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Synthesis of 2,3-Dihydro-1,4-benzodioxin Derivatives. I. 2-Substituted-5(and 6)-sulfamoyl-2,3-dihydro-1,4-benzodioxins

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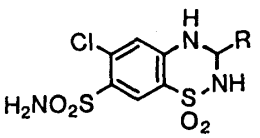
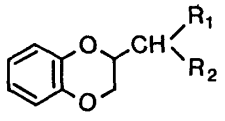
In order to study new sulfonamide diuretics, two series of 6- and 5-sulfamoyl-2,3-dihydro-1,4-benzodioxins were synthesized and tested for diuretic and antihypertensive activities in rats. Starting from 4-chloro(or 3,4-dichloro)-1,2-dihydroxybenzene, these sulfamoyl compounds were prepared by two different routes. In method A, 6-sulfamoyl compounds (**8** or **11**) were obtained by conversion of the nitro function into sulfonamide *via* the Sandmeyer reaction. In method B, 5-sulfamoyl compounds (**16**) were synthesized by direct introduction of sulfonyl chloride into the dihydrobenzodioxin, followed by amination. The sulfamoyl dihydrobenzodioxins showed lower diuretic and antihypertensive activities than trichloromethiazide.

Keywords——sulfonamide diuretic; 2,3-dihydro-1,4-benzodioxin; phenoxyacetic acid; α-blocker; β-blocker; antihypertensive; uricosuric

The most important first-line drug therapy for essential hypertension employs diuretics, especially sulfonamide diuretics[1] such as thiazides (I). However, the drawback of thiazide diuretics is uric acid retention, causing hyperuricemia. We have been interested in the development of sulfonamide diuretics having new profiles such as uricosuric properties. Prosympal (III) and piperoxan (IV) have been reported as α-blocker dihydrobenzodioxin antihypertensive agents having the 2-(alkylamino)methyl function.[2] Dihydrobenzodioxinyl-ethanolamine[3] (V) is a β-blocker, and phenoxyacetic acid diuretics, such as tienilic acid[4a]

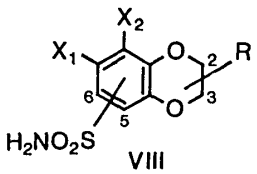


I : thiazide
II : R=$CHCl_2$ TCM

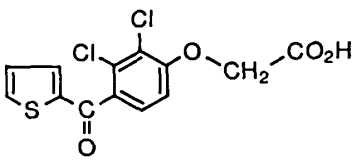


III : prosympal
IV : piperoxan
V :

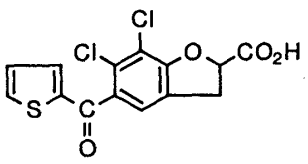
R_1	R_2
H	NEt_2
H	N⟨ ⟩
OH	CH_2NHPr^i



VIII



VI : tienilic acid



VII : dihydrobenzofuran carboxylic acid (Merck)

X_1=Cl, X_2=H
X_1=X_2=Cl
X_1=PhO, X_2=H

R = CH_2OH, CO_2H, $CH_2NR_1R_2$, $CONR_1R_2$

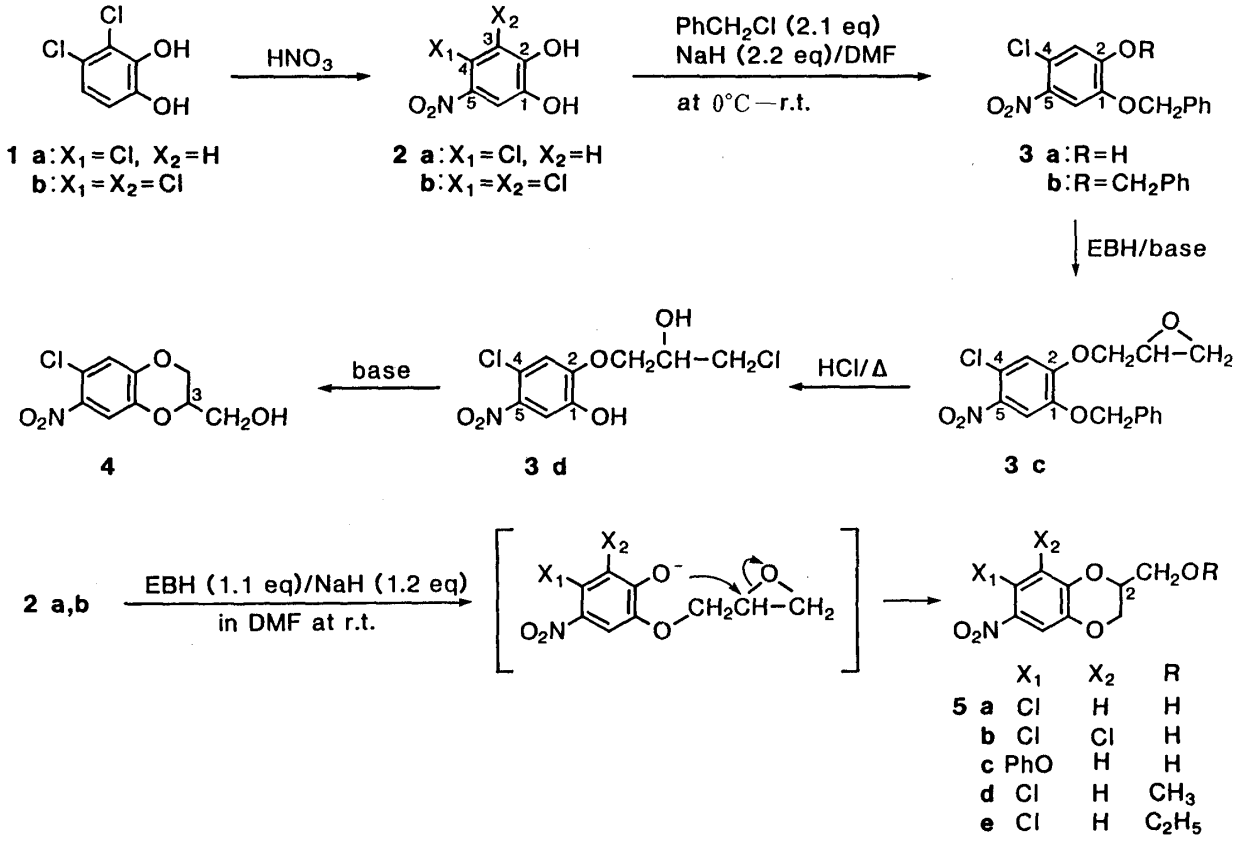
Fig. 1

(VI and VII),[4b] are uricosuric diuretic agents. From this point of view, we have synthesized two series of 6(and 5)-sulfamoyl 2(or 3)-substituted dihydrobenzodioxins, possessing chloro and phenoxy functions at position 7 or 8, as shown in Fig. 1. These compounds were tested for diuretic and antihypertensive properties.

Chemistry

It is well known that 1,2-dihydroxybenzenes reacts with epibromohydrin (EBH) in the presence of a base to give 2,3-dihydro-1,4-benzodioxin-2-ylmethanol.[5] This method has been applied to obtain dihydrobenzodioxins with various substituents at position 2, because the hydroxymethyl function is easily converted into carboxylic acid, alkylamino, carboxylamide and ethanolamine moieties. However, if unsymmetrically substituted 1,2-dihydroxybenzenes are subjected to the above reaction, two isomers will arise and regioselective synthetic methods will be needed for their synthesis. Therefore, a strongly electronegative nitro group in 1,2-dihydroxybenzene is expected to control the regioselectivity of the construction of the dihydrobenzodioxin ring. In addition, the nitro function can be smoothly converted into sulfonyl chloride through Meerwein's variant of the Sandmeyer reaction[6] of the amino analogue obtained by reduction of the nitro compound, followed by amination to yield the desired sulfonamide (method A). The other method was the regioselective construction of 7,8-dichlorodihydrobenzodioxin-2-ylmethanol acetate (**13**) from 3,4-dichloro-1,2-dihydroxybenzene (**1b**), following direct introduction of the chlorosulfonyl function, then its conversion into the sulfonamide by amination (method B). In general, 6-sulfamoyl dihydrobenzodioxins (**8** and **11**) were prepared by method A. However, the 5-sulfamoyl compounds (**16**) were obtained by method B.

Chart 1 depicts the regioselective construction of the dihydrobenzodioxin ring starting from both 4-chloro-1,2-dihydroxy-5-nitrobenzene (**2a**) and the 3,4-dichloro compound (**2b**).



1 a: X_1=Cl, X_2=H; b: X_1=X_2=Cl

2 a: X_1=Cl, X_2=H; b: X_1=X_2=Cl

3 a: R=H; b: R=CH_2Ph

4

3 d

3 c

	X_1	X_2	R
5 a	Cl	H	H
b	Cl	Cl	H
c	PhO	H	H
d	Cl	H	CH_3
e	Cl	H	C_2H_5

Chart 1

Compound **2a** was treated with benzyl chloride (2.1 eq) and sodium hydride (2.2 eq) in *N*,*N*-dimethylformamide (DMF) at room temperature for 10 min to give the 1-benzyl ether (**3a**) in 77.4% yield along with the dibenzyl ether (**3b**) in 8.6% yield. The monobenzyl ether (**3a**) was treated with EBH in the presence of base, and the resulting glycide ether (**3c**) was cleaved by acid to afford the chloride (**3d**). The ring closure was effected with a base to give 7-chloro-6-nitrodihydrobenzodioxin-3-ylmethanol (**4**) (66% overall yield from **3a**).[5]

Alternatively, the regioisomer (**5a**) has been obtained as follows. 4-Chloro-1,2-dihydroxy-5-nitrobenzene (**2a**) was directly treated with EBH (1.1 eq) in the presence of sodium hydride (1.2 eq) in DMF at room temperature for 30 min followed by heating at 80 °C for 3 h, to give 7-chloro-6-nitrodihydrobenzodioxin-2-ylmethanol (**5a**) in 81% yield. The structure of **5a** was unequivocally determined on the basis of X-ray crystal analysis[7] of 7-chloro-6-sulfamoyldihydrobenzodioxin-2-yl-methanol (**8a**), which was derived from **5a**. The reason for this regioselectivity may be as follows. In general, the phenoxy anion derived from a less acidic hydroxy group is kinetically more reactive than the phenoxy anion from a more acidic hydroxy group. As the 1-hydroxy group is less acidic than the 2-hydroxy one in the nitro compound (**2a**), an electrophilic reagent such benzyl chloride or EBH reacts preferentially with the 1-hydroxy group to give predominantly the 1-benzyl ether (**3a**) or dihydrobenzodioxin-2-ylmethanol (**5a**) under the reaction condition used.

7,8-Dichloro-6-nitrodihydrobenzodioxin-2-ylmethanol (**5b**) was obtained from compound **2b** in 74% yield, by the same procedure. The 7-phenoxy analogue (**5c**) has been synthesized from the 7-chloro compound (**5a**) by a substitution reaction.[8] Heating **5a** at 170 °C for 4 h with phenol and potassium hydroxide in the presence of copper as a catalyst gave **5c** in 75% yield. The 7-chloro-2-methoxymethyl (and 2-ethoxymethyl) compounds (**5d** and **5e**) were synthesized from **5a** by reaction with alkyl halide and sodium hydride in DMF.

These 6-nitrodihydrobenzodioxin-2(or 3)-ylmethanols (**5** and **4**) were converted into the corresponding sulfonamides as shown in Chart 2. The nitro compound (**5a**) was reduced by catalytic hydrogenation or by using metallic iron and hydrochloric acid to give the corresponding amino compound (**6a**) in good yield. The conversion of **6a** into the sulfonyl chloride (**7a**) was performed according to Meerwein's variant of the Sandmeyer process. The sulfonyl chloride (**7a**), without special purification, was converted into the sulfonamide (**8a**) by treatment with aqueous ammonia in acetone in 73% yield. In the above reaction, the amino dihydrobenzodioxins (**6a** and **6b**) bearing a chloro group at the *ortho* position to the amino

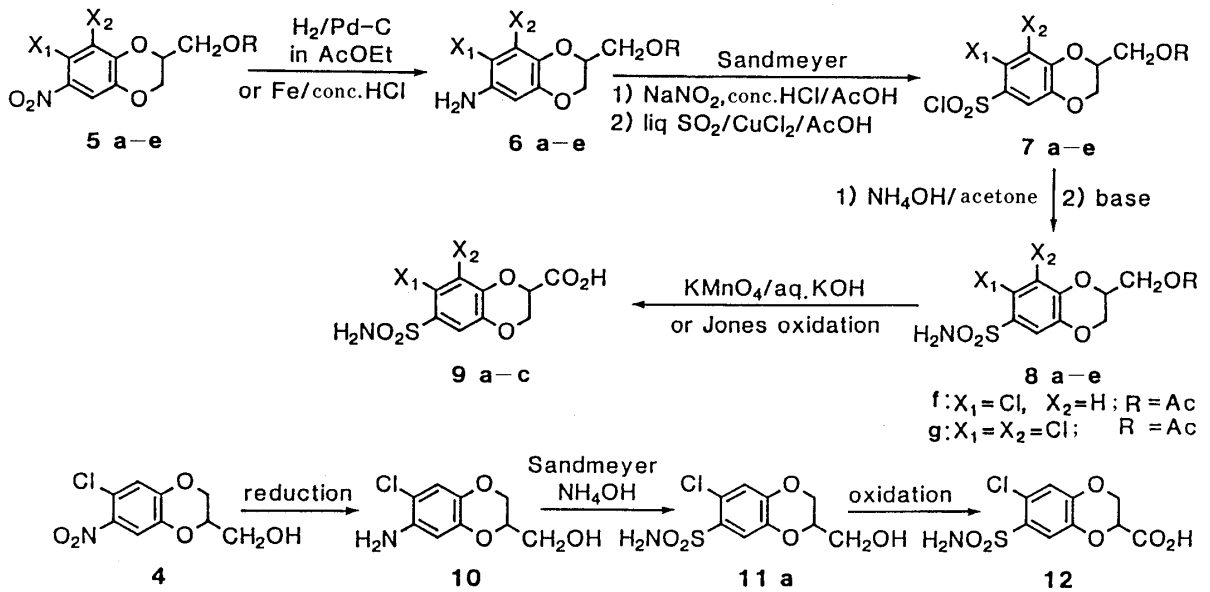


Chart 2

group were converted into the sulfonamides in good yield, while compound **6c** having a phenoxy group at the *ortho* position afforded the sulfonamide (**8c**) in only 11.5% yield. The 3-hydroxymethyl analogue (**11a**) was prepared from **4** by the same procedure. These 6-sulfamoyl-2(or 3)-hydroxymethyl compounds (**8a—c**) and (**11a**) were converted into the corresponding carboxylic acids (**9a—c**) and (**12**) by oxidation with $KMnO_4$ or Jones reagent in good yield. 5-Acyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2-carboxylic acids have been found to show a strong diuretic activity in the course of our study. A series of 5-sulfamoyl analogues (**17**) was produced from 7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2-ylmethanol acetate (**13**), which was prepared from **1b**.[9] Reaction of **13** with chlorosulfonic acid and thionyl chloride at room temperature gave a mixture of 5- and 6-sulfonyl chlorides, which were separated by chromatography on a Lobar column (Merck) and to give **14** (50%) and **15** (28.2%). These sulfonyl chlorides were treated with amines to afford 2-acetoxymethyl com-

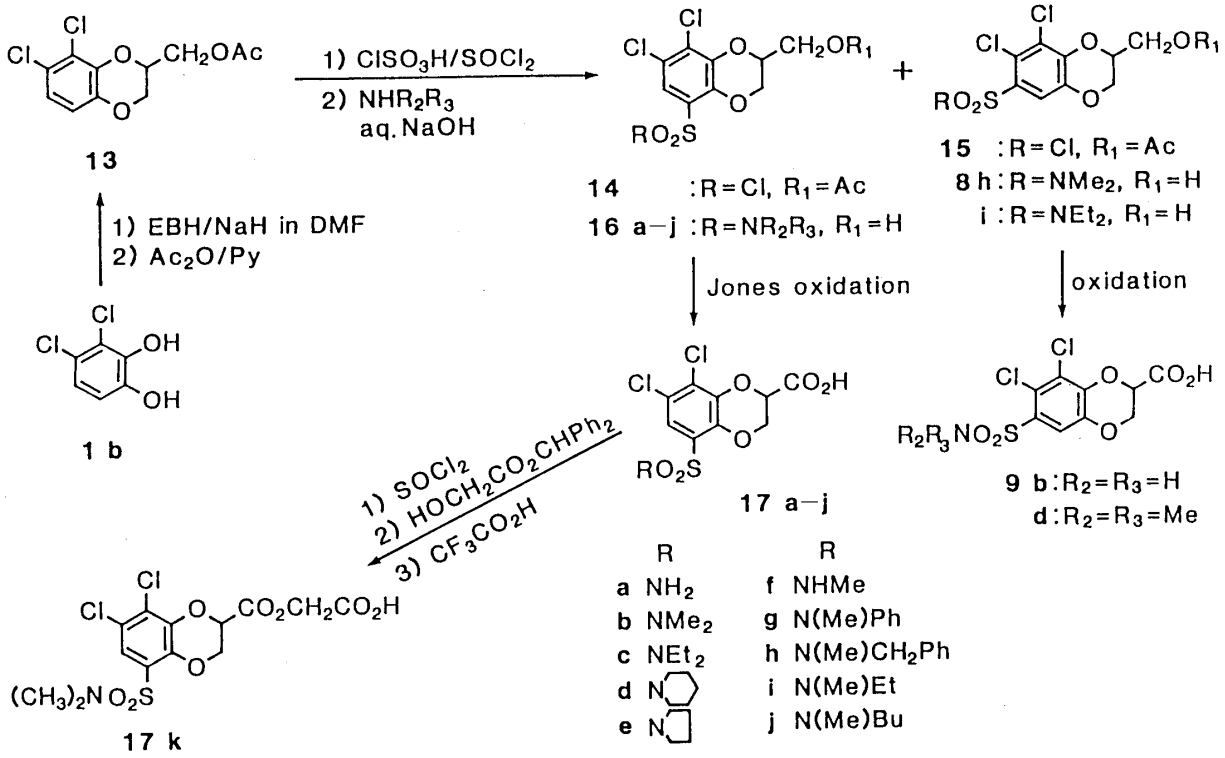


Chart 3

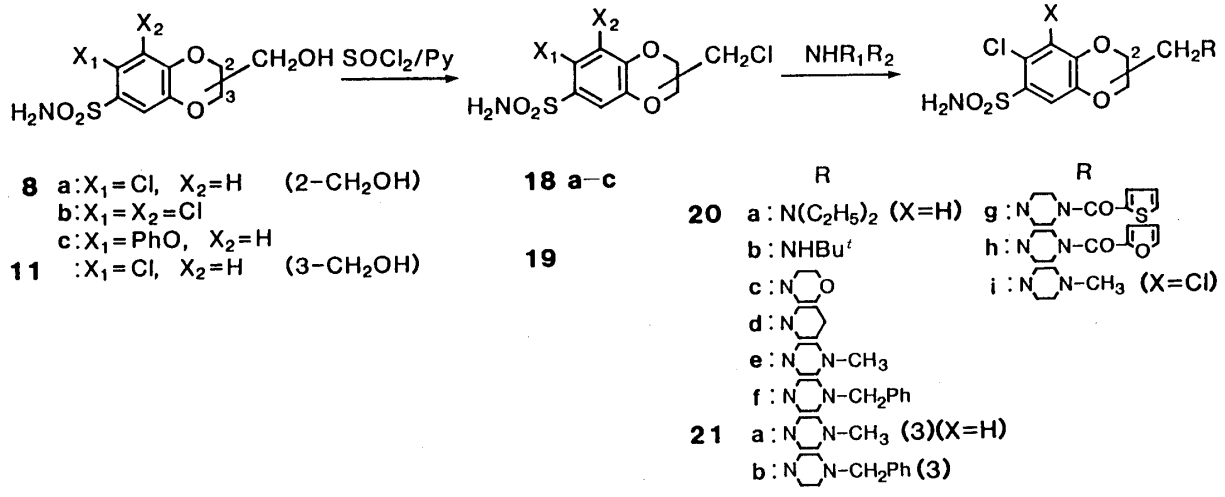


Chart 4

pounds, which were hydrolyzed with aqueous NaOH to the corresponding hydroxymethyl sulfonamides (**16**) or (**8**). On oxidation of **16** or **8** with Jones reagent, the corresponding carboxylic acids (**17** or **9**) were prepared as shown in Chart 3.

As illustrated in Charts 4 and 5, various (alkylamino)methyl (**20** and **21**), carboxyamide (**22**) and ethanolamine (**27** and **28**) analogues were obtained from these hydroxymethyl compounds (**8** and **11**) and carboxylic acids (**9** and **12**) by conventional methods.

6-Sulfamoyl dihydrobenzodioxin-2(or 3)-ylmethanols (**8** and **11**) were converted into the corresponding chloromethyl compounds (**18** and **19**, respectively) by treatment with thionyl chloride in pyridine. Compounds **18** and **19** were converted into 2(or 3)-(alkylamino)methyl compounds (**20** and **21**) by reaction with amines as shown in Chart 4. 2(or 3)-Carboxyamides (**22**) were obtained by treatment of 2(or 3)-carboxylic acids (**9** or **12**) with phosphorus trichloride and amines by the known method.[10]

6-Sulfamoyl dihydrobenzodioxinylethanolamines (**27** and **28**) were obtained from the corresponding carboxylic acids (**9a** and **9b**) as follows. 7-Chloro-6-sulfamoyldihydrobenzodioxin-2-carboxylic acid (**9a**) was treated with thionyl chloride to afford the corresponding acid chloride, which was reacted with diazomethane and HCl/AcOEt to yield the chloroacetyl compound (**23**). Reduction of **23** with sodium borohydride afforded a mixture of stereoisomers, which were separated by chromatography on a Lobar column to give **25a**

TABLE I. 7-Chloro(or 7,8-Dichloro or 7-Phenoxy)-2(or 3)-substituted-2,3-dihydro-1,4-benzodioxin-6-sulfonamides

Compound No.	Diuretic (rat) Na meq/kg body weight (Treated/control)	Antihypertensive[a]
8a	No	
8b	2.63[b]/0.74 (50 mg/kg)	
8f	No	+(84)
8g	0.83[b]/0.50 (23 mg/kg)	
9a	No	+(50)
9b	No	
9c	No	
11a	1.39[b]/0.50 (42 mg/kg)	+(78)
11b	No	
15	No	
18a	1.26[b]/0.59 (50 mg/kg)	+(100)
18b	No	
18c	No	
19	No	
20d	No	
20e	No	+(103)
20g	0.97[b]/0.55 (20 mg/kg)	
20k	1.13[b]/0.55 (12 mg/kg)	
22c	1.01[b]/0.55 (20 mg/kg)	
28a	0.22 /0.43 (50 mg/kg)	
28b	1.24[b]/0.43 (50 mg/kg)	
TCM (reference)	1.26[b]/0.67 (1 mg/kg)	100
Indacrinon (reference)	3.51[b]/0.67 (50 mg/kg)	

a) 0.2 mg/d, after 15th day (rat) see Experimental. *b*) Statistically significant difference.

TABLE II. 7,8-Dichloro-2-substituted-5-sulfamoyl-2,3-dihydro-1,4-benzodioxins

Compound No.	Diuretic (rat)[a] Na meq/kg body weight (Treated/control)
16a	0.95 /0.64
16b	0.87 /0.59
16c	0.64 /0.53
17a	0.47 /0.64
17b	1.39[b]/0.59
17c	1.46[b]/0.53
17d	1.34[b]/0.75
17e	0.90 /0.75
17g	0.71 /0.73
17i	1.65[b]/0.55
17j	1.24[b]/0.73
17k	1.43[b]/0.51
TCM (1 mg/kg) (reference)	1.26[b]/0.67
Indacrinone[a] (reference)	3.51[b]/0.67

a) Dose: 50 mg/kg. *b*) Statistically significant difference.

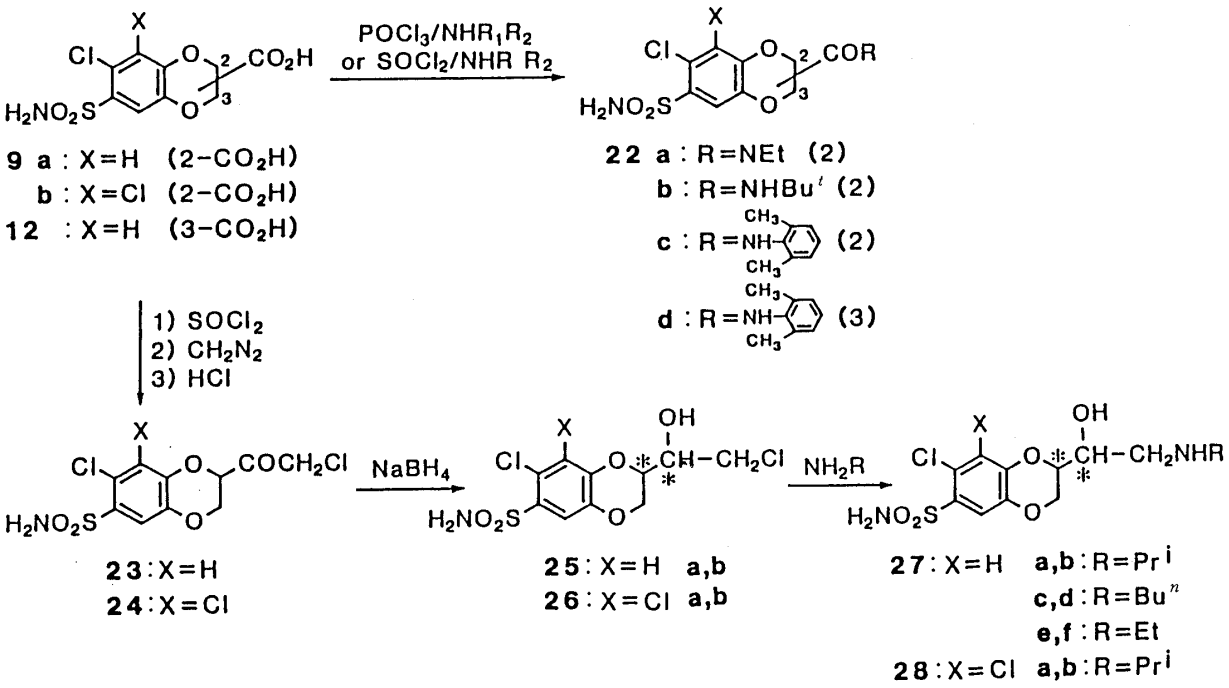


Chart 5

and **25b**. These were converted into the corresponding ethanolamines (**27**) by reaction with amines. 7,8-Dichloro analogues (**28a** and **28b**) were prepared from **9b** by the same method, as shown in Chart 5.

Biological Activities

Table I shows the diuretic activities of the 6-sulfamoyl-2,3-dihydro-1,4-benzodioxin derivatives and Table II shows those of the 5-sulfamoyl compounds. In general, the 5-sulfamoyl compounds were more diuretic than the 6-sulfamoyl derivatives, but they showed less potent diuretic and antihypertensive activities[11] than trichloromethiazide (TCM).

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. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken in dimethyl sulfoxide-d_6 (DMSO-d_6) solution on a Varian EM-390 or T-60 spectrophotometer, unless otherwise noted. Chemical shifts were expressed as δ values (ppm) from tetramethylsilane. Column chromatography was conducted using silica gel (E. Merck, 70—230 mesh ASTM) or a Lobar column (Merck). When the products were isolated by solvent extraction, the procedure generally followed was to extract the aqueous layer with two or three portions of the indicated solvent, then wash the organic layer with saturated NaCl–H_2O or H_2O, dry it over Na_2SO_4 or $MgSO_4$, and evaporate the solvent *in vacuo*.

Preparation of 7-Chloro-6-nitro-2,3-dihydro-1,4-benzodioxin-3-ylmethanol (4)

1) 1-Benzyloxy-4-chloro-2-hydroxy-5-nitrobenzene (3a)——A solution of **2a** (10.0 g) in dry DMF (25 ml) was added to a suspension of NaH (50% in oil, 5.32 g, 2.1 eq) in dry DMF (25 ml) with stirring under cooling on an ice bath for 10 min. Next, a solution of benzyl chloride (14.07 g) in dry DMF (10 ml) was added. The resulting mixture was stirred at room temperature for 30 min and then heated at 50—60 °C for an additional 45 min. The mixture was diluted with water, and the resulting solid (2.5 g) (dibenzyl ether) (**3b**) was removed by filtration. The filtrate was extracted with ether to remove the neutral fraction (5.28 g). The mother liquor was acidified with concentrated HCl and then extracted with ether. The extracts (13.08 g) were passed over SiO_2 with benzene/CH_2Cl_2 and the crude products were recrystallized from benzene–petroleum ether (PE) to give **3a** (9.85 g, mp 85—88 °C, as the first crop and 1.59 g, mp 75—78 °C, as the second one, yield 77.4%). The dibenzyl ether fraction (**3b**) (2.5 g) was recrystallized from CH_2Cl_2–ether to afford crystals, 1.674 g (mp 107—109 °C, yield 8.6%).

The 1-Benzyl Ether (**3a**): *Anal.* Calcd for $C_{13}H_{10}ClO_4 \cdot 1/4H_2O$ (M_r 270.172): C, 54.94; H, 3.54; Cl, 12.47; N, 4.93.

Found: C, 54.88; H, 3.46; Cl, 13.08; N, 4.90. IR cm^{-1}: 3497, 3383, 1573. ^{1}H-NMR δ: 7.67 (1H, s), 7.41 (5H, s, Ph), 7.07 (1H, s), 6.12 (1H, br, OH), 5.17 (2H, s, CH_2Ph).

The Dibenzyl Ether (**3b**): ^{1}H-NMR ($CDCl_3$) δ: 7.81 (1H, s), 7.40 (11H, s), 5.30, 5.23 (each 2H, s, CH_2Ph).

2) 1-Benzyloxy-4-chloro-2-(2,3-epoxypropoxy)-5-nitrobenzene (3c)——A solution of **3a** (5.0 g) in dry DMF (10 ml) was added to a suspension of NaH (50% in oil, 0.943 g, 1.1 eq) in dry DMF (40 ml) under stirring and cooling on an ice bath over 5 min. After 15 min, a solution of EBH (3.42 g, 1.4 eq) in dry DMF (10 ml) was added at room temperature and the resulting reaction mixture was heated at 76 °C for 5 h. After cooling, the reaction mixture was diluted with water and 2 N NaOH. The resulting crystals were collected by filtration and then dissolved with CH_2Cl_2. The CH_2Cl_2 solution was washed with water and dried over Na_2SO_4. The solvent was evaporated off *in vacuo*, giving a neutral fraction (4.77 g), which was passed through an SiO_2 column with benzene/CH_2Cl_2 (4 : 1)–CH_2Cl_2 as the eluent. Recrystallization of the residue obtained from the eluate from CH_2Cl_2–ether–PE afforded **3c** (3.809 g, mp 91—93 °C). *Anal.* Calcd for $C_{16}H_{14}ClNO_5$ (M_r 335.747): C, 57.24; H, 4.20; Cl, 10.56; N, 4.17. Found: C, 57.04; H, 4.31; Cl, 10.78; N, 4.26. IR cm^{-1}: 1578. ^{1}H-NMR ($CDCl_3$) δ: 7.62 (1H, s), 7.40 (5H, s, Ph), 7.02 (1H, s), 5.15 (2H, m), 4.57—3.87 (2H, m), 3.60—3.20 (1H, m), 3.00—2.67 (2H, m).

3) 4-Chloro-2-(3-chloro-2-hydroxypropoxy)-1-hydroxy-5-nitrobenzene (3d)——A solution of **3c** (5.0 g) in concentrated HCl (200 ml) was heated at 110—115 °C for 1 h. The cooled reaction mixture was extracted with ether. Recrystallization of the residue from benzene–PE gave **3d** (3.475 g, mp 119—121 °C, yield 82.7%). *Anal.* Calcd for $C_9H_9Cl_2NO_5$ (M_r 282.087): C, 38.32; H, 3.22; Cl, 25.14; N, 4.97. Found: C, 38.60; H, 3.17; Cl, 25.23; N, 4.79. IR cm^{-1}: 3402, 3262, 1606, 1587. ^{1}H-NMR ($CDCl_3$) δ: 7.53 (1H, s), 6.92 (1H, s), 4.57—4.17 (1H, m), 4.30 (2H, s), 3.82 (2H, d, J=4 Hz).

4) 7-Chloro-6-nitro-2,3-dihydro-1,4-benzodioxin-3-ylmethanol (4)——A mixture of **3d** (6.0 g) and KOH (1.02 g, 1.2 eq) in EtOH (300 ml) was refluxed under an atmosphere of nitrogen for 20 min. The cooled reaction mixture was neutralized with concentrated HCl, then the solvent was removed *in vacuo* at room temperature. The resultant syrup was extracted with CH_2Cl_2. The residue (5.21 g) was crystallized from ether–PE to give **4** (4.68 g, mp 99—101 °C, yield 89.6%). *Anal.* Calcd for $C_9H_8ClNO_5$ (M_r 245.622): C, 44.01; H, 3.28; Cl, 14.44; N, 5.70. Found: C, 44.27; H, 3.57; Cl, 14.45; N, 5.77. IR cm^{-1}: 3395, 3290, 1608, 1573. ^{1}H-NMR δ: 7.64 (1H, s), 7.22 (1H, s), 5.11 (1H, br, OH), 4.58—4.07 (3H, m), 3.70 (2H, br, CH_2OH).

7-Chloro-6-nitro-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (5a)——4-Chloro-1,2-dihydroxy-5-nitrobenzene (**2a**) (11.92 g) was added dropwise to a suspension of NaH (50% in oil, 4.56 g, 1.2 eq, the oil was removed by PE) in dry DMF (250 ml) under cooling in an ice bath. The mixture was stirred at the same temperature until evolution of hydrogen gas ceased, and then a solution of EBH (11.92 g, 1.1 eq) in dry DMF (50 ml) was added. The reaction mixture was stirred at room temperature for 30 min, the then heated at 80 °C for 3 h. The cooled reaction mixture was poured into ice water and extracted with ether. The residue (16.8 g) was recrystallized from ether to give **5a** (14.0 g, mp 103—105 °C). A second crop (1.88 g, mp 99—102 °C) of **5a** was obtained by recrystallization of the crystalline residue, after passage through a column of SiO_2. The yield of crystalline **5a** totaled 15.88 g (yield 81.7%). *Anal.* Calcd for $C_9H_8ClNO_5$ (M_r 245.622): C, 44.01; H, 3.28; Cl, 14.44; N, 5.70. Found: C, 43.92; H, 3.39; Cl, 14.58; N, 5.76. IR cm^{-1}: 3306—3206, 1612, 1578. ^{1}H-NMR δ: 7.68 (1H, s), 7.27 (1H, s), 5.12 (1H, t, J=6 Hz, OH), 4.30—4.08 (3H, m), 3.65 (2H, d, J=6 Hz, CH_2OH).

7,8-Dichloro-6-nitro-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (**5b**): mp 108—111 °C (from EtOH–PE, yield 74%). *Anal.* Calcd for $C_9H_7Cl_2NO_5$ (M_r 280.071): C, 38.60; H, 2.52; Cl, 25.32; N, 5.00. Found: C, 38.90; H, 2.44; Cl, 25.13; N, 5.01. IR cm^{-1}: 3567, 1570. ^{1}H-NMR δ: 7.75 (1H, s), 5.20 (1H, br, OH), 4.63—4.07 (3H, m), 3.87—3.60 (2H, br, CH_2OH).

6-Nitro-7-phenoxy-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (5c)——A mixture of phenol (19.52 g, 1.7 eq) and NaOH (10.00 g, 1.46 eq) was heated on an oil bath at 130—140 °C for 15 min. After the mixture had cooled to 100—110 °C, **5a** (30 g) and Cu powder (610 g) were added. The resulting mixture was heated at 150—170 °C for 4 h. The cooled reaction mixture was mixed with ice water and extracted with CH_2Cl_2. The organic layer was washed with 2 N NaOH, and evaporated *in vacuo*. The residue (36.93 g) was passed through a column of SiO_2 (200 g) with CH_2Cl_2 and gave a yellow oil (**5c**) (27.86 g, yield 75.3%). *Anal.* Calcd for $C_{15}H_{13}NO_6$ (M_r 303.27). MS *m/z*: 303 (M^+). IR ($CHCl_3$) cm^{-1}: 3620, 1628, 1587. ^{1}H-NMR δ: 7.67 (11H, s), 7.19 (5H, br, PhO), 6.65 (1H, s), 5.08 (1H, t, J=5 Hz, OH), 4.30 (3H, m), 3.67 (2H, d, J=5 Hz), 3.32 (3H, s).

7-Chloro-6-nitro-2,3-dihydro-1,4-benzodioxin-2-ylmethanol Ethyl Ether (5e)——A mixture of **5a** (5.0 g) in dry DMF (10 ml) was added to a suspension of NaH (50% in oil, 1.07 g, 1.12 eq) in dry DMF (50 ml) with stirring and cooling, over 10 min. After 20 min, EtBr (3.33 g, 1.5 eq) was added to the mixture. The resulting mixture was stirred at room temperature for 20 min, and then heated at 40 °C for 3 h. The cooled reaction mixture was diluted with water and extracted with ether. The residue (5.82 g) obtained from the extract was passed through a column of SiO_2 with benzene–benzene/CH_2Cl_2 (5 : 1) and gave an oil (**5e**) (4.927 g, yield 89.0%). *Anal.* Calcd for $C_{11}H_{12}ClNO_5$ (M_r 273.67). MS *m/z*: 273 (M^+). IR ($CHCl_3$) cm^{-1}: 2980, 1583. ^{1}H-NMR δ: 7.72 (1H, s), 7.32 (1H, s), 4.65—3.95 (3H, m), 3.67 (2H, d, J=5 Hz), 3.52 (2H, q, J=7 Hz), 1.13 (3H, t, J=7 Hz).

7-Chloro-6-nitro-2,3-dihydro-1,4-benzodioxin-2-ylmethanol Methyl Ether (**5d**): mp 67—68 °C (from EtOH, yield 84%). *Anal.* Calcd for $C_{10}H_{10}ClNO_5$ (M_r 259.649). MS *m/z*: 259 (M^+). IR ($CHCl_3$) cm^{-1}: 1616, 1583. ^{1}H-NMR

δ: 7.68 (1H, s), 7.28 (1H, s), 4.58—3.90 (3H, m), 3.60 (2H, d, J=5 Hz), 3.32 (3H, s).

Preparation of 6-Amino-7-chloro-2,3-dihydro-1,4-benzodioxin-2(or 3)-ylmethanols (6 and 10)

6-Amino-7-chloro-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (6a)——1) A mixture of **5a** (13 g) and 5% Pd–C (2.75 g) in AcOEt (300 ml) was hydrogenated by a conventional procedure until the starting material (**5a**) had disappeared on thin layer chromatography (TLC). The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*, leaving a residue (12.0 g), which when recrystallized from MeOH–ether gave **6a** (8.37 g, mp 119—122 °C, yield 73%).

2) Metallic iron (5.5 g) was added portionwise to a mixture of **5a** (8.0 g) in MeOH (35 ml) and concentrated HCl (23 ml). The reaction mixture was refluxed with stirring for 10 h until **5a** had disappeared on TLC. Conventional work-up gave a residue, and recrystallization from MeOH–ether gave **6a** (5.91 g, mp 119—122 °C, yield 84%). *Anal.* Calcd for $C_9H_{10}ClNO_3$ (M_r 215.640): C, 50.13; H, 4.67; Cl, 16.44; N, 6.50. Found: C, 50.28; H, 4.80; Cl, 16.34; N, 6.66. IR cm^{-1}: 3448, 3368, 3230, 1625, 1607, 1581. ^{1}H-NMR δ: 6.80 (1H, s), 6.42 (1H, s), 5.02 (1H, t, J=6 Hz, OH), 4.83 (2H, s, NH_2), 4.38—3.88 (3H, m), 3.65 (2H, d, J=6 Hz, CH_2OH).

6-Amino-7,8-dichloro-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (**6b**): (Oil, yield 95%). ^{1}H-NMR δ: 7.33 (2H, s, NH_2), 6.27 (1H, s), 4.40—3.60 (6H, m).

6-Amino-7-phenoxy-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (**6c**): (Oil, yield 91.1%). *Anal.* Calcd for $C_{15}H_{15}NO_4$ (M_r 273.28). MS m/z: 273 (M^+). IR ($CHCl_3$) cm^{-1}: 3600, 3450, 3370, 1680, 1592. ^{1}H-NMR δ: 7.17 (5H, br, PhO), 6.37 (2H, s), 4.92 (1H, t, J=6 Hz, OH), 4.37 (2H, br, NH_2), 4.05 (3H, br), 3.57 (2H, d, J=6 Hz, CH_2OH).

6-Amino-7-chloro-2,3-dihydro-1,4-benzodioxin-2-ylmethanol Methyl Ether (**6d**): mp 60.5—62 °C (from ether–PE, yield 76%). *Anal.* Calcd for $C_{10}H_{12}ClNO_3$ (M_r 229.667): C, 52.30; H, 5.27; Cl, 15.44; N, 6.10. Found: C, 52.74; H, 5.28; Cl, 15.37; N, 6.01. IR cm^{-1}: 3301, 3280, 3192, 1634, 1588. ^{1}H-NMR δ: 6.75 (1H, s), 6.35 (1H, s), 4.95 (2H, br, NH_2), 4.38—3.83 (3H, m), 3.52 (2H, d, J=5 Hz), 3.30 (3H, s, CH_3).

6-Amino-7-chloro-2,3-dihydro-1,4-benzodioxin-2-ylmethanol Ethyl Ether (**6e**): mp 62—63.5 °C (from ether, yield 83%). *Anal.* Calcd for $C_{11}H_{14}ClNO_3$ (M_r 243.694): C, 54.22; H, 5.79; Cl, 14.55; N, 5.75. Found: C, 53.92; H, 5.72; Cl, 14.49; N, 5.75. IR cm^{-1}: 3420, 3290, 3180, 1635, 1590. ^{1}H-NMR δ: 6.73 (1H, s), 6.35 (1H, s), 4.72 (2H, br, NH_2), 4.38—3.83 (3H, m), 3.57 (2H, d, J=5 Hz), 3.48 (2H, q, J=7 Hz), 1.12 (3H, t, J=7 Hz).

6-Amino-7-chloro-2,3-dihydro-1,4-benzodioxin-3-ylmethanol (**10**): mp 117—118 °C (from ether–PE, yield 80%). *Anal.* Calcd for $C_9H_{10}ClNO_3$ (M_r 215.640): C, 50.13; H, 4.67; Cl, 16.44; N, 6.50. Found: C, 50.28; H, 4.57; Cl, 16.40; N, 6.55. IR cm^{-1}: 3470, 3370, 3190, 3090, 1601, 1576. ^{1}H-NMR δ: 6.72 (1H, s), 6.35 (1H, s), 4.95 (1H, t, J=6 Hz, OH), 4.77 (2H, br, NH_2), 4.33—3.80 (3H, m), 3.70—3.45 (2H, d, J=6 Hz, CH_2OH).

Preparation of 7(and 8)-(Di)substituted-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2(or 3)-ylmethanols (8 and 11)

7-Chloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (8a)——A solution of $NaNO_2$ (3.81 g) in H_2O (6 ml) was added dropwise to a mixture of **6a** (10.83 g) in AcOH (35 ml) and concentrated HCl (40 ml) under stirring and cooling on an ice-NaCl bath at −15 to −5 °C (internal temperature) over 35 min. After 15 min, a solution of $CuCl_2 \cdot 2H_2O$ (5 g) in H_2O (5 ml) and 33% SO_2–AcOH (SO_2 34 g in AcOH 66 g) was added. The reaction mixture was gradually warmed to 33 °C (internal temperature) under stirring and maintained at the same temperature for an additional 50 min until gas evolution ceaed. The reaction mixture was poured into ice water and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* at room temperature to give a residue of the sulfonyl chloride (**7a**). Concentrated NH_4OH (70 ml) was added to a solution of the residue (**7a**) in acetone (80 ml) with stirring and cooling on an ice bath, then the mixture was refluxed for 30 min. After acidification with concentrated HCl, the reaction mixture was evaporated *in vacuo* and extracted with AcOEt. The residue from the extract was diluted with 2 N NaOH (100 ml) and the mixture was heated at 70—80 °C for 15 min. Next, the reaction mixture was extracted with CH_2Cl_2 to remove the neutral fraction (0.7 g), and the solid was collected (8.8 g), then recrystallized from EtOH–ether to afford **8a** (8.7 g, mp 168—169 °C). The filtrate was acidified with concentrated HCl and extracted with AcOEt. The residue (3.8 g) was passed through a column of SiO_2 with AcOEt/MeOH (100 : 1) and the product was recrystallized from the same solvent to give **8a** (1.51 g, mp 163—165 °C). The total yield of **8a** amounted to 10.21 g (73%). **8a**: *Anal.* Calcd for $C_9H_{10}ClNO_5S$ (M_r 279.7): C, 38.65; H, 3.60; Cl, 12.68; N, 5.01; S, 11.46. Found: C, 38.79; H, 3.63; Cl, 12.70; N, 5.08; S, 11.30. IR cm^{-1}: 3547, 3298, 1570. ^{1}H-NMR δ: 7.47 (3H, s), 7.17 (1H, s), 5.12 (1H, t, J=5 Hz), 4.50—4.00 (3H, m), 3.50 (2H, br).

7-Chloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2-ylmethanol Acetate (**8f**): mp 181—182 °C (from CH_2Cl_2–ether). *Anal.* Calcd for $C_{11}H_{12}ClNO_6S$ (M_r 321.737): C, 41.06; H, 3.76; Cl, 11.02; N, 4.35; S, 9.97. Found: C, 40.99; H, 3.70; Cl, 11.43; N, 4.35; S, 9.91. IR cm^{-1}: 3465, 3258, 1748, 1732. ^{1}H-NMR δ: 7.43 (1H, s), 7.40 (2H, br, SO_2NH_2), 7.16 (1H, s), 2.05 (3H, s, $OCOCH_3$).

7,8-Dichloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (**8b**): mp 234—235 °C (from acetone, yield 74%). *Anal.* Calcd for $C_9H_9Cl_2NO_5S$ (M_r 314.15): C, 34.41; H, 2.89, Cl, 22.57, N, 4.46; S, 10.21. Found: C, 34.45; H, 2.83; Cl, 22.43; N, 4.37; S, 10.47. IR cm^{-1}: 3510, 3340, 3205, 3085, 1566. ^{1}H-NMR δ: 7.44 (1H, s), 8.00—7.00 (2H, br, SO_2NH_2), 4.50—4.00 (3H, m), 3.67 (2H, d, J=5 Hz), 3.28 (1H, br, OH).

7-Phenoxy-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (**8c**): mp 140.5 °C (from ether, yield 11.5%). *Anal.* Calcd for $C_{15}H_{15}NO_6S$ (M_r 337.35): C, 53.41; H, 4.48; N, 4.15; S, 9.50. Found: C, 53.40; H, 4.49; N, 4.15; S, 9.71. IR cm^{-1}: 3560, 3419, 3360, 3312, 3260, 1566. ^{1}H-NMR δ: 7.32 (1H, s), 6.38 (1H, s), 7.25 (5H, br), 5.08 (1H, t,

$J=6$ Hz), 4.18 (3H, br), 3.60 (2H, t, $J=6$ Hz).

7-Chloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2-ylmethanol Methyl Ether (**8d**): mp 181.5—182 °C (from ether, yield 73%). *Anal.* Calcd for $C_{10}H_{12}ClNO_5S$ (M_r 293.725): C, 40.89; H, 4.12; Cl, 12.07; N, 4.77; S, 10.92. Found: C, 41.04; H, 4.06; Cl, 12.21; N, 4.75; S, 10.88. IR cm^{-1}: 3351, 3240, 1609, 1577. ^{1}H-NMR δ: 7.43 (1H, s), 7.17 (1H, s), 7.40 (2H, br, SO_2NH_2), 4.55—3.88 (3H, br), 3.62 (2H, d, $J=5$ Hz), 3.34 (3H, s, OCH_3).

7-Chloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2-ylmethanol Ethyl Ether (**8e**): mp 173—175 °C (from acetone–EtOH, yield 67%). *Anal.* Calcd for $C_{11}H_{14}ClNO_5S$ (M_r 307.752): C, 42.93; H, 4.59; Cl, 11.52; N, 4.55; S, 10.42. Found: C, 42.96; H, 4.51; Cl, 11.54; N, 4.54; S, 10.61. IR cm^{-1}: 3380, 3270, 1575. ^{1}H-NMR δ: 7.42 (1H, s), 7.15 (1H, s), 7.40 (2H, br, SO_2NH_2), 4.55—3.88 (3H, br), 3.62 (2H, d, $J=5$ Hz), 3.50 (2H, q, $J=7$ Hz), 1.12 (3H, t, $J=7$ Hz).

7,8-Dichloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2-ylmethanol Acetate (**8g**): mp 202—203 °C (acetone–ether). *Anal.* Calcd for $C_{11}H_{11}Cl_2NO_6S$ (M_r 356.184): C, 37.09; H, 3.11; Cl, 19.91; N, 3.93; S, 9.00. Found: C, 37.09; H, 3.02; Cl, 19.80; N, 3.81; S, 8.95. IR (Nujol) cm^{-1}: 3380, 3310, 3270, 1738, 1715. ^{1}H-NMR δ: 7.60 (2H, br, SO_2NH_2), 7.47 (1H, s), 2.05 (3H, s).

7-Chloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-3-ylmethanol (**11a**): mp 159—160 °C (from EtOH, yield 78%). *Anal.* Calcd for $C_9H_{10}ClNO_5S$ (M_r 279.698): C, 38.65; H, 3.60; Cl, 10.68; N, 5.01; S, 11.49. Found: C, 38.68; H, 3.49; Cl, 12.97; N, 4.92; S, 11.35. IR cm^{-1}: 3470, 3370, 3190, 3090, 1601. ^{1}H-NMR δ: 7.42 (3H, s, $SO_2NH_2+C_5$-H), 7.12 (1H, s), 5.33—4.73 (1H, br, OH), 4.57—4.00 (3H, br), 3.75—3.50 (2H, br).

7-Chloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-3-ylmethanol Acetate (**11b**): mp 170—173 °C (from EtOH). *Anal.* Calcd for $C_{11}H_{12}ClNO_6S$ (M_r 321.735): C, 41.07; H, 3.76; Cl, 11.02; N, 4.35; S, 9.97. Found: C, 41.24; H, 3.66; Cl, 11.26; N, 4.38; S, 9.85. IR cm^{-1}: 3380, 3260, 1717, 1609. ^{1}H-NMR δ: 7.45 (1H, s), 7.42 (2H, br, SO_2NH_2), 7.17 (1H, s), 4.67—3.93 (5H, br), 2.05 (3H, s, $OCOCH_3$).

Preparation of 6-Sulfamoyl-2,3-dihydro-1,4-benzodioxin-2(or 3)-carboxylic Acids (9 and 12)

7-Chloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (9a)——A stirred mixture of **8a** (2.00 g) and KOH (800 g) in H_2O (20 ml) was treated with $KMnO_4$ (1.50 g) under cooling on an ice bath. The reaction mixture was allowed to stand overnight at 0 °C. Next, it was diluted with water, and the resulting precipitate was removed by filtration. The filtrate was acidified with concentrated HCl and extracted with AcOEt. The neutral fraction (**8a**) (640 mg) and the acidic one (**9a**) (1520 mg) were separated by treating the organic layer with saturated $NaHCO_3$. Recrystallization of the product in the neutral fraction from ether gave the starting material (**8a**) (600 mg, mp 168—170 °C, yield 30%). The acidic fraction afforded the carboxylic acid (**9a**) (1260 mg, mp 208—210 °C, yield 60%) by recrystallization from benzene. *Anal.* Calcd for $C_9H_8ClNO_6S$ (M_r 293.681): C, 36.81; H, 2.75; Cl, 12.07; N, 4.77; S, 10.92. Found: C, 36.76; H, 2.63; Cl, 12.27; N, 4.07; S, 10.82. IR cm^{-1}: 3425, 3313,1742, 1729, 1607. ^{1}H-NMR δ: 7.38 (1H, s), 7.20 (1H, s), 7.38 (2H, br, NH_2), 5.15 (1H, t, $J=3$ Hz), 4.71—4.15 (3H, br).

7,8-Dichloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (**9b**): mp 208—211 °C (from benzene–CH_2Cl_2, yield 91.4%). *Anal.* Calcd for $C_9H_7Cl_2NO_6S$ (M_r 328.130): C, 32.94; H, 2.15; Cl, 21.61; N, 4.27; S, 9.77. Found: C, 32.69; H, 2.29; Cl, 22.25; N, 4.07; S, 9.77. IR cm^{-1}: 3380, 3263, 1750. ^{1}H-NMR δ: 7.62 (2H, br, SO_2NH_2), 7.43 (1H, s), 5.43 (1H, t, $J=3$ Hz), 4.47 (2H, dd, $J=12$, 3 Hz).

7-Phenoxy-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (**9c**): mp 218—219.5 °C (from ether, yield 89.4%). *Anal.* Calcd for $C_{15}H_{13}NO_7S$ (M_r 351.33): C, 51.28; H, 3.73; N, 3.99; S, 9.13. Found: C, 51.49; H, 3.69; N, 3.77; S, 8.63. IR cm^{-1}: 3418, 3300, 1751, 1720, 1616. ^{1}H-NMR δ: 7.30 (1H, s), 7.20 (5H, br, PhO), 6.45 (1H, s), 5.10 (1H, m), 4.37 (2H, m).

7-Chloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-3-carboxylic Acid (**12**): mp 211—213 °C (from MeOH–ether, yield 78%). *Anal.* Calcd for $C_9H_8ClNO_6S$ (M_r 293.681): C, 36.81; H, 2.75; Cl, 12.07; N, 4.77; S, 10.92. Found: C, 36.97; H, 2.83; Cl, 11.89; N, 4.73; S, 10.62. IR cm^{-1}: 3318, 3240, 1740, 1604. ^{1}H-NMR δ: 7.48 (1H, s), 7.15 (1H, s), 7.45 (2H, br, SO_2NH_2), 5.17 (1H, t, $J=3$ Hz), 4.72—4.17 (3H, br).

Preparation of 7,8-Dichloro 2-Substituted 5-Sulfamoyl-2,3-dihydro-1,4-benzodioxin

2-Acetoxymethyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin 5(and 6)-Sulfonyl Chlorides (14 and 15)——Chlorosulfonic acid (14 ml) was added dropwise to a mixture of **13** (5.954 g) and $SOCl_2$ (35 ml) under cooling by an ice bath. After being stirred at room temperature for 2 h, the reaction maixture was poured into ice water and extracted with ether–AcOEt. The residue (8.37 g) obtained from the extract was recrystallized from ether to give both crystals of the 6-sulfonyl chloride (**15**) (1.75 g, mp 136—139 °C) and a crystalline residue (6.482 g). Chromatography of this crystalline residue on a Lobar column B with benzene/acetone (25 : 1) gave a fraction (4.29 g) with a low *Rf* and a polar farction (0.66 g) with a higher *Rf*. Recrystallization of the first fraction from ether–hexane afforded the 5-sulfonyl chloride (**14**) (4.05 g, mp 123—124 °C, 50.1%). Recrystallization of the polar fraction from ether–hexane gave the 6-sulfonyl chloride (**15**) (0.563 g, mp 142—145 °C), total yield, 28.2%. **14**: *Anal.* Calcd for $C_{11}H_9Cl_3O_6S$ (M_r 375.618): C, 35.17; H, 2.42; Cl, 28.32; S, 8.54. Found: C, 35.00; H, 2.59; Cl, 28.22; S, 8.40. IR cm^{-1}: 1744, 1580. ^{1}H-NMR ($CDCl_3$) δ: 7.66 (1H, s), 4.73—4.13 (5H, m), 2.11 (3H, s, $OCOCH_3$). **15**: *Anal.* Calcd for $C_{11}H_9Cl_3O_6S$ (M_r 375.618): C, 35.17: H, 2.42; Cl, 28.32; S, 8.54. Found: C, 35.14; H, 2.57; Cl, 28.58; S, 8.38. IR cm^{-1}: 1747, 1585. ^{1}H-NMR ($CDCl_3$) δ: 7.68 (1H, s), 4.73—4.00 (5H, m), 2.11 (3H, s, $COCH_3$).

Preparation of 7,8-Dichloro-5(or 6)-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2-ylmethanols (16 and 8) and Carboxylic

TABLE III. 7,8-Dichloro-5(or 6)-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2-ylmethanols

Compound No.	SO_2R (5) R	mp (°C) (Solv.)	Yield (%)	Analysis (%) Calcd (Found) C	H	Cl	N	S	IR (Nujol) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ
16a	NH_2	172—174 (Acetone–Et_2O)	95.0	$C_9H_9Cl_2NO_5S$ (M_r 314.147) 34.41 (34.15)	2.89 (2.88)	22.57 (22.24)	4.46 (4.46)	10.21 (10.20)	3300, 3240, 1566	8.00—6.50 (2H, br), 7.41 (1H, s), 4.64—4.04 (3H, m), 3.71 (2H, d, J=5), 3.29 (1H, br)
16b	NMe_2	169—172 (Acetone–Et_2O)	92.0	$C_{11}H_{13}Cl_2NO_5S$ (M_r 342.201) 38.61 (38.48)	3.83 (3.86)	20.72 (20.05)	4.09 (4.13)	9.37 (9.36)	3540, 1564	7.39 (1H, s), 5.13 (1H, t, J=5), 4.58—4.13 (3H, m), 3.68 (1H, t, J=5), 2.73 (6H, s)
16c	NEt_2	84—88 (CH_2Cl_2–hexane)	90.0	$C_{13}H_{17}Cl_2NO_5S$ (M_r 370.255) 42.17 (42.06)	4.63 (4.55)	19.15 (19.22)	3.78 (3.86)	8.66 (8.79)	3500, 1560	7.58 (1H, s), 4.57—4.14 (3H, m), 3.92 (2H, t, J=5), 3.32 (2H, q, J=7), 2.31 (1H, t, J=5), 1.12 (3H, t, J=7)
16d		141—144 (Hexane)	95.0	$C_{14}H_{17}Cl_2NO_5S$ (M_r 382.266) 43.99 (43.81)	4.48 (4.53)	18.55 (18.63)	3.66 (3.71)	8.39 (8.29)	3590, 3100, 1567	7.54 (1H, s), 4.53—4.14 (3H, m), 3.95 (2H, br), 3.18 (4H, br), 2.33 (1H, br), 1.55 (6H, br)
16e		154—157 (Et_2O)	97.0	$C_{13}H_{15}Cl_2NO_5S$ (M_r 368.239) 42.40 (42.18)	4.11 (4.11)	19.26 (19.17)	3.80 (3.54)	8.71 (8.56)	3420, 1580, 1565	7.58 (1H, s), 4.57—4.13 (3H, m), 3.93 (2H, br), 3.43—3.27 (4H, m), 2.35 (1H, br), 1.92—1.77 (4H, m)
16f	N(Me)Ph	Oil	96.0	$C_{16}H_{15}Cl_2NO_5S$ (M_r 404.272) 47.54 (46.94)	3.74 (3.87)	17.54 (17.64)	3.46 (3.51)	7.97 (7.74)	[a] 3610, 1597	7.45 (1H, s), 7.25 (5H, m), 4.30—3.80 (5H, m), 3.30 (3H, s), 2.25 (1H, br)
16g	$N(Me)CH_2Ph$	108—111 (Et_2O)	89.8	$C_{17}H_{17}Cl_2NO_5S$ (M_r 418.299) 48.81 (48.48)	4.10 (4.02)	16.95 (17.01)	3.35 (3.35)	7.66 (7.45)	3530, 1565	7.61 (1H, s), 7.28 (5H, s), 4.53—4.10 (3H, m), 4.31 (2H, s), 3.95 (2H, br), 2.73 (3H, s), 2.23 (1H, br)
16h	NH(Me)	168—170 (CH_2Cl_2–Et_2O)	85.0	$C_{10}H_{11}Cl_2NO_5S$ (M_r 328.174) 36.60 (36.53)	3.38 (3.42)	21.61 (21.72)	4.27 (4.23)	9.77 (9.61)	3570, 3290, 1565	[b] 7.48 (1H, s), 6.30 (1H, br), 4.67—4.20 (4H, m), 3.92 (2H, t, J=5), 2.60 (3H, d, J=5)
16i	N(Me)Et	84—86 (Et_2O–hexane)	90.1	$C_{12}H_{15}Cl_2NO_5S$ (M_r 356.228) 40.46 (40.34)	4.24 (4.19)	19.91 (19.71)	3.93 (3.97)	9.00 (8.82)	3510, 1560	7.59 (1H, s), 4.57—4.18 (3H, m), 3.94 (2H, t, J=5), 3.25 (2H, q, J=7), 2.86 (3H, s), 2.28 (1H, t, J=5), 1.15 (3H, t, J=7)
16j	N(Me)Bu	Oil	99.2	$C_{14}H_{19}Cl_2NO_5S$ (M_r 384.282) 43.76 (43.26)	4.98 (4.99)	18.45 (18.50)	3.65 (3.67)	8.34 (8.20)	[a] 2970, 1566	7.58 (1H, s), 4.57—4.17 (3H, m), 3.94 (2H, br), 3.11 (2H, t, J=7), 2.83 (3H, s), 2.38 (1H, b), 1.87—1.20 (4H, m), 0.91 (3H, t, J=7)
8h	NMe_2 (6)	108—110 (CH_2Cl_2–Et_2O)	95.0	$C_{11}H_{13}Cl_2NO_5S$ (M_r 342.201) 38.61 (38.41)	3.83 (3.85)	20.72 (20.62)	4.09 (4.12)	9.37 (9.31)	3540, 1564	[c] 7.40 (1H, s), 5.14 (1H, t, J=5), 4.53—4.03 (3H, m), 3.70 (2H, t, J=5), 2.79 (6H, s)
8i	NEt_2 (6)	104—106 (CH_2Cl_2–PE)	75.0	$C_{13}H_{17}Cl_2NO_5S$ (M_r 370.255) 42.17 (42.20)	4.63 (4.53)	19.15 (19.33)	3.78 (3.77)	8.66 (8.65)	3500, 3400, 1562	7.62 (1H, s), 4.47—4.08 (3H, m), 3.92 (2H, t, J=5), 3.33 (4H, q, J=8), 2.19 (1H, t, J=5), 1.12 (3H, t, J=8)

Coupling constants (J) are given in Hz. *a*) In $CHCl_3$. *b*) In acetone-d_6. *c*) In DMSO-d_6.

TABLE IV. 7,8-Dichloro-5(or 6)-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acids

Compound No.	SO_2R (5) R	mp (°C) (Solv.)	Yield (%)	Analysis (%) Calcd (Found)					IR (Nujol) cm^{-1}	^{1}H-NMR (acetone-d_6) δ
				C	H	Cl	N	S		
17a	NH_2	210—212 (Acetone–CH_2Cl_2)	77.8	$C_9H_7Cl_2NO_6S$ (M_r 328.130)					3340, 3260, 1745, 1714	[a] 7.60—7.10 (2H, br), 7.43 (1H, s), 5.36 (1H, t, J=3), 4.73—4.27 (3H, m)
				32.94 (32.76)	2.15 (2.54)	21.61 (22.26)	4.27 (4.12)	9.77 (9.53)		
17b	NMe_2	242—245 (Acetone–CH_2Cl_2)	85.8	$C_{11}H_{11}Cl_2NO_6S$ (M_r 356.184)					3270, 1770	7.48 (1H, s), 7.10—6.10 (1H, br), 5.36 (1H, t, J=3), 4.88—4.43 (2H, m), 2.78 (6H, s)
				37.09 (36.84)	3.11 (3.16)	19.91 (20.12)	3.93 (3.90)	9.00 (8.84)		
17c	NEt_2	170—172 (Acetone–CH_2Cl_2)	78.1	$C_{13}H_{15}Cl_2NO_6S$ (M_r 384.238)					3100, 1760, 1582	7.53 (1H, s), 7.20—6.00 (1H, br), 5.35 (1H, t, J=3), 4.90—4.40 (2H, m), 3.32 (4H, q, J=7), 1.07 (6H, t, J=7)
				40.64 (40.57)	3.94 (4.07)	18.46 (18.73)	3.65 (3.67)	8.34 (8.38)		
17d		199—200 (Acetone–Et_2O)	78.9	$C_{14}H_{15}Cl_2NO_6S$ (M_r 396.249)					1740, 1584	7.47 (1H, s), 6.70—5.80 (1H, br), 5.36 (1H, t, J=3), 4.87—4.42 (2H, m), 3.16 (4H, br), 1.52 (6H, br)
				42.44 (42.53)	3.82 (3.87)	17.90 (17.61)	3.53 (3.49)	8.09 (7.99)		
17e		176—179 (CH_2Cl_2–hexane)	91.8	$C_{13}H_{13}Cl_2NO_6S$ (M_r 382.222)					1740, 1583	8.90—8.10 (1H, br), 7.52 (1H, s), 5.38 (1H, t, J=3), 4.91—4.44 (2H, m), 3.43—3.17 (4H, m), 1.88—1.73 (4H, m)
				40.85 (40.65)	3.43 (3.53)	18.55 (18.84)	3.66 (3.42)	8.39 (8.17)		
17f	NH(Me)	249—252 (Et_2O–hexane)	88.0	$C_{10}H_9Cl_2NO_6S$ (M_r 342.157)					3520, 3310, 1743	8.40—7.30 (1H, br), 7.51 (1H, s), 6.60—6.10 (1H, br), 5.36 (1H, t, J=3), 4.86—4.43 (2H, m), 2.55 (3H, d, J=5)
				35.10 (35.31)	2.65 (2.89)	20.73 (20.57)	4.09 (4.04)	9.37 (9.12)		
17g	N(Me)Ph	Oil	93.2	$C_{16}H_{13}Cl_2NO_6S$ (M_r 418.255)					[b] 3500, 1740, 1590	7.46 (1H, s), 7.30—7.07 (5H, m), 6.47 (1H, br), 4.98 (1H, t, J=3), 4.43—4.00 (2H, m), 3.27 (3H, s)
				45.95 (45.72)	3.13 (3.66)	16.95 (16.64)	3.35 (3.34)	7.67 (7.24)		
17h	$N(Me)CH_2Ph$	169—171 (CH_2Cl_2–hexane)	86.4	$C_{17}H_{15}Cl_2NO_6S$ (M_r 432.282)					1740, 1713, 1567	7.90—6.20 (1H, br), 7.56 (1H, s), 7.32 (5H, br), 5.38 (1H, t, J=3), 4.92—4.46 (2H, m), 4.35 (2H, s), 2.70 (3H, s), 2.70 (3H, s)
				47.23 (46.88)	3.50 (3.62)	16.40 (16.57)	3.24 (3.37)	7.42 (7.24)		
17i	N(Me)Et	168—171 (Et_2O–hexane)	88.6	$C_{12}H_{13}Cl_2NO_6S$ (M_r 370.211)					3200, 1773, 1572	9.30—8.20 (1H, br), 7.50 (1H, s), 5.35 (1H, t, J=3), 4.87—4.43 (2H, m), 3.21 (2H, q, J=7), 2.82 (3H, s), 1.07 (3H, t, J=7)
				38.93 (38.96)	3.54 (3.73)	19.16 (18.97)	3.78 (3.96)	8.66 (8.43)		
17j	N(Me)Bu	152—154 (CH_2Cl_2–hexane)	91.6	$C_{14}H_{17}Cl_2NO_6S$ (M_r 398.265)					1740, 1710, 1570	8.80—7.20 (1H, br), 7.51 (1H, s), 5.35 (1H, t, J=3), 4.87—4.43 (2H, m), 3.14 (2H, q, J=8), 2.79 (3H, s), 1.60—1.12 (4H, m), 0.88 (3H, t, J=8)
				42.22 (41.89)	4.30 (4.23)	17.81 (17.59)	3.52 (3.64)	8.05 (7.94)		
17k	NMe_2 {$COOCH_2$-COOH (2)}	149—151 (Et_2O)	98.9	$C_{13}H_{13}Cl_2NO_8S$ (M_r 414.220)					1760, 1730, 1577	7.20—6.00 (1H, br), 7.50 (1H, s), 5.49 (1H, t, J=3), 4.90—4.47 (2H, m), 4.78 (2H, s), 2.78 (6H, s)
				37.70 (37.81)	3.16 (3.27)	17.12 (17.07)	3.38 (3.38)	7.74 (7.56)		
9d	NMe_2 (6)	219—222 (Acetone–CH_2Cl_2)	87.4	$C_{11}H_{11}Cl_2NO_6S$ (M_r 356.184)					1730, 1556	7.48 (1H, s), 7.00—6.00 (1H, br), 5.36 (1H, t, J=3), 4.80—4.36 (2H, m), 2.86 (6H, s)
				37.09 (36.83)	3.11 (3.21)	19.91 (20.02)	3.93 (3.92)	9.00 (8.83)		

a) In $CDCl_3$. *b*) In $CHCl_3$.

TABLE V. 7-Chloro-2(or 3)-alkylamino-6-sulfamoyl-2,3-dihydro-1,4-benzodioxins

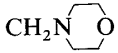
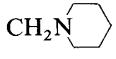
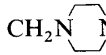
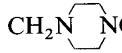
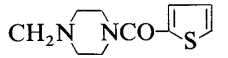
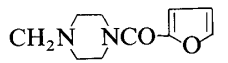
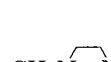
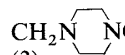
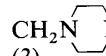
Compound No.	R (2)	mp (°C) (Solv.)	Yield (%)	Analysis (%) Calcd (Found) C	H	Cl	N	S	IR (Nujol) cm^{-1}	^{1}H-NMR (DMSO-d_6) δ
20a	CH_2NEt_2	128—131 (Et_2O)	73.0	$C_{13}H_{19}ClN_2O_4S$ (M_r 334.822) 46.63 (46.53)	5.72 (5.65)	10.59 (10.42)	8.37 (8.30)	9.58 (9.47)	3345, 1606, 1576	7.42 (1H, s), 7.37 (2H, br, SO_2NH_2), 7.10 (1H, s), 4.18 (3H, br), 2.53 (6H, br), 0.95 (6H, t, $J=7$)
20b	CH_2NHBut	233—235 (MeOH–CH_2Cl_2)	28.0	$C_{13}H_{19}ClN_2O_4S$ (M_r 334.822) 46.63 (46.55)	5.72 (5.51)	10.59 (10.80)	8.37 (8.29)	9.58 (9.60)	3340, 3295, 1574	7.43 (1H, s), 7.30 (3H, br, SO_2NH_2, NH), 7.14 (1H, s), 4.20 (3H, br), 2.73 (2H, br), 1.01 (9H, s)
20c		182—184 (Et_2O)	70.0	$C_{13}H_{17}ClN_2O_5S$ (M_r 348.805) 44.77 (44.83)	4.91 (5.09)	10.17 (10.22)	8.03 (8.05)	9.19 (9.01)	3320, 3210, 1606	7.42, 7.13 (each 1H, s), 7.38 (2H, br, SO_2NH_2), 4.67—3.87 (3H, br), 3.57 (4H, m)
20d		194—195 (Acetone–Et_2O)	70.0	$C_{14}H_{19}ClN_2O_4S$ (M_r 346.833) 48.47 (48.70)	5.52 (5.69)	10.22 (—)	8.08 (8.28)	9.24 (—)	3335, 3170, 1602	7.43 (3H, s, SO_2NH_2), 7.15 (1H, s)
20e		165—166 (Benzene)	62.0	$C_{14}H_{20}ClN_3O_4S \cdot 1/3\,C_6H_6$ (M_r 387.886) 49.54 (49.01)	5.72 (5.63)	9.14 (9.31)	10.83 (10.89)	8.27 (8.76)	3324, 1598	7.43, 7.15 (each 1H, s), 7.37 (2H, br, SO_2NH_2), 2.15 (3H, s)
20f		181—183 (Acetone–MeOH–Et_2O)	81.0	$C_{20}H_{24}ClN_3O_4S$ (M_r 437.946) 54.85 (54.48)	5.52 (5.66)	8.10 (7.87)	9.60 (9.33)	7.32 (7.82)	3360, 1576	7.42, 7.12 (1H, s), 7.27 (2H, br, SO_2NH_2), 4.55—3.83 (3H, br), 3.45 (2H, s, CH_2–Ph)
20g		206—208 (Acetone–MeOH–Et_2O)	73.0	$C_{19}H_{20}ClN_3O_5S_2$ (M_r 457.951) 47.21 (47.28)	4.40 (4.42)	7.74 (7.93)	9.18 (9.11)	14.00 (13.75)	3160, 3090, 1596	7.78—7.00 (5H, br), 7.40 (2H, br, SO_2NH_2), 4.67—3.87 (3H, br), 3.63 (4H, t, $J=5$), 2.75—2.33 (6H, br)
20h		199—201 (MeOH–Et_2O)	77.0	$C_{18}H_{20}ClN_3O_6S$ (M_r 441.890) 48.93 (48.47)	4.56 (4.57)	8.02 (8.31)	9.51 (9.26)	7.26 (7.46)	1626, 1576	7.78, 7.13 (each 1H, s), 7.42 (2H, br, SO_2NH_2), 7.40 (1H, br), 6.39 (1H, br), 6.52 (1H, br), 4.23 (3H, br), 3.63 (4H, t, $J=5$), 2.55 (6H, br)
20i	 (7,8-diCl)	234—236 (Acetone–Et_2O)	71.0	$C_{14}H_{19}Cl_2N_3O_4S$ (M_r 396.297) 42.43 (42.20)	4.83 (4.84)	17.89 (17.68)	10.60 (10.29)	8.09 (7.94)	3330, 1566	7.45 (3H, s, SO_2NH_2), 4.67—3.83 (3H, br), 2.15 (3H, s, N–CH_3)
21a	 (3)	194—196 (Benzene–Et_2O)	62.0	$C_{14}H_{20}ClN_3O_4S$ (M_r 361.848) 46.47 (46.46)	5.57 (5.55)	9.80 (9.93)	11.61 (11.40)	8.86 (8.79)	3351, 1575	7.43 (2H, s, SO_2NH_2), 7.42, 7.13 (each 1H, s), 4.57—3.83 (3H, br), 2.15 (3H, s, N–CH_3)
21b	 (3)	148—150 (CH_2Cl_2–Et_2O)	76.0	$C_{20}H_{24}ClN_3O_4S$ (M_r 437.946) 54.85 (54.93)	5.52 (5.57)	8.10 (8.40)	9.60 (9.30)	7.32 (7.17)	3340, 1606, 1576	7.40, 7.12 (each 1H, s), 7.27 (7H, s, SO_2NH_2, Ph), 3.45 (2H, s)

TABLE VI. 7-Chloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2(or 3)-carboxyamides

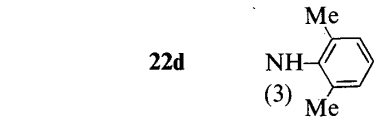
Compound No.	COR (2) R	mp (°C) (Solv.)	Yield (%)	Analysis (%) Calcd (Found)					IR (Nujol) cm^{-1}	^{1}H-NMR (DMSO-d_6) δ
				C	H	Cl	N	S		
22a	NEt_2	183—186 (Et_2O)	67.0	$C_{13}H_{17}ClN_2O_5S$ (M_r 348.805)					3368, 3228, 1633, 1575	7.40, 7.17 (each 1H, s), 7.40 (2H, s, SO_2NH_2), 5.28 (1H, br), 4.35 (2H, br), 3.35 (4H, t, $J=8$), 1.12 (6H, t, $J=8$)
				44.77	4.91	10.17	8.03	9.19		
				(44.65	4.80	10.18	7.95	9.07)		
22b	$NHBu^t$	238—239 (MeOH)	33.0	$C_{13}H_{17}ClN_2O_5S$ (M_r 348.805)					3380, 3200, 1670, 1580	7.62 (1H, br, NH), 7.40, 7.22 (each 1H, s), 7.40 (2H, br, SO_2NH_2), 4.80 (1H, br), 4.32 (2H, br), 1.27 (9H, s)
				44.76	4.91	10.17	8.03	9.19		
				(44.62	5.08	10.43	8.04	9.36)		
22c		250—252 (Acetone–Et_2O–MeOH)	74.0	$C_{17}H_{17}ClN_2O_5S$ (M_r 396.849)					3340, 3242, 1683	9.52 (1H, br, NH), 7.45, 7.25 (each 1H, s), 7.45 (2H, s, SO_2NH_2), 7.05 (3H, s), 5.28 (1H, t, $J=3$), 4.53 (2H, br), 2.05 (6H, s)
				51.45	4.32	8.93	7.06	8.08		
				(51.52	4.31	8.99	6.95	8.09)		
22d		217—218 (MeOH–Et_2O)	74.0	$C_{17}H_{17}ClN_2O_5S$ (M_r 396.849)					3360, 3270, 3230, 1665	7.67, 7.18 (each 1H, s), 7.43 (2H, br, SO_2NH_2), 7.03 (3H, s), 5.23 (1H, t, $J=3$), 4.53 (2H, t, $J=3$), 2.03 (6H, s)
				51.45	4.32	8.93	7.06	8.08		
				(51.58	4.29	9.18	6.97	8.33)		

TABLE VII. 7-Chloro(or 7,8-dichloro)-2-(2-alkylamino-1-hydroxymethyl)-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin Derivatives

Compound No.	R (2)	mp (°C) (Solv.)	Yield (%)	Analysis (%) Calcd (Found)					IR (Nujol) cm^{-1}	^{1}H-NMR (pyridine-d_6) δ
				C	H	Cl	N	S		
23	$COCH_2Cl$	155—157 (AcOEt–Et_2O)	73.8	$C_{10}H_9Cl_2NO_5$ (M_r 326.158)					3375, 3270, 1722, 1604	[a] 7.50 (1H, s), 7.20 (1H, s), 6.57 (2H, br, SO_2NH_2), 5.31 (1H, t, $J=3$), 4.95—4.35 (4H, m)
				36.83	2.78	21.74	4.29	9.83		
				(36.78	3.00	21.44	4.35	9.63)		
24	$COCH_2Cl$ (7,8-diCl)	218—221 (Et_2O)	55.0	$C_{10}H_8Cl_3NO_5S$ (M_r 360.607)					3364, 3272, 1736, 1564	[b] 7.64 (2H, br), 7.45 (1H, s), 5.60 (1H, t, $J=3$), 4.83 (2H, d, $J=6$), 4.86—4.37 (2H, m)
				33.31	2.24	29.50	3.88	8.89		
				(33.52	2.51	29.78	3.77	8.58)		
25a	$CH(OH)CH_2Cl$	167—168 (Et_2O)	41.8	$C_{10}H_{11}Cl_2NO_5S$ (M_r 328.174)					3420, 3320, 3230, 3130, 3050, 1604	[a] 7.49 (1H, s), 7.07 (1H, s), 6.50 (2H, br, SO_2NH_2), 5.00 (1H, br, OH), 4.67—3.67 (6H, m)
				36.60	3.38	21.61	4.27	9.77		
				(36.59	3.54	21.71	4.48	9.47)		
25b	$CH(OH)CH_2Cl$	167—168 (Et_2O)	27.4	$C_{10}H_{11}Cl_2NO_5S$ (M_r 328.174)					3484, 3228, 3108, 1604	[a] 7.50 (1H, s), 7.06 (1H, s), 6.55 (2H, br, SO_2NH_2), 4.83 (1H, br, OH), 4.67—3.59 (6H, m)
				36.60	3.38	21.61	4.27	9.77		
				(36.68	3.33	21.75	4.22	9.69)		
26a	$CH(OH)CH_2Cl$ (7,8-diCl)	260—262 (Acetone–Et_2O)	27.2	$C_{10}H_{10}Cl_3NO_5S$ (M_r 362.623)					3500, 3408, 3312, 1565	9.10—8.10 (2H, br), 8.00—7.40 (1H, br), 7.98 (1H, s), 4.63—4.24 (4H, m), 4.20—3.87 (2H, m)
				33.12	2.78	29.33	3.86	8.84		
				(32.89	2.92	29.12	3.86	8.78)		
26b	$CH(OH)CH_2Cl$ (7,8-diCl)	181—184 (CH_2Cl_2)	32.7	$C_{10}H_{10}Cl_3NO_5S$ (M_r 362.623)					3404, 3244, 3092	9.18 (2H, br), 8.27—7.73 (1H, br), 7.99 (1H, s), 4.69—3.93 (6H, m)
				33.12	2.78	29.33	3.86	8.84		
				(33.05	2.89	28.92	3.83	8.83)		
27a	$CH(OH)CH_2NHPr^i$	170—172 (AcOEt–Et_2O)	53.6	$C_{13}H_{19}ClN_2O_5S$ (M_r 350.821)					3316, 3176, 3056, 2688, 1606, 1574	7.96 (1H, s), 7.10 (1H, s), 6.80—4.50 (4H, br, SO_2NH_2, NH, OH), 4.68—4.23 (3H, m), 4.22—3.97 (1H, m), 3.20—2.64 (3H, m), 1.03 (6H, s)
				44.51	5.46	10.11	7.99	9.14		
				(44.70	5.31	10.03	7.87	8.84)		

27b	$CH(OH)CH_2NHPr^i$	201—203 (AcOEt)	42.4	$C_{13}H_{19}ClN_2O_5S$ (M_r 350.821)					3500, 3364, 3320, 2596, 1603, 1574	7.98, 7.04 (each 1H, s), 6.80—4.60 (4H, br, SO_2NH_2, NH, OH), 4.58—4.00 (3H, m), 3.01 (2H, d, $J=7$), 2.79 (1H, m), 1.03 (6H, d, $J=7$)
				44.51	5.46	10.11	7.99	9.14		
				(44.23	5.36	9.96	7.77	9.01)		
27c	$CH(OH)CH_2NHBu^t$	192—193 ($AcOEt–Et_2O$)	63.6	$C_{14}H_{21}ClN_2O_5S \cdot 1/4\,H_2O$ (M_r 371.352)					3456, 3320, 3196, 3084, 1605, 1574	8.03, 7.20 (each 1H, s), 4.98 (1H, br, NH), 4.65—4.34 (4H, m, SO_2NH_2, OH), 4.20—4.07 (1H, m), 3.15—2.89 (1H, m), 1.11 (9H, s)
				45.53	5.87	9.60	7.58	8.68		
				(45.75	5.74	9.70	7.28	8.57)		
27d	$CH(OH)CH_2NHBu^t$	188—190 (AcOEt)	40.0	$C_{14}H_{21}ClN_2O_5S$ (M_r 364.848)					3040, 3208, 3080	8.04, 7.11 (each 1H, s), 4.97 (1H, br, NH), 4.60—4.31 (4H, br, SO_2NH_2, NH, OH), 4.20—4.08 (1H, m), 3.04 (1H, d, $J=3$), 1.11 (9H, s)
				46.09	5.80	9.72	7.68	8.79		
				(45.81	5.69	9.66	7.51	8.57)		
27e	$CH(OH)CH_2NEt_2$	134—135 (AcOEt)	35.3	$C_{14}H_{21}ClN_2O_5S$ (M_r 364.848)					3308, 3288, 3216, 3100, 2676, 1599	9.10 (2H, br), 8.08, 7.20 (each 1H, s), 4.98 (1H, br), 4.70—4.58 (1H, m), 4.44—4.33 (2H, m), 4.13 (1H, q, $J=3$), 2.91—2.66 (2H, qq, $J=3$, 4), 2.58 (4H, q, $J=7$), 0.98 (6H, t, $J=7$)
				46.09	5.80	9.72	7.68	8.79		
				(46.04	5.82	9.96	7.56	9.09)		
27f	$CH(OH)CH_2NEt_2$	179—182 (AcOEt)	80.0	$C_{14}H_{21}ClN_2O_5S$ (M_r 364.848)					3364, 3272, 1606, 1574	9.07 (2H, br), 8.06 (1H, s), 7.18 (1H, s), 4.99 (1H, br, OH), 4.56—4.40 (3H, m), 4.10 (1H, t, $J=6$), 3.00—2.76 (2H, m), 2.55 (4H, q, $J=7$), 0.98 (6H, t, $J=7$)
				46.09	5.80	9.72	7.68	8.79		
				(46.03	5.63	9.82	7.61	8.71)		
28a	$CH(OH)CH_2NHPr^i$ (7,8-diCl)	195—198 (AcOEt)	63.1	$C_{13}H_{18}Cl_2N_2O_5S$ (M_r 385.270)					3600, 3344, 3096, 1563	7.99 (1H, s), 7.50—4.90 (4H, br), 4.62—4.09 (4H, m), 3.12 (2H, d, $J=7$), 2.95—2.68 (1H, m), 1.08 (3H, s), 1.03 (3H, s)
				40.53	4.71	18.41	7.27	8.32		
				(40.24	4.75	18.55	7.11	8.21)		
28b	$CH(OH)CH_2NHPr^i$ (7,8-diCl)	169—172 (iso-Pr_2O)	81.0	$C_{13}H_{18}Cl_2N_2O_5S$ (M_r 385.270)					3504, 3336, 1564	8.00 (1H, s), 7.10—4.80 (4H, br), 4.72—4.06 (4H, m), 3.27—2.65 (3H, m), 1.09 (3H, m), 1.02 (3H, m)
				40.53	4.71	18.41	7.27	8.32		
				(40.46	4.69	18.56	7.04	8.07)		

Pr^i, isopropyl; Bu^t, *tert*-butyl. *a*) In acetone-d_6. *b*) In DMSO-d_6.

Acids (17 and 9)

General Procedure——Step A: Amination of the 5(or 6)-sulfonyl chloride. An amine (5.05 mmol, 4 eq) was added to a solution of 2-acetoxymethyl-7,8-dichloro-2,3-dihydro-1,4-benzodioxin 5(or 6)-sulfonyl chloride (**14** or **15**) (480 mg) in acetone (5 ml) under cooling by an ice bath. After refluxing for 1 h, the reaction mixture was concentrated *in vacuo* and extracted with CH_2Cl_2. The residue obtained from the extract was recrystallized from an appropriate solvent, affording a pure substance.

Step B: Hydrolysis of the 2-acetoxymethyl 5(or 6)-sulfonamide. A mixture of the above product in EtOH (10 ml) and 1 N NaOH (5 ml) was refluxed for 10 min. The reaction mixture was concentrated *in vacuo*, and extracted with CH_2Cl_2 or AcOEt. The residue obtained from the extract was recrystallized from an appropriate solvent, giving the 2-hydroxymethyl sulfonamide (**16** or **8**). See Table III.

Step C: Oxidation of the 2-hydroxymethyl sulfonamide. The Jones reagent (1 ml) was added dropwise to a solution of **16** or **8** (450—500 mg) in acetone (20 ml) over 1 h, and then the reaction mixture was stirred at room temperature for 4—6 h until the strating material had disappeared on TLC. After the reaction had reached completion, methanol was added to the reaction mixture until its color changed from red to green. The resulting precipitate was removed by filtration, then the filtrate was concentrated *in vacuo*, mixed with water, and extracted with EtOAc or ether. The residue obtained from the extract was recrystallized from an appropriate solvent to afford the corresponding carboxylic acid (**17** or **9**). See Table IV.

Preparation of 7-Chloro-2(or 3)-chloromethyl-6-sulfamoyldihydrobenzodioxins (18 and 19)

7-Chloro-2-chloromethyl-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin (18a)——Thionyl chloride (1 ml) was added to a solution of 7-chloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (**8a**) (1.5 g) in dry pyridine (15 ml) under cooling on an ice bath, and then the reaction mixture was allowed to stand overnight at room temperature. After the excess thionyl chloride had been decomposed by adding water under cooling on an ice bath, the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with 2 N HCl, and H_2O, and dried over Na_2SO_4, then evaporated *in vacuo*. The residue (1.2 g) was passed through an SiO_2 column with CH_2Cl_2/AcOEt (10 : 1) to yield a product (1050 mg). Recrystallization from benzene gave **18a** (990 mg, mp 147—148 °C, as the first crop, and 135 mg, mp 141—143 °C, as the second crop, yield 70%). *Anal.* Calcd for $C_9H_9Cl_2NO_4S$ (M_r 298.15): C, 36.26; H, 3.04; Cl, 23.78; N, 4.70; S, 10.75. Found: C, 36.54; H, 2.91; Cl, 23.62; N, 4.82; S, 11.03. IR cm^{-1}: 3284, 3384. ^{1}H-NMR δ: 7.45 (1H, s), 7.18 (1H, s), 7.42 (2H, br, SO_2NH_2).

7,8-Dichloro-2-chloromethyl-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin (**18b**): mp 188—189 °C (from EtOH, yield 70%). *Anal.* Calcd for $C_9H_8Cl_3NO_4S$ (M_r 332.597): C, 32.50; H, 2.42; Cl, 31.98; N, 4.21; S, 9.64. Found: C, 32.73; H, 2.53; Cl, 30.98; N, 4.35; S, 9.77. IR cm^{-1}: 3375, 3265, 1602, 1591. ^{1}H-NMR δ: 7.58 (2H, br, SO_2NH_2), 7.48 (1H, s), 4.92—3.55 (5H, m).

2-Chloromethyl-7-phenoxy-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin (**18c**): mp 175—177 °C (from benzene–CH_2Cl_2, yield 76%). *Anal.* Calcd for $C_{15}H_{14}ClO_5S$ (M_r 355.79): C, 50.64; H, 3.97; N, 3.94. Found: C, 50.80; H, 3.71; N, 3.73. IR cm^{-1}: 3375, 3265, 1602, 1591. ^{1}H-NMR δ: 7.33 (1H, s), 7.18 (5H, br), 6.40 (1H, s), 4.32 (3H, m), 3.90 (2H, br).

7-Chloro-3-chloromethyl-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin (**19**): mp 132.5—135 °C (from benzene, yield 50%). *Anal.* Calcd for $C_9H_9Cl_2NO_4S$ (M_r 298.15): C, 36.26; H, 3.04; Cl, 23.78; N, 4.70; S, 10.75. Found: C, 36.51; H, 3.00; Cl, 23.60; N, 4.59; S, 10.78. IR cm^{-1}: 3340, 3250, 1605. ^{1}H-NMR δ: 7.47 (1H, s), 7.43 (2H, br, SO_2NH_2), 7.18 (1H, s), 4.67—4.08 (3H, br), 4.00—3.82 (2H, br).

Preparation of 2(or 3)-(Alkylamino)methyl-7-chloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin (20 or 21)——A mixture of the 2(or 3)-chloromethyl compound (**18** or **19**) (300 mg) and an amine (10—15 vol.) was heated at 100 °C for 24—48 h; if necessary, a sealed tube was used. The cooled reaction mixture was diluted with water and extracted with AcOEt. The residue obtained from the extract was purified by chromatography on SiO_2 or crystallization from an appropriate solvent to obtain the product as listed in Table V.

Preparation of 6-Sulfamoyl-2,3-dihydro-1,4-benzodioxin-2(or 3)-carboxyamides (22)——A stirred mixture of 7-chloro-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin-2(or 3)-carboxylic acid (**9a** or **12**), an amine (1.05 eq) and PCl_3 (5 eq) in chlorobenzene (6 ml) was heated at 100—130 °C on an oil bath for 8—18 h.[10] The product was obtained by conventional work-up. See Table VI.

Preparation of 2-(2-Alkylamino-1-hydroxyethyl)-7-chloro(or 7,8-dichloro)-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin (27 and 28)

1) 7-Chloro-2-chloroacetyl-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin (23)——A stirred mixture of 7-chloro-6-sulfamoyl dihydrobenzodioxin-2-carboxylic acid (**9a**) (2.20 g) and thionyl chloride (3 ml) in dry benzene (10 ml) and dry tetrahydrofuran (THF) (4 ml) was refluxed for 2.5 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in dry THF (4 ml), then the solution was added to a solution of diazomethane [prepared from nitrosomethylurea (6 g) in ether (60 ml) and aqueous 50% KOH (20 ml)] with stirring under cooling on an ice bath over 15 min. The mixture was stirred for an additional 15 min, then a solution of 2 N HCl/AcOEt was added. The resulting mixture was stirred for 30 min under cooling on an ice bath. After the reaction had reached completion, the mixture was extracted with AcOEt, and the extract was washed with aqueous $NaHCO_3$, dried over $MgSO_4$ and evaporated. The residue was passed through a Lobar column B with AcOEt/CH_2Cl_2 (2 : 3) and the eluate was

collected. Recrystallization of the product from AcOEt–ether afforded **23** (1.80 g, mp 155—157 °C, yield 73.8%). By the same procedure, 7,8-dichloro-2-chloroacetyl-6-sulfamoyl dihydrobenzodioxin (**24**) was obtained from **9b** in 55% yield.

2) 7-Chloro-2-(2-chloro-1-hydroxyethyl)-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin (25a and 25b)——Sodium borohydride (0.70 g, 18.9 mmol) was added portionwise to a mixture of **23** (5.30 g, 16.2 mM) in EtOH (106 ml) under cooling on an ice bath for 45 min and the reaction mixture was stirred for an additional 1.5 h at the same temperature, then concentrated *in vacuo*. The residue was diluted with aqueous NH_4Cl and extracted with AcOEt. The residue (5.32 g) obtained from this extract was separated on a Lobar column B with AcOEt/benzene/CH_2Cl_2 (1 : 1 : 1) and to give **25a** (2.23 g, mp 167—168 °C, from ether, yield 41.8%) with lower *Rf* and **25b** (1.46 g, mp 167—168 °C from ether, yield 27.4%) with higher *Rf*.

3) 2-(2-Alkylamino-1-hydroxyethyl)-7-chloro(or 7,8-dichloro)-6-sulfamoyl-2,3-dihydro-1,4-benzodioxin (27 and 28)——General Procedure: A mixture of **25** or **26** and NHR_1R_2 (5 vol.) in hexamethylphosphoramide (HMPA) (10 vol.) was stirred at 60 °C on an oil bath under an atmosphere of nitrogen for 20 h. The cooled reaction mixture was acidified with aqueous 20% HCl at pH 3 and extracted with AcOEt to remove the starting material. The water layer was adjusted to pH 10 with aqueous 20% NaOH and extracted with AcOEt. The extract was evaporated, and the residue was passed through a column of SiO_2 using $CHCl_3$ (to remove HMPA) and then AcOEt to obtain **27** or **28**. See Table VII.

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 in the afternoon (at approximately 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 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.

Antihypertensive Effect on Rats[11]——Male Wistar rats, six weeks old (120—140 g), were uninephrecotomized (one group, 6 rats). After one week, they were maintained on stock chow (Na: 2.4 mg/g) with 1% saline solution for drinking during the experimental period (3 weeks) and given desoxycorticosterone acetate (DOCA) at a dose of 15 mg/kg per week, while s.c. TCM (1% suspension of gum arabic) as the reference compound and a test sample were administered at a dose 0.2 mg/kg *p.o.* daily. The control group was orally administered 1% gum arabic alone. The systolic blood pressure of rats after warming (50 °C, 2 min) was measured on both the 8th day and 15th day after the administration. [A physiograph and electrosphygmomanometer (DMP-4B and PE-300, Narco Biosystems, Houston) were used to measure the blood pressure]. The antihypertensive effect was expressed by the relative ratio of potencies to that of TCM, which was taken as 100.

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