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Studies in the 5-Halo-2-thiouracil Series. I. An Improved Method of Debenzylation of 5-Iodo-2-benzylthiouracil and Homologs

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An improved method for the debenzylation of 5-iodo-2-benzylthiouracil and homologs is described, involving reaction with anhydrous aluminum bromide in toluene. The scope and limitations of this reaction are briefly discussed. The monosodium salts of 5-iodo-2-thiouracil and some of its homologs have been prepared and characterized.

Derivatives of 2-thiouracil have aroused considerable interest in recent years as potent antithyroid agents.[3] 5-Halo-2-thiouracils, including the 5-iodo and 6-methyl-5-iodo derivatives, were first synthesized by Barrett, *et al.*[4] Their method involved: (1) protection of the thiol group of thiouracil, by preparation of the methyl, ethyl or benzyl derivative, (2) iodination with iodine in aqueous alkaline solution, and (3) removal of the protecting group on the sulfur atom by treatment with anhydrous hydrogen iodide in glacial acetic acid solution. In this manner, these authors obtained 57% of the theoretical amount of 5-iodo-2-thiouracil from the cleavage of 5-iodo-2-benzylthiouracil. This cleavage reaction was not satisfactory for large-scale operation because of its potentially hazardous nature and the low yield afforded, and a safer and more efficient method was required.

Harnish and Tarbell[5] investigated the efficacy of a considerable number of acidic reagents in the cleavage of benzyl phenyl sulfide. They found most of these to be relatively inefficient; however, anhydrous aluminum bromide gave high yields of thiophenol under optimum conditions. These findings suggested the possible utility of this reagent in the cleavage of 5-iodo-2-benzylthiouracil and its homologs, even though consideration of the structure of these substances suggested the possibility of prior reactions with other functional groups of the molecule. The postulated mechanism[5] of this cleavage involves a rapid coördination of the sulfur atom of the benzylthio derivative with aluminum bromide, followed by a rate-determining decomposition of the resulting complex to form a second complex which upon treatment with a hydroxylic solvent decomposes to yield the free thiol. Harnish and Tarbell[5] found that oxygenated solvents inhibited or entirely prevented cleavage, depending upon the amount of such solvents present. Presumably, donor solvents of this type preferentially coördinate with the aluminum bromide. The thiouracil derivatives under consideration contain such a donor group. Furthermore, it is well known[6] that the Friedel–Crafts reaction catalyzed by anhydrous aluminum halides generally fails when applied to heterocyclic ring systems containing nitrogen, and also that halogen atoms are often labile[7] in this same reaction. As previously stated, these considerations made the success of the aluminum bromide cleavage method uncertain when applied to benzyliodothiouracils. In actual fact, however, the reaction was found to proceed smoothly, affording about 82% of the theoretical amount of 5-iodo-2-uracil from the S-benzyl derivative after purification.

With regard to scope and limitations, it has been found that this reaction could also be applied successfully to similar derivatives of certain other thiol-substituted nitrogen-containing heterocycles, including 2-benzylmercaptobenzothiazole, 2-benzylmercaptobenzoxazole and 2-benzylmercapto-4,5-diiodoimidazole.[8] However, it failed when applied to 4-benzal-2-benzylthiohydantoin, possibly because of cleavage of the heterocyclic ring. It was also applied successfully to certain other derivatives containing the α-naphthylmethyl protecting group on the sulfur atom, but failed when this group was alkyl or allyl; cleavage of these derivatives did not occur and starting material was recovered.

5-Iodo-2-thiouracil was found to exhibit a rather peculiar type of photosensitivity. On exposure to light it developed a pronounced reddish to red-brown color which disappeared for the most part on storage in the dark. A method was developed for the preparation of the monosodium salt which was found to be quite stable and insensitive to light.

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Experimental[9]

5-Iodo-2-thiouracil.[4]—A solution of 88.3 g. (0.33 mole) of anhydrous aluminum bromide in 500 ml. of dry toluene was prepared in a 1-liter, three-necked, round-bottomed flask having ground-glass joints and equipped with a mechanical stirrer, reflux condenser protected with a calcium chloride tube, and thermometer. 5-Iodo-2-benzylthiouracil[4] (103 g., 0.30 mole) was then added rapidly to the clear, orange solution with stirring. The temperature rose to about 66° within about five minutes and a yellow precipitate was formed. After cessation of the spontaneous evolution of heat, the temperature was permitted to fall to 60° and then maintained at this point for six hours with continued stirring.

The reaction mixture was then cooled to 25° and 40 ml. of water was added over a period of about 30 minutes with

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(3) See reference 4 for early references.

(4) H. W. Barrett, I. Goodman and K. Dittmar, THIS JOURNAL, **70**, 1753 (1948).

(5) D. P. Harnish and D. S. Tarbell, *ibid.*, **70**, 4123 (1948).

(6) See, for example, C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publ. Corp., New York, N. Y., 1941, pp. 194, 386.

(7) See, for example, W. Baker and C. Evans, *J. Chem. Soc.*, 372 (1938).

(8) C. F. Huebner and C. R. Scholz, U. S. Patent 2,654,761; 2,654,762.

(9) Melting points were determined by the capillary tube method in a stirred liquid bath and are uncorrected. We are indebted to Mr. L. Dorfman and associates for the microanalyses.

stirring. An additional 60 ml. of water was then added in one portion and stirring was continued for 20 minutes. The mixture was then allowed to stand until the liquid layers had separated, and the upper toluene layer was decanted and discarded. The lower aqueous slurry was then filtered with suction. The resulting cake of crude product was removed from the funnel, slurried with 250 ml. of water and the slurry was again filtered. The cake was then digested with 200 ml. of boiling 95% ethanol and the slurry was filtered hot, washed with cold 95% ethanol and dried in the vacuum oven at 55°. The resulting crude product weighed 66 g., m.p. 220–222° dec. The purity by titration with standard iodine solution was 95%. It was purified by solution in dilute aqueous sodium hydroxide, treatment with decolorizing carbon, filtration and reprecipitation by acidification with acetic acid. After filtration, washing with water and drying, the purified product weighed 62.3 g. (81.6% of theory), m.p. 228–230° dec.; purity by iodine titration, 98.2%.

5-Iodo-2-thiouracil Monosodium Salt Monohydrate.—A solution of 4.4 g. (0.11 mole) of sodium hydroxide in 89 ml. of water was heated to 65° and to it was added 35.4 g. (0.1 mole) of 5-iodo-2-thiouracil. The mixture was stirred at 65–70° until solution was complete. The solution was then treated with decolorizing carbon and the mixture was filtered hot. The filtrate was cooled slowly to 5° and the resulting crop of white crystals was collected on a Büchner funnel. It was washed with 10 ml. of ice-water, then with 15 ml. of ice-cold 95% ethanol and 20 ml. of ether. After drying for 18 hours in a vacuum oven at 50° the product had the composition of the monosodium salt monohydrate. The yield was 25.4 g. or 86.5%, m.p. 235° dec.; purity by iodine titration, 99.4% as monosodium salt monohydrate.

Anal. Calcd. for $C_4H_4N_2O_2ISNa$: N, 9.52; I, 43.16. Found: N, 9.61; I, 43.15.

Acidification of the mother liquor from the salt preparation yielded 1.65 g. (6.5%) of recovered 5-iodo-2-thiouracil. According to the same procedure, monosodium salts of the following compounds were prepared from the corresponding 5-iodo-2-thiouracils.

(1) 6-Methyl-5-iodo-2-thiouracil[4]: Obtained as the monohydrate; yield 66%, m.p. 233° dec.; purity by iodine titration, 100%. *Anal.* Calcd. for $C_5H_6N_2O_2ISNa$: N, 9.09; I, 41.20. Found: N, 9.02; I, 41.55.

(2) 6-Ethyl-5-iodo-2-thiouracil: yield 70%, m.p. 234–235° dec. *Anal.* Calcd. for $C_6H_6N_2OISNa$: N, 9.21; I, 41.74. Found: N, 9.34; I, 41.93.

(3) 6-*n*-Propyl-5-iodo-2-thiouracil: yield 83%, m.p. 215–216° dec. *Anal.* Calcd. for $C_7H_8N_2OISNa$: N, 8.81; I, 39.89. Found: N, 8.58; I, 40.02.

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Polyazobenzenes. II. Synthesis and Ultraviolet Absorption Spectra of Polyazobenzenes Containing Nitro, Amino and Hydroxyl Groups

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Polyazobenzenes containing nitro, amino and hydroxyl groups and polyazostilbenes were synthesized and their ultraviolet absorption spectra determined.

In order to study the effect of substituents on the absorption spectra of polyazobenzenes, a number of polyazobenzenes with nitro, amino and hydroxyl groups, and of azostilbenes have been synthesized and their absorption spectra determined.

Hartley[2a] and Brode[2b] reported that the absorption spectra of substituted azobenzenes, especially those having amino or hydroxyl groups in the *para* position, are considerably affected by light because of their photochemical *cis–trans* isomerism. The higher *p*-substituted polyazo homologs have similar phototropic properties. The phototropism of unsubstituted polyazobenzenes is so slow that the pure *trans* isomers could be obtained by chromatographic separation,[3] but the pure *trans* form of substituted polyazobenzenes could not be obtained by this method. In this study, therefore, the absorption spectra were determined on benzene solutions of the polyazobenzenes, which were kept in the dark and which were believed to contain mainly the *trans* forms.[2]

Experimental

The polyazobenzenes were synthesized as previously reported,[3] by condensation of nitronitrosobenzene with an amino compound, followed by reduction of the nitro group. Some polyazophenols were prepared by the coupling of diazotized amines with phenol. In the case of the azostilbenes, nitronitroso- or nitrosobenzene was condensed with aminostilbene in glacial acetic acid. All the compounds studied are listed in Tables I, II and III.

4-Phenylazo-4′-nitroazobenzene (II). (a) **From 4-Aminoazobenzene.**—Hot solutions of 3.8 g. of 4-aminoazobenzene in 20 ml. of glacial acetic acid and 3.2 g. of *p*-nitronitrosobenzene in 20 ml. of glacial acetic acid were mixed. After a few minutes, the mixture became nearly solid due to the formation of 4-phenylazo-4′-nitroazobenzene, which was recrystallized from glacial acetic acid and then from nitrobenzene. The orange crystals, m.p. 223.5–224.5°, weighed 4.2 g.

(b) **From 4-Nitro-4′-aminoazobenzene.**—A mixture of 0.5 g. of 4-nitro-4′-aminoazobenzene (m.p. 210–212°)[4] dissolved in 10 ml. of glacial acetic acid and 0.2 g. of nitrosobenzene in glacial acetic acid was kept at room temperature for two days. The crystals, recrystallized as above, weighed 0.4 g. A mixed melting point of both samples showed no depression.

Anal. Calcd. for $C_{18}H_{13}O_2N_5$: N, 21.13. Found: N, 21.09.

4-Phenylazo-4′-aminoazobenzene (VIII).—A suspension of 2.0 g. of the nitroazo compound (II) in 20 ml. of ethanol was heated on a water-bath with 5 ml. of 30% NaSH in 5 ml. of water for 15 minutes. After cooling, an equal volume of water was added and the solid material separated. After initial purification as the hydrochloride, the free amine was recrystallized from toluene to give orange crystals; 1.0 g., m.p. 186–187°.[5] They dissolved in concentrated sulfuric acid to give a red solution which turned violet.

Anal. Calcd. for $C_{18}H_{15}N_5$: N, 23.24. Found: N, 22.90.

4-Phenylazo-4′-(*p*-nitrophenylazo)-azobenzene (III) and 4-Phenylazo-4′-(*p*-aminophenylazo)-azobenzene (IX).—These compounds were synthesized from 4-phenylazo-4′-

(1) Department of Chemistry, Clark University, Worcester, Mass.

(2) (a) G. S. Hartley, *Nature*, **140**, 281 (1937); *J. Chem. Soc.*, 633 (1938); (b) W. R. Brode, J. H. Gould and G. M. Wyman, THIS JOURNAL, **74**, 4641 (1952).

(3) K. Ueno, THIS JOURNAL, **74**, 4508 (1952).

(4) German Patent 134,860; *Frdl.*, **16**, 873 (1900).

(5) The material reported by R. Nietzki and J. Diesterweg, *Ber.*, **21**, 2146 (1888), is quite different from our sample. Its structure is doubtful because it failed to give the expected 4-phenylazoazobenzene upon deamination.