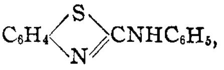
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

RESEARCHES ON THIAZOLES. XVIII. THE SYNTHESIS OF 2-PHENYLBENZOTHIAZOLE-5-CARBOXYLIC ACID AND DERIVATIVES

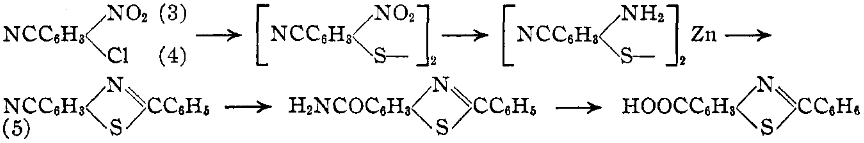
BY MARSTON TAYLOR BOGERT AND HELEN G. HUSTED[1]

RECEIVED APRIL 29, 1932 PUBLISHED AUGUST 5, 1932

In the course of certain pharmacological experiments in the benzothiazole field with which we have been occupied lately, we had occasion to prepare some of the well-known benzothiazoles by new methods and some new compounds by old methods. For the benefit of other workers in this field, these experimental results are here recorded.

In place of the processes heretofore used, we found it most convenient to prepare *o*-aminophenyl mercaptan hydrochloride, $HSC_6H_4NH_2HCl$, by treating the zinc mercaptide with concentrated hydrochloric acid, and the 2-anilinobenzothiazole,  $C_6H_4\overset{S}{\underset{N}{\langle\rangle}}CNHC_6H_5$, from the *o*-aminophenyl disulfide and phenyl isothiocyanate.

From 3-nitro-4-chlorobenzonitrile, a series of new compounds was synthesized by the following steps



From the 2-phenyl-5-cyanobenzothiazole, a mononitro derivative was obtained, but the location of the nitro group was not determined. The methyl ester was prepared from the 2-phenylbenzothiazole-5-carboxylic acid. Both the acid and its methyl ester were too difficultly soluble to be used in our pharmacological experiments.

Experimental

From *o*-nitrochlorobenzene, there were prepared, as described in the literature and with similar results, *o*-**nitrophenyl disulfide,**[2] **zinc** *o*-**aminophenyl mercaptide**[3] **and** *o*-**aminophenyl disulfide.**[3]

o-**Aminophenyl mercaptan hydrochloride** was obtained most conveniently by treating the zinc mercaptide (8.5 g.) with concentrated hydrochloric acid (sp. gr. 1.2) (75 cc.). The zinc salt dissolved with evolution of heat and of a trace of hydrogen sulfide. The warm solution was filtered through asbestos and the filtrate cooled in an ice pack. The hydrochloric acid salt separated rapidly in colorless needles, which were crystallized from concentrated hydrochloric acid, the crystals washed with ether, recrystallized from

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[1] Ferguson Fellow, Columbia University, 1928–1929.

[2] (a) Blanksma, *Rec. trav. chim.*, **20**, 121 (1901); (b) Wohlfahrt, *J. prakt. Chem.*, [2] **66**, 555 (1902); (c) Bogert and Stull, THIS JOURNAL, **47**, 3080 (1925).

[3] Bogert and Snell, *ibid.*, **46**, 1309 (1924).

water, and then melted with decomposition at 217° (corr.) in agreement with the literature;[2c,4] yield, 80.3%.

3-Nitro-4-chlorobenzonitrile was obtained, by nitration of *p*-chlorobenzonitrile, in a yield of 61% by the Mattaar[5] method, m. p. 100–101° (corr.). Mattaar recorded the m. p. as 99–100°. It formed odorless, colorless, lustrous spangles or fine needles, readily soluble in alcohol or toluene.

Anal. Calcd. for $C_7H_3O_2N_2Cl$: C, 46.03; H, 1.64; N, 15.34. Found: C, 46.60; H, 1.63; N, 15.17.

2-Nitro-4-cyanophenyl disulfide was prepared from 3-nitro-4-chlorobenzonitrile and sodium disulfide in essentially the same way as the *o*-nitrophenyl disulfide,[2] except that refluxing of the solution was not necessary, as the disulfide separated almost immediately in fine canary yellow needles or granules, which were thoroughly washed with boiling water and then with hot alcohol; yield, 86%. When heated, these crystals began to char around 235°, and liquefied at about 335°.

Anal. Calcd. for $C_{14}H_6O_4N_4S_2$: C, 46.65; H, 1.67; N, 15.64. Found: C, 46.92; H, 1.68; N, 15.56.

2-Amino-4-cyanophenyl Mercaptan (3-Amino-4-mercaptobenzonitrile).—The zinc salt was obtained by reduction of the corresponding nitro disulfide, as described by Bogert and Snell[3] for *o*-aminophenyl mercaptan. Owing to the very slight solubility of the disulfide in hot glacial acetic acid, the reduction was carried out by intimately mixing (in a mortar) the finely pulverized disulfide with a very pure zinc dust (the purity of the zinc dust influenced the yield markedly), adding this mixture to the acid and refluxing for an hour. The product was pulverulent and pale cream colored; yield, 49%. When heated, it began to decompose at about 250°.

Anal. Calcd. for $C_{14}H_{10}N_4S_2Zn$: C, 46.28; H, 2.75. Found: C, 46.48; H, 3.39.

Benzothiazole.—*o*-Aminophenyl mercaptan hydrochloride was condensed with formaldehyde, as recorded by Claasz[6] and by Bogert and Stull.[2c]

Considerable difficulty was encountered in purifying the crude thiazole satisfactorily by distillation. At atmospheric pressure, there was much decomposition, so that the distillation had to be conducted under reduced pressure, and then the maintenance of a fairly constant pressure proved troublesome even when all connections were carefully sealed.

The fraction (A) collected at 97–100° at 18.6 mm. was used for some of the pharmacological experiments which will appear shortly in the *J. Pharmacol. and Exptl. Therapeutics*, and when tested by the Siwoloboff[7] method showed a b. p. of 231° (corr.) at atmospheric pressure, in accordance with the figure given by Hofmann[4a] and by Bogert and Stull.[2c] From another run, the fraction (C) boiling at 87–91° at 11 mm., 231° (corr.) at 760 mm. was used for pharmacological tests, some carried out by ourselves, and some by Professor S. W. Clausen, of the University of Rochester, in connection with his studies on experimental eczema.

The carefully purified material (b. p. 231°, corr.) showed the following constants: $n_D^{24.6}$ 1.6370; d^{22} 1.23.

Methiodide.—Fine colorless needles, melting with decomposition at 210° (corr.), in agreement with the literature.[4a]

Anal. Calcd. for C_8H_8NSI: N, 5.06. Found: N, 5.08.

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[4] (a) Hofmann, *Ber.*, **20**, 2251 (1887).

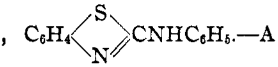
[5] Mattaar, *Rec. trav. chim.*, **41**, 24 (1922).

[6] Claasz, *Ber.*, **49**, 1141 (1916).

[7] Siwoloboff, *ibid.*, **19**, 795 (1886).

Nitrate.—Prepared as described by Mills,[8] formed colorless crystals, but the aqueous solution of these crystals was too acidic to be suitable for our pharmacological experiments.

2-Anilinobenzothiazole,



$C_6H_4\langle S, N \rangle CNHC_6H_5$.—A mixture of 0.01 mole of *o*-aminophenyl disulfide and 0.02 mole of phenyl isothiocyanate was heated for forty minutes at 100°, with or without 95% alcohol as solvent. A small amount of precipitate separated and some hydrogen sulfide was evolved. Evaporation of the alcohol and crystallization of the residue from toluene gave fine colorless needles; yield, 30%; m. p., 159.2° (corr.), as compared with the figure 159° recorded by Hofmann,[9] and by Jacobson and Frankenbacher,[10] who prepared it by other methods.

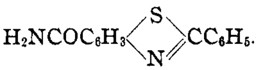
Anal. Calcd. for $C_{13}H_{10}N_2S$: C, 69.03; H, 4.43. Found: C, 68.88; H, 4.71.

2-Phenyl-5-cyanobenzothiazole.—When prepared by the Bogert and Snell[3] method from the zinc aminocyanophenyl mercaptide (7.5 g.) and benzoyl chloride (12 cc.), crystallized from toluene in odorless silvery spangles, light and bulky, which melted at 197° (corr.). The yield was only 20%, as there was considerable loss in recrystallization.

Following the process of Bogert and Stull,[2c] and using benzaldehyde (2 cc.) instead of benzoyl chloride upon the zinc mercaptide (2.55 g.), the yield of thiazole was 30% and its m. p. 196.6–197.7° (corr.).

Anal. Calcd. for $C_{14}H_8N_2S$: C, 71.18; H, 3.39; N, 11.86; S, 13.59. Found: C, 71.16; H, 3.52; N, 11.76; S, 13.42.

2-Phenylbenzothiazole-5-carbamide,



$H_2NCOC_6H_3\langle S, N \rangle CC_6H_5$.—When the above nitrile (3 g.) was suspended in 75% sulfuric acid (80 cc.), the mixture heated for about forty-five minutes at 80°, then cooled and the brown solution poured into 900 cc. of ice water, a copious white precipitate separated which was decolorized and crystallized repeatedly from 95% alcohol. There were thus obtained colorless small needles, m. p. 247.2° (corr.), insoluble in *N* sodium hydroxide solution; yield, 23%.

Anal. Calcd. for $C_{14}H_{10}ON_2S$: N, 11.02; S, 12.59. Found: N, 10.91; S, 12.15.

Nitro-2-phenyl-5-cyanobenzothiazole.—2-Phenyl-5-cyanobenzothiazole (0.5 g.) was warmed for eighteen hours at 25° with fuming nitric acid (20 cc. of sp. gr. 1.6), and the cooled solution then poured slowly upon cracked ice. The curdy pale yellow precipitate was purified by dissolving it in a large volume of boiling 95% alcohol and adding water to incipient turbidity. The product was a colorless pulverulent solid, m. p. 256° (corr.); yield, 10%.

Anal. Calcd. for $C_{14}H_7O_2N_3S$: C, 59.78; H, 2.49. Found: C, 59.66; H, 2.71.

Not enough of this derivative was obtained to enable us to ascertain the location of the nitro group.

2-Phenylbenzothiazole-5-carboxylic Acid.—When 2-phenyl-5-cyanobenzothiazole (0.51 g.) was heated at 80° for fifteen minutes with sulfuric acid (10 cc. of a mixture of three parts by weight of concentrated acid to one of water) and then for fifteen minutes at 205°, the nitrile was saponified and on dilution with ice the thiazole acid separated. It crystallized from 95% alcohol as an odorless, colorless microcrystalline powder, and from ether in minute colorless silky needles which began to decompose around 250° and melted at about 273° (corr.); yield, 80%.

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[8] Mills, *J. Chem. Soc.*, **121**, 460 (1922).

[9] Hofmann, *Ber.*, **13**, 12 (1880).

[10] Jacobson and Frankenbacher, *ibid.*, **24**, 1410 (1891).

Anal. Calcd. for $C_{14}H_9O_2NS$: C, 65.88; H, 3.53; N, 5.49. Found: C, 65.76; H, 3.60; N, 5.55.

It was practically insoluble in water and only slightly soluble in hot alcohol, but dissolved readily in ether or in caustic alkali solutions.

The same product was obtained by digesting 0.29 g. of the corresponding amide with 10 cc. of hydrochloric acid (sp. gr. 1.19) for a few minutes. The acid separated in crystalline form. It was removed, washed thoroughly with water, dissolved in aqueous sodium hydroxide solution, reprecipitated by sulfuric acid, this solution and reprecipitation being repeated several times and the purified acid then decolorized and crystallized from 95% alcohol, and finally from absolute alcohol; yield, 80%. The carboxyl content was determined by a Pregl micro-titration with $N/100$ sodium hydroxide solution.

Anal. Calcd. for $C_{13}H_8NSCOOH$: COOH, 17.6. Found: COOH, 18.0

Methyl Ester.—The silver salt was prepared by treating the sodium salt with silver acetate in aqueous solution. The solution was made faintly acid with nitric acid, the silver salt filtered out, washed with water, then with alcohol, dried, suspended in a methyl alcohol solution of methyl iodide, the mixture refluxed for ten minutes, diluted with methyl alcohol, the silver iodide filtered out of the hot solution, the filtrate concentrated and cooled. The methyl ester which separated was purified by recrystallization from methyl alcohol. The crystals were colorless and finely granular, m. p. 171–172° (corr.), with some previous sintering; yield, 5%.

Anal. Calcd. for $C_{15}H_{11}O_2NS$: N, 5.20. Found: N, 5.38.

Attempts to prepare the ester directly from the nitrile by the action of hydrochloric acid and methyl alcohol were unsuccessful, the original nitrile being recovered unaltered.

Summary

1. 2-Phenyl-5-cyanobenzothiazole has been synthesized from *p*-chlorobenzonitrile, by nitration of the latter, reduction of the nitrochloro compound, through the disulfide, to the 3-amino-4-mercaptobenzonitrile and the condensation of the zinc salt of the latter with either benzoyl chloride or benzaldehyde.

2. This cyanobenzothiazole has been hydrolyzed to the corresponding amide and acid, and some derivatives prepared from the latter.

3. The work was incidental to pharmacological studies which will appear elsewhere.

NEW YORK, N. Y.