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Aminobenzoic Acid Diuretics. 4.[1] 4-Benzyl-5-sulfamylanthranilic Acid Derivatives and Related 1,2-Benzisothiazole 1,1-Dioxides

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A series of *N*-substituted 4-benzyl-5-sulfamylanthranilic acids and a series of 5-substituted amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxides have been synthesized and screened for their diuretic properties. The results for some of the compounds are summarized and compared with those of selected anthranilic acid diuretics and bumetanide. The most potent diuretic compound in both series had the *N*-2-furylmethyl side chain and showed a diuretic profile almost similar to that of bumetanide. The existence of an equilibrium between the benzisothiazole dioxides and the corresponding benzoylsulfamylanthranilic acids has been investigated. The structure–activity relationship is discussed in these terms.

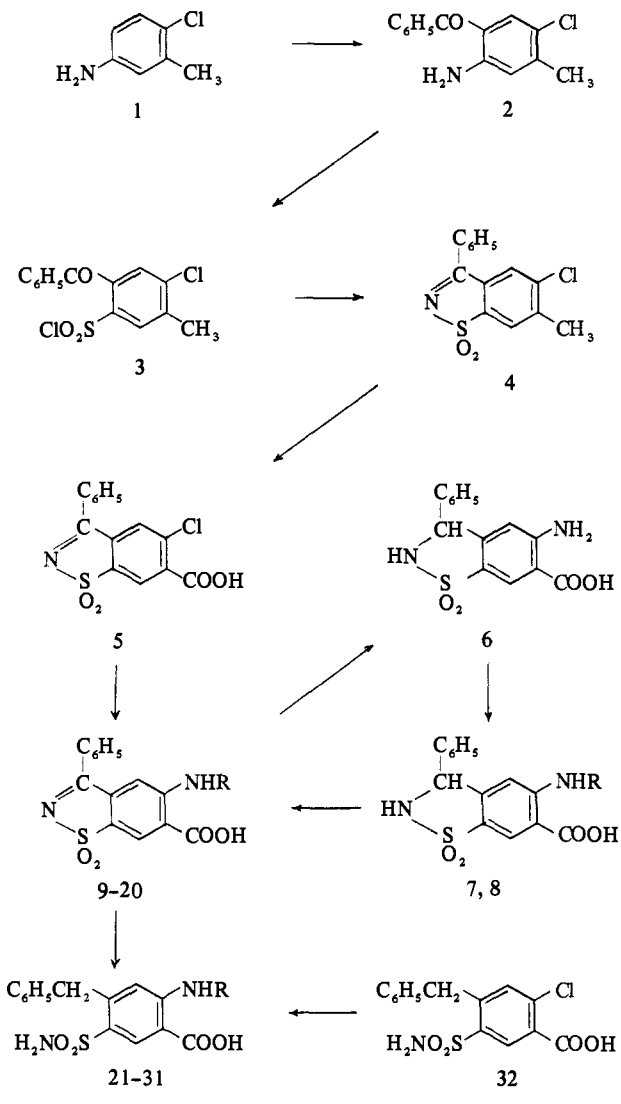
Previous studies in this laboratory have revealed that certain 4-substituted 3-amino-5-sulfamylbenzoic acid[2] and 5-sulfamylanthranilic acid[1] derivatives exhibit high ceiling diuretic activity superior in potency to the corresponding 4-Cl compounds. In continuation of our studies on the structural requirements for this activity, we report the synthesis and diuretic screening results of *N*-alkylated 4-benzyl-5-sulfamylanthranilic acids (**21–30**). In connection with this search we prepared a series of *N*-alkylated 5-amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxides (**9–20**). As cyclodehydration products of the corresponding 4-benzoyl-5-sulfamylanthranilic acid derivatives, these compounds represent a structure modification of considerable interest.

Chemistry. The synthesis of the *N*-alkylated 4-benzyl-5-sulfamylanthranilic acids (**21–31**) and the related *N*-alkylated 5-amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxides (**10–20**) is outlined in Scheme I and detailed in the Experimental Section. The sequence resulting in the key intermediate **5** involved cyclodehydration subsequent to the amidation of the sulfochloride **3**. This type of cyclization has previously been described by Wright[3] and is supported by spectroscopic evidence in the present case.

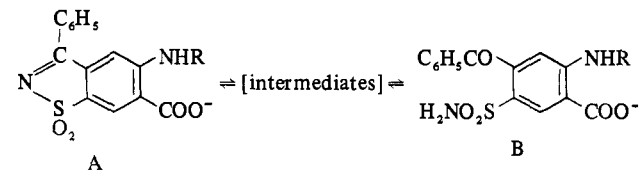
Replacement of the Cl in **5** with different amines resulted in the 5-substituted aminobenzisothiazoles (**10–19**) (Table II). For the reaction with benzylamine the corresponding benzisothiazoline **7** was formed as by-product. It was therefore convenient to prepare 5-amino-6-carboxy-3-phenyl-1,2-benzisothiazoline 1,1-dioxide (**6**) from the crude mixture by catalytic hydrogenation and simultaneous debenzylation. Benzylation and reductive alkylation provided the benzisothiazolines **7** and **8** (Table I) which could as well as **6** be dehydrogenated to the benzisothiazoles **9**, **10**, and **20**, respectively. The anthranilic acid derivatives **21–29** (Table III) were obtained from **10–20** by Wolff-Kishner reduction, except for **22** which was conveniently achieved by benzylation of the anthranilic acid **21**. The Wolff-Kishner reaction was probably made possible by hydrolytic ring cleavage to the corresponding benzophenones prior to the reduction due to the alkaline reaction conditions. **30** and **31** (Table III) were provided from the corresponding 2-chlorobenzoic acid derivative **32** by replacement reaction.

Diuretic Effect and Structure–Activity Relationship. **6**, **7**, and **8** (Table I), the 5-substituted amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxides (Table II), and the *N*-alkylated 4-benzyl-5-sulfamylanthranilic acids (Table III) prepared in this study were screened for their diuretic properties in dogs. The urinary volume and electrolyte excretion following iv administration (solution in NaOH) were determined hourly. The urinary volume and the electrolyte excretion from the 3-hr test period for those compounds resulting in a Na^+ excretion >1.0 mequiv after iv administration of 1 mg/kg or less are summarized in Table IV and compared with relevant anthranilic acid diuretics, including furosemide, and with 3-*n*-butylamino-4-phenoxy-5-sulfamylbenzoic acid (bumetanide). In relation to diuretic profile, high potency, and the advantage of the *N*-2-furylmethyl substitution over the benzyl and alkyl substitution, the data

Scheme I



Scheme II



compounds B due to formation of the sulfonamide anion. The equal activity observed after injection of both the alkaline solution of **10** and the neutral solution of the Na salt of **10** (**10** Na salt, Table IV) could be adequately explained by assuming such an equilibrium adjusting at a sufficiently high rate under physiologic conditions and pH. However, on this basis no suggestion concerning the ratio A/B in solution at this pH could be made.

A realistic tool to differentiate between A and B in aqueous solutions could be based on the C=O and C=N stretching vibration in the ir area. For this reason the ir spectra of **10** Na salt (recrystallized from D_2O) were taken in D_2O and 1 *N* NaOD. The most prominent line in the D_2O spectrum was a line situated at 1609 cm^{-1}, which could be assigned to the C=O stretching vibration in the COO^- group. A line at 1578 cm^{-1} could be assigned to the C=N stretching vibration. In the NaOD spectrum a new line at 1659 cm^{-1} proved the existence of a diaryl C=O group. Furthermore, the 1578-cm^{-1} line found in the D_2O spectrum was absent in the NaOD spectrum. Repetitions of the infrared experiments showed that a very weak shoulder at 1659 cm^{-1} in the D_2O spectrum was genuine and not assignable to the water background. This observation indicates the existence of a few per cent of B during the infrared experiment in neutral D_2O.

Altogether it can therefore be postulated that the potent diuretic effect observed after administration of the benzisothiazoles is effected by interaction of the corresponding benzoylsulfamylanthranilic acids with the receptor enabled by a dynamic equilibration in plasma. This would bring the structure of these diuretics in consistence with those of the 4-benzylanthranilic acids. On the other hand, the benzisothiazoline 8 which is not able to undergo hydrolytic ring cleavage was not devoid of activity. 8 showed at a dose of 1 mg/kg the following urinary excretion per kilogram in the 3-hr test period: 6 ml of urine, 0.7 mequiv of Na^+, 0.3 mequiv of K^+, and 0.9 mequiv of Cl^-. For this reason a certain activity of structure A cannot be excluded.

on the described 4-benzylanthranilic acids and benzisothiazoles equaled those of the previously reported[1,2] high-ceiling diuretics of the sulfamylanthranilic acid and 3-aminobenzoic acid series. In consideration of the absent free sulfonamide function, the high potency of the listed carboxybenzisothiazoles is rather interesting. However, a consideration of the following points led to an investigation into whether the diuretic activity should be based on this new structure. The course of the Wolff-Kishner reaction described in the chemical part of this paper could indicate the existence of an equilibrium between the benzisothiazoles and the corresponding 4-benzoyl-5-sulfamylanthranilic acids in the presence of water as outlined in Scheme II. Consequently, the basicity of the injection fluid used in the screening procedure should produce the ring-opened

Experimental Section

Analyses were performed by G. Cornali and W. Egger of these labs. Melting points were corrected and taken in open glass capillaries using a Hershberg apparatus. Nmr spectra were taken on a Varian A-60A spectrometer. Ir spectra were obtained on a Perkin-Elmer PE 457 spectrometer. Infrared liquid spectra were taken in a 0.033-mm BaF_2 cell using D_2O and NaOD from Merck (Uvasole 99.9% deuterated); other ir spectra were taken 0.3% in KBr. Anal-

Table I. Physical Properties of Compounds 6-8

No.	R	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula[d]
6	H	A	281-284 dec	Methyl cellosolve		$C_{14}H_{12}N_2O_4S$
7	$CH_2C_6H_5$	B	270-272 dec	EtOH	29	$C_{21}H_{18}N_2O_4S \cdot H_2O$[e]
8	$CH_2CCHCHCHO$	C	245-246	*f*	12	$C_{19}H_{16}N_2O_5S$

[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 the analytically pure compounds is given, and 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, S, and, if present, halogen. Analytical results are within ±0.4% of the theoretical values unless otherwise stated. [e] Also analyzed for H_2O. [f] A mixture of EtOH (two parts) and methyl cellosolve (one part) was used.

Table II. Physical Properties of Compounds 9-20

No.	R	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula[d]
9	H	D	>285	*e*	80	$C_{14}H_{10}N_2O_4S$
10	$CH_2C_6H_5$	D, E	263-265 dec	*f*	29[g]	$C_{21}H_{16}N_2O_4S$
10 Na salt[h]	$CH_2C_6H_5$	F	296-298 dec	H_2O	50	$C_{21}H_{15}N_2NaO_4S \cdot 3H_2O$[i]
11	$CH_2C_6H_4$, 3-Me	E	213-214 dec	EtOH	17	$C_{22}H_{18}N_2O_4S \cdot C_2H_5OH$
12	$CH_2C_6H_4$, 4-OMe	E	240-241 dec	EtOH	9	$C_{22}H_{18}N_2O_5S \cdot C_2H_5OH$
13	$CH_2C_6H_4$, 4-Cl	E	271-273 dec	EtOH	9	$C_{21}H_{15}ClN_2O_4S \cdot C_2H_5OH$
14	$CH_2CH_2C_6H_5$	E	241-244 dec	EtOH	52	$C_{22}H_{18}N_2O_4S$
15	*n*-Bu	E	254-257 dec	EtOH	52	$C_{18}H_{18}N_2O_4S$
16	*n*-Am	E	249-251 dec	EtOH	54	$C_{19}H_{20}N_2O_4S$
17	*i*-Am	E	232-235 dec	EtOH	43	$C_{19}H_{20}N_2O_4S$
18	$CH_2CH_2CH_2OCH_3$	E	211-212 dec	EtOH	42	$C_{18}H_{18}N_2O_5S$
19	$CH_2CCHNCHCHCH$	E	285-286 dec	DMF-H_2O	58	$C_{20}H_{15}N_3O_4S \cdot 0.25H_2O$[j]
20	$CH_2CCHCHCHO$	D	228-231 dec	*k*	6	$C_{19}H_{14}N_2O_5S$

[a-d]See corresponding footnotes in Table I. [e]A mixture of EtOH (five parts) and methyl cellosolve (one part) was used. [f]A mixture of EtOH (three parts) and methyl cellosolve (one part) was used. [g]The yield obtained following method D is given. [h]Ir (KBr) 1608 and 1572 cm^{-1} (COO^- and C=N stretching). [i]H_2O: calcd, 11.54; found, 12.21. [j]H: calcd, 3.93; found, 4.39. [k]A mixture of EtOH (two parts) and methyl cellosolve (one part) was used.

Table III. Physical Properties of Compounds 21-31

No.	R	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula[d]
21	H	G	253-255 dec	EtOH	87	$C_{14}H_{14}N_2O_4S$
22	$CH_2C_6H_5$	H	256-258 dec	Methyl cellosolve	38	$C_{21}H_{20}N_2O_4S$[e]
23	$CH_2C_6H_4$, 3-Me	G	232-234 dec	EtOH	20	$C_{22}H_{22}N_2O_4S$
24	$CH_2C_6H_4$, 4-Cl	G	259-261 dec	*f*	20	$C_{21}H_{19}ClN_2O_4S$
25	$CH_2CH_2C_6H_5$	G	245-246 dec	*f*	67	$C_{22}H_{22}N_2O_4S$
26	*n*-Bu	G	248-249 dec	EtOH	33	$C_{18}H_{22}N_2O_4S$
27	*n*-Am	G	251-252 dec	*f*	60	$C_{19}H_{24}N_2O_4S$
28	*i*-Am	G	251-252 dec	*f*	65	$C_{19}H_{24}N_2O_4S$
29	$CH_2CH_2CH_2OCH_3$	G	224-225 dec	EtOH	70	$C_{18}H_{22}N_2O_5S$
30	$CH_2CCHCHCHO$	I	229-229.5 dec	EtOH	8	$C_{19}H_{18}N_2O_5S$
31	$CH_2CCHCHCHS$	I	229-230 dec	EtOH	25	$C_{19}H_{18}N_2O_4S_2$

[a-d]See corresponding footnotes in Table I. [e]N: calcd, 7.07; found, 6.65. [f]A mixture of EtOH (three parts) and methyl cellosolve (one part) was used.

Table IV. Diuretic and Saluretic Activity of Some 5-Substituted Amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-Dioxides and of Some *N*-Substituted 4-Benzyl-5-sulfamylanthranilic Acids

Compd	R	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
5-Substituted amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxides						
10	$CH_2C_6H_5$	1	23	2.8	0.5	3.4
		0.25	17	1.9	0.3	2.4
10 Na salt		0.25[d]	22	1.9	0.4	2.3
14	$CH_2CH_2C_6H_5$	1	9	1.0	0.2	1.2
15	*n*-Bu	1	13	1.6	0.4	1.9
		0.25	8	0.8	0.7	1.1
20	$CH_2CCHCHCHO$	1	44	4.8	0.7	5.9
		0.1	26	2.7	0.8	3.3
		0.01	10	1.0	0.4	1.4
N-Substituted 4-benzyl-5-sulfamylanthranilic acids						
22	$CH_2C_6H_5$	1	13	1.7	0.4	1.9
30	$CH_2CCHCHCHO$	0.25	19	2.1	0.4	2.7
31	$CH_2CCHCHCHS$	0.25	11	1.2	0.3	1.6
N-Benzyl-4-chloro-5-sulfamylanthranilic acid[e]		10	15	1.6	0.4	2.1
		1	5	0.4	0.2	0.7
N-(2-Furylmethyl)-4-chloro-5-sulfamylanthranilic acid (furosemide)[e]		10	33	3.7	0.8	4.8
		1	20	1.9	0.5	2.3
N-(2-Furylmethyl)-4-phenoxy-5-sulfamylanthranilic acid[f]		1	43	5.0	0.8	6.4
		0.01	8	0.6	0.3	0.8
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 by E. H. Oestergaard, M. P. Magnussen, Chr. Kaergaard Nielsen, E. Eilertsen, and H.-H. Frey, *Arzneim.-Forsch.*, 22, 66 (1972); 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]K. Sturm, W. Siedel, R. Weyer, and H. Ruschig, *Chem. Ber.*, 99, 328 (1966). [f]P. W. Feit and O. B. Tvaermose Nielsen, *J. Med. Chem.*, 15, 79 (1972). [g]P. W. Feit, *J. Med. Chem.*, 14, 432 (1971). [h]Average of four tests.

ytical data are given as defined in footnote *d*, Table I. Technical assistance was given by Hanne Hollensen.

5-Amino-4-benzoyl-2-chlorotoluene (2). To BzCl (300 ml, 2.6 mol) 1[4] (142 g, 1 mol) was added in portions during about 30 min while stirring at 120–130°. The temperature of the resulting solution was raised to 180–190° followed by the slow addition of anhydrous $ZnCl_2$ (170 g, 1.25 mol) during about 1 hr. Finally the mixture was stirred at 200–210° for a further 2 hr and was then, still hot, poured into ice. The precipitated lumpy material was pulverized and washed twice with hot 2 *N* HCl and with H_2O. The crude 4-benzoyl-5-benzoylamino-2-chlorotoluene obtained was hydrolyzed with a mixture of concentrated H_2SO_4 (400 ml) and H_2O (180 ml) by stirring at 150–160° for about 2 hr. The resulting solution was poured into ice and the precipitated material collected and washed with 2 *N* NaOH (about 2 l.) to remove BzOH. The remaining material was dissolved in Et_2O. After filtration, the solution was washed with 2 *N* NaOH, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was triturated with EtOH (150 ml) to give almost pure 2 (60–70 g, 24–29%). Recrystallization from EtOH yielded 2, mp 122–123.5°. *Anal.* ($C_{14}H_{12}ClNO$) C, H, Cl, N.

5-Chloro-6-methyl-3-phenyl-1,2-benzisothiazole 1,1-Dioxide (4). 2 was converted to the corresponding 5-chlorosulfonyl derivative 3 adapting a procedure described[1] for the preparation of 2,5-dichloro-4-phenoxy-3-sulfamylbenzoic acid. The crude 3 (obtained in about 85% yield) was air-dried and was then added in portions to liquid NH_3 (about 4 ml/g). When the excess of NH_3 had evaporated, the residue was triturated with 2 *N* HCl and collected. It was recrystallized from methyl cellosolve to yield 4 (49% based on 2): mp 216–218°; ir (KBr) no absorptions 1600–1800 cm^{-1}. *Anal.* ($C_{14}H_{10}ClNO_2S$) C, H, Cl, N, S.

6-Carboxy-5-chloro-3-phenyl-1,2-benzisothiazole 1,1-Dioxide (5). To a stirred suspension of 4 (65 g, 0.22 mol) in refluxing 2 *N* NaOH (650 ml), a hot solution of $KMnO_4$ (110 g, 0.70 mol) in H_2O (1100 ml) was added dropwise during about 45 min. The stirring and refluxing was continued for a further 30 min and the hot mixture was then filtered. The filtrate was acidified with concentrated HCl to precipitate crude 5 (about 55 g). It was recrystallized from aqueous EtOH and dried *in vacuo* at 65° for about 6 hr to give 5 (30%), mp 224–226°. *Anal.* ($C_{14}H_8ClNO_4S$) C, H, Cl, N, S.

5-Substituted Amino-6-carboxy-3-phenyl-1,2-benzisothiazoline 1,1-Dioxide (6–8, Table I). Method A. A mixture of 5 (20 g, 62 mmol) and $C_6H_5CH_2NH_2$ (80 ml, 0.75 mol) was stirred at 150° for 3 hr and was then poured into 4 *N* HCl (200 ml). After cooling, the precipitated mixture of 7 and 10 was collected and washed with H_2O. The dried mixture (about 12.5 g) was suspended in methyl cellosolve (100 ml) and hydrogenated in the presence of concentrated HCl (0.7 ml) and Pd (10%)–C (0.3 g). After about 6 hr the H_2 uptake became negligible and a clear solution had been formed. The catalyst was removed by filtration and the solvent evaporated *in vacuo*. The residue was triturated with H_2O, collected, and air-dried to give almost pure 6 (8.9 g, 47%).

Method B. A solution of 6 (1.0 g, 3.3 mmol) and $C_6H_5CH_2Br$ (1.0 ml, 8.4 mmol) in methyl cellosolve (10 ml) was heated on a steam bath for 24 hr. After cooling, the resulting solution was diluted with H_2O (10 ml) to precipitate crude 7.

Method C. 6 (1.2 g, 4 mmol) was allowed to react with furfural (1.2 ml, 14.5 mmol) and the intermediate Schiff base reduced with $NaBH_4$ (1.2 g, 38 mmol) following a described procedure.[2]

5-Substituted Amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-Dioxide (9–20, Table II). Method D. To a stirred solution of the corresponding 1,2-benzisothiazoline derivative in 2 *N* NaOH (10 ml/g), a solution of $KMnO_4$ (0.3 g/g) in H_2O (10 ml/g) was added dropwise during 5 min. After additional stirring for 5 min, the mixture was filtered and the filtrate acidified with AcOH to precipitate the crude reaction product.

Method E. A stirred mixture of 5 and the appropriate RNH_2 (4 ml/g) was heated to 100–140° for 18–22 hr. For 10 the reaction time was decreased to 3 hr in order to minimize the formation of 7 (see method A). The mixture was then poured into cold 4 *N* AcOH and the precipitated crude reaction product was collected, washed with H_2O, and air-dried.

Sodium Salt of 5-Benzylamino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-Dioxide (10 Na Salt, Table II). Method F. 10 (0.25 g) was dissolved in boiling saturated $NaHCO_3$. On cooling crude 10 Na salt crystallized.

4-Benzyl-*N*-substituted 5-Sulfamylanthranilic Acids (21–30, Table III). Method G. A mixture of the appropriate 5-substituted amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxide (1.0 g), hydrazine hydrate (2 ml, 80%), KOH (0.5 g) in H_2O (1.5 ml), and diethylene glycol (8 ml) was stirred at about 125° for 2 hr. The temperature was then during about 2 hr raised to 215° allowing volatile material to distill off, and finally the mixture was stirred at 215° until the N_2 evolution had ceased (3–5 hr). After cooling, the mixture was diluted with H_2O (15 ml) and acidified with 4 *N* HCl (8 ml) to precipitate the crude reaction product.

Method H. Method B was followed using 21 as starting material.

4-Benzyl-2-chloro-5-sulfamylbenzoic Acid (32). A solution of 21 (3.0 g, 10 mmol) and $NaNO_2$ (0.76 g, 11 mmol) in 1 *N* NaOH (30 ml) was added dropwise to concentrated HCl (30 ml) while stirring at 0 to −5°. After additional stirring at this temperature for 15 min the resulting diazonium mixture was poured into a solution of CuCl (6.0 g, 60 mmol) in concentrated HCl (30 ml). The mixture was stirred at room temperature for about 20 hr and the precipitated material was collected, washed with H_2O, and air-dried to give crude 32 (3.0 g, 92%, mp 208–211°). It was recrystallized from aqueous EtOH and from aqueous AcOH to yield analytically pure 32 with mp 217–218°. *Anal.* ($C_{14}H_{12}ClNO_4S$) C, H, Cl, N, S.

Method I. A mixture of 32 (1.6 g, 5 mmol) and the appropriate RNH_2 (6.0 ml) was stirred at 140° for 3 hr and was then poured into ice-cold 4 *N* AcOH (50 ml) to precipitate the crude reaction product. For 30, the first precipitate was extracted with hot saturated $NaHCO_3$ and filtered hot in the presence of charcoal, and crude 30 was reprecipitated by acidification with AcOH.

Spectra of 10 Na Salt. 10 Na salt was recrystallized from D_2O in order to minimize background from undeuterated water. The spectra of the resulting Na salt were taken in ca. 4% w/v in D_2O or 10% w/v in 1 *N* NaOD, respectively.

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