uid extractor. The residue obtained on concentration of the extracts was chromatographed on silica gel (25 g) using ethyl acetate as the eluent. The combined fractions of product were concentrated on a rotary evaporator. The residue obtained was recrystallized from the appropriate solvent. The recrystallization solvent, yield (from lactone 4), and physical constants for each individual isomers of 2 are given in Table I.

5-Alkyl-5-(3′-hydroxy-1′-methylbutyl)-2-thiobarbituric Acids (3). A solution of sodium methoxide was prepared from 0.17 g (0.0075 g-atom) of sodium and 3 ml of MeOH. To this cooled solution was added 0.27 g (0.0035 mol) of dried thiourea, followed by lactone 6 (amount prepared from 0.004 g of lactone 4). The mixture was heated at 55–58° for 21 hr. The reaction mixture was cooled, diluted with 4 ml of H_2O, and extracted with 2 × 5 ml of Et_2O. The aqueous layer was cooled in an ice bath, acidified to pH 5 with concentrated HCl, and extracted with 3 × 5 ml portions of Et_2O. Concentration of the dried (Na_2SO_4) Et_2O extracts gave an oil. This oil was chromatographed on silica gel (150 g) using first $CHCl_3$, followed by $CHCl_3$–EtOAc (1:1), and then EtOAc as the eluent. Fractions containing pure product (by tlc) were combined and recrystallized from the appropriate solvent. The recrystallization solvent, yield (from lactone 4), and physical constants for each of the individual isomers of 3 are given in Table I.

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Aminobenzoic Acid Diuretics. 7.[1] 3-Substituted 4-Phenyl-, 4-Arylcarbonyl-, and 4-Arylmethyl-5-sulfamoylbenzoic Acids and Related Compounds

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Various 4-substituted 3-alkylamino-, 3-alkoxy-, 3-alkylthio-, and 3-alkyl-5-sulfamoylbenzoic acids related to known aminobenzoic acid diuretics were synthesized and screened for their diuretic properties in dogs. The tabulated results from a 3-hr test period revealed that generally the diuretic profile and potency could be retained when 3-alkoxy, 3-alkylthio, and 3-phenethyl were substituted for the 3-alkylamino moiety. The high potency of several 3-alkoxy-, 3-alkylthio-, and 3-phenethyl-4-benzoyl-5-sulfamoylbenzoic acids confirmed previous suggestions that the apparent diuretic effect of 4- and 5-alkylamino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxides originates from the corresponding 4-benzoyl-5-sulfamoylbenzoic acid derivatives due to an existing equilibrium in plasma. 4-Benzoyl-5-sulfamoyl-3-(3-thenyloxy)benzoic acid (118) is among the most potent benzoic acid diuretics hitherto synthesized and shows significant diuretic activity in dogs at 1 μg/kg. The results obtained with different 3-substituted 4-phenyl-5-sulfamoylbenzoic acids supported the earlier concept regarding the steric influence of the 4-substituent on the diuretic potency of sulfamoylbenzoic acid diuretics.

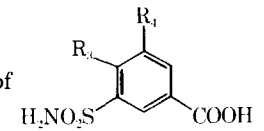
We concluded previously[2] that substituted or unsubstituted phenyl attached by NH, O, S, SO, SO_2, CO, or CH_2 to the 4 position of 2- or 3-alkylamino-5-sulfamoylbenzoic acids contributed to high-ceiling diuretic activity of high potency. We suggested that the influence of the 4-substituent is of steric rather than physicochemical nature. In order to obtain more precise information on the steric requirements for high-ceiling diuretic activity, we decided to investigate some 3-alkylamino-4-phenyl-5-sulfamoylbenzoic acids (7–11).

In the preceding paper of this series[1] it was shown that certain 3-alkylthio-4-phenoxy- and 3-alkylthio-4-phenylthio-5-sulfamoylbenzoic acids possess diuretic activity of the same level of potency as previously reported[3] for the corresponding 3-alkylaminobenzoic acids. This observation prompted us to extend our synthetic program in order to elucidate extensively the effect on the diuretic activity of a departure from the amino function in different 4-substituted 3-alkylamino-5-sulfamoylbenzoic acids. Consequently, we synthesized the title compounds having various 3-alkoxy, 3-alkylthio, and 3-alkyl side chains.

Chemistry. The preparation of the 3-alkylamino-4-phenyl-5-sulfamoylbenzoic acids 7–11 (Table I) was based on the Ullman reaction and is given in Scheme I. The synthesis of the 4-substituted 3-alkoxy-, 3-alkylthio-, and 3-alkyl-5-sulfamoylbenzoic acids 103–150 (Table I) is outlined in Scheme II. The introduction of the oxygen and sulfur function in the 3 position was performed by means of generally known reactions with the diazonium salts of 4 and 12–15. The Meerwein alkylation reaction[4] with the diazonium chloride of 12 and cinnamic acid followed by hydrogenation of the resulting styrene intermediate 28 to the 3-phenethyl compound 65 was the key reaction in the preparation of the 3-phenethylbenzoic acids 139 and 150. The influence of the 4-substituents on the chemical behavior resulted in the different sequences.

It is remarkable that the different 3-substituted 4-benzoyl-5-sulfamoylbenzoic acids prepared in this study could be isolated as such while under similar conditions the corresponding 3-alkylaminobenzoic acids as well as the 4-benzoyl-5-sulfamoylanthranilic acid derivatives underwent spontaneous cyclodehydration to the corresponding benz-

Table I. Physical Properties and Diuretic and Saluretic Activity of



No.	R_3	R_4 (NHR_2, OR_2, SR_2, CH_2R_2)	Method[b]	Mp, °C[c]	Yield,[d] %	Formula[e]	Treatment,[f] mg/kg	Urinary excretion[a] ml/kg per 3 hr, H_2O	Urinary excretion[a] mequiv/kg per 3 hr Na^+	K^+	Cl^-
Control								0.93[g] ± 0.35	0.10[g] ± 0.02	0.16[g] ± 0.01	0.08[g] ± 0.02
6	C_6H_5	NH_2	S	237–239[h]	61	$C_{13}H_{12}N_2O_4S$[i]	1	As control			
7	C_6H_5	$NHCH_2CH{=}CHCH_3$	T	186–187	16	$C_{17}H_{18}N_2O_4S$	1	As control			
8	C_6H_5	NH-*n*-Bu	U	134–136	61	$C_{17}H_{20}N_2O_4S$	1	7	0.6	0.35	0.9
9	C_6H_5	$NHCH_2C_6H_5$	T	221–222	65	$C_{20}H_{18}N_2O_4S$	1	23	3.3	0.81	3.4
							0.1	5	0.3	0.26	0.4
10	C_6H_5	$NHCH_2CCHCHCHO$	V	110–112, 166–168	13	$C_{18}H_{16}N_2O_5S{\cdot}H_2O$	1	10	0.8	0.37	1.5
11	C_6H_5	$NHCH_2CH_2CCHCHNCHCH$	W	216–218	6	$C_{20}H_{19}N_3O_4S$[j]	1	12	1.3	0.41	1.4
103	COC_6H_5	OEt	X	236–239, 267–269[k]	6	$C_{16}H_{15}NO_6S{\cdot}1.5H_2O$	1	9	1.2	0.32	1.5
104	COC_6H_5	O-*n*-Pr	Y	175–177, 214–216	32	$C_{17}H_{17}NO_6S$	0.1	8	1.1	0.23‡	1.5
105	COC_6H_5	$OCH_2CH{=}CH_2$	Y	170–175, 203–205	11	$C_{17}H_{15}NO_6S$[l]	1	14	1.5	0.48	2.0
							0.1	6	0.5	0.23‡	0.6
106	COC_6H_5	$OCH_2C{\equiv}CH$	X	151–154, 211–213[m]	4	$C_{17}H_{13}NO_6S{\cdot}C_2H_5OH$[j]	0.25	11	1.1	0.29	1.3
							0.1	4	0.3	0.24	0.6
107	COC_6H_5	O-*n*-Bu	Y	173–178, 200–202[k]	36	$C_{18}H_{19}NO_6S$	0.1	19	2.0	0.44	2.9
108	COC_6H_4-4-Me	O-*n*-Bu	X	129–133, 272–274[k]	26	$C_{19}H_{21}NO_6S{\cdot}H_2O$[n]	0.1	27	2.6	0.78	4.1
							0.01	9	1.1	0.32	1.3
109	COC_6H_4-4-Cl	O-*n*-Bu	X	142–146, 209–211[k]	16	$C_{18}H_{18}ClNO_6S{\cdot}0.75H_2O$	0.1	17	2.1	0.67	2.8
110	COC_6H_5	O-*n*-Am	Y	168–170[o]	15	$C_{19}H_{21}NO_6S$	0.1	22	2.3	0.90	3.0
111	COC_6H_5	$O(CH_2)_5CH_3$	X	143–150, 233–235[k]	13	$C_{20}H_{23}NO_6S{\cdot}H_2O$	1	17	2.0	0.43	2.7
							0.25	7	0.9	0.25	1.4
112	COC_6H_5	$OCH_2C_6H_5$	Y	193–195	10	$C_{21}H_{17}NO_6S$	0.25	33	3.6	0.89	4.4
							0.1	12	1.0	0.42	2.0
113	COC_6H_4-4-Me	$OCH_2C_6H_5$	X	164–167, 222–225	36	$C_{22}H_{19}NO_6S{\cdot}0.25H_2O$[j]	0.1	27	2.6	0.63	3.3
							0.01	15	1.9	0.36	2.6
							0.01 po	7	0.5	0.15‡	1.2
114	COC_6H_4-4-Cl	$OCH_2C_6H_5$	X	196–200, 228–230[k]	12	$C_{21}H_{16}ClNO_6S$[p]	0.1	30	3.6	0.66	4.0
115	COC_6H_5	$OCH_2C_6H_4$-4-Cl	X	224–225[k,q]	44	$C_{21}H_{16}ClNO_6S$	0.1	10	1.1	0.78	1.4
116	COC_6H_5	$OCH_2CH_2C_6H_5$	Y	172–174	14	$C_{22}H_{19}NO_6S$[l]	0.1	20	1.6	0.28	2.0
117	COC_6H_5	$O(CH_2)_3C_6H_5$	X	166–170, 219–222[k]	7	$C_{23}H_{21}NO_6S{\cdot}H_2O$	1	5	0.7	0.19‡	0.8
118	COC_6H_5	$OCH_2CCHCHSCH$	X	177–178[k]	54	$C_{19}H_{15}NO_6S_2{\cdot}0.5H_2O$	0.1	38	4.4	0.97	4.9
							0.01	23	2.5	0.53	3.5
							0.01 po	16	1.9	0.27	2.4
							0.0025	13	1.0	0.53	1.9
							0.001	4	0.7	0.28	0.7

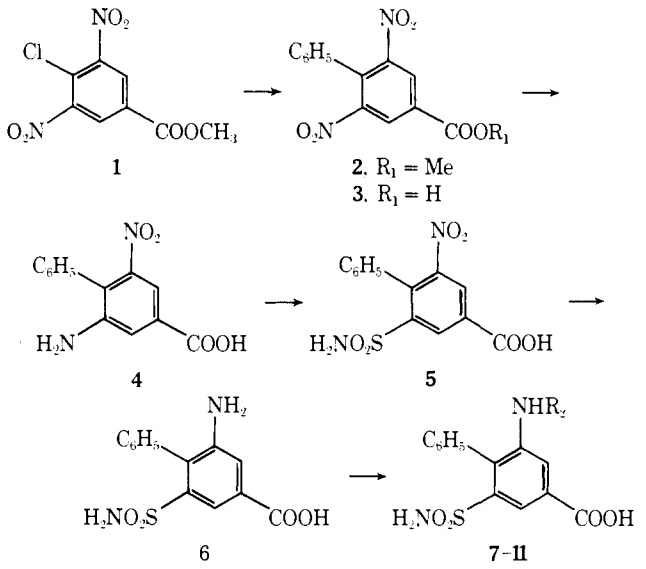
119	COC_6H_5	$OCH_2CCHCHCHCHN$	Y	274–276 dec[k]	23	$C_{20}H_{16}N_2O_6S$	1	21	1.8	0.43	2.7
							0.1	7	0.7	0.15[†]	0.8
120	C_6H_5	O-*n*-Pr	X	155–157	51	$C_{16}H_{17}NO_5S$	1	As control			
121	C_6H_5	O-*n*-Bu	X	145–147	31	$C_{17}H_{19}NO_5S \cdot 0.25H_2O$	1	12	1.2	0.32	1.6
122	C_6H_5	O-*n*-Am	X	152–155	42	$C_{18}H_{21}NO_5S$	1	5	0.6	0.26	0.8
123	C_6H_5	$OCH_2C_6H_5$	X	207–208	33	$C_{20}H_{17}NO_5S$	1	28	3.2	0.64	4.1
							0.1	12	1.6	0.30	1.8
124	C_6H_5	$OCH_2CH_2C_6H_5$	X	108–110	34	$C_{21}H_{19}NO_5S \cdot 0.25H_2O$	1	10	1.0	0.26	1.2
125	C_6H_5	$OCH_2CCHCHSCH$	X	222–223	39	$C_{18}H_{15}NO_5S_2$[r]	1	22	2.3	0.46	2.7
126	CH_3	O-*n*-Pr	X	217–218	21	$C_{11}H_{15}NO_5S \cdot 0.25H_2O$[l]	1	9	0.7	0.25	0.9
127	CH_3	O-*n*-Bu	X	211–212	48	$C_{12}H_{17}NO_5S$[l]	1	12	1.7	0.44	1.9
128	CH_3	$OCH_2C_6H_5$	X	259–260	36	$C_{15}H_{15}NO_5S$	1	15	1.5	0.48	2.1
129	CH_3	$OCH_2CCHCHSCH$	X	223–224	10	$C_{13}H_{13}NO_5S_2$[s]	1	9	0.9	0.21[†]	1.3
130	COC_6H_5	SMe	X	182–184, 249–251[k]	20	$C_{15}H_{13}NO_5S_2$[j]	1	8	0.7	0.24	1.1
131	COC_6H_5	S-*n*-Pr	X	154–156[k]	14	$C_{17}H_{17}NO_5S_2$	0.1	17	1.7	0.34	2.4
132	COC_6H_5	$SCH_2CH{=}CH_2$	X	141–143	5	$C_{17}H_{15}NO_5S_2$[j]	0.1	8	0.8	0.33	1.2
133	COC_6H_5	S-*n*-Bu	X	161–162[k]	22	$C_{18}H_{19}NO_5S_2$	0.1	26	2.7	0.51	3.3
134	COC_6H_5	S-*i*-Am	X	159–161	15	$C_{19}H_{21}NO_5S_2$[l]	0.1	17	1.8	0.38	2.5
135	COC_6H_5	$SCH_2C_6H_5$	X	172–174[k]	23	$C_{21}H_{17}NO_5S_2$[t]	0.1	28	2.2	0.73	4.2
							0.01	17	1.5	0.38	1.9
136	C_6H_5	S-*n*-Pr	X	85–87	25	$C_{16}H_{17}NO_4S_2 \cdot H_2O$[u]	1	5	0.4	0.35	0.5
137	C_6H_5	S-*n*-Bu	X	75–77	33	$C_{17}H_{19}NO_4S_2 \cdot 0.67H_2O$[u,v]	1	13	1.5	0.50	1.9
138	C_6H_5	$SCH_2C_6H_5$	X	114–120	41	$C_{20}H_{17}NO_4S_2 \cdot 0.5H_2O$[w]	1	13	1.4	0.37	1.6
139	COC_6H_5	$CH_2CH_2C_6H_5$	Y	146–149	48	$C_{22}H_{19}NO_5S \cdot H_2O$[j,x]	0.1	31	2.9	0.79	4.1
140	$CH_2C_6H_5$	OEt	Z	235–236	39	$C_{16}H_{17}NO_5S$[l]	1	23	2.7	0.87	3.6
							0.1	4	0.5	0.13[†]	0.6
141	$CH_2C_6H_5$	O-*n*-Pr	Z	230–233	57	$C_{17}H_{19}NO_5S$	0.1	25	2.5	0.75	3.2
142	$CH_2C_6H_5$	$OCH_2CH{=}CH_2$	Z	238–240 dec	21	$C_{17}H_{17}NO_5S$[j]	0.25	18	2.0	0.32	2.7
							0.1	13	0.9	0.32	1.9
143	$CH_2C_6H_5$	O-*n*-Bu	Z	228–229	58	$C_{18}H_{21}NO_5S$[j]	0.1	17	1.8	0.47	2.8
							0.01	10	0.9	0.51	1.3
							0.01 po	10	1.2	0.40	1.7
144	$CH_2C_6H_4$-4-Cl	O-*n*-Bu	Z	227–229	39	$C_{18}H_{20}ClNO_5S$[l]	0.1	14	1.9	0.37	2.3
145	$CH_2C_6H_5$	O-*n*-Am	Z	223–225	50	$C_{19}H_{23}NO_5S$	0.1	6	0.7	0.19[†]	0.8
146	$CH_2C_6H_5$	$O(CH_2)_5CH_3$	Z	213–215	35	$C_{20}H_{25}NO_5S \cdot 0.25H_2O$[j]	1	As control			
147	$CH_2C_6H_5$	$OCH_2C_6H_5$	Z	249–251[m]	37	$C_{21}H_{19}NO_5S$[j]	0.1	26	3.0	0.59	4.1
							0.01	12	1.5	0.31	1.7
							0.01 po	8	0.6	0.20[†]	1.0
148	$CH_2C_6H_4$-4-Me	$OCH_2C_6H_5$	Z	262–263[m]	36	$C_{22}H_{21}NO_5S$[l]	0.1	21	2.3	0.29	2.3
149	$CH_2C_6H_4$-4-Cl	$OCH_2C_6H_5$	Z	262–264[m]	13	$C_{21}H_{18}ClNO_5S$[l]	0.1	8	1.3	0.19[†]	1.5
150	$CH_2C_6H_5$	$CH_2CH_2C_6H_5$	Z	208–211	30	$C_{22}H_{21}NO_4S$[y]	0.1	10	1.2	0.27	1.5
168	$CH_2C_6H_5$	SMe	ZA	232–234	25[z]	$C_{15}H_{15}NO_4S_2 \cdot H_2O$[l]	1	15	1.6	0.41	2.1
169	$CH_2C_6H_5$	SEt	ZA	234–235	12[z]	$C_{16}H_{17}NO_4S_2 \cdot 0.25C_2H_5OH$[l]	1	37	3.6	0.77	5.0
							0.1	19	1.1	0.50	2.7
170	$CH_2C_6H_5$	S-*n*-Pr	ZA	205–206	9[z]	$C_{17}H_{19}NO_4S_2$[l]	0.1	31	3.2	0.76	5.1
							0.01	11	0.9	0.27	1.1
171	$CH_2C_6H_5$	$SCH_2CH{=}CH_2$	ZA	187–188	45[z]	$C_{17}H_{17}NO_4S_2 \cdot 0.5H_2O$[l]	0.25	26	2.3	0.54	3.1
							0.1	17	1.7	0.43	2.1

Table I *(Continued)*

No.	R_3	R_4 (NHR_2, OR_2, SR_2, CH_2R_2)	Method[b]	Mp, °C[c]	Yield,[d] %	Formula[e]	Treatment,[f] mg/kg	Urinary excretion[a]: ml/kg per 3 hr, H_2O	mequiv/kg per 3 hr: Na^+	K^+	Cl^-
172	$CH_2C_6H_5$	S-*n*-Bu	ZA	205–206	8[z]	$C_{18}H_{21}NO_4S_2$[l]	0.1	18	2.0	0.52	3.0
173	$CH_2C_6H_5$	S-*n*-Am	ZA	210–212	6[z]	$C_{19}H_{23}NO_4S_2 \cdot 0.25H_2O$[l]	0.1	9	0.9	0.22	1.3
174	$CH_2C_6H_5$	$SCH_2C_6H_5$	ZA	222–224	8[z]	$C_{21}H_{19}NO_4S_2$[l]	0.1	28	2.8	0.66	3.6
175	$CH_2C_6H_5$	$SCH_2C_6H_4$-3-OMe	ZA	188–189	31[z]	$C_{22}H_{21}NO_5S_2$[l]	1	5	0.6	0.20‡	0.8
176	$CH_2C_6H_5$	$SCH_2CCHCHCHO$	ZB	206–207 dec	3	$C_{19}H_{17}NO_5S_2$[j,aa]	0.1	23	2.3	0.51	3.4
177	$CH_2C_6H_5$	$SCH_2CCHCHSCH$	ZA	198–199	23[z]	$C_{19}H_{17}NO_4S_3 \cdot 0.5H_2O$[j]	0.1	38	4.1	0.78	4.9
178	$CH_2C_6H_5$	$SCH_2CCHCHNCHCH$	ZA	198–201 dec	8[z]	$C_{20}H_{18}N_2O_4S_2 \cdot 0.5C_2H_5OH$[j]	1	23	2.5	0.55	3.5
							0.25	12	0.6	0.38	1.6
179	$CH_2C_6H_5$	$SCH_2CH_2CCHCHNCHCH$	ZA	180–182	6[z]	$C_{21}H_{20}N_2O_4S_2 \cdot 0.5H_2O$	0.1	19	2.5	0.61	2.8
180	CH_3	S-*n*-Pr	ZA	215–216	13[bb]	$C_{11}H_{15}NO_4S_2 \cdot 0.5C_2H_5OH$	1	4	0.5	0.34	0.3
181	CH_3	S-*n*-Bu	ZA	209–210	33[bb]	$C_{12}H_{17}NO_4S_2$	1	15	1.6	0.39	2.4
182	CH_3	$SCH_2C_6H_5$	ZA	234–236	45[bb]	$C_{15}H_{15}NO_4S_2$	1	13	1.2	0.32	1.7
183	CH_3	$SCH_2CCHCHSCH$	ZA	215–217	20[bb]	$C_{13}H_{13}NO_4S_3$[cc]	1	13	1.4	0.40	1.7
3-*n*-Butylamino-4-phenoxy-5-sulfamoylbenzoic acid (bumetanide)							0.1	26[dd] ± 8.3	2.4[dd] ± 0.4	0.44[dd] ± 0.11	3.5[dd] ± 0.8
							0.1 po	31[dd] ± 7.6	3.3[dd] ± 0.9	0.49[dd] ± 0.16	4.5[dd] ± 1.4
							0.01	10[dd] ± 4.8	0.92[dd] ± 0.42	0.27[dd] ± 0.05	1.4[dd] ± 0.5
4-Benzyl-3-*n*-butylamino-5-sulfamoylbenzoic acid (besumide)							0.1	21[dd] ± 3.6	2.1[dd] ± 0.5	0.57[dd] ± 0.15	2.9[dd] ± 0.6
							0.01	9[dd] ± 2.2	0.92[dd] ± 0.27	0.27[dd] ± 0.03	1.2[dd] ± 0.3

[a]The procedure is described in ref 7. In this reference the term metanilic acid has been used erroneously for 3-aminobenzoic acid throughout; when not otherwise stated single test only. Values not significantly different from controls (one-sided 95% confidence limits) are marked with ‡. Where three or more tests were performed the average ±S.D. of the mean is given. [b]The letters relate to the general procedures given in the Experimental Section. [c]Unless otherwise stated the compounds were recrystallized from aqueous EtOH, if necessary while treating with decolorizing C. The 4-COAr compounds 103–119, 130–135, and 139 melt with dehydration to give the corresponding benzisothiazoles; the melting points observed were therefore often unsharp and in many cases the benzisothiazoles crystallized from the initial melt, so that a double melting point was observed. [d]The yield of analytically pure compounds is given, and in most cases no attempts were made to optimalize the yield. [e]The compounds were analyzed for C, H, N, and, if present, S and Cl. Analytical results are within 0.4% of the theoretical values unless otherwise stated. Except when otherwise stated, the compounds were dried *in vacuo* (10–14 mm) for 16–24 hr in the presence of P_2O_5. [f]When not otherwise stated iv injection in NaOH solution. [g]Average of three tests. [h]Recrystallized from AcOH. [i]Dried *in vacuo* (10–14 mm) for 24 hr in the presence of KOH. [j]Dried in air. [k]To avoid partly dehydration to the corresponding benzisothiazole, the last purification was the dropwise addition of a solution of the previously recrystallized (aqueous EtOH or EtOH) compound in 1 *N* NaOH to a slight excess of ice-cold 1 *N* AcOH or HCl to precipitate the compounds tabulated. [l]Dried *in vacuo* (10–14 mm) at 65° for 6–8 hr. [m]Recrystallized from EtOH. [n]S: calcd, 7.83; found, 7.09. [o]Recrystallized from $CHCl_3$–petroleum ether. [p]Not analyzed for Cl. [q]Recrystallized from a mixture of EtOH (three parts) and methyl cellosolve (one part). [r]S: calcd, 16.47; found, 15.90. [s]S: calcd, 19.59; found, 19.02. [t]C: calcd, 59.00; found, 59.68. [u]The compounds crystallize as labile hydrates, the amount of H_2O being dependent on the atmospheric moisture. The values given were obtained after leaving the compounds submitted to the atmosphere of the analytically laboratory (50–54% relative humidity, 25°) for 2 weeks prior to analysis. [v]S: calcd, 16.99; found, 16.16. [w]S: calcd, 15.70; found, 15.26. [x]Not analyzed for N and S. [y]Dried *in vacuo* (10–14 mm) for 5 hr at 100° in the presence of P_2O_5. [z]Based on crude 166. [aa]S: calcd, 15.89; found, 15.10. [bb]Based on crude 167. [cc]S: calcd, 28.01; found, 27.38. [dd]Average of four tests.

Scheme I



isothiazole 1,1-dioxide derivatives.[2,5] However, the cyclization proceeds smoothly by melting of the 4-benzoyl-5-sulfamoylbenzoic acids to give the benzisothiazoles **151-158** and **160-163** (Table II) almost quantitatively. **159** was obtained in an attempt to recrystallize **119**. The existence of an equilibrium between 4-benzoyl-5-sulfamoylanthranilic acid derivatives and the corresponding 1,2-benzisothiazole 1,1-dioxides in aqueous solution has been reported previously and it was observed that in neutral solution the benzisothiazoles are predominating.[5] In contrast, thin-layer chromatographic examination of a freshly prepared solution of the benzisothiazole **153** in phosphate buffer at pH 7.4 and 37° revealed that the corresponding benzoylsulfamoylbenzoic acid **107** prevailed.

For the 3-alkylthiobenzoic acids **168-183** (Table I) it was found convenient to introduce the sulfamoyl function prior to the 3-substituent as shown in Scheme III. For further details see the Experimental Section.

Diuretic Effect and Structure-Activity Relationship. The title compounds prepared in this study were screened in dogs for their diuretic properties after intraveneous and in some cases after oral administration.

The urinary volume and electrolyte excretion from the 3-hr test period are summarized in Table I and compared with those of 3-*n*-butylamino-4-phenoxy-5-sulfamoylbenzoic acid (bumetanide) and 4-benzyl-3-*n*-butylamino-5-sulfamoylbenzoic acid (besunide). For the active compounds the observed onset and duration of diuresis as well as the diuretic profile were similar to those described in previous papers of this series for benzoic acid diuretics of comparable potency. The data demonstrate that a great

Scheme II

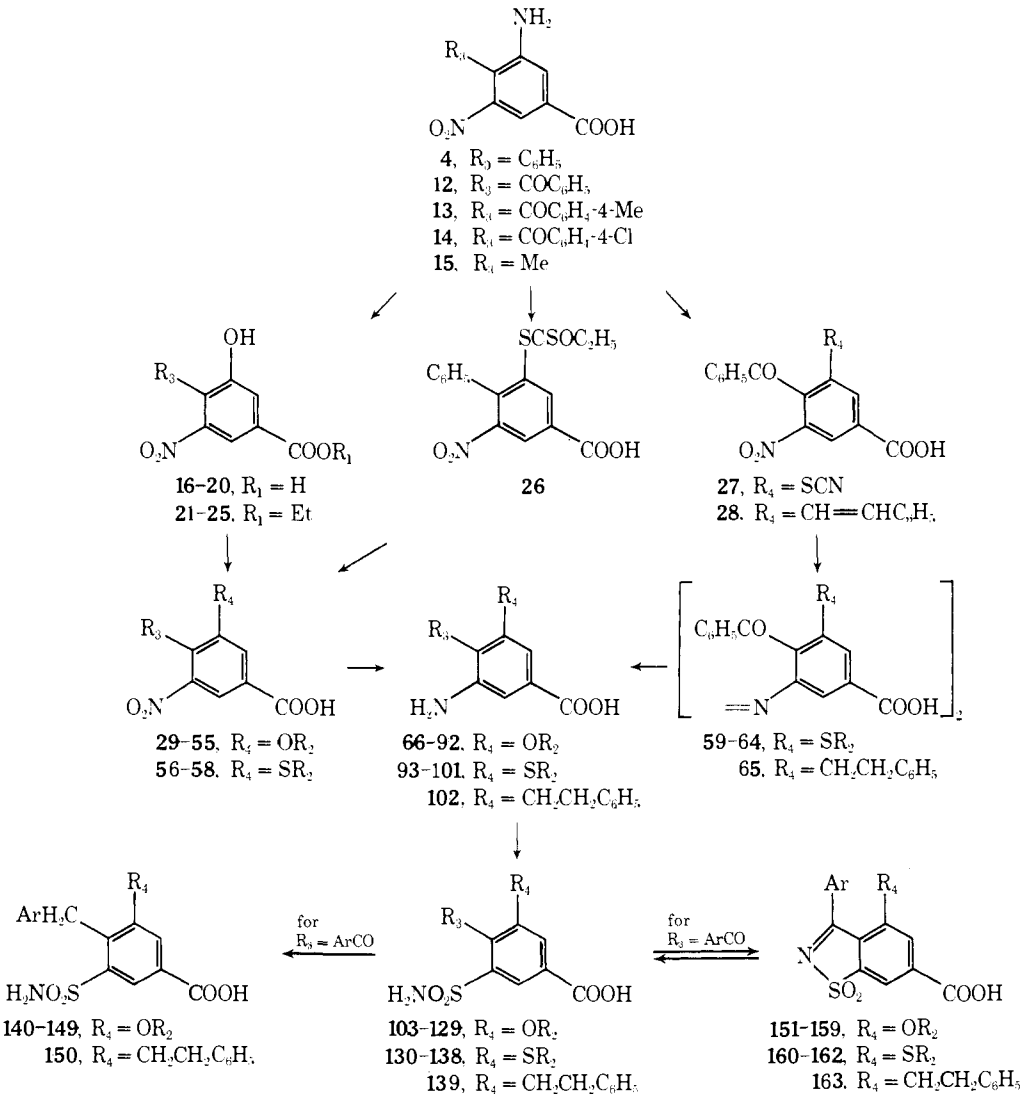
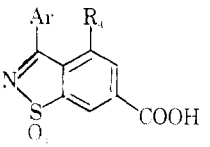
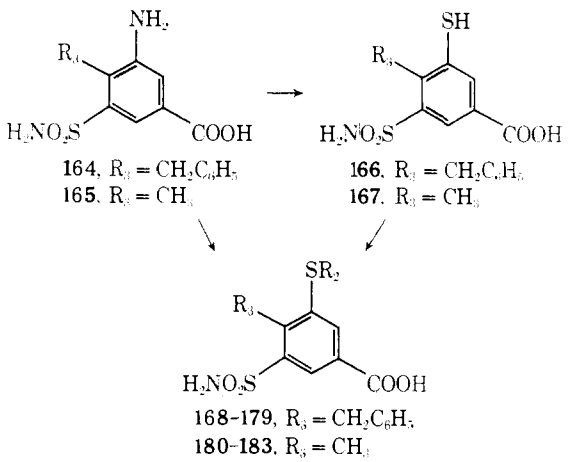


Table II. Physical Properties of 

No.	Ar	R_4	Temp of dehydration, C[a]	Mp, C	Formula[b]
151	C_6H_5	O-*n*-Pr	220–225	213–216	$C_{17}H_{15}NO_5S$
152	C_6H_5	$OCH_2CH{=}CH_2$	205–215	196–198	$C_{17}H_{13}NO_5S$
153	C_6H_5	O-*n*-Bu	210–215	207–210	$C_{18}H_{17}NO_5S$
154	C_6H_4-4-Cl	O-*n*-Bu	190–195	208–210	$C_{18}H_{16}ClNO_5S$
155	C_6H_5	O-*n*-Am	170–175	180–181	$C_{19}H_{19}NO_5S$
156	C_6H_5	$OCH_2C_6H_5$	205–210	229–231	$C_{21}H_{15}NO_5S$
157	C_6H_4-4-Me	$OCH_2C_6H_5$	170–185	220–221	$C_{22}H_{17}NO_5S$[c]
158	C_6H_5	$OCH_2CH_2C_6H_5$	170–175	208–210	$C_{22}H_{17}NO_5S$[c]
159	C_6H_5	$OCH_2CCHCHCHCHN$		276–278	$C_{20}H_{14}N_2O_5S$
160	C_6H_5	SMe	185–190	247–249	$C_{15}H_{11}NO_4S_2$
161	C_6H_5	S-*n*-Pr	160–165	181–183	$C_{17}H_{15}NO_4S_2$
162	C_6H_5	S-*i*-Am	160–175	160–162	$C_{19}H_{19}NO_4S_2$
163	C_6H_5	$CH_2CH_2C_6H_5$	200	189–193	$C_{22}H_{17}NO_4S$

[a] The compounds were prepared according to method ZC at the temperatures defined, except 159, which was obtained on recrystallization (methyl cellosolve) of crude **119**. [b] The compounds were analyzed for C and H; the analytical results were within 0.4% of the theoretical values. The compounds were dried *in vacuo* (10–14 mm) for 16–24 hr in the presence of P_2O_5. [c] Crystallized from C_6H_6.

Scheme III



number of the compounds exhibit excellent diuretic activity. A comparison including previous results[2] for some of the corresponding 4-substituted 3-alkylamino-5-sulfamoylbenzoic acids revealed that high diuretic potency could be retained when the 3-alkoxy, 3-alkylthio, or even a 3-phenethyl side chain is substituted for the 3-alkylamino moiety.

A comparison of the different 3-substituted 4-phenyl-5-sulfamoylbenzoic acids **7–11**, **120–125**, and **136–138** with the various 3-substituted 4-anilino-, 4-phenoxy-, 4-phenylthio-, 4-benzyl-, and 4-benzoyl-5-sulfamoylbenzoic acids of the present and previous investigations[1-3] showed that abolishment of the connecting link to the phenyl in the 4 position leads to a marked decrease in potency down to the level obtainable with the corresponding 4-methylbenzoic acid derivatives. Owing to the restricted possibilities of spatial positions for the 4-phenyl group, this supports our earlier suggestion that steric factors may be of importance for the influence of the 4-substituent on the diuretic potency.

The results obtained with the 4-benzoyl-5-sulfamoylbenzoic acids **103–119**, **130–135**, and **139** are of considerable interest in the light of the previously reported diuretic activity of certain 4- and 5-alkylamino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxides. It has been suggested[2,5] that the activity of these benzisothiazole dioxides is attributable to an interaction of their corresponding 4-benzoyl-5-sulfamoylbenzoic acids with the receptor enabled by a dynamic equilibrium between the benzisothiazole dioxide and the benzoyl compound in plasma. The fact that the 4-benzoyl substituent, evaluated as such for the first time in the present series, contributed to high diuretic potency can be taken as a confirmation of this suggestion.

4-Benzoyl-5-sulfamoyl-3-(3-thenyloxy)benzoic acid (**118**) and 4-benzyl-5-sulfamoyl-3-(3-thenylthio)benzoic acid (**177**) are among the most potent benzoic acid diuretics ever reported. **118** shows significant diuretic activity in dogs at 1 μg/kg, which represents a potency approximately five times as high as that of bumetanide.

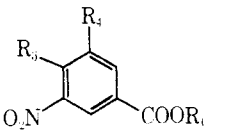
Experimental Section

Technical assistance was given by Mrs. Hanne Hollensen, A. Fogh, and K. Holm. Analyses were performed by G. Cornali and W. Egger of these laboratories. Melting points were corrected and taken in open glass capillaries using a Hershberg apparatus. For the typical compounds nmr spectra were taken by N. Rastrup Andersen on a Varian A-60A spectrometer. Spectral features were in accord with structures. Analytical data are given as defined in footnote *c*, Table I.

Methyl 3,5-Dinitro-4-phenylbenzoate (2, Table III). Method A. A mixture of **1** (60.0 g, 0.23 mol), iodobenzene (36.0 ml, 0.32 mol), and Cu powder (60.0 g, 0.94 g-atom) was stirred at 145–155° for 4.5 hr. After cooling, extraction of the solids with $CHCl_3$, evaporation *in vacuo*, and trituration with MeOH (150 ml), followed by cooling, almost pure **2** was obtained.

3,5-Dinitro-4-phenylbenzoic Acid (3, Table III). Method B. **2** was saponified according to a described method (see ref 2, method B) using methyl cellosolve as solvent.

4-R_3-3-Amino-5-nitrobenzoic Acids (4 and 15, Table III). Method C. 3 or 3,5-dinitro-4-methylbenzoic acid was partially reduced according to a described method (see ref 2, method C) using 2.5 mol of $Na_2S_2O_4$ per mole of dinitro compound and 10–12 ml of 50% pyridine–H_2O per gram of dinitro compound as sol-

Table III. Physical Properties of 

No.	R_1	R_3	R_4	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula[d]
2	CH_3	C_6H_5	NO_2	A	147–148	Methyl cellosolve	73	$C_{14}H_{10}N_2O_6$[e]
3	H	C_6H_5	NO_2	B	219–221	Aq EtOH	97	$C_{13}H_8N_2O_6$
4	H	C_6H_5	NH_2	C	247–249 dec	Aq EtOH	51	$C_{13}H_{10}N_2O_4$[e]
5	H	C_6H_5	SO_2NH_2	D	119–121	Aq EtOH	66	$C_{13}H_{10}N_2O_6S\cdot H_2O$
15	H	CH_3	NH_2	C	213–214	Aq EtOH	70	$C_8H_8N_2O_4$
16	H	COC_6H_5	OH	E	264–266	Aq EtOH	77 (11)	$C_{14}H_9NO_6\cdot H_2O$[e]
17	H	COC_6H_4-4-Me	OH	E	249–251	Aq EtOH	94 (8)	$C_{15}H_{11}NO_6\cdot 0.5H_2O$[f]
18	H	COC_6H_4-4-Cl	OH	E	266–268	MeCN	80 (7)	$C_{14}H_8ClNO_6\cdot 0.5H_2O$[e]
19	H	C_6H_5	OH	E	215–217	Aq MeOH	67 (5)[g]	$C_{13}H_9NO_5$
20	H	CH_3	OH	E	214–215	H_2O	53	$C_8H_7NO_5$
21	C_2H_5	COC_6H_5	OH	F	(167–168)		86[h]	
22	C_2H_5	COC_6H_4-4-Me	OH	F	(124–131)		90[h]	
23	C_2H_5	COC_6H_4-4-Cl	OH	F	(188–192)		91[h]	
24	C_2H_5	C_6H_5	OH	F	128–130	CCl_4	92	$C_{15}H_{13}NO_5\cdot 0.25H_2O$[f]
25	C_2H_5	CH_3	OH	F	137–139	Aq EtOH	80	$C_{10}H_{11}NO_5$
26	H	C_6H_5	$SCSOC_2H_5$	G			*i*	
27	H	COC_6H_5	SCN	H	183–185	Aq EtOH	72	$C_{15}H_8N_2O_5S\cdot 0.25H_2O$[f]
28	H	COC_6H_5	$CH{=}CHC_6H_5$	I	288–289 dec	*j*	16	$C_{22}H_{15}NO_5$[k]

[a] See footnote *b* in Table I. [b] Several recrystallizations were usually performed, if necessary, while treating with decolorizing C. [c] The yield of fairly pure material as used in the following step, usually obtained after one recrystallization, is given. In cases where the yield of a rather impure product (used in the next step) is given, the yield of analytically pure compound is given in parentheses. A sample was, unless otherwise stated, purified to give the analytically pure compound. No attempts were made to optimalize the yields. [d] See footnote *e* in Table I. [e] Dried in air. [f] Dried *in vacuo* (10–14 mm) at 65° for 6–8 hr. [g] Almost pure **19** (62%) was also obtained by acetolysis of the diazonium salt described under method G with a mixture of Ac_2O and AcOH followed by hydrolysis of the intermediate phenol-ester, adapting a method described in ref 9. [h] Not purified; the yield of crude material is given. [i] Not purified. [j] Purified by acidification of a solution of the Na salt in hot H_2O with AcOH. [k] Dried *in vacuo* (40 mm) at 60° for 2 hr in the presence of P_2O_5.

vent. Almost pure **4** or **15** crystallized on acidification with 4 *N* HCl or with 4 *N* AcOH, respectively.

3-Nitro-4-phenyl-5-sulfamoylbenzoic Acid (5, Table III). Method D. **4** was converted to the 5-sulfamoyl derivative **5** adapting a procedure described[6] for the preparation of 2,5-dichloro-4-phenoxy-3-sulfamoylbenzoic acid.

4-R_3-3-Hydroxy-5-nitrobenzoic Acids 16–20 (Table III). Method E. To a stirred mixture of concentrated H_2SO_4 (875 ml) and H_2O (280 ml), the appropriate amine **4** or **12–15**[2] (0.34 mol) was added in portions at 90–100° (in the case of **4** at 15–20°). To the vigorously stirred suspension of the amine sulfate thus obtained a solution of $NaNO_2$ (45 g, 0.66 mol) in H_2O (280 ml) was added dropwise during 1–1.5 hr at 0–5° to give a suspension of the diazonium sulfate (in the case of **15** a solution was obtained). The mixture was stirred for a further 30–60 min allowing the temperature to rise to 15–20° and was then heated on a steam bath (or in the case of **4** in an oil bath kept at 115–120°) until the N_2 evolution had ceased (2–6 hr). Cooling and dilution with H_2O (about 1500 ml) precipitated crude **16–20**. It was convenient to use the thus obtained material in the subsequent steps.

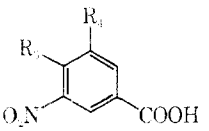
Ethyl 4-R_3-3-Hydroxy-5-nitrobenzoates 21–25 (Table III). Method F. Crude **16–20** were esterified with EtOH using concentrated H_2SO_4 as catalyst. Concentration *in vacuo* to a small volume and trituration with saturated $NaHCO_3$ gave crude **21–25**.

Ethylxanthic Acid 5-Carboxy-3-nitro-2-phenyl Phenyl Ester (26, Table III). Method G. **4** (15.5 g, 60 mmol) and concentrated HCl (80 ml) were heated on a steam bath for a few minutes. To the suspension of the amine hydrochloride thus obtained a solution of $NaNO_2$ (4.8 g, 68 mmol) in H_2O (20 ml) was added dropwise during about 30 min at 0–5°. After additional stirring at 0° for 10–15 min, 50% aqueous HBF_4 (40 ml) was added, and the mixture was stirred at about −10° for 1 hr to precipitate the diazonium tetrafluoroborate. The moist salt was added at 60–70° in portions to a vigorously stirred solution of $KSCSOC_2H_5$ (20 g, 125 mmol) in H_2O (200 ml), followed by heating on a steam bath until the N_2 evolution had ceased (about 30 min) to give, after cooling, **26** as a heavy oil, which was used as such in the next step.

4-Benzoyl-5-nitro-3-thiocyanobenzoic Acid (27, Table III). Method H. **12**[2] was diazotized and the diazonium tetrafluoroborate prepared adapting the procedure given in method G. The air-dried diazonium salt was added at 45–50° in portions to a vigorously stirred mixture of KSCN (about 8 mmol/mmol of salt), CuSCN (about 5.6 mmol/mmol of salt), and H_2O (about 15 ml/g of salt). After the N_2 evolution had ceased (4–5 hr), the stirring was continued for a further 16 hr at room temperature. The solids were dried in air and extracted with boiling EtOH. Evaporation of the extract *in vacuo* and trituration with aqueous EtOH gave almost pure **27**.

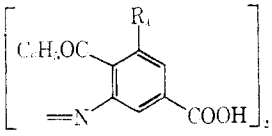
4-Benzoyl-5-nitro-3-styrylbenzoic Acid (28, Table III). Method I. **12**[2] (22.8 g, 0.08 mol) was diazotized at 0–5° with $NaNO_2$ (6.2 g, 0.09 mol) using AcOH (110 ml) and concentrated HCl (170 ml) as solvents. The precipitated diazonium chloride was collected and without drying added to a vigorously stirred solution of cinnamic acid (8.4 g, 0.057 mol) in MeCN (400 ml), immediately followed by a solution of $NaOAc\cdot 3H_2O$ (26 g, 0.19 mol) in H_2O (330 ml) and a solution of $CuCl_2\cdot 2H_2O$ (2.7 g, 0.016 mol) in H_2O (25 ml), successively. After additional stirring for 2 hr, dilution with H_2O (200 ml) and Et_2O (200 ml), and filtration, the aqueous layer was extracted five times with Et_2O. Evaporation of the Et_2O extracts *in vacuo* followed by trituration with aqueous EtOH gave crude **28**. It was dissolved in hot 1 *N* $NaHCO_3$ (60 ml) and cooled to precipitate the Na salt of **28**. Redissolving in hot H_2O and acidification with AcOH yielded analytically pure **28**.

4-R_3-3-R_4-5-Nitrobenzoic Acids 29–58 (Table IV). Method J. Crude **21–25** (30 mmol) was added to a solution of NaOEt (40 mmol) in dry EtOH (100 ml) followed by the appropriate alkyl iodide or alkyl bromide (40 mmol, in the case of 3-thenyl bromide[8] dissolved in 40 ml of C_6H_6) and the mixture was refluxed for 12–72 hr. The reaction was controlled by tlc, and if necessary additional amounts of NaOEt and/or alkyl halogenide were added. When the alkylation was completed, the solvents were re-

Table IV. Physical Properties of 

No.	R_3	R (OR_2, SR_2)	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula[d]
29	COC_6H_5	OEt	J	188–191	EtOH	61	$C_{16}H_{13}NO_6 \cdot 0.5C_2H_5OH$[e]
30	COC_6H_5	O-*n*-Pr	J	160–162	Aq EtOH	65	$C_{17}H_{15}NO_6$[e]
31	COC_6H_5	$OCH_2CH{=}CH_2$	J	192–193	EtOH	51	$C_{17}H_{13}NO_6$[e]
32	COC_6H_5	$OCH_2C{\equiv}CH$	J	169–172	Aq EtOH	37	$C_{17}H_{11}NO_6$[e]
33	COC_6H_5	O-*n*-Bu	J	183–185	Aq EtOH	65	$C_{18}H_{17}NO_6$[e]
34	COC_6H_4-4-Me	O-*n*-Bu	J	162–163	EtOH	60	$C_{19}H_{19}NO_6 \cdot 0.5C_2H_5OH$[f]
35	COC_6H_4-4-Cl	O-*n*-Bu	J	180–182	EtOH	55	$C_{18}H_{16}ClNO_6$[f]
36	COC_6H_5	O-*n*-Am	J	163–165	Aq EtOH	56 (13)	$C_{19}H_{19}NO_6$[f]
37	COC_6H_5	$O(CH_2)_5CH_3$	J	165–166	EtOH	74 (9)	$C_{20}H_{21}NO_6 \cdot 0.25H_2O$[e]
38	COC_6H_5	$OCH_2C_6H_5$	K	205–207	EtOH	67	$C_{21}H_{15}NO_6$[e]
39	COC_6H_4-4-Me	$OCH_2C_6H_5$	J	222–223	EtOH	63	$C_{22}H_{17}NO_6 \cdot 0.25H_2O$[e]
40	COC_6H_4-4-Cl	$OCH_2C_6H_5$	J	137–139	EtOH	50	$C_{21}H_{14}ClNO_6$[e]
41	COC_6H_5	$OCH_2C_6H_4$-4-Cl	J	253–254	EtOH	56 (9)	$C_{21}H_{14}ClNO_6 \cdot 0.25H_2O$[f]
42	COC_6H_5	$OCH_2CH_2C_6H_5$	J	168–171	Aq EtOH	22	$C_{22}H_{17}NO_6$
43	COC_6H_5	$O(CH_2)_3C_6H_5$	J	186–187	Aq EtOH	24	$C_{23}H_{19}NO_6 \cdot 0.5C_2H_5OH$[f]
44	COC_6H_5	$OCH_2CCHCHSCH$	K	201–203	Aq EtOH	2	$C_{19}H_{13}NO_6S \cdot 2H_2O$[e]
45	COC_6H_5	$OCH_2CCHCHCHCHN$	J	225–226	Methyl cellosolve	5	$C_{20}H_{14}N_2O_6$[f]
46	C_6H_5	O-*n*-Pr	J	142–144	Aq EtOH	72	$C_{16}H_{15}NO_5$
47	C_6H_5	O-*n*-Bu	J	133–134	HCOOH	40	$C_{17}H_{17}NO_5$[g]
48	C_6H_5	O-*n*-Am	J	144–146	Aq EtOH	83	$C_{18}H_{19}NO_5$
49	C_6H_5	$OCH_2C_6H_5$	K	188–190	*i*-PrOH	42	$C_{20}H_{15}NO_5$[e]
50	C_6H_5	$OCH_2CH_2C_6H_5$	J	172–173	HCOOH	45	$C_{21}H_{17}NO_5$[g]
51	C_6H_5	$OCH_2CCHCHSCH$	J	184–186	EtOH	19	$C_{16}H_{13}NO_5S$
52	CH_3	O-*n*-Pr	J	172–173	Aq EtOH	85	$C_{11}H_{13}NO_5$
53	CH_3	O-*n*-Bu	J	147–149	Aq EtOH	87	$C_{12}H_{15}NO_5$
54	CH_3	$OCH_2C_6H_5$	K	188–190	EtOH	61	$C_{15}H_{13}NO_5$
55	CH_3	$OCH_2CCHCHSCH$	J	152–154	Aq EtOH	29	$C_{13}H_{11}NO_5S \cdot H_2O$
56	C_6H_5	S-*n*-Pr	L	178–180	Aq EtOH	60[h]	$C_{16}H_{15}NO_4S$
57	C_6H_5	S-*n*-Bu	L	147–148	Aq EtOH	46[h]	$C_{17}H_{17}NO_4S \cdot 0.67H_2O$
58	C_6H_5	$SCH_2C_6H_5$	L	179–181	Aq EtOH	71[h]	$C_{20}H_{15}NO_4S \cdot 0.5H_2O$

[a] See footnote *b* in Table I. [b,c] See corresponding footnotes in Table III. [d] See footnote *e* in Table I. [e,f] See corresponding footnotes in Table III. [g] Dried *in vacuo* (10–14 mm) for 24 hr in the presence of KOH. [h] Yield over two steps based on 4.

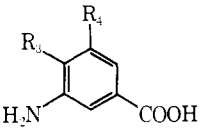
Table V. Physical Properties of 

No.	R_4 (SR_2, CH_2R_2)	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula[d]
59	SMe	M	232–234 dec	EtOH	67	$C_{30}H_{22}N_2O_6S_2$[e]
60	S-*n*-Pr	M	164–165	Aq EtOH	53	$C_{34}H_{30}N_2O_6S_2$[f]
61	$SCH_2CH{=}CH_2$	M	161–163	EtOH	61	$C_{34}H_{26}N_2O_6S_2$[e]
62	S-*n*-Bu	M	102–103	Aq EtOH	43	$C_{36}H_{34}N_2O_6S_2$[f]
63	S-*i*-Am	M	143–144	EtOH	54	$C_{38}H_{38}N_2O_6S_2$[e]
64	$SCH_2C_6H_5$	M	219–220	[g]	70	$C_{42}H_{30}N_2O_6S_2$[e]
65	$CH_2CH_2C_6H_5$	N	172–173	Aq EtOH	31	$C_{44}H_{34}N_2O_6$[h]

[a] See footnote *b* in Table I. [b,c] See corresponding footnotes in Table III. [d] See footnote *e* in Table I. [e,f] See corresponding footnotes in Table III. [g] A mixture of EtOH (three parts) and methyl cellosolve (two parts) was used. [h] Dried *in vacuo* (10 mm) at 60° for 2 hr in the presence of P_2O_5.

moved *in vacuo* and the residue was saponified by heating with 2 *N* NaOH (100 ml) on a steam bath for 45–50 min. After charcoaling and cooling the Na salt separated. Redissolving in hot H_2O and acidification (4 *N* HCl or AcOH) precipitated the fairly pure acids.

Method K. A mixture of crude **16**, **19**, or **20** (16.5 mmol), $C_6H_5CH_2Br$ (2.5 ml, 21 mmol), or 3-thenyl bromide[8] (about 30 mmol in 30 ml of C_6H_6) and 1 *N* NaOH (50 ml) was stirred at room temperature for 24 hr. After cooling, the separated Na salt was worked up adapting method J.

Table VI. Physical Properties of 

No.	R_3	R_4 (OR_2, SR_2, CH_2R_2)	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula[d]
66	COC_6H_5	OEt	O	229–231	EtOH	91	$C_{16}H_{15}NO_4$[e]
67	COC_6H_5	O-*n*-Pr	O	220–222	EtOH	66	$C_{17}H_{17}NO_4$
68	COC_6H_5	$OCH_2CH{=}CH_2$	O	206–208	EtOH	49	$C_{17}H_{15}NO_4$[f]
69	COC_6H_5	$OCH_2C{\equiv}CH$	O	191–193	Aq EtOH	78	$C_{17}H_{13}NO_4$[e]
70	COC_6H_5	O-*n*-Bu	O	202–204	EtOH	73	$C_{18}H_{19}NO_4$[f]
71	COC_6H_4-4-Me	O-*n*-Bu	O	168–172	Aq EtOH	61	$C_{19}H_{21}NO_4$[f]
72	COC_6H_4-4-Cl	O-*n*-Bu	O	286–288	Aq EtOH	92	$C_{18}H_{18}ClNO_4$[e]
73	COC_6H_5	O-*n*-Am	O	168–170	Aq EtOH	55	$C_{19}H_{21}NO_4$[e]
74	COC_6H_5	$O(CH_2)_5CH_3$	O	168–169	Aq EtOH	80	$C_{20}H_{23}NO_4$[e]
75	COC_6H_5	$OCH_2C_6H_5$	O	216–218	EtOH	98	$C_{21}H_{17}NO_4$[e]
76	COC_6H_4-4-Me	$OCH_2C_6H_5$	O	182–185	EtOH	41	$C_{22}H_{19}NO_4 \cdot 0.25H_2O$[e]
77	COC_6H_4-4-Cl	$OCH_2C_6H_5$	O	191–193	EtOH	94	$C_{21}H_{16}ClNO_4 \cdot 0.25H_2O$[f]
78	COC_6H_5	$OCH_2C_6H_4$-4-Cl	O	248–249	Methyl cellosolve	90	$C_{21}H_{16}ClNO_4$[e]
79	COC_6H_5	$OCH_2CH_2C_6H_5$	O	162–163	Aq EtOH	65	$C_{22}H_{19}NO_4 \cdot 0.5H_2O$
80	COC_6H_5	$O(CH_2)_3C_6H_5$	O	157–158	Aq EtOH	83	$C_{23}H_{21}NO_4$[e]
81	COC_6H_5	$OCH_2CCHCHSCH$	O	227–229	*g*	93	$C_{19}H_{15}NO_4S$[e]
82	COC_6H_5	$OCH_2CCHCHCHCHN$	O	212–213	Methyl cellosolve	61	$C_{20}H_{16}N_2O_4$[f]
83	C_6H_5	O-*n*-Pr	O	102–104	Aq EtOH	48	$C_{16}H_{17}NO_3$
84	C_6H_5	O-*n*-Bu	P	122–124	Aq EtOH	38	$C_{17}H_{19}NO_3$
85	C_6H_5	O-*n*-Am	P	134–135	Aq EtOH	37	$C_{18}H_{21}NO_3 \cdot 0.25H_2O$
86	C_6H_5	$OCH_2C_6H_5$	P	161–162	Aq EtOH	72	$C_{20}H_{17}NO_3 \cdot 0.5H_2O$[e]
87	C_6H_5	$OCH_2CH_2C_6H_5$	P	159–160	EtOH	54	$C_{21}H_{19}NO_3$
88	C_6H_5	$OCH_2CCHCHSCH$	O	139–140	Aq EtOH	71	$C_{18}H_{15}NO_3S \cdot 0.5H_2O$
89	CH_3	O-*n*-Pr	P	164–165	Aq EtOH	72	$C_{11}H_{15}NO_3$
90	CH_3	O-*n*-Bu	P	137–139	Aq EtOH	80	$C_{12}H_{17}NO_3$
91	CH_3	$OCH_2C_6H_5$	P	167–169	Aq EtOH	89	$C_{15}H_{15}NO_3$
92	CH_3	$OCH_2CCHCHSCH$	O	*h*			
93	COC_6H_5	SMe	Q	158–159	Aq EtOH	96	$C_{15}H_{13}NO_3S$[e]
94	COC_6H_5	S-*n*-Pr	Q	124–126	Aq EtOH	60	$C_{17}H_{17}NO_3S$[e]
95	COC_6H_5	$SCH_2CH{=}CH_2$	Q	152–154	EtOH	67	$C_{17}H_{15}NO_3S$[e]
96	COC_6H_5	S-*n*-Bu	Q	144–145	Aq EtOH	70	$C_{18}H_{19}NO_3S \cdot 0.25H_2O$[e]
97	COC_6H_5	S-*i*-Am	Q	143–144	Aq EtOH	95	$C_{19}H_{21}NO_3S$
98	COC_6H_5	$SCH_2C_6H_5$	Q	141–142	Aq EtOH	65	$C_{21}H_{17}NO_3S$[e]
99	C_6H_5	S-*n*-Pr	P	190–191	Aq EtOH	83	$C_{16}H_{17}NO_2S$
100	C_6H_5	S-*n*-Bu	P	143–144	Aq EtOH	80	$C_{17}H_{19}NO_2S$
101	C_6H_5	$SCH_2C_6H_5$	P	173–174	Aq EtOH	42	$C_{20}H_{17}NO_2S$
102	COC_6H_5	$CH_2CH_2C_6H_5$	R	153–155	Aq EtOH	57	$C_{22}H_{19}NO_3$[i]

[a] See footnote *b* in Table I. [b,c] See corresponding footnotes in Table III. [d] See footnote *e* in Table I. [e,f] See corresponding footnotes in Table III. [g] A mixture of EtOH (five parts) and methyl cellosolve (one part) was used. [h] Not obtained analytically pure. [i] Dried *in vacuo* (10 mm) at 78° for 2 hr in the presence of P_2O_5.

Method L. A mixture of crude **26** (prepared from 10 mmol of **4**) and 2 *N* NaOH (35 ml) in a N_2 atmosphere was heated on a steam bath for 15 min. The appropriate alkyl iodide or alkyl bromide (20–25 mmol) was added, and the mixture was stirred for 16–20 hr in a N_2 atmosphere. After cooling, the separated Na salt was worked up adapting method J.

3,3′-(R_4)$_2$-2,2′-Dibenzoyl-5,5′-dicarboxyazobenzenes 59–65 (Table V). Method M. A mixture of **27** (6.65 g, 20 mmol), glucose monohydrate (4.0–5.0 g, 20–25 mmol), and 2 *N* NaOH (65 ml) was heated on a steam bath for a few minutes. The appropriate alkyl iodide or alkyl bromide (22–35 mmol) was added and the mixture was stirred in a N_2 atmosphere, in the case of **59**, **61**, and **64** at room temperature for 3–5 hr, and in the case of **60**, **62**, and **63** at 50–60° for 5 hr. After cooling, the separated Na salt was worked up adapting method J.

Method N. **28** (7.4 g, 20 mmol) was suspended in EtOH (375 ml) and hydrogenated using (10%) Pd/C (0.7 g) as catalyst. Filtration and dilution with H_2O precipitated crude **65**.

4-R_3-3-R_4-5-Aminobenzoic Acids 66–102 (Table VI). Method O. The appropriate NO_2 derivative was reduced according to a described procedure (see ref 2, method E), except that the heating following the acidification was omitted.

Method P. The appropriate NO_2 derivative was reduced according to a described procedure given under method O, except that the reaction mixture without removal of the solvents was poured into an excess of 4 *N* AcOH and/or HCl. In the case of **89–91** a hydrated sulfite resulted. The free amine was obtained by addition of an alkaline solution of the sulfite to an excess of 1 *N* AcOH.

Method Q. A mixture of the appropriate azobenzene **59–64** (5 mmol), $SnCl_2 \cdot 2H_2O$ (4.5–6.0 g, 20–27 mmol), concentrated HCl (9–12 ml), and AcOH (50 ml) was heated on a steam bath for 1.5–2 hr. Evaporation *in vacuo* and trituration with H_2O (about 50 ml) yielded crude **93–98**.

Method R. To a stirred, hot solution of **65** (2.8 g, 8 mmol) in AcOH (80 ml), Fe powder (2.8 g, 0.05 g-atom) was added in por-

tions during 45 min. Additional stirring for 15 min and cooling precipitated crude **102**. Redissolving in hot saturated $NaHCO_3$, charcoaling, and acidification with AcOH precipitated **102**.

4-R_3-3-R_4-5-Sulfamoylbenzoic Acids 6–11, 103–150, and 168–183 (Table I). Method S. 5 was in AcOH solution hydrogenated using PtO_2 as catalyst.

Method T. 6 was alkylated adapting a described procedure (see ref 3, method 3A), in the case of 7 using $CH_3CH{=}CHCH_2Br$ instead of $C_6H_5CH_2Br$. The intermediate Et esters were saponified (2 *N* NaOH) without purification.

Method U. 7 was in EtOH solution hydrogenated using PtO_2 as catalyst.

Method V. 6 was reductively alkylated adapting a method described in ref 3, method 4K.

Method W. 4-Vinylpyridine was in MeOH solution allowed to react with 6, using AcOH as catalyst.

Method X. A solution of the appropriate amino derivative (3 mmol) and KNO_2 or $LiNO_2{\cdot}H_2O$ (3.3–3.5 mmol) in 1 *N* KOH or LiOH (6.5–7.5 ml) was added at −2–2° dropwise to a stirred mixture of concentrated HCl (7–10 ml) and AcOH (7–10 ml). To the diazonium mixture was added AcOH saturated with SO_2 (10 ml) and containing $CuCl_2{\cdot}2H_2O$ (0.3–0.4 g) in H_2O (1–1.5 ml). The stirring was continued for a further 2–4 hr at room temperature to precipitate the sulfochloride, if necessary after cooling and/or dilution with H_2O. It was added at 10–15° in portions to stirred concentrated aqueous NH_3 (about 10 ml/g of sulfochloride). Additional stirring at room temperature for 16–20 hr followed by cooling precipitated the NH_4 salt. Redissolving in 1 *N* NaOH (about 10 ml/g of salt) and acidification with a slight excess of ice-cold 1 *N* AcOH or HCl gave the crude reaction product. For 106, 120–121, 130–133, and 135–138 the reaction mixture after the amidation process was acidified without isolation of an NH_4 salt.

Method Y. A described process given under method D was adapted except that the solvent was a mixture of concentrated HCl and AcOH. The crude reaction product was (except in the case of 110, 112, and 139) dissolved in hot saturated $NaHCO_3$ (about 10 ml/g of sulfamoyl derivative) and, after cooling, the Na salt thus obtained was worked up as described under method X for similar NH_4 salts.

Method Z. The Wolff–Kishner reduction described in ref 5, method G, was adapted.

Method ZA. 164[2] or 165[2] (0.1 mol) was diazotized according to method X using $NaNO_2$ (7.0 g, 0.1 mol) and 1 *N* NaOH (150 ml). The filtered diazonium solution at 60–70° was carefully added to a vigorously stirred solution of $KSCSOC_2H_5$ (24 g, 0.15 mol) and $NaHCO_3$ (250 g) in H_2O (900–1100 ml). Stirring at 60–70° for a further 1–1.5 hr, cooling, and cautious acidification with concentrated HCl precipitated the crude xanthate, which was dissolved in 2 *N* NaOH (about 10 ml/g of xanthate) and in a N_2 atmosphere heated on a steam bath for 1–1.5 hr. Cooling and acidification with a slight excess of 4 *N* HCl (in a N_2 atmosphere) precipitated crude 166 (80–85% based on 164) or crude 167 (30–35% based on 165) contaminated with various amounts of the corresponding disulfides. The crude thiol (166 or 167, 5 mmol) was dissolved in stirred saturated $NaHCO_3$ (12–15 ml) followed by addition of $NaHCO_3$ (1.0 g, 12 mmol) and, in small portions, $Na_2S_2O_4$ (1.0 g, 6 mmol). The appropriate alkyl iodide or alkyl bromide, for 178 4-chloromethylpyridine and for 179 4-vinylpyridine (6–10 mmol), was added, and the mixture was stirred at room temperature for 2–4 hr. In the case of 178, 180, and 181 the reaction time was extended to 18–20 hr and in the case of 169, 170, 172, 173, and 179 the reaction was performed at 65–70° for 3–4 hr. After cooling, the separated Na salt was worked up as described under method X for similar NH_4 salts. For 179 the reaction mixture was acidified (4 *N* AcOH) without isolation of a salt.

Method ZB. 164[2] (6.12 g, 20 mmol) was diazotized as given in method ZA. The filtered diazonium solution was added to a stirred mixture of furfurylmercaptan (3.8 g, 33 mmol), Cu powder (2.0 g), and 2 *N* NaOH (125 ml). After additional stirring at room temperature for 1 hr, the mixture was heated on a steam bath for 1.5 hr, charcoaled, and, after cooling, acidified with AcOH (12 ml) to precipitate an oil. Redissolving in hot saturated $NaHCO_3$ (35 ml) and cooling yielded the Na salt of 176, which was worked up as described under method X for similar NH_4 salts.

3-Aryl-4-R_4-6-carboxy-1,2-benzisothiazole 1,1-Dioxides 151–158 and 160–163 (Table II). Method ZC. A pure sample (25–100 mg) of the appropriate 4-aroyl-5-sulfamoyl derivative was heated for 5–10 min in an oil bath kept at the temperature defined in Table II. On cooling, the pure anhydro compound usually crystallized in quantitative yield. In a few cases (see Table II) where an amorphous material resulted, crystallization from C_6H_6 was performed.

Hydrolytic Ring Cleavage of 153. To 153 (10 mg) was added phosphate buffer of pH 7.4 (10 ml) preheated to 37°, and the mixture was stirred at 37 ± 0.5°; 153 dissolved within 1–2 min. After 1.5, 5, 15, 30, and 60 min samples (2.0 ml) were rapidly cooled in ice, acidified with 4 *N* AcOH (0.3 ml), and extracted with EtOAc (0.5 ml). The extracts were analyzed by tlc [silica gel (HF 254, Merck), $CHCl_3$ (80), AcOH (10), C_6H_{12} (10), MeOH (2.5)]. As reference compounds were used 107 and 153 both proved to be stable under the chromatographical conditions. Examination of the plates in uv (254 and 366 nm) revealed that all time samples had the same composition in showing only 107 besides traces of 153.

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Antiinflammatory Sydnones. 2

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A series of derivatives of 3-(2-phenylthio)ethylsydnone has been synthesized. Several of these compounds are more potent than hydrocortisone and phenylbutazone *vs.* adjuvant arthritis.

We have recently reported that sydnone 1 and several closely related analogs possess potent antiarthritic activity as measured in the adjuvant arthritis assay. It was shown that the structural features consistent with maximum activity included an aromatic ring at R_2, X = S or SO, and a two-carbon link between sulfur and the sydnone ring. Where X = SO_2 or O, activity was maintained but at diminished levels. The study described here was designed to determine the structural limits on R_1 and R_2 consistent with biological activity and to determine which of these impart maximum potency.

The sydnones were synthesized according to the general