Synthetic Studies on Diuretics. 5-(3,3-*N*,*S*-Substituted-2-propenoyl)-2,3-dihydro-2-benzo[*b*]furancarboxylic Acids

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6,7-Dichloro-2,3-dihydro-2-benzo[*b*]furancarboxylic acid derivatives having a 3,3-*N*,*S*-disubstituted-2-propenoyl group at the 5-position were prepared by alkylation of 5-(thiocarbamoyl)acetyl derivatives of the 2,3-dihydro-2-benzo[*b*]furancarboxylic acid ester or by acetal exchange reaction of 5-[3,3-bis(alkylthio)-2-propenoyl] derivatives. Synthesis of 5-[4 and/or 5-(di)substituted-4-thiazolin-2-ylidene]acetyl-2,3-dihydro-2-benzo[*b*]furancarboxylic acids was also achieved by the reaction of 2-halo-1-methoxyethyl isothiocyanate with the 5-acetyl derivative in the presence of base or through sulfide contraction of 2-[((6,7-dichloro-2-methoxycarbonyl-2,3-dihydrobenzo[*b*]furan-5-yl)carbonyl)-methylthio]thiazolium bromide. Some of the compounds which were synthesized showed potent natriuretic activities in rats and mice. The structure–activity relationship is also discussed.

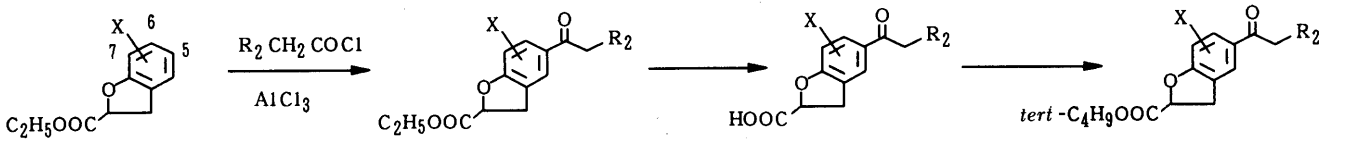
Keywords 6,7-dichloro-2,3-dihydro-2-benzo[*b*]furancarboxylic acid; α-oxoketene-*N*,*S*-acetal; β-oxothioamide; acetal exchange reaction; 2-halo-1-methoxyethyl isothiocyanate; sulfide contraction; thiazole synthesis; natriuretic activity; structure–activity relationship

Ethacrynic acid is a loop diuretic which shows a high ceiling character and a potent short-term activity.[1] It belongs to the phenoxyacetic acid diuretic family. The phenoxyacetic acid diuretics have been developed to uricosuric diuretics such as tienilic acid[2] and indacrinone.[3] These compounds relieve hyperuricemia caused by a urate-retaining side effect during antihypertensive therapy using diuretics. The basic phenoxyacetic acid structure substituted with an acyl group at the 4-position has been shown to be 5-acyl-2,3-dihydro-2-benzo[*b*]furancarboxylic acid, and many diuretic compounds having this structure have been reported.[1,4] We also reported on the synthesis and pharmacological characteristics of 6,7-dichloro-5-(*N*,*N*-dimethylsulfamoyl)-2,3-dihydro-2-benzo[*b*]furancarboxylic acid, S-8666, as a candidate uricosuric diuretic.[4e,5] Now we report on the syntheses and diuretic activities of the 2,3-dihydro-2-benzo[*b*]furancarboxylic acid derivatives having a 5-propenoyl (or its α-methyl derivative) moiety substituted with nitrogen or sulfur at the β position. As most compounds showing diuretic activity in this family have dichloro substitution at the 6 and 7 positions, derivatization was mainly done from 6,7-dichloro-2,3-dihydro-2-benzo[*b*]-furancarboxylic acid.

Chemistry Compounds used for this study and their saluretic activities in rats and mice are listed in Tables I—III. The synthetic pathways to 2,3-dihydro-2-benzo[*b*]-furancarboxylic acids having an α-oxoketene-*N*,*S*-acetal moiety at the 5-position are shown in Charts 1—9. Compounds **4a**, **4b** and **5**, which were used as starting materials, were obtained by the ester exchange reaction of the acylated products (**2a**,[6] **2b** and **3**) of **1a**[6] and **1b**. The use of *tert*-butyl esters led to stability against strong base at the 2-position compared with the use of ethyl esters (Chart 1).

Reaction of the *tert*-butyl esters (**4a**, **4b** and **5**) with methyl, ethyl and phenyl isothiocyanate in the presence of sodium hydride as a base, followed by alkylation of the resultant sodium salts of the β-oxothioamides (**8**) with alkyl halides (methyl iodide, propargyl bromide, allyl bromide and 1,2-dibromoethane) gave the *N*,*S*-acetal derivatives in a one-pot procedure.[7] Hydrolysis of the *tert*-butyl esters using trifluoroacetic acid (TFA) gave the free acids (**9a**, **9b**, **10**, **11** and **13**—**17**). The thioamide compound (**18**) was obtained by quenching the sodium salt (**8**, R_2=H, R_4=Me), which precipitated from the reaction mixture, with aqueous ammonium chloride. Reaction of propargyl bromide with **18** followed by hydrolysis gave **12**. The geometry of **9a**, **9b** and **10**—**16** is concluded to be of the *E*-form (which can form intramolecular hydrogen bonds) based on the following findings.

The infrared (IR) spectra of the *tert*-butyl esters of **9a**, **9b**, and **10**—**16** showed a weak broad NH absorption band at 3100—3200 cm^{-1} attributable to the intramolecular hydrogen bond in a dilute chloroform ($CHCl_3$) solution and no free NH or enolic OH absortpion band. The proton magnetic resonance (^{1}H-NMR) spectrum of the *tert*-butyl ester of **9a** showed a broad signal attributable to NH at δ 11.38 in a chloroform-*d* ($CDCl_3$) solution coupled with NCH_3 protons appearing at δ 3.06 as a doublet. A similar NH proton was observed in the *tert*-butyl ester of **14** at δ 11.40—11.87 in various solvents (benzene-d_6, $CDCl_3$, acetonitrile-d_3, acetone-d_6) regardless of the polarity. According to Dudek *et al.*[8] and Boberg and Gentzkow,[9] these low field signals are due to NH protons forming intramolecular hydrogen bonds. *tert*-Butyl esters of other com-



1a: X = 6,7-di-Cl
1b: X = 7-CH_3

2a: X = 6,7-di-Cl, R_2 = H
2b: X = 7-CH_3, R_2 = H
3 : X = 6,7-di-Cl, R_2 = CH_3

6a: X = 6,7-di-Cl, R_2 = H
6b: X = 7-CH_3, R_2 = H
7 : X = 6,7-di-Cl, R_2 = CH_3

4a: X = 6,7-di-Cl, R_2 = H
4b: X = 7-CH_3, R_2 = H
5 : X = 6,7-di-Cl, R_2 = CH_3

Chart 1

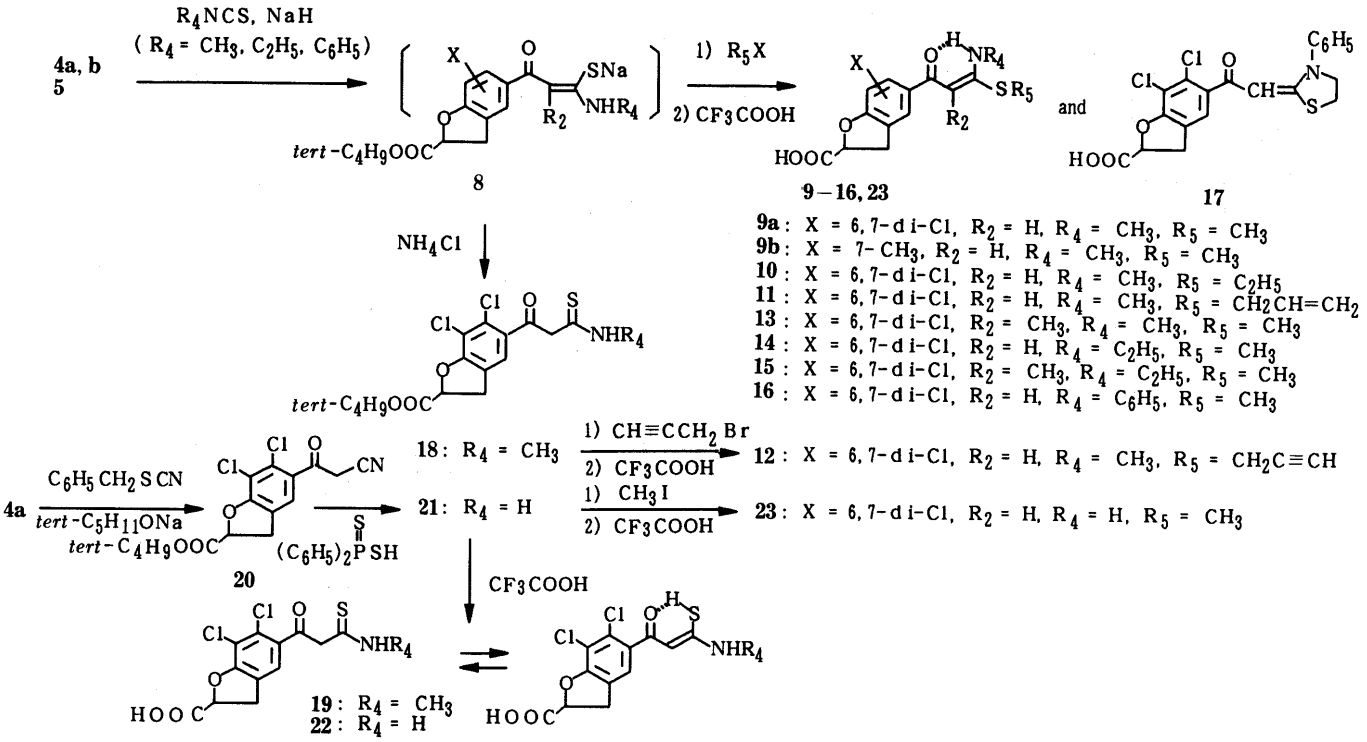
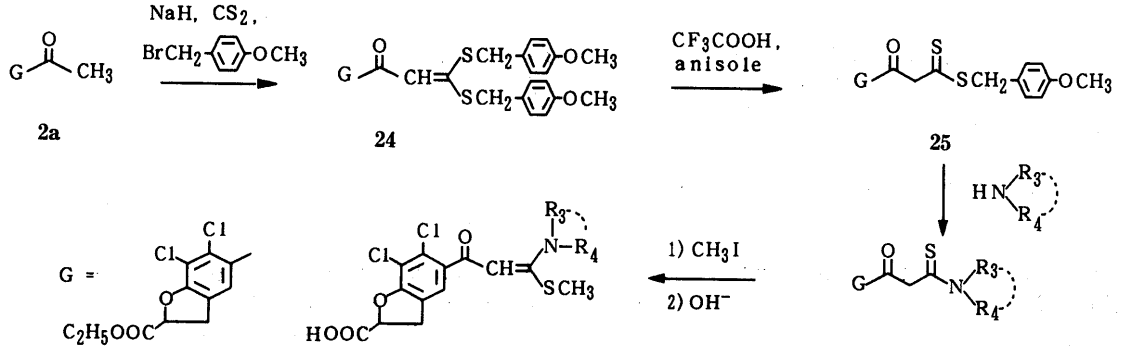


Chart 2

pounds (**9b**, **10**—**13**, **15** and **16**) showed lowfield NH proton signals at below δ 11.38 in $CDCl_3$ solution.

The thioamide (**21**) in which there is no substituent on the nitrogen atom was synthesized in high yield by the reaction of diphenyldithiophosphonic acid[10] with the reaction product (**20**) of **4a** with benzyl thiocyanate in the presence of sodium *tert*-amylate according to the procedure of Rodriguez *et al.*,[11] while reaction of hydrogen sulfide with the same compound (**20**) failed to yield **21**. Compounds **18** and **21** were converted to the free acids (**19** and **22**) using TFA. Both free acids (**19** and **22**) and *tert*-butyl esters (**18** and **21**) having a β-oxothioamide structure were shown to exist as a tautomeric mixture of a thioamide form and a thioenol form in $CDCl_3$ solution by ^{1}H-NMR spectroscopy (see experimental section). Compound **21** was methylated with methyl iodide in the presence of potassium carbonate to afford an *N*,*S*-acetal derivative (**23**) (Chart 2).

Compounds **31**—**35** in which substituents R_3 and R_4 on the nitrogen atom are H and 2-butenyl, propargyl and cyclopropyl and in which substituents R_3, R_4 are methyl and R_3, R_4 and the nitrogen atom constitute a morpholine ring, were synthesized by the route shown in Chart 3. Compound **24** was obtained from **2a** and carbon disulfide in the presence of sodium hydride followed by alkylation with *p*-methoxybenzyl bromide. Treatment of **24** with TFA and anisole selectively eliminates only one *p*-methoxybenzyl group to give **25**. The dithiocarboxylic acid *p*-methoxybenzyl ester (**25**) was substituted with the corresponding amines to obtain thioamides (**26**—**30**). Methylation of these thioamides followed by hydrolysis gave compounds **31**—**35**. In the ethyl esters of **32**—**34**, NH groups forming intramolecular hydrogen bonds were observed in the IR



31: $R_3 = R_4 = CH_3$
32: R_3 = H, $R_4 = CH_2CH{=}CHCH_3$
33: R_3 = H, $R_4 = CH_2C{\equiv}CH$
34: R_3 = H, R_4 = cyclo-C_3H_5
35: $R_3 - R_4 = (CH_2)_2\text{-}O\text{-}(CH_2)_2$

26: $R_3 = R_4 = CH_3$
27: R_3 = H, $R_4 = CH_2CH{=}CHCH_3$
28: R_3 = H, $R_4 = CH_2C{\equiv}CH$
29: R_3 = H, R_4 = cyclo-C_3H_5
30: $R_3 - R_4 = (CH_2)_2\text{-}O\text{-}(CH_2)_2$

Chart 3

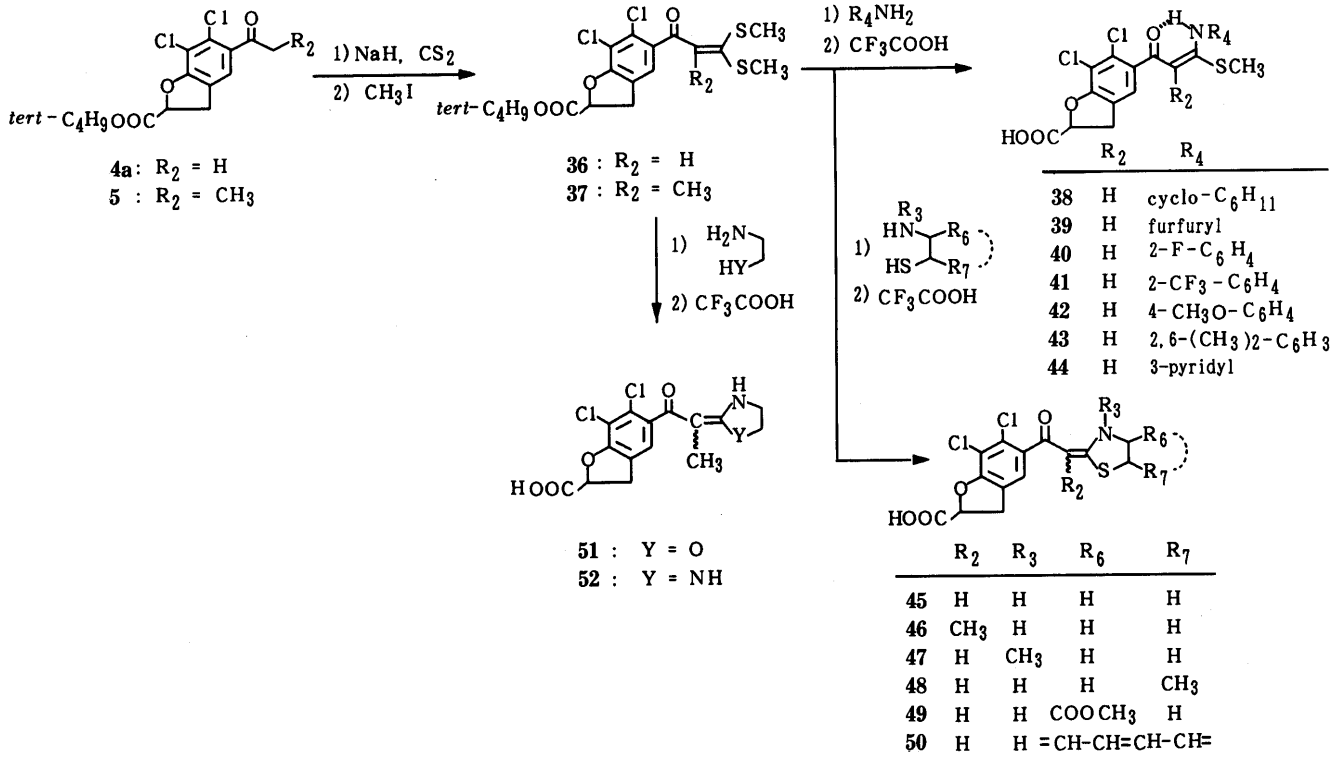


Chart 4

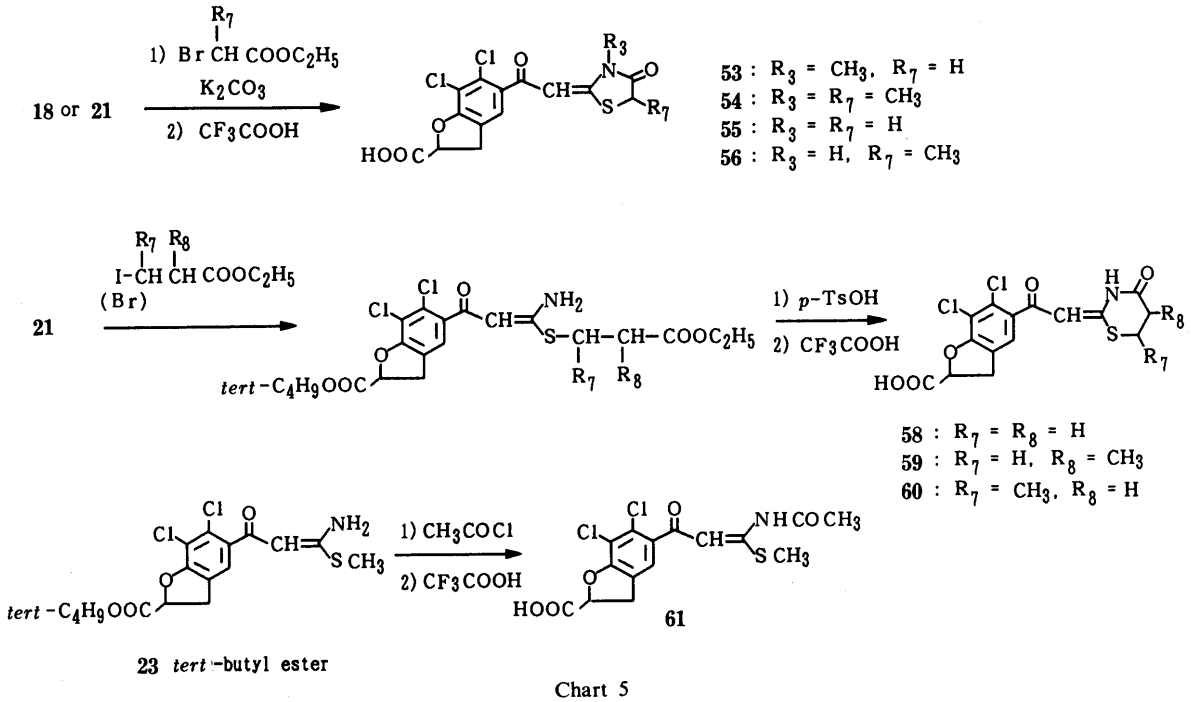


Chart 5

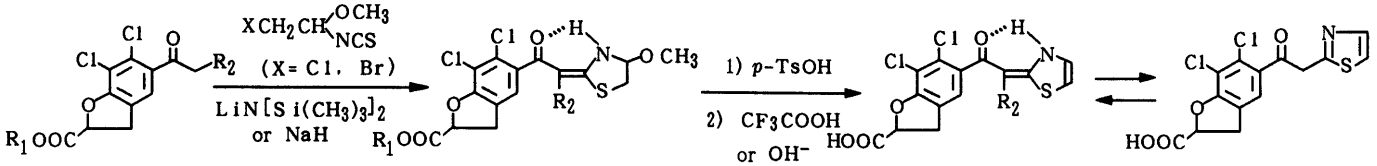
spectra as in the cases of **9a**, **9b** and **10**—**16**. Accordingly, carboxylic acids (**32**—**34**) and their esters may exist in the *E*-form.

An acetal exchange reaction[7] was applied to the syntheses of **38**—**52** (Chart 4). Aminolysis of the *S*,*S*-acetals (**36** and **37**) with cyclohexylamine, arylamines, and furfurylamine gave the corresponding *N*,*S*-acetals (**38**—**44**). In this reaction, use of 2-mercaptoalkylamines, *o*-mercaptoaniline, ethanolamine and ethylenediamine gave cyclic acetals: thiazolidine (**45**—**49**), benzothiazoline (**50**), oxazolidine (**51**) and imidazolidine (**52**) derivatives, respectively. The compounds **38**—**46**, **48** and **49** may also exist in the *E*-form on the basis of the IR spectra and ^{1}H-NMR spectra of their esters as in the cases of **9a**, **9b** and **10**—**16**.

4-Oxo-1,3-thiazolidines[7] (**53**—**56**) and 4-oxoperhydro-1,3-thiazines (**58**—**60**) were synthesized by the route shown in Chart 5. The reaction of ethyl bromoacetate or ethyl 2-bromopropionate with 5-thiocarbamoylacetyl derivatives (**18** and **21**) in the presence of potassium carbonate followed by hydrolysis with TFA gave compounds **53**—**56**. Similar

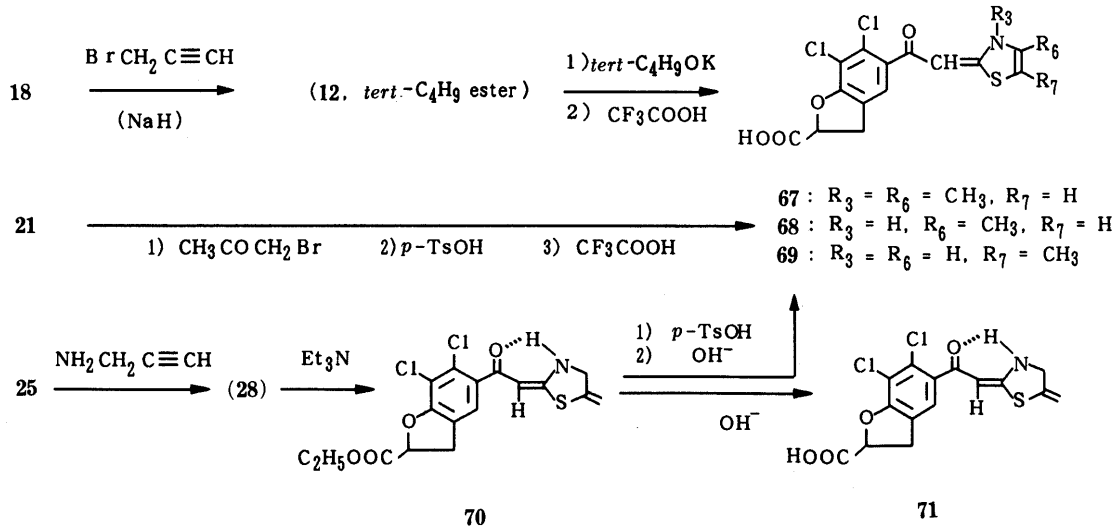
treatment of ethyl 3-bromopropionate, ethyl 3-iodobutylate or ethyl 3-iodo-2-methylpropionate to **21** gave acyclic intermediates (**57**), which were cyclized by refluxing in benzene in the presence of *p*-toluenesulfonic acid. Hydrolysis of the esters gave the free acids **58**—**60**. Compound **61** was obtained by acetylation of the *tert*-butyl ester of **23** using acetyl chloride followed by hydrolysis of the ester.

The 5-(4-thiazolin-2-ylidene)acetyl derivatives were synthesized by the routes shown in Charts 6—8. Reaction of the carbanion, which was generated from **4a** with lithium hexamethyldisilazide in tetrahydrofuran (THF), with 2-chloro-1-methoxyethyl isothiocyanate[12] gave the 4-methoxythiazolidine (**63**) which was converted to the thiazoline derivative (*tert*-butyl ester of **65**) by acid treatment. The resultant thiazoline ester was hydrolyzed to the free acid (**65**). Compound **65** exists as a tautomeric mixture of the thiazoline form (**65a**) and the thiazole form (**65b**), because signals of a vinylic methine proton and methylene protons which were exchangeable with deuterium by addition of deuterioxide were observed in its ^{1}H-NMR



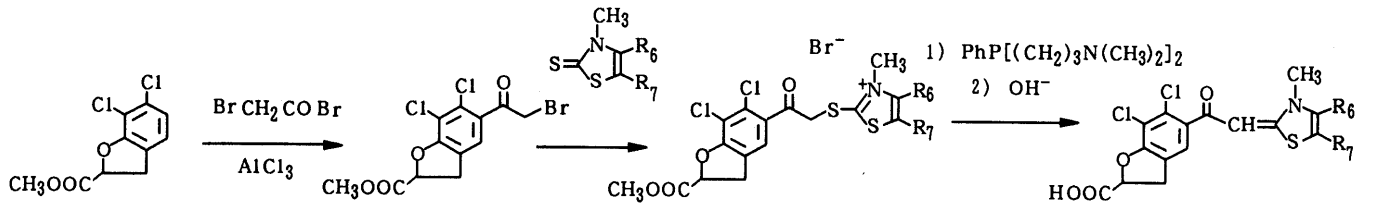
4a : R_1 = *tert*-C_4H_9, R_2 = H
62 : R_1 = C_2H_5, R_2 = $COOC_2H_5$
63 : R_1 = *tert*-C_4H_9, R_2 = H
64 : R_1 = C_2H_5, R_2 = $COOC_2H_5$
65a : R_2 = H
66 : R_2 = $COOC_2H_5$
65b

Chart 6



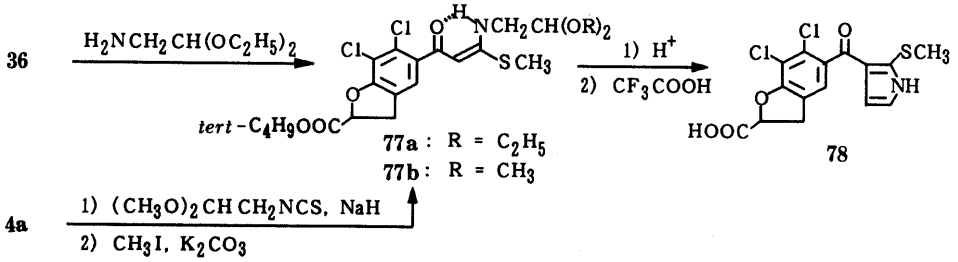
70 **71**

Chart 7



1c **72**
73 : R_6 = R_7 = H
74 : R_6 = R_7 = CH=CH-CH=CH
75 : R_6 = R_7 = H
76 : R_6 = R_7 = CH=CH-CH=CH

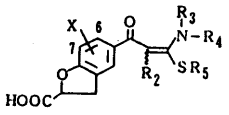
Chart 8



78

Chart 9

TABLE I. 5-(3,3-*N*,*S*-Substituted Propenoyl)-2,3-dihydro-2-benzofurancarboxylic Acids



Compd. No.	X	R_2	R_3	Substitutent R_4	R_5	mp (°C)	Yield (%) [from]	Recrystn. solvent[a]	Formula	Analysis (%) Calcd (Found) C	H	Cl	N	S	Oral natriuretic activities[b] Rats[c]	Mice[d]
9a	6,7-DiCl	H	H	CH_3	CH_3	263—265 (dec.)	45 [4a]	D–E	$C_{14}H_{13}Cl_2NO_4S$	46.42 (46.44	3.62 3.70	19.57 19.32	3.87 3.96	8.85 8.66)	1.7	7.2
9b	7-CH_3	H	H	CH_3	CH_3	219—220 (dec.)	6 [4b]	E	$C_{15}H_{17}NO_4S$	58.62 (58.30	5.57 5.67		4.56 4.61	10.43 10.21)	—	N
10	6,7-DiCl	H	H	CH_3	C_2H_5	249—251 (dec.)	40 [4a]	D–E	$C_{15}H_{15}Cl_2NO_4S$	47.88 (47.79	4.02 4.04	18.84 18.57	3.72 3.82	8.52 8.30)	N[e]	2.1
11	6,7-DiCl	H	H	CH_3	CH_2CHCH_2	178—180 (dec.)	47 [4a]	E	$C_{16}H_{15}Cl_2NO_4S$	49.50 (49.44	3.89 3.86	18.26 18.33	3.61 3.64	8.26 8.10)	N[e]	2.5
12	6,7-DiCl	H	H	CH_3	$CH{\equiv}CCH_2$	180—183 (dec.)	34 [4a]	E	$C_{16}H_{13}Cl_2NO_4S$	49.75 (49.50	3.39 3.58	18.36 18.51	3.63 3.57	8.30 8.15)	2.4[e]	4.2
13	6,7-DiCl	CH_3	H	CH_3	CH_3	206—207 (dec.)	60 [5]	D–W	$C_{15}H_{15}Cl_2NO_4S$	47.88 (47.66	4.02 4.00	18.85 18.56	3.72 3.88	8.52 8.44)	2.1[e]	4.2
14	6,7-DiCl	H	H	C_2H_5	CH_3	247—249 (dec.)	53 [4a]	A	$C_{15}H_{15}Cl_2NO_4S$	47.88 (47.76	4.02 3.90	18.85 19.03	3.72 3.80	8.52 8.33)	2.5[e]	7.8
15	6,7-DiCl	CH_3	H	C_2H_5	CH_3	194—196 (dec.)	68 [5]	A	$C_{16}H_{17}Cl_2NO_4S$	49.24 (49.12	4.39 4.45	18.17 18.28	3.56 3.59	8.21 8.48)	N[e]	2.8
16	6,7-DiCl	H	H	C_6H_5	CH_3	223—225 (dec.)	62 [4a]	A	$C_{19}H_{15}Cl_2NO_4S$	53.78 (53.93	3.63 3.83	16.71 14.49	3.30 3.15	7.55 7.70)	N[e]	N
17	6,7-DiCl	H	C_6H_5	CH_2–CH_2		225—228 (dec.)	35 [4a]	E	$C_{20}H_{15}Cl_2NO_4S \cdot C_2H_5OH$	54.78 (54.42	4.39 4.35	14.79 15.05	2.90 3.03	6.65 6.60)	N[e]	N
19	6,7-DiCl	H	H	CH_3	H	121—124	33 [4a]	B	$C_{13}H_{11}Cl_2NO_4S$	44.84 (44.92	3.18 3.29	20.36 20.14	4.02 4.10	9.21 8.96)	3.8[e]	6.1
22	6,7-DiCl	H	H	H	H	120—125	46 [21]	ET	$C_{12}H_9Cl_2NO_4S \cdot 1/2(C_2H_5)_2O$	45.29 (45.07	3.80 3.79	19.10 19.34	3.77 3.80	8.63 8.47)	N	6.2
23	6,7-DiCl	H	H	H	CH_3	254—257 (dec.)	94 [21]	E	$C_{13}H_{11}Cl_2NO_4S$	44.84 (44.67	3.18 3.26	20.36 20.19	4.02 3.97	9.21 9.09)	2.6	5.0
31	6,7-DiCl	H	CH_3	CH_3	CH_3	230—232 (dec.)	18 [25]	E	$C_{15}H_{15}Cl_2NO_4S$	47.88 (47.64	4.02 4.02	18.85 18.81	3.72 3.69	8.52 8.21)	—	3.6
32	6,7-DiCl	H	H	$CH_3CH{=}CHCH_2$	CH_3	213—216	27 [25]	E	$C_{17}H_{17}Cl_2NO_4S$	50.76 (50.71	4.26 4.28	17.63 17.75	3.48 3.49	7.97 7.74)	1.7	5.9
33	6,7-DiCl	H	H	$CH{\equiv}CH_2$	CH_3	202—204	5 [25]	E	$C_{16}H_{13}Cl_2NO_4S \cdot 1/2\,C_2H_5OH$	48.93 (49.15	3.87 4.06	16.99 16.76	3.36 3.41	7.68 7.66)	2.7	4.9
34	6,7-DiCl	H	H	cyclo-C_3H_5	CH_3	242—246 (dec.)	62 [25]	A–EA	$C_{16}H_{15}Cl_2NO_4S$	49.44 (49.26	3.89 3.96	18.26 18.15	3.61 3.66	8.26 8.26)	N	4.4
35[f]	6,7-DiCl	H		$(CH_2)_2O(CH_2)_2$	CH_3	230—232 (dec.)	37 [25]	E–EA	$C_{17}H_{16}Cl_2NNaO_5S \cdot 1/2\,H_2O$	45.44 (45.47	3.81 3.84	15.78 15.88	3.12 3.19	7.13 7.38)	N	2.4
38	6,7-DiCl	H	H	cyclo-C_6H_{11}	CH_3	167—168	50 [36]	E	$C_{19}H_{21}Cl_2NO_4S$	53.03 (52.92	4.92 4.95	16.84 16.37	3.25 3.30	7.45 7.38)	2.0	2.6
39	6,7-DiCl	H	H	Furfuryl	CH_3	214—216 (dec.)	52 [36]	E	$C_{18}H_{15}Cl_2NO_5S$	50.48 (50.29	3.53 3.61	16.55 16.38	3.27 3.22	7.48 7.39)	1.8	4.4
40	6,7-DiCl	H	H	2-F-C_6H_4	CH_3	237—242 (dec.)	36 [36]	E	$C_{19}H_{14}Cl_2FNO_4S$	51.60 (51.38	3.19 3.33	16.03 16.06	3.17 3.08	7.25 7.48)	N	N
41	6,7-DiCl	H	H	2-CF_3-C_6H_4	CH_3	226—228 (dec.)	18 [36]	E	$C_{20}H_{14}Cl_2F_3NO_4S$	48.79 (48.74	2.87 3.04	14.40 14.13	2.85 2.80	6.51 6.65)	N	N
42	6,7-DiCl	H	H	4-CH_3O–C_6H_4	CH_3	240—243 (dec.)	34 [36]	DO	$C_{20}H_{17}Cl_2NO_5S$	52.87 (52.74	3.77 3.77	16.51 15.95	3.08 2.84	7.06 7.21)	N	3.5
43	6,7-DiCl	H	H	2,6-$(CH_3)_2C_6H_3$	CH_3	252—255 (dec.)	29 [36[g]]	E	$C_{21}H_{19}Cl_2NO_4S$	55.76 (55.60	4.23 4.32	15.67 15.47	3.10 3.11	7.09 6.94)	N	N
44	6,7-DiCl	H	H	3-Pyridyl	CH_3	227—232 (dec.)	29 [36]	E	$C_{18}H_{14}Cl_2N_2O_4S$	50.84 (50.63	3.32 3.57	16.67 16.67	6.59 6.58	7.54 7.30)	N	1.7
45	6,7-DiCl	H	H	CH_2–CH_2		252—254 (dec.)	56 [36]	E	$C_{14}H_{11}Cl_2NO_4S$	46.68 (46.50	3.08 3.21	19.68 19.58	3.89 3.88	8.90 8.69)	2.5	8.2
46	6,7-DiCl	CH_3	H	CH_2–CH_2		264—266 (dec.)	23 [37]	D–W	$C_{15}H_{13}Cl_2NO_4S$	48.14 (47.99	3.50 3.64	18.95 18.89	3.74 4.00	8.57 8.26)	2.0[e]	N
47	6,7-DiCl	H	CH_3	CH_2–CH_2		272—275 (dec.)	70 [36]	D–E	$C_{15}H_{13}Cl_2NO_4S$	48.14 (47.93	3.50 3.57	18.95 18.55	3.74 3.79	8.57 8.45)	2.3[e]	1.7
48	6,7-DiCl	H	H	CH_2–$CH(CH_3)$		237—247 (dec.)	75 [36]	E	$C_{15}H_{13}Cl_2NO_4S$	48.14 (48.22	3.50 3.58	18.95 18.82	3.74 3.79	8.57 8.57)	3.3	10.5
49	6,7-DiCl	H	H	(*R*)CH(COOCH$_3$)–CH_2		205—215	23 [36]	EA	$C_{16}H_{13}Cl_2NO_6S$	45.95 (45.81	3.13 3.24	16.95 16.77	3.35 3.38	7.66 7.58)	N	N
50	6,7-DiCl	H	H			259—261 (dec.)	25 [36]	D–E	$C_{18}H_{11}Cl_2NO_4S$	52.96 (52.66	2.72 2.91	17.37 17.37	3.43 3.31	7.85 7.98)	—	N
Tienilic acid															2.5[e]	5.4
Indacrinone															2.3[e]	8.4

a) A=acetone, B=benzene, D=*N*,*N*-dimethylformamide, DO=dioxane, E=ethanol, EA=ethyl acetate, ET=ether, W=water. *b*) The experimental details are described in the experimental section. Ratio to control (treated/control value) is shown; N indicates that the difference from the control is not statistically significant and — indicates that the difference was not determined. *c*) Dose: 10 mg/kg. *d*) Dose: 30 mg/kg. *e*) Dose: 50 mg/kg. *f*) Sodium salt. *g*) Yield was calculated from the ethyl ester of **36** which was used as a starting material.

spectrum. Similarly, **62**, which was formed by the Friedel–Crafts acylation reaction of ethyl malonyl chloride with **1a**, was allowed to react with 2-bromo-1-methoxyethyl isothiocyanate[12] in the presence of sodium hydride as a base in *N*,*N*-dimethylformamide (DMF). The resultant 4-methoxythiazolidine derivative (**64**) was converted to **66** by a treatment similar to that described above (Chart 6).

5-(Substituted-4-thiazolin-2-ylidene)acetyl derivatives (**67**—**69**) were synthesized by the route shown in Chart 7. Introduction of an *S*-propargyl group into **18**, isomerization of the *S*-propargyl group to an *S*-allenyl group with potassium *tert*-butoxide, then cyclization according to the procedure of Bhattacharjee *et al.*[13] gave **67** (geometry unknown). Compound **68** was obtained from thioamide (**21**) by Hantzsch thiazole synthesis followed by hydrolysis. Treatment of *n*-propargylthioamide (**28**) with triethylamine formed **70**, which was converted to **69** in high yield by heating with *p*-toluenesulfonic acid in benzene followed by hydrolysis. Both compounds (**68** and **69**) were found from their ^{1}H-NMR spectra to exist as a tautomeric mixture of the thiazole and thiazoline forms, as in the case of **65**. Compound **70** showed the intramolecularly hydrogen-bonded NH group at 3200 cm^{-1} in its IR spectrum and at δ 10.4 in its ^{1}H-NMR spectrum. Therefore, **70** and **71** may exist as the *E*-form, as in the cases of **9a**, **9b** and **10**—**16**.

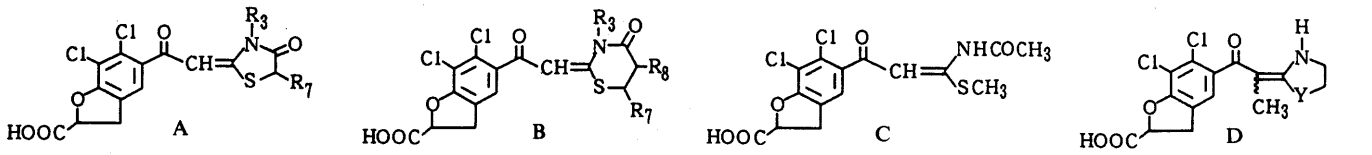
The synthetic pathway to compounds **75** and **76** is shown in Chart 8. A Friedel–Crafts acylation product (**72**) of **1c** with bromoacetyl bromide reacted with 3-methyl-4-thiazoline-2-thione to give the 2-thiothiazolium salt (**73**), the bridged sulfur atom of which was abstracted with bis(3-*N*,*N*-dimethylaminopropyl)phenylphosphine.[14] Hydrolysis of the resultant ester gave **75**. A similar procedure with 3-methylbenzothiazoline-2-thione (**74**) gave **76**. Compounds **75** and **76** each seemed to be a single isomer on the basis of the ^{1}H-NMR spectra, but the geometry is not known (Chart 8).

The *tert*-butyl ester of the 5-(3-pyrrolylcarbonyl) derivative (**78**) was obtained by acid cyclization of **77a**, which was obtained by the acetal exchange reaction of **36**. It was converted to the free acid (**78**) by hydrolysis. The same compound (**78**) was also obtained by similar treatment of a dimethylacetal derivative (**77b**) which was the methylated derivative of the reaction product of **4a** and 2-dimethoxyethylisothiocyanate in the presence of sodium hydride (Chart 9).

Natriuresis Oral natriuretic activities of the compounds synthesized in this study were tested in rats and mice. The results are shown in the last columns in Tables I—III. Data are shown as the ratio to the control. Natriuresis of the control groups was 0.60 meq/kg·B.W. for rats and 0.62 meq/kg·B.W. for mice. Tienilic acid and indacrinone were used as reference compounds. Indacrinone showed more potent activity than tienilic acid in mice, but both showed almost the same activity in rats. Diuretic and kaliuretic activities paralleled the natriuretic activity (data not shown).

Most of the compounds exhibited natriuretic activity. The 7-methyl derivative showed markedly lower natriuretic activity compared with the 6,7-dichloro-substituted derivative (**9a** ≫ **9b**). Among the *N*,*S*-acetal compounds (Table I),

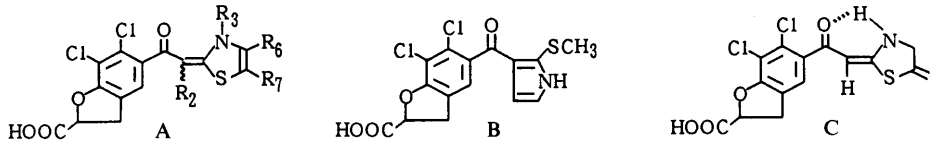
TABLE II. 6,7-Dichloro-5-[2-(1,3-oxazolidin and imidazolidin-2-ylidene)propionyl], 5-[(4-Oxo-1,3-thiazolidin-2-ylidene)acetyl] and 5-[(4-Oxoperhydro-1,3-thiazin-2-ylidene)acetyl]-2,3-dihydro-2-benzofurancarboxylic Acids



Compd. No.	Structure	Substituent R_3	R_7	R_8	Y	mp (°C)	Yield (%) [from]	Recrystn. solvent[a]	Formula	Analysis (%) Calcd (Found) C	H	Cl	N	S	Oral natriuretic activities[b] Rats[c]	Mice[d]
51	D				O	241—242 (dec.)	9 [37]	ET	$C_{15}H_{13}Cl_2NO_5$	50.29 (49.99	3.66 3.76	19.80 20.07	3.91 3.88)		N[e]	N
52	D				NH	273—276 (dec.)	26 [37]	A	$C_{15}H_{14}Cl_2N_2O_4$	50.44 (50.49	3.95 4.08	19.85 19.78	7.84 7.59)		N[e]	N
53	A	H	H			242—258 (dec.)	44 [21]	E	$C_{14}H_9Cl_2NO_5S$	44.94 (44.83	2.42 2.58	18.95 19.18	3.74 3.66	8.57 8.47)	3.6	6.4
54	A	H	CH_3			212—214 (dec.)	32 [21]	EA	$C_{15}H_{11}Cl_2NO_5S$	46.41 (46.20	2.86 3.08	18.26 18.33	3.61 3.62	8.26 8.06)	7.0	12.1
55	A	CH_3	H			253—256 (dec.)	57 [18]	E	$C_{15}H_{11}Cl_2NO_5S$	46.41 (46.31	2.86 2.96	18.26 18.12	3.61 3.54	8.26 8.07)	3.0	5.1
56	A	CH_3	CH_3			248—256 (dec.)	37 [18]	E	$C_{16}H_{13}Cl_2NO_5S \cdot 1/2H_2O$	46.73 (46.91	3.43 3.43	17.24 17.35	3.41 3.41	7.79 7.79)	3.8	10.7
58	B	H	H	H		226—228	67 [21]	E	$C_{15}H_{11}Cl_2NO_5S$	46.41 (46.19	2.86 3.02	18.26 18.32	3.61 3.52	8.26 8.12)	2.6	4.8
59	B	H	H	CH_3		213—217	46 [21]	E	$C_{16}H_{13}Cl_2NO_5S$	47.78 (47.50	3.26 3.25	17.63 17.50	3.48 3.46	7.97 7.84)	4.0	4.0
60	B	H	CH_3	H		198—202	50 [21]	EA	$C_{16}H_{13}Cl_2NO_5S$	47.78 (47.62	3.26 3.33	17.63 17.69	3.48 3.67	7.97 8.02)	4.8	8.9
61	C					217—220 (dec.)	66 [23[f]]	E	$C_{15}H_{13}Cl_2NO_5S$	46.17 (46.01	3.36 3.49·	18.17 18.14	3.59 3.61	8.21 8.07)	2.0	2.8

a—*e*) See footnotes *a*—*e*) in Table I. *f*) Yield was calculated from the *tert*-butyl ester of **23** which was used as a starting material.

TABLE III. 6,7-Dichloro-5-[(1,3-thiazolin-2-ylidene)acetyl] and 5-(3-Pyrrolylcarbonyl)-2,3-dihydro-2-benzofurancarboxylic Acids



Compd. No.	Structure	Substituent R_2	R_3	R_6	R_7	mp (°C)	Yield (%) [From]	Recrystn. solvent[a]	Formula	Analysis (%) Calcd (Found) C	H	Cl	N	S	Oral natriuretic activities[b] Rats[c]	Mice[d]
65	A	H	H	H	H	214—216	17 [**4a**]	E	$C_{14}H_9Cl_2NO_4S$	46.94 (46.85	2.53 2.70	19.80 19.95	3.91 3.96	8.95 8.87)	1.5	4.1
66	A	$COOC_2H_5$	H	H	H	212—215	7 [**1a**]	A	$C_{17}H_{13}Cl_2NO_6S$	47.46 (47.47	3.05 3.33	16.48 16.34	3.25 3.22	7.45 7.18)	N[e]	N
67	A	H	CH_3	CH_3	H	277—279 (dec.)	60 [**18**]	D–E	$C_{16}H_{13}Cl_2NO_4S$	49.75 (49.51	3.39 3.61	18.36 18.09	3.63 3.78	8.30 8.04)	N[e]	N
68	A	H	H	CH_3	H	252—256 (dec.)	68 [**21**]	E	$C_{15}H_{11}Cl_2NO_4S$	48.40 (48.38	2.98 3.27	19.05 18.75	3.76 3.70	8.61 8.60)	N	2.0
69	A	H	H	H	CH_3	232—234 (dec.)	69 [**70**]	E	$C_{15}H_{11}Cl_2NO_4S$	48.40 (48.40	2.98 3.08	19.05 18.74	3.76 3.89	8.61 8.44)	4.4[e]	7.3
71	C					146—147	81 [**70**]	E	$C_{15}H_{11}Cl_2NO_4S \cdot H_2O$	46.16 (46.36	3.35 3.48	18.17 18.38	3.56 3.78	8.21 8.27)	2.1	7.4
75	A	H	CH_3	H	H	282—285 (dec.)	73 [**72**]	D–E	$C_{15}H_{11}Cl_2NO_4S$	48.40 (48.28	2.98 3.11	19.05 18.98	3.75 3.77	8.61 8.71)	N[e]	N
76	A	H	CH_3	CH=CH –CH=CH		283—285 (dec.)	44 [**72**]	D–E	$C_{19}H_{13}Cl_2NO_4S$	54.04 (53.67	3.10 3.37	16.79 16.74	3.32 3.54	7.59 7.41)	1.8[e]	N
78	B					246—248 (dec.)	25 [**36**]	E	$C_{15}H_{11}Cl_2NO_4S$	48.40 (48.26	2.98 3.27	19.05 18.93	3.76 3.70	8.61 8.43)	4.5	8.1

a—e) See footnotes *a—e*) in Table I.

substituent effects on the natriuretic activities are as follows: the potency increases when R_2 is hydrogen rather than a methyl group (**9a** > **13**, **14** > **15**, and **45** > **46**), when the substitution on the nitrogen atom is mono-substitution (R_3 = H) and its R_4 substituent is a lower alkyl group (**9a** ≫ **31** and **35**, **9a** ≒ **14** > **32**—**34** and **38**—**44**, and **45** ≫ **47** > **17**), and when the substituent on the sulfur atom (R_5) is hydrogen or a smaller alkyl group (**19** ≒ **9a** ≫ **12**, **10** and **11**, and **22** > **23**). Among the cyclic acetals, the *N,S*-acetals **45** and **48** showed potent activities, but **49**, **50** and the *N,N*- and *N,O*-acetals (**50** and **51** in Table II) were inactive. The 4-oxo-2-thiazolinylidene and perhydrothiazinylidene compounds listed in Table II showed moderate or potent activities. Introduction of a methyl group at the position adjacent to the sulfur atom potentiated their activities markedly (**54** > **53**, **56** > **55**, and **60** > **58**). On the other hand, introduction of a methyl group (R_8) at the 5-position of the thiazinylidene derivative (**59**) did not potentiate its activity (**58** ≒ **59**). Introduction of a methyl group at the 3- and 4-position of the 1,3-thiazolinylidene compounds listed in Table III had no effect on the activities. The 5-methyl derivative (**69**) showed intermediate potency between tienilic acid and indacrinone. Compound **78** showed nearly the same activity as that of **69**.

The compounds with the natriuretic activities equivalent to or more potent than that of indacrinone were **9a**, **14**, **45**, **48**, **54**, **56**, **60**, **69**, **71** and **78**. Further evaluation of these compounds, including tests of antihypertensive and uricosuric activities and toxicity, is in progress.

Experimental

Melting points were determined on a Yanagimoto hot plate micro melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were taken on a Varian EM-390 spectrometer with tetramethylsilane (TMS) as an internal standard. Signal multiplicities are represented by s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), br (broad), and m (multiplet). Chemical shifts are expressed in δ values and the coupling constants in herz (Hz). For column chromatography, Silica gel 60 (E. Merck, 0.063—0.200 mm) was used and elution was carried out with 1—10% ethyl acetate (EA)–dichloromethane unless otherwise noted.

Ethyl 7-Methyl-2,3-dihydro-2-benzo[*b*]furancarboxylate (1b) This was prepared by esterification of the free acid.[4a]

Ethyl 5-Acetyl-7-methyl-2,3-dihydro-2-benzo[*b*]furancarboxylate (2b) and Ethyl 6,7-Dichloro-5-propionyl-2,3-dihydro-2-benzo[*b*]furancarboxylate (3) These compounds were obtained by a procedure similar to that used for **2a**.[6] **2b**: Yield 99%, oil. ^{1}H-NMR (in $CDCl_3$) δ: 1.30 (3H, t, J = 7), 2.29 (3H, s), 2.52 (3H, s), 3.35 (1H, dd, J = 16, 6), 3.63 (1H, dd, J = 16, 10), 4.26 (2H, q, J = 7), 5.25 (1H, dd, J = 10, 6), 7.17 (2H, br s). **3**: Yield 98%, mp 71—72 °C from ether–hexane. *Anal.* Calcd for $C_{14}H_{14}Cl_2O_4$: C, 53.02; H, 4.45; Cl, 22.36. Found: C, 52.97; H, 4.47; Cl, 22.49.

***tert*-Butyl 5-Acetyl-6,7-dichloro-2,3-dihydro-2-benzo[*b*]furancarboxylate (4a)** A suspension of **2a** (23.4 g, 0.0766 mol), ethanol (100 ml), water (100 ml) and potassium hydroxide (5.2 g, 0.929 mol) was allowed to react at room temperature for 1 h, then concentrated under reduced pressure. The aqueous solution was acidified and the precipitated crystalline material was collected by filtration, washed with water and dried, giving **6a** (20.6 g, 98%). A suspension of **6a** (20.6 g, 0.075 mol), thionyl chloride (19.3 ml, 0.26 mol) in dry benzene (188 ml) was refluxed for 2.5 h, then evaporated under reduced pressure. The residue was dissolved in dry ether (80 ml) and the solution was added to a stirred solution of *tert*-butanol (28 g, 0.38 mol), triethylamine (8.3 g, 0.082 mol), 4-(*N,N*-dimethylamino)-pyridine (0.9 g, 0.0074 mol) in dry ether (80 ml) at −10 °C, then the reaction was allowed to proceed at room temperature for 0.5 h. The ethereal solution was washed with water and an aqueous sodium bicarbonate solution, dried and evaporated. The residue was purified by column chromatography, giving **4a** (22.0 g, 87% from **2a**), which was recrystallized from ether–hexane, mp 60—61 °C. *Anal.* Calcd for $C_{15}H_{16}Cl_2O_4$: C, 54.40; H, 4.87; Cl, 21.41. Found: C, 54.12; H, 4.87; Cl, 21.29.

4b and **5** were obtained in a similar manner. **4b**: Yield 89%, oil. ^{1}H-NMR (in $CDCl_3$) δ: 1.48 (9H, s), 2.29 (3H, s), 2.52 (3H, s), 3.16—3.74 (2H, m), 5.15 (1H, dd, J = 10, 7), 7.67 (2H, br s). **5**: Yield 92%, mp 57—58 °C from Hx. *Anal.* Calcd for $C_{16}H_{18}Cl_2O_4$: C, 55.67; H, 5.26; Cl, 20.54. Found: C, 55.78; H, 5.18; Cl, 20.64.

6,7-Dichloro-5-(3-ethylamino-3-methylthio-2-propenoyl)-2,3-dihydro-2-benzo[*b*]furancarboxylic Acid (14) A solution of **4a** (1.65 g, 5 mmol) in

TABLE IV. ^{1}H-NMR Data for the Compounds Listed in Tables I—III in DMSO-d_6 Solution

9a 2.43 (3H, s), 3.0 (3H, d, J=5), 3.20—3.85 (2H, m), 5.22 (1H, s), 5.42 (1H, dd, J=10, 6), 7.30 (1H, s), 11.15 (1H, br)
9b 2.20 (3H, s), 2.50 (3H, s), 2.98 (3H, d, J=5), 3.1—3.8 (2H, m), 5.27 (1H, dd, J=10, 6), 5.66 (1H, s), 7.60 (1H, s), 11.50 (1H, br)
10 1.29 (3H, t, J=7), 2.84—3.1 (5H, m), 3.15—3.85 (2H, m), 5.25 (1H, s), 5.42 (1H, dd, J=10, 6), 7.28 (1H, s), 11.20 (1H, br)
11 3.0 (3H, d, J=5), 3.68 (2H, d, J=6), 3.2—3.83 (2H, m), 5.1—5.5 (4H, m), 5.65—6.1 (1H, m), 7.26 (1H, s), 11.20 (1H, br)
12 2.99 (3H, d, J=5), 3.2—3.7 (3H, m), 3.90 (2H, d, J=3), 5.42 (1H, dd, J=10, 6), 5.40 (1H, s), 7.30 (1H, s), 11.16 (1H, br)
13 1.80 (3H, s), 2.42 (3H, s), 3.16—3.85 (5H, m, s), 5.45 (1H, dd, J=10, 6), 7.08 (1H, s), 11—12 (1H, br)
14 1.23 (3H, t, J=7), 2.42 (3H, s), 3.2—3.8 (4H, m), 5.21 (1H, s), 5.41 (1H, dd, J=10, 6), 7.29 (1H, s), 11.30 (1H, br)
15[a] 1.28 (3H, t, J=7), 1.49 (9H, s), 1.87 (3H, s), 2.40 (3H, s), 3.2—3.8 (4H, m), 5.18 (1H, dd, J=10, 6), 6.93 (1H, brs), 12.03 (1H, br)
16 2.40 (3H, s), 3.10—3.85 (2H, m), 5.42 (1H, dd, J=10, 6), 5.53 (1H, s), 7.38 (6H, m), 13.03 (1H, br)
17 1.06 (3H, t, J=7), 3.2—3.8 (6H, m), 4.10 (2H, t, J=7), 5.42 (1H, dd, J=10, 6), 5.09 (1H, s), 7.19—7.45 (6H, m)
19 2.30 (s) and 2.96 (s) (3H), 3.2—3.9 (2H, m), 4.28 (2/3 H, s), 5.40—5.65 (1H, m), 5.76 (2/3 H, s), 7.39 (2/3 H, s), 7.66 (1/3 H, s), 9.95 (2/3 H, br), 10.3 (1/3 H, br), 13.4 (1H, br), 14.38 (2/3 H, s)
22 3.2—3.9 (2H, m), 4.22 (2/4 H, s), 5.47 (1H, dd, J=10, 6), 5.75 (3/4 H, s), 7.38 (3/4 H, s), 7.66 (1/4 H, s), 9.1 (2H, br)
23 2.40 (3H, s), 3.2—3.8 (2H, m), 5.23 (1H, s), 5.42 (1H, dd, J=10, 6), 7.26 (1H, s), 7.5—10 (2H, br)
31 2.40 (3H, s), 3.13 (s) and 3.2—3.8 (m) (8H), 5.14 (1H, s), 5.40 (1H, dd, J=10, 6), 7.25 (1H, s)
32 1.67 (3H, d, J=6), 2.40 (3H, s), 3.2—3.8 (2H, m), 3.9 (2H, m), 5.2—5.8 (4H, m, s), 7.30 (1H, s), 11.35 (1H, br)
33 2.43 (s) and 2.48 (d, J=3) (4H), 3.2—3.8 (2H, m), 4.22 (2H, dd, J=6, 3), 5.27 (1H, s), 5.40 (1H, dd, J=10, 6), 7.30 (1H, s), 11.27 (1H, brt)
34[b] 0.60—1.07 (4H, m), 1.32 (3H, t, J=7), 2.37 (3H, s), 2.40 (1H, br), 3.03—3.77 (2H, m), 4.25 (2H, q, J=7), 5.13—5.47 (2H, m), 7.13 (1H, s)
35[b] 1.30 (3H, t, J=7), 2.40 (3H, s), 3.10—3.93 (10H, m), 4.23 (2H, q, J=7), 5.12—5.45 (2H, m), 7.15 (1H, s)
38 1.1—2.0 (10H, m), 2.40 (3H, s), 3.17—3.80 (3H, m), 5.21 (1H, m), 5.42 (1H, dd, J=10, 6), 7.30 (1H, s), 11.55 (1H, d, J=9)
39 2.45 (3H, s), 3.20—3.84 (2H, m), 4.60 (2H, d, J=6), 5.30 (1H, s), 5.42 (1H, dd, J=10, 6), 6.42 (2H, m), 7.32 (1H, s), 7.65 (1H, m), 11.53 (1H, t, J=6)
40 2.43 (3H, s), 3.2—3.9 (2H, m), 5.45 (1H, dd, J=10, 6), 5.61 (1H, s), 7.2—7.7 (5H, m), 12.81 (1H, s)
41 2.46 (3H, s), 3.2—3.9 (2H, m), 5.45 (1H, dd, J=10, 6), 5.63 (1H, s), 7.43—7.75 (5H, m), 13.0 (1H, s)
42 2.38 (3H, s), 3.2—3.9 (5H, s, m), 5.43 (1H, dd, J=10, 6), 5.48 (1H, s), 6.95, 7.25 (4H, ABq, J=10), 7.39 (1H, s), 12.85 (1H, s)
43 2.20 (6H, s), 2.33 (3H, s), 3.2—3.9 (2H, m), 5.45 (1H, dd, J=10, 6), 5.49 (1H, s), 7.17 (3H, s), 7.43 (1H, s), 12.4 (1H, s)
44 2.44 (3H, s), 3.2—3.9 (2H, m), 5.45 (1H, dd, J=10, 6), 5.62 (1H, s), 7.4 (2H, m, s), 7.83 (1H, m), 8.55 (2H, m), 12.87 (1H, s)
45 3.1—3.9 (6H, m), 5.43 (1H, dd, J=10, 6), 5.75 (1H, s), 7.25 (1H, s), 8.55 (1/2 H, br), 10.2 (1/2 H, br)
46 1.64 (3H, s), 3.0—4.0 (6H, m), 5.40 (1H, dd, J=10, 6), 7.01 (1H, brs), 7.75, 10.50 (1H, br)
47 2.95 (3H, s), 2.9—3.8 (6H, m), 5.42 (1H, dd, J=10, 6), 5.56 (1H, s), 7.25 (1H, s)
48 1.35 (3H, m), 3.28—3.73 (4H, m), 3.93 (1H, m), 5.37—5.48 (1H and 3/5 H, s and m), 5.70 (2/5 H, s), 7.22 (s) and 7.27 (s) (1H), 8.52 (2/5 H, br), 10.09 (3/5 H, br), 13.75 (1H, brs)
49 3.30—3.72 (4H, m), 3.72 (3H, s), 4.78, 4.97 (1H, m), 5.45 (1H, m), 5.51 (s) and 5.91 (s) (1H), 7.24 (s) and 7.33 (s) (1H), 9.02 (brs) and 10.30 (brs) (1H), 13.5 (1H, br)
50 3.2—3.85 (2H, m), 5.45 (1H, dd, J=10, 6), 6.27 (1H, s), 7.1—7.9 (5H, m), 12—13 (1H, br)
51[a] 1.47 (9H, s), 1.62 (3H, s), 3.07—3.63 (2H, m), 3.85 (2H, t, J=5), 4.55 (2H, t, J=5), 5.05—5.35 (1H, m), 6.85—6.98 (1H), 9.0—10.4 (1H, br)

TABLE IV. (continued)

52[a] 1.45 (12H, s), 3.03—3.97 (6H, m), 5.20—5.65 (1H, m), 6.98 (1H, s), 7.18 (1H, br), 9.7 (1H, br)
53 3.2—3.8 (2H, m), 3.80 (2H, s), 5.45 (1H, dd, J=10, 6), 6.33 (1H, s), 7.32 (1H, brs), 11.85 (1H, br)
54 1.48 (3H, d, J=7), 3.23—3.86 (2H, m), 4.08 (1H, q, J=7), 5.47 (1H, dd, J=10, 6), 6.37 (1H, s), 7.34 (1H, brs), 11.8 (1H, br)
55 3.17 (3H, s), 3.2—3.8 (2H, m), 3.90 (2H, s), 5.49 (1H, dd, J=10, 6), 6.46 (1H, s), 7.46 (1H, brs)
56 1.50 (3H, d, J=7), 3.18 (3H, s), 3.2—3.9 (2H, m), 4.15 (1H, q, J=7), 5.50 (1H, dd, J=10, 6), 6.46 (1H, s), 7.46 (1H, brs)
58 2.70—3.85 (6H, m), 5.46 (1H, m), 5.90 (2/5 H, s), 6.30 (3/5 H, s), 7.26 (3/5 H, s), 7.40 (2/5 H, s), 11.02 (3/5 H, s), 12.45 (2/5 H, s)
59 1.20—1.30 (3H, m), 2.7—3.9 (5H, m), 5.45 (1H, m), 5.87 (1/3 H, s), 6.29 (2/3 H, s), 7.27 (2/3 H, s), 7.40 (1/3 H, s), 11.0 (2/3 H, s), 12.46 (1/3 H, s)
60 1.30 (d, J=7) and 1.35 (d, J=7) (3H), 2.65—3.85 (5H, m), 5.45 (1H, m), 5.88 (1/3 H, s), 6.30 (2/3 H, s), 7.28 (2/3 H, s), 7.40 (1/3 H, s), 11.12 (2/3 H, s), 12.50 (1/3 H, s)
61 2.21 (3H, s), 2.35 (3H, s), 3.2—3.8 (2H, m), 5.45 (1H, dd, J=10, 6), 5.77 (1H, s), 7.46 (1H, brs), 13.30 (1H, brs)
65 3.2—3.85 (2H, m), 5.45 (1H, m), 4.76 (2×1/3 H, s), 6.12 (2/3 H, s), 7.14—7.74 (3H, m)
66 0.74 (3H, t, J=7), 3.18—3.90 (4H, m), 5.42 (1H, dd, J=10, 6), 7.04 (1H, s), 7.28 (1H, d, J=5), 7.62 (1H, d, J=5), 13.7 (1H, br)
67 2.26 (3H, s), 3.45 (3H, s), 3.20—3.85 (2H, m), 5.44 (1H, dd, J=10, 6), 6.00 (1H, s), 6.50 (1H, brs), 7.33 (1H, brs)
68[a] 1.50 (9H, s), 2.40 (3H, brs), 3.20—3.77 (2H, m), 5.10—5.33 (1H, m), 4.62 (2×1/3 H, s), 6.00 (2/3 H, s), 6.11 (2/3 H, brs), 6.83 (1/3 H, brs), 7.32 (2/3 H, s), 7.35 (1/3 H, s)
69 2.33 (3×2/3 H, s), 2.42 (3×1/3 H, s), 3.22—3.86 (2H, m), 4.68 (2×1/3 H, s), 5.46 (1H, m), 6.04 (2/3 H, s), 7.25 (2/3 H, m), 7.35 (1/3 H, brs), 7.42 (2/3 H, brs), 7.76 (1/3 H, m)
71 3.2—3.85 (2H, m), 4.40 (2×2/3 H, m), 4.65 (2×1/3 H, m), 5.30—5.53 (3H and 2×1/3 H, m), 5.78 (2/3 H, s), 7.23 (1H, br), 8.75 (2/3 H, brs)
75 3.2—3.85 (2H, m), 3.56 (3H, s), 5.42 (1H, dd, J=10, 6), 5.99 (1H, s), 6.82 (1H, d, J=4), 7.33 (1H, brs), 7.38 (1H, d, J=4)
76 3.68 (3H, s), 3.20—3.86 (2H, m), 5.45 (1H, dd, J=10, 6), 6.30 (1H, s), 7.16—7.86 (5H, m)
78 2.48 (3H, s), 3.2—3.9 (2H, m), 5.50 (1H, dd, J=10, 6), 6.18 (1H, m), 6.85 (1H, m), 7.23 (1H, brs), 11.60 (1H, br)

a) *tert*-Butyl ester in $CDCl_3$ solution. *b*) Ethyl ester in $CDCl_3$ solution.

dry DMF (4 ml) was added to a stirred mixture of 60% oily sodium hydride (0.20 g, 5 mmol), ethyl isothiocyanate (0.53 g, 6 mmol) and DMF (1 ml) under a nitrogen atmosphere at 5—10 °C, then the reaction mixture was kept at the same temperature for 2.5 h. Methyl iodide (0.85 g, 6 mmol) was added and the mixture was allowed to react for 2.5 h. After addition of an aqueous ammonium chloride solution, the mixture was extracted with ether. The organic layer was washed with brine, dried, and then evaporated under reduced pressure. The residue was purified by column chromatography, giving an oily *tert*-butyl ester of **14** (1.6 g, 76.5%). TFA (13 ml) was added to the ester (1.3 g) obtained above and the mixture was stirred for 0.5 h at room temperature. TFA was evaporated off under reduced pressure, leaving a crystalline residue, which was treated with ether. Recrystallization from acetone gave **14** (0.81 g, 70%, yield from **4a** was 53%).

Compounds **9a**, **9b**, **10**, **11**, **13** and **15**—**17** were obtained in a similar manner. ^{1}H-NMR spectral data for **9a**, **9b**, **10**, **11**, **13**—**17** are given in Table IV.

***tert*-Butyl 6,7-Dichloro-5-(*N*-methylthiocarbamoylacetyl)-2,3-dihydro-2-benzo[*b*]furancarboxylate (18)** **4a** (0.993 g, 3 mmol) was allowed to react with methyl isothiocyanate by a procedure similar to that described above. A saturated aqueous ammonium chloride solution was added to the reaction mixture and the mixture was extracted with ether. The organic layer was washed with brine, dried and evaporated under reduced pressure. The residue was purified by column chromatography, giving oily **18** (0.65 g, 54%), which was found to exist as a tautomeric mixture (an enol form/a keto form = 1/1) from its ^{1}H-NMR spectrum. ^{1}H-NMR (in $CDCl_3$) δ: 1.49 (9H, s), 3.1—3.8 (5H, m), 4.39 (1H, s), 5.60 (0.5H, s), 8.9 (0.5H, br), 14.45 (0.5H, brs).

6,7-Dichloro-5-(3-methylamino-3-propargylthio-2-propenoyl)-2,3-dihydro-2-benzo[*b*]furancarboxylic Acid (12) A solution of **18** (0.30 g, 0.74 mmol) in acetonitrile (6 ml) was allowed to react with propargyl bromide (0.097 g, 0.82 mmol) in the presence of potassium carbonate (0.15 g, 1.09 mmol) at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, then the residue was purified by column chromatography, giving the *tert*-butyl ester of **12** (0.30 g, 92%). The ester was hydrolyzed with TFA by a procedure similar to that described above to obtain **12** (0.18 g, 70%). ^{1}H-NMR spectral data for **12** are given in Table IV.

6,7-Dichloro-5-(*N*-methylthiocarbamoylacetyl)-2,3-dihydro-2-benzo[*b*]-furancarboxylic Acid (19) A solution of **18** (0.65 g, 1.61 mmol) in TFA (6.5 ml) was allowed to react at room temperature for 1 h then TFA was evaporated off under reduced pressure. Treatment of the crystalline residue with ether gave **19** (0.34 g, 61%).

***tert*-Butyl 6,7-Dichloro-5-cyanoacetyl-2,3-dihydro-2-benzo[*b*]furancarboxylate (20)** A solution of **4a** (3.03 g, 10 mmol) in benzene (5 ml) was added under ice cooling to a solution of sodium *tert*-amylate, which was prepared by refluxing a mixture of 60% oily sodium hydride (0.48 g, 12 mmol), *tert*-amyl alcohol (1.06 g, 12 mmol) and dry benzene (25 ml). The mixture was stirred for 0.5 h. A solution of benzyl thiocyanate (2.24 g, 15 mmol) in benzene (10 ml) was then added under ice cooling. The reaction mixture was kept at room temperature overnight, then an aqueous ammonium chloride solution was added. The organic layer was separated, washed, dried and evaporated under reduced pressure. The residue was purified by column chromatography and treated with isopropyl ether to obtain crystalline **20** (1.08 g, 30%), which showed a melting point of 73—74 °C and was used for the next reaction without further purification. ^{1}H-NMR (in $CDCl_3$) δ: 1.50 (9H, s), 3.24—3.85 (2H, m), 4.17 (2H, s), 5.30 (1H, dd, J=10, 7), 7.46 (1H, s).

***tert*-Butyl 6,7-Dichloro-5-thiocarbamoylacetyl-2,3-dihydro-2-benzo[*b*]-furancarboxylate (21)** A soluion of **20** (1.21 g, 3.39 mmol) and diphenylphosphinodithioic acid[15] (1.87 g, 7.46 mmol) in 2-propanol (50 ml) was allowed to react at 40 °C overnight. The precipitated crystalline material was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography, giving resinous **21** (1.1 g, 83%), which was found to exist as a tautomeric mixture (enol form/keto form=3/2) from its ^{1}H-NMR spectrum. ^{1}H-NMR (in $CDCl_3$) δ: 1.49 (9H, s), 3.2—3.8 (2H, m), 5.25 (1H, m), 7.27 (1H, m), [enol form: 5.76 (0.6H, s), 6.70 (1.2H, br s), 14.54 (0.6H, s), keto form: 4.39 (0.8H, s), 7.8 (0.4H, br), 8.45 (0.4H, br)].

6,7-Dichloro-5-thiocarbamoylacetyl-2,3-dihydro-2-benzo[*b*]furancarboxylic Acid (22) Hydrolysis of **21** was carried out by a procedure similar to that described for **19**. Yield 46%. ^{1}H-NMR spectral data for **22** are given in Table IV.

6,7-Dichloro-5-methylthiocarbamoylacetyl-2,3-dihydro-2-benzo[*b*]-furancarboxylic Acid (23) A solution of **21** (0.16 g, 0.41 mmol) in acetonitrile (3 ml) was allowed to react with methyl iodide (0.07 g, 0.49 mmol) in the presence of potassium carbonate (0.085 g, 0.61 mmol) at room temperature for 1 h. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography to obtain the *tert*-butyl ester of **23** (0.16 g, 96%). A solution of the ester in TFA (1.6 ml) was allowed to react at room temperature for 1 h, then the mixture was evaporated under reduced pressure and the residue was treated with ether, giving **23** (0.134 g, 98%). ^{1}H-NMR spectral data for **23** are given in Table IV.

Ethyl 5-[3,3-Bis(4-methoxybenzyl)-2-propenoyl]-6,7-dichloro-2,3-dihydro-2-benzo[*b*]furancarboxylate (24) A mixture of **2a** (6.06 g, 20 mmol), freshly distilled *p*-methoxybenzyl bromide (10.0 g, 50 mmol), carbon disulfide (3.81 g, 50 mmol), 60% oily sodium hydride (1.76 g, 44 mmol), *N*,*N*-dimethylacetamide (DMA, 4.1 ml), potassium iodide (0.1 g) and dry ether (106 ml) was stirred at room temperature for 72 h under a nitrogen atmosphere. The mixture was poured into ice water, then the precipitated crystals were collected by filtration and washed with ether. The crystals were dissolved in dichloromethane, then purified by column chromatography, giving **24** (6.8 g, 55%). ^{1}H-NMR (in $CDCl_3$) δ: 1.28 (3H, t, J=7), 3.08—3.83 (8H, m), 4.03—4.43 (6H, m), 5.12—5.40 (1H, m), 6.50 (1H, s), 6.63—7.37 (10H, m).

Ethyl 6,7-Dichloro-5-[(4-methoxybenzylthio)thiocarbonylacetyl]-2,3-dihydro-2-benzo[*b*]furancarboxylate (25) A mixture of **24** (6.8 g, 10.97 mmol), anisole (13.6 ml) and TFA (13.6 ml) was stirred at room temperature for 2 h, then concentrated under reduced pressure. The residue was subjected to column chromatography and eluted with ethyl acetate–benzene (1 : 9), giving syrupy **25** (5.0 g, 91%). ^{1}H-NMR (in $CDCl_3$) δ: 1.29 (3H, t, J=7), 3.25—3.85 (m) and 3.78 (s) (5H), 4.27 (2H, q, J=7), 4.43 (2H, s), 5.32 (1H, dd, J=7, 10), 6.55 (1H, s), 6.8—7.3 (m) and 7.25 (s) (5H), 14.94 (1H, s).

6,7-Dichloro-5-(3-dimethylamino-3-methylthio-2-propenoyl)-2,3-dihydro-2-benzo[*b*]furancarboxylic Acid (31) A solution of **25** (0.524 g, 1.024 mmol) and dimethylamine (0.07 g, 1.54 mmol) in dry acetonitrile (5 ml) was allowed to react at room temperature overnight, then the solution was concentrated under reduced pressure. The residue was purified by column chromatography to obtain **26** (0.16 g, 39%). A solution of **26** (0.15 g, 0.385 mmol) in dry acetonitrile (3 ml) was allowed to react with methyl iodide (0.08 g, 0.56 mmol) in the presence of potassium carbonate (0.08 g, 0.58 mmol) at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane. The solution was washed, dried and evaporated. The extract was purified by column chromatography to obtain the ethyl ester of **31** (0.155 g, 100%).

A solution of the ester in dichloromethane (2 ml) and ethanol (5 ml) was hydrolyzed with 1 N NaOH (0.6 ml) at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and neutralized with 1 N HCl. The precipitated crystalline material was collected by filtration and washed with water and a small amount of ethanol to obtain **31** (0.105 g, 73%).

Compounds **32**—**35** were obtained in a similar manner. ^{1}H-NMR spectral data for **31**—**35** are given in Table IV.

***tert*-Butyl 5-(3,3-Bismethylthio-2-propenoyl)-6,7-dichloro-2,3-dihydro-2-benzo[*b*]furancarboxylate (36)** A solution of **4a** (7.0 g, 21.1 mmol), carbon disulfide (4.0 g, 53 mmol) and methyl iodide (7.5 g, 53 mmol) in dry ether (80 ml) was added to a stirred suspension of 60% oily sodium hydride (1.85 g, 46.4 mmol), DMA (4.4 ml) and dry ether (30 ml) under a nitrogen atmosphere at room temperature. The mixture was allowed to react for 72 h then was poured into ice water and extracted with benzene. The organic layer was washed, dried and evaporated under reduced pressure then the residue was subjected to column chromatography. Elution with ethyl acetate–benzene (1 : 9) gave oily **36** (6.0 g, 65%). ^{1}H-NMR (in $CDCl_3$) δ: 1.49 (9H, s), 2.48 (3H, s), 2.53 (3H, s), 3.2—3.8 (2H, m), 5.22 (1H, dd, J=6, 10), 6.47 (1H, s), 7.27 (1H, s). **37** was obtained in a similar manner. Yield 90%, oil. ^{1}H-NMR (in $CDCl_3$) δ: 1.49 (9H, s), 1.98 (3H, s), 2.32 (3H, s), 2.37 (3H, s), 3.2—3.8 (2H, m), 5. 25 (1H, dd, J=7, 10), 7.40 (1H, br s).

6,7-Dichloro-5-(3-furfurylamino-3-methylthio-2-propenoyl)-2,3-dihydro-2-benzo[*b*]furancarboxylic Acid (39) A solution of **36** (0.435 g, 1 mmol) and furfurylamine (0.117 g, 1.2 mmol) in dry toluene (1 ml) was refluxed for 9 h, then evaporated under reduced pressure. The residue was purified by column chromatography, giving the resinous *tert*-butyl ester of **39** (0.36 g, 75%). A mixture of the ester and TFA (3.6 ml) was stirred at room temperature for 0.5 h. Evaporation under reduced pressure and treatment of the residue with ether gave **39** (0.22 g, 69%; 52% from **36**).

Compounds **38** and **40**—**44** were obtained in a similar manner. Compounds **45**—**52** were obtained in a similar manner using the corresponding 2-aminoethanethiols, 2-aminoethanol and 1,2-diaminoethane instead of furfurylamine. ^{1}H-NMR spectral data for **38**—**52** are summarized in Table IV.

6,7-Dichloro-5-(4-oxothiazolidin-2-ylidene)acetyl-2,3-dihydro-2-benzo-[*b*]furancarboxylic Acid (55) A mixture of **21** (0.4 g, 1.025 mmol), ethyl bromoacetate (0.205 g, 1.23 mmol), potassium iodide (0.017 g, 0.01 mmol) and potassium carbonate (0.212 g, 1.54 mmol) in dry acetonitrile (3 ml) was allowed to react at room temperature for 3 h with stirring. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography. The ester obtained above was hydrolyzed with TFA (4 ml) at room temperature for 1 h. Evaporation and treatment of the residue with ether gave **55** (0.16 g, 42%).

Compounds **53**, **54** and **56** were obtained in a similar manner. ^{1}H-NMR spectral data for **53**—**56** are given in Table IV.

6,7-Dichloro-5-(4-oxoperhydro-1,3-thiazin-2-ylidene)acetyl-2,3-dihydro-2-benzo[*b*]furancarboxylic Acid (58) A mixture of **21** (0.39 g, 1 mmol), ethyl 3-bromopropionate (0.21 g, 1.2 mmol), potassium carbonate (0.21 g, 1.5 mmol), potassium iodide (0.017 g, 0.1 mmol) and dry acetonitrile (3 ml) was allowed to react at room temperature for 5 h, then concentrated under reduced pressure. The residue was extracted with dichloromethane, and the material soluble in dichloromethane was purified by column chromatography. **57a** ($R_7=R_8=H$): ^{1}H-NMR (in $CDCl_3$) δ: 1.26 (3H, t, J=7), 1.47 (9H, s), 2.70 (2H, t, J=6), 3.07—3.73 (4H, m), 4.15 (2H, q, J=7), 5.18 (1H, dd, J=10, 6), 5.47 (1H, s), 7.0—8.7 (2H, br), 7.18 (1H, s). The oily **57** obtained was dissolved in dry benzene (10 ml) containing *p*-toluenesulfonic acid (0.009 g, 0.05 mmol), and the solution was refluxed for 1 h through a water separator packed with Molecular Sieve 3A. The reaction

mixture was washed with aqueous sodium bicarbonate, dried and evaporated. The residue was purified by column chromatography to give the *tert*-butyl ester of **58** (0.32 g, 72%).

A solution of the ester (0.32 g) in TFA (3 ml) was stirred at room temperature for 1 h then evaporated. Treatment of the residue with ether gave **58** (0.235 g, 92.5%; 67% from **21**).

Compounds **59** and **60** were obtained in a similar manner. **57b** (R_7 = H, R_8 = CH_3): ^{1}H-NMR (in $CDCl_3$) δ: 1.27 (3H, t, J=7), 1.48 (9H, s), 1.80 (3H, d, J=7), 2.18—3.27 (5H, m), 4.17 (2H, q, J=7), 5.18 (1H, dd, J=10, 6), 5.50 (1H, s), 7.2—8.7 (2H, br), 7.20 (1H, s). **57c** (R_7 = CH_3, R_8 = H): ^{1}H-NMR (in $CDCl_3$) δ: 1.2—1.9 (15H, m), 2.50—2.95 (2H, m), 3.10—3.93 (3H, m), 4.20 (2H, q, J=7), 5.20 (1H, m), 5.55, 5.86 (each s, 1H), 7.22 (1H, br s). ^{1}H-NMR spectral data for **58**—**60** are given in Table IV.

5-(3-Acetylamino-3-methylthio-2-propenoyl)-6,7-dichloro-2,3-dihydro-2-benzo[*b*]furancarboxylic Acid (61) Potassium carbonate (0.3 g, 2.2 mmol) and acetyl chloride (0.17 g, 2.2 mmol) were added to a stirred solution of the *tert*-butyl ester of **23** (0.175 g, 0.43 mmol) in dry acetonitrile (3 ml) at room temperature. The mixture was allowed to react for 2 h, then the precipitate was filtered off and the filtrate was evaporated under reduced pressure. When the residue was subjected to column chromatography, elution with acetonitrile–dichloromethane (1 : 20) gave the *tert*-butyl ester of **61** (0.125 g), which was hydrolyzed with TFA (1.3 ml) to obtain **61** (0.11 g, 66%). ^{1}H-NMR spectral data for **61** are given in Table IV.

2-Chloro-1-methoxyethyl Isothiocyanate[12] A mixture of chloroacetaldehyde dimethyl acetal (4.0 g, 32 mmol) and silicon tetraisothiocyanate [$Si(NCS)_4$] (4.4 g, 16.8 mmol) was allowed to react at 80—85 °C for 6 h. The reaction mixture was poured onto ice and extracted with ether. The ether layer was washed with an aqueous sodium bicarbonate solution, dried and evaporated under reduced pressure. Distillation of the residue gave the desired compound (4.34 g, 90.5%). bp 92—93 °C (28 mmHg). IR (in CCl_4) ν_{max} cm^{-1}: 2000 (br, NCS). ^{1}H-NMR (in $CDCl_3$) δ: 3.60 (3H, s), 3.7 (2H, d, J=6), 5.00 (1H, t, J=6).

2-Bromo-1-methoxyethylisothiocyanate[12] was obtained from bromoacetaldehyde dimethyl acetal in a similar manner. Yield 85%, bp 86 °C (10 mmHg). ^{1}H-NMR (in $CDCl_3$) δ: 3.52 (2H, d, J=6), 3.57 (3H, s), 4.95 (1H, t, J=6).

6,7-Dichloro-5-(4-thiazolin-2-ylidene)acetyl-2,3-dihydro-2-benzo[*b*]-furancarboxylic Acid (65) A solution of **4a** (1.99 g, 6 mmol) in dry THF (6 ml) was added at −78 °C under a nitrogen atmosphere to a solution of lithium hexamethyldisilazide, which was prepared from hexamethyl disilazane (1.3 ml, 6.3 mmol) and a 1.5 N solution of butyllithium in hexane (4.2 ml, 6.3 mmol). The mixture was allowed to react at −70 to −78 °C for 0.5 h and then a solution of 2-chloro-1-methoxyethylisothiocyanate (1.0 g, 6.6 mmol) in THF (2 ml) was added. The temperature of the reaction mixture was raised slowly and kept at 5—7 °C for 3 h, then at 10—15 °C for 2 h. Next, an aqueous ammonium chloride solution was added and the resulting mixture was extracted with ether. The organic layer was washed with brine, dried and evaporated at below 0 °C under reduced pressure. The residue was purified by chromatography to obtain a mixture of **63** and the starting material (**4a**). [Successive chromatographic separation gave pure **63**. ^{1}H-NMR (in $CDCl_3$) δ: 1.49 (9H, s), 3.10—3.76 (m) and 3.38 (s) (7H), 5.1—5.4 (2H, m), 5.66 (1H, s), 7.22 (1H, br s).] The mixture was dissolved in 1,2-dichloroethane (15 ml) containing *p*-toluenesulfonic acid (50 mg) and the solution was refluxed for 0.2 h. After cooling, the solution was washed with aqueous sodium bicarbonate, dried and evaporated under reduced pressure. Purification of the residue by column chromatography gave the starting material (**4a**, 0.85 g, 42%) and the *tert*-butyl ester of **65** (0.78 g, 31%). Hydrolysis of the ester with TFA was carried out by a procedure similar to that described for **58** to obtain **65** (0.31 g, 46%). **65** was found to exist as a tautomeric mixture (thiazoline form/thiazole form = 3/1) from its ^{1}H-NMR spectrum. ^{1}H-NMR spectral data for **68** are given in Table IV.

6,7-Dichloro-5-[2-ethoxycarbonyl-2-(4-thiazolin-2-ylidene)acetyl]-2,3-dihydro-2-benzo[*b*]furancarboxylic Acid (66) A mixture of **1a** (2.6 g, 10 mmol), ethyl malonyl chloride (1.96 g, 13 mmol), anhydrous aluminum chloride (4.8 g, 36 mmol) and dry dichloromethane (30 ml) was allowed to react at room temperature overnight then poured onto ice. Dichloromethane was added, and the organic layer was washed, dried and evaporated. Purification of the residue by column chromatography gave **62** (0.75 g, 20%) and the starting material (**1a**, 0.81 g, 31%).

A solution of **62** (1.0 g, 2.67 mmol) in a mixture of DMA and THF (1 : 3, 3 ml) was added to a solution of 60% oily sodium hydride (0.107 g, 2.67 mmol) in DMA–THF (1 : 3, 1 ml) at 5—7 °C under a nitrogen atmosphere. The mixture was stirred for 0.25 h, and 2-bromo-1-methoxyethyl isothiocyanate (0.575 g, 2.95 mmol) was added at −30 °C. The reaction mixture was kept at 0—10 °C for 3 h, at 5 °C overnight, and at 20—25 °C for 3 h, then it was worked up by a procedure similar to that described for **65** to obtain **64**. Yield 0.77 g, 63%, oil. ^{1}H-NMR (in $CDCl_3$) δ: 0.80 (3H, br t, J=7), 1.8 (3H, t, J=7), 3.05—3.75 (7H, m), 3.91 (2H, q, J=7), 4.23 (2H, q, J=7), 5.2—5.5 (2H, m), 6.95 (1H, br), 10.8 (br s) and 12.3 (br s) (1H).

64 was hydrolyzed with NaOH in the usual way to give **66** (0.4 g, 58.5%, 7.4% from **1a**. ^{1}H-NMR spectral data for **66** are given in Table IV.

6,7-Dichloro-5-(3,4-dimethyl-4-thiazolin-2-yliden)acetyl-2,3-dihydro-2-benzo[*b*]furancarboxylic Acid (67) Propargyl bromide (0.29 ml, 3.6 mmol) was added to a solution of **18** (0.65 g, 1.61 mmol) and 60% oily sodium hydride (0.065 g, 1.61 mmol) in DMF–THF (1 : 3, 9 ml) and the solution was allowed to react at room temperature for 3 h. Potassium *tert*-butoxide (0.07 g, 0.6 mmol) was added, and then the reaction mixture was kept at room temperature overnight. A saturated aqueous ammonium chloride solution was added to the reaction mixture and whole was extracted with ether. The ether extracts were purified by column chromatography and treated with ether to obtain the crystalline *tert*-butyl ester of **67** (0.50 g, 70%), which was hydrolyzed with TFA by a procedure similar to that described for **58**, to obtain **67** (0.375 g, 86%).

6,7-Dichloro-5-[(4-methyl-4-thiazolin-2-yliden)acetyl]-2,3-dihydro-2-benzo[*b*]furancarboxylic Acid (68) A solution of bromoacetone (90%, 0.18 g, 1.2 mmol) in acetonitrile (2 ml) was added to a stirred suspension of **21** (0.39 g, 1.0 mmol), potassium carbonate (0.21 g, 1.5 mmol) and potassium iodide (0.017 g, 0.1 mmol) in dry acetonitrile (3 ml) at room temperature. The reaction mixture was stirred for 0.5 h, and, after addition of water, extracted with ether. The ethereal layer was washed, dried and evaporated. *p*-Toluenesulfonic acid (0.01 g, 0.05 mmol) was added to a solution of the residue in benzene (10 ml) and the solution was refluxed for 0.2 h. The reaction mixture was washed with an aqueous sodium bicarbonate solution, dried and evaporated under reduced pressure. The residue was submitted to column chromatography and elution with acetonitrile–dichloromethane (1 : 20) gave the *tert*-butyl ester of **68** (0.3 g, 75%), which was hydrolyzed with TFA (3 ml) as described above to give **68** (0.25 g, 90%). ^{1}H-NMR spectral data for **68** are given in Table IV.

Ethyl 6,7-Dichloro-5-[(5-methylene-1,3-thiazolidin-2-ylidene)acetyl]-2,3-dihydro-2-benzo[*b*]furancarboxylate (70) A solution of **25** (4.05 g, 8.12 mmol) and propargylamine (0.54 g, 9.75 mmol) in dry acetonitrile (9 ml) was allowed to react at room temperature under a nitrogen atmosphere for 6 h, then diluted with ether. The precipitate was collected by filtration and washed with ether to obtain **70** (1.15 g). The filtrate was evaporated under reduced pressure and the residue was dissolved in dry acetonitrile (8 ml) containing triethylamine (2 drops). The solution was allowed to react at room temperature for 17 h, then diluted with ether. Collection by filtration gave **70** (1.25 g). Yield 74% (2.4 g). ^{1}H-NMR (in $CDCl_3$) δ: 1.29 (3H, t, J=7), 3.25—3.80 (2H, m), 4.26 (2H, q, J=7), 4.64 (2H, t, J=2.5), 5.20—5.40 (3H, m), 5.50 (1H, s), 7.20 (1H, br s), 10.40 (1H, br).

6,7-Dichloro-5-[(5-methyl-4-thiazolin-2-ylidene)acetyl]-2,3-dihydro-2-benzo[*b*]furancarboxylic Acid (69) A solution of **70** (1.1 g, 2.75 mmol) and *p*-toluenesulfonic acid (0.52 g, 3.0 mmol) in dry benzene (55 ml) was refluxed for 0.5 h with separation of water as the benzene azeotrope. After cooling, precipitated crystalline materials were collected and washed with benzene. The crystals were suspended in an aqueous sodium bicarbonate solution and extracted with ether–dichloromethane (1 : 1). The organic layer was dried and evaporated. The residue was subjected to column chromatography and elution with ether gave the ethyl ester of **69** (0.99 g, 90%), which was hydrolyzed with 1 N NaOH to obtain **69** (0.71 g, 77%). ^{1}H-NMR spectral data for **69** are given in Table IV.

6,7-Dichloro-5-[(5-methylene-1,3-thiazolidin-2-ylidene)acetyl]-2,3-dihydro-2-benzo[*b*]furancarboxylic Acid (71) A suspension of **70** (3.5 g, 8.75 mmol) and 1 N NaOH (13 ml, 13 mmol) in ethanol–dichloromethane (2 : 1, 100 ml) was stirred for 0.5 h at room temperature. The organic solvents were evaporated off under reduced pressure and the resulting aqueous solution was acidified with 1 N HCl (13 ml). Precipitates were collected by filtration and washed with small amounts of cold ethanol, giving **71** (2.75 g, 81%). ^{1}H-NMR spectral data for **71** are listed in Table IV.

6,7-Dichloro-5-(3-methyl-4-thiazolin-2-ylidene)acetyl-2,3-dihydro-2-benzo[*b*]furancarboxylic Acid (75) Anhydrous aluminum chloride (8.6 g, 65 mmol) was added to a solution of methyl 6,7-dichloro-2,3-dihydro-2-benzofurancarboxylate (6.2 g, 25 mmol) and bromoacetyl bromide (6.56 g, 32.5 mmol) in dry dichloromethane (62 ml) under ice cooling. The mixture was allowed to react at room temperature for 3 h, then the reaction

mixture was poured into a mixture of ice and dilute HCl and extracted with dichloromethane. The organic layer was washed, dried and evaporated under reduced pressure, leaving crude crystalline **72** (8.5 g), which, when recrystallized from benzene–hexane, gave **72** (7.5 g, 81.5%), mp 111—112 °C. ^{1}H-NMR (in $CDCl_3$) δ: 3.3—3.9 (2H, m), 3.82 (3H, s), 4.48 (2H, s), 5.40 (1H, dd, J=10, 6), 7.35 (1H, s).

3-Methylthiazoline-2-thione[16] (1.31 g, 10 mmol) was added to a solution of **72** (3.68 g, 10 mmol) in dry acetone (10 ml) and the mixture was allowed to react at 40—45 °C for 5 h. Benzene (10 ml) was added to the reaction mixture and the precipitated crystals were collected by filtration. Washing of the crystalline materials with small amounts of acetone gave **73** (4.73 g, 95%), mp 126—128 °C. ^{1}H-NMR (in DMSO-d_6) δ: 3.2—4.0 (2H, m), 3.73 (3H, s), 4.07 (3H, s), 5.60 (2H, s), 5.68 (1H, dd, J=10, 6), 7.96 (1H, s), 8.16 (1H, d, J=4), 8.43 (1H, d, J=4).

A solution of phenyl bis(3-*N*,*N*-dimethylaminopropyl)phosphine[14,17] (0.31 g, 3.3 mmol) in acetonitrile (1 ml) was added to a suspension of **73** (1.50 g, 3 mmol) in acetonitrile (10 ml) under ice cooling with stirring. The mixture was allowed to react for 0.5 h at room temperature then evaporated under reduced pressure. The residue was dissolved in dichloromethane and the solution was washed with 1 N sodium dihydrogen phosphate and then water, dried and evaporated under reduced pressure. The residue was purified by column chromatography (Lobar column, size B, E. Merck, eluted with ethyl acetate–dichloromethane (1 : 4—1 : 1) to give the oily methyl ester of **75** (0.94 g, 81%).

A 1 N NaOH solution (4.7 ml, 4.7 mmol) was added to a solution of the ester (1.2 g, 2.75 mmol) in a mixture of ethanol and dichloromethane (2 : 1, 15 ml) and the mixture was stirred at room temperature for 1 h. After concentration of the organic solvent under reduced pressure, the aqueous residue was adjusted to pH 3 with dilute HCl and acetic acid. The precipitated crystalline materials were collected by filtration, and washed with water and small amounts of ethanol to give **75** (1.09 g, 95%, 73% from **72**).

Compound **76** was obtained in a similar manner. Compound **74**: mp 121—122 °C. ^{1}H-NMR (in DMSO-d_6) δ: 3.2—4.1 (5H, m), 4.20 (3H, s), 5.4—5.8 (3H, m), 7.3—8.5 (5H, m). ^{1}H-NMR spectral data for **75** and **76** are given in Table IV.

6,7-Dichloro-5-(2-methylthiopyrrol-3-ylcarbonyl)-2,3-dihydro-2-benzo[*b*]furancarboxylic Acid (78) A mixture of **36** (1.09 g, 2.5 mmol), 2,2-diethoxyethylamine (0.33 g, 2.5 mmol) and dry toluene (2 ml) was refluxed for 16 h, then the solvent was evaporated off under reduced pressure. The residue was purified by column chromatography, giving **77a** (1.02 g, 81%). ^{1}H-NMR (in $CDCl_3$) δ: 1.26 (6H, t, J=7), 1.48 (9H, s), 2.40 (3H, s), 3.20—3.86 (8H, m), 4.69 (1H, t, J=6), 5.19 (1H, dd, J=10, 6), 5.30 (1H, s), 7.22 (1H, s), 11.45 (1H, br t). A 1 N hydrogen chloride solution in anhydrous ether (8 ml, 8 mmol) was added to a solution of **77a** (0.9 g, 1.78 mmol) in a mixture of ether and dichloromethane (1 : 1, 30 ml) and the solution was allowed to react at 5—25 °C overnight then evaporated under reduced pressure. The residue was dissolved in dichloromethane and the solution was washed with an aqueous sodium bicarbonate solution, dried and evaporated. The residue was purified by column chromatography to obtain the crystalline *tert*-butyl ester of **78** (0.445 g, 58%). mp 187—188 °C.

The ester obtained above was dissolved in TFA (5 ml) and the solution was allowed to react at room temperature for 1 h, then evaporated under reduced pressure. The crystalline residue was washed with a small amount of 50% aqueous ethanol, giving **78** (0.21 g, 54%).

***tert*-Butyl 6,7-Dichloro-5-[3-(2,2-dimethoxyethylamino)-3-methylthio-2-propenoyl]-2,3-dihydro-2-benzo[*b*]furancarboxylate (77b)** A solution of **4a** (3.31 g, 10 mmol) in dry DMF (10 ml) was added dropwise to a stirred suspension of 60% oily sodium hydride (0.4 g, 10 mmol) and 2,2-dimethoxyethylisocyanate[18] (2.0 g, 15 mmol) in dry DMF (5 ml) at 0—5 °C. The mixture was stirred for 1 h at 10—13 °C, then quenched with an aqueous ammonium chloride solution, and extracted with ether. The ethereal layer was washed with brine, dried and evaporated. The residue was subjected to column chromatography and elution with acetonitrile–dichloromethane (1 : 20) gave the thioamide derivative (3.7 g). A suspension of the thioamide derivative (3.7 g, 8 mmol), potassium carbonate (1.65 g, 12 mmol) and methyl iodide (1.36 g, 9.6 mmol) in dry acetonitrile (15 ml) was allowed to react at room temperature for 1 h, then evaporated under reduced pressure. The residue was dissolved in ether and the ethereal solution was washed with brine, dried and evaporated, giving **77b** (3.85 g, 77% from **4a**). ^{1}H-NMR (in $CDCl_3$) δ: 1.48 (9H, s), 2.40 (3H, s), 3.15—3.75 (m) and 3.45 (s) (10H), 4.56 (1H, t, J=6), 5.18 (1H, dd, J=10, 7), 5.31 (1H, s), 7.22 (1H, br s), 11.47 (1H, br t). **77b** gave **78** when a similar procedure to that for **77a** was applied. Yield 28%.

Natriuresis Natriuretic activities on rats and mice were evaluated by the reported methods.[4e]

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