[Contribution from the Medical-Research Division, Sharp and Dohme, Inc.]

Substituted Sulfanilamides. III. N^4-Acyl-N^1-hydroxy Derivatives

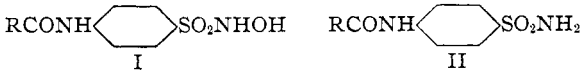
By Maurice L. Moore, Charles S. Miller and Ellis Miller

The first paper[1] of this series described the preparation of a number of acyl derivatives of sulfanilamide, certain of which were found to possess low toxicity and to be more or less effective in combating experimental streptococcic infections in mice.

We undertook to prepare and investigate derivatives of sulfanilamide which might be more soluble in water than the acylsulfanilamides.

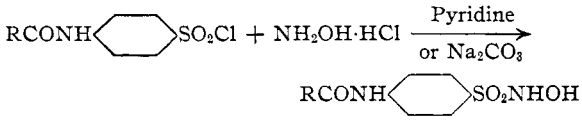
Kharasch and Reinmuth[2] have reported the preparation of sulfanilhydroxamide through the intermediate acetyl derivative and have indicated that it possesses useful therapeutic activity in the treatment of streptococcic and other infections.

This paper describes the preparation, properties and antistreptococcal activity of a series of acyl derivatives of sulfanilhydroxamide I (Table II) for comparison with the acylsulfanilamides II.



I II

The aliphatic monocarboxylic acid derivatives of sulfanilhydroxamide were prepared from the acylanilides by the action of chlorosulfonic acid and subsequent treatment of the 4-acylaminobenzenesulfonyl chloride (Table I) thus produced with hydroxylamine hydrochloride in pyridine or in an aqueous suspension with sodium carbonate.



4-Nitrobenzenesulfonhydroxamide was prepared from 4-nitrobenzenesulfonyl chloride by the same procedure.

The dicarboxylic acid derivatives were prepared by refluxing an alcoholic solution of the appropriate dicarboxylic acid anhydride with sulfanilhydroxamide, as previously described for the sulfanilamide derivatives.[1] Condensation of benzoyl chloride with sulfanilhydroxamide in pyridine or sodium bicarbonate solution led to the preparation of N^4-benzoylsulfanilamide instead of the expected N^4-benzoylsulfanilhydroxamide.

(1) Miller, Rock and Moore, This Journal, **61**, 1198 (1939).

(2) Kharasch and Reinmuth, U. S. Patent 2,097,414.

N^4-Acylaminobenzenesulfinic acids were obtained by treating the acylsulfanilhydroxamides with sodium hydroxide solution.

The N^4-acylsulfanilhydroxamides are more soluble in water than the corresponding N^4-acylsulfanilamides. However, they are less soluble in water than the unacylated sulfanilhydroxamide or sulfanilamide. The antistreptococcal activity of these compounds was determined by the oral administration of daily doses of 5 mg. for four days to 20-g. mice experimentally infected with a virulent strain of β-hemolytic streptococcus of such strength that all controls died within forty-eight hours. The results, thus obtained, showed considerable variation. The aliphatic monocarboxylic acid derivatives of sulfanilhydroxamide were more active than the corresponding acylsulfanilamides and in several instances the activity was greater than that of sulfanilamide itself. It is interesting to note that sulfanilhydroxamide was less active in our tests than sulfanilamide and that several of the higher acyl derivatives showed greater activity than the parent compound. The dicarboxylic acid derivatives were less effective.

The toxicity of these compounds was greatly below that of sulfanilamide so that the therapeutic index was generally more favorable.

The preliminary antistreptococcal and toxicity tests were carried out with the coöperation of Dr. Bettylee Hampil and Mr. G. W. Webster and will be reported elsewhere.

The comparative results, as given in Table II with the activity of sulfanilamide expressed as +++, are based on the number of animals surviving a period of observation of seven days.

Experimental

The acylanilides used in this experiment were prepared by the action of the appropriate acid or acid chloride on aniline according to the usual procedures.

Preparation of 4-Acylaminobenzenesulfonyl Chlorides.—The series of 4-acylaminobenzenesulfonyl chlorides was synthesized according to the procedure of Smiles and Stewart,[3] which in general involved the treatment of chlorosulfonic acid (5 moles) with the appropriate acylanilide (1 mole) at 5–20° with stirring. In every case, the reactions were subsequently raised to a temperature of 55–65°

(3) Smiles and Stewart, "Organic Syntheses," Coll. Vol. I, p. 8.

TABLE I

4-ACYLAMINOBENZENESULFONYL CHLORIDES[a]

No.	Acyl group	Yield, %[b]	M. p., °C.[c]	Formula	Nitrogen, % Calcd.	Found		Chlorine, % Calcd.	Found	
1	CH_3CO	80	147–148							
2[d]	CH_3CH_2CO	82	112–113	$C_9H_{10}O_3NSCl$	5.66	5.72	5.71	14.34	14.35	
3[d]	$CH_3CH_2CH_2CO$	80	118–119	$C_{10}H_{12}O_3NSCl$	5.35	5.35	5.20	13.58	13.39	13.40
4[d]	$CH_3(CH_2)_3CO$	63	111–112	$C_{11}H_{14}O_3NSCl$	5.08	5.19	5.16	12.89	13.07	12.87
5	$CH_3(CH_2)_4CO$	75	92	$C_{12}H_{14}O_3NSCl$	4.84	4.88	5.00	12.26	12.14	12.00
6	$CH_3(CH_2)_5CO$	80	85–86	$C_{13}H_{18}O_3NSCl$	4.61	4.61	4.48	11.70	11.60	11.50
7	$CH_3(CH_2)_6CO$	60	69–70	$C_{14}H_{20}O_3NSCl$	4.41	4.21	4.37			
8	$CH_3(CH_2)_7CO$	35	72–72.5	$C_{15}H_{22}O_3NSCl$	4.22	4.17	4.14	10.71	10.65	10.81
9[d]	$(CH_3)_2CHCO$	65	131–132.5	$C_{10}H_{12}O_3NSCl$	5.35	5.27	5.30			
10[d]	$(CH_3)_2CHCH_2CO$	80	123–124	$C_{11}H_{14}O_3NSCl$	5.08	5.12	5.06	12.89	12.80	12.81
11	$(CH_3)_2CH(CH_2)_2CO$	72	78.5–79.5	$C_{12}H_{16}O_3NSCl$	4.84	4.64	4.73	12.26	12.03	

[a] White crystalline solids from benzene which decompose upon standing after a few days. [b] The yields are based upon the crude solid. [c] All melting points reported are uncorrected. [d] These compounds have been described recently by Adams, Long and Johnson, THIS JOURNAL, **61**, 2342 (1939).

and continued for three hours. The sulfonyl chlorides were obtained as gummy masses when poured into an ice-water mixture. They solidified after standing and were used directly as obtained, in the condensation reactions. A portion of each product was purified by crystallization from benzene, as a white crystalline solid, for identification and analysis. The yields, based on crude solid, and properties of the sulfonyl chlorides are summarized in Table I.

Preparation of Monocarboxylic Acid Derivatives of Sulfanilhydroxamide.—(1) To 10 g. (0.14 mole) of hydroxylamine hydrochloride dissolved in 100 cc. of pyridine was added 20 g. (0.07 mole) of crude 4-*n*-hexanaminobenzenesulfonyl chloride, with stirring, over a period of one hour. The solution was allowed to cool to room temperature and then poured into 300 cc. of 10% hydrochloric acid solution. A white crystalline product formed which was easily purified by decolorizing with Norit and recrystallizing from 50% alcohol. The yield of N^4-hexanoylsulfanilhydroxamide was about 75%, melting at 175–179° with decomposition.

(2) Thirty-five grams of 4-acetaminobenzenesulfonyl chloride and 52.5 g. of hydroxylamine hydrochloride were suspended in 100 cc. of water and 32 g. of sodium carbonate added slowly with vigorous stirring. The mixture was allowed to stand for several hours and the N^4-acetylsulfanilhydroxamide[2] collected on the filter. A yield of 68% was obtained and after recrystallizing from dilute alcohol as glistening prisms it melted at 194–196° with decomposition.

This product could be converted easily into the free base, sulfanilhydroxamide,[2] by hydrolyzing with dilute hydrochloric acid, neutralizing with sodium bicarbonate and recrystallizing from dilute alcohol, as glistening prismatic crystals. The yield was about 80%, melting at 170.5–173° with decomposition.

The aliphatic monocarboxylic acid derivatives of sulfanilhydroxamide were readily soluble in acetone, alcohol, propylene glycol, and sodium hydroxide solution. They were soluble in sodium bicarbonate solution, without effervescence, upon heating.

Preparation of Dicarboxylic Acid Derivatives of Sulfanilhydroxamide.—These derivatives were prepared by refluxing the necessary acid anhydride (0.05 mole) with sulfanilhydroxamide (0.05 mole) in alcohol (70 cc.) according to the previously reported procedure.[1] The products were readily soluble in sodium bicarbonate solution with effervescence and were purified by crystallization from water.

Reaction of Benzoyl Chloride with Sulfanilhydroxamide.—Sulfanilhydroxamide, 9 g. (0.05 mole), was dissolved in 40 cc. of pyridine and treated with 7 g. (0.05 mole) of benzoyl chloride. The solution was warmed on the steam-bath for one and one-half hours and then poured into 250 cc. of cold 10% hydrochloric acid solution. An orange solid separated which was insoluble in water, acetone, benzene, ether and only slightly soluble in anhydrous alcohol. It was soluble in benzyl alcohol and propylene glycol. Crystallization from propylene glycol gave colorless glistening prism-like crystals melting at 182–183°. This product was shown to be N^4-benzoylsulfanilamide[1] by mixed melting point with a known sample.

Several attempts to prepare N^4-benzoylsulfanilhydroxamide by condensation of benzoyl chloride with sulfanilhydroxamide in pyridine or aqueous sodium carbonate solution, with or without heat, have been unsuccessful.

4 - Nitrobenzenesulfonhydroxamide.—Hydroxylamine hydrochloride, 14.8 g. (0.213 mole), was dissolved in 50 cc. of pyridine and 23.6 g. (0.206 mole) of 4-nitrobenzenesulfonyl chloride added slowly with stirring. Considerable heat was involved during the reaction and the mixture was allowed to cool to room temperature before pouring into a mixture, of twice its volume, of ice and hydrochloric acid. A light yellow precipitate was formed and collected on the filter. The crude product, 16.4 g., melted with decomposition at 144–146°. Immediate recrystallization from alcohol gave a product melting at 145–149° with decomposition. The compound was so unstable that the melting point had to be determined immediately after crystallization and drying and even then there was evidence of decomposition. Nitrogen analysis of a sample melting at 145–149° gave results about 1% lower than the calculated for the desired product.

4-*n*-Hexanaminobenzenesulfinic Acid.[4]—N^4-Hexanoyl sulfanilhydroxamide, 6.9 g., dissolved slowly, at room temperature, in 50 cc. of water, containing 5.3 cc. of 4.6 *N* sodium hydroxide, with the evolution of a gas. The

(4) We are indebted to Mr. L. F. McBurney for carrying out this reaction.

TABLE II

N⁴-ACYLSULFANILHYDROXAMIDES

No.	Acyl group	Yield, %	M. p., °C.,[a] dec.	Antistrep. activity	Formula	Nitrogen, % Calcd.	Nitrogen, % Found		Sulfur, % Calcd.	Sulfur, % Found	
1[b,c]	H	80	170.5–173	++	$C_6H_8O_3N_2S$	14.90			17.02	17.19	17.11
2[b,d]	CH_3CO	44–68	194–196	+	$C_8H_{10}O_4N_2S$	12.17	12.05	12.09	13.92	13.96	14.07
3[d]	CH_3CH_2CO	44	174–178	+	$C_9H_{12}O_4N_2S$	11.48	11.42	11.41	13.12	13.28	
4[d]	$CH_3(CH_2)_2CO$	79	172–178	+++	$C_{10}H_{14}O_4N_2S$	10.85	10.85	10.78	12.40	12.26	12.43
5[d]	$CH_3(CH_2)_3CO$	80	178–179.5	++++	$C_{11}H_{16}O_4N_2S$	10.29	10.32	10.34	11.76	11.90	11.87
6[d]	$CH_3(CH_2)_4CO$	75	173–179	++++	$C_{12}H_{18}O_4N_2S$	9.79	9.82	9.89	11.19	11.29	11.25
7[d]	$CH_3(CH_2)_5CO$	65	166–169	++++	$C_{13}H_{20}O_4N_2S$	9.33	9.27	9.39	10.67	10.67	10.60
8[d]	$CH_3(CH_2)_6CO$	..	160–163	+++	$C_{14}H_{22}O_4N_2S$	8.91	8.84	8.75	10.19	10.34	10.20
9[d]	$CH_3(CH_2)_7CO$	50	168–172	+	$C_{15}H_{24}O_4N_2S$	8.54	8.46	8.44	9.76	10.01	9.92
10[d]	$(CH_3)_2CHCO$	70	172–176	+	$C_{10}H_{14}O_4N_2S$	10.85	10.60				
11[d]	$(CH_3)_2CHCH_2CO$	75	168.5–173	+	$C_{11}H_{16}O_4N_2S$	10.29	10.45	10.42	11.76	11.92	
12[d]	$(CH_3)_2CH(CH_2)_2CO$	55	153–157	+	$C_{12}H_{18}O_4N_2S$	9.79	9.70	9.80	11.19	11.15	
13[e]	$HOOCCH_2CH_2CO$	50	170–174	0	$C_{10}H_{12}O_6N_2S$	9.72	9.73	9.66			
14[e]	HOOCCH=CHCO	63	184–185	0	$C_{10}H_{10}O_6N_2S$	9.79	9.62	9.57			
15[f]		38	145–149	++	$C_6H_6O_5N_2S$						

[a] These compounds start to darken slightly on top, in the melting point tube, a few degrees before this range is reached, and then bubble up the tube as a brown liquid at the range indicated. [b] Previously reported by Kharasch and Reinmuth.[2] [c] Recrystallized from water as glistening prismatic plates. [d] Recrystallized from dilute ethanol, usually as glistening crystals. Slightly soluble in water. [e] Recrystallized from water as small glistening platelets. Decomposed with vigorous effervescence. [f] Recrystallized from alcohol. Too unstable for satisfactory analysis as it decomposes during the process. Appreciably soluble in water.

sodium salt of 4-*n*-hexanaminobenzenesulfinic acid, 4.9 g. (74% yield), was obtained when the solution was poured into a large volume of acetone. Neutralization of the sodium salt with dilute sulfuric acid gave the free acid, which upon crystallization from dilute ethanol, as feathery needles, melted at 113–116°.

Anal. Calcd. for $C_{12}H_{17}O_3NS$: N, 5.49. Found: N, 5.35.

The identity of the product was further established by the reduction of 4-*n*-hexanaminobenzenesulfonyl chloride with sodium sulfite.[5] The resulting 4-*n*-hexanaminobenzenesulfinic acid, m. p. 113–116°, gave no depression in melting point when mixed with the above product.

(5) "Organic Syntheses," Coll. Vol. I, p. 7.

Summary

The preparation, properties and some reactions of a series of N⁴-acyl derivatives of sulfanilhydroxyamide are described, together with the preliminary results of their chemotherapeutic activity against experimental streptococcic infections in mice.

Certain of the aliphatic acyl derivatives have been found to possess unusual activity as antistreptococcal agents. The dicarboxylic acid derivatives are less effective in this respect.

GLENOLDEN, PENNSYLVANIA RECEIVED MAY 11, 1940

[CONTRIBUTION FROM THE MEDICAL-RESEARCH DIVISION OF SHARP AND DOHME, INC.]

The Preparation of Some Amino Sulfonamides

BY ELLIS MILLER, JAMES M. SPRAGUE, L. W. KISSINGER AND LANE F. MCBURNEY

The results of many studies[1] on the chemotherapy of experimental streptococcal infections indicate that the maximum therapeutic effect is obtained with those compounds which have a nitrogen and sulfur attached to a benzene nucleus in the 1,4 positions. Although the results of variations in the structure of sulfanilamide and related compounds support this conclusion, it has not been shown definitely that it is necessary for the nitrogen and sulfur to be attached directly to an aromatic nucleus. However, Shaeffer[2] has reported that β-(*p*-sulfamylphenyl)-alanine has a greater antistreptococcal activity than sulfanilamide.

In order to determine the effect upon therapeutic value of the separation of the amino group and the sulfonamide group from the benzene nucleus, several compounds of the general structure I have been synthesized.

II and III were prepared by the catalytic re-

(1) Fourneau, *et al.*, *Compt. rend. soc. biol.*, **122**, 258 (1936); Butler, *et al.*, *Biochem. J.*, **32**, 1101 (1938); Crossley, *et al.*, THIS JOURNAL, **60**, 2217 (1938); for a review, *cf.* Marshall, *Physiol. Rev.*, **19**, 252 (1939).

(2) Shaeffer, *Proc. Soc. Exptl. Biol. Med.*, **37**, 648 (1938).