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RESEARCHES ON THIAZOLES. IX. FURTHER STUDIES ON DERIVATIVES OF 2-PHENYL-BENZOTHIAZOLE[1]

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In continuation of our studies in this field, and as introductory to other papers soon to appear, the present article records the preparation and properties of some chloro, nitro, amino and hydroxy derivatives of 2-phenyl-benzothiazole.

In a footnote to an article describing various thiazole derivatives, Hofmann[2] reported that phosphorus pentachloride reacted vigorously with 2-phenyl-benzothiazole with formation of a crystalline chlorinated derivative, which he did not investigate or identify.

We have repeated the experiment and find that Hofmann's product is the 6-chloro-2-phenyl-benzothiazole, since the same product can be obtained from 6-amino-2-phenyl-benzothiazole or by fusing benzal-*p*-chloro-aniline with sulfur.

Direct nitration of 2-phenyl-benzothiazole yielded the 6-mononitro and a dinitro derivative. By the action of the appropriate nitrobenzoyl-chloride upon zinc *o*-aminophenyl-mercaptide, the 2-(*m*- and *p*-nitrophenyl)-benzothiazoles were obtained. Amines were prepared by reduction of these nitro derivatives.

Because of the fact that some azo dyes like Trypan Blue and Afridol Violet, prepared with "H Acid" as coupler, have been found to possess valuable therapeutic properties, we diazotized 6-amino-2-phenyl-benzothiazole and coupled it with "H Acid," but the purification of the resultant dye was so troublesome that only a few preliminary pharmacological tests were made.

Bogert and Stull[3] recently have shown that Hofmann[4] was correct in stating that benzothiazoles are formed by the interaction of *o*-aminophenyl-mercaptan and aldehydes, and that Claasz[5] was wrong in assigning to these products a benzothiazoline structure. Our syntheses of the 2-(*o*-hydroxyphenyl)- and 2-(*p*-hydroxyphenyl)benzothiazoles from the corresponding aldehydes, and of the 2-(*p*-hydroxyphenyl) compound from the corresponding 2-(*p*-aminophenyl) derivative, are in entire agreement with the work of Hofmann and of Bogert and Stull, but at variance with that of Claasz.

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[1] Presented in abstract at the Baltimore Meeting of the American Chemical Society, April 9, 1925.

[2] Hofmann, *Ber.*, **13**, 1223 (1880).

[3] Bogert and Stull, THIS JOURNAL, **47**, 3078 (1925).

[4] Hofmann, *Ber.*, **13**, 1236 (1880).

[5] Claasz, (a) *Ber.*, **45**, 1031 (1912); (b) **49**, 1141 (1916).

The 6-hydroxy was produced from the 6-amino compound. Nitration of the 2-(*p*-hydroxyphenyl) gave a mononitro derivative which was reduced to the corresponding amine.

Experimental Part

6-Chloro-2-phenyl-benzothiazole. (*a*) *By the Hofmann Method.*[2]—An intimate mixture of 62.5 g. of phosphorus pentachloride and 21.1 g. of 2-phenyl-benzothiazole was heated at 185° until the evolution of hydrogen chloride ceased (usually about three hours), and was then allowed to cool. The crude product was washed thoroughly with water and crystallized from *n*-butyl alcohol, when it appeared in small, lustrous, colorless platelets; m. p., 156.7° (corr.); yield, 30–35%. A qualitative test showed the presence of chlorine.

Anal. Calcd. for $C_{13}H_8ClNS$: C, 63.55; H, 3.26. Found: C, 62.96; H, 3.40.

The compound was readily soluble in toluene, ethyl or *n*-butyl alcohol, or in carbon tetrachloride.

The same reaction was carried out in the presence of a few crystals of iodine, but the yield was lower and the product less pure, although the velocity of the reaction appeared greater.

(*b*) *From 6-Amino-2-phenyl-benzothiazole.*—A suspension of 5.6 g. of the amino derivative in 50 cc. of concd. hydrochloric acid was diazotized at 0° with 2 g. of sodium nitrite in 50 cc. of water, and 5 g. of copper bronze[6] was added in small portions. When the temperature of the mixture was allowed to rise to that of the laboratory, nitrogen was evolved copiously. After standing for eight hours, the mixture was boiled, the insoluble material collected, washed twice with 1% hydrochloric acid containing a few drops of nitric acid, then with hot water, dried, dissolved in hot alcohol, the solution decolorized and allowed to cool. The yellow-orange crystals so obtained (m. p., 156.2–156.7°, corr.; yield, 1.3 g., or 21.4%) were crystallized from glacial acetic acid, in the presence of a suitable decolorizing carbon, and then appeared in yellowish flakes; m. p., 157.7–158.3° (corr.); yield, 0.88 g. Mixed with the product of the phosphorus pentachloride method, no appreciable lowering of the melting point occurred. A qualitative test disclosed the presence of chlorine.

(*c*) *From Benzal-p-chloro-aniline.*—An intimate mixture of 14.5 g. of benzal-*p*-chloro-aniline (m. p., 60°, corr.) with 6.5 g. of sulfur was fused at about 252°, first at ordinary pressure and finally under reduced pressure (245 mm.) until the evolution of hydrogen sulfide ceased (about 90 minutes). The cold pulverized melt was extracted thrice with hot, concd. hydrochloric acid and the acid poured into a large volume of cold water. The crude product so precipitated was purified by crystallization from ethyl and then from *n*-butyl alcohol, and melted at 155.7°; yield, very low. It gave a positive Beilstein test for halogen. When this product was mixed with a sample of the chloro derivative from Method *a* which melted at 156.2°, the melting point of the latter was not lowered perceptibly.

(*d*) *Experiments with the Chloro Derivative.*—To discover whether or not further chlorination could be effected by phosphorus pentachloride, 3.2 g. of the chloro derivative was subjected to the action of 15 g. of this reagent, but no higher chlorination products were detected and 2.5 g. of the original monochloro derivative was recovered unaltered.

In an effort to replace the chlorine by bromine, an alcoholic solution of the chloro derivative was refluxed for eleven hours with lithium bromide, but no exchange of halogens occurred.

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[6] Morgan and Webster, *J. Chem. Soc.*, **119**, 1070 (1921).

6-Nitro-2-phenyl-benzothiazole has been described by Hofmann,[2] by Naegeli,[7] and by Bogert and Abrahamson,[8] as melting at 188° (corr.). We followed the process of Bogert and Abrahamson, except that the nitration was conducted at 45–50° instead of at 75°, because the higher temperature tended to increase the amount of dinitro derivative. By repeated crystallization from carbon tetrachloride and from glacial acetic acid, in the presence of a decolorizing carbon, the melting point was raised finally to 196° (corr.).

Anal. Calcd. for $C_{13}H_8O_2N_2S$: C, 61.0; H, 3.10. Found: C, 61.05; H, 3.08.

Dinitro-phenyl-benzothiazole was isolated from a nitration in which a 20% excess of nitric acid was used. It was separated from the mononitro derivative by the greater solubility of the latter in glacial acetic acid, carbon tetrachloride and alcohol. It formed small, pale, lemon-yellow needles which felted together on the filter, and melted at 223° (corr.). Oehler[9] gives a melting point of 218–220° for a mixture of isomers. In our product, one of the nitro groups is probably at Position 6, but the location of the other has not been determined.

Anal. Calcd. for $C_{13}H_7O_4N_3S$: C, 51.9; H, 2.32. Found: C, 52.01; H, 2.2.

2-(*m*-Nitrophenyl)-benzothiazole, prepared from zinc *o*-aminophenyl-mercaptide and *m*-nitrobenzoyl chloride, and purified by crystallization from glacial acetic acid and then from alcohol in the presence of a decolorizing carbon, formed colorless needles; m. p., 186.8–187.3° (corr.); yield, about 35%.

Anal. Calcd. for $C_{13}H_8O_2N_2S$: C, 61.0; H, 3.1. Found: C, 61.31; H, 3.27.

2-(*p*-Nitrophenyl)-benzothiazole was prepared as described by Bogert and Snell,[10] from zinc *o*-aminophenyl-mercaptide and *p*-nitrobenzoyl chloride; yield, 62.2%. By crystallization from glacial acetic acid, the melting point of the product was raised to 233° (corr.). Bogert and Snell reported a melting point of 231° (corr.) for their product.

6-Amino-2-phenyl-benzothiazole was prepared by the method of Bogert and Abrahamson,[8] by reduction of the nitro derivative by tin and hydrochloric acid, except that after treating the mixed hydrochlorides of tin and the amine with excess of 4 *M* sodium hydroxide, the alkaline solution was extracted immediately with hot toluene, and the extracts were decolorized and filtered hot. The amine separated as the solution cooled; m. p., 206.6° (corr.) (Bogert and Abrahamson give 207°, corr.); yield, 60%. Bogert and Abrahamson reported that this reduction proceeded exothermically, but our experience indicated that this was true only when the mononitro was contaminated with some dinitro derivative.

2-Phenyl-benzothiazole-6-azo-"H Acid."—The diazotized aminothiazole was coupled with "H Acid" in dil. sodium hydroxide solution and the dye salted out in the usual manner. No satisfactory method of purification was found, but some preliminary dye tests were conducted on the partially purified dye, through the courtesy of Mr. R. V. Revson, of the H. A. Metz Dye Testing Laboratory, the most interesting result of which was the unusual light-fastness of the bright rose-lavender dyeing on artificial silk. Preliminary tests on rabbit blood smears showed that the red blood cells were stained faintly by a 0.1% neutral solution of the dye, and that it stained the plasma but not the nucleus of leucocytes.

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[7] Naegeli, *Bull. soc. chim.*, [3] **11,** 895 (1894).

[8] Bogert and Abrahamson, This Journal, **44,** 832 (1922).

[9] Oehler, (a) Ger. pat. 50,486 (1889); (b) Friedländer, "Die Fortschritte der Teerfarbenfabrikation," **2,** 303 (1891); (c) Winther, "Patente der organischen Chemie," **2,** 911 (1889). See also (d) Remy, Ehrhart, and Co., Ger. pat. 54,921 (1889); (e) Ref. 9 b, p. 305; (f) Ref. 9 c, p. 1448.

[10] Bogert and Snell, This Journal, **46,** 1310 (1924).

2-(*m*-Aminophenyl)-benzothiazole was prepared by the reduction of the corresponding nitro derivative (3.5 g.) with tin (5.6 g.) and concd. hydrochloric acid (25 cc.). After a brief preliminary heating, the reaction proceeded exothermically, so that the flame was removed. Upon the termination of this vigorous reaction, the mixture was diluted and boiled until a clear solution was obtained. This solution was filtered, the filtrate made strongly alkaline with 3 *N* sodium hydroxide, the precipitate redissolved in concd. hydrochloric acid and the solution again made strongly alkaline with sodium hydroxide. This second precipitate was extracted with hot alcohol, the solution decolorized and the crude product recrystallized from dil. alcohol. The purified compound appeared in colorless needles; m. p., 140.4–140.9° (corr.); yield, 1 g., or 32.3%. Its alcoholic solution showed a greenish-blue fluorescence.

Anal. Calcd. for $C_{13}H_{10}N_2S$: C, 69.03; H, 4.42. Found: C, 69.25; H, 4.65.

2-(*p*-Aminophenyl)-benzothiazole.—The process of Bogert and Snell[10] was varied in several particulars. When 13 g. of the nitro derivative was treated with 90 cc. of concd. hydrochloric acid, it dissolved at first and then separated again as a finely divided, yellow-brown solid suspended in the acid. After 21 g. of granular tin had been added to this mixture, it was heated for two hours at 60–70°. Two volumes of water were added and the solution was boiled until clear. As the solution cooled, the double tin chloride of the amine separated in glistening, golden-yellow platelets.

Since it was found difficult to free the base completely from tin by the action of caustic alkali, the difficultly soluble sulfate of the amine was precipitated from a weakly acid solution by the addition of sodium sulfate. The small quantity of amine passing into the filtrate was recovered subsequently. The base, liberated from the sulfate by the action of sodium hydroxide, decolorized and crystallized from alcohol, melted at 156.2–156.7° (corr.). Bogert and Snell, and French pat. 216,086, reported the melting point as 155°.

The double tin chloride of the amine is largely hydrolyzed when boiled with water, and the amine may be partially separated from the tin in this way.

Diazotized and coupled with β-naphthol, the amine yielded a bright red azo dye.

6-Hydroxy-2-phenyl-benzothiazole.—A solution of 5.6 g. of the 6-amino derivative in 100 g. of concd. sulfuric acid was poured into ice water. This finely divided suspension was diazotized at low temperature by the addition of a solution of 2 g. of sodium nitrite in 50 cc. of water. The mixture was stirred for 30 minutes longer, the temperature allowed to rise to that of the room, the mixture poured into an equal volume of boiling water and the whole boiled vigorously for a short time. Some tar collected on the surface, while the solution itself became turbid and a heavy, yellow, flocculent precipitate separated. The mixture was cooled to 60°, made strongly alkaline with sodium hydroxide and filtered. The filtrate was deep red by reflected and reddish-green by transmitted light, but upon dilution the fluorescence became a pure green. The alkaline solution was acidified with hydrochloric acid, and 2.2 g. (39.3%) of crude product obtained. After repeated crystallization, the pure compound appeared in nearly colorless crystals; m. p., 228–229° (corr.).

Anal. Calcd. for $C_{13}H_9ONS$: C, 68.75; H, 3.97. Found: C, 68.46; H, 4.24.

It dissolved quite freely in alcohol or glacial acetic acid, less readily in chloroform or toluene, and was practically insoluble in water. Its solution in aqueous alkali exhibited a beautiful green fluorescence.

2-(*o*-Hydroxyphenyl)-benzothiazole, prepared from zinc *o*-aminophenyl-mercaptide and salicyl aldehyde in the same way as was the isomeric *p*-hydroxy derivative, formed glistening colorless or pale yellowish crystals, m. p. 131.1–131.7° (corr.), which melting point was not changed by further crystallization; yield, about 50%. Its alkali solution, especially in the presence of some alcohol, exhibits a beautiful blue fluorescence, as noted by Hofmann,[11] who discovered this compound by the direct condensation of salicyl aldehyde and *o*-aminophenyl mercaptan, and recorded its melting point as 129°.

Claasz[5b] carried out a similar condensation, using the hydrochloride of the amino mercaptan and salicyl aldehyde and obtained a similar product, m. p. 130°, but which he believed to be the 2-(*o*-hydroxyphenyl)-benzothiazoline.

2-(*p*-Hydroxyphenyl)-benzothiazole. (*a*) *From the 2-(p-aminophenyl) Derivative.*—The amine was diazotized as described for the 6-hydroxy isomer. The diazonium salt did not all remain in solution. When the temperature of the diazotized mixture was raised, evolution of nitrogen began at 50°, the solution largely cleared at about 75°, but became turbid again at 90°, separated a flocculent precipitate and no longer coupled with β-naphthol to give a red dye. The mixture was made alkaline and filtered, the filtrate acidified with hydrochloric acid, and the precipitate collected, washed and dried; yield of crude (m. p., 220.5–222.7°) product, 69%. It was further purified by crystallization from dil. alcohol and from dil. acetic acid, and then appeared in small, pale, cream-colored needles; m. p., 228.6–229° (corr.). A trace of impurity was still present in these crystals and sublimed in a thin red film above the solid in the melting point tubes.

(*b*) *From p-Hydroxy-benzaldehyde.*—A hot solution of 16 g. of zinc *o*-aminophenylmercaptide and 12.5 g. of *p*-hydroxy-benzaldehyde in 1 liter of glacial acetic acid, was treated with hydrogen sulfide for two hours, filtered hot, the filtrate decolorized, diluted with an equal volume of water and allowed to cool. The crystals obtained melted at 228.6–229.1° (corr.), and were identical with those described in Method *a*, except that no red sublimate formed in the melting point tubes; yield, 11 g., or 47.1%. The melting point was not altered by further crystallization. Dilute solutions, when cooled slowly, separated the compound in long, cream-colored, feathery scales. Its solution in dilute aqueous alkali possessed a violet fluorescence with a yellowish tinge.

Anal. Calcd. for $C_{13}H_9ONS$: C, 68.72; H, 3.96. Found: C, 68.52; H, 4.23.

When a technical grade of *p*-hydroxy-benzaldehyde was substituted for the C. P. grade, the yield of product was 41.6%, the melting point 227–228° (corr.), and the color much darker.

Nitration of 2-(*p*-Hydroxyphenyl)-benzothiazole.—A solution of 8.5 g. of the hydroxy derivative (from the aldehyde condensation) in 60 cc. of concd. sulfuric acid was nitrated at room temperature by the slow (18 minutes) addition of 2.37 cc. of concd. nitric acid dissolved in 15 cc. of the same solvent. After being warmed for 20 minutes at 45°, the mixture was poured into an excess of ice water and the yellow precipitate collected; yield, 8.7 g., or 85%. When this precipitate was dissolved in hot glacial acetic acid, the solution decolorized, diluted and cooled, a yield of 4.1 g. (47.1%) of crystals, m. p. 198.1–198.7° (corr.), was obtained. A further crystallization from dilute acetic acid raised this melting point to 199.2–199.7° (corr.). Because of paucity of highly purified material, the analysis was run on a sample melting at 198.1–198.7° (corr.).

Anal. Calcd. for $C_{13}H_8O_3N_2S$: C, 57.4; H, 2.94. Found: C, 55.32; H, 2.82.

The pure compound formed a bright yellow product, very light and difficult to handle because of its adherence to the sides of the container. With caustic alkali, it gave a bright red color and on dilution dissolved to form a yellowish-red solution. It was slightly soluble in alcohol. The behavior in the melting point tube was peculiar. Prior to melting, a slow decomposition appeared to occur, with formation of a red sublimate, and not all of the material liquefied at the initial melting point, complete liquefaction occurring only 20–30° above that point.

In the course of a nitration conducted at 10–15°, followed by crystallization of the

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[11] Hofmann, *Ber.*, **13**, 1237 (1880).

crude product from glacial acetic acid, a difficultly soluble fraction was obtained, m. p. 252–256.8° (corr.), slightly darker in color than the foregoing; its analysis indicated that it was probably mainly a dinitro derivative.

Anal. Calcd. for $C_{13}H_7O_5N_3S$: C, 49.21; H, 2.25. Found: C, 51.68; H, 2.15.

Monoamino-2-(*p*-hydroxyphenyl)-benzothiazole was prepared by reduction of the corresponding nitro derivative (4 g.) with tin (6 g.) and concd. hydrochloric acid (60 cc.). After the mixture had been warmed for 30 minutes most of the tin was dissolved. The solution was diluted with 100 cc. of water and boiled until clear. As it cooled, fine golden-yellow needles of a double tin salt separated, which liquefied at 179–180° (corr.), resolidifying immediately to a red substance which browned at higher temperatures but was unmelted at 255° (corr.). This double tin salt was quite freely soluble in water. Its aqueous solution was de-tinned by the action of hydrogen sulfide, and the filtrate from the tin sulfide exactly neutralized with sodium carbonate. The voluminous, cream-colored precipitate thus obtained was dissolved in alcohol, the solution decolorized and water added until the hot solution began to cloud. As it cooled, bunches of fine, nearly colorless needles separated; m. p., 234.5–235.5° (corr.); yield, about 20%.

Anal. Calcd. for $C_{13}H_{10}ON_2S$: C, 64.46; H, 4.13. Found: C, 64.46; H, 4.43.

In a later experiment, the nitro derivative was reduced with iron filings and concd. hydrochloric acid. The yield (42.7%) of crude product was good, but the melting point (210.5–211.6°, corr.) low, and further purification was not attempted.

The pure compound was easily soluble in alcohol, the solution exhibiting a weak bluish fluorescence. Its solutions darkened on exposure to the air. Diazotized in the usual way, it yielded an insoluble reddish-orange diazonium salt, which coupled with alkaline β-naphthol solution to give a rich violet or purple precipitate.

Summary

1. The following new derivatives of 2-phenyl-benzothiazole have been prepared and studied: 6-hydroxy, 2-*p*-hydroxy, dinitro, 2-*m*-nitro, 2-*m*-amino, a mononitro-2-*p*-hydroxy and monoamino-2-*p*-hydroxy.

2. The following derivatives, already described in the literature, were produced by new methods: 6-chloro and 2-*o*-hydroxy.

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