[CONTRIBUTION FROM THE RESEARCH CENTER, PURE OIL CO.]

Synthesis of Bisbenzothiazoles[1]

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A number of new bisbenzothiazoles have been synthesized by the polyphosphoric acid-catalyzed intermolecular condensation of dibasic acids with *o*-aminothiophenol. Bisbenzothiazole, bis(2-benzothiazolyl)alkanes containing up to ten methylene groups, 1,2-bis(2-benzothiazolyl)ethylene, and 1,2-bis(2-benzothiazolyl)-1,2-ethanediol have been synthesized in yields of 56–99% of the theory. 1,2-Bis(2-benzothiazolyl)benzene and 1,4-bis(2-benzothiazolyl)benzene were synthesized similarly in 85 and 46% yields, respectively. 2,2′-Bis(2-benzothiazolyl)diethyl sulfide and 1,2,3-trisbenzothiazolylpropane were also prepared readily in polyphosphoric acid medium in quantitative yields. Possible reaction mechanisms for the polyphosphoric acid catalyzed intermolecular condensation of dibasic acids and *o*-aminothiophenol are also suggested.

In recent years the use of polyphosphoric acid, as an effective agent in intermolecular condensations, has been extensively demonstrated. Hein, Alheim, and Leavitt[2] extended its application to the Phillips benzimidazole synthesis[3] and to similar reactions leading to benzoxazoles and benzothiazoles. Shriner and Upson[4] modified Phillips' method by using a longer reflux time in the synthesis of bisbenzimidazoles. Later Wang and Joulee[5] synthesized bisbenzimidazoles by polyphosphoric acid catalyzed condensation. They showed further that the polyphosphoric acid method was fairly general and successfully catalyzed the preparation of some benzimidazoles which could not be prepared by conventional methods.

A review of the literature indicated that Hofmann[6] prepared bisbenzothiazole by the reaction of 2-aminothiophenol and cyanogen in an alcoholic medium in 18% yield.[7] Mills[8] in 1922 prepared bis(2-benzothiazolyl)methane by heating *o*-aminothiophenol and malonic ester in a carbon dioxide atmosphere for four hours. 1,2-Bis(2-benzothiazolyl) ethane was first prepared by Hofmann[9] by heating *o*-aminothiophenol with succinimide and later Reisser and More[10] prepared it by the oxidation of benzothiazolylpropiothioanilide with alkaline potassium ferricyanide. The present study was undertaken to investigate if polyphosphoric acid would be useful in the synthesis of these and related compounds.

Bis(2-benzothiazolyl)alkanes were prepared by the polyphosphoric acid catalyzed condensation of dicarboxylic acids with *o*-aminothiophenol. As the length of the alkylene chain between the two benzothiazole nuclei was increased, the reaction took place under milder conditions and, in some cases, the yields of the compounds also increased. In the literature, a reaction temperature of 250°, and a reaction time of four hours is reported for similar condensations.[2] However, in the present study, high yields of the product were obtained by carrying out the reaction for two hours or less at 125–150°.

The synthesis of 1,2-bis(2-benzothiazolyl)ethylene and 1,2-bis(2-benzothiazolyl)-1,2-ethanediol required milder conditions. The condensation of maleic acid with *o*-aminothiophenol took place readily in polyphosphoric acid medium at 125° in one hour to give 1,2-bis(2-benzothiazolyl)ethylene in 88% yield. 1,2-Bis(2-benzothiazolyl)-1,2-ethanediol was obtained in 82% yield by heating tartaric acid and *o*-aminothiophenol at 100°, for less than half an hour, whereas prolonged heating at higher temperatures gave an unknown product which was insoluble in alcohol and did not melt below 300°.

The condensation reaction involving aromatic dicarboxylic acids required higher temperatures (150–175°) and a longer reaction period (three hours). 1,2-Bis(2-benzothiazolyl)benzene was readily formed in 85% yield, but 1,4-bis(2-benzothiazolyl)benzene was obtained in a yield of only 46%. It was found preferable from the standpoint of yield, to use phthalic anhydride instead of phthalic acid for the preparation of 1,2-bis(2-benzothiazolyl)benzene.

In the synthesis of these compounds, dicarboxylic acids were condensed with *o*-aminothiophenol; however, it was found that if the acids were replaced by esters, nitriles or anhydrides, the polyphosphoric acid still catalyzed the reaction. 1,2-Bis(2-benzothiazolyl)ethane was obtained in improved yields when succinic acid was replaced by succinonitrile or succinic anhydride. Hofmann[6] reported that condensation of *o*-aminothiophenol with succinic anhydride or succinic acid ester did not take place.

(1) Presented at The Twelfth Annual Kansas City Chemistry Conference, sponsored by the Kansas City Section of American Chemical Society, on November 18, 1960.

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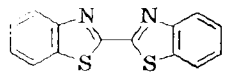
TABLE I

BISBENZOTHIAZOLES



Acid (or Other) Reagent Used with *o*-Aminothiophenol	Connecting Unit	Crude Yield, %	M.P.	Formula	Found				Calcd.			
					C	H	N	S	C	H	N	S
Oxalic	—	56.0	306[7]	$C_{14}H_8N_2S_2$	62.71	3.04	10.38	24.02	62.70	2.98	10.42	23.90
Malonic	CH_2	99.0	95.5–95[8]	$C_{15}H_{10}N_2S_2$	63.89	3.62	9.68	22.70	63.82	3.54	9.94	22.70
Succinic	$(CH_2)_2$	93.0	137.5–138[9,10]	$C_{16}H_{12}N_2S_2$	65.25	4.15	9.20	21.82	64.90	4.05	9.46	21.62
Succinonitrile	$(CH_2)_2$	99.8	137.5	$C_{16}H_{12}N_2S_2$	65.31	4.11	9.36	21.71	64.90	4.05	9.46	21.62
Succinic anhydride	$(CH_2)_2$	97.0	137.5	$C_{16}H_{12}N_2S_2$	65.00	4.08	9.40	21.90	64.90	4.05	9.46	21.62
Glutaric	$(CH_2)_3$	88.0	77–78	$C_{17}H_{14}N_2S_2$	65.76	4.45	8.88	20.65	65.82	4.52	9.04	20.62
Adipic	$(CH_2)_4$	99.0	103.5–104	$C_{18}H_{16}N_2S_2$	66.30	5.20	8.65	20.01	66.70	4.94	8.66	19.76
Pimelic	$(CH_2)_5$	87.2	60	$C_{19}H_{18}N_2S_2$	67.49	5.41	7.88	19.20	67.52	5.36	8.29	18.93
Suberic	$(CH_2)_6$	87.5	75	$C_{20}H_{20}N_2S_2$	67.69	6.20	7.66	18.20	68.30	5.68	7.94	18.18
Azelaic	$(CH_2)_7$	97.0	48.5	$C_{21}H_{22}N_2S_2$	68.88	6.21	7.51	17.50	68.90	6.02	7.65	17.50
Sebacic	$(CH_2)_8$	95.0	49.5	$C_{22}H_{24}N_2S_2$	69.61	6.51	7.15	17.00	69.50	6.32	7.37	16.85
Dodecanedioic	$(CH_2)_{10}$	68.5	59.5–60.5	$C_{24}H_{28}N_2S_2$	70.32	6.78	6.85	15.70	70.54	6.91	6.85	15.69
Maleic	CH=CH	88.1	245–248	$C_{16}H_{10}N_2S_2$	65.12	3.40	9.40	21.14	65.27	3.42	9.51	21.78
Tartaric	CHOH CHOH	82.2	222–225	$C_{16}H_{12}N_2S_2O_2$	57.61	3.70	8.22	19.51	58.51	3.68	8.53	19.52
Phthalic	*o*-C_6H_4	84.7	111.5[6]	$C_{20}H_{12}N_2S_2$	69.72	3.45	8.30	18.80	69.75	3.48	8.12	18.65
Phthalic anhydride	*o*-C_6H_4	92.4	112.0	$C_{20}H_{12}N_2S_2$	69.80	3.41	8.19	18.71	69.75	3.48	8.12	18.65
Terephthalic	*p*-C_6H_4	46.0	257–258	$C_{20}H_{12}N_2S_2$	69.81	3.61	8.21	18.44	69.75	3.48	8.12	18.65
Thiodipropionic	$CH_2CH_2SCH_2CH_2$	99.1	158.5	$C_{18}H_{16}N_2S_3$	60.87	4.56	7.80	26.98	60.77	4.49	7.86	26.88
1,2,3-Propanetricarboxylic	CH_2 –CH—CH_2[a]	99.5	97–98	$C_{33}H_{17}S_3N_3$	65.12	4.08	9.70	21.80	65.00	3.84	9.48	21.68

[a] 1,2,3-Trisbenzothiazolylpropane.

The reaction of β,β'-thiodipropionic acid and *o*-aminothiophenol gave a quantitative yield of 2,2'-bis(2-benzothiazolyl)diethyl sulfide in polyphosphoric acid medium. 1,2,3-Propanetricarboxylic acid also condensed readily with *o*-aminothiophenol in a one:three molar ratio to give a quantitative yield of 1,2,3-tris(2-benzothiazolyl)propane in the polyphosphoric acid catalyzed reaction.

As polyphosphoric acid is a complex mixture, it does not lend itself to the cryoscopic methods which have been so successfully used in the study of mechanisms of the organic chemical reactions in pure sulfuric acid. Because polyphosphoric acid is highly viscous, and a poor medium for crystallization, it is not surprising that reaction intermediates have not been isolated by this means. At the present time only speculation may be made concerning the mechanisms by which it operates on organic compounds. The most obvious possibilities are that it functions as a protonic acid, as a Lewis acid, or as a phosphorylating agent. The intermolecular condensation of *o*-aminothiophenol and dibasic acids may be rationalized on the basis of an initial step which is either a protonation followed by elimination of water or conversion to mixed anhydride which cyclizes in the usual manner to give a benzothiazole nucleus.

EXPERIMENTAL[11]

The procedure for the preparation of bisbenzothiazole and the related compounds is described below. The data on the preparation, yields, melting points and analyses are summarized in Table I. All melting points reported here are uncorrected. Commercial polyphosphoric acid, obtained from Victor Chemical Works, was used in this investigation.

Preparation of bis(2-benzothiazolyl)alkanes. *o*-Aminothiophenol (0.2 mole) was mixed with the dicarboxylic acid, anhydride or nitrile (0.1 mole) and the mixture was poured into well stirred polyphosphoric acid (125 ml.) contained in a three neck flask at 70°. The reaction mixture was heated at 125–150° for 2 hr. with efficient stirring. It was then allowed to cool to room temperature and was then poured into ice cold water. The precipitate was removed by filtration, washed three times with dilute sodium bicarbonate solution, and dried in a vacuum desiccator. The crude product was crystallized preferentially from ethanol and in some cases from benzene until a constant melting point was obtained.

Preparation of 1,2- and 1,4-bis(2-benzothiazolyl)benzenes. A mixture of *o*-aminothiophenol (0.1 mole) and phthalic acid or terephthalic acid (0.05 mole) was added to polyphosphoric acid (100 ml.) at 100°. The reaction mixture was heated at 175° for 3 hr. for 1,2-bis(2-benzothiazolyl)benzene and 4 hr. for 1,4-bis(2-benzothiazolyl)benzene. The 1,2-bis(2-benzothiazolyl)benzene was isolated according to the procedure previously described.

Preparation of 2,2'-bis(2-benzothiazolyl)diethyl sulfide. This compound was prepared by treating *o*-aminothiophenol (0.2 mole) with β,β'-thiodipropionic acid (0.1 mole) in polyphosphoric acid (100 ml.) at 125°. The reaction was complete in 1 hr. and the product was worked up by the procedure described for bis(2-benzothiazolyl)alkanes.

Preparation of 1,2,3-trisbenzothiazolylpropane. 1,2,3-Propanetricarboxylic acid (0.1 mole) was mixed with *o*-aminothiophenol (0.3 mole) and added to well stirred warm polyphosphoric acid (125 ml.). The reaction mixture was heated for 2 hr. at 125°. 1,2,3-Trisbenzothiazolylpropane was obtained in 92% yield as shiny tan crystals following the normal isolation and crystallization method.

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(11) Analyses were performed by the Analytical Research & Service Division of the Pure Oil Research Center.

[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, NITRO RESEARCH DEPARTMENT, MONSANTO CHEMICAL CO.]

Derivatives of 2-Benzothiazolesulfenamides. I. Novel Method for Preparation of *N*-Substituted Benzothiazolesulfenamides

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A novel method, the reduction of *N*-alkylidene- (or arylidene)-benzothiazolesulfenamides (I–XIII) with sodium borohydride, has been developed for the preparation of benzothiazolesulfenamides in 76–99% yields. This new method avoids the use of an amine as a reactant and also furnishes the benzothiazolesulfenamides with greater stability than those prepared by conventional known methods. During the course of this investigation the following interesting reactions were encountered: (1) The reaction of 2-benzothiazolesulfenamide with cyclohexanone or 2,4-pentanedione under basic conditions gave 2-(2-oxocyclohexylthio)benzothiazole (XIV) and 2-diacetylmethylthiobenzothiazole (XXXVIII), respectively; (2) the attempted reduction of *N*-isopropylidene-2-benzothiazolesulfenamide (XI) with (a) formic acid, (b) sulfur or hydrogen sulfide in isopropylamine-ethyl alcohol solvent, and (c) hydrogen sulfide in ethyl alcohol, gave 2,2'-dithiobis(benzothiazole) (XXXVI), the isopropylamine salt of 2-mercaptobenzothiazole (XXXVII), and 2-mercaptobenzothiazole (XXXV), respectively; (3) the reaction of *N*-cyclohexyl-2-benzothiazolesulfenamide (XXXII) with 4,4'-methylenebis(phenyl isocyanate) or toluene 2,4-diisocyanate furnished 1,1'-(*p*-methylenediphenylene)bis(3-cyclohexylurea) (XXXXI) and 1-cyclohexyl-3-(3-isocyanato-*p*-tolyl)urea (XXXXII), respectively. A possible mechanism for reaction (1) is discussed.

The discovery that 2-mercaptobenzothiazoles are accelerators for the vulcanization of rubber with sulfur[1,2] has stimulated many workers to prepare and extensively evaluate their derivatives. Among the many derivatives prepared and evaluated, the benzothiazolesulfenamide, in particular,

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