Studies on Sulfabenzothiazoles

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(Received September 15, 1961)

With a view to examining the medicinal and industrial importance of "benzothiazole derivatives", sulfabenzothiazole, sulfa-6-methyl-, -6-chloro-, -6-methoxy-, -6-nitro-benzothiazoles and sulfa-β-naphthothiazole, have been synthesized. As an extension of the previous work on 2-aminobenzothiazole derivatives[1], acetylamino-, benzoylamino-, 2-(2-hydroxy-1-naphthylazo)- and 2,2'-azobisbenzothiazole derivatives from the substituted 2-aminobenzothiazoles have also been prepared.

The starting compound, 2-aminobenzothiazole[2] was obtained by the action of liquid bromine on asymmetrical phenylthiourea in an inert medium like chloroform. Similarly other substituted, 2-amino-4-methyl-[3], -5-methyl-[1], -6-methyl-[4], -5-chloro-, -6-chloro-[4], -4-methoxy-, -6-methoxy-[1], -4-ethoxy-[4], -6-nitro-[1]benzothiazoles and 2-amino-α-naphtho-[1], -β-naphtho-[1]thiazoles have been prepared from the corresponding substituted asymmetrical arylthioureas and the latter were subsequently prepared[5,6] by the interaction of ammonium thiocyanate with the corresponding amine hydrochlorides.

The compound, sulfathiazole[7] was obtained by the condensation of acetylsulfanilyl chloride[8] (ASC) and 2-aminothiazole in pyridine and

1) P. N. Bhargava and B. T. Baliga, *J. Ind. Chem. Soc.*, 35, 807 (1958).
2) A. Hugershoff, *Ber.*, **36**, 3121 (1903).
3) R. F. Hunter, *J. Chem. Soc.*, **129**, 1385 (1926).
4) P. N. Bhargava and K. A. Jose, *J. Ind. Chem. Soc.*, **37**, 314 (1960).
5) De. Clermont., *J. Chem. Soc.*, **31**, 70 (1877).
6) J. M. Berkebile and A. H. Fries, *J. Chem. Educ.*, **25**, 617 (1948).
7) J. Laudon and B. S. Svensk, *Kem. Tid.*, **52**, 64 (1940), in German.
8) M. L. Moore, C. S. Miller and E. Miller, *J. Am. Chem. Soc.*, **62**, 2097 (1940).

by subsequent alkaline hydrolysis of the condensed product. Following the same procedure all the sulfabenzothiazoles and sulfanaphthothiazoles have been synthesized and tested for bactericidal activity[9]. Further an absorption spectra study of these sulfabenzothiazoles has been made as a physical evidence in confirmation of structure of these compounds.

Experimental

2-(*p*-Aminobenzenesulfonamido)-benzothiazole.—Into a flask 3 g. of 2-aminobenzothiazole, 4.4 g. of acetylsulfanilyl chloride and 18 ml. of pyridine were taken and heated under reflux on a water bath for about two and a half hours. The contents were poured on cooling into water and the solid was filtered and crystallized from dilute ethanol. This intermediate product was heated under reflux on a low flame with 20 ml. of alcoholic 10% sodium hydroxide solution for two hours. The solution of the flask was poured into cold water and the solid substance filtered, dried and finally crystallized from ethanol into a white crystalline form, m. p. 213°C.

Similarly other substituted sulfabenzothiazoles were prepared. Their proprties and analytical data are recorded in Table I. However, with this procedure, the synthesis of sulfabenzothiazoles was not successful with 2-amino-4-methyl-, -5-methyl-, -5-chloro-, -4-methoxy-, -4-ethoxy-benzothiazoles and 2-amino-α-naphthothiazole.

2-Acetylamino-6-methylbenzothiazole.—One gram of 2-amino-6-methylbenzothiazole and 4 ml. of acetic anhydride were heated under reflux for 15 min. and then on cooling poured into cold water. The solid substance was filtered, dried and crystallized from ethanol into a white crystalline form, m. p. 202°C.

Similarly acetylamino derivatives of 2-amino-5-chloro-, -6-chloro-, -4-methoxy-benzothiazoles were prepared and on analysis the number of acetyl group in these derivatives was found to be one. Their properties and analytical data are given in Table II.

2-Benzoylamino-6-methylbenzothiazole. — Into a flask 1 g. of 2-amino-6-methylbenzothiazole was dissolved in 10 ml. of 20% sodium hydroxide solution and then it was treated with 1.5 ml. of benzoyl chloride, small quantity at a time with vigorous shaking and cooling. After the addition of the latter, the flask was warmed on a water bath under reflux to hydrolyze the excess of benzoyl chloride. The solid was cooled, filtered, washed with water, dried and crystallized from ethanol into a colorless crystalline from, m. p. 178°C.

Similarly, 2-benzoylamino derivatives of 5-chloro-, -6-chloro-, -4-methoxy-, -6-methoxy-benzothiazoles were prepared and on analysis the number of benzoyl groups in these derivatives was found to be one. Their properties and analytical data are mentioned in Table III.

6-Methyl-2-(2-hydroxy-1-naphthylazo)-benzothiazole.—Into a flask 20 ml. of dilute hydrochloric acid 1 g. of 2-amino-6-methylbenzothiazole was dissolved and diazotized as usual. The diazotized product was coupled with 0.9 g. of β-naphthol dissolved in 10 ml. of 4% sodium hydroxide solution. The orange brown azo compound on extraction with ether and crystallization in vacuum gave chocolate crystals, m. p. 124°C. It developed rosy red color in glacial acetic acid and gave the original

Table I. 2-(*p*-Aminobenzenesulfonamido)-benzothiazoles

No.	Compound	Yield %	Color	M. p. °C	Molecular formula	S, % Found	S, % Calcd
1	*A-B	61	Colorless	213	$C_{13}H_{11}O_2N_3S_2$	20.75	20.98
2	A-6-methyl-B	63	Colorless	200	$C_{14}H_{13}O_2N_3S_2$	19.66	20.06
3	A-6-chloro-B	67	Colorless	212	$C_{13}H_{10}O_2N_3S_2Cl$	18.98	18.85
4	A-6-nitro-B	48	Yellow	253	$C_{13}H_{10}O_4N_4S_2$	18.41	18.28
5	A-6-methoxy-B	64	Colorless	198	$C_{14}H_{13}O_3N_3S_2$	18.85	19.10
6	A-β-naphothiazole	62	Light grey	above 300	$C_{17}H_{13}O_2N_3S_2$	17.86	18.03

*A : -2-(*p*-aminobenzenesulfonamido)-
B : Benzothiazole

Table II. Acetyl derivatives of substituted 2-aminobenzothiazoles

No.	Compound	Color	M. p. °C	Molecular formula	N, % Found	N, % Calcd.
1	A-6-methyl-B	Colorless	202	$C_{10}H_{10}ON_2S$	13.37	13.59
2	A-5-chloro-B	Colorless	227	$C_9H_7ON_2SCl$	12.43	12.36
3	A-6-chloro-B	Colorless	224	$C_9H_7ON_2SCl$	12.29	12.36
4	A-4-methoxy-B	Colorless	245	$C_{12}H_{10}O_2N_2S$	12.51	12.73

A : 2-Acetylamino B : Benzothiazole

9) A. Mukherji, *Ind. Med. Gaz.*, **31**, 415 (1954).

TABLE III. BENZOYL DERIVATIVES OF SUBSTITUTED 2-AMINOBENZOTHIAZOLES

No.	Compound	Color	M. p. °C	Molecular formula	N, % Found	N, % Calcd.
1	A-6-methyl-B	Colorless	178	$C_{15}H_{12}ON_2S$	10.19	10.41
2	A-5-chloro-B	Colorless	Above 300, changes to black at 218	$C_{14}H_9ON_2SCl$	9.54	9.70
3	A-6-chloro-B	Colorless	Above 300, changes to black at 225	$C_{14}H_9ON_2SCl$	9.57	9.70
4	A-4-methoxy-B	Colorless	174	$C_{15}H_{12}O_2N_2S$	9.98	9.86
5	A-6-methoxy-B	Colorless	202	$C_{15}H_{12}O_2N_2S$	10.02	9.86

A: 2-Benzoylamino B: Benzothiazole

TABLE IV. 2-(2-HYDROXY-1-NAPHTHYLAZO)-BENZOTHIAZOLE DERIVATIVES

No.	Compound	Color	M. p. °C	Color in glacial acetic acid	Molecular formula	N, % Found	N, % Calcd.
1	5-Methyl-A	Dark violet	147	Yellowish pink	$C_{18}H_{13}ON_3S$	12.84	13.17
2	6-Methyl-A	Chocolate	124	Rosy red	$C_{18}H_{13}ON_3S$	12.73	13.17
3	5-Chloro-A	Brown	101	Orange	$C_{17}H_{10}ON_3SCl$	12.12	12.37
4	6-Chloro-A	Dark grey	156	Dirty yellow	$C_{17}H_{10}ON_3SCl$	12.61	12.37
5	6-Nitro-A	Dark brown	133	Pink	$C_{17}H_{10}O_3N_4S$	15.63	15.82
6	4-Methoxy-A	Dark violet	105	Red	$C_{18}H_{13}O_2N_3S$	12.31	12.54
7	6-Methoxy-A	Chocolate	96	Red	$C_{18}H_{13}O_2N_3S$	12.29	12.54

A: 2-(2-Hydroxy-1-naphthylazo)-benzothiazole

TABLE V. 2,2'-AZOBISBENZOTHIAZOL DERIVATIVES FROM SUBSTITUTED 2-AMINOBENZOTHIAZOLES

No.	Compound	Color	M. p. °C	Color in glacial acetic acid	Molecular formula	N, % Found	N, % Calcd.
1	2,2'-Azobis(6-methyl-A)	Dark black	Above 300	Brownish red	$C_{16}H_{12}N_4S_2$	16.82	17.28
2	2,2'-Azobis(5-chloro-A)	Reddish black	Above 300	Yellow	$C_{14}H_6S_2Cl_2N_4$	14.97	15.34
3	2,2'-Azobis(6-chloro-A)	Chocolate	191	Orange yellow	$C_{14}H_6N_4S_2Cl_2$	15.21	15.34
4	2,2'-Azobis(4-methoxy-A)	Dark pink	Above 300	Light chocolate	$C_{16}H_{12}O_2N_4S_2$	15.13	15.73
5	2,2'-Azobis(6-ethyl-A)	Dark violet	Above 300	Pink	$C_{18}H_{16}O_2N_4S_2$	14.33	14.58

A: Benzothiazole

TABLE VI. ULTRAVIOLT ABSORPTION OF SULFABENZOTHIAZOLES

Solvent: Absolute ethanol Concn.: 0.01 g./l.

No.	Compound	1st peak mμ	2nd peak mμ	3rd peak mμ
1	Sulfabenzothiazole	226.00	269.50	—
2	Sulfa-6-methylbenzothiazole	228.75	268.75	—
3	Sulfa-6-chlorobenzothiazole	230.25	268.25	—
4	Sulfa-6-nitrobenzothiazole	224.00	352.00	—
5	Sulfa-6-methoxybenzothiazole	227.50	269.50	—
6	Sulfa-β-naphthothiazole	229.75	257.50	299.50

2-amino-6-methylbenzothiazole on reduction with tin and concentrated hydrochloric acid.

Similarly six more azo-compounds were prepared from different substituted 2-aminobenzothiazoles. Their properties and analytical data are recorded in Table IV.

2,2'-Azobis(6-methylbenzothiazole). — One gram of 2-amino-6-methylbenzothiazole was suspended in 30 ml. of water taken in a beaker and was gradually treated with 50 ml. of 0.3 N solution of sodium hypochlorite and kept for half an hour. The brown solid, after being washed with ether, was extracted with a mixture of chloroform and light petroleum ether (1 : 1). After evaporation of the solvents the products was left as dark brown crystals, m. p. above 300°C. It developed brownish red color in glacial acetic acid and gave the original benzothiazole on reduction with tin and concentrated hydrochloric acid.

Similarly other azobisbenzothiazole derivatives were prepared from 2-amino-5-chloro-, -6-chloro-, -4-methoxy-, -4-ethoxy-benzothiazoles and their properties and analytical data are given in Table V.

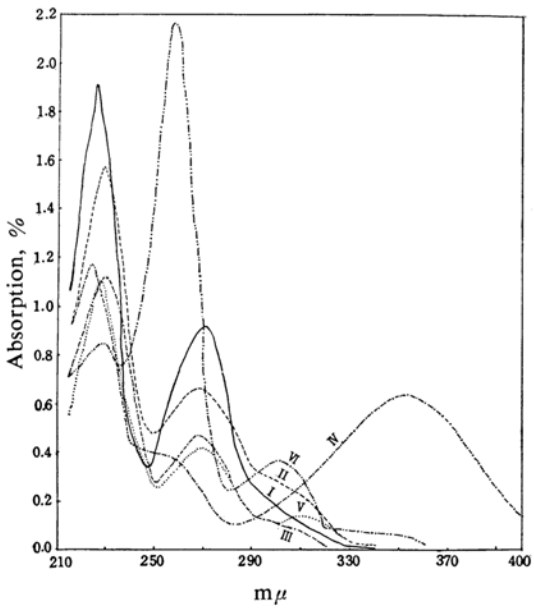

Fig. 1. Ultraviolet absorption curves of sulfabenzothiazoles.
I Sulfabenzothiazole
II Sulfa-6-methylbenzothiazole
III Sulfa-6-chlorobenzothiazole
IV Sulfa-6-nitrobenzothiazole
V Sulfa-6-methoxybenzothiazole
VI Sulfa-β-naphthothiazole

Absorption Spectra Measurements of Sulfabenzothiazoles.—The study of ultraviolet spectra of sulfabenzothiazoles was carried out in spectroscopically pure absolute ethanol on Beckman D. U. spectrophotometer. The values of λ_{max} for different peaks observed from the curves are given in Table VI.

The λ_{max} at 226 mμ in 2-(*p*-aminobenzenesulfonamido)-benzothiazole is due to the presence of benzenesulfonamido nucleus and the second peak at 269.5 mμ is due to the presence of 2-aminobenzothiazole (a shift of λ_{max} from 262 to 269.5 mμ due to the presence of benzenesulfonamido nucleus). Substituents like chlorine atom, methyl and methoxy groups in 2-aminobenzothiazoles at position 6 have little effect on the shift. But in sulfa-6-nitrobenzothiazole a tendency of absorption peak to appear at higher wavelength is observed because of the presence of chromophoric group like nitro group which has pronounced effect to increase absorption from ultraviolet to visible region and thus cause for the appearance of color (yellow). So in this case the second absorption peak appeared at 352 mμ. In the case of sulfa-β-naphthothiazole absorption peaks are found at 229.75, 257.5 and 299.5 mμ, as the latter two are due to the presence of β-naphthothiazole.

Assay of Sulfabenzothiazoles for Bactericidal Activity.—The compounds were tested in Central Drug Research Institute, Lucknow, India, for bactericidal activity according to the method[9] and it was found that sulfa-6-methyl-, -6-chloro-, -6-methoxy-, -6-nitro-benzothiazoles were inactive upto a dilution of 1 : 1000 against Klebsilla pneumonial; Salmonella paratyphi; Salmonella typhi; Escherichia coli; Shigella dysenteriae (Shiga); Micrococcus pyrogenes Var aureus; Acrobactor aerogenes and B. subtillis.

Thanks of the authors are due to Professor Gurbakhsh Singh, head of the Department of Chemistry and other authorities of the Banaras Hindu University for providing necessary facilities and also to Dr. Dashrath Lal Srivastava, Deputy Director C. D. R. I., Lucknow for the assaying of sulfabenzothiazoles.

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