of the product from pentane afforded **12a** (5.464 g, mp 61 °C, yield 40.1%).

2) **2-Benzylloxy-3,4-dichloro-1-(2,3-epoxypropoxy)benzene (13a)**—A suspension of NaH (60% in oil, 480 mg, 1.1 eq) and EBH (1.685 g, 1.1 eq) were added to a solution of 2-benzyl ether (**12a**) (2.69 g) in dry DMF (100 ml) and the mixture was stirred at 80 °C for 6 h. Next, it was poured into ice water and extracted with ether. Recrystallization of the residue (3.5 g) from hexane afforded **13a** (2.569 g, mp 65 °C, yield 79%). *Anal.* Calcd for C₁₆H₁₄Cl₂O₃ (M_r 325.199): C, 59.09; H, 4.34; Cl, 21.81. Found: C, 58.87; H, 4.24; Cl, 22.06. IR cm⁻¹: 1581. ¹H-NMR δ : 7.59—7.23

(5H, m), 7.13, 6.78 (each 1H, d, $J=9$ Hz), 5.05 (2H, s), 4.33—3.81 (2H, m), 3.32 (1H, br), 2.90—2.64 (2H, m).

3) 3,4-Dichloro-1-(2,3-epoxypropoxy)-2-hydroxybenzene (14a)—A mixture of **13a** (5.595 g) and 5% Pd-C in AcOEt (140 ml) was hydrogenated in the conventional way with absorption of 625 ml of hydrogen gas in 20 min. After removal of the catalyst by filtration, evaporation of the solvent gave **14a** (4.3 g, yield 100%). $^1\text{H-NMR}$ δ : 6.93, 6.74 (each 1H, d, $J=9$ Hz), 4.41—3.91 (2H, m), 3.47—3.30 (1H, m), 3.01—2.79 (2H, m).

4) A solution of **14a** (4.3 g) in 2 N NaOH (10 ml) and EtOH (50 ml) was heated at 80 °C for 5 min. The reaction mixture was concentrated and mixed with water, and then extracted with ether. The residue (3.16 g) obtained from the extract was passed through a column of SiO₂ (20 g) and eluted with CH₂Cl₂ to afford 7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (**15a**) (3.16 g, mp 53—54 °C from hexane, yield 76.7%).

Preparation of 7,8-Dichloro-2,3-dihydro-1,4-benzodioxin-3-ylmethanol (16a)

Method B-1—A mixture of **2** (5 g), K₂CO₃ (15.5 g, 4 eq) and EBH (5.75 g, 1.5 eq) in acetone (150 ml) was refluxed for about 10 h with stirring until the starting material had disappeared on thin layer chromatography (TLC) (CH₂Cl₂–acetone, 20:1). The reaction mixture was filtered in order to remove the insoluble material, and evaporation of the filtrate gave a residue, which was extracted with CH₂Cl₂. The organic layer was washed with 2 N NaOH followed by water, dried and evaporated. The residue (6.95 g) was passed through a column of SiO₂ (10 g) with CH₂Cl₂ to decolorize it, giving **16a** (6.30 g, yield 80%). IR (CHCl₃) cm^{-1} : 3590, 3380, 1580. $^1\text{H-NMR}$ δ : 6.96, 6.75 (each 1H, d, $J=9$ Hz), 4.72—4.01 (3H, m), 3.93—3.80 (2H, m), 2.04 (1H, t, $J=7$ Hz).

Method B-2. 1) 1-Benzyloxy-3,4-dichloro-2-hydroxybenzene (12b)—Benzyl bromide (10.25 g, 1.3 eq) was added to a suspension of 3,4-dichloro-1,2-dihydroxybenzene (**2**) (8.95 g) and NaH (50% in oil, 4.80 g, 2 eq) in dry DMF (250 ml) and the mixture was stirred for 10 min at room temperature, then poured into water. Sparingly soluble crystals were collected by filtration and recrystallized from hexane, giving the dibenzyl ether (**12c**) (2.096 g, mp 74—75 °C, yield 21.1%). The filtrate was acidified with concentrated HCl and extracted with ether. The residue (10.40 g) obtained from the extract was chromatographed on a column of SiO₂ (30 g) with CH₂Cl₂ to afford **12b** (8.637 g, yield 64.2%) as an oil. IR (CHCl₃) cm^{-1} : 3520, 1600, 1580. $^1\text{H-NMR}$ δ : 7.40 (5H, m), 6.92, 6.73 (each 1H, d, $J=9$ Hz), 6.00 (1H, s, OH), 5.09 (2H, s).

The Dibenzyl Ether (**12c**): *Anal.* Calcd for C₂₀H₁₆Cl₂O₂ (M_r 359.260): C, 66.87; H, 4.49; Cl, 19.74. Found: C, 67.49; H, 4.75; Cl, 19.44. IR cm^{-1} : 1585. $^1\text{H-NMR}$ δ : 7.36 (10H, m), 7.12, 6.78 (each 1H, d, $J=9$ Hz), 5.07, 5.04 (each 2H, s).

2) 1-Benzyloxy-3,4-dichloro-2-(2,3-epoxypropoxy)benzene (13b)—A mixture of **12b** (9.73 g), NaH (50% in oil, 1.91 g, 1.1 eq) and EBH (5.45 g, 1.1 eq) in dry DMF (150 ml) was stirred at 80 °C for 4 h. The cooled reaction mixture was poured into water and extracted with ether. The residue (11.5 g) obtained from the extract was passed through a column of SiO₂ (40 g) with CH₂Cl₂ to afford **13b** (9.64 g, mp 59—61 °C, from hexane, yield 82.0%). *Anal.* Calcd for C₁₆H₁₄Cl₂O₃ (M_r 325.199): C, 59.09; H, 4.34; Cl, 21.81. Found: C, 59.06; H, 4.27; Cl, 21.86. IR cm^{-1} : 1580. $^1\text{H-NMR}$ δ : 7.36 (5H, m), 7.08, 6.78 (each 1H, d, $J=9$ Hz), 5.05 (2H, s), 4.28—3.93 (2H, m), 3.41—3.23 (1H, m), 2.81—2.53 (2H, m).

3) 3,4-Dichloro-2-(2,3-epoxypropoxy)-1-hydroxybenzene (14b)—Compound **13b** (1.626 g) in EtOAc (50 ml) was catalytically hydrogenated with 5% Pd-C (500 mg) under atmospheric pressure with absorption of 153 ml of hydrogen gas in 2 h. After removal of the catalyst by filtration, evaporation of the solvent gave **14b** (1.151 g, mp 92—94 °C from cyclohexane, yield 98%). *Anal.* Calcd for C₉H₈Cl₂O₃ (M_r 235.074): C, 45.99; H, 3.43; Cl, 30.17. Found: C, 45.36; H, 3.54; Cl, 29.78. IR cm^{-1} : 3270—3210 (br), 1590. $^1\text{H-NMR}$ δ : 7.12, 6.78 (each 1H, d, $J=9$ Hz), 7.9—6.3 (1H, br), 4.62—3.98 (2H, m), 3.43—3.30 (1H, m), 3.36—2.96 (2H, m).

4) A mixture of **14b** (1.128 g), EtOH (10 ml), and 2 N NaOH (4 ml) was heated at 80 °C for 5 min. The cooled reaction mixture was diluted with water and extracted with ether. Recrystallization of the residue from hexane gave 7,8-dichloro-2,3-dihydro-1,4-benzodioxin-3-ylmethanol (**16a**) (1.120 g, mp 72—74 °C, yield 99%).

Friedel-Crafts Acylation: General Procedure—Method A: A mixture of **15a** or **16a** (8 mmol) in CH₂Cl₂ or CCl₄ (25—30 ml) and acyl halide/aluminum chloride (4.0:3.0 or 5.0:4.0 eq) was stirred at room temperature for 30 min and refluxed for 2 h on an oil bath. The cooled reaction mixture was poured into ice/concentrated HCl, and extracted with CH₂Cl₂. The organic layer was washed with 2 N NaOH, then with water, and saturated NaCl, dried and evaporated to obtain 5(and 6)-acyl-2-(or 3)-hydroxymethyl ester. Subsequently, the ester was refluxed in 2 N NaOH/EtOH for 10 min, and the reaction mixture was extracted with CH₂Cl₂, giving a mixture of 5(and 6)-acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2(or 3)-ylmethanol. The mixture was, if necessary, separated into 5(and 6)-acyl compounds after acetylation.

Method B: A mixture of **15a** or **16a** (8 mmol) and acyl chloride/aluminum chloride (4.0:3.0 eq) in dry CH₂Cl₂ (10—30 ml) was stirred at room temperature for 30 min, then placed on an oil bath and kept at 90 °C for 2.5 h to remove the solvent. The 5(and 6)-acyl compounds were obtained by the same work-up procedure. See Tables IX, X and XI.

7,8-Dichloro-5(and 6)-propionyl-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (17e and 10e)—Method A: A mixture of **15a** (20 g) in CH₂Cl₂ (150 ml), propionyl chloride (39.4 g, 5 eq) and aluminum chloride (45.3 g, 4 eq) was stirred at room temperature for 30 min and then refluxed for 2 h. The cooled reaction mixture was poured into ice/concentrated HCl and extracted with CH₂Cl₂. The organic layer was washed with saturated NaCl, 2 N NaOH, and

then saturated NaCl, and evaporated. The residue (30.0 g) was immediately taken up in EtOH (200 ml) and 2 N NaOH (150 ml), and the mixture was refluxed for 30 min. The concentrated reaction mixture was diluted with water and extracted with CH_2Cl_2 . The residue (24.6 g) was crystallized from CH_2Cl_2 -ether, giving the 5-propionyl compound **17e** (10.930 g, mp 124–126 °C, yield 44.2%) and another residue (14 g). This residue was mixed with dry pyridine (80 ml) and Ac_2O (50 ml), and left standing overnight at room temperature. The reaction mixture was concentrated and extracted with CH_2Cl_2 . The residue obtained from the extract was separated into two fractions using two columns of Lobar B with hexane/acetone (4:1) as the eluent. Recrystallization of the former fraction from ether-hexane gave the 5-propionyl-2-acetoxymethyl compound (**17e-2**) (4.11 g, mp 67–70 °C, yield 14.5%). The later fraction afforded the 6-isomer (**10e-2**) (9.10 g, mp 74–77 °C, yield 32.1%) upon recrystallization from the same solvent. Deacetylation of these acetates with 2 N NaOH afforded **17e** and **10e**, respectively, in quantitative yield.

7,8-Dichloro-5(and 6)-thenoyl-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (17a and 10a)—Method B: A mixture of **15a** (3.0 g), thenoyl chloride (7.5 g, 4 eq) and aluminum chloride (5.2 g, 3 eq) in CH_2Cl_2 (100 ml) was stirred at room temperature for 30 min, and then refluxed to 90 °C on an oil bath. The solvent was removed and the resultant mixture was kept at the same temperature for 2.5 h. A residue (9.50 g) was obtained by conventional work-up. A mixture of the residue and 2 N NaOH (50 ml) in EtOH (100 ml) was refluxed for 30 min, and then concentrated and extracted with CH_2Cl_2 . The residue was separated into two fractions by chromatography on a Lobar column B with CH_2Cl_2 /acetone (20:1) as an eluent. The first fraction (1.99 g) was recrystallized from EtOH-hexane to afford the 6-thenoyl compound (**10a**) (1.86 g, mp 113–114 °C, yield 42%) and the second fraction (2.01 g) gave the 5-thenoyl compound (**17a**) (1.985 g, mp 122–125 °C, yield 45%).

Compound **19b** was prepared from **15a**.

7,8-Dichloro-2,3-dihydro-1,4-benzodioxin-2-carboxylic acid (19a): mp 159–161 °C (from CH_2Cl_2 -hexane, yield 52.1%). *Anal.* Calcd for $\text{C}_9\text{H}_6\text{Cl}_2\text{O}_4$ (M_r 249.057): C, 43.40; H, 2.43; Cl, 28.47. Found: C, 43.20; H, 2.55; Cl, 28.57. IR cm^{-1} : 3040, 1747, 1600, 1580. $^1\text{H-NMR}$ (acetone- d_6) δ : 7.88 (1H, br), 7.02, 6.80 (each 1H, d, $J=9$ Hz), 5.20 (1H, t, $J=3$ Hz), 4.70–4.23 (2H, m).

Ethyl **7,8-Dichloro-2,3-dihydro-1,4-benzodioxin-2-carboxylate (19b)**: mp 92–94 °C (from CH_2Cl_2 -PE). *Anal.* Calcd for $\text{C}_{11}\text{H}_{10}\text{Cl}_2\text{O}_4$ (M_r 277.111): C, 47.68; H, 3.64; Cl, 25.59. Found: C, 47.54; H, 3.72; Cl, 25.71. IR cm^{-1} : 1742, 1600, 1580. $^1\text{H-NMR}$ δ : 7.00, 6.72 (each 1H, d, $J=8$ Hz), 4.98 (1H, t, $J=8$ Hz), 4.67–4.17 (2H, m), 4.27 (2H, q, $J=8$ Hz), 1.27 (3H, t, $J=8$ Hz).

Preparation of 5(or 6)-Acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2(or 3)-carboxylic Acids (20–23) by Oxidation of 5(or 6)-Acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2(or 3)-ylmethanols (17, 10, 18 and 11)

General Procedure—Jones reagent (8 N chromic acid/sulfuric acid solution) was added dropwise to a solution of a 2(or 3)-dihydrobenzodioxinylmethanol (**17**, **10**, **18** or **11**) (2.0 g) in acetone (100 ml) over a 2 h period. (The reaction solution was red immediately after the addition, and the reagents was added when the color turned green.) The reaction mixture was allowed to stand overnight at room temperature. The excess chromic acid was decomposed with MeOH, and the resulting precipitate was removed by filtration. The organic solvent of the filtrate was evaporated off *in vacuo*, giving a solid, which was collected by filtration or extraction with EtOAc or CH_2Cl_2 . The collected solid or residue obtained from the extract was recrystallized from an appropriate solvent to afford the corresponding 2(or 3)-carboxylic acid (**20–23**). See Tables XII, XIII and XIV.

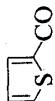
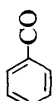
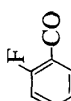
Preparation of 5(or 6)-Aroyl-7,8-dichloro-1,4-benzodioxin-2(or 3)-carboxylic Acids (30–32)

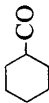
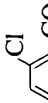
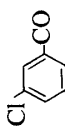
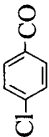
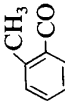
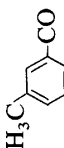
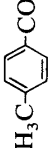
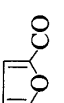
General Procedure—A mixture of an ethyl 5(or 6)-aroyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2(or 3)-carboxylate (**24–26**) (1.5 g), NBS (3.5 eq) and benzoyl peroxide (230 mg) in dry CCl_4 (80 ml) was refluxed for 20 h. The resulting precipitate was removed by filtration, and the solvent of the filtrate was evaporated off *in vacuo* at room temperature. A mixture of the residue and NaI (3 g) in acetone (100 ml) was refluxed for 1 h. The resultant precipitate was removed from the reaction mixture by filtration, the organic solvent was evaporated off, and the residue was extracted with CH_2Cl_2 . The organic layer was washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$, then with water, and evaporated *in vacuo*. Recrystallization of the residue from an appropriate solvent afforded the corresponding benzodioxin ethyl ester (**27–29**). A mixture of the residue in 2 N NaOH and THF or dioxane was heated at 70 °C for 5 min, and then allowed to stand at room temperature for 1 h. The reaction mixture was neutralized with aqueous HCl and diluted with water, and then extracted with AcOEt. Recrystallization of the product from an appropriate solvent gave the corresponding free carboxylic acid (**30–32**). See Tables XVI and XVII.

Preparation of 5(or 6)-(2-Alkylacryloyl) Derivatives (33–35)

1) 7,8-Dichloro-5-(2-ethylacryloyl)-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (33b)—A mixture of the 5-butyryl compound (**20f**) (1194 mg), paraformaldehyde (449 mg), and *p*-TsOH (710 mg) in dioxane (15 ml) was stirred at 90 °C for 27 h. After completion of the reaction, the reaction mixture was concentrated and then mixed with benzene. The acidic portion of the mixture was extracted into aqueous saturated NaHCO_3 , made acidic with aqueous HCl, and extracted with benzene. The residue (1474 mg) was chromatographed on SiO_2 (30 g) with CH_2Cl_2 /ether (9:1). The fraction obtained (748 mg) was recrystallized from isopropyl ether-hexane and afforded **33b** (565 mg, mp 142–143 °C, yield 45.6%). *Anal.* Calcd for $\text{C}_{14}\text{H}_{12}\text{Cl}_2\text{O}_5$ (M_r 331.15): C, 50.78; H, 3.65; Cl, 21.41. Found: C, 50.60; H, 3.82; Cl, 21.33. IR cm^{-1} : 3500–2800, 1765, 1630. $^1\text{H-NMR}$ (acetone- d_6) δ : 7.9–6.9 (1H, br, COOH), 6.97 (1H, s), 5.91, 5.64 (each 1H, s), 5.25 (1H, t, $J=3$ Hz), 4.59, 4.37 (each 1H, dd, $J=13, 3$ Hz), 2.37 (1H, q, $J=7$ Hz), 1.06 (3H, t,

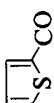
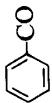
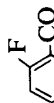
TABLE IX. 6-Acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2-ylmethanols

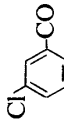
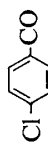
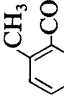
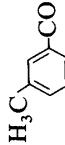
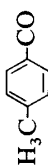
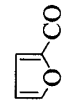
Compound	Acyl	mp (°C) (Solvent) ^{a)}	Yield (%)	Analysis (%)					IR (Nujol) cm ⁻¹	¹ H-NMR (CDCl ₃) δ	
				Calcd	Found	C	H	Cl			S (F)
10a		113–114 (Et ₂ O)	45.0	C ₁₄ H ₁₀ Cl ₂ O ₄ S (M _r 345.2)		48.71	2.92	20.54	9.29	3420, 1630, 1600, 1560	7.73 (1H, dd, J = 5, 1), 7.45 (1H, dd, J = 5, 1), 7.17 (1H, t, J = 5), 6.97 (1H, s), 3.72–4.28 (1H, m), 4.30 (2H, m), 3.95 (2H, m), 2.13 (1H, t, J = 7)
10b		Oil	43.0			48.62	3.16	20.54	9.31	^{b)} 3590, 3400, 1665, 1595	7.86–7.09 (5H), 6.89 (1H, s), 4.46–4.13 (3H), 4.03–3.90 (2H), 2.32 (1H, t, J = 7)
10c		109–110 (iso-Pr ₂ O)	33.2	C ₁₆ H ₁₁ Cl ₂ FO ₄ (M _r 357.168)		53.81	3.10	19.85	5.32	3420, 1665, 1610	7.80–7.08 (4H, m), 6.99 (1H, s), 4.46–4.11 (1H, m), ca. 4.33 (2H), ca. 3.95 (2H), 2.20 (1H, t, J = 6)
10d	CH ₃ CO	72–73 (iso-Pr ₂ O)	58.6	C ₁₁ H ₁₀ Cl ₂ O ₄ (M _r 277.111)		47.68	3.64	25.59		3560, 1680, 1598, 1550	7.10 (1H, s), 4.45–4.10 (3H, m), ca. 3.94 (2H), 2.60 (1H, s), 2.39 (1H, t, J = 7)
10d-2	CH ₃ CO (2-acetate)	95–96 (Benzene-hexane)		C ₁₃ H ₁₂ Cl ₂ O ₅ (M _r 319.148)		47.44	3.70	25.55		1740, 1680, 1590, 1560	7.07 (1H, s), 4.63–3.95 (5H, m), 2.58 (3H, s), 2.10 (3H, m)
10e	C ₂ H ₅ CO	96–100 (Benzene-cyclohexane)	32.0	C ₁₂ H ₁₂ Cl ₂ O ₄ (M _r 291.138)		48.82	3.74	22.17		3520, 1685, 1595, 1559	^{c)} 7.07 (1H, s), 4.70–3.50 (6H, m), 2.90 (2H, q, J = 7), 1.12 (3H, t, J = 7)
10e-2	C ₂ H ₅ CO (2-acetate)	70–73 (Et ₂ O-hexane)		C ₁₄ H ₁₄ Cl ₂ O ₅ (M _r 333.165)		49.51	4.15	24.36		1742, 1688, 1595, 1558	7.00 (1H, s), 4.67–3.90 (5H, m), 2.90 (2H, q, J = 7), 2.10 (3H, s), 1.17 (3H, t, J = 7)
10f	C ₃ H ₇ CO	66–68 (iso-Pr ₂ O-hexane)	28.2	C ₁₃ H ₁₄ Cl ₂ O ₄ (M _r 305.161)		50.47	4.24	21.28		3440, 1690, 1595	6.96 (1H, s), 4.44–4.08 (3H, m), ca. 3.93 (2H), 2.86 (2H, t, J = 7), 2.30 (1H, t, J = 6), 1.75 (2H, m), 0.95 (3H, t, J = 8)
10h	C ₄ H ₉ CO	Oil	22.1	C ₁₄ H ₁₆ Cl ₂ O ₄ (M _r 319.192)		51.17	4.62	23.24		^{b)} 3580, 3400, 1693, 1600	6.97 (1H, s), 4.46–4.11 (3H), ca. 3.94 (2H), 2.90 (2H, t, J = 7), 2.30 (1H, t, J = 6), 1.74–1.25 (2 × 2H), 0.93 (3H, t, J = 7)

10j		Oil	27.3		^{b)} 3570, 3370 (br), 1690, 1600	^{c)} 6.82 (1H, s), 4.42—4.06 (3H), <i>ca.</i> 3.92 (2H), <i>ca.</i> 3.0 (1H), <i>ca.</i> 2.18 (1H), 1.95—1.24 (10H)
10k		117—122 (Et ₂ O)	5.6	C ₁₇ H ₁₄ Cl ₂ O ₄ (<i>M_r</i> 353.209)	3520, 1686, 1606, 1592	7.23 (5H, s), 6.90 (1H, s), 4.47—4.00 (3H, m), 4.17 (2H, s), 4.00—3.73 (2H, m), 2.27—1.86 (1H, m)
10l		Oil	40.3		^{b)} 3600, 3450—3400 (br), 1682	<i>ca.</i> 7.38 (4H), 7.00 (1H, s), 4.42—4.07 (3H), <i>ca.</i> 3.92 (2H), 2.29 (1H, br)
10m		144—146 (iso-Pr ₂ O)	30.6	C ₁₆ H ₁₁ Cl ₃ O ₄ (<i>M_r</i> 373.631)	3530, 1655	7.75—7.24 (4H), 6.87 (1H, s), 4.45—4.11 (3H), <i>ca.</i> 3.94 (2H), 2.22 (1H, t, <i>J</i> =6)
10n		Oil	42.4		^{b)} 3590, 3400—3350 (br), 1673	^{c)} 7.78, 7.53 (2 × 2H, d, <i>J</i> =9), 6.96 (1H, s), 4.56—4.07 (3H), <i>ca.</i> 3.90 (2H), 2.75 (1H, s)
10o		Oil	43.8		^{b)} 3570, 3400—3350, 1662	7.47—7.06 (4H), 6.91 (1H, s), 4.42—4.07 (3H), <i>ca.</i> 3.91 (2H), 2.51 (3H, s), 2.39 (1H, t, <i>J</i> =6)
10p		Oil	38.9		^{b)} 3580, 3420—3350, 1665	7.62—7.23 (4H), 6.86 (1H, s), 4.44—4.09 (3H), <i>ca.</i> 3.95 (2H), 2.38 (3H, s), <i>ca.</i> 2.24 (1H)
10q		Oil	27.8		^{b)} 3580, 3410—3360, 1662	7.68, 7.22 (2 × 2H, d, <i>J</i> =8), 6.85 (1H, s), 4.43—4.08 (3H), <i>ca.</i> 3.93 (2H), 2.40 (3H, s), 2.25 (1H, t, <i>J</i> =6)
10r		112—114 (Benzene-hexane)	48.0	C ₁₄ H ₁₀ Cl ₂ O ₅ (<i>M_r</i> 329.143)	3320—3270, 3100, 1648, 1598	7.64 (1H, dd, <i>J</i> =0.5, 2.0), 7.07 (1H, dd, <i>J</i> =0.5, 4.0), 6.95 (1H, s), 6.50 (1H, dd, <i>J</i> =2.0, 4.0), 4.43—4.08 (3H), <i>ca.</i> 3.93 (2H), 2.33 (1H, t, <i>J</i> =6)
10s	HCO	127—128 (Acetone-Et ₂ O-PE)	22.4 (42.3)	C ₁₀ H ₈ Cl ₂ O ₄ (<i>M_r</i> 263.076)	3450, 1690—1670, 1591, 1560	^{c)} 10.30 (1H, s), 7.33 (1H, s), 4.70—4.17 (3H, m), 4.07—3.83 (2H, m)
10s-2	HCO (2-acetate)	90—92 (Et ₂ O)		C ₁₂ H ₁₀ Cl ₂ O ₅ (<i>M_r</i> 305.121)	1732, 1590, 1578, 1558	^{c)} 10.23 (1H, s), 7.33 (1H, s), 4.73—4.07 (5H, m), 2.07 (3H, s)

Coupling constants (*J*) are given in Hz. *a*) Solvent: ethyl ether = Et₂O, isopropyl ether = iso-Pr₂O, petroleum ether = PE. *b*) In CHCl₃. *c*) In acetone-*d*₆.

TABLE X. 5-Acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2-ylmethanols

Compound	Acyl	mp (°C) (Solvent) ^{a)}	Yield (%)	Analysis (%)				IR (Nujol) cm ⁻¹	¹ H-NMR (CDCl ₃) δ		
				Calcd	Found	C	H			Cl	S
17a		136—137 (Et ₂ O— hexane)	45.7	C ₁₄ H ₁₀ Cl ₂ O ₄ S (<i>M_r</i> 345.204)		48.71	2.92	20.54	9.29	3480—3430 (br), 1630, 1582	7.75 (1H, dd, <i>J</i> = 1.5, 5.5), 7.52 (1H, dd, <i>J</i> = 1.5, 4.5), 7.13 (1H, dd, <i>J</i> = 5.5, 4.5), 7.14 (1H, s), 4.91—4.06 (3H, m), 3.92 (2H, d, <i>J</i> = 6), 2.75 (1H, t, <i>J</i> = 7)
17b		158—159 (Benzene)	45.0	C ₁₆ H ₁₂ Cl ₂ O ₄ (<i>M_r</i> 339.182)		56.66	3.57	20.91		3430, 1643, 1590, 1572	7.83—7.23 (5H), 7.07 (1H, s), 4.44—4.03 (3H, m), <i>ca.</i> 3.89 (2H, m), 2.25 (1H, t, <i>J</i> = 7)
17c		Oil	49.4	C ₁₆ H ₁₁ Cl ₂ FO ₄ (<i>M_r</i> 357.172)		56.55	3.76	20.98)	^{b)} 3590, 3380, 1685, 1610	7.77—6.94 (4H), 7.23 (1H, s), 4.42—4.00 (3H), 3.87 (2H, t, <i>J</i> = 7), 2.33 (1H, t, <i>J</i> = 7)	
17d	CH ₃ CO	101—102 (iso-Pr ₂ O)	39.6	C ₁₁ H ₁₀ Cl ₂ O ₄ (<i>M_r</i> 277.111)		47.68	3.64	25.59		3500, 1683, 1580, 1550	7.45 (1H, s), 4.56—4.18 (3H, m), <i>ca.</i> 3.96 (2H), 2.57 (3H, s), 2.47 (1H, t, <i>J</i> = 7)
17d-2	CH ₃ CO (2-acetate)	69—71 (Benzene— hexane)		C ₁₃ H ₁₂ Cl ₂ O ₅ (<i>M_r</i> 319.148)		47.53	3.64	25.45)		1750, 1685, 1662, 1582	7.44 (1H, s), 4.59—4.02 (5H, m), 2.56 (3H, s), 2.11 (3H, m)
17e	C ₂ H ₅ CO	126—128 (Benzene)	60.0	C ₁₂ H ₁₂ Cl ₂ O ₄ (<i>M_r</i> 291.138)		48.69	3.82	22.11)		3480, 1675, 1585	^{c)} 7.34 (1H, s), 4.65—4.23 (3H, m), 3.96—3.85 (2H, m), 2.98 (2H, q, <i>J</i> = 8), 2.77 (1H, s), 1.08 (3H, t, <i>J</i> = 8)
17e-2	C ₂ H ₅ CO (2-acetate)	75—76 (Hexane)		C ₁₄ H ₁₄ Cl ₂ O ₅ (<i>M_r</i> 333.175)		49.36	4.17	24.58)		1730, 1675, 1580	^{c)} 7.34 (1H, s), 4.73—4.17 (5H, m), 2.96 (2H, q, <i>J</i> = 8), 2.03 (3H, s), 1.09 (3H, t, <i>J</i> = 8)
17f	C ₃ H ₇ CO	116—118 (Benzene— hexane)	46.8	C ₁₃ H ₁₄ Cl ₂ O ₄ (<i>M_r</i> 305.165)		50.47	4.24	21.28		3470, 1655, 1575	7.39 (1H, s), 4.53—4.16 (3H, m), 4.01—3.88 (2H, m), 2.90 (2H, t, <i>J</i> = 7), 2.36 (1H, t, <i>J</i> = 6), 1.88—1.47 (2H, m), 0.94 (3H, t, <i>J</i> = 7)
17g	iso-C ₃ H ₇ CO	Oil	36.8	C ₁₃ H ₁₄ Cl ₂ O ₄ (<i>M_r</i> 305.165)		51.17	4.62	23.24	^{b)} 3600, 3400 (br), 1685, 1580	^{c)} 7.23 (1H, s), 4.63—4.13 (3H), <i>ca.</i> 3.90 (2H), 2.75 (1H, s), 3.47 (1H, m), 1.08 (6H, d, <i>J</i> = 6)	

17h	<chem>C4H9CO</chem>	80—81 (iso-Pr ₂ O— hexane)	17.1	C ₁₄ H ₁₆ Cl ₂ O ₄ (<i>M_r</i> 319.192) 52.68 5.05 22.22 (52.53 4.85 22.37)	3500, 1663, 1578	7.40 (1H, s), 4.53—4.15 (3H), <i>ca.</i> 3.95 (2H), 2.92 (2H, t, <i>J</i> =7), 2.30 (1H, t, <i>J</i> =6), 1.79—1.15 (2×2H), 0.90 (3H, t, <i>J</i> =7)
17i		Oil	8.3	C ₁₆ H ₁₆ Cl ₂ O ₄ (<i>M_r</i> 343.214)	^{b)} 3590, 3400, 1700, 1582	^{c)} 7.24 (1H, s), 4.63—4.14 (3H), <i>ca.</i> 3.88 (2H), 3.70 (1H, m), 2.89 (1H, s), 1.86—1.59 (8H)
17k	<chem>c1ccc(cc1)CC(=O)O</chem>	148—151 (AcOEt— hexane)	21.0	C ₁₇ H ₁₄ Cl ₂ O ₄ (<i>M_r</i> 353.209) 57.81 4.00 20.08 (57.98 4.08 19.83)	3480, 1670, 1575	^{c)} 7.27 (1H, s), 7.22 (5H, s), 4.66—4.14 (3H, m), 4.26 (2H, s), <i>ca.</i> 3.87 (2H, m), 2.72 (1H, s)
17l		Oil	51.4		^{b)} 3600, 3450—3350, 1675	<i>ca.</i> 7.36 (4H), 7.29 (1H, s), 4.37—3.97 (3H), <i>ca.</i> 3.85 (2H), 2.22 (1H, t, <i>J</i> =6)
17m		96—98 (iso-Pr ₂ O— hexane)	21.0	C ₁₆ H ₁₁ Cl ₃ O ₄ (<i>M_r</i> 373.631) 51.43 2.97 28.47 (51.13 3.10 28.45)	^{b)} 3560, 3400—3350 (br), 1660	7.73—7.22 (4H), 7.07 (1H, s), 4.36—4.03 (3H), <i>ca.</i> 3.89 (2H), 2.17 (1H, t, <i>J</i> =6)
17n		Oil	46.6		^{b)} 3590, 3400—3350 (br), 1670	^{c)} 7.85, 7.52 (2×2H, d, <i>J</i> =9), 7.12 (1H, s), 4.50—3.97 (3H), <i>ca.</i> 3.85 (2H), 2.74 (1H, s)
17o		Oil	38.0		^{b)} 3410—3350 (br), 1660	7.49—7.18 (4H), 7.11 (1H, s), 4.43—4.02 (3H), <i>ca.</i> 3.89 (2H), 2.6—2.3 (1H, br), 2.46 (3H, s)
17p		Oil	40.9		^{b)} 3570, 3420—3350, 1662	7.61—7.23 (4H), 7.05 (1H, s), 4.39—3.98 (3H), <i>ca.</i> 3.90 (2H), 2.39 (3H, s), <i>ca.</i> 2.31 (1H)
17q		Oil	23.1		^{b)} 3580, 3410—3360, 1660	7.68, 7.22 (2×2H, d, <i>J</i> =8), 7.03 (1H, s), 4.39—3.99 (3H), <i>ca.</i> 3.89 (2H), 2.40 (3H, s), 2.30 (1H, t, <i>J</i> =6)
17r		143—145 (Benzene— hexane)	47.0	C ₁₄ H ₁₀ Cl ₂ O ₅ (<i>M_r</i> 329.143) 51.09 3.06 21.55 (51.25 3.19 21.78)	3280, 1642, 1588, 1560	7.67 (1H, dd, <i>J</i> =0.5, 2.0), 7.17 (1H, s), 7.13 (1H, dd, <i>J</i> =0.5, 4.0), 6.56 (1H, dd, <i>J</i> =2.0, 4.0), 4.42—4.06 (3H), 3.93 (2H, t, <i>J</i> =5), 2.43 (1H, t, <i>J</i> =6)
17s	HCO	99—100 (Et ₂ O—PE)	33.4 (20)	C ₁₀ H ₈ Cl ₂ O ₄ (<i>M_r</i> 263.084) 45.66 3.07 26.95 (45.58 3.19 26.67)	3440, 1680, 1585	^{c)} 10.30 (1H, s), 7.40 (1H, s), 4.77—4.25 (3H, m), 4.07—3.87 (2H, m)
17s-2	HCO (2-acetate)	142—144 (Acetone— Et ₂ O)		C ₁₂ H ₁₀ Cl ₂ O ₅ (<i>M_r</i> 305.121) 47.24 3.30 23.24 (47.06 3.26 22.99)	1758, 1678, 1580	^{c)} 10.25 (1H, s), 7.40 (1H, s), 4.73—4.17 (5H, m), 2.07 (3H, s)

a) Solvent: ethyl ether = Et₂O, isopropyl ether = iso-Pr₂O, ethyl acetate = AcOEt, petroleum ether = PE. b) In CHCl₃. c) In acetone-*d*₆.

TABLE XI. 5- and 6-Acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-3-ylmethanols

Compound	Acyl	mp (°C) (Solvent) ^{a)}	Analysis (%)				IR (Nujol) cm ⁻¹	¹ H-NMR (CDCl ₃) δ
			C	H	Cl	S (F)		
11a		137–139 (Et ₂ O–PE)	C ₁₄ H ₁₀ Cl ₂ O ₄ S (<i>M_r</i> 345.2)	48.71	2.92	20.54	9.29	7.73 (1H, dd, <i>J</i> = 5, 1), 7.45 (1H, dd, <i>J</i> = 5, 1), 7.10 (1H, t, <i>J</i> = 5), 6.95 (1H, s), 4.13–4.58 (3H, m), 3.77–4.00 (2H, m), 2.20 (1H, t, <i>J</i> = 7)
11b		Oil	C ₁₆ H ₁₂ Cl ₂ O ₄ (<i>M_r</i> 339.182)	(48.89	3.02	20.35	9.20)	^{a)} 7.87–7.37 (5H, m), 6.91 (1H, s), 4.70–4.17 (3H, m), 3.93–3.78 (2H, m), 2.97–2.63 (1H, br)
11c		108–109 (Et ₂ O)	C ₁₆ H ₁₁ Cl ₂ FO ₄ (<i>M_r</i> 357.168)	53.81	3.10	19.85	5.32	7.80–6.98 (4H, m), 7.00 (1H, s), 4.64–4.12 (1H, m), 4.56–4.19 (2H, m), <i>ca.</i> 3.89 (2H), 2.03 (1H, t, <i>J</i> = 6)
11d		84–86 (Et ₂ O–PE)	C ₁₂ H ₁₂ Cl ₂ O ₄ (<i>M_r</i> 291.13)	(53.62	3.14	19.97	5.40)	7.00 (1H, s), 4.55–4.07 (3H, m), 3.67–3.57 (2H, m), 2.87 (2H, q, <i>J</i> = 7), 2.00 (1H, t, <i>J</i> = 7), 1.17 (3H, t, <i>J</i> = 7)
11e		Oil	C ₁₂ H ₁₂ Cl ₂ O ₄ (<i>M_r</i> 291.13)	49.51	4.30	24.36	(49.20	6.98 (1H, s), 4.53–4.09 (3H, m), 3.94–3.83 (2H, m), 2.86 (2H, t, <i>J</i> = 7), 2.20 (1H, t, <i>J</i> = 7), 1.90–1.50 (2H, m), 0.95 (3H, t, <i>J</i> = 7)
18a		Oil	C ₁₂ H ₁₂ Cl ₂ O ₄ (<i>M_r</i> 291.13)	49.51	4.15	24.36	(49.25	^{b)} 3450–3400 (br), ^{c)} 7.95 (1H, dd, <i>J</i> = 1.5, 5.5), 7.64 (1H, dd, <i>J</i> = 1.5, 4.5), 7.17 (1H, dd, <i>J</i> = 5.5, 4.5), 7.13 (1H, s), 4.67–4.16 (3H, m), 4.68 (2H, d, <i>J</i> = 4)
18b		112–114 (Et ₂ O–PE)	C ₁₂ H ₁₂ Cl ₂ O ₄ (<i>M_r</i> 291.13)	49.51	4.15	24.36	(49.25	7.40 (1H, s), 4.60–4.17 (3H, m), 4.05–3.80 (2H, m), 2.63–2.47 (1H, t, <i>J</i> = 7), 2.93 (2H, q, <i>J</i> = 7), 1.15 (3H, t, <i>J</i> = 7)

a) Solvent: ethyl ether = Et₂O, petroleum ether = PE. b) In CHCl₃. c) In acetone-*d*₆.

$J = 7$ Hz).

7,8-Dichloro-5-(2-methacryloyl)-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (33a): mp 160—162 °C (from benzene-hexane, yield 32%). *Anal.* Calcd for $C_{13}H_{10}Cl_2O_5$ (M_r 317.132): C, 49.24; H, 3.18; Cl, 22.36. Found: C, 49.39; H, 3.36; Cl, 22.06. IR cm^{-1} : 3500—2300 (br), 1765, 1635, 1622. 1H -NMR (acetone- d_6) δ : 9.4—8.3 (1H, br), 6.98 (1H, s), 5.64 (1H, m), 5.26 (1H, t, $J = 3$ Hz), 4.59, 4.35 (each 1H, dd, $J = 13, 3$ Hz), 1.92 (3H, d, $J = 1.5$ Hz).

7,8-Dichloro-6-(2-methacryloyl)-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (34a): mp 155—158 °C (from isopropyl ether-hexane, yield 21%). *Anal.* Calcd for $C_{13}H_{10}Cl_2O_5$ (M_r 317.132): C, 49.24; H, 3.18; Cl, 22.36. Found: C, 49.35; H, 3.46; Cl, 21.82. IR (CHCl₃) cm^{-1} : 1754, 1710, 1560. 1H -NMR δ : 8.53 (1H, s, COOH), 6.76 (1H, s), 5.99, 5.52 (each 1H, s, =CH₂), 5.03 (1H, t, $J = 3$ Hz), 4.63—4.22 (2H, m), 2.02 (3H, s).

7,8-Dichloro-6-(2-ethylacryloyl)-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (34b): mp 134—135 °C (from isopropyl ether-hexane, yield 40%). *Anal.* Calcd for $C_{14}H_{12}Cl_2O_5$ (M_r 331.15): C, 50.78; H, 3.65; Cl, 21.41. Found: C, 50.65; H, 3.56; Cl, 21.85. IR cm^{-1} : 3500—2800, 1760, 1650. 1H -NMR (acetone- d_6) δ : 8.00—5.30 (1H, br, COOH), 6.83 (1H, s), 6.00, 5.60 (each 1H, m), 5.27 (1H, t, $J = 3$ Hz), 4.66, 4.42 (each 1H, dd, $J = 13, 3$ Hz), 2.42 (2H, q, $J = 7$ Hz), 1.11 (3H, t, $J = 7$ Hz).

7,8-Dichloro-6-(2-ethylacryloyl)-2,3-dihydro-1,4-benzodioxin-3-carboxylic Acid (35): mp 187—189 °C (from AcOEt-benzene), yield 47%. *Anal.* Calcd for $C_{14}H_{12}Cl_2O_5$ (M_r 331.15): C, 50.78; H, 3.65; Cl, 21.41. Found: C, 50.66; H, 3.60; Cl, 21.49. IR cm^{-1} : 3600—2200 (br), 1710, 1650. 1H -NMR (acetone- d_6) δ : 7.6—6.9 (1H, br, COOH), 6.93 (1H, s), 6.01 (1H, t, $J = 1.5$ Hz), 5.63 (1H, s), 5.16 (1H, t, $J = 3$ Hz), 4.75, 4.53 (each 1H, dd, $J = 13, 3$ Hz), 2.43 (2H, q, $J = 7$ Hz), 1.12 (3H, t, $J = 7$ Hz).

Optical Resolution of Racemic 7,8-Dichloro-5-propionyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (20e)

1) A mixture of **20e** (3.0 g) and SOCl₂ (6 ml) in dry benzene (20 ml) was refluxed for 1.5 h and then the reaction mixture was evaporated to dryness. The resulting residue was dissolved in dry dioxane (20 ml), and then the solution was added to a mixture of D-(–)-phenylglycinol (1347 mg, 1.0 eq) and triethylamine (1191 mg, 1.2 eq) in dry dioxane (20 ml). After being stirred at room temperature for 2 h, the reaction mixture was concentrated and mixed with 1 N HCl and benzene. The resulting precipitate was collected by filtration and recrystallized from benzene, giving a diastereomer (**36a**) (1058 mg, mp 122—123 °C, yield 25.4%). The mother residue was mixed with the above filtrate and the mixed filtrate was extracted with benzene. Chromatography of the residue (2.90 g) on a Lobar column B with hexane/AcOEt (1:1) gave two fractions. Recrystallization of the first fraction (606 mg) from benzene provided **36a** (564 mg, mp 122—123 °C, total yield 38.9%). The later fraction (1739 mg) was recrystallized from benzene and afforded another diastereoisomer (**36b**) (1513 mg, mp 127—128 °C, yield 36.2%).

36a: $[\alpha]_D - 62.5^\circ \pm 0.7$ ($c = 1.4$, EtOH). *Anal.* Calcd for $C_{20}H_{19}Cl_2NO_5$ (M_r 424.288): C, 56.62; H, 4.51; Cl, 16.71; N, 3.30. Found: C, 56.41; H, 4.39; Cl, 16.51; N, 3.30. IR cm^{-1} : 3400, 3370, 1680 (sh), 1670. 1H -NMR (acetone- d_6) δ : 7.40—7.23 (6H, m), 5.13—4.93 (2H, m), 4.03 (1H, t, $J = 6$ Hz), 3.80 (2H, d, $J = 6$ Hz), 2.93 (2H, q, $J = 7$ Hz), 2.75 (1H, s), 1.07 (3H, t, $J = 7$ Hz).

36b: $[\alpha]_D + 35.2^\circ \pm 0.8$ ($c = 1.0$, EtOH). *Anal.* Calcd for $C_{20}H_{19}Cl_2NO_5$ (M_r 424.288): C, 56.62; H, 4.51; Cl, 16.71; N, 3.30. Found: C, 56.49; H, 4.45; Cl, 16.85; N, 3.31. IR cm^{-1} : 3500, 3265, 1681, 1668, 1657. 1H -NMR δ : 7.43—7.09 (6H, m), 5.20—4.86 (2H, m), 4.70—4.20 (2H, m), *ca.* 3.94 (2H), 2.89 (2H, q, $J = 7$ Hz), *ca.* 2.45 (2H), 1.10 (3H, t, $J = 7$ Hz).

2) (–)-7,8-Dichloro-5-propionyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (37a)—A mixture of **36a** (1525 mg) and 2 N H₂SO₄/dioxane (12 ml) was heated at 90 °C for 1.5 h. The cooled reaction mixture was diluted with water, and extracted with AcOEt. The acidic portion of the mixture was extracted into saturated NaHCO₃, made acidic with aqueous HCl, and extracted with AcOEt. Recrystallization of the product (839 mg) from AcOEt gave an optically active compound (**37a**) (674 mg, mp 236 °C, yield 61.5%). $[\alpha]_D^{23} - 83.5^\circ \pm 0.5$ ($c = 2.5$, EtOH). *Anal.* Calcd for $C_{12}H_{10}Cl_2O_5$ (M_r 305.121): C, 47.24; H, 3.30; Cl, 23.24. Found: C, 47.05; H, 3.43; Cl, 23.24.

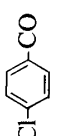
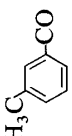
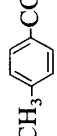
3) (+)-7,8-Dichloro-5-propionyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (37b)—Compound **36b** (1462 mg) was hydrolyzed with 2 N H₂SO₄/dioxane (12 ml) and afforded another optically active compound (**37b**) (640 mg, mp 236 °C from AcOEt, yield 60.9%) $[\alpha]_D^{23} + 83.8^\circ \pm 0.5$ ($c = 2.5$, EtOH) as in the above procedure. *Anal.* Calcd for $C_{12}H_{10}Cl_2O_5$ (M_r 305.121): C, 47.24; H, 3.30; Cl, 23.24. Found: C, 47.18; H, 3.41; Cl, 22.77.

Diuretic Effect—Diuretic Effect on Rats: Slc: SD 8-week-old rats (males, weighing about 250 g each) were used for the test. On the morning of the day before the test, a few lumps of sugar were given in place of the ordinary diet, and 5% glucose solution was given orally at a rate of 20 ml/kg on the afternoon (approximately at 4 p.m.). On the morning of the test, the sample was prepared by suspending or dissolving a test compound in 2% gum arabic and orally administered at a dose of 20 ml/kg. The control group was given an oral dose of 2% gum arabic alone at 20 ml/kg. Immediately after the administration, the test animals were put in plastic cages for the metabolic tests and urine samples were collected for 5 h. The cumulative urine volume, urinary sodium, and urinary potassium were quantitatively determined.

Diuretic Effect on Mice: Slc: ddy 5-week-old mice (females weighing about 20 g each) were used for the test. From the morning of the day before the test day, the mice were made to fast but were allowed water. On the morning of the test, the sample was prepared by suspending or dissolving a test compound in 2% gum arabic and then orally administered to each animal at 30 ml/kg. The control group was given an oral dose of 2% gum arabic alone at

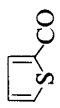
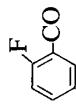
TABLE XII. 5-Acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acids

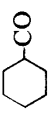
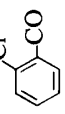
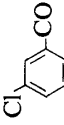
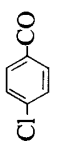
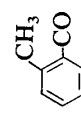
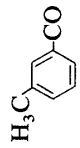
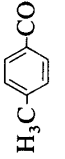
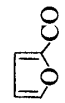
Compound	Acyl	mp (°C) (Solvent) ^{a)}	Yield (%)	Analysis (%)				IR (Nujol) cm ⁻¹	¹ H-NMR (acetone-d ₆) δ
				Calcd	Found	C	H	Cl	S (F)
20a		215–217 (AcOEt–hexane)	85	C ₁₄ H ₈ Cl ₂ O ₅ S (M _r 359.187)		46.82	2.25	19.74	8.93
				(47.10	2.65	19.41	8.52)		
20b		218–219 (AcOEt–hexane)	80.7	C ₁₆ H ₁₀ Cl ₂ O ₅ (M _r 353.165)		54.42	2.85	20.08	
				(54.35	3.13	19.99)			
20c		225–227 (AcOEt–hexane)	76	C ₁₆ H ₉ Cl ₂ FO ₅ (M _r 371.155)		51.78	2.44	19.11	5.12
				(51.85	2.56	19.01	5.09)		
20d	CH ₃ CO	206–208 (AcOEt–benzene)	87.4	C ₁₁ H ₈ Cl ₂ O ₅ (M _r 291.09)		45.39	2.77	24.36	
				(45.14	2.98	24.56)			
20e	C ₂ H ₅ CO	231–232 (AcOEt–benzene)	92.0	C ₁₂ H ₁₀ Cl ₂ O ₅ (M _r 305.121)		47.24	3.30	23.24	
				(47.28	3.48	23.11)			
20f	C ₃ H ₇ CO	177–178 (AcOEt–benzene)	86.7	C ₁₃ H ₁₂ Cl ₂ O ₅ (M _r 319.148)		48.92	3.79	22.22	
				(49.13	3.89	22.17)			
20g	iso-C ₃ H ₇ CO	150–152 (Benzene)	34.2	C ₁₃ H ₁₂ Cl ₂ O ₅ (M _r 319.148)		48.92	3.79	22.22	
				(49.08	3.73	22.45)			
20h	C ₄ H ₉ CO	151–152 (Benzene)	81.2	C ₁₄ H ₁₄ Cl ₂ O ₅ (M _r 333.175)		50.47	4.24	21.28	
				(50.23	4.21	21.28)			

20i		149—150 (Benzene- hexane)	79.3	C ₁₅ H ₁₄ Cl ₂ O ₅ (M _r 345.186) 52.19 4.09 20.54 (52.13 4.01 20.56)	3550—2200 (br), 1722, 1672	7.26 (1H, s), 6.0—4.9 (1H, br), 5.29 (1H, t, J=3), 4.76, 4.48 (each 1H, dd, J=3, 13), 3.65 (1H, m), 1.85—1.57 (8H)
20k		171—173 (Benzene)	85.3	C ₁₇ H ₁₂ Cl ₂ O ₅ (M _r 367.192) 55.61 3.29 19.31 (55.93 3.35 19.25)	3300—2400 (br), 1730, 1683	7.7—6.8 (1H, br), 7.30 (1H, s), 7.22 (5H, s), 5.30 (1H, t, J=3), 4.71, 4.48 (2 × 1H, dd, J=3, 13), 4.25 (2H, s)
20l		214—215 (Benzene)	81.9	C ₁₆ H ₉ Cl ₃ O ₅ (M _r 387.614) 49.58 2.35 27.44 (49.76 2.53 27.67)	3600—2300 (br), 1758, 1622	10.3—9.0 (1H, br), ca. 7.46 (4H), 7.33 (1H, s), 5.22 (1H, t, J=3), 4.41, 4.22 (2 × 1H, dd, J=3, 12)
20m		176—177 (Benzene)	87.5	C ₁₆ H ₉ Cl ₃ O ₅ (M _r 387.614) 49.58 2.34 27.44 (49.68 2.62 27.11)	3600—2000 (br), 1760, 1640	7.77—7.30 (4H), 8.5—7.1 (1H, br), 7.17 (1H, s), 5.27 (1H, t, J=3), 4.51, 4.32 (2 × 1H, dd, J=3, 12)
20n		241—242 (AcOEt- hexane)	87.5	C ₁₆ H ₉ Cl ₃ O ₅ (M _r 387.614) 49.58 2.34 27.44 (49.67 2.60 27.25)	3600—2400 (br), 1768, 1642	8.1—6.7 (1H, br), 7.81, 7.52 (2 × 2H, d, J=9), 7.17 (1H, s), 5.29 (1H, t, J=3), 4.53, 4.33 (2 × 1H, dd, J=3, 12)
20o		212—213 (AcOEt- hexane)	76.8	C ₁₇ H ₁₂ Cl ₂ O ₅ (M _r 367.192) 55.61 3.29 19.31 (56.32 3.42 18.79)	3600—2200 (br), 1758, 1620	9.3—7.8 (1H, br), 7.53—7.26 (4H), 7.19 (1H, s), 5.25 (1H, t, J=3), 4.46, 4.27 (2 × 1H, dd, J=3, 12), 2.46 (3H, s)
20p		194—195 (AcOEt- hexane)	72.7	C ₁₇ H ₁₂ Cl ₂ O ₅ (M _r 367.192) 55.61 3.29 19.31 (55.44 3.40 19.22)	3500—2100 (br), 1765, 1637	10.1—8.7 (1H, br), 7.61—7.31 (4H), 7.11 (1H, s), 5.26 (1H, t, J=3), 4.49, 4.30 (2 × 1H, dd, J=3, 12), 2.35 (3H, s)
20q		212—214 (AcOEt- hexane)	59.7	C ₁₇ H ₁₂ Cl ₂ O ₅ (M _r 367.192) 55.61 3.29 19.31 (55.68 3.34 19.19)	3400—2100 (br), 1755, 1623	9.4—7.4 (1H, br), 7.67, 7.27 (2 × 2H, d, J=8), 7.09 (1H, s), 5.26 (1H, t, J=3), 4.48, 4.30 (2 × 1H, dd, J=3, 12), 2.38 (3H, s)
20r		160—162 (Benzene)	77.1	C ₁₄ H ₈ Cl ₂ O ₆ (M _r 343.126) 49.01 2.35 20.66 (49.41 2.70 20.43)	3140, 1760, 1638, 1585	8.5—7.5 (1H, br), 7.87 (1H, dd, J=0.5, 2.0), 7.19 (1H, s), 7.18 (1H, dd, J=0.5, 2.0), 6.66 (1H, dd, J=2.0, 4.0), 5.31 (1H, t, J=3), 4.61, 4.39 (2 × 1H, dd, J=3, 13)
20s		254—257 (AcOEt- ether)		C ₁₀ H ₆ Cl ₂ O ₅ (M _r 277.059) 43.35 2.18 25.59 (43.29 2.58 25.20)	1718, 1683, 1583	9.27 (1H, s), 7.42 (1H, s), 6.43 (1H, m), 5.36 (1H, t, J=3), 4.90—4.47 (2H, m)

a) Solvent: ethyl acetate = AcOEt, ethyl ether = Et₂O, isopropyl ether = iso-Pr₂O, petroleum ether = PE.

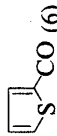
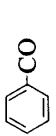
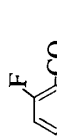
TABLE XIII. 6-Acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acids

Compound	Acyl	mp (°C) (Solvent) ^{a)}	Yield (%)	Analysis (%)				IR (Nujol) cm ⁻¹	¹ H-NMR (acetone-d ₆) δ
				Calcd	Found	C	H	Cl	S (F)
21a		192–194 (CH ₂ Cl ₂ –benzene)	75.0	C ₁₄ H ₈ Cl ₂ O ₅ S (<i>M_r</i> 359.187)		46.82	2.25	8.93	19.74
				(46.88	2.36	8.90	19.58)		
21b		201–204 (Acetone–CH ₂ Cl ₂)	74.7	C ₁₆ H ₁₀ Cl ₂ O ₅ (<i>M_r</i> 353.165)		54.42	2.85	20.08	
				(54.13	2.93	20.36)			
21c		197–199 (Benzene)	80.0	C ₁₆ H ₈ Cl ₂ FO ₅ (<i>M_r</i> 371.155)		51.78	2.44	19.11	5.12
				(51.52	2.64	19.30	5.16)		
21d		199–200 (AcOEt–benzene)	66.8	C ₁₁ H ₈ Cl ₂ O ₅ (<i>M_r</i> 291.094)		45.39	2.77	24.39	
				(45.11	2.92	24.09)			
21e		177–179 (Et ₂ O–CH ₂ Cl ₂)	70.0	C ₁₃ H ₁₀ Cl ₂ O ₄ (<i>M_r</i> 305.121)		47.24	3.30	23.24	
				(47.02	3.07	23.45)			
21f		132–133 (Benzene)	60.6	C ₁₃ H ₁₂ Cl ₂ O ₅ (<i>M_r</i> 319.148)		48.92	3.79	22.22	
				(48.63	3.59	22.12)			
21h		Oil	100	C ₁₄ H ₁₄ Cl ₂ O ₅ (<i>M_r</i> 333.175)					

2lj		Oil	95.0	$C_{16}H_{16}Cl_2O_5$ (M_r 359.214) Mass M^+ 358	^{b)} 3600–2300 (br), ^{c)} 7.73 (1H, br), 6.82 (1H, s), 5.03 (1H, t, $J=3$), 4.56, 4.29 (2 × 1H, dd, $J=3$, 12), <i>ca.</i> 2.98 (1H), 1.95–1.24 (10H) 1735, 1690 3600–2200 (br), 11.0–9.3 (1H, br), <i>ca.</i> 7.51 (4H), 7.01 (1H, s), 5.33 (1H, t, $J=3$), 4.68, 4.42 (2 × 1H, dd, $J=3$, 12) 1723, 1675
2ll		149–150 (Benzene–hexane)	78.0	$C_{16}H_9Cl_3O_5$ (M_r 387.614) Mass M^+ 386	
2lm		198–200 (Benzene)	89.7	$C_{16}H_9Cl_3O_5$ (M_r 387.614) 49.58 2.34 27.44 (49.47 2.48 27.25)	3600–2000 (br), 8.8–7.7 (1H, br), 7.76–7.43 (4H), 7.01 (1H, s), 5.33 (1H, t, $J=3$), 4.69, 4.45 (2 × 1H, dd, $J=3$, 12) 1758, 1667
2ln		152–154 (Benzene–cyclohexane)	74.4	$C_{16}H_9Cl_3O_5$ (M_r 387.614) 49.58 2.34 27.44 (49.26 2.67 27.21)	3650–2200 (br), 7.77, 7.53 (2 × 2H, d, $J=9$), 7.4–6.3 (1H, br), 6.96 (1H, s), 5.30 (1H, t, $J=3$), 4.67, 4.42 (2 × 1H, dd, $J=3$, 12) 1765, 1660
2lo		187–188 (Benzene–cyclohexane)	85.8	$C_{17}H_{12}Cl_2O_5$ (M_r 367.192) 55.61 3.29 19.31 (55.59 3.33 19.47)	3500–2300 (br), 10.0–8.5 (1H, br), 7.57–7.16 (4H), 6.96 (1H, s), 5.33 (1H, t, $J=3$), 4.69, 4.44 (2 × 1H, dd, $J=3$, 12), 2.49 (3H, s) 1758, 1645
2lp		205–206 (AcOEt–hexane)	73.9	$C_{17}H_{12}Cl_2O_5$ (M_r 367.192) 55.61 3.29 19.31 (55.71 3.34 19.06)	3210–3180, 1760, 10.4–8.9 (1H, br), 7.63–7.23 (4H), 6.93 (1H, s), 5.31 (1H, t, $J=3$), 4.68, 4.44 (2 × 1H, dd, $J=3$, 12), 2.37 (3H, s) 1652
2lq		188–189 (AcOEt–hexane)	65.6	$C_{17}H_{12}Cl_2O_5$ (M_r 367.192) 55.61 3.29 19.31 (55.53 3.33 19.35)	3400–2100 (br), 9.5–8.3 (1H, br), 7.64, 7.30 (2 × 2H, d, $J=8$), 6.89 (1H, s), 5.28 (1H, t, $J=3$), 4.66, 4.42 (2 × 1H, dd, $J=3$, 12), 2.37 (3H, s) 1750, 1640
2lr		142–145 (AcOEt–hexane)	90.6	$C_{14}H_8Cl_2O \cdot H_2O$ (M_r 361.141) 46.56 2.79 19.64 (47.30 2.84 19.62)	3480, 3410, 1720, 7.88 (1H, dd, $J=0.5$, 2.0), 7.16 (1H, dd, $J=0.5$, 4.0), 7.04 (1H, s), 6.67 (1H, dd, $J=2.0$, 4.0), <i>ca.</i> 5.80 (1H), 5.30 (1H, t, $J=3$), 4.68, 4.42 (2 × 1H, dd, $J=3$, 13) 1650
2ls	HCO	262–263 (Acetone)		$C_{10}H_6Cl_2O_5$ (M_r 277.059) 43.35 2.18 25.59 (43.07 2.36 25.53)	1755, 1658, 1593, 10.33 (1H, s), 7.35 (1H, s), 5.40 (1H, t, $J=3$), 4.75–4.33 (2H, m) 1558

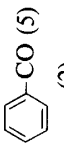
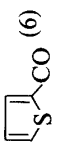
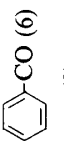
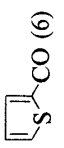
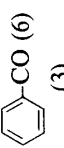
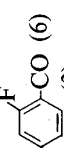
a) Solvent: dichloromethane = CH_2Cl_2 , ethyl acetate = AcOEt, ethyl ether = Et₂O. b) In $CHCl_3$. c) In $CDCl_3$.

TABLE XIV. 5- and 6-Acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-3-carboxylic Acids

Compound	Acyl	mp (°C) (Solvent) ^{a)}	Yield (%)	Analysis (%)				IR (Nujol) cm ⁻¹	¹ H-NMR (acetone-d ₆) δ
				Calcd (Found)					
				C	H	Cl	S (F)		
22a		Amorphous	80.9	C ₁₄ H ₈ Cl ₂ O ₅ S (<i>M_r</i> 359.187) Mass M ⁺ 358				3600—2200 (br), 1730, 1630	9.0—8.0 (1H, br), 7.94 (1H, dd, <i>J</i> = 1.5, 5.5), 7.78 (1H, dd, <i>J</i> = 1.5, 4.5), 7.17 (1H, s), 7.16 (1H, dd, <i>J</i> = 4.5, 5.5), 5.12 (1H, t, <i>J</i> = 3), 4.78, 4.47 (2 × 1H, dd, <i>J</i> = 3, 12)
22b	C ₂ H ₅ CO (5)	173—175 (Et ₂ O-PE)	95.2	C ₁₂ H ₁₀ Cl ₂ O ₅ (<i>M_r</i> 305.117) 47.24 3.30 23.24 (47.17 3.46 23.18)				3080, 1740, 1715, 1682, 1580	8.33—7.50 (1H, br), 7.40 (1H, s), 5.37 (1H, t, <i>J</i> = 3), 4.43—4.95 (2H, m), 3.08 (2H, q, <i>J</i> = 7), 1.10 (3H, t, <i>J</i> = 7)
23a		220—222 (Et ₂ O)	78.0	C ₁₄ H ₈ Cl ₂ O ₅ S (<i>M_r</i> 359.187) 46.82 2.24 19.74 8.93 (46.74 2.56 19.80 8.85)				1730, 1620, 1600	8.03 (1H, dd, <i>J</i> = 5, 1), 7.53 (1H, dd, <i>J</i> = 5, 1), 7.23 (1H, t, <i>J</i> = 5), 7.17 (1H, s), 5.23 (1H, t, <i>J</i> = 4), 4.68 (2H, t, <i>J</i> = 4)
23b		207—209 (Acetone- CH ₂ Cl ₂)	80.0	C ₁₆ H ₁₀ Cl ₂ O ₅ (<i>M_r</i> 353.161) 54.42 2.85 20.08 (54.19 3.03 20.23)				1720, 1670, 1590	8.22—7.48 (5H, m), 7.07 (1H, s), 5.22 (1H, t, <i>J</i> = 3), 4.95—4.45 (2H, m)
23c		162—163 (Benzene)	86.0	C ₁₆ H ₈ Cl ₂ FO ₅ (<i>M_r</i> 371.151) 51.78 2.44 19.10 5.12 (51.55 2.65 19.65 4.95)				3600—2209 (br), 1758, 1630	9.4—7.3 (1H, br), 7.83—7.23 (4H, m), 7.15 (1H, s), 5.12 (1H, t, <i>J</i> = 3), 4.79, 4.58 (2 × 1H, dd, <i>J</i> = 3, 13)
23d	C ₃ H ₇ CO (6)	124—125 (Benzene- cyclohexane)	78.4	C ₁₃ H ₁₂ Cl ₂ O ₅ (<i>M_r</i> 319.144) 48.93 3.79 22.22 (48.84 3.54 22.20)				3600—2200 (br), 1710, 1690	^{b)} 9.65 (1H, s), 7.07 (1H, s), 4.94 (1H, t, <i>J</i> = 3), 4.67, 4.46 (2 × 1H, dd, <i>J</i> = 3, 13), 2.87 (2H, t, <i>J</i> = 7), 1.91—1.50 (2H, m), 0.95 (3H, t, <i>J</i> = 7)

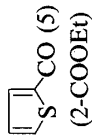
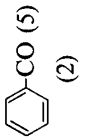
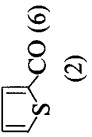
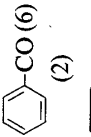
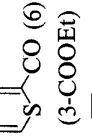
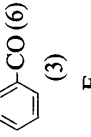
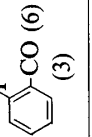
a) Solvent: petroleum ether = PE, ethyl ether = Et₂O, dichloromethane = CH₂Cl₂. b) In CDCl₃.

TABLE XV. Ethyl 5(or 6)-Acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2(or 3)-carboxylates

Compound	Acyl	mp (°C) (Solvent) ^{a)}	Yield (%)	Analysis (%)				IR (Nujol) cm ⁻¹	¹ H-NMR (CDCl ₃) δ
				C	H	Cl	S (F)		
24a	 CO (5)	124—125 (EtOH)	84.0	C ₁₆ H ₁₂ Cl ₂ O ₃ S (<i>M_r</i> 387.241)	49.63	3.12	18.31	1745, 1640, 1582, 1570	7.72 (1H, dd, <i>J</i> = 6, 2), 7.47 (1H, dd, <i>J</i> = 6, 2), 7.10 (1H, t, <i>J</i> = 6), 7.17 (1H, s), 5.00 (1H, t, <i>J</i> = 4), 4.62—4.17 (2H, m), 4.27 (2H, q, <i>J</i> = 8), 1.27 (3H, t, <i>J</i> = 8)
24b	 CO (5)	171—172 (AcOEt—hexane)	94.5	C ₁₈ H ₁₄ Cl ₂ O ₃ (<i>M_r</i> 381.219)	56.71	3.70	18.60	1742, 1658	^{b)} 7.85—7.42 (5H), 7.16 (1H, s), 5.29 (1H, t, <i>J</i> = 3), 4.49, 4.31 (2 × 1H, dd, <i>J</i> = 3, 12), 4.22 (2H, q, <i>J</i> = 7), 1.20 (3H, t, <i>J</i> = 7)
24c	C ₂ H ₅ CO (5)	108—109 (Cyclohexane)	92.5	C ₁₄ H ₁₄ Cl ₂ O ₃ (<i>M_r</i> 333.175)	50.47	4.24	21.28	1735, 1670, 1580	^{b)} 7.34 (1H, s), 5.29 (1H, t, <i>J</i> = 3), 4.75, 4.48 (2 × 1H, dd, <i>J</i> = 3, 13), 4.21, 2.91 (2 × 2H, q, <i>J</i> = 8), 1.23, 1.07 (2 × 3H, t, <i>J</i> = 8)
24d	HCO (5)	110—113 (EtOH)	48.0 (19)	C ₁₂ H ₁₀ Cl ₂ O ₃ (<i>M_r</i> 305.121)	47.24	3.30	23.24	3080, 1755, 1690, 1588, 1575	^{b)} 10.20 (1H, s), 7.40 (1H, s), 5.37 (1H, t, <i>J</i> = 2), 4.73—4.40 (2H, m), 4.27 (2H, q, <i>J</i> = 8), 1.25 (3H, t, <i>J</i> = 8)
25a	 CO (6)	134—135 (Et ₂ O)	92.0	C ₁₆ H ₁₂ Cl ₂ O ₃ S (<i>M_r</i> 387.241)	49.63	3.12	18.28	8.31	^{b)} 7.01 (1H, s), 8.03 (1H, dd, <i>J</i> = 5, 1), 7.52 (1H, dd, <i>J</i> = 5, 1), 7.22 (1H, t, <i>J</i> = 5), 5.33 (1H, t, <i>J</i> = 4), 4.33—4.87 (2H, m), 4.27 (2H, q, <i>J</i> = 7), 1.27 (3H, t, <i>J</i> = 7)
25b	 CO (6)	71—73 (EtOH-PE)	90.0	C ₁₈ H ₁₄ Cl ₂ O ₃ (<i>M_r</i> 381.219)	56.71	3.70	18.60		6.80 (1H, s), 7.90—7.17 (5H, m), 5.00 (1H, t, <i>J</i> = 5), <i>ca.</i> 4.43 (2H, m), 4.27 (2H, q, <i>J</i> = 7), 1.30 (3H, t, <i>J</i> = 7)
25c	HCO (6)	101—102 (EtOH)	47.0 (39)	C ₁₂ H ₁₀ Cl ₂ O ₃ (<i>M_r</i> 305.121)	47.24	3.30	23.24	3070, 3040, 1757, 1690, 1597, 1560	^{b)} 10.33 (1H, s), 7.33 (1H, s), 5.40 (1H, t, <i>J</i> = 2), 4.70—4.30 (2H, m), 4.25 (2H, q, <i>J</i> = 8), 1.25 (3H, t, <i>J</i> = 8)
26a	 CO (6)	137—138 (Et ₂ O)	70.0	C ₁₆ H ₁₂ Cl ₂ O ₃ S (<i>M_r</i> 387.241)	49.63	3.12	18.28	1750, 1658, 1588	^{b)} 7.23 (1H, s), 8.10 (1H, dd, <i>J</i> = 5, 1), 7.58 (1H, dd, <i>J</i> = 5, 1), 7.30 (1H, t, <i>J</i> = 5), 5.27 (1H, t, <i>J</i> = 4), 4.70 (2H, t, <i>J</i> = 4), 4.30 (2H, q, <i>J</i> = 7), 1.27 (3H, t, <i>J</i> = 7)
26b	 CO (6)	112—113 (Benzene—hexane)	90.0	C ₁₈ H ₁₄ Cl ₂ O ₃ (<i>M_r</i> 381.219)	56.71	3.70	18.60	1743, 1667, 1600, 1557	^{b)} 7.05 (1H, s), 7.88—7.47 (5H, m), 5.20 (1H, t, <i>J</i> = 4), 4.90—4.43 (2H, m), 4.23 (2H, q, <i>J</i> = 7), 1.23 (3H, t, <i>J</i> = 7)
26c	 CO (6)	139—140 (Cyclohexane)	90.0	C ₁₈ H ₁₃ Cl ₂ FO ₃ (<i>M_r</i> 399.209)	54.16	3.28	17.76	1775, 1670, 1605	7.82—6.98 (4H, m), 7.10 (1H, s), 4.86 (1H, t, <i>J</i> = 3), <i>ca.</i> 4.53 (2H), 4.27 (2H, q, <i>J</i> = 7), 1.27 (3H, t, <i>J</i> = 7)

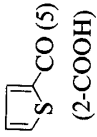
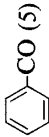
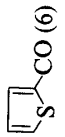
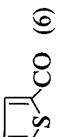
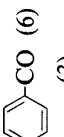
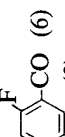
a) Solvent: ethyl acetate = AcOEt, ethyl ether = Et₂O, petroleum ether PE. b) In acetone-*d*₆.

TABLE XVI. Ethyl-5(or 6)-acyl-7,8-dichloro-1,4-benzodioxin-2(or 3)-carboxylates

Compound	Acyl	mp (°C) (Solvent) ^{a)}	Yield (%)	Analysis (%)				IR (Nujol) cm ⁻¹	¹ H-NMR (CDCl ₃) δ
				Calcd	Found	C	H	Cl	S (F)
27a	 (5) (2-COOEt)	165—166 (EtOH)	73.0	C ₁₆ H ₁₀ Cl ₂ O ₅ S (<i>M_r</i> 385.225)		49.89	2.62	18.41	8.32
				(49.91		2.75	18.70	8.32)	
27b	 (5) (2)	153—155 (EtOH)	80.6	C ₁₈ H ₁₂ Cl ₂ O ₅ (<i>M_r</i> 379.203)		57.02	3.19	18.70	
				(56.51		3.33	18.56)		
28a	 (6) (2)	128—130 (Et ₂ O)	64.0	C ₁₆ H ₁₀ Cl ₂ O ₅ S (<i>M_r</i> 385.225)		49.89	2.62	18.41	8.32
				(49.85		2.92	18.41	8.32)	
28b	 (6) (2)	95—96 (EtOH-PE)	60.0	C ₁₈ H ₁₂ Cl ₂ O ₅ (<i>M_r</i> 379.203)		57.02	3.19	18.70	
				(56.50		3.25	19.00)		
29a	 (6) (3-COOEt)	171—173 (CH ₂ Cl ₂ - Et ₂ O)	50.0	C ₁₆ H ₁₀ Cl ₂ O ₅ S (<i>M_r</i> 385.225)		49.89	2.62	18.41	8.32
				(49.69		2.74	18.38	8.13)	
29b	 (6) (3)	155—157 (CH ₂ Cl ₂ - MeOH)	80.6	C ₁₈ H ₁₂ Cl ₂ O ₅ (<i>M_r</i> 379.203)		57.02	3.19	18.70	
				(57.22		3.26	18.59)		
29c	 (6) (3)	169—171 (Acetone- Et ₂ O-PE)	85.6	C ₁₈ H ₁₁ Cl ₂ FO ₅ (<i>M_r</i> 397.193)		54.43	2.79	17.85	4.78
				(54.14		2.90	17.75	4.82)	

a) Solvent: ethyl ether = Et₂O, petroleum ether = PE, dichloromethane = CH₂Cl₂. b) In acetone-*d*₆.

TABLE XVII. 5(or 6)-Acyl-7,8-dichloro-1,4-benzodioxin-2(or 3)-carboxylic Acids

Compound	Acyl	mp (°C) (Solvent) ^{a)}	Yield (%)	Analysis (%)				IR (Nujol) cm ⁻¹	¹ H-NMR (acetone-d ₆) δ
				Calcd	Found	C	H	Cl	S (F)
30a	 (2-COOH)	233—236 (CH ₂ Cl ₂ -PE)	77.8	C ₁₄ H ₆ Cl ₂ O ₅ S (M _r 357.171)		47.08	1.69	19.85	8.98
				(46.92	1.95	19.85	8.79)		
30b	 (2)	265—268 (AcOEt)	83.2	C ₁₆ H ₈ Cl ₂ O ₅ (M _r 351.149)		54.73	2.30	20.19	
				(54.65	2.53	20.02)			
31a	 (2)	274—276 (Et ₂ O)	94.0	C ₁₄ H ₆ Cl ₂ O ₅ S (M _r 357.171)		47.08	1.69	19.85	8.98
				(46.99	2.00	19.86	9.02)		
31b	 (2)	232—234 (Acetone-Et ₂ O)	75.0	C ₁₆ H ₈ Cl ₂ O ₅ (M _r 351.149)		54.73	2.30	20.19	
				(53.97	2.51	20.08)			
32a	 (3)	281—283 (CH ₂ Cl ₂ -Et ₂ O)	80.0	C ₁₄ H ₆ Cl ₂ O ₅ S (M _r 357.171)		47.08	1.69	19.85	8.98
				(46.87	2.12	20.04	8.71)		
32b	 (3)	250—252 (Acetone-Et ₂ O)	94.0	C ₁₆ H ₈ Cl ₂ O ₅ (M _r 351.149)		54.73	2.30	20.19	
				(54.39	2.53	19.96)			
32c	 (3)	238—239 (Acetone-Et ₂ O)	95.0	C ₁₆ H ₇ Cl ₂ FO ₅ (M _r 369.139)		52.06	1.91	19.21	5.17
				(51.96	2.24	19.51	5.22)		

a) Solvent: ethyl ether = Et₂O, petroleum ether = PE, dichloromethane = CH₂Cl₂, ethyl acetate = AcOEt. b) In DMSO-d₆.

30 ml/kg. Immediately after the administration, the metabolic tests were conducted and urine samples were collected for 4 h. The cumulative urine volume, urinary sodium, and urinary potassium were quantitatively determined.

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