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Organoboron Compounds. X. On the Reaction of *o*-Hydroxybenzeneboronic Acid Anhydride with Some Sulfonamides

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Several new azo compounds containing boron atoms have been synthesized by the use of sulfonamides; these compounds have an excellent effect on bacilli. It was expected that the antibiotic effect would be very remarkable, since it had been reported that boron-containing azo dyes are useful for therapy on brain tumors. A mixed solvent of ethanol-water (1 : 1) and acetone was found useful for recrystallizing this class of compounds. The infrared spectra of these compounds show absorption bands at the 1090—1100 cm^{-1}, 1375—1380 cm^{-1} and 1600—1610 cm^{-1} regions these bands may be assigned to the carbon-boron, boron-oxygen and nitrogen-nitrogen bonds respectively.

Some azo compounds containing boron atoms were found to be effective in the medical treatment of brain tumors by Kruger$^{1)}$ and by Zall et al.$^{2)}$ It had been known that a number of azo compounds containing negative atoms or groups such as halogens, as well as hydroxyl, nitro and trifluoro groups, are also effective, if irradiated, even without boron atoms; however, the azo compounds containing boron atoms are more effective with respect to the absorption by tumors than the compounds without boron atoms. Gilman et al.$^{3)}$ obtained a number of azo compounds containing boron atoms by coupling *o*-hydroxybenzeneboronic acid anhydride with the diazonium chlorides of benzene, *p*-bromobenzene and nitrobenzene. It was expected that if boron atoms were introduced into sulfonamides by coupling them with boronic acid, the antibiotic effect would be even more remarkable. This paper will deal with some studies of the reactions of *o*-hydroxybenzeneboronic acid anhydride with certain sulfonamides which contain at least one amino group capable of being diazotized, namely, sulfanilamide, N^1-2-thiazolylsulfanilamide, N^1-(2, 6-dimethoxy-4-pyrimidinyl)sulfanilamide and N^1-(6-methoxy-3-pyridazinyl)sulfanilamide. This coupling could occur at the position either ortho or para to the hydroxy group, but primarily at the para position.

Figure 1 illustrates the compounds of this class thus obtained.

The solubility of these products was tested with a solvent such as that used by Gilman$^{3)}$ for the azo dyes from *o*-hydroxybenzeneboronic acid anhydride (Table I).

A solvent system including ethanol-water (1 : 1) was always found to be a better solvent for recrystallization than acetone.

Although melting point determination has been profitably employed as a criterion of purity for most organic compounds, it does not seem to hold generally true for azo boron compounds. The

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* Died April 9, 1965.

1) P. G. Kruger, *Radiation Research*, **3**, 1 (1955).

2) P. A. Zall and F. S. Cooper, *Science*, **93**, 64 (1941).

3) H. Gilman, L. Santucci, D. R. Swayampati and R. O. Ranck, *J. Am. Chem. Soc.*, **79**, 2889 (1957).

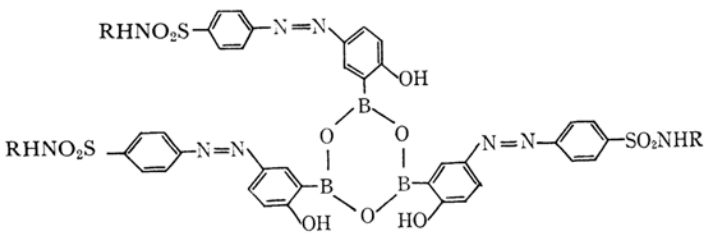

Fig. 1. Azo compound of *o*-hydroxybenzeneboronic acid anhydride.

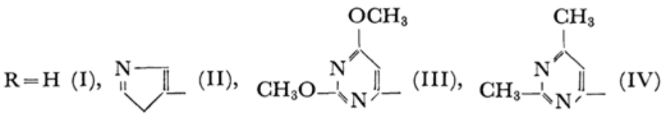

Table I. The solubility of products

Solvent	R			
	I[a]	II[b]	III[c]	IV[d]
Chloroform - Carbon tetrachloride (1 : 1)	i	i	i	i
Acetone	s	hs	hs	hs
Benzene - Petroleum ether (1 : 1)	i	i	i	i
Ethanol-Water (1 : 1)	hs	hs	hs	hs
Benzene	i	i	i	i
Ethylene chloride	i	i	ls	i

i : insoluble, s : soluble, hs : soluble by heating, ls : a little soluble

a) 2-Hydroxy-5-(sulfonamidophenylazo)benzeneboronic acid anhydride

b) 2-Hydroxy-5-(N^1-2-thiazolylsulfonamidophenylazo)benzeneboronic acid anhydride

c) 2-Hydroxy-5-(N^1-(2,6-dimethoxy-4-pyrimidinyl)-sulfonamidophenylazo)benzeneboronic acid anhydride

d) 2-Hydroxy-5-(N^1-(6-methoxy-3-pyridazinylsulfonamidophenylazo))benzeneboronic acid anhydride

materials obtained also decomposed over 200°C before melting.

The infrared spectra of these azo boronic acids showed absorption bands at two regions, from 1090 to 1100 cm^{-1} and from 1375 to 1380 cm^{-1}, as have many of the boronic acids already reported; these bands may be assigned to the carbon-boron and the boron-oxygen bonds respectively. A band of a weak intensity appeared at 1600 to 1610 cm^{-1} in all the azo derivatives of boronic acid; this band may be due to the azo group.

Experimental

***o*-Hydroxybenzeneboronic Acid Anhydride.**—*o*-Hydroxybenzeneboronic acid anhydride was prepared from 35.0 g. (0.2 mol.) of *o*-bromophenol and an equivalent quantity of tri-*n*-butyl borate (98.6 g.) in an atmosphere of nitrogen, almost exactly according to Gilman's method.[4] The ethereal solution of lithium *o*-lithiophenoxide was sucked up through a glass tube into a graduated dropping funnel which had previously been flushed with nitrogen. The crude material was then recrystallized three times from toluene using activated charcoal. This represents ca. a 44% yield of a nearly pure material with a melting point range of 176—179°C.

Diazotization and Coupling.—*With Sulfanilamide* (R=I).—The diazotization of sulfanilamide (1.7 g., 0.01 mol.) was carried out according to Datta's method.[5] The diazotized sulfanilamide solution was then slowly added to a stirred solution composed of 0.9 g. (0.0225 mol.) of sodium hydroxide, 1.4 g. (0.01 mol.) of *o*-hydroxybenzeneboronic acid anhydride, and 10 ml. of water, and cooled to 5°C by means of an ice-salt bath. Agitation was continued for two hours at 0—5°C following the completion of the addition. The reaction mass was then filtered, and the filter cake was suspended in 100 ml. of water at 40°C and acidified by adding 10% hydrochloric acid. After it had been cooled to room temperature, the precipitated solid was removed by filtration and dried in a vacuum oven; yield, 2.9 g. (96%). This solid does not change until 300°C. The crude product was recrystallized twice from an ethanol-water (1 : 1) mixture.

Found: C, 47.88; H, 3.79; B, 3.37; N, 13.90. Calcd. for $C_{12}H_{10}BN_3O_4S$: C, 47.52; H, 3.33; B, 3.58; N, 13.87%.

With N^1-2-Thiazolylsulfanilamide (R=II). — N^1-2-Thiazolylsulfanilamide (2.5 g., 0.01 ml.) was diazotized according to the method of Datta.[5] This diazonium chloride solution was then stirred over a 15-min. period into a solution composed of 1.1 g. (0.0275 mol.) of sodium hydroxide, 1.4 g. (0.01 mol.) of *o*-hydroxybenzeneboronic acid anhydride, and 10 ml. of water; then the solution was cooled in an ice-salt bath. Agitation was continued for 2 hr. following the completion of the addition, with the temperature maintained at 0—5°C. The reaction mixture was then filtered, and the filter cake was suspended in 100 ml. of water at 40°C and then acidified with 10% hydrochloric acid. The solid thus precipitated was removed by filtration after it had been cooled to room temperature;

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4) H. Gilman, L. Santucci, D. R. Swayampati and R. O. Ranck, ibid., **79**, 3077 (1957).

5) S. K. Datta and S. N. Saha, *Z. anal. Chem.*, **174**, 38 (1960).

it was then dried in a vacuum oven. The brown crude material was recrystallized twice from an ethanol-water (1 : 1) mixture to give 2.5 g. of a pure, bitter, orange product decomposing at 220°C. Yield, 66%.

Found: C, 46.27; H, 2.62; B, 2.64; N, 14.77. Calcd. for $C_{15}H_{11}BN_4O_4S_2$: C, 46.62; H. 2.88; B, 2.80. N, 14.52%.

With N^1-(2, 6-Dimethoxy-4-pyrimidinyl) sulfanilamide (R = III). — N^1-(2, 6-Dimethoxy - 4 - pyrimidinyl)sulfanilamide (4.3 g., 0.01 mol.) was dissolved in 3 ml. of 30% hydrochloric acid and diazotized with 0.7 g. of sodium nitrite and 25 ml. of water at −1 to −3°C. The diazonium chloride solution was added to a stirred solution composed of 1.4 g. of *o*-hydroxybenzeneboronic acid anhydride, 1.1 g. (0.01 mol.) of sodium hydroxide, and 10 ml. of water cooled to 0—5°C by means of an ice-salt bath. Agitation was continued for 2 hr. following the completion of the addition, with the temperature maintained below 5°C. The reaction mass was then filtered, and the residue was suspended in 100 ml. of water and acidified by adding 10% hydrochloric acid. The product was filtered, washed, and recrystallized from an ethanol-water (1 : 1) mixture. The yield was 3.8 g. (86%). This product decomposes at 210°C.

Found: C, 49.60; H, 3.69; B, 2.62; N, 16.09. Calcd. for $C_{18}H_{15}BN_5O_6S$: C, 49.08; H, 3.44; B, 2.46; N, 15.92%.

With N^1-(6-Methoxy-3-pyridazinyl) sulfanilamide (R = IV). —To a stirred solution of 1.4 g. (0.01 mol.) of *o*-hydroxybenzeneboronic acid anhydride and 1.2 g. (0.03 mol.) of sodium hydroxide in 10 ml. of water, cooled to 0—5°C in an ice-salt bath, there was slowly added a solution containing 2.8 g. of N^1-(6-methoxy-3-pyridazinyl)-sulfanilamide, 4.8 ml. of 30% hydrochloric acid, 0.7 g. sodium nitrite, and 25 ml. of water. The alkaline reaction mixture was stirred for 2 hr. at 0—5°C and was then filtered. The filter cake was suspended in 100 ml. of water and acidified with 10% hydrochloric acid. A product with a decomposition point of 210°C was thus obtained in a 70% yield. The crude product was recrystallized twice from an ethanol-water (1 : 1) mixture.

Found: C, 49.26; H, 3.12; B, 2.80; N, 16.93. Calcd. for $C_{17}H_{14}BN_5O_5S$: C, 49.62; H, 3.44; B, 2.63; N, 17.04%.