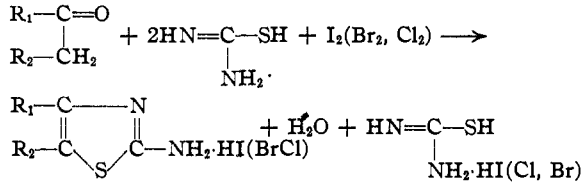
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Reaction of Ketones with Halogens and Thiourea[1]

BY R. M. DODSON AND L. CARROLL KING

In a study of the reactions of compounds containing reactive hydrogen atoms with halogens in the presence of a base, it was observed that ketones react with thiourea and a halogen[2] to give substituted 2-aminothiazoles.

The reaction may be formulated as



R_1 = methyl-, phenyl-, *m*-nitrophenyl-
R_2 = H-, methyl-, carbethoxy-

In order to establish the generality of the above reaction it was used to prepare thiazoles from a variety of ketones, namely, acetophenone, propiophenone, *m*-nitroacetophenone, acetone and ethyl acetoacetate. In each case the thiazole obtained from the reaction mixture agreed in chemical and physical properties with the data reported in the literature for the corresponding substance obtained by other methods. The structure of the substance described as 2-amino-4-phenyl-5-methylthiazole depends on its formation according to the above reaction and on correct elementary analysis of the compound and its acetyl derivative.

using each of the common halogens. The yield of thiazole varied significantly with the halogen used. The yields, properties and analyses of the thiazoles prepared in this study are listed in Table I.

The general procedure for effecting the reaction may be illustrated by several examples.

To a slurry consisting of 0.2 mole of acetophenone and 0.4 mole of thiourea, 0.2 mole of halogen was added; when iodine was used it was added all at once, bromine was added dropwise, chlorine in weighed amount was distilled into the reaction mixture. After this addition, the reaction mixture was heated overnight on the steam-bath. It was then diluted with water, heated until most of the solid had gone into solution, filtered,[3] cooled and made alkaline with concentrated ammonium hydroxide. The precipitated 2-amino-4-phenylthiazole was separated and crystallized from ethyl alcohol to constant melting point.

For the preparation of 2-amino-4-methylthiazole from acetone, 0.5 mole of halogen was added to a suspension of 1 mole of thiourea in 100 ml. of acetone. After the addition was complete, the reaction mixture was refluxed for two hours; the reflux condenser was then removed and the open vessel heated on the steam-bath overnight. The 2-amino-4-methylthiazole was recovered from the reaction mixture according to the directions of Byers and Dickey.[4]

The acetyl derivatives of these thiazoles were prepared by the reaction of acetic anhydride on about 1 g. of each of the substituted 2-aminothiazoles, the products being recrystallized from ethyl alcohol.

The above reaction can be carried out in a much shorter time if the reaction mixture is heated strongly until a vigorous reaction begins. However, this procedure results in a lowered yield of the thiazole and is accompanied by the separation of much free sulfur and by olfactory evidence of mercaptans. In order to obtain the yield of

TABLE I

Thiazole	Formula	M. p., °C./ Found	M. p., °C. Reported	N analyses, % Found	Calcd.	% Yield[g] obtained using Cl_2	Br_2	I_2
2-Amino-4-methyl-	.....	.....	42[a]	...	...	51	36	77
Acetyl derivative	$C_6H_8N_2OS$	136–137	134[a]	18.48	17.94			
Picrate		229–230 (dec.)	229.5[b]					
2-Amino-4-methyl-5-carbethoxy-	$C_7H_{10}N_2O_2S$	176–177	175[c]	14.89	15.05	60	82	63
Acetyl derivative	$C_9H_{12}N_2O_3S$	225–225.5	[e]	12.31	12.28			
2-Amino-4-phenyl-	$C_9H_8N_2S$	151–152	147[a]	15.84	15.90	49	85	94
Acetyl derivative	$C_{11}H_{10}N_2OS$	214–214.5	208[a]	12.74	12.84			
2-Amino-4-(3-nitrophenyl)-	$C_9H_7N_3O_2S$	188–190	188–191[d]	19.57	19.00	75	95	52
Acetyl derivative[h]	$C_{11}H_9N_3O_3S$	308–313 (dec.)	310–314[d]	17.75 17.65[h]	15.96			
-Amino-4-phenyl-5-methyl-	$C_{10}H_{10}N_2S$	116–118	[e]	14.36	14.73	68	84	94
Acetyl derivative	$C_{12}H_{12}N_2OS$	223	[e]	12.23	12.07			

[a] V. Traumann, *Ann.*, **249**, 31 (1888). [b] E. Otiai, *C. A.*, **33**, 3791[4] (1939). [c] M. Steude, *Ann.*, **261**, 22 (1891). [d] N. Kharasch, Ph. D. Thesis, Northwestern University, 1944, p. 65. [e] Not previously reported. [f] All melting points were observed on a Fischer–Jones melting point block. [g] Based on the ketone, or on the halogen added to the reaction mixture except in the case of 2-amino-4-methylthiazole which is based only on the halogen. [h] This substance has a surprisingly low solubility in most solvents.

A synthesis of each of the substituted 2-aminothiazoles under consideration was carried out

(1) For other papers in this series, see L. C. King, THIS JOURNAL, **66**, 894 (1944); 1612 (1944).

(2) The use of bromine to form benzothiazoles from substituted phenylthioureas has been reported by A. Hugershoff, *Ber.*, **36**, 3121 (1903); L. M. White and R. Q. Brewster, *C. A.*, **34**, 5447 (1940); H. Erlenmeyer and H. Ueberwasser, *Helv. Chim. Acta*, **23**, 328 (1940); M. Dyson and T. Harrington, *J. Chem. Soc.*, 374 (1942).

(3) A small amount of free sulfur separated.

(4) J. R. Byers and J. B. Dickey, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 31.

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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Derivatives of Sulfanilamide. I. N^4-(*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 N^4-(*p*-aminobenzoyl)-sulfanilamide and related compounds and their action on several organisms.

N^4-(*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. N^4-(*p*-Nitrobenzoyl)-sulfanilamide,[4] N^4-(*p*-nitrobenzoyl)-albucid[5] and N^4-(*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.

(1) On leave from the University of Peking, China. The present address is the Department of Medicine, University of Minnesota, Minneapolis, Minn.

(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

N^4-(*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. N^4-(*p*-Nitrobenzoyl)-albucid was also prepared by acetylation of N^4-(*p*-nitrobenzoyl)-sulfanilamide with acetic anhydride and pyridine in a quantitative yield.

N^4-(*p*-Aminobenzoyl)-sulfanilamide and Analogs.—The most satisfactory means for reducing N^4-(*p*-nitrobenzoyl)-sulfanilamide thus far tried is Raney nickel in alcohol or pyridine. A mixture of 2 g. of N^4-(*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 N^4-(*p*-aminobenzoyl)-sulfanilamide was recrystallized from acetone. It melts at 276° first, solidifies and then melts again at 313° dec.

N^4-(*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.

N^4-(*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).