sealed tube for five hours with a large excess of concentrated hydrochloric acid. The excess hydrochloric acid was evaporated on a steam-bath and the residue made basic with sodium hydroxide. The methylamine was removed by steam distillation. The solution was treated with decolorizing charcoal, acidified with hydrochloric acid, and again evaporated on a steam-bath. Sodium chloride was separated by treating the residue with alcohol and filtering. On evaporation of the alcohol the crude hydrochloride of hygric acid was obtained. This was dried and purified by precipitation from its alcohol solution with either. From alcohol the material crystallized as colorless rhombic plates of m. p. 182–186°.

By treating the hydrochloride with silver carbonate and hydrogen sulfide, hygric acid was obtained and recrystallized from chloroform as white needles of m. p. 168–170° (dec.) (Willstätter,[7] 169–170°). The copper and gold salts of this substance melted at 208–209° and 190–197°, respectively.

Hygric Acid Amide.—Fifteen grams of the methyl ester of hygric acid (b. p. 64–67° at 9 mm.) was dissolved in 100 cc. of methanol–ammonia (saturated at 0°). The solution was let stand overnight in a pressure bottle and then heated to 70–80° for twenty hours. Methyl alcohol and excess ammonia were removed by evaporation in a vacuum desiccator. A white crystalline residue remained. The yield was 12 g. or 90%. The compound was very soluble in water and in most organic solvents except ether, petroleum ether and benzene. It was recrystallized from benzene as fine white needles of m. p. 135.5–137° (corr.).

Anal. Calcd. for $C_6H_{12}ON_2$: C, 56.22; H, 9.44; N, 21.86. Found: C, 56.32, 56.19; H, 9.11, 9.05; N, 21.75, 21.77.

Chloroaurate.—Yellow crystalline precipitate from dilute hydrochloric acid; m. p. 173–174° (corr.) (softens lower).

Anal. Calcd. for $C_6H_{13}ON_2AuCl_4$: Au, 42.12. Found: Au, 41.89.

Chloroplatinate.—Fine orange needles and plates from 50% alcohol; very soluble in water; m. p. 196–197° (dec.) (corr.).

Anal. Calcd. for $C_{12}H_{26}O_2N_4PtCl_6$: Pt, 29.30. Found: Pt, 28.93.

Picrate.—Small yellow prisms or needles from alcohol; m. p. 132.5–133.5° (corr.).

Anal. Calcd. for $C_{12}H_{15}O_8N_5$: N, 19.60. Found: N, 19.52.

Summary

1. A synthesis for hygric acid, involving the catalytic reduction of a pyrrole compound, has been described.

2. Hygric acid amide and (1-methylpyrrolidyl-2)-methanol have been prepared.

3. Several tertiary pyrrolidine and quaternary pyrrolidinium derivatives have been prepared for pharmacological testing.

NEW YORK, N. Y. RECEIVED MARCH 13, 1939

[CONTRIBUTION FROM THE TECHNICAL DIVISION, SHARP & DOHME, INC.]

Substituted Sulfanilamides. I. N^4-Acyl Derivatives[1]

BY ELLIS MILLER, HENRY J. ROCK AND MAURICE L. MOORE

Following the announcement of Domagk[2] that certain sulfonamide compounds were specific remedies in the treatment of experimental streptococcic infections, a large number of derivatives and analogs of sulfanilamide have been prepared and tested in the search for other compounds which would be effective as chemotherapeutic agents.[3–9]

Fourneau, *et al.*,[10] and others have indicated that the antistreptococcic activity of sulfanilamide was reduced greatly by the introduction of an acyl group, such as the formyl or acetyl, on the 4-amino nitrogen. We have found, however, that the N^4-*n*-caproyl derivative of sulfanilamide is as active as the parent compound itself, but much less toxic, in the protection of mice against B. hemolytic streptococci. This paper describes the preparation of a series of N^4-acyl derivatives of sulfanilamide, and other analogs, some of which have been found to be very active as anti-streptococcal agents.

The monocarboxylic acid derivatives were prepared, preferably by the action of the desired acid chloride on a suspension of sulfanilamide in an inert solvent, with or without the presence of an organic base such as pyridine, or by condensing the appropriate 4-acylaminobenzenesulfonyl chloride with ammonia or ammonium carbonate, according to the following equations

(1) In naming these compounds, we have followed the nomenclature described by Crossley, Northey and Hultquist[3] which was suggested by Austin M. Patterson.

(2) Domagk, *Deut. med. Wochschr.*, **61**, 250 (1935).

(3) See Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2217 (1938), for references to the previous literature on these derivatives; also Crossley, *et al.*, *ibid.*, **60**, 2222, 2225 (1938).

(4) Choudhury, *et al.*, *J. Ind. Chem. Soc.*, **14**, 733 (1937); *C. A.* **32**, 4150 (1938).

(5) Whitby, *Lancet*, **1**, 1210 (1938).

(6) Smyth and Carpenter, *Science*, **87**, 350 (1938).

(7) Kolloff, THIS JOURNAL, **60**, 950 (1938).

(8) Stuart, U. S. Patent 2,117,260; *C. A.*, **32**, 5160 (1938).

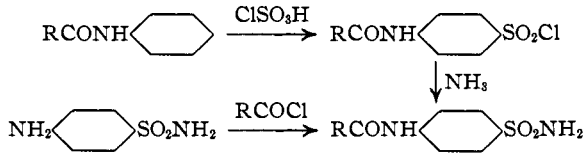
(9) Webster and Powers, THIS JOURNAL, **60**, 1553 (1938).

(10) Fourneau, *et al.*, *Compt. rend. soc. biol.*, **122**, 258 (1938).

Table I

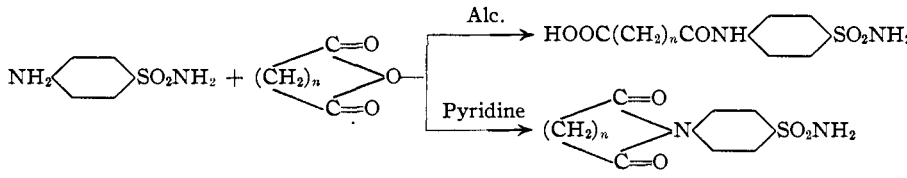
Compound	AcNH–C₆H₄–SO₂NH₂ where Ac is	Therap. effect	Yield, %	M. p., °C.	% nitrogen Calcd.	% nitrogen Found	
Sulfanilamide	H—	+++	..	165	...	...	
N⁴-Acetylsulfanilamide	CH_3CO—	+	..	215–216	...	...	
N⁴-Propionylsulfanilamide	C_2H_5CO—	++	..	220–221	12.28	12.26	12.30
N⁴-*n*-Butyrylsulfanilamide	C_3H_7CO—	++	82	230–231	11.57	11.9	
N⁴-Valerylsulfanilamide[a]	C_4H_9CO—	+++	90	197–198	10.94	10.78	10.67
N⁴-Caproylsulfanilamide[a]	$C_5H_{11}CO$—	+++	62	200–201	10.37	10.15	10.16
N⁴-Heptoylsulfanilamide	$C_6H_{13}CO$—	++	49	192–203	9.86	9.77	9.62
N⁴-Octoylsulfanilamide[a]	$C_7H_{15}CO$—	+	95	200	9.39	9.26	9.16
N⁴-Laurylsulfanilamide[a]	$C_{11}H_{23}CO$—	0	68	205–205.5	7.91	7.92	7.76
N⁴-Benzoylsulfanilamide	C_6H_5CO—	0	90	280	10.14	10.01	9.92
N⁴-Isobutyrylsulfanilamide	*i*-C_3H_7CO—	+	42	241.5–242.5	11.57	11.17	10.93
N⁴-Isovalerylsulfanilamide[a]	*i*-C_4H_9CO—	+	90	216–217	10.94	10.66	10.45
N⁴-Isocaproylsulfanilamide	*i*-$C_5H_{11}CO$—	0	59	193–194	10.37	10.10	10.07
N⁴-Maleylsulfanilamide	$HOOCCH{=}CHCO$—	+	78	208–209	10.37	10.34	
N⁴-Succinylsulfanilamide[b]	$HOOC(CH_2)_2CO$—	+	78	212.5–213.5	10.28	10.28	
N⁴-Benzylsulfanilamide[c]	$C_6H_5CH_2NHC_6H_4SO_2NH_2$	++	..	169–174	...	...	
4-Benzoylaminobenzenesulfonanilide	$C_6H_5CONHC_6H_4SO_2NHC_6H_5$	0	..	222–222.5	7.96	7.90	7.99
4-Succinimidobenzenesulfonamide	$CH_2{-}C{=}O$ / $CH_2{-}C{=}O$ $NC_6H_4SO_2NH_2$	..	30	282.3	11.02	10.92	
3-Sulfonamidobenzamide	$NH_2COC_6H_4SO_2NH_2$	0	..	171–173	...	...	

[a] I. G. F., French Patent 820,546; *C. A.*, **32**, 2958 (1938). [b] Mentioned by Sweet at Dallas meeting, A. C. S., April, 1938. [c] Goissedet and Despois, U. S. Patent 2,111,768; *C. A.*, **32**, 3910 (1938).



N⁴-Benzoyl-N¹-phenylsulfanilamide and *m*-sulfonamidobenzamide are included for comparison.

The dicarboxylic acid derivatives were prepared by refluxing an alcoholic solution of the corresponding dicarboxylic acid anhydride with sulfanilamide. The mono-acylamido derivatives with a free carboxyl group were obtained by this method, as indicated by analytical and solubility data. Refluxing succinic anhydride with sulfanilamide in the presence of pyridine gave the succinimido derivative.



The properties of the derivatives synthesized and their comparative effectiveness against β-hemolytic streptococcal infections in mice are given in the table, where sulfanilamide = + + +.[11] The pharmacological data were obtained on white mice experimentally infected with a virulent strain of β-hemolytic streptococci of such strength that all controls died within forty-eight hours. The reported results are based on the number of animals surviving a period of observation of five days after treatment with a single protective dose of the drug.

The results of our tests indicate that the monocarboxylic acid derivatives are more effective than the dicarboxylic acid derivatives. This activity appears to increase with the increase in length of the acyl group up to and including six carbon atoms, after which it falls off rapidly. The normal acyl derivatives are more active than the corresponding iso compounds. The aromatic group (C_6H_5CO—) appears to be less active than the saturated straight chain acyl group ($C_6H_{13}CO$—) or the benzyl group ($C_6H_5CH_2$—).

(11) We are indebted to Messrs. G. W. Webster and Harry J. Pratt for technical assistance in the pharmacological testing of these compounds.

Experimental

Preparation of Monocarboxylic Acid Derivatives. 1 — To 17.2 g. (0.1 mole) of sulfanilamide suspended in 200 cc. of benzene was added dropwise 7 g. (0.06 mole) of isovaleryl chloride over a period of ten minutes. The mixture was refluxed for seven hours on a water-bath, cooled, and the precipitated product filtered. This was washed three times with benzene and dried thoroughly. The product was then washed with dilute hydrochloric acid and water, and recrystallized from dilute alcohol.

2.—To 17.2 g. (0.1 mole) of sulfanilamide suspended in 200 cc. of toluene was added 15.8 g. (0.2 mole) of pyridine. Fifteen grams (0.11 mole) of *n*-caproyl chloride was then added dropwise and the material refluxed for six hours on an oil-bath at a temperature of 130°. The cooled solution was added to 250 cc. of 10% hydrochloric acid with vigorous agitation and the precipitated material collected, washed several times with water and recrystallized from alcohol.

3.—To 106.5 g. (1 mole) of chlorosulfonic acid in a 300-cc. three-necked flask, equipped with a reflux condenser and mechanical stirrer, cooled to 5–15°, was added 32 g. (0.2 mole) of *n*-caproanilide in small portions with vigorous stirring.[12] After the addition, the mixture was allowed to warm up to room temperature and then heated at 55–60° for two hours, cooled and poured into approximately 200 cc. of an ice–water mixture. The sticky semi-solid reaction product which formed was washed several times with water and then added slowly to 200 cc. of a cold concentrated ammonia solution (28%) with stirring. Stirring was continued until a homogeneous suspension was obtained. The suspended product was filtered, triturated and washed several times with water, and recrystallized from propylene glycol.

The sodium salts of the above N^4-acylsulfanilamides were obtained readily by suspending metallic sodium chips in boiling pyridine and adding dropwise a pyridine solution of the amide. Boiling was continued, after the addition, until no sodium remained visible. The reaction mixture was cooled, filtered and the solid product washed several times with boiling alcohol. The sodium salts thus obtained were completely soluble in water.

Preparation of Dicarboxylic Acid Derivatives.—Ten grams (0.1 mole) of succinic anhydride and 17.2 g. (0.1 mole) of sulfanilamide in 100 cc. of alcohol was refluxed for ten minutes when a crystalline solid began to precipitate. Gentle refluxing was continued for five minutes and the solution filtered hot. The remainder of the product was obtained by chilling the filtrate and then recrystallizing the combined material from water. The product was readily soluble in sodium carbonate solution.

The derivative from maleic anhydride appeared to undergo partial decomposition upon recrystallization, as the crystals were of indefinite structure with a wide and much lower melting range (150–170°). Rapid recrystallization proved satisfactory.

When 10 g. (0.1 mole) of succinic anhydride was refluxed with 17.2 g. (0.1 mole) of sulfanilamide in 70 cc. of pyridine for two and one-half hours, no solid separated on chilling, but a gray solid, soluble in sodium hydroxide but insoluble in sodium carbonate, was obtained by dilution with three volumes of dilute hydrochloric acid and recrystallized from a large volume of hot water as small prisms. This corresponds to 4-succinimidobenzenesulfonamide.

(12) Smiles and Stewart, *Org. Syntheses*, **5**, 3 (1925).

Summary

The preparation and properties of a series of N^4-acyl derivatives of sulfanilamide are described, together with the preliminary results of the pharmacological study of their effect against experimental streptococcic infections in mice.

Certain of the aliphatic acyl derivatives have been found to possess activity as antistreptococcic agents, of which the *n*-caproyl derivative is the most effective.

GLENOLDEN, PENNA. RECEIVED JANUARY 27, 1939

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Alkylaminoalkyl Esters of Aminonaphthoic Acids as Local Anesthetics[1,2]

BY F. F. BLICKE AND H. C. PARKE

Ever since the discovery of novocaine,[3] attempts have been made to find a local anesthetic which will possess not only all of the favorable properties of this substance but which will exhibit, in addition, vasoconstrictor activity and anesthetize, effectively, mucous membranes when applied topically. Naturally, an increase in anesthetic action and a decrease in toxicity is sought also.[4]

Several years ago a study of alkylaminoalkyl esters of aminonaphthoic acids was begun since naphthyl analogs of novocaine had not been described in the literature. In this paper we have described esters which represent combinations of eight different dialkylamino alcohols with 3-, 4-, 5- and 6-amino-1-naphthoic acid.

Pharmacological tests, conducted by Mr. L. W. Rowe in the Parke, Davis and Company Laboratories, have shown that all of the esters which have been prepared possess definite local anesthetic power when tested in the form of their salts.[5] However, some of the hydrochlorides are quite irritating and are rather insoluble in water.

The dialkylaminoalkyl esters were prepared by

(1) This paper represents part of a dissertation to be submitted to the Horace H. Rackham School of Graduate Studies by H. C. Parke in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) We wish to express our indebtedness to Parke, Davis and Company, whose support made this investigation possible.

(3) Einhorn, *Ann.*, **371**, 162 (1909).

(4) Recent articles on local anesthetics of the novocaine type are those of Sergievskava and Nesvad'ba [*J. Gen. Chem.* (U. S. S. R.), **8**, 924 (1938); *C. A.*, **33**, 1307 (1939)] and Burnett, Jenkins, Peet, Dreger and Adams, THIS JOURNAL, **59**, 2248 (1937). We also wish to call attention to the excellent summary on local anesthetics by Elton S. Cook, *Studies of the Institutum Divi Thomae*, **2**, 63 (1938).

(5) A detailed pharmacological report will be published in another journal.