mole) of salicylic acid dissolved by 4 g. of sodium hydroxide in 200 cc. of water. The azo dyestuff was precipitated by dropping its alkaline solution slowly into a solution of 20 cc. of concd. hydrochloric acid in 300 cc. of water; vigorous stirring caused the separation of a flocculent precipitate. The latter was filtered, washed, and dried *in vacuo* for twenty-four hours. The weight, 4.4 g., represents a yield of 96% of the theoretical.

The resulting dyestuff was a light tan-colored solid which developed an extreme electrical charge when reduced to an amorphous powder by grinding. It exhibited the following behavior when heated: namely, its color deepened at 80–90°, and the solid began to melt at about 110° to a gummy solid. Above this temperature there was progressive softening, and at about 125–130° the material evolved a gas causing much expansion of the mass. No definite melting point or decomposition point could be recognized.

This azo derivative could not be recrystallized from any of the common organic solvents by dilution with water, for such addition of water caused separation of a gum which would not harden subsequently. It fuses in hot water at about 80°. The dyestuff was recrystallized from tetralin, yielding yellow-orange colored microscopic crystals. The latter could be dried at 110° and melted at 133–134°, although darkening occurred at about 125°; gas evolution took place above the melting point. Analysis was made of the recrystallized azo compound.

Anal. Calcd. for $C_{25}H_{22}N_4O_5$: C, 65.49; H, 4.84; N, 12.22. Found: C, 65.88; H, 4.77; N, 12.10.

It is assumed that salicylic acid couples para to the hydroxyl group in forming this derivative in analogy to its behavior in forming Crumpsall Yellow.

Summary

1. Nirvanol has been converted into colored derivatives. The latter contain a substituted aryl-azo-benzyl grouping attached to the nitrogen in the 3-position of the heterocycle.

AUSTIN, TEXAS RECEIVED MAY 8, 1939

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE MALTBIE CHEMICAL CO.]

Sulfanilamido Derivatives of Heterocyclic Amines[1]

BY RUSSEL J. FOSBINDER AND L. A. WALTER

Since the discovery by Domagk[2] that compounds containing the sulfanilamido structure are more or less effective in combating streptococcic infections in animals, hundreds of modifications of the parent structure have been prepared and tested for anti-bacterial activity.

This paper describes sulfanilamido derivatives of the pyridine and thiazole series, some of which were prepared before the especially interesting announcement by Whitby[3] that 2-sulfanilamidopyridine was effective against pneumococcic infections.

Through the kindness of Dr. Ralph Mellon and Mr. Frank B. Cooper at Western Pennsylvania Hospital, Pittsburgh, several of the compounds were tested pharmacologically in mice to determine their anti-streptococcic and anti-pneumococcic activity.

TABLE I

PROPERTIES OF THE NEW COMPOUNDS AND ANALYTICAL DATA

Compound[a]	M. p., °C.	Formula	% Nitrogen Calcd.	% Nitrogen Found[b]
2-*p*-Nitrobenzenesulfonamido-6-aminopyridine	228–230	$C_{11}H_{10}N_4O_4S$	19.04	18.75
2-Sulfanilamido-6-aminopyridine	204–206	$C_{11}H_{12}N_4O_2S$	21.20	20.93
2-N⁴-acetylsulfanilamido-6-aminopyridine	194–196[c] 237–239	$C_{13}H_{14}N_4O_3S$	18.29	18.19
2-*p*-Nitrobenzenesulfonamido-4-methylthiazole	197–199	$C_{10}H_9N_3O_4S_2$	14.04	13.91
2-N⁴-acetylsulfanilamido-4-methylthiazole	259–260	$C_{12}H_{13}N_3O_3S_2$	13.47	13.17
2-N⁴-acetylsulfanilamidothiazole	256–257	$C_{11}H_{11}N_3O_3S_2$	14.14	13.90
2-Sulfanilamido-4-methylthiazole	236–238	$C_{10}H_{11}N_3O_2S_2$	15.61	15.55
2-Sulfanilamidothiazole	194–196	$C_9H_9N_3O_2S_2$	16.46	16.31

[a] Nomenclature according to Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2217 (1938). [b] Kjeldahl. [c] Melts, then crystallizes and melts with decomposition at the higher temperature.

TABLE II

PHARMACOLOGICAL ACTIVITY OF THE NEW COMPOUNDS

Compound	Effect: Anti-streptococcic	Effect: Anti-pneumococcic
2-N⁴-acetylsulfanilamido-6-aminopyridine	Slight	None
2-Sulfanilamido-6-aminopyridine	Good	Good
2-Sulfanilamido-4-methylthiazole	Good	Good
2-Sulfanilamidothiazole	Good	Good
2,6-Diamino-3-*p*-sulfonamidophenylazopyridine[a]	None	None
Sulfanilamide	Good	Fair
Sulfapyridine (2-sulfanilamidopyridine)	Good	Good

[a] Mietzsch and Klarer, U. S. Patent 2,148,705.

(1) Presented before the Division of Medicinal Chemistry, A. C. S., Baltimore, April 6, 1939.

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

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

coccic activity as compared to the action of sulfanilamide and sulfapyridine. A sulfonamidophenylazopyridine derivative also tested, is included in Table II.

The observations on chemotherapeutic efficacy are of interest and justify a detailed study of the toxicological properties of the most active compounds. The results seem to indicate that heterocyclic amino compounds, other than 2-aminopyridine, may be coupled with the sulfanilyl radical without great change in physiological activity.

Experimental

2-Aminothiazole and 2-amino-4-methylthiazole were prepared by treating thiourea with α,β-dichloroethyl ether, and with chloroacetone, respectively.[4]

The nitro and acetamino sulfonamides were prepared by treating two moles of heterocyclic amine with one mole of the required sulfonyl chloride in ethyl acetate or dioxane solution, as shown in the following preparation.

2 - *p* - Nitrobenzenesulfonamido - 6 - aminopyridine.—Twenty-one and eight-tenths grams of 2,6-diaminopyridine in 200 cc. of ethyl acetate was poured into a solution of 22.1 g. of *p*-nitrobenzenesulfonyl chloride in 75 cc. of ethyl acetate. The solution was kept in cold water for several hours with an occasional shaking and then let stand overnight at room temperature. The solvent was distilled on a steam-bath and the oily residue shaken with 200 cc. of cold water until it crystallized. The product was filtered off and recrystallized from alcohol with the use of a little decolorizing charcoal. The yield was 22 g. It was soluble in dilute alkalies.

2 - Sulfanilamido - 6 - aminopyridine. 1.—Twenty-two grams of the above nitro compound was stirred with 200 cc. of 10% hydrochloric acid and an excess of finely divided tin. The mixture was kept at 50° for half an hour, filtered while still warm and diluted with water. The tin salts were precipitated with hydrogen sulfide and the filtered solution neutralized with sodium bicarbonate to precipitate the sulfanilamide. The crude material was recrystallized from alcohol, yield 15.5 g. (80%). It was soluble in dilute acids and dilute alkali.

2.—Attempts to hydrolyze the acetyl group from 2-N^4-acetylsulfanilamido-6-aminopyridine by refluxing with 10% hydrochloric acid gave chiefly sulfanilic acid. The acetyl group was removed with practically quantitative yields of the desired sulfanilamide by refluxing with ten times its weight of 5–10% sodium hydroxide for forty-five minutes.

Sulfanilamidothiazoles.—Reduction of 2-*p*-nitrobenzenesulfanilamido-4-methylthiazole with tin and hydrochloric acid as described for the pyridine compound gave only 30% of 2-sulfanilamido-4-methylthiazole.

The acetyl group was hydrolyzed from the 2-N^4-acetylsulfanilamidothiazole by refluxing with ten times its weight of 10% hydrochloric acid for half an hour. The yield of 2-sulfanilamidothiazole was about 70%. Longer refluxing gave a much lower yield. The 2-sulfanilamido-4-methylthiazole was also prepared in this manner. The sulfanilamidothiazoles were soluble in dilute acids and dilute alkali.

Summary

Some 2-sulfanilamido thiazoles and pyridines have been prepared and their chemotherapeutic activity against experimental streptococcic and pneumococcic infections in mice has been determined.

Several of the compounds appear to possess anti-streptococcic and anti-pneumococcic efficacy comparable to sulfanilamide and sulfapyridine, respectively.

NEWARK, N. J. RECEIVED APRIL 18, 1939

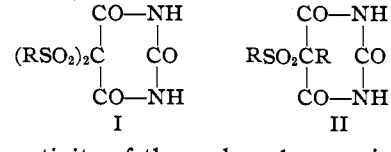
(4) Traumann, *Ann.*, **249**, 36 (1888).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING AT THE UNIVERSITY OF PENNSYLVANIA]

5-Sulfonylbarbituric Acids[1]

BY EDMOND L. D'OUVILLE,[2] FREDERICK J. MYERS AND RALPH CONNOR

α-Sulfonylamides[3] were effective enough as hypnotics to encourage a continued investigation of compounds containing the sulfone group combined with other groups that are present in some of the common hypnotics. Attention was naturally directed toward the synthesis of 5,5-disulfonyl (I) and 5-alkyl-5-sulfonyl (II) derivatives of barbituric acid.



I II

The reactivity of the carbonyl group in alloxan (III) suggested that it might react with thiol compounds to give mercaptols (IV) which could be oxidized to the desired products (I).

(1) A portion of the communication is abstracted from a thesis submitted by Edmond L. d'Ouville in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Pennsylvania in June, 1937.

(2) Chemical Foundation Fellow.

(3) d'Ouville and Connor, THIS JOURNAL, **60**, 33 (1938).