

## Diuretics. 4-Substituted 3-Sulfamoylbenzoic Acid Hydrazides

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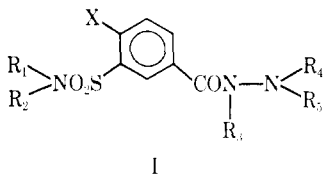
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A series of 4-substituted 3-sulfamoylbenzoic acid hydrazides was prepared and examined for diuretic activity. Chlorine was the preferred substituent in the 4 position, and the 2,2-dialkylhydrazides were found to be the most potent diuretic agents in this class. The corresponding benzohydroxamic acid and methyl ester was found to be equipotent with 4-chloro-3-sulfamoylbenzoic acid hydrazide.

A series of 4-substituted 3-sulfamoylbenzoic acid hydrazides was prepared and the 4-halo compounds (I, X = Cl, Br) were found to be particularly potent diuretic agents.<sup>1</sup> Subsequently, Jucker and coworkers<sup>2,3</sup> reported the preparation of various hydrazides of this type and confirmed the diuretic activity. In this paper the variation of activity with different types of ring substituents and the introduction of lower alkyl groups on both the hydrazide and sulfamoyl functions is discussed.



**Synthesis.**—The desired hydrazides were obtained from the corresponding acid chlorides or esters by treatment with an excess of hydrazine. In general, it was found to be most convenient to prepare the activated cyanomethyl esters which were then allowed to react with the hydrazine at room temperature. This route avoided the formation of the acylated hydrazides which were obtained as by-products when the acid chlorides were used.

When monomethyl hydrazine was used as a reactant, the expected substituted 1-methylhydrazides were obtained, except in the case of 2,4-dichloro-5-sulfamoylbenzoic acid cyanomethyl ester (IIa) where 2,4-dichloro-5-sulfamoylbenzoic acid 2-methylhydrazide (III) was isolated (Scheme I). However, the addition of 2,4-dichloro-5-sulfamoylbenzoyl chloride (IIb) to a chilled aqueous solution of monomethylhydrazine yielded the expected 2,4-dichloro-5-sulfamoylbenzoic acid 1-methylhydrazide (IV). The structure of IV was confirmed by preparing the isopropylidene derivative V.

The hydrazides III, IV, and VII differed greatly in their ease of cyclization *via* displacement of the chlorine atom in the 2 position. When a solution of III in ethyl Cellosolve was heated at reflux for 15 min, the expected 6-chloro-1-methyl-3-oxo-5-indazolesulfonamide (VI) was obtained. The same product was also obtained when 2,4-dichloro-5-sulfamoylcarboxamide (IIc) was treated with monomethylhydrazine in an autoclave at 140°. However, IV was recovered unchanged after heating at reflux in ethyl Cellosolve overnight. On the other hand, the cyclization of 2,4-dichloro-5-sul-

famoylbenzoic acid hydrazide (VII) to 6-chloro-3-oxo-5-indazolesulfonamide<sup>4</sup> (VIII) was effected by refluxing in ethanol.

The derivatives bearing a single substituent on the terminal nitrogen atom were conveniently prepared from the unsubstituted hydrazides. Thus, 4-chloro-3-sulfamoylbenzoic acid, isopropylidene hydrazide was obtained by refluxing the hydrazide in acetone. This product was then reduced to yield 4-chloro-3-sulfamoylbenzoic acid 2-isopropylhydrazide. 4-Chloro-3-sulfamoylbenzoic acid 2-(1-cyano-1-methyl)ethylhydrazide was obtained by heating the hydrazide and acetone cyanohydrin at reflux.

**Pharmacology.**—Each of the compounds listed in Table I was assayed for saluretic and diuretic potency in rats at several dose levels. Following familiarization and experience with this series of compounds, it was decided that a convenient and meaningful comparison of relative potencies might be accomplished best by a two-point dose comparison of natriuretic response. Accordingly, the treatment described below was employed.

Young adult, male Holtzman rats, weighing 140–240 g were used. The animals were allowed at least 1 week in their new environment prior to test and were maintained on Rockland rat pellets and water *ad libitum*. Food and water were withdrawn 18 hr prior to testing. The animals were placed in stainless steel metabolism cages for urine collection after drug and/or vehicle administration, three rats per cage and three cages per dose. Urine volumes were recorded at 2, 5, and 24 hr postdosage, and the urine samples representing the periods 0–5 hr and 5–24 hr postdose were assayed for Na<sup>+</sup> and K<sup>+</sup> concentrations. Test compounds and/or vehicle were administered by oral intubation as a solution or suspension in 2% gum acacia–0.9% NaCl solution. A volume of 25 ml of vehicle/kg of body weight was administered. Most of the compounds were tested at five dose levels, *i.e.*, 2, 10, 50, 100, and 250 mg/kg of body weight; however, some of the more recently tested congeners were examined at 2, 20, and 100 mg/kg.

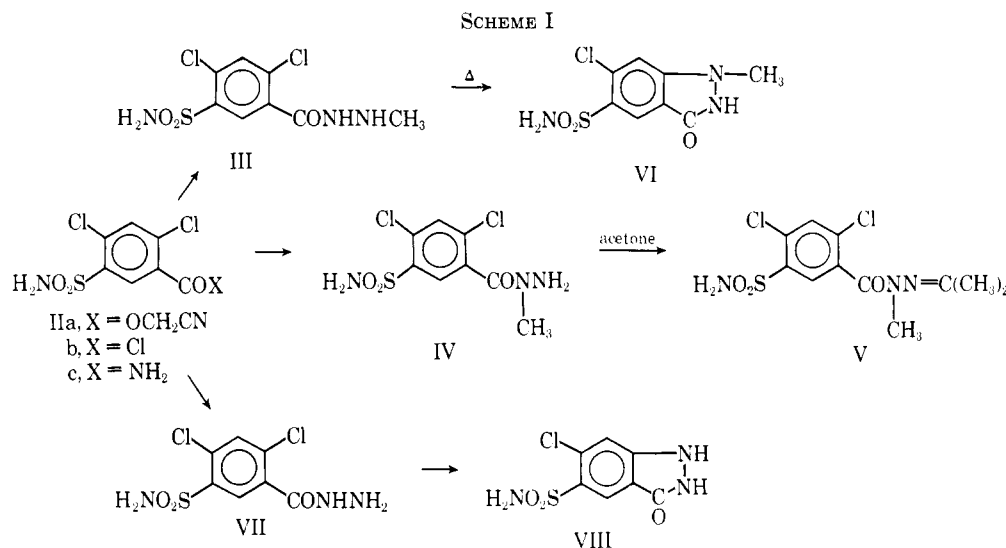
The dose-response curves for this series reflect multiple renal activities and hence are not of the classical so-called “S-shape.” Consequently, log dose-response curves for urinary Na<sup>+</sup> excretion during the first 5 hr after dosage were constructed. The responses at the 5- and 50-mg/kg dose levels were chosen as representing the most clearly descriptive picture for the entire group of compounds, and these values were taken from the

(1) M. L. Hoefle and H. A. DeWald, U. S. Patent 3,043,874 (1962).

(2) E. Jucker and A. Lindenmann, *Helv. Chim. Acta*, **45**, 2316 (1962).

(3) E. Jucker, A. Lindenmann, E. Schenker, E. Flückiger, and M. Tschler, *Arzneim.-Forsch.*, **13**, 269 (1963).

(4) K. Sturm, W. Siedel, R. Weyer, and H. Ruschig, *Chem. Ber.*, **99**, 328 (1966).



curves. The net increase in sodium excretion caused by the test compounds relative to that caused by the reference compound (1) was used as the basis of potency comparison. The per cent activity relative to that of 1 at the 5- and 50-mg/kg doses is given in the last two columns of Table I. Compound 32 is included for comparison.

**Biological Results and Discussion.**—The chemical structure and relative natriuretic activity of the compounds prepared are shown in Table I. 4-Chloro-3-sulfamoylbenzoic acid 2,2-dimethylhydrazide (1) was used as the reference compound since it was selected for clinical studies.<sup>5</sup>

A halogen substituent in the 4 position yielded the most active compound with the activity decreasing in the order chloro > bromo (1, 15 and 2, 3). Removal of the 4-halogen substituent (5) or replacing it with an *n*-propylamino group (6) resulted in greatly decreased activity. Shifting the halogen from the 4 to the 6 position (8) also resulted in a decrease of activity. The 4-methyl compound (4) proved to be quite active in rats, but this relatively high activity was not found in subsequent testing in dogs. The introduction of an additional chloro substituent in the 6 position (7) or ring closure of the hydrazide function to the 6 position also resulted in decreased activity.

The introduction of an alkyl substituent on the nitrogen atom adjacent to the carbonyl group of the hydrazide function resulted in decreased activity (19, 21), whereas terminal substitution generally enhanced the activity (1, 15, 17). However, it appears that steric factors may also have some effect since 4-chloro-*N*-morpholine-3-sulfamoylbenzamide (18) showed decreased activity. Similarly, 4-chloro-3-sulfamoylbenzoic acid 2-(1-cyano-1-methyl)ethylhydrazide (25) was more active than the analogous compound where the cyano group was replaced by hydrogen (24). The presence of an electron-attracting group on the terminal nitrogen atom also decreased activity (13, 14). In the case of the isopropylidene derivatives (9, 11, 12, 20) it is believed that the variation of activity may have been due to differences in the rates of hydrolysis. Alkyl substitution on the sulfamoyl group clearly decreased

activity (26–29). The corresponding benzohydroxamic acid (30) and methyl ester (31) had about the same activity as the parent 4-chloro-3-sulfamoylbenzoic acid hydrazide (2).

### Experimental Section<sup>6,7</sup>

**Intermediates (Table II).** **A. Acid Chlorides.**—The desired acid chlorides were obtained by heating the required acid and SOCl<sub>2</sub> at reflux. It was found advisable to hold the reaction time to 4 hr or less in order to minimize the formation of the corresponding *N*-sulfinylsulfonamides.<sup>8</sup> Excess SOCl<sub>2</sub> was removed by distillation under reduced pressure, and the crude acid chloride was used directly in the next step.

**B. Cyanomethyl Esters.**—The cyanomethyl esters were prepared by the method of Schwyzer, *et al.*<sup>9</sup> The esters were isolated as solids and purified by recrystallization from Me<sub>2</sub>CO-H<sub>2</sub>O unless otherwise noted.

**General Procedure for the Preparation of 4-Substituted 3-Sulfamoylbenzoic Acid Hydrazides.**—Footnote *a* in Table I indicates the methods by which the benzoic acid hydrazides were prepared. Representative examples of each of these methods follows.

**Method A. 2,4-Dichloro-5-sulfamoylbenzoic Acid 1-Methylhydrazide (IV).**—A suspension of 10.7 g of 2,4-dichloro-5-sulfamoylbenzoyl chloride in 100 ml of Et<sub>2</sub>O was added in portions to a stirred solution consisting of monomethylhydrazine in 100 ml of Et<sub>2</sub>O. The reaction mixture was cooled during the addition and then stirred at room temperature for 0.5 hr. The Et<sub>2</sub>O was decanted, and the residue was triturated with warm H<sub>2</sub>O and filtered; yield 7.8 g, mp 230–234°. Recrystallization from aqueous EtOH (1:1) gave colorless crystals, mp 242–243°. *Anal.* (C<sub>8</sub>H<sub>6</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S) C, H, N.

The isopropylidene derivative (V) of the above product was prepared by boiling a small sample in Me<sub>2</sub>CO for several minutes. H<sub>2</sub>O was added and the solution was concentrated by heating on the steam bath for an additional 5 min. After cooling a white solid separated which upon recrystallization from aqueous Me<sub>2</sub>CO melted at 194–195°. *Anal.* (C<sub>11</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S) C, H, N.

**4-Chloro-3-sulfamoylbenzohydroxamic Acid (30).**—A solution of 22.0 g of 4-chloro-3-sulfamoylbenzoyl chloride in 40 ml of THF was added dropwise to a chilled solution of HONH<sub>2</sub> (prepared by dissolving 17 g of NaOH in 70 ml of H<sub>2</sub>O and then adding 10.5 g of HONH<sub>3</sub><sup>+</sup>Cl<sup>−</sup>). The reaction mixture was kept at 0–5° for 0.5 hr following this addition, and it was then allowed to stand

(6) All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected.

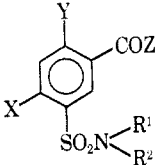
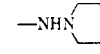
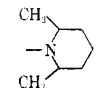
(7) Where analyses are indicated by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

(8) G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H. P. Patzschke, H. Smalla, and A. Trede, *Angew. Chem. Intern. Ed. Engl.*, **1**, 89 (1962).

(9) R. Schwyzer, B. Iselin, W. Rittel, and P. Sieber, *Helv. Chim. Acta*, **39**, 872 (1956).

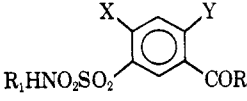
(5) D. H. Kaump, R. L. Fransway, L. T. Blouin, and D. Williams, *J. New Drugs*, **4**, 21 (1964).

TABLE I  
 4-SUBSTITUTED 3-SULFAMOYL BENZOIC ACID HYDRAZIDES

										% diuretic act. rel to 1:	
No.	X	Y	Z	R <sub>1</sub>	R <sub>2</sub>	Prepn method <sup>a</sup>	RS <sup>b</sup>	Mp, °C	Formula <sup>c</sup>	50 mg/kg	5 mg/kg
1 <sup>r</sup>	Cl	H	NHN(CH <sub>3</sub> ) <sub>2</sub>	H	H	A	E	190-191 <sup>r</sup>	C <sub>9</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>3</sub> S	100	100
2 <sup>e</sup>	Cl	H	NHNH <sub>2</sub>	H	H	E	E-W	211-212	C <sub>7</sub> H <sub>8</sub> ClN <sub>3</sub> O <sub>3</sub> S	52	111
3	Br	H	NHNH <sub>2</sub>	H	H	E	E-W	202-203	C <sub>7</sub> H <sub>8</sub> BrN <sub>3</sub> O <sub>3</sub> S	45	74
4	CH <sub>3</sub>	H	NHNH <sub>2</sub>	H	H	E	E-W	206-208	C <sub>8</sub> H <sub>10</sub> N <sub>3</sub> O <sub>3</sub> S	38	73
5	H	H	NHNH <sub>2</sub>	H	H	E	E-W	200-201	C <sub>7</sub> H <sub>9</sub> N <sub>3</sub> O <sub>3</sub> S	0	15
6	<i>n</i> -C <sub>8</sub> H <sub>7</sub> NH	H	NHNH <sub>2</sub>	H	H	P	E-W	224-225	C <sub>10</sub> H <sub>16</sub> N <sub>3</sub> O <sub>3</sub> S	0	9
7	Cl	Cl	NHNH <sub>2</sub>	H	H	E	W	248-249	C <sub>7</sub> H <sub>7</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>3</sub> S	9	48
8	H	Cl	NHNH <sub>2</sub>	H	H	E	E-W	180-181	C <sub>7</sub> H <sub>8</sub> ClN <sub>3</sub> O <sub>3</sub> S	11	16
9	Cl	H	NH=C(CH <sub>3</sub> ) <sub>2</sub>	H	H	P	A	250-252	C <sub>10</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>3</sub> S	58	116
10	Cl	H	NH=CHC <sub>6</sub> H <sub>5</sub>	H	H	P	D-W	225-226	C <sub>10</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>3</sub> S	20	39
11	Br	H	NHN=C(CH <sub>3</sub> ) <sub>2</sub>	H	H	P	E	246-248	C <sub>10</sub> H <sub>12</sub> BrN <sub>3</sub> O <sub>3</sub> S	46	72
12	CH <sub>3</sub>	H	NHN=C(CH <sub>3</sub> ) <sub>2</sub>	H	H	P	A	236-238	C <sub>11</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub> S	25	86
13	Cl	H	NHNHCHO	H	H	P	E-W	210-212	C <sub>8</sub> H <sub>8</sub> ClN <sub>3</sub> O <sub>3</sub> S	27	69
14	Cl	H	NHNHCONH <sub>2</sub>	H	H	P	E	220-221	C <sub>8</sub> H <sub>9</sub> ClN <sub>4</sub> O <sub>3</sub> S·0.5H <sub>2</sub> O	16	35
15	Br	H	NHN(CH <sub>3</sub> ) <sub>2</sub>	H	H	E	E	183-184	C <sub>9</sub> H <sub>12</sub> BrN <sub>3</sub> O <sub>3</sub> S	95	81
16	<i>n</i> -C <sub>8</sub> H <sub>7</sub> NH	H	NHN(CH <sub>3</sub> ) <sub>2</sub>	H	H	P	E-W	176-177	C <sub>12</sub> H <sub>20</sub> N <sub>3</sub> O <sub>3</sub> S	0	19
17	Cl	H	NHN(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	H	H	E	E-W	180-182	C <sub>11</sub> H <sub>16</sub> ClN <sub>3</sub> O <sub>3</sub> S	92	102
18 <sup>e</sup>	Cl	H		H	H	E	D-W	274-275	C <sub>10</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>3</sub> S	74	57
19	Cl	H	N(CH <sub>3</sub> )NH <sub>2</sub>	H	H	A	E-W	158-159	C <sub>8</sub> H <sub>10</sub> ClN <sub>3</sub> O <sub>3</sub> S	14	93
20	Cl	H	N(CH <sub>3</sub> )N=C(CH <sub>3</sub> ) <sub>2</sub>	H	H	P	E-W	156-158	C <sub>11</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>3</sub> S	11	67
21	Cl	Cl	N(CH <sub>3</sub> )NH <sub>2</sub>	H	H	A	E-W	249-250	C <sub>8</sub> H <sub>9</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>3</sub> S	0	32
22	Cl	Cl	N(CH <sub>3</sub> )N=C(CH <sub>3</sub> ) <sub>2</sub>	H	H	P	A-W	194-195	C <sub>11</sub> H <sub>13</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>3</sub> S		
23	Cl	Cl	NHNHCH <sub>3</sub>	H	H	E	W	238-240	C <sub>8</sub> H <sub>9</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>3</sub> S		
24 <sup>e</sup>	Cl	H	NHNHCH(CH <sub>3</sub> ) <sub>2</sub>	H	H	P	W	187-189	C <sub>10</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>3</sub> S	82	41
25	Cl	H	NHNHC(CN)(CH <sub>3</sub> ) <sub>2</sub>	H	H	P	E-W	166-167	C <sub>11</sub> H <sub>13</sub> ClN <sub>4</sub> O <sub>3</sub> S	110	107
26	Cl	H	NHNH <sub>2</sub>	CH <sub>3</sub>	H	E	E-W	139-141	C <sub>8</sub> H <sub>10</sub> ClN <sub>3</sub> O <sub>3</sub> S	29	65
27	Cl	H	NHNH <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	A	W	189-190	C <sub>9</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>3</sub> S	0	38
28	Cl	H	NHN(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub>	H	E	E-W	214-215	C <sub>10</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>3</sub> S	63	74
29	Cl	H	NHN(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	A	E-W	146-147	C <sub>11</sub> H <sub>16</sub> ClN <sub>3</sub> O <sub>3</sub> S	26	48
30	Cl	H	NHOH	H	H	A	W	155-157	C <sub>7</sub> H <sub>7</sub> ClN <sub>3</sub> O <sub>3</sub> S <sup>d</sup>	44	97
31	Cl	H	NHOCH <sub>3</sub>	H	H	A	E-W	232-234	C <sub>8</sub> H <sub>9</sub> ClN <sub>3</sub> O <sub>3</sub> S	77	109
32 <sup>f</sup>	Cl	H		H	H					82	66

<sup>a</sup> Method of preparation: A, *via* the acid chloride; E, *via* the ester; P, derived from the hydrazide. <sup>b</sup> Recrystallization solvents: A, acetone; D, dimethylformamide; E, ethanol; W, water. <sup>c</sup> Satisfactory analytical data were obtained for C, H, N. <sup>d</sup> An early laboratory preparation of this compound<sup>1</sup> was recrystallized from H<sub>2</sub>O and was found to melt at 185-188°. <sup>e</sup> These compounds have been reported in the literature.<sup>1,2</sup> <sup>f</sup> Clopamide (Sandoz).<sup>3</sup> <sup>g</sup> C: calcd, 33.5; found, 33.0.

 TABLE II  
 INTERMEDIATE ACID CHLORIDES AND ESTERS

						Yield, %	Mp, °C	Formula <sup>b</sup>
X	Y	R <sub>1</sub>	R <sub>2</sub>	RS <sup>a</sup>				
Cl	H	H	Cl	Et <sub>2</sub> O		78	170-171	C <sub>7</sub> H <sub>5</sub> Cl <sub>2</sub> NO <sub>3</sub> S
Cl	Cl	H	Cl	Et <sub>2</sub> O		81.5	176-177	C <sub>7</sub> H <sub>4</sub> Cl <sub>3</sub> NO <sub>3</sub> S
Cl	H	H	OCH <sub>2</sub> CN	EtOH		72	185-187	C <sub>9</sub> H <sub>7</sub> ClN <sub>2</sub> O <sub>4</sub> S
CH <sub>3</sub>	H	H	OCH <sub>2</sub> CN	CH <sub>3</sub> CN		69	138-140	C <sub>10</sub> H <sub>10</sub> N <sub>2</sub> O <sub>4</sub> S
Br	H	H	OCH <sub>2</sub> CN	H <sub>2</sub> O-Me <sub>2</sub> O		74	201-202	C <sub>9</sub> H <sub>7</sub> BrN <sub>2</sub> O <sub>4</sub> S
Cl	H	CH <sub>3</sub>	OCH <sub>2</sub> CN	H <sub>2</sub> O-Me <sub>2</sub> O		70.8	105-106	C <sub>10</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>4</sub> S
Cl	Cl	H	OCH <sub>2</sub> CN	H <sub>2</sub> O-Me <sub>2</sub> O		90.2	150-151	C <sub>9</sub> H <sub>6</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S

<sup>a</sup> Recrystallization solvent. <sup>b</sup> Satisfactory analyses were obtained for C, H.

at room temperature for 0.5 hr. The THF was removed under reduced pressure and the resulting solution was treated with charcoal and then acidified with concentrated HCl.  $\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$  (12.0 g) was added and the solution was treated with concentrated  $\text{NH}_4\text{OH}$  until the resulting suspension was slightly basic. The barium salt was collected by filtration and after drying at  $60^\circ$  in a vacuum oven weighed 22.85 g. It was recrystallized from  $\text{H}_2\text{O}$ . *Anal.* ( $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_8\text{S}_2\text{Ba}$ ) C, H.

The barium salt was treated with 6 *N* HCl, and a solid separated, mp  $151^\circ$ . Two recrystallizations from  $\text{H}_2\text{O}$  raised the melting point to  $155\text{--}157^\circ$ . However, this material had a low carbon analysis even after prolonged drying at  $100^\circ$  and it was assumed that this was due to tightly bound  $\text{H}_2\text{O}$ .

**Method E. 2,4-Dichloro-5-sulfamoylbenzoic Acid 2-Methylhydrazide (III).**—2,4-Dichloro-5-sulfamoylbenzoic acid cyanomethyl ester (15.4 g) was mixed with 100 ml of monomethylhydrazine and the resulting solution was allowed to stand at room temperature for 18 hr. The reaction mixture was concentrated to one-half of its original volume by heating on a steam bath, 100 ml of  $\text{H}_2\text{O}$  was added, and the solution was neutralized with concentrated HCl. Upon cooling the solid was removed by filtration and washed with cold  $\text{H}_2\text{O}$ ; yield 6.8 g, mp  $220\text{--}225^\circ$ . One recrystallization from  $\text{H}_2\text{O}$  raised the melting point to  $238\text{--}240^\circ$ . *Anal.* ( $\text{C}_8\text{H}_6\text{Cl}_2\text{N}_3\text{O}_3\text{S}$ ) C, H, N.

**6-Chloro-1-methyl-3-oxo-5-indazolinylsulfonamide (VI).**—A solution of 5.0 g of 2,4-dichloro-5-sulfamoylbenzoic acid 2-methylhydrazide in 30 ml of ethyl Cellosolve was heated at reflux for 4 hr. The reaction mixture was cooled and the product was removed by filtration; yield 2.55 g, mp  $314\text{--}315^\circ$ . The analytical sample was recrystallized from aqueous EtOH (1:1), mp  $315^\circ$ . *Anal.* ( $\text{C}_8\text{H}_7\text{ClN}_3\text{O}_3\text{S}$ ) C, H, N.

The same product was obtained when a solution of 10.0 g of 2,4-dichloro-5-sulfamoylbenzamide and 10 ml of monomethylhydrazine in 50 ml of EtOH was heated in an autoclave at  $140^\circ$  for 4 hr; yield 5.8 g, mp  $314\text{--}315^\circ$ .

A solution of 5.0 g of 2,4-dichloro-5-sulfamoylbenzoic acid 1-methylhydrazide in 50 ml of ethyl Cellosolve was heated at reflux for 8 hr. The solution was concentrated under reduced pressure and  $\text{H}_2\text{O}$  was added to the residue. The solid was collected by filtration; yield 4.3 g, mp  $234\text{--}236^\circ$ . There was no mixture melting point depression of this product and the starting material.

**4-Chloro-3-sulfamoylbenzoic Acid 2-Isopropylhydrazide (24).**—The isopropylidene derivative of 4-chloro-3-sulfamoylbenzoic acid hydrazide was prepared by dissolving 3.0 g of the hydrazide in 50 ml of  $\text{Me}_2\text{CO}$ . The reaction mixture was heated on a steam bath for 5 min, and product which had separated was removed by filtration; yield 3.0 g, mp  $250\text{--}252^\circ$ . This product was re-

duced by the method of Kollonitsch, *et al.*<sup>10</sup> Three grams was dissolved in 200 ml of THF containing 4.0 g of  $\text{CaI}_2$  and then 1.4 g of  $\text{NaBH}_4$  was added. The clear solution was stirred at room temperature overnight during which time a solid separated. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in a mixture of 20 ml of  $\text{H}_2\text{O}$  and 20 ml of 7 *N* methanolic HCl. The solution was again evaporated to dryness under reduced pressure, and the residue was dissolved in 40 ml of  $\text{H}_2\text{O}$ . A small amount of insoluble material was removed by filtration and the pH of the filtrate was adjusted to 7.5. The solid which precipitated was collected by filtration and weighed 3.5 g, mp *ca.*  $190^\circ$ . The solid was triturated with 15 ml of 1 *N* NaOH and the mixture was filtered. Neutralization of the filtrate with HOAc yielded 1.7 g of product as tan needles, mp  $183\text{--}185^\circ$ . The analytical sample was prepared by recrystallization from  $\text{H}_2\text{O}$  yielding colorless needles melting at  $187\text{--}189^\circ$ .

**4-Chloro-3-sulfamoylbenzoic Acid 2-(1-Cyano-1-methyl)ethylhydrazide (25).**—A mixture of 10.0 g of 4-chloro-3-sulfamoylbenzoic acid hydrazide and 3.4 g of acetone cyanohydrin was heated at reflux for 0.5 hr. The mixture was cooled and poured into 100 ml of  $\text{Et}_2\text{O}$ . The gummy product slowly solidified upon standing; mp  $154\text{--}160^\circ$ . Recrystallization from aqueous EtOH (1:1) yielded 3.61 g of product, mp  $166\text{--}167^\circ$ .

**4-(*n*-Propylamino)-3-sulfamoylbenzoic Acid 2,2-Dimethylhydrazide (16).**—A solution of 4-chloro-3-sulfamoylbenzoic acid 2,2-dimethylhydrazide (5.0 g) in 30 ml of *n*-propylamine was heated in an autoclave at  $130^\circ$  for 4 hr. The excess amine was removed by distillation under reduced pressure and 50 ml of  $\text{H}_2\text{O}$  was added. The viscous oil that separated was dissolved in 1 *N* HCl, treated with charcoal, and filtered. The filtrate was made slightly basic with concentrated  $\text{NH}_4\text{OH}$  and a solid was obtained and recrystallized ( $\text{H}_2\text{O}$ ); yield 2.55 g, mp  $176\text{--}177^\circ$ .

**4-Chloro-3-sulfamoylbenzohydroxamic Acid Methyl Ester (31).**—4-Chloro-3-sulfamoylbenzoyl chloride (10.0 g) was added in small portions to a chilled solution of 6.3 g of methoxyamine hydrochloride in 30 ml of  $\text{H}_2\text{O}$  containing 3.0 g of NaOH. Following this addition, the reaction mixture was allowed to stand at room temperature for 1.5 hr. The crude product was collected by filtration and recrystallized (1:1  $\text{H}_2\text{O}\text{--EtOH}$ ); yield 5.4 g, mp  $232\text{--}234^\circ$ .

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(10) J. Kollonitsch, O. Fuchs, and V. Gabor, *Nature*, **175**, 346 (1955).