Professor Helmut Bredereck, Dr. Wolfgang Pfleiderer, and their associates of the Technischen Hochschule, Stuttgart, Germany, for their interest and information. They also wish to express their appreciation to Mr. Hal P. Van Fossen, Mrs. Margaret L. Rounds, and Miss Phyllis G. Shaul for their valuable assistance in performing analytical and instrumental measurements.

2-Sulfobenzoic Acid Esters. II. 4-Amino Derivatives

BERNARD LOEV AND MINERVA KORMENDY

Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pa.

Received December 8, 1961

An improved synthesis of 4-amino-2-sulfamylbenzoates (I) is described along with a number of substituted derivatives These compounds show marked anticonvulsant activity.

The preceding paper in this series[1] described the preparation of a series of sulfamylbenzoates, some of which possessed marked anticonvulsant activity. This activity[2] was initially discovered in a series of 4-amino-2-sulfamylbenzoates, and this paper describes improved methods of synthesis for these compounds (I) and their derivatives.

Hamor and Janfaza[3] synthesized I (R = CH_3, C_2H_5, and i-C_3H_7) by a sequence that involved the reaction of 6-nitrosaccharin with the appropriate alcohol followed by reduction of the resulting 4-nitro-2-sulfamylbenzoate. The 6-nitrosaccharin was prepared by the permanganate oxidation of 4-nitro-2-sulfamyltoluene. In our hand, the yields of 6-nitrosaccharin obtained from this oxidation step were quite low. In addition to this drawback, such a route restricted the variations in chemical structure that could be carried out. Attempts to improve the oxidation step by the use of manganese dioxide[4] or ammonium persulfate[5] as oxidizing agents were unsuccessful. In both cases the starting material was recovered unchanged. In attempts to prepare a more readily oxidized compound (ethyl 4-nitro-2-sulfocinnamate), ethyl *p*-nitrocinnamate was treated with fuming sulfuric or chlorosulfonic acids. At low temperature no sulfonation occurred; at higher temperatures decomposition resulted.

The nitration of saccharin was next considered as a means of eliminating the oxidation step. (Direct substitution reactions on saccharin have not been reported.) However, reaction of saccharin with nitric acid gave either no reaction or tars depending on the severity of conditions.

Syntheses based on the reaction sequence employed by Hamor were then abandoned, and an improved reaction sequence was developed related to the one previously described for the synthesis of unsubstituted sulfamylbenzoates. This sequence is rapid, facile, and gives high over-all yields. It also provides a large variety of structural modifications from a single intermediate (II).

The reaction sequence is outlined in Fig. 1. The yield in the oxidation and in the conversion of the resulting diacid to the dichloride (II) is 60 to 80% in each step. The reaction of the dichloride with aliphatic alcohols gives only the carboxylic ester, III. (Attempts to synthesize aromatic esters led to anomalous results which will be described in Part III of this series.) There was no evidence of sulfonic ester formation, even when an excess of alcohol was used. Compound IV (R = isopropyl) was found to exist in polymorphic forms, m.p. 128–130° and 153–154°. The three steps from the phosphorus pentachloride reaction through to the isolation of IV, can be carried out without isolation or purification of the intermediates, and over-all yields in this sequence often approach 80%.

Catalytic reduction of IV proceeded in high yield. However, in connection with other work, a study of the action of various chemical reducing agents on IV was made. Of the following reduction systems—stannous chloride in acetic acid, stannous chloride and hydrochloric acid in isopropyl alcohol, ferrous hydroxide in aqueous or isopropyl alcoholic solution, zinc and calcium chloride in ethanol, titanium trichloride or sodium hydrosulfite in ethanol, and sodium hydrosulfite in aqueous pyridine—only the hydrosulfite–pyridine procedure was successful (60% yield).

The sulfamyl *N*-alkyl or aryl substituted derivatives were prepared by substituting the appropriate amine for ammonia in the reaction with III. When III (R = isopropyl) was treated with hydrazine, the sulfamyl *N*-amino derivative (a sulfonhydrazide, Table I, compound 10) was ob-

(1) B. Loev and M. Kormendy, Part I, *J. Org. Chem.*, **27**, 1703 (1962).

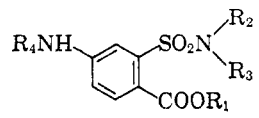
(2) We are indebted to Dr. A. Kandel and co-workers for carrying out the pharmacological examination of these compounds. A detailed presentation of their results will be published elsewhere.

(3) G. H. Hamor and M. Janfaza. Thesis of M. Janfaza, 1957, School of Pharmacy, University of Southern California. These, and certain related compounds, were made available to us for pharmacological testing by Dr. Hamor.

(4) I. K. Fel'dman *et al.*, *J. Gen. Chem., USSR*, **15**, 962 (1945); *Chem. Abstr.*, **40**, 6443 (1946).

(5) C. Beck, German Patent 80.165 (1894).

TABLE I
4-AMINO-2-SULFAMYLBENZOIC ACID ESTERS



No.	R_1	R_2	R_3	R_4	M.P., °C.	Calcd. C	Calcd. H	Found C	Found H
1	*i*-Pr	H	H	H	121–122[a,b]	46.50	5.46	46.68	5.40
2	Cyclopentyl	H	H	H	127–128	50.69	5.67	50.52	5.74
3	*i*-Pr	CH_3	H	H	122–123.5	48.51	5.92	48.22	6.02
4	*i*-Pr	CH_3	CH_3	H	147	50.33	6.34	50.55	6.61
5	*i*-Pr	H	H	CH_3	135–145 dec.	48.51	5.92	48.54	5.70
6	*i*-Pr	Ac	H	H (V)	197–198	47.99	5.37	48.26	5.67
7	*i*-Pr	H	H	Ac (VI)	256–257 dec.	47.99	5.37	48.19	5.51
8	*i*-Pr	C_6H_5	H	H	162–163	57.47	5.43	57.86	5.88
9	*i*-Pr	$C_6H_5CH_2$	$C_6H_5CH_2$	H	108–110	65.73	5.98	65.64	6.12
10	*i*-Pr	NH_2	H	H	80 dec.	43.94	5.53	43.62	5.76

[a] Hydrochloride, m.p. 189–192°. [b] Lit.,[3] m.p. 120–121°.

tained. This synthesis was complicated by the ease with which the product decomposes when warmed in hydroxylic solvents.[6]

The *N,N*-dibenzylsulfamyl derivative (compound 9) was prepared in the hope that the dibenzyl group would serve as a removable blocking agent; however, neither chemical nor catalytic reduction techniques led to any debenzylation.

The sulfamyl *N*-acyl derivative (V) was prepared by acylation of the sulfamyl group *prior* to reduction of the nitro group. When V was treated under Clarke-Eschweiler alkylating conditions,[7] the 4-(*N*-methyl) derivative of I was obtained.[8] If acylation is carried out *after* reduction, the aromatic *amino* group is selectively acylated (VI). When VI is dissolved in base and the solution acidified, the product is the acetamidosaccharin.

The various 4-amino-2-sulfamylbenzoates which were prepared are listed in Table I.

Modification of the literature procedure[9] provided 5-nitro-2-sulfobenzoic anhydride (IX). Attempted conversion of this intermediate to the 5-aminosulfamylbenzoates, using the procedure employed for the 4-isomer (Fig. 1), was not successful. All attempts to convert IX or its hydrolysis product (VII) to the dichloride reported by Stubbs,[9] resulted in quantitative recovery of the anhydride (Fig. 2). An alternate route was then investigated, in which the anhydride was treated with isopropyl alcohol giving a quantitative yield of isopropyl 5-nitro-2-sulfobenzoate (VIII). When this ester was treated with phosphorus pentachloride,[10] thionyl chloride, or phosphorus oxychloride, the original anhydride was recovered

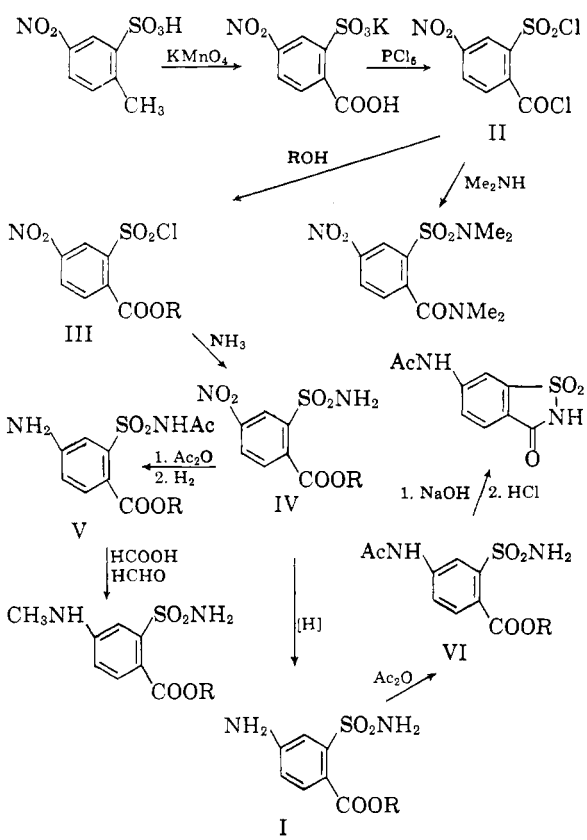


Figure 1

quantitatively. The 5-amino isomer has since been synthesized by another route.[11]

Structure-Activity Relationship.[2]—The most potent anticonvulsant compound in this series, as indicated by potency in preventing the effect of strychnine or maximal electric shock in mice, was compound I (R = isopropyl). The methyl and ethyl esters were much less potent in that order.

(6) Recrystallization from alcohol, for example, partially converts it to a new substance that appears to correspond to a cyclic compound such as described in Part I of this series[1] (compound IIIb).

(7) M. L. Moore, *Org. Reactions*, **5**, 301 (1949).

(8) The only previous instance where Clarke-Eschweiler reaction conditions gave only monomethylation was with *t*-butylamine, A. F. Meimers *et al.*, *J. Org. Chem.*, **23**, 1122 (1958).

(9) M. B. Stubbs, *Am. Chem. J.*, **50**, 193 (1913).

(10) This procedure worked well in the des nitro series, see ref. 1.

(11) G. H. Hamor, University of Southern California unpublished results.

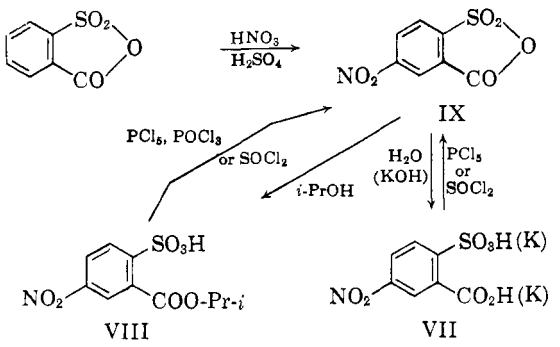


Figure 2

The mono- and dimethylsulfamyl derivatives showed markedly increased side effects.

Experimental[12]

Potassium 2-Carboxy-5-nitrobenzenesulfonate.—Potassium permanganate (748 g.) was added over 2 hr. to a solution of 327 g. (1.36 moles) sodium 2-methyl-5-nitrobenzenesulfonate (E. I. du Pont de Nemours and Co.) in 7.4 l. of water containing 101 g. of potassium hydroxide maintained at 90–100°. The manganese dioxide was filtered hot, then the filtrate and hot water rinses were neutralized with concd. hydrochloric acid and concentrated to 3 l. The solution was then made strongly acidic with hydrochloric acid and chilled. The precipitated potassium 2-carboxy-5-nitrobenzenesulfonate (172.8 g.) was filtered and used in the next step without further purification.

4-Nitro-2-(chlorosulfonyl)benzoyl Chloride (II).—Potassium 2-carboxy-5-nitrobenzenesulfonate (95.1 g.) and 190 g. (0.91) mole of phosphorus pentachloride were thoroughly mixed and heated at 120–130° for 2.5 hr. The phosphorus oxychloride was distilled under reduced pressure, and the yellow residue was rinsed with ice water, dissolved in ether, rinsed again with ice water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residual oil solidified on cooling, m.p. 44°, yield 80 g. (80%).

This material was suitable for use in the subsequent reactions. It could be recrystallized only with considerable difficulty. A sample was recrystallized from isopropyl ether, m.p. 49–55° (lit.,[13] m.p. 59°).

Esters of 4-Nitro-2-sulfamylbenzoic Acid (IV).—A solution of 34 g. (0.12 mole) of 4-nitro-2-chlorosulfonylbenzoyl chloride in 100 ml. of isopropyl alcohol was heated at 50–60° for 45 min. The solution was concentrated under reduced pressure, then the residual oil (crude isopropyl 4-nitro-2-chlorosulfonylbenzoate) was dissolved in ether and poured into an ethereal solution containing excess ammonia. The excess ammonia and ether were blown off in a nitrogen stream, and the residue was stirred with water to dissolve the ammonium chloride, leaving the organic product in fairly pure form. The product was recrystallized from isopropyl alcohol to give 26 g. of isopropyl 4-nitro-2-sulfamylbenzoate. The first time this reaction was carried out, the product had a melting point of 127–128° (lit.,[3] m.p. 128°). Every time thereafter, however, the m.p. was 153°.

Anal. Calcd. for $C_{10}H_{12}N_2O_6S$: C, 41.66; H, 4.20; N, 9.72. Found: C, 41.69; H, 4.50; N, 9.87.

Reduction of either compound gave the same amino derivative. It was concluded, therefore, that they were polymorphic substances.

By a similar procedure, the methyl ester (61% yield,[14] m.p. 186–191°, lit.,[3] m.p. 193°) and the cyclopentyl ester (84% yield,[14] m.p. 170–172°) were prepared.

Anal. Calcd. for $C_{12}H_{14}N_2O_6S$: C, 45.85; H, 4.49. Found: C, 45.79; H, 4.55.

The intermediate cyclopentyl 5-nitro-2-chlorosulfonylbenzoate (III. R = cyclopentyl) was a solid, m.p. 92–94°.

When isopropyl 4-nitro-2-chlorosulfonylbenzoate was treated with ethereal solutions of amines instead of ammonia, sulfamyl *N*-substituted derivatives resulted. The following were prepared (amine used, melting point of product, per cent yield[14]): CH_3NH_2, 142–145°, 65%; $(CH_3)_2NH$, 82–84°, 61%; $C_6H_5NH_2$, 104–106°, 77%; $(C_6H_5CH_2)_2NH$, 100–101°, 34%.

4-Amino-2-sulfamylbenzoic Acid Esters (I). a. *Via* **Catalytic Reduction.**—The nitro compound was dissolved in ethyl acetate and reduced at 50 p.s.i.g. using 10% palladium-on-carbon catalyst. When the reduction was complete, the catalyst was filtered off, and the solvent distilled. The residual solid was recrystallized from alcohol–hexane. The yield of pure product was 60–80%. The compounds so prepared are described in Table I.

b. *Via* **Chemical Reduction.**—One gram of the nitro compound (IV. R = isopropyl) dissolved in 4.5 ml. of pyridine was mixed with a solution of 2.7 g. of sodium hydrosulfite in 8 ml. of water. The temperature spontaneously rose to 40° as the color of the solution changed from dark red to light red and then dark again. Another 2.5 ml. of pyridine was added and the two phase mixture was heated at reflux for 2 hr. The solution was cooled, diluted with water, and extracted with ether. After drying, the organic layer was concentrated giving 0.6 g. of an oil that solidified to a glass. It was recrystallized from a mixture of ethanol–petroleum ether, giving 0.4 g. of isopropyl 4-amino-2-sulfamylbenzoate, m.p. 118–120°, identical with that prepared by catalytic reduction.

Isopropyl 4-Amino-2[*N*-acetylsulfamyl]benzoate (V. R = isopropyl).—A suspension of isopropyl 4-nitro-2-sulfamylbenzoate (5.9 g., 0.02 mole) in 10 ml. of acetic anhydride was refluxed for 30 min. On cooling the solution a solid precipitated and was filtered, 1.5 g.; the filtrate was concentrated under reduced pressure and the residue suspended in water to give an additional 4 g., total yield 81%. The combined solids were recrystallized from ethyl acetate–petroleum ether, giving 5.1 g. (73%) of isopropyl 4-nitro-2-(*N*-acetylsulfamyl)benzoate (IV. R = isopropyl), m.p. 137–138°.

A solution of 6.7 g. of isopropyl 4-nitro-2-[*N*-acetylsulfamyl]benzoate in 60 ml. of ethyl acetate was hydrogenated using 10% palladium-charcoal catalyst. The catalyst was filtered, and the filtrate was concentrated under reduced pressure to give an oil which crystallized on standing, m.p. 184–188°; this was recrystallized from isopropyl alcohol–petroleum ether to give 2.6 g. (43%) of product, m.p. 197–198°.

Anal. Calcd. for $C_{12}H_{16}N_2O_5S$: C, 47.99; H, 5.37. Found: C, 48.26; H, 5.67.

Isopropyl 4-Nitro-2-sulfhydrazylbenzoate.—An ethereal solution of hydrazine was added to an ethereal solution containing 0.04 mole of III (R = isopropyl) until the mixture reached pH 8; a dark yellow oil formed which solidified on standing. The solid was separated by filtration, suspended in water and the excess of hydrazine neutralized with a few drops of hydrochloric acid. The resulting suspension was filtered giving 7.3 g. (62%) of 4-nitro-2-sulfhydrazylbenzoic acid, isopropyl ester, which was recrystallized from ethyl acetate–hexane without heating, m.p. 123–124.5° dec., 5.5 g. (47% yield).

Anal. Calcd. for $C_{10}H_{13}N_3O_6S$: C, 39.60; H, 4.32; N, 13.86. Found: C, 39.83; H, 4.63; N, 14.05.

Isopropyl 4-Amino-2-sulfhydrazylbenzoate.—Reduction of 4-nitro-2-sulfhydrazylbenzoic acid, isopropyl ester, 3.5 g. (0.0115 mole) was carried out in presence of 10% palladium-charcoal (0.5 g.) in tetrahydrofuran solution; the reduction proceeded smoothly. The suspension was filtered and the filtrate concentrated under reduced pressure to give an oil

(12) All melting points are corrected. The analyses were performed by Mrs. D. Rolston and her staff of these laboratories.

(13) J. H. Kastle, *Am. Chem. J.*, **11**, 177 (1889).

(14) Based on dichloride II.

which solidified when triturated with isopropyl ether in a mortar and was separated by filtration, m.p. 80° dec., 1.8 g. (60%).

Isopropyl 4-[*N*-Methylamino]-2-sulfamylbenzoate.—A solution of 3.6 g. (0.012 mole) of isopropyl 4-amino-2-[*N*-acetyl-sulfamyl]-benzoate (V, R = isopropyl) in 25 ml. of methanol was added to 6.0 g. of 98% formic acid, while keeping the mixture in an ice bath; after 10–15 min., 10 ml. of a 37% solution of formaldehyde in methanol–water was added and the solution was refluxed for 24 hr. The solution was cooled and acidified with 5 ml. of concd. hydrochloric acid and concentrated under reduced pressure. A solid separated which dissolved on neutralization with 10% sodium hydroxide to give a yellow solution. Upon addition of concd. hydrochloric acid the product separated and was filtered; it was recrystallized from isopropyl ether, 1.8 g.

Isopropyl 4-Acetamido-2-sulfamylbenzoate (VI. R = isopropyl).—A mixture of 1.9 g. (0.015 mole) of 4-amino-2-sulfamylbenzoic acid, isopropyl ester and 0.75 g. (0.073 mole) acetic anhydride in 10 ml. of tetrahydrofuran was left at room temperature for several hours. The white solid which separated was recrystallized from acetonitrile, m.p. 256–257° dec.

6-Acetamidosaccharin.—When a solution of isopropyl 4-acetamido-2-sulfamylbenzoate in 10% sodium hydroxide was neutralized with 4 *N* hydrochloric acid, 6-acetamidosaccharin separated as a pink solid which was recrystallized from a mixture of methanol, ethyl acetate, and hexane, m.p. 295–298° dec.

Anal. Calcd. for $C_9H_8N_2O_4S$: C, 45.00; H, 3.36. Found: C, 45.06; H, 3.68, 3.67.

4-Nitro-2-(dimethylsulfamyl)-*N*,*N*-dimethylbenzamide.—An ethereal solution containing 10 g. (0.035 mole) of the di-acid chloride (II) was added to a solution of 7.9 g. of dimethylamine (0.175 mole) in 100 cc. of ether. An immediate yellow precipitate and gum formed. The ethereal solution was decanted, and proved to contain only 1 g. of an oil, which was discarded. The insoluble solid and gum were washed with water leaving a pale yellow solid, 9 g., m.p. 165–169°, very soluble in benzene and hot ethanol, insoluble in ether. It was recrystallized from ethanol to give 6 g. of yellow solid, m.p. 168–170.5°.

Anal. Calcd. for $C_{11}H_{15}N_3O_5S$: C, 43.84; H, 5.02. Found: C, 43.55; H, 5.05.

5-Nitrosulfobenzoic Anhydride (IX).—A mixture of 50 g. (30 cc.) of fuming nitric acid and 40 g. (25 cc.) of concd. sulfuric acid was added to 25 g. of sulfobenzoic anhydride (Eastman Organic Chemicals). After about 60 sec. the solution turned red and became very hot and was then cooled in ice water (30–45 sec.) and left at room temperature. After 15 min., the solution was poured on ice, and the white solid product was filtered, 6 g., m.p. 210–212° (lit.,[9] m.p. 212°). The anhydride was used without further purification.

There was undoubtedly more product and 5-nitrosulfobenzoic acid in the filtrate, but no attempt was made to isolate it. A small sample of the anhydride was purified and analyzed.

Anal. Calcd. for $C_7H_3NO_6S$: C, 36.68; H, 1.32. Found: C, 36.47; H, 1.69.

5-Nitrosulfobenzoic Acid (VII).—A suspension of 16 g. (0.07 mole) of nitrosulfobenzoic anhydride in 250 ml. of water was boiled until all the solid dissolved. The clear solution was concentrated under reduced pressure to give a solid corresponding to the 5-nitrosulfobenzoic acid, m.p. 156° (lit., 153°).[15]

Attempted Synthesis of 2-Chlorosulfonyl-5-nitrobenzoic Acid, Isopropyl Ester.—A suspension of 7.7 g. (0.0336 mole) of 5-nitro-sulfobenzoic anhydride in 30 ml. of isopropyl alcohol was heated on the steam bath. Heating was continued for 20 min. after the anhydride had dissolved. The solution was cooled and concentrated under reduced pressure to give a sirup which failed to crystallize. When heated with phosphorus pentachloride (18 g., 0.0865 mole), a solid separated, m.p. 215–217° (identical to starting material, 216–219°); the filtrate was concentrated and the residue was diluted with ether and filtered, giving an additional quantity of anhydride. A total of 88% of the nitrosulfobenzoic anhydride was recovered. The filtrate was concentrated but a dark tar was the only isolable product.

Attempted Synthesis of 2-Chlorosulfonyl-5-nitrobenzoyl Chloride.—a. A mixture of 17.3 g. (0.07 mole) of 5-nitrosulfobenzoic acid and 75 g. (0.36 mole) of phosphorus pentachloride was heated at 120° for five hours. (There was an exothermic reaction when the solids were mixed.) The phosphorus oxychloride was removed *in vacuo* and the residue was suspended in ether. A solid separated and was filtered, 13.3 g. (83%) of 5-nitrosulfobenzoic anhydride were recovered, m.p. 215–218°. Attempts to isolate another product were successful.

b. A suspension of 13.3 g. (0.0582 mole) of 5-nitrosulfobenzoic anhydride in 100 ml. of water was heated to boiling until all the anhydride had dissolved. To this solution was added 9.0 g. (0.0654 mole) of potassium carbonate and the solution was concentrated *in vacuo*. The resulting potassium salt was dried and treated with 25 g. (0.12 mole) of phosphorus pentachloride and the mixture heated at 120° for 14 hr. The phosphorus oxychloride was distilled *in vacuo* and the semisolid residue suspended in ether and filtered, 7.7 g. (58%) of 5-nitrosulfobenzoic anhydride, m.p. 215–218°, were recovered. The filtrate gave an unworkable tar.

Similar results were obtained on reaction of isopropyl 5-nitro-2-sulfobenzoate with phosphorus oxychloride, thionyl chloride, or thionyl chloride in dimethylformamide.

---

(15) After this work was completed, G. H. Hamor, *J. Am. Pharm. Assoc.*, **49**, 280 (1960), reported results differing from ours. On nitration of sulfobenzoic anhydride, we isolated a compound whose melting point (m.p. 215°) and analysis corresponds to that of compound IX (m.p. 212°) first isolated by Stubbs[9] from the nitration of sulfobenzoic acid. On hydrolysis, our compound was converted to another substance whose melting point (m.p. 156°) agrees with that (m.p. 153°) described by H. J. Taverne, *Rec. trav. chim.*, **25**, 64 (1906), for VII. The structure of VII was clearly established by Taverne, who converted it to the known 2-chloro-5-nitrobenzoic acid. In contrast, Hamor (v.s.) reported that nitration of sulfobenzoic acid gave a mixture of 4- and 6-nitrosulfobenzoic acids, m.p. 90–125° (the structures were established by conversion, *via* the dichlorides, to the corresponding nitrosaccharins). A possible explanation for the discrepancies in the two results is that as a result of the difference in the work-up of the reaction mixture we each isolated different constituents of a multicomponent system (our yield is only 25%; Hamor does not report experimental procedure or yield in his paper).