thiazole indicated, 2 moles of thiourea must be present in the reaction mixture for each mole of halogen. In an experiment where 1 mole of thiourea was used for each mole of halogen the yield of thiazole was poor and the product was difficult to purify.

Preliminary experiments indicate that the above reaction is a convenient general synthetic method for preparation of substituted thiazoles. Extension of this reaction to other ketones and to thioamides is in progress.

Summary

It has been demonstrated that acetophenone, propiophenone, *m*-nitroacetophenone, acetone and ethyl acetoacetate react directly with 1.0 mole of a halogen and 2.0 moles of thiourea to give in excellent yield, 2-amino-4-phenylthiazole, 2-amino-4-phenyl-5-methylthiazole, 2-amino-4-(3-nitrophenyl)-thiazole, 2-amino-4-methylthiazole, and 2-amino-4-methyl-5-carbethoxythiazole, respectively.

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[CONTRIBUTION FROM THE BIOCHEMICAL INSTITUTE AND THE CLAYTON RESEARCH FOUNDATION, THE UNIVERSITY OF TEXAS]

Derivatives of Sulfanilamide. I. N⁴-(*p*-Aminobenzoyl)-sulfanilamide and Related Compounds

BY EDITH JU-HWA CHU[1]

Since the discovery and establishment of antagonism between sulfonamide drugs and *p*-aminobenzoic acid, a normal constituent of cells, a number of *p*-aminobenzoic acid derivatives and analogs have been investigated and described. Hirsch[2] demonstrated that *p*-aminobenzamide also possessed bacteriostatic properties, while Johnson and co-workers[3] indicated that in the molecule of *p*-aminobenzoic acid variation of the carbonyl group by replacement or by derivative formation might give compounds exhibiting *p*-aminobenzoic acid activity, bacteriostatic activity, or neither. It was interesting to study the physiological action of a combination of sulfanilamide and *p*-aminobenzoic acid in a simple molecule. The present paper reports syntheses of N⁴-(*p*-aminobenzoyl)-sulfanilamide and related compounds and their action on several organisms.

N⁴-(*p*-Aminobenzoyl)-sulfanilamide and analogs from albucid, sulfapyridine, sulfadiazine, sulfathiazole and sulfaguanidine have been synthesized by reduction of corresponding nitro derivatives. The most suitable reducing agent is Raney nickel in alcohol or pyridine. N⁴-(*p*-Nitrobenzoyl)-sulfanilamide,[4] N⁴-(*p*-nitrobenzoyl)-albucid[5] and N⁴-(*p*-nitrobenzoyl)-sulfapyridine[6] were previously reported.

These compounds have been tested on *Lactobacillus arabinosus 17-5*, *Streptococcus lactis R*, *Staphylococcus aureus* and *Escherichia coli* and found to be more or less toxic to these organisms; but the action is not reversed by presence of *p*-aminobenzoic acid in most cases.

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(2) J. Hirsch, *Science*, **96**, 140 (1942).

(3) O. H. Johnson, D. E. Green and R. Pauli, *J. Biol. Chem.*, **153**, 37 (1944).

(4) C. Siebenmann and R. J. Schnitzer, THIS JOURNAL, **65**, 2126 (1943).

(5) S. M. Mistry and P. C. Guha, *J. Indian Inst. Sci.*, **15A**, 25 (1932).

(6) Société des usines chimiques Rhône-Poulenc, French Patent 846,191, Sept. (1939).

Preparation and Properties

N⁴-(*p*-Nitrobenzoyl)-sulfanilamide and Analogs.—A mixture of one millimole each of *p*-nitrobenzoyl chloride and sulfanilamide in 5 ml. of dry pyridine was refluxed for an hour, cooled and then poured into ice water. The precipitate thus obtained was recrystallized from acetic acid or pyridine, yielding pale yellow fine needles. It is difficultly soluble in benzene or 1,4-dioxane, slightly soluble in acetic acid, acetone or alcohol, moderately soluble in isobutyl acetate, and soluble in pyridine, ethanolamine, diethanolamine and triethanolamine. It is recovered unchanged by boiling with 10% sodium hydroxide or concentrated hydrochloric acid for ten–fifteen minutes, but is hydrolyzed by refluxing with 10% sodium hydroxide for two hours, *p*-nitrobenzoic acid being identified. It was also synthesized from *p*-nitrobenzanilide by treatment with chlorosulfonic acid and reaction of the aromatic sulfonyl chloride with ammonium hydroxide; yield, 75%.

Analogs were prepared from albucid, sulfapyridine, sulfathiazole, sulfadiazine and sulfaguanidine, respectively. N⁴-(*p*-Nitrobenzoyl)-albucid was also prepared by acetylation of N⁴-(*p*-nitrobenzoyl)-sulfanilamide with acetic anhydride and pyridine in a quantitative yield.

N⁴-(*p*-Aminobenzoyl)-sulfanilamide and Analogs.—The most satisfactory means for reducing N⁴-(*p*-nitrobenzoyl)-sulfanilamide thus far tried is Raney nickel in alcohol or pyridine. A mixture of 2 g. of N⁴-(*p*-nitrobenzoyl)-sulfanilamide and 10 g. of Raney nickel in 20 ml. of alcohol was refluxed on a steam-bath for an hour and then filtered. The precipitate of N⁴-(*p*-aminobenzoyl)-sulfanilamide was recrystallized from acetone. It melts at 276° first, solidifies and then melts again at 313° dec.

N⁴-(*p*-Nitrobenzoyl) derivatives of sulfathiazole, sulfapyridine, sulfadiazine and sulfaguanidine were similarly reduced to amino derivatives by Raney nickel except that pyridine was used as the solvent instead of alcohol and the product was washed with acetic acid.

N⁴-(*p*-Aminobenzoyl)-sulfathiazole was insoluble in most solvents and difficultly purified and the analysis of nitrogen content always was 2% lower. It was acetylated to acetyl derivative, prisms, m. p. 314° dec.

Physiological Action on Microörganisms.—These compounds have been tested on *Lactobacillus arabinosus 17-5*, *Streptococcus lactis R*, *Staphylococcus aureus* and *Escherichia coli*, respectively. For testing with *Lactobacillus arabinosus 17-5* a medium described by Lewis[7] was modified by

(7) J. C. Lewis, *J. Biol. Chem.*, **146**, 441 (1942).

TABLE I

Compounds	Solvent for recrystn.	Cryst. form	Yield, %	M. p., °C.	Formula	% Nitrogen Calcd.	% Nitrogen Found	Toxicity: *Lactobacillus arabinosus 17-5*	Toxicity: *Streptococcus lactis R*	Toxicity: *Staphylococcus aureus*	Toxicity: *Escherichia coli*
N^4-(*p*-Nitrobenzoyl)-											
sulfanilamide	Acet. acid.	Fine need.	89[a], 75[b]	263 dec.[c]	$C_{13}H_{11}N_3O_5S$	...	...	†NR[g]	...	...	...
albucid	Pyridine	Prisms	78[d], 100[e]	279–280 dec.	$C_{14}H_{13}N_3O_5S$	11.57	11.53	†NR	...	...	..
sulfapyridine	Pyridine	Prisms	82	272 dec.	$C_{18}H_{14}N_4O_5S$	...	...	††R	O	†NR	†NR
sulfathiazole	Pyridine	Prisms	90	281–282 dec.	$C_{16}H_{12}N_4O_5S_2$	13.86	13.74	††R	††NR	††NR	††NR
sulfadiazine	Pyrid. + alc.	Needles	74	282 dec.	$C_{17}H_{13}N_5O_5S$	17.54	17.51	††R	††NR	††NR	††NR
sulfaguanidine	Pyridine	Prisms	78	266–267	$C_{14}H_{13}N_5O_5S$	19.28	19.14	O	...	...	...
acetylsulfaguanidine	Acetone	Plates	82	238–239 dec.	$C_{16}H_{15}N_5O_6S$	17.28	17.15	...	...	...	...
N^4-(*p*-Aminobenzoyl)-											
sulfanilamide	Acetone	Prisms	50	276, 313 dec.	$C_{13}H_{13}N_3O_3S$	14.43	14.21	†NR	...	...	...
albucid	Pyridine	Prisms	67	230	$C_{14}H_{15}N_3O_3S$	12.61	12.80	O	...	...	...
sulfapyridine	Acetone	Prisms	78	255–256	$C_{18}H_{16}N_4O_3S$	15.21	15.10	††R	††NR	††NR	††NR
sulfathiazole	.....	....	90	265 dec.	$C_{16}H_{14}N_4O_3S_2$						
sulfadiazine	Acet. + pyrid.	Cubes	49	233 dec.	$C_{17}H_{15}N_5O_3S$	18.97	18.71	††R	††NR	††NR	††NR
sulfaguanidine	Pyridine	Prisms	67	253–254	$C_{14}H_{15}N_5O_3S$	21.01	20.98	O	...	...	...
N^4-(*p*-Acetylaminoben-											
zoyl)-sulfathiazole	Acet. acid	Prisms	..	314 dec.	$C_{18}H_{18}N_4O_4S_2$	13.46	13.30	...	...	...	..

[a] From *p*-nitrobenzoyl chloride and sulfanilamide. [b] From *p*-nitrobenzanilide. [c] Siebenmann and Schnitzer[4] reported a m. p. 260°. [d] From *p*-nitrobenzoyl chloride and albucid. [e] Acetylation of N^4-(*p*-nitrobenzoyl)-sulfanilamide. [f] Mistry and Guha[5] reported a m. p. 293°. [g] † = slightly toxic; †† = toxic; R = reversed and NR = not reversed by *p*-aminobenzoic acid.

addition of 1 γ (gamma) of *p*-aminobenzoic acid per 10 ml. For *Streptococcus lactis R*, *Staphylococcus aureus* and *Escherichia coli* the same medium was modified by addition of 1 γ of *p*-aminobenzoic acid and 1 γ of folic acid concentrate per 10 ml. The medium containing the testing substance (200 γ per 10 ml.) was inoculated with the respective organism, incubated at 30° for twenty-four hours and the turbidity was read as usual.

The properties, analyses and toxicity action of these compounds are collected in the following table.

Summary

N^4-(*p*-Aminobenzoyl)-sulfanilamide and analogs derived from albucid, sulfapyridine, sulfadiazine, sulfathizole and sulfaguanidine have been synthesized by reduction of corresponding nitro compounds. Among reducing agents tried, Raney nickel in alcohol or pyridine is the most satisfactory.

N^4-(*p*-Nitrobenzoyl) derivatives of sulfapyridine, sulfadiazine, sulfathiazole and N^4-(*p*-aminobenzoyl) derivatives of sulfapyridine and sulfadiazine inhibit growth of *Lactobacillus arabinosus 17-5* and the inhibition action is reversed by *p*-aminobenzoic acid. The action of N^4-(*p*-nitrobenzoyl) derivatives of sulfanilamide and of albucid and N^4-(*p*-aminobenzoyl)-sulfanilamide are not reversed by *p*-aminobenzoic acid, while N^4-(*p*-nitrobenzoyl)-sulfaguanidine, N^4-(*p*-am-inobenzoyl)-albucid and N^4-(*p*-aminobenzoyl-sulfaguanidine are indifferent.

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[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY,[1] ALBANY, CALIFORNIA]

The Thermal Degradation of Pectin

BY REYNOLD C. MERRILL[2] AND MARY WEEKS

The most obvious change that occurs when a solution of pectin is heated is the rapid irreversible decrease in viscosity[3] which is denoted in this paper by the term degradation. Kertesz[4] has shown that most of this change in viscosity occurs before appreciable changes in the methoxyl content and reducing power of the pectin solutions are detected. He postulated a structure for pectin in solution described by the formula $[(G)_m]_n$. $(G)_m$ represents a polymer of *m* galacturonic acid units which forms aggregates containing *n* of these units held together by secondary valence forces. These "secondary aggregates," he believes, are mostly responsible for the high viscosity of pectin solutions, and the rapid initial decrease in viscosity on heating is due to the destruction of these aggregates, held together by secondary forces.

One method of testing this theory and of establishing the type of bond broken during the rapid initial decrease in viscosity on heating is to measure the activation energy of the process. The secondary forces holding such an aggregate to-

(1) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

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(3) See *e. g.*, P. B. Myers and G. L. Baker, *Agr. Expt. Sta. (Del.) Bull.*, **149**, 26 (1927).

(4) Z. I. Kertesz, THIS JOURNAL, **61**, 2544 (1939).