

Institut für Pharmazeutische Chemie der Philipps-Universität, Marburg, Germany

1,3-Dibromo-5,5-dimethylhydantoin (DBH) as oxidant and precipitant for drug identification according to PH. EUR.

Analytical methods of pharmacopoeias with DBH in respect to environmental and economical concern, part 15¹

M. HILP

Elemental bromine serves as oxidant for the identification of propylthiouracil, 2-thiouracil and sulphur according to PH. EUR. 2002. Phenol is identified according to PH. EUR. 2002 with bromine water as the sparingly water-soluble 2,4,4,6-tetrabromo-2,5-cyclohexadiene-1-one. These tests can be performed better using 1,3-dibromo-5,5-dimethylhydantoin (DBH).

1. Introduction

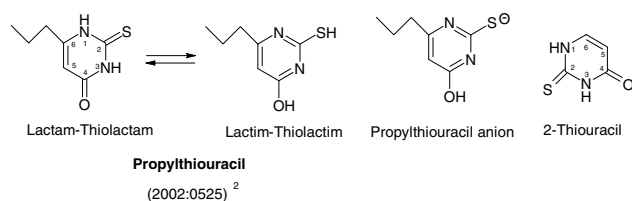
Bromine is a very toxic substance with a MAC value [2] of 0.7 mg/m³ resp. 0.1 ml/m³, whose vapours are still dangerous to life [3] in a concentration of 1 : 10,000. Bromine vapours violently irritate mucous membranes and cause severe eye damage, bronchospasms and pulmonary oedema depending on the concentration [4]. Liquid bromine rapidly attacks the skin and other tissues to produce irritation and necrosis. The burns are not only painful but also slow to heal [5]. Therefore, working with bromine requires an exhaust hood and appropriate precautions. PH. EUR. 2002 use bromine water as oxidant for the identification of propylthiouracil and sulphur and as precipitant for the identification of phenol.

DBH is in contrast to elemental bromine a stable and easy to handle crystalline compound [1, 6–19] and contains about 110% active bromine. It has been qualified in many cases for pharmaceutical analysis [1, 6–19].

2. Investigations and results

2.1. Identification using DBH as oxidant instead of bromine water

2.1.1. Propylthiouracil, 2-thiouracil



Propylthiouracil (PTU) and 2-thiouracil [20] exist in solid form as lactam-thiollactam tautomer, whereas in aqueous solutions the lactim-thiollactim form [21] is predominant. Propylthiouracil (PTU) dissolves as a weak acid with a pK_a-value of 8.2 in alkaline solutions, whereby the sulphhydryl group is deprotonated [21].

For the identification of PTU according to PH. EUR. 2002 heating with bromine water is required. The sulphur of thiourea is oxidized to sulphate by bromine. A barium chloride solution precipitates barium sulphate [20, 21]. After the addition of sodium hydroxide the precipitate shall not become violet. A violet colouring indicates non substituted thiouracils and uracils in 6 position.

The sulphur of the thiouracils is oxidized to sulphate already at room temperature by dissolution of the test sub-

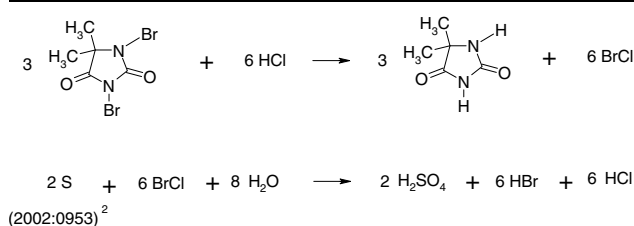
stance in acetic acid as well as in alkaline DBH solution. Barium chloride forms a precipitate of barium sulphate. For the colour test of unsubstituted thiouracils the test material has to be dissolved in alkaline DBH solutions and elemental bromine has to be liberated by acidification with hydrochloric acid. Boiling of the test solution is not necessary. The excess of bromine must be removed by boiling away or with 5-sulphosalicylic acid [7, 22] at room temperature. The violet colourant formed by unsubstituted thioureas is sparingly soluble in alkaline medium. The precipitate is dissolved and discoloured after acidification. A violet precipitate occurs again, when the acidic solution is alkalinized. The colour identification test of thiouracils is not sensitive, so that a content of about 25% in a mixture with propylthiouracil can still be detected, a content of 10% cannot be found [6].

2.1.2. Sulphur for external use

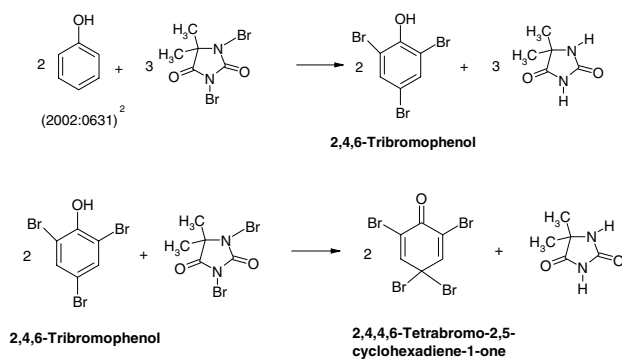
PH. EUR. 1997 boils sulphur with bromine water for identification (Scheme 1). Arising sulphuric acid is precipitated as barium sulphate [20].

Solid DBH or an alkaline DBH solution can replace bromine water. 2 M HCl is added and heated to boiling until the total excess of bromine resp. bromine chloride is expelled. A fermentation tube whose lower part is filled with 0.5 M sulfosalicylic acid solution (SSS) is put on the test tube to absorb the bromine vapours quantitatively. To work in an exhaust hood is not required. Acetic acid DBH solutions are unqualified. Colloid sulphur is formed, when cooled to room temperature, and is not retained by the filtration with paper filters. A turbidity exists already before the addition of barium chloride. Furthermore, it is impossible to work with a Bunsen burner and a free flame, when using DBH/HAC.

Scheme 1



Scheme 2



2.2. Identification using DBH as precipitant instead of bromine water

2.2.1. Phenol

PH. EUR. 1997 identifies phenol by converting it with bromine water to the sparingly soluble 2,4,4,6-tetrabromo-2,5-cyclohexadiene-1-one [24–26]. 2,4,6-Tribromophenol arises as intermediate. At first, a milky turbidity can be observed, which gives a voluminous weak yellow precipitate of the tetrabromo derivative after a short period (Scheme 2).

The test solution of phenol gives a more or less yellow coloured solution, when reacting with DBH/NaOH and following acidification with hydrochloric acid as well as with DBH/HAc and following dilution with water. However, if a DBH/NaOH solution is acidified with hydrochloric acid and the test solution of phenol is added afterwards, a milky turbidity arises, which yields a voluminous, weak yellow precipitate analogous to the reaction with bromine according to PH. EUR. 1997.

3. Discussion

The present investigations demonstrate, that all identification tests of PH. EUR. 2002 using elemental bromine resp. sodium hypobromite solutions can be performed advantageously by DBH, a stable and easy to handle compound [1, 6, 10, 11, 15–19]. The application of DBH is able to improve the prescriptions of the pharmacopoeia. The tests can also be performed in the semi-micro range and for spot-test analysis in the micro range. A lower consumption of chemicals is of economic benefit and is also a contribution to environmental protection.

4. Experimental

4.1. Chemicals and drugs

Acetic acid [64-19-7], min. 99.8% p.a., Riedel-de Haën art. 33209 = HAc; barium chloride [10326-27-9], p.a. Riedel-de Haën art. 31125; bromine [7726-95-6], extra pure DAB 6, Merck art. 1945; 1,3-dibromo-5,5-dimethylhydantoin = 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione [77-48-5], for synthesis Merck art. 803600 = DBH (for analytical purpose qualified); hydrochloric acid [7647-01-0], fuming, 37%, extra pure Merck, art. 100314; phenol PH. EUR. 1997, USP 24 [108-95-2], chem. extra pure, Riedel-de Haën art. 16017; propylthiouracil [51-52-5], PH. EUR. 1997, USP 2000, Kali-Chemie; sodium hydroxide, Rotipuran 99% [1310-73-2], Roth, art. 9356; sulphur [7704-34-9] for external use PH. EUR. 1997, USP 2000, purified, Merck art. 107983; 5-sulphosalicylic acid dihydrate [5965-83-3], extra pure, Merck, art. 689 = SSS; 2-thioracil [141-90-2], for synthesis, Merck Art. 821120

4.2. Solutions

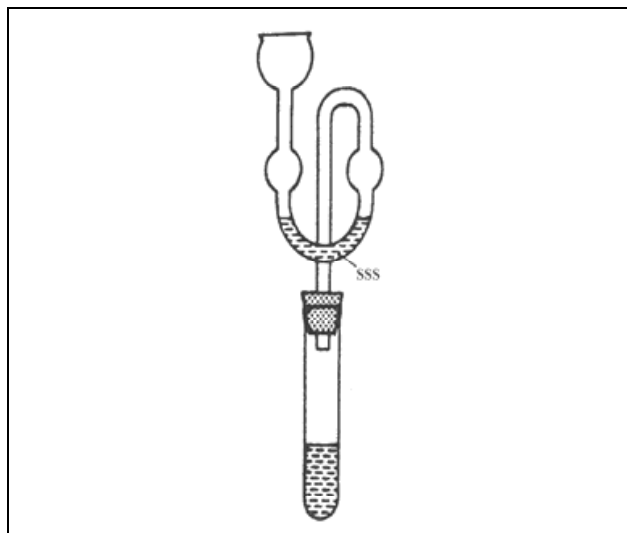


Fig.: Fermentation tube filled with SSS³

0.01 M DBH/HAc: 0.29 g (1 mmol) of DBH are dissolved in glacial acetic acid with stirring to 100 ml; 0.05 M DBH/0.5 M NaOH: 1.43 g (5 mmol) of DBH are dissolved with stirring in 0.5 M NaOH to 100.0 ml; 0.2 M SSS: 5.08 g (0.02 mol) of 5-sulphosalicylic acid are dissolved in water to 100 ml; 0.5 M SSS is prepared analogously.

4.3. Identification tests

For comparisons according to PH. EUR. and under other conditions see Hilp [6]. Solutions marked with R correspond to PH. EUR. In contrast to PH. EUR. molar concentrations are used preferably.

4.3.1. Identification of propylthiouracil and 2-thiouracil

About 9 mg (50 μmol) of propylthiouracil are dissolved in 5 ml of 0.05 M DBH/0.5 M NaOH and acidified with 1 ml of 5 M HCl. The arising brownish yellow solution is discoloured immediately with 0.5 ml of 0.2 M SSS. Add 1 ml of 0.1 M BaCl₂. A white precipitate is formed, whose colour does not change, when 1 ml of 10 M NaOH is added. In the presence of 2-thiouracil the precipitate becomes violet after alkalization.

4.3.2. Identification of sulphur

About 32 mg (1 mmol) of sulphur are added to 2.5 ml of 0.05 M DBH/0.5 M NaOH or to about 29 mg (0.1 mmol) of solid DBH and 2.5 ml of 2 M HCl. The expelled bromine is removed by boiling. A fermentation tube filled in the lower part with 0.5 M SSS (see Fig.) is put on the test tube to absorb the bromine vapours quantitatively. After filtration of the unconverted sulphur and addition of 0.5 ml of 0.1 M BaCl₂ a white precipitate is formed.

4.3.3. Identification of phenol

0.1 ml of 0.05 M DBH/0.5 M NaOH are mixed with 0.5 ml of 0.1 M HCl and then 0.1 ml 0.01 M test solution are added immediately. A milky turbidity arises, which is converted slowly to a voluminous precipitate, when allowed to stand.

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¹ Part 14: [1]

² Year of the monograph published in PH. EUR.: Monograph reference number

³ Modified according to Jander, G.; Blasius, E.; Strähle, J.; Schweda, E.: Einführung in das anorganisch-chemische Praktikum, 14. ed, p.67, S. Hirzel, Stuttgart, Leipzig, 1995

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Dr. Manfred Hilp
Institut für Pharmazeutische Chemie
der Philipps-Universität
Marbacher Weg 6
D-35032 Marburg
Hilp@mail.uni-marburg.de