Aminobenzoic Acid Diuretics. 5.[1] 3-Amino-4-arylmethyl-5-sulfamylbenzoic Acid Derivatives and Related Compounds

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A series of 3-substituted amino-4-arylmethyl-5-sulfamylbenzoic acids and a series of 4-substituted amino-6-carboxy-3-aryl-1,2-benzisothiazole 1,1-dioxides have been synthesized and screened for their diuretic properties in the dog assay. The screening results from a 3-hr test period are summarized. For investigation of the structure–activity relationship, selected derivatives of 4-methyl- and 4-phenethyl-3-amino-5-sulfamylbenzoic acid were synthesized. 5-Benzylamino-7-carboxy-4-phenyl-1,2,3-benzothiadiazine 1,1-dioxide, an aza homolog of the corresponding 1,2-benzisothiazole, was prepared and found to be devoid of diuretic activity. It is concluded that substituted or unsubstituted phenyl attached by NH, O, S, SO, SO_2, CO, or CH_2 to the 4 position of N-substituted 2- or 3-amino-5-Benzylamino-7-carboxy-4-phenyl-1,2,3-benzothiadiazine 1,1-dioxide, an aza homolog of the corresponding 1,2- to steric rather than to physicochemical parameters. 4-Benzyl-3-*n*-butylamino-5-sulfamylbenzoic acid (besunide, pINN) was selected for further investigation. At an almost equal dose level, the diuretic profile and behavior of the compound were shown to be similar to that of bumetanide in dogs. In the rat the compound was rapidly inactivated by metabolization. LD_{50}'s in mice were found to be 186 mg/kg and >2 g/kg after iv and oral administration, respectively.

In the preceding paper[1] of this series the synthesis and diuretic activity of 4-benzyl-5-sulfamylanthranilic acid derivatives and related N-alkylated 5-amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxides were reported. A tentative explanation of the rather high diuretic and saluretic potency of these benzisothiazoles was based on the existing equilibrium between these compounds and the corresponding N-alkylated 4-benzoyl-5-sulfamylanthranilic acids in aqueous solution. An examination of the results found in earlier studies[2,3] revealed that the dependence of the diuretic potency on structural changes tended to be less pronounced in the 3-amino-5-sulfamylbenzoic acid series than in the 5-sulfamylanthranilic acids.

With this background in mind, we decided to investigate the title compounds, including some 4-substituted amino-6-carboxy-3-aryl-1,2-benzisothiazole 1,1-dioxides **35–43** as cyclodehydration products of the corresponding 3-substituted amino-4-benzoyl-5-sulfamylbenzoic acids. Due to the expected equilibrium in aqueous solution, it could not be foreseen whether these benzoyl compounds or the benzisothiazoles would be stable and isolable.

After the diuretic effect and structure of the benzisothiazoles had been established, it seemed justifiable to synthesize 5-benzylamino-7-carboxy-4-phenyl-1,2,3-benzothiadiazine 1,1-dioxide (**79**) as an aza ring homolog of **35**.

Furthermore, in connection with our studies on the structural requirements of high ceiling diuretic activity, we found it of interest to investigate selected derivatives of 4-methyl- and 4-phenethyl-3-amino-5-sulfamylbenzoic acid.

Chemistry. The synthesis of the 3-substituted amino-4-arylmethyl-5-sulfamylbenzoic acids **57–74** (Table IV) and the related 4-substituted amino-6-carboxy-3-aryl-1,2-benzisothiazole 1,1-dioxides **35–43** (Table III) is outlined in Scheme I and detailed in the Experimental Section.

The key reaction in the sequence consists in a partial reduction of the symmetrical dinitro compounds **6–9** to the corresponding nitroamines **10–13** (Table I) by means of sodium dithionite. This reaction was sensitive as both the amount of dithionite and the temperature are involved. It is remarkable that the 4-arylcarbonyl-3-nitro-5-sulfamylbenzoic acids **14–17** (Table I) were isolable, since following the reduction of the nitro group, cyclodehydration to the corresponding benzisothiazoles **18–21** (Table III) occurs spontaneously as described for similar compounds.[1] The benzisothiazoles **35–38** and **40** were prepared by alkylation of the appropriate amines *via* their ethyl esters. The alternative route involving alkylation of the probably less sterically hindered benzisothiazolines and subsequent dehydrogenation was advantageous in cases where the direct alkylation proceeded at a low rate. The 3-amino-4-arylmethyl-5-sulfamylbenzoic acid derivatives **53–74** (Table IV) were achieved from the corresponding benzisothiazoles by Wolff–Kishner reduction and alkylation in arbitrary order according to methods dealt with in previous papers of this series.

The preparation of the 1,2,3-benzothiadiazine derivative **79** is outlined in Scheme II and implies cyclization as described for the parent compound.[4]

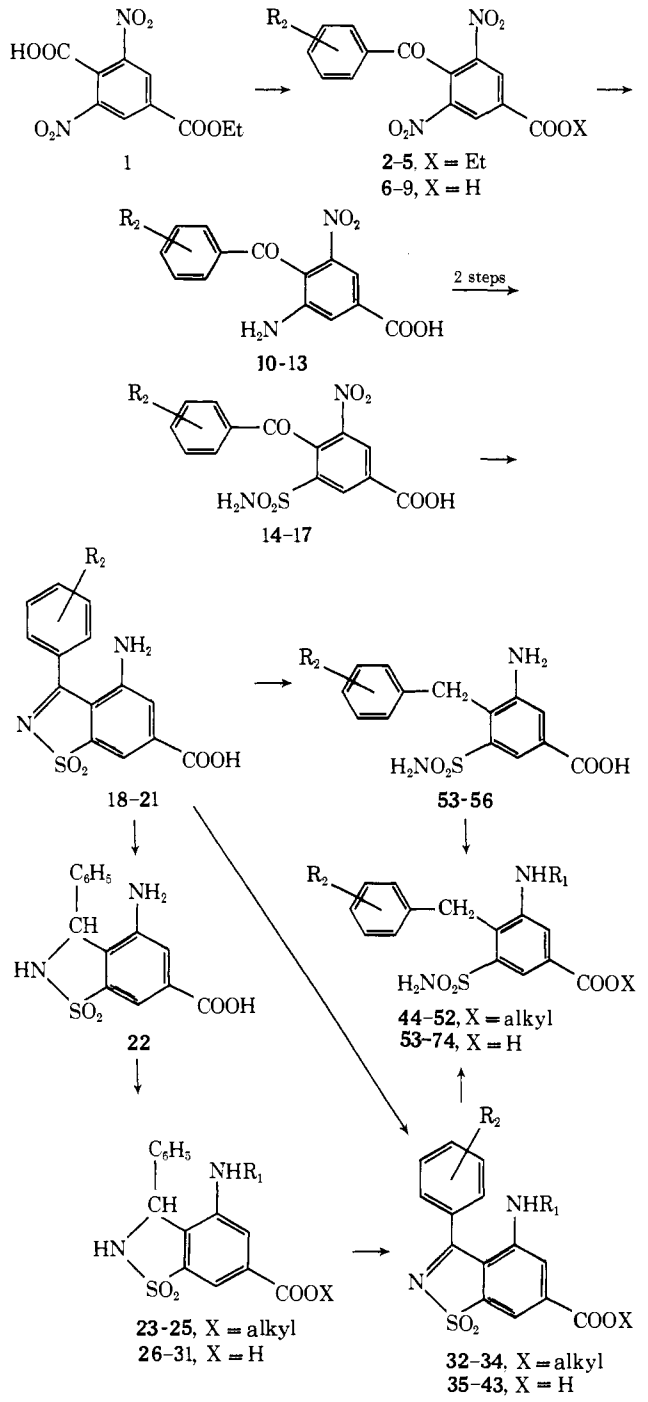
The 3-substituted amino-4-(2-phenethyl)-5-sulfamylbenzoic acids **87** and **89** were available as indicated in Scheme III. The deprotonation of the 4-methyl group in **80** was sufficiently facilitated by the nitro groups to allow C-alkylation by means of benzyl bromide and sodium hydride in hexamethyl phosphoric triamide. The partial reduction to **83**, the introduction of the sulfonamide function to yield **84**, and the subsequent reduction to the amino acid **85** followed by alkylation were performed as detailed in the Experimental Section.

The 3-benzylamino-4-methyl-5-sulfamylbenzoic acid was provided *via* 4-methyl-3-nitro-5-sulfamylbenzoic acid, mainly by adapting methods described in preceding papers of this series.[2,5,†]

Diuretic Effect and Structure–Activity Relationship. The 3-substituted amino-4-arylmethyl-5-sulfamylbenzoic acids **57–74** (Table IV), the 3-substituted amino-4-phenethyl-5-sulfamylbenzoic acids **87** and **89**, 3-benzylamino-4-methyl-5-sulfamylbenzoic acid, the 4-substituted amino-6-carboxy-3-aryl-1,2-benzisothiazole 1,1-dioxides **35–43** (Table III), and the benzothiadiazine dioxide **79** prepared in this study were screened for their diuretic properties in dogs. Excellent diuretic potency was found for many of the 4-arylmethyl-5-sulfamylbenzoic acid derivatives both after iv and oral administration. In this respect these compounds were superior to the benzisothiazoles. The urinary volume and electrolyte excretion from the 3-hr test period following iv administration (solution

† In ref 5 the term metanilic acid has been used erroneously for 3-aminobenzoic acid throughout.

Scheme I

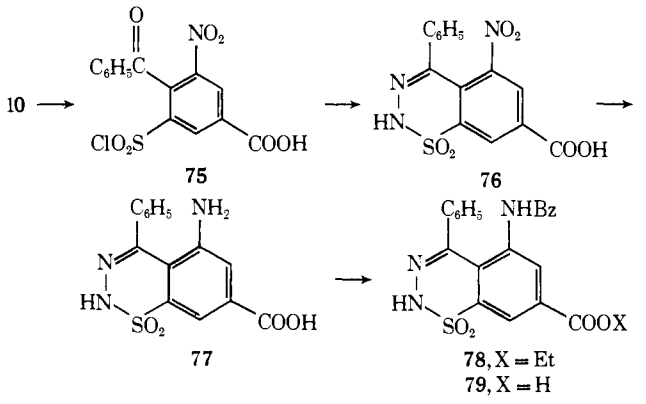


in NaOH) are tabulated in Table V and compared with furosemide and bumetanide (3-*n*-butylamino-4-phenoxy-5-sulfamylbenzoic acid). Due to an existing equilibrium in aqueous solution, as previously shown for the 5-substituted amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxide diuretics,[1] the benzisothiazoles of the present study should exhibit their diuretic effect by interaction of the corresponding 3-substituted amino-4-arylcarbonyl-5-sulfamylbenzoic acids with the receptor. This is supported by the equal diuretic effect of **35**, following oral administration and iv administration in alkaline solution, where in the latter case the compound is present as the benzoyl derivative. Furthermore, **41** showed a diuretic effect after iv administration of both the alkaline solution and the neutral solution of the sodium salt of **41**. In this connection it is interesting that the benzothiadiazine **79** is completely devoid of activity.

The phenethyl compounds **87** and **89**, investigated in an attempt to delineate the structural requirements for the 4 substituent, were considerably less potent than the corresponding 4-benzyl compounds **57** and **66**, respectively. Intravenous administration of 1 mg/kg of **87** resulted in a 3-hr test period in the following urinary excretion per kilogram: 11 ml of urine, 1.2 mequiv of Na^+, 0.3 mequiv of K^+, and 1.6 mequiv of Cl^-. The corresponding results for **89** have been: 6 ml of urine, 0.62 mequiv of Na^+, 0.2 mequiv of K^+, and 0.92 mequiv of Cl^-. For control values see Table V. The 3-benzylamino-4-methyl-5-sulfamylbenzoic acid showed significant diuresis under these conditions, increasing at a dose of 10 mg/kg to the following excretion: 38 ml of urine, 4.5 mequiv of Na^+, 1.0 mequiv of K^+, and 5.2 mequiv of Cl^-.

In this series we have examined some of the structural features required for potent high ceiling diuretic activity. The influence of the N-substituent and its difference in the 2-amino- and 3-aminobenzoic acid series have already been discussed in our earlier papers. Regarding the substituent in the 4 position, substituted phenyl attached by NH, O, S, SO, SO_2, CO, or CH_2 to N-substituted 2- or 3-amino-5-sulfamylbenzoic acids obviously contributed to the high potency, which is in contrast to selected thiazide-type diuretics where corresponding substitution resulted in inactive compounds.[6] From a physicochemical point of view it might appear surprising that despite the variation in the connecting link to aryl, almost equal diuretic potency is obtainable. This led to the conclusion that steric parameters are of importance for this part of

Scheme II



Scheme III

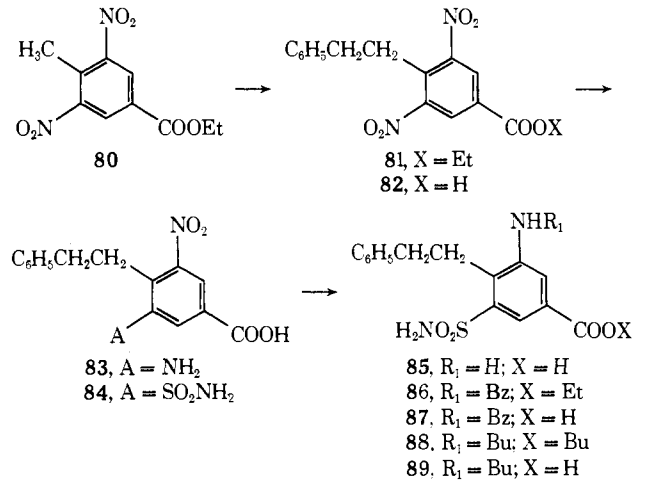
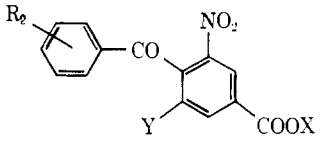


Table I. Physical Properties of



No.	R_2	X	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula[d]
				Y = NO_2			
2	H	Et	A	172–173	Me cellosolve	46	$C_{16}H_{12}N_2O_7$
3	4-Me	Et	A	177.5–179	*e*	67	$C_{17}H_{14}N_2O_7$
4	2,4-Me_2	Et	A	155.5–157.5	Me cellosolve	46	$C_{18}H_{16}N_2O_7$
5	4-Cl	Et	A	162.5–164	EtOH	18	$C_{16}H_{11}ClN_2O_7$
6	H	H	B	264–265 dec	Aqueous EtOH	89	$C_{14}H_8N_2O_7$
7	4-Me	H	B	266–268 dec	EtOH	84	$C_{15}H_{10}N_2O_7$
8	2,4-Me_2	H	B	243–245 dec	EtOH	78	$C_{16}H_{12}N_2O_7$
9	4-Cl	H	B	266–267 dec	Aqueous EtOH	51	$C_{14}H_7ClN_2O_7$
				Y = NH_2			
10	H	H	C	203–204 dec	MeCN	59	$C_{14}H_{10}N_2O_5$[f]
11	4-Me	H	C	223.5–225 dec	MeCN	45	$C_{15}H_{12}N_2O_5$
12	2,4-Me_2	H	C	245–247 dec	MeCN	86	$C_{16}H_{14}N_2O_5$
13	4-Cl	H	C	239–241 dec	MeCN	53	$C_{14}H_9ClN_2O_5 \cdot CH_3CN$
				Y = SO_2NH_2			
14	H	H	D	234–235 dec	Aqueous EtOH	60	$C_{14}H_{10}N_2O_7S$
15	4-Me	H	D	231–232.5 dec	Aqueous EtOH	53	$C_{15}H_{12}N_2O_7S$
16	2,4-Me_2	H	D	236–238 dec	MeCN	44	$C_{16}H_{14}N_2O_7S \cdot CH_3CN$
17	4-Cl	H	D	234.5–235.5 dec	Aqueous EtOH	24	$C_{14}H_9ClN_2O_7S$

[a] The letters relate to the general procedure given in the Experimental Section. [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. A sample was further purified to give the analytically pure compound. In most cases no attempts were made to optimalize the yield. The compounds were dried in air. [d] The compounds were analyzed for C, H, N, and, if present, S and halogen. Analytical results are within ±0.4% of the theoretical values unless otherwise stated. [e] A mixture of EtOH (two parts) and methyl cellosolve (one part) was used. [f] C: calcd, 58.74; found, 58.32.

Table II. Physical Properties of Compounds **22–31**

No.	X	R_1	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula[d]
22	H	H	F	290–292.5	EtOH	68	$C_{14}H_{12}N_2O_4S$
23	Et	$CH_2C_6H_5$	G	171.5–173.5	EtOH	81	$C_{23}H_{22}N_2O_4S$
24	Et	$CH_2CH{=}CH_2$[e]	H	(157.5–159.5)	Aqueous EtOH	(80)	
25	*n*-Bu	*n*-Bu	I	117.5–119	EtOH	32	$C_{22}H_{28}N_2O_4S$
26	H	$CH_2C_6H_5$	J	222–223.5	EtOH	33	$C_{21}H_{18}N_2O_4S \cdot 0.9C_2H_5OH$[f]
27	H	*n*-Pr	K	237–239	Aqueous EtOH	76	$C_{17}H_{18}N_2O_4S \cdot H_2O$[g]
28	H	$CH_2CH{=}CH_2$[e]	J	(226–228)	Aqueous EtOH	(76)	
29	H	*n*-Bu	J	238–240	EtOH	94	$C_{18}H_{20}N_2O_4S$
30	H	*n*-Am	L	227–230	Aqueous EtOH	30	$C_{19}H_{22}N_2O_4S$
31	H	$CH_2CCHCHCHO$	M	205.5–206.5	Aqueous EtOH	34	$C_{19}H_{16}N_2O_5S \cdot H_2O$

[a,b] See corresponding footnotes in Table I. [c] The yield of analytically pure compound is given and in most cases no attempts were made to optimalize the yield. The compounds were dried in air. [d] See footnote *d*, Table I. [e] Nmr (DMSO) showed the presence of various amounts of the *n*-propylamino compound, which could not be removed on recrystallization. Crude **28** was therefore hydrogenated to give **27**. [f] Nmr showed the presence of 0.9 mol of EtOH, which could not be removed on drying *in vacuo*. [g] Also analyzed for H_2O.

the molecule. The hydrophobic nature of this substituent can be of minor influence only, since, for example, phenoxy and *p*-hydroxyphenoxy groups in the 4 position of 3-benzylamino-5-sulfamylbenzoic acid resulted in compounds with the same level of potency.[2] The participation of the entire molecule should depend on the carboxylic function being present as carboxylic anion under physiological pH.

Pharmacology. 4-Benzyl-3-*n*-butylamino-5-sulfamylbenzoic acid (**66**) (besunide, pINN) was selected for further investigation for the following reasons. (**a**) Apart from the 4 substituent being benzyl instead of phenoxy, **66** is similar to bumetanide in structure. It was therefore of interest to discover whether the diuretic profile, dose response, and toxicity deviated in any way. (b) From a synthetic point of view **66** is one of the best available potent compounds of the present series. (**c**) Compound **66** has the *n*-butylamino side chain which should be superior to the benzylamino side chain in respect to oral absorption in man in accordance with preliminary volunteer studies with compounds of the previously reported 3-aminobenzoic acid diuretics.

Regarding the dose response, diuretic profile (see Table V), level of potency, and duration of action in dogs, **66** was found to be almost equal to bumetanide. The dose-response curves for urinary sodium and potassium over a 6-hr period after iv and oral administration are shown in Figure 1. Serum levels of **66** following oral administration of 0.25 mg/kg to four dogs were determined by means of fluorometric spectroscopy. Peak values were reached 60–90 min after administration, the same time range in which maximal diuresis occurred.

Table III. Physical Properties of Compounds **18–21** and **32–43**

No.	X	R_1	R_2	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula[d]
18	H	H	H	E	287–288 dec	*e*	25	$C_{14}H_{10}N_2O_4S$
19	H	H	4-Me	E	321.5–324.5 dec	*f*	48	$C_{15}H_{12}N_2O_4S$
20	H	H	2,4-Me_2	E	269.5–272 dec	Aqueous EtOH	10[g]	$C_{16}H_{14}N_2O_4S \cdot 0.5H_2O$
21	H	H	4-Cl	E	321–323 dec	Aqueous EtOH	12[h]	$C_{14}H_9ClN_2O_4S$
32	*n*-Bu	H	H	N	124.5–125.5	Aqueous EtOH	33	$C_{18}H_{18}N_2O_4S$
33	Et	$CH_2C_6H_5$	4-Me	G	153.5–155.5	EtOH	40	$C_{24}H_{22}N_2O_4S$
34	Et	$CH_2C_6H_5$	2,4-Me_2	G	149–150	EtOH	11	$C_{25}H_{24}N_2O_4S$
35	H	$CH_2C_6H_5$	H	O	235–236 dec	EtOH	8	$C_{21}H_{16}N_2O_4S \cdot C_2H_5OH$
36	H	$CH_2C_6H_5$	4-Me	J	247–248.5	EtOH	71	$C_{22}H_{18}N_2O_4S$
37	H	$CH_2C_6H_5$	2,4-Me_2	J	206–208	Aqueous EtOH	66	$C_{23}H_{20}N_2O_4S \cdot C_2H_5OH$
38	H	$CH_2C_6H_5$	4-Cl	O	237–239	Aqueous EtOH	18	$C_{21}H_{15}ClN_2O_4S \cdot C_2H_5OH$
39	H	*n*-Pr	H	P	214–215.5	EtOH	16	$C_{17}H_{16}N_2O_4S$
40	H	$CH_2CH{=}CH_2$	H	Q	200.5–202	EtOH	2	$C_{17}H_{14}N_2O_4S$
41	H	*n*-Bu	H	P	190–191.5	Aqueous EtOH	30	$C_{18}H_{18}N_2O_4S \cdot 0.5H_2O$
41, Na salt	H	*n*-Bu	H	R	>290	H_2O	32	$C_{18}H_{17}N_2NaO_4S \cdot 1.5H_2O$[i]
42	H	*n*-Am	H	P	167.5–170	Aqueous EtOH	19	$C_{19}H_{20}N_2O_4S$[j]
43	H	$CH_2CCHCHCHO$	H	P	195.5–196.5	EtOH	6	$C_{19}H_{14}N_2O_5S$

[a,b] See corresponding footnotes in Table I. [c] See footnote *c*, Table II. [d] See footnote *d*, Table I. [e] A mixture of MeCN (five parts) and methyl cellosolve (one part) was used. [f] A mixture of EtOH (eight parts) and methylcellosolve (one part) was used. [g] Crude material (mp *ca.* 255°) sufficiently pure for use in the alkylation step was obtained in 90% yield. [h] Crude material (mp *ca.* 300°) sufficiently pure for use in the alkylation step was obtained in 84% yield. [i] H_2O: calcd, 6.64; found, 6.74. [j] C: calcd, 61.28; found, 60.86.

Table IV. Physical Properties of Compounds **44–74**

No.	X	R_1	R_2	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula[d]
44	*n*-Bu	H	H	N	114–115	Aqueous EtOH	57	$C_{18}H_{22}N_2O_4S$
45	Et	$CH_2C_6H_5$	4-Me	G	151.5–153.5	EtOH	40	$C_{24}H_{26}N_2O_4S$
45	Et	$CH_2C_6H_5$	2,4-Me_2	G	150–151	Aqueous EtOH	21	$C_{25}H_{28}N_2O_4S$
47	Et	$CH_2C_6H_5$	4-Cl	G	168.5–170.5	EtOH	25	$C_{23}H_{23}ClN_2O_4S$
48	Et	$CH_2CH_2C_6H_5$	H	S	132–134	Aqueous EtOH	12	$C_{24}H_{26}N_2O_4S$
49	Et	Et	H	T	149–151	Aqueous EtOH	46	$C_{18}H_{22}N_2O_4S$
50	Et	$CH_2CH{=}CH_2$	H	H	131.5–133.5	Aqueous EtOH	41	$C_{19}H_{22}N_2O_4S$
51	*n*-Bu	*n*-Bu	H	I	110–112	Aqueous EtOH	37	$C_{22}H_{30}N_2O_4S$
52	*n*-Bu	*n*-Bu	4-Me	I	116–118	Aqueous EtOH	47	$C_{23}H_{32}N_2O_4S$
53	H	H	H	U, V	292–294 dec	*e*	65[f]	$C_{14}H_{14}N_2O_4S$
54	H	H	4-Me	U	296–298 dec	EtOH	28	$C_{15}H_{16}N_2O_4S$
55	H	H	2,4-Me_2	V	265–267 dec	Aqueous EtOH	8[g]	$C_{16}H_{18}N_2O_4S \cdot H_2O$[h]
56	H	H	4-Cl	V	304–306 dec	EtOH	13[i]	$C_{14}H_{13}ClN_2O_4S \cdot 0.5H_2O$[j,k]
57	H	$CH_2C_6H_5$	H	O	248–249 dec	EtOH	30	$C_{21}H_{20}N_2O_4S$
58	H	$CH_2C_6H_5$	4-Me	J	236–237	EtOH	65	$C_{22}H_{22}N_2O_4S$
59	H	$CH_2C_6H_5$	2,4-Me_2	J	245–248	EtOH	67	$C_{23}H_{24}N_2O_4S$
60	H	$CH_2C_6H_5$	4-Cl	J	263.5–265	Aqueous EtOH	14	$C_{21}H_{19}ClN_2O_4S \cdot H_2O$[l]
61	H	$CH_2CH_2C_6H_5$	H	J	235–237	Aqueous EtOH	61	$C_{22}H_{22}N_2O_4S$
62	H	Et	H	J	230.5–231.5	Aqueous EtOH	33	$C_{16}H_{18}N_2O_4S$
63	H	*n*-Pr	H	K	237–238	MeCN	33	$C_{17}H_{20}N_2O_4S$[m]
64	H	$CH_2CH{=}CH_2$	H	J	216–218	Aqueous EtOH	87	$C_{17}H_{18}N_2O_4S$
65	H	$CH_2CBr{=}CH_2$	H	W	230–232	Aqueous EtOH	17	$C_{17}H_{17}BrN_2O_4S$[n]
66	H	*n*-Bu	H	J	236–237	Aqueous EtOH	71	$C_{18}H_{22}N_2O_4S$
67	H	*n*-Bu	4-Me	J	246–248	EtOH	69	$C_{19}H_{24}N_2O_4S$
68	H	*n*-Am	H	L	231.5–233	Aqueous EtOH	9	$C_{19}H_{24}N_2O_4S$
69	H	$CH_2CCHCHCHO$	H	M	201–202 dec	Aqueous EtOH	25	$C_{19}H_{18}N_2O_5S$
70	H	$CH_2CCHCHCHO$	4-Me	M	234–236 dec	EtOH	4	$C_{20}H_{20}N_2O_5S$
71	H	$CH_2CCHCHCHS$	H	X	231–233	Aqueous EtOH	5	$C_{19}H_{18}N_2O_4S_2$[o]
72	H	$CH_2CNCHCHCHCH$	H	Y	248–249 dec	Me cellosolve	15	$C_{20}H_{19}N_3O_4S \cdot 0.25H_2O$
73	H	$CH_2CH_2CCHCHNCHCH$	H	Z	195.5–196.5	EtOH	4	$C_{21}H_{21}N_3O_4S$
74	H	$CH_2CH_2CCHCHNCHCH$	4-Me	Z	227–228	Me cellosolve	10	$C_{22}H_{23}N_3O_4S$

[a,b] See corresponding footnotes in Table I. [c] See footnote *c*, Table II. [d] See footnote *d*, Table I. [e] A mixture of EtOH (seven parts), methyl cellosolve (five parts), and H_2O (five parts) was used. [f] The yield obtained following method U is given. [g] Crude material sufficiently pure for use in the alkylation step was obtained in about 40% yield. [h] C: calcd, 54.53; found, 55.00. [i] Crude material sufficiently pure for use in the alkylation step was obtained in about 50% yield. [j] C: calcd, 48.09; found, 48.52. [k] N: calcd, 8.01; found, 8.45. [l] C: calcd, 56.18; found, 56.80. [m] Not analyzed for S. [n] Br: calcd, 18.79; found, 20.26. [o] S: calcd, 15.90; found, 15.28.

After iv administration of 0.1 mg/kg the diuresis and osmolal clearance over time were investigated. The results were similar to those seen after 0.05 mg/kg of bumetanide and 2 mg/kg of furosemide, indicating that the site of ac-

Table V. Diuretic and Saluretic Activity of Some 4-Substituted Amino-6-carboxy-3-R_2-phenyl-1,2-benzisothiazole 1,1-Dioxides and of Some 3-Substituted Amino-4-(R_2-benzyl)-5-sulfamylbenzoic Acids

Compound	R_1	R_2	Treatment,[b] mg/kg	Urinary excretion[a] ml/kg per 3 hr, H_2O	mequiv/kg per 3 hr Na^+	K^+	Cl^-
Control[c]				2	0.2	0.13	0.13
4-NHR$_1$-6-carboxy-3-R$_2$-phenyl-1,2-benzisothiazole 1,1-dioxides							
35	$CH_2C_6H_5$	H	0.25	17	1.8	0.5	2.5
			0.25 po	18	1.8	0.6	2.4
			0.1 po	6	0.8	0.3	1.2
36	$CH_2C_6H_5$	4-CH_3	0.25	21	2.3	0.6	3.1
			0.1	13	1.0	0.8	1.5
37	$CH_2C_6H_5$	2,4-CH_3	1.0	10	1.2	0.3	1.3
38	$CH_2C_6H_5$	4—Cl	0.1	11	1.3	0.4	1.8
39	*n*-Pr	H	0.25	6	0.3	0.2	0.6
40	$CH_2CH{=}CH_2$	H	1.0	7	0.7	0.3	1.7
41	*n*-Bu	H	0.25	18	2.4	0.4	2.9
			0.1	13	1.7	0.5	2.1
41, Na salt			0.1[d]	11[e]	1.2[e]	0.3[e]	1.6[e]
42	*n*-Am	H	1.0	13	1.3	0.3	1.7
43	$CH_2CCHCHCHO$	H	0.25	19	2.0	0.6	2.7
3-NHR$_1$-4-(R$_2$-benzyl)-5-sulfamylbenzoic acids							
57	$CH_2C_6H_5$	H	0.25	38	4.7	0.9	5.6
			0.1	18	2.1	0.4	2.5
			0.01	9	1.1	0.2	1.3
			0.01 po	8	1.3	0.3	1.3
58	$CH_2C_6H_5$	4-Me	0.25	42	4.0	1.0	6.8
			0.05	16	1.8	0.4	2.2
59	$CH_2C_6H_5$	2,4-Me	0.25	11	1.3	0.2	1.7
60	$CH_2C_6H_5$	4-Cl	0.25	23	2.3	0.6	3.3
61	$CH_2CH_2C_6H_5$	H	0.25	17	1.5	0.5	2.4
62	Et	H	0.25	10	0.7	0.3	1.1
63	*n*-Pr	H	0.25	13	1.6	0.3	1.8
			0.1	10	1.1	0.3	1.2
64	$CH_2CH{=}CH_2$	H	0.25	17	1.6	0.3	2.0
65	$CH_2CBr{=}CH_2$	H	0.25	35	3.1	0.5	4.8
			0.05	15	1.8	0.4	2.3
66	*n*-Bu	H	0.25	28	3.1	0.7	4.2
			0.25 po	29	3.3	0.6	4.1
67	*n*-Bu	4-Me	0.25	33	3.8	0.6	4.5
			0.1	21	2.3	0.4	3.0
68	*n*-Am	H	0.25	14	1.6	0.5	2.2
69	$CH_2CCHCHCHO$	H	0.25	38	3.3	0.6	4.6
			0.025	17	1.7	0.5	2.3
			0.025 po	11	1.2	0.2	1.6
70	$CH_2CCHCHCHO$	4-Me	0.25	45	5.0	0.9	6.4
			0.1	23	2.6	0.5	3.3
71	$CH_2CCHCHCHS$	H	0.25	38	4.1	0.9	5.4
			0.25 po	36	3.4	1.0	4.4
			0.01	17	1.1	0.3	2.0
			0.01 po	7	0.8	0.2	1.1
72	$CH_2CNCHCHCHCH$	H	0.25	17	1.9	0.4	2.4
			0.1	15	1.5	0.2	1.9
73	$CH_2CH_2CCHCHNCHCH$	H	0.25	17	1.5	0.5	2.2
74	$CH_2CH_2CCHCHNCHCH$	4-Me	0.25	30	3.2	0.8	4.1
			0.1	14	1.3	0.4	1.9
N-(2-Furylmethyl)-4-chloro-5-sulfamylanthranilic acid (furosemide)[f]			10	33	3.7	0.8	4.8
			1	20	1.9	0.5	2.3
3-*n*-Butylamino-4-phenoxy-5-sulfamylbenzoic acid (bumetanide)[g]			0.25	39[h]	4.1[h]	0.8[h]	5.7[h]
			0.01	10[h]	1.0[h]	0.3[h]	1.4[h]

[a] The procedure is described in ref 7; when not otherwise stated single test only. [b] When not otherwise stated iv injection in NaOH solution. [c] Average of three tests. [d] Iv injection in aqueous solution. [e] Average of two tests. [f] K. Sturm, W. Siedel, R. Weyer, and H. Ruschig, *Chem. Ber.*, **99**, 328 (1966). [g] See ref 2. [h] Average of four tests.

tion is mainly in the ascending limb of Henle's loop.

The half-life time in plasma following iv administration of 0.25 mg of **66** to four dogs was found to be 7 min (5–9.5), increasing to 21 and 35 min in two dogs pretreated with probenecid. The protein binding of **66** in 25% dog serum was 91.1 ± 1.0% (four dogs). These results revealed that **66** in the kidney is excreted mainly by tubular secretion.

After oral administration of **66** to rats, a significant diuretic effect was observed only after doses exceeding 20

mg/kg. Urine analysis by thin-layer and gas-liquid chromatography revealed that the compound is metabolized rapidly in this species. After 100 mg/kg less than 2% of the drug administered was found unchanged in the urine and at least six metabolites were detected.

The LD_{50}'s for 66 in mice (7 days) were 186 mg/kg and >2 g/kg after iv and oral administration, respectively.

Experimental Section

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. Nmr spectra were performed by N. Rastrup Andersen and taken on a Varian A-60A spectrometer. Ir spectra were obtained on a Perkin-Elmer PE 457 spectrometer. Spectral features were in accord with structures. Analytical data are given as defined in footnote *d*, Table I.

Ethyl 4-Arylcarbonyl-3,5-dinitrobenzoates 2-5 (Table I). Method A. Crude ethyl 3,5-dinitro-4-chlorocarbonylbenzoate (obtained from 1 by reaction with an excess of $SOCl_2$ followed by evaporation *in vacuo*) was treated at 80-100° for 2-3 hr with the appropriate aromatic hydrocarbon (C_6H_6 and $2,4\text{-}Me_2C_6H_4$, 1.5 ml/g of 1; C_6H_5Cl, 3.0 ml/g of 1) using anhydrous $AlCl_3$ (1.25 mol/mol of 1) as catalyst. When C_6H_5Me was added, 7.5 ml/g of 1 and 2.0 mol of $AlCl_3$/mol of 1 were used and the reaction was performed at room temperature for 2.5 hr. The reaction mixture was hydrolyzed with dilute HCl and the crude reaction product was extracted with $CHCl_3$ or with CH_2Cl_2. After evaporation *in vacuo*, it was crystallized by trituration with EtOH.

4-Arylcarbonyl-3,5-dinitrobenzoic Acids 6-9 (Table I). Method B. To a stirred suspension of the Et ester 2-5 in EtOH or methyl cellosolve (5-10 ml/g of ester), 2 *N* NaOH (1.1 mol/mol of ester) was added during about 10 min. After additional stirring for about 10 min, the resulting solution was clarified by filtration and acidified with a slight excess of 4 *N* HCl to precipitate the crude reaction product, eventually after further dilution with H_2O.

5-Amino-4-arylcarbonyl-3-nitrobenzoic Acids 10-13 (Table I). Method C. A mixture of the 3,5-dinitro derivative 6-9 and pyridine (2 ml/g of dinitro compound) was heated on a steam bath for a few minutes and was then diluted with H_2O (4 ml/g of dinitro compound). To the stirred and cooled mixture, solid $Na_2S_2O_4$ (1.65-1.80 mol/mol of dinitro compound) was added during 10 min, keeping the temperature at 20-22°. After additional stirring for 5 min, the resulting solution was acidified with an excess of concentrated HCl, keeping the temperature below 25°. The separated oil crystallized on standing at room temperature in the mother liquors for 18-24 hr. The material was collected and recrystallized from MeCN to give the almost pure reaction product.

4-Arylcarbonyl-3-nitro-5-sulfamylbenzoic Acids 14-17 (Table I). Method D. The 5-amino compounds 10-13 were converted to the corresponding 5-sulfamyl derivatives 14-17 adapting a procedure described[3] for the preparation of 2,5-dichloro-4-phenoxy-3-sulfamylbenzoic acid.

4-Amino-3-aryl-6-carboxy-1,2-benzisothiazole 1,1-Dioxides 18-21 (Table III). Method E. To a stirred solution of the 4-arylcarbonyl-3-nitro-5-sulfamylbenzoic acid 14-17 in a mixture of pyridine (2-5 ml/g of acid) and H_2O (5-10 ml/g of acid), solid $Na_2S_2O_4$ (3.5-4.5 mol/mol of acid) was added during about 30 min. After additional stirring for about 1 hr the resulting solution was evaporated *in vacuo* and the residue was dissolved in H_2O (about 10 ml/g). The solution was acidified with an excess of concentrated HCl and was then heated on a steam bath for 30 min in order to complete the cyclization process. After cooling, the precipitated crude reaction product was collected, washed with H_2O, and air-dried.

4-Amino-6-carboxy-3-phenyl-1,2-benzisothiazoline 1,1-Dioxide (22, Table II). Method F. To a stirred solution of 18 (20 g, 64 mmol) in 2 *N* NaOH (200 ml), $NaBH_4$ (5.0 g, 140 mmol) was added in portions during about 15 min. After additional stirring for 4 hr, the solution was carefully acidified with 4 *N* AcOH to precipitate crude 22.

4-Substituted amino-6-carbethoxy- (or carboxy-) 3-aryl-1,2-benzisothiazoline 1,1-dioxides 23-25, 26-31 (Table II), 4-substituted amino-6-carbalkoxy- (or carboxy-) 3-aryl-1,2-benzisothiazole 1,1-dioxides 32-34, 35-43 (Table III), alkyl 3-substituted amino-4-arylmethyl-5-sulfamylbenzoates 44-52 (Table IV), and 3-substituted amino-4-arylmethyl-5-sulfamylbenzoic acids 53-74 (Table IV) were in most cases prepared adapting methods described in earlier papers of this series. References are given under methods G-Z.

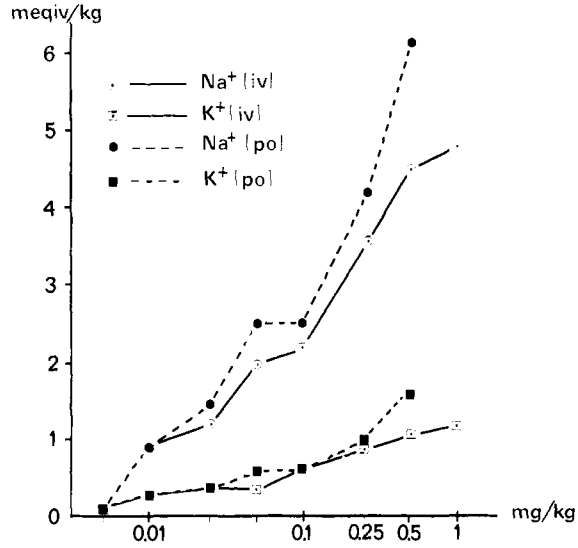


Figure 1. Urinary excretion of sodium and potassium during a 6-hr period after intravenous injection (solution in NaOH) and oral administration (gelatin capsules) of 66. Each dose level is represented by the mean value of four experiments in dogs.

Method G. For the benzylation process see ref 2, method 3A. 34 and 45-47 were obtained after evaporation *in vacuo*, followed by trituration with petroleum ether.

Method H. The alkylation method of ref 2, method 3A, was adapted, except that $CH_2{=}CHCH_2Br$ was used instead of $C_6H_5CH_2Br$. The crude reaction products were obtained after evaporation *in vacuo*, followed by trituration with petroleum ether.

Method I. A solution of the appropriate NH_2 compound (10 g) and *n*-BuI (10 g) in *n*-BuOH (200 ml) was refluxed for several days using a water trap. The alkylation and esterification processes were controlled by tlc. 52 crystallized from the solution on cooling. For 25 and 51 the solution was evaporated *in vacuo* and the residue washed with petroleum ether and with ice-cold EtOH to yield the crude reaction product.

Method J. The saponification process of ref 2, method 4C, was adapted, except that 2 *N* NaOH was used.

Method K. For the hydrogenation process see ref 2, method 3D.

Method L. To a solution of 22 or 53 (2.0 g) in *n*-AmOH (20 ml), concentrated H_2SO_4 (0.2 ml) was carefully added, and the mixture was refluxed for 3-4 days. The alkylation and esterification processes were controlled by tlc. The solution was then evaporated *in vacuo* and the obtained crude *n*-Am ester saponified with 2 *N* NaOH (20 ml) as described in ref 2, method 4C, to yield crude 30 and 68, respectively.

Method M. For the reductive alkylation see ref 2, method 4K. For 31 MeOH was replaced by methyl cellosolve and the Na salt was not isolated.

Method N. The corresponding carboxy compound was esterified with *n*-BuOH using concentrated H_2SO_4 as catalyst. 32 crystallized from the solution on cooling, while 44 was isolated after evaporation *in vacuo* and trituration with petroleum ether.

Method O. The benzylation process of ref 2, method 3A, was adapted, except that the obtained crude Et ester was saponified without purification.

Method P. The dehydrogenation process of ref 1, method D, was adapted, except that the Na salts were isolated.

Method Q. The alkylation process of ref 2, method 3A, was adapted using $CH_2{=}CHCH_2Br$ instead of $C_6H_5CH_2Br$ and without purification of the intermediate crude Et ester.

Method R. 41 (3.0 g) was dissolved in boiling saturated $NaHCO_3$ (30 ml). On cooling crude 41 Na salt crystallized from the solution.

Method S. The alkylation process of ref 2, method 3A, was

adapted except that $C_6H_5CH_2CH_2Br$ was used instead of $C_6H_5CH_2Br$. Crude **48** was obtained after evaporation *in vacuo* and trituration with petroleum ether.

Method T. The ethylation process of ref 2, method 4I, was adapted, except that the intermediate Et ester **49**, obtained after evaporation *in vacuo*, was isolated and purified.

Method U. The Wolff–Kishner reduction described in ref 1, method G, was adapted.

Method V. The Wolff–Kishner reduction described in ref 1, method G, was adapted using the NO_2 derivatives **14**, **16**, or **17** as starting material. The amount of hydrazine hydrate could be reduced to 1 ml (80% in H_2O)/g of starting material without lowering the yields. Under the reaction conditions used, the NO_2 group was simultaneously reduced.

Method W. Br_2 was added to **64**, adapting the bromination process of ref 2, method 3F, except that AcOH was used as solvent instead of $CHCl_3$. The intermediate 2,3-dibromopropyl compound (obtained slightly impure with mp 176–177°) was at room temperature dehydrobrominated with 2 *N* NaOH (20 ml/g of dibromo derivative) and crude **65** precipitated by acidification with 4 *N* HCl.

Method X. The reductive alkylation described in ref 2, method 4K, was adapted, except that 2-thiophenealdehyde was used instead of furfural.

Method Y. **53** was in AcOH solution reductively alkylated with 2-pyridinealdehyde using PtO_2 as catalyst.

Method Z. 4-Vinylpyridine was allowed to react with **53** (in methyl cellosolve solution) or with **54** (in MeOH solution) using AcOH as catalyst to yield **73** and **74**, respectively.

7-Carboxy-5-nitro-4-phenyl-1,2,3-benzothiadiazine 1,1-Dioxide (76). **75** [0.8 g; prepared according to method **D** and recrystallized from MeCN, mp 224.5–226.5° dec. *Anal.* ($C_{14}H_8ClNO_7S \cdot CH_3CN$) C, H, Cl, N, S] was added to a mixture of hydrazine hydrate (2.15 ml, 24% in H_2O) and H_2O (6.45 ml). After additional stirring at about 5° for 1.5 hr, the solution was acidified with 4 *N* HCl to precipitate crude **76**. It was recrystallized twice from aqueous EtOH to give **76** (42%) crystallizing with 1 mol of EtOH, mp 208–211° dec. *Anal.* ($C_{14}H_9N_3O_6S \cdot C_2H_5OH$) C, H, N, S.

5-Amino-7-carboxy-4-phenyl-1,2,3-benzothiadiazine 1,1-Dioxide (77). A solution of **76** (4.2 g, 11 mmol) in diluted NH_3 (45 ml, about 5% in H_2O) was added dropwise at room temperature to a stirred solution of $FeSO_4 \cdot 7H_2O$ (21 g, 75 mmol) in H_2O (50 ml). To the resulting mixture concentrated NH_3 (25% in H_2O) was added in portions until a persistent alkaline pH was obtained. After additional stirring for 30 min, the mixture was filtered and the filtrate was acidified with concentrated HCl to precipitate crude **77**. It was recrystallized several times from aqueous EtOH and from MeCN to give **77** (35%), mp 229.5–231°. *Anal.* ($C_{14}H_{11}N_3O_4S \cdot 0.33H_2O$) C, H, N, S.

5-Benzylamino-7-carbethoxy-4-phenyl-1,2,3-benzothiadiazine 1,1-Dioxide (78). **77** was benzylated according to a described process (see ref 2, method 3A) to yield, after recrystallization twice from a mixture of EtOH and methyl cellosolve, **78** (32%), mp 184–187°. *Anal.* ($C_{23}H_{21}N_3O_4S$) C, H, N, S.

5-Benzylamino-7-carboxy-4-phenyl-1,2,3-benzothiadiazine 1,1-Dioxide (79). **78** was saponified with 2 *N* NaOH to yield, after recrystallization from EtOH and from MeCN, **79** (25%), mp 226.5–227° dec. *Anal.* ($C_{21}H_{17}N_3O_4S$) C, H, N, S.

Ethyl 3,5-Dinitro-4-(2-phenylethyl)benzoate (81). To hexamethyl phosphoric triamide (50 ml) NaH (5.3 g; 50% suspended in oil, 0.11 mol) was added in portions during about 15 min while stirring at 0–5°. To the stirred mixture **80** (25.4 g, 0.10 mol) was added in portions during 30 min, keeping the temperature at 0–5°; after additional stirring at this temperature for 1 hr, $C_6H_5CH_2Br$ (34.2 g, 0.20 mol) was added within a few minutes, and the mixture was then stirred at 0–5° for 3 hr and at room temperature for 1 hr. The mixture was poured into ice and the precipitate was collected and washed with H_2O and with ice-cold EtOH to give, after filtration and air-drying, almost pure **81** (19.6–21.6 g). It was recrystallized from EtOH and from methyl cellosolve to yield **81** (26%), mp 123–125°. *Anal.* ($C_{17}H_{16}N_2O_6$) C H, N.

3,5-Dinitro-4-(2-phenylethyl)benzoic Acid (82). **81** was saponified according to method B (using methyl cellosolve as solvent) to give, after recrystallization twice from EtOH, **82** (33%), mp 236–238°. *Anal.* ($C_{15}H_{12}N_2O_6$) C, H, N.

5-Amino-3-nitro-4-(2-phenylethyl)benzoic Acid (83). **82** was partially reduced according to method C, except that 0.5 *N* $NaHCO_3$ (20 ml/g of **82**) was used as solvent instead of pyridine-H_2O and that the amount of $Na_2S_2O_4$ was increased to 3 mol/mol of **82**. The crude product was esterified with EtOH using dry HCl as catalyst; the hydrochloride of the Et ester of **83** was slightly soluble in EtOH and could be isolated and saponified to give almost pure **83** (about 40% based on **82**, mp 194–195°). Recrystallization from aqueous EtOH and from MeCN yielded **83** (3%), mp 194–196°. *Anal.* ($C_{15}H_{14}N_2O_4$) C, H, N.

3-Nitro-4-(2-phenylethyl)-5-sulfamylbenzoic Acid (84). **83** was converted to **84** adapting a published procedure given under method **D**. Recrystallization several times from aqueous EtOH yielded **84** (16%), mp 257–259°. *Anal.* ($C_{15}H_{14}N_2O_6S$) C, H, N, S.

3-Amino-4-(2-phenylethyl)-5-sulfamylbenzoic Acid (85). **84** was reduced according to method E to yield, after recrystallization several times from aqueous EtOH, **85** (12%), mp 244–246°. *Anal.* ($C_{15}H_{16}N_2O_4S$) C, H, N, S.

Ethyl 3-Benzylamino-4-(2-phenylethyl)-5-sulfamylbenzoate (86). **85** was benzylated according to a described procedure (see ref 2, method 3A) to give, after recrystallization from aqueous EtOH, **86** (55%), mp 175.5–177°. *Anal.* ($C_{24}H_{26}N_2O_4S$) C, H, N, S.

3-Benzylamino-4-(2-phenylethyl)-5-sulfamylbenzoic Acid (87). **86** was saponified with 2 *N* NaOH to yield, after recrystallization several times from EtOH, **87** (63%), mp 237.5–239.5°. *Anal.* ($C_{22}H_{22}N_2O_4S$) C, H, N, S.

***n*-Butyl 3-*n*-Butylamino-4-(2-phenylethyl)-5-sulfamylbenzoate (88).** **85** was butylated according to method I to yield, after recrystallization from aqueous EtOH, **88** (12%), mp 100–101°. *Anal.* ($C_{23}H_{32}N_2O_4S$) C, H, N, S.

3-*n*-Butylamino-4-(2-phenylethyl)-5-sulfamylbenzoic Acid (89). **88** was saponified with 2 *N* NaOH to yield, after recrystallization twice from aqueous EtOH, **89** (48%), mp 208–210°. *Anal.* ($C_{19}H_{24}N_2O_4S$) C, H, N, S.

4-Methyl-3-nitro-5-sulfamylbenzoic Acid. This intermediate was prepared in three steps from *p*-toluic acid as described[5] for the corresponding 4-Cl derivative. Recrystallization from aqueous EtOH yielded 4-methyl-3-nitro-5-sulfamylbenzoic acid (30%, yield over three steps), mp 225–226°. *Anal.* ($C_8H_8N_2O_6S$) C, H, N, S.

3-Amino-4-methyl-5-sulfamylbenzoic Acid. 4-Methyl-3-nitro-5-sulfamylbenzoic acid was reduced according to method E, to yield, after recrystallization twice from aqueous EtOH, 3-amino-4-methyl-5-sulfamylbenzoic acid (40%), mp 261.5–263°. *Anal.* ($C_8H_{10}N_2O_4S$) C, H, N, S.

Ethyl 3-Benzylamino-4-methyl-5-sulfamylbenzoate. 3-Amino-4-methyl-5-sulfamylbenzoic acid was benzylated according to a described process (see ref 2, method 3A) to yield, after recrystallization from EtOH, ethyl 3-benzylamino-4-methyl-5-sulfamylbenzoate (39%), mp 176–177.5°. *Anal.* ($C_{17}H_{20}N_2O_4S$) C, H, N, S.

3-Benzylamino-4-methyl-5-sulfamylbenzoic Acid. Ethyl 3-benzylamino-4-methyl-5-sulfamylbenzoate was saponified using 2 *N* NaOH and adapting a described process (see ref 2, method 4C) to yield, after recrystallization twice from methyl cellosolve, 3-benzylamino-4-methyl-5-sulfamylbenzoic acid (66%), mp 268.5–269.5. *Anal.* ($C_{15}H_{16}N_2O_4S$) C, H, N, S.

Diuretic Clearance and Half-Life Time Studies. Methods described[7] for the investigation of bumetanide were used.

Determination of 66 in Biological Material. (a) Spectrofluorometric Determination. The described[7] method for bumetanide was adapted. The fluorescence maxima are 465 and 420 nm at the activation maxima of 360 and 335 nm in acidic and alkaline solution, respectively. Maximum fluorescence is obtained at pH 3 and 11, respectively. **(b) Gas–Liquid Chromatographic Determination.** A described method[8] was adapted using bumetanide as internal reference compound.

Thin-Layer Chromatography. Precoated plates (E. Merck, Darmstadt) were used in the following solvent systems: cyclohexane (10)–chloroform (80)–methanol (2.5)–acetic acid (10); cyclohexane (40)–ethyl acetate (40)–acetic acid (20). Multirun technique was performed with cyclohexane (1)–ethyl acetate (1) and methylene chloride (65)–methanol (35).

Serum Protein Binding. A described[9] gel filtration method was used.

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References

(1) P. W. Feit, O. B. T. Nielsen, and N. Rastrup-Andersen, *J. Med. Chem.*, 16, 127 (1973) (paper 4).
(2) P. W. Feit, *ibid.*, 14, 432 (1971).
(3) P. W. Feit and O. B. T. Nielsen, *ibid.*, 15, 83 (1972).
(4) J. B. Wright, *J. Heterocycl. Chem.*, 5, 453 (1968).
(5) P. W. Feit, H. Bruun, and C. K. Nielsen, *J. Med. Chem.*, 13, 1071 (1970).
(6) P. W. Feit, O. B. T. Nielsen, and H. Bruun, *ibid.*, 15, 437 (1972).
(7) E. H. Østergaard, M. P. Magnussen, C. K. Nielsen, E. Eilertsen, and H.-H. Frey, *Arzneim.-Forsch.*, 22, 66 (1972).
(8) P. W. Feit, K. Roholt, and H. Sørensen, *J. Pharm. Sci.*, 62, 375 (1973).
(9) J. Krieglstein and G. Kuschinsky, *Arzneim.-Forsch.*, 18, 287 (1968).

Analgetics Based on the Pyrrolidine Ring. 8

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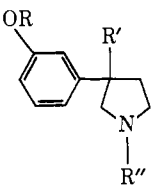
A group of *m*-[3-alkyl-1-(cyclopropylmethyl)-3-pyrrolidinyl]phenols and related compounds has been synthesized for evaluation as potential nonaddicting analgesic drugs. The compounds have been tested in mice and many show an antinociceptive effect in an abdominal constriction (writhing) test and, in addition, antagonize morphine in the tail pressure test. The biological results are discussed in relation to chemical structure.

The present paper describes some chemical and pharmacological properties of a series of 1-(cycloalkylalkyl)pyrrolidines [particularly 1-(cyclopropylmethyl)pyrrolidines of type (I)] (where, for example, R″ = CH_2-c-C_3H_5). Many of these compounds proved to be antinociceptive agents in abdominal constriction (writhing) tests and simultaneously have the ability to antagonize the effects of morphine in the tail pressure test. Pertinent structure–activity relationships are discussed. A detailed report on the pharmacological and chemical properties of *levo*-*m*-[1-(cyclopropylmethyl)-3-isobutyl-3-pyrrolidinyl]phenol monosuccinate (I, R = H; R′ = CH_2CHMe_2; R″ = CH_2-c-C_3H_5), also referred to as CI 747 succinate, is being published elsewhere.[1]



I

Chemistry and Experimental Section

The synthetic procedures used are summarized below. More detailed descriptions for some particular examples have been previously given.[2] The preparation of 3-alkyl-3-*m*-methoxyphenylpyrrolidines has been previously described.[3,4]

m-[3-Alkyl-1-(cyclopropylmethyl)-3-pyrrolidinyl]phenols. **Method A.** N-Acylation of a 3-alkyl-3-(*m*-methoxyphenyl)pyrrolidine [or a 3-alkyl-3-(*m*-isopropoxyphenyl)pyrrolidine] with cyclopropanecarboxylic acid chloride (or with cyclopropanecarboxylic acid using the mixed anhydride method) was followed by reduction of the amide with $LiAlH_4$. Subsequent conversion of the 3-alkyl-1-(cyclopropylmethyl)-3-(*m*-methoxyphenyl)pyrrolidine [or the 3-alkyl-1-(cyclopropylmethyl)-3-(*m*-isopropoxyphenyl)pyrrolidine] to the *m*-[3-alkyl-1-(cyclopropylmethyl)-3-pyrrolidinyl]-phenol was effected by the use of boron tribromide[5] or, in the case of the (*m*-isopropoxyphenyl)pyrrolidine (compounds 18 and 19), with refluxing 6 *N* HCl.

Method B. N-Acylation of a 3-alkyl-3-(*m*-methoxyphenyl)pyrrolidine was followed by O-demethylation using boron tribromide. The phenolic amide was reduced to the corresponding *m*-[3-alkyl-1-(cycloalkylalkyl)3-pyrrolidinyl]phenol using $LiAlH_4$.

Method C. O-Demethylation of a 3-alkyl-3-*m*-(methoxyphenyl)-pyrrolidine with boron tribromide at −60°, or with refluxing HBr, afforded the corresponding *m*-(3-alkyl-3-pyrrolidinyl)phenol which, on N-acylation followed by reduction with $LiAlH_4$, gave the required *m*-[3-alkyl-1-(cyclopropylmethyl)-3-pyrrolidinyl]phenol.

Method D. 3-Alkyl-3-(*m*-methoxyphenyl)pyrrolidines were N-alkylated by a method similar to that previously described.[6] O-Demethylation was effected with boron tribromide.

Optical Resolution of *m*-[1-(Cyclopropylmethyl)-3-isobutyl-3-pyrrolidinyl]phenol. Method E. *m*-[1-(Cyclopropylmethyl)-3-isobutyl-3-pyrrolidinyl]phenol was resolved by fractional crystallization of its salt with (−)-di-*p*-toluoyl-D-tartaric acid from EtOH. The salt of the (−) enantiomer crystallized first. Liberation of the base enriched in the (+) enantiomer from the salt in the mother liquors, followed by fractional crystallization of its salt with (+)-di-*p*-toluoyl-L-tartaric acid, led to the isolation of the (+) enantiomer.

O Esters. Method F. *m*-[3-Alkyl-1-(cyclopropylmethyl)-3-pyrrolidinyl]phenols were converted to the O esters by the action of an acid anhydride in pyridine.

Method G. As an alternative route to the O esters, the *m*-(3-pyrrolidinyl]phenols were converted to the O esters by the action with the acid chloride in the presence of triethylamine.

m-(1-Cyclopropyl-3-propyl-3-pyrrolidinyl)phenol. **Method H.** 2-(*m*-Methoxyphenyl)-2-propylsuccinic acid (prepared from the corresponding imide by alkaline hydrolysis) was converted to the anhydride by a method similar to that described by Horning and Finelli.[7] Refluxing the anhydride with cyclopropylamine for 30 min afforded *N*-cyclopropyl-2-(*m*-methoxyphenyl)-2-propylsuccinimide which was O-demethylated with boron tribromide and the succinimide converted to the pyrrolidine by reduction with $LiAlH_4$ in Et_2O.

3-[*m*-(Allyloxy)phenyl]-1-(cyclopropylmethyl)-3-propylpyrrolidine. **Method I.** *m*-[1-(Cyclopropylmethyl)-3-propyl-3-pyrrolidinyl]phenol was converted to the O-allyl derivative by the action of allyl bromide in the presence of NaH.

The physicochemical properties of the compounds prepared for biological evaluation are listed in Table I.

Pharmacological Methods. Antinociceptive activity was measured using the mouse abdominal constriction test as described by Collier, *et al.*,[8] in which acetylcholine (3.2 mg/kg) was the intraperitoneal challenge substance. Antimorphine activity was measured in a mouse tail pressure test based on the method of Bianchi and Franceschini,[9] using a special apparatus described by Collier.[10] The test drug was administered subcutaneously in solution together with a dose of morphine (22.2 mg/kg) having an antinociceptive effect in 95% of animals treated. A median effec-

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