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Determination of phenol and resorcinol using 1,3-dibromo-5,5-dimethylhydantoin (DBH) analogous to the Koppeschaar reaction

Analytical methods of pharmacopoeias with DBH in respect to environmental and economical concern, part 6[1]

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PH. EUR. 1997 determines phenol and resorcinol according to the Koppeschaar reaction using hepatotoxic and environmentally hazardous chloroform. Chlorinated hydrocarbons are not required when applying 1,3-dibromo-5,5-dimethylhydantoin (DBH). The reaction time for phenol can be reduced from 45 to 5 min. Blind values according to PH. EUR. 1997 result a systematic error of about −1.8%.

1. Introduction

The Koppeschaar reaction [2, 3] is known as the bromometric determination of aromatics such as phenol [2]. Thereby elemental bromine is liberated from a bromate solution of known content and an excess of bromide in strong acidic medium (Scheme 1).

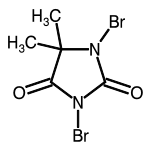
Scheme 1

$$BrO_3^- + 5\ Br^- + 6\ H_3O^+ \rightarrow 3\ Br_2 + 9\ H_2O$$

On the addition of potassium iodide excessive bromine is mostly converted to iodine, which is titrated afterwards with sodium thiosulphate.

This method is used predominantly in the pharmacopoeias for the determination of phenols (chlorocresol, phenol, phenolsulfonphthalein, resorcinol PH. EUR. 1997, thymol DAB 9, USP/NF 2000, hydroxyethyl salicylate PH. EUR. Suppl. 1998) and aromatic amines (benzocaine 2 AB/DDR, sulfacetamide sodium, sulfaguanidine, sulfisomidine, sulfathiazole DAB 7/DDR).

1,3-Dibromo-5,5-dimethylhydantoin (DBH), a stable and easy to handle crystalline compound, has been qualified in many cases for pharmaceutical analysis [1, 4–8]. A strong acidic pH value (phenol PH. EUR. 1997 about 1.3) is required to liberate bromine according to the Koppeschaar reaction [2, 3]. DBH can be used in an acetic acid solution instead of a bromide-bromate solution and reacts at an essentially higher, for iodimetry more suitable pH value [9] of about 2–3. Furthermore potassium bromate and potassium bromide are only soluble in water. Problems arise with sparingly water-soluble analytes and conversion products such as phenol resp. resorcinol. On the other hand DBH is soluble in acetic acid and diluted acetic acid [1, 4–8]. Numerous publications [compare 4, 10] show that it is possible to titrate directly analytes, which can be brominated with DBH in acetic acid as titrant. However for practicable reasons an aqueous standard solution e.g. sodium thiosulphate is preferred to a titrant in acetic acid. Consequently the iodometric determination of a DBH-excess is more suitable. Moreover high concentrated bromine solutions are formed, when determining blind values according to PH. EUR. 1997 after the bromide-bromate solution is acidified with hydrochloric acid. A systematic error is observed (see 2.1. phenol). In contrast large amounts of elemental bromine are only released, if DBH/HAc is intensively exposed to light. Otherwise it has to be mentioned that the titer of a potassium bromate standard solution is significantly more stable than those of DBH solutions [4, 6].



DBH

2. Investigations, results and discussion

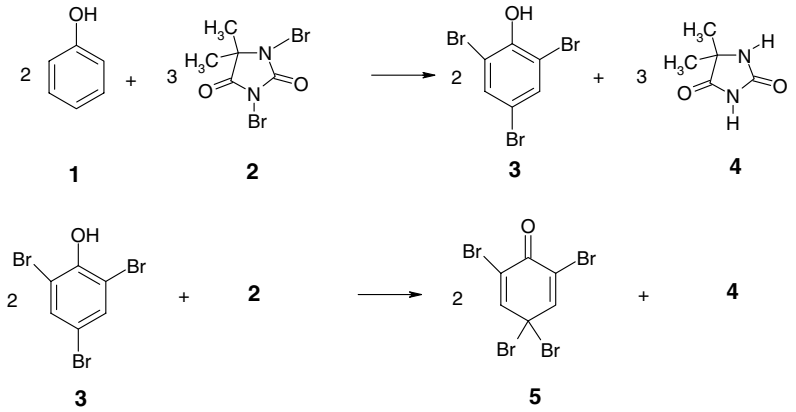
Phenol and resorcinol were selected from the large amount of analytes, which can be determined according to Koppeschaar, because PH. EUR. 1997 uses hepatotoxic and environmentally hazardous chloroform for the determination of these two substances.

2.1. Phenol

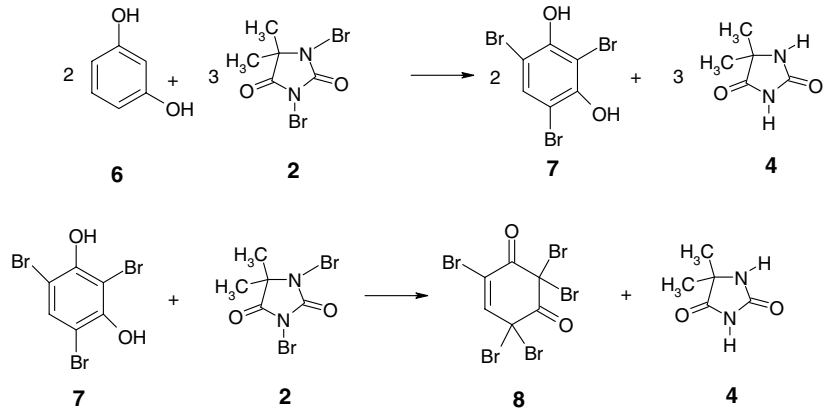
Phenol is converted with a bromide-bromate solution, when performing the determination according to PH. EUR. 1997 [2, 11]. After acidification with concentrated hydrochloric acid the analytical solution is allowed to stand for 30 min with occasionally swirling and is than allowed to stand for further 15 min. Tribromophenol (**3**) and 2,4,4,6-tetrabrom-2,5-cyclohexadiene-1-one (**5**) [12, 13] are precipitated (Scheme 2). To improve the recognition of the end point PH. EUR. 1997 demands the addition of chloroform, because the arising precipitate is not completely discoloured [11].

According to PH. EUR. 1997 the determination of blind values is required. Performing the blank titration in the same manner as the analysis without the analyte a systematic error of about −1.8% is obtained. In the absence of phenol a concentrated bromine solution arises after acidification of 0.0167 M bromide-bromate. Bromine vapours get lost, when the ground-glass-stoppered flask is opened for the addition of potassium iodide. Moreover, when performing the titration, sodium thiosulphate can partly be oxidized to sodium sulphate by bromine vapour existing above the solution of the analysis. However, if potassium iodide is added to the bromate bromide solution before acidification with concentrated hydrochloric acid, significantly higher blind values are found. DAB 9 has not demanded the determination of blind values. Potassium

Scheme 2



Scheme 3



bromate is a primary standard for volumetric solutions according to PH. EUR. 1997. For the manufacture of the 0.0167 M bromide-bromate exact weighing of potassium bromate is prescribed. Thus, the determination of blind values is not reasonable. Sodium thiosulphate has to be standardized according to the pharmacopoeia with 0.033 M potassium bromate or preferably with potassium iodate [4, 5].
The addition of chloroform is not required, if DBH is used in acetic acid. The reaction time can be reduced from 45 min to 5 min. If the concentration of acetic acid is too low 2,4,4,6-tetrabrom-2,5-cyclohexadien-1-on (**5**) [12, 13] is precipitated as fine, pale yellow coloured and analytical pure needles.
The analytical values of phenol using DBH are found with a relative standard deviation of 0.13% ($\bar{x} = 100.3\%$, $n = 7$).

2.2. Resorcinol

In contrast to phenol, resorcinol [14, 15] has been determined already in DAB 7 (1968) by addition of chloroform. Bromine liberated in strong acidic medium from bromate and bromide reacts with resorcinol to tribromoresorcinol (**7**) (Scheme 3) and partly to pentabromocyclohexene-1,3-dione **8** [15–18]. Compound **8** is converted to iodine with added potassium iodide and thus does not affect the titration.
In the case of resorcinol using DBH/HAc the addition of acetic acid is not required. A mean error of −0.3% ($n = 7$, $\bar{x} = 99{,}7$, $s_{rel} = 0.18$) for a reaction time of 15 min was found only with resorcinol freshly sublimated in vacuo. The values of the same sample were about 1% ($n = 7$, $\bar{x} = 98{,}7$, $s_{rel} = 0.25$) lower after a reaction time of only 5 min. The reaction time cannot be reduced by addition of acetic acid. A not purified sample yields a mean error of −1.0% (15 min) resp. −2.3% (5 min). Using TLC PH. EUR. 1997 restricts the content of related substances to 0.5%. A 1% loss on drying is permitted.
A freshly sublimated sample of resorcinol yields according to PH. EUR. 1997 a mean value of 100,9% ($n = 8$, $s_{rel} = 0.19$) with stirring, protection from light [15] and a prescribed reaction time of 15 min. In contrast to phenol PH. EUR. 1997 demands no blank titration. Both determinations of PH. EUR. are carried out by different prescriptions.

3. Experimental

3.1. Reagents

Acetic acid [64-19-7], min. 99.8% p.a., Riedel-de Haën art. 33209 = HAc; chloroform, trichloromethane [67-66-3], extra pure, DAB 9, Merck art. 159129; hydrochloric acid [7647-01-0], fuming, 37%, extra pure Merck, art. 100314; phenol, Phenolum PH. EUR. 1997, USP 24 [108-95-2], chem. extra pure, Riedel-de Haën art. 16017; purified by micro distillation (18 mbar, 90 °C); potassium bromate [7758-01-2] extra pure FCC, Merck

art. 104914; potassium bromide [7758-02-3], extra pure DAB, PH. EUR, BP, Merck art. 104900; potassium iodide 99,5%, p.a., Roth, D-76185 Karlsruhe, art. 6750; resorcinol, Resorcinolum PH. EUR. 1997, USP 2000 [108-46-3], chem. pure, Riedel-deHaën art. 16101, purified by sublimation (0,01 mbar, 100 °C, colourless needles); sodium thiosulfate pentahydrate 98,5%, Roth art. 8649; starch soluble extra pure Erg. B. 6, Merck, art. 1253.

3.2. Solutions

0.05 M DBH/HAc: 3.57g (0.0125 mol) of DBH are dissolved in glacial acetic acid with stirring to 250 ml; Starch solution, iodide-free according to PH. EUR. 1997 without HgI_2, is used and stable at a temperature of about 4 °C for six weeks. Avoid a temperature below 0 °C.

3.3. Assays

3.3.1. Determination of phenol

3.3.1.1. Determination of blind values according to PH. EUR. 1997

Hydrochloric acid is added before potassium iodide.
0.1 M $Na_2S_2O_3$: $\bar{x} = 49.20$ ml; $n = 7$; $s_{rel} = 0.45\%$.

3.3.1.2. Modified determination of blind values

Potassium iodide is added before hydrochloric acid.
0.1 M $Na_2S_2O_3$: $\bar{x} = 49.82$ ml; $n = 7$; $s_{rel} = 0.048\%$.
(Comparison to 3.3.1.1.: F-Test $\alpha = 2.9 \cdot$ E-5; t-Test, two-sided, $\alpha = 2.3 \cdot$ E-4).

3.3.1.3. Determination of phenol using blind values according to PH. EUR. 1997

Found: $n = 8$; $\bar{x} = 98.2\%$ phenol; mean error $= -1.83\%$; $s_{rel} = 0.20\%$.

3.3.1.4. Determination of phenol using modified blind values

Found: $n = 8$; $\bar{x} = 100.2\%$ phenol; mean error $= 0.15\%$; $s_{rel} = 0.22\%$.
(Comparison to 3.3.1.3.: F-Test $\alpha = 0.79$; t-Test, two-sided, $\alpha = 7.1 \cdot$ E-13).

3.3.1.5. Determination of phenol using DBH / HAc

About 470 mg (5×10^{-3} mol) of phenol, accurately weighed, are diluted with H_2O to 250.0 ml. 25.00 ml of the solution (5×10^{-4} mol) are mixed with 10.0 ml of glacial acetic acid and 20.00 ml of 0.05 M DBH/HAc in a ground-glass-stoppered Erlenmeyer flask and allowed to stand in the dark for 5 min. After addition of 5 ml of 1 M KI the expelled iodine is titrated with 0.1 M $Na_2S_2O_3$/starch solution, iodide-free. A blind value is determined with 25 ml of H_2O, 10.0 ml of glacial acetic acid and 20.00 ml 0.05 M DBH/HAc without a waiting time. 1 ml of 0.1 M $Na_2S_2O_3$ (difference of blind value and analytical value) is equivalent to 1.569 mg of C_6H_6O.
Waiting time after addition of DBH:
immediately: $n = 7$; $\bar{x} = 99.2\%$ phenol; mean error $= -0.77\%$, $s_{rel} = 7.3\%$.
5 min: $n = 7$; $\bar{x} = 100.3\%$ phenol; mean error $= -0.3\%$; $s_{rel} = 0.13\%$.
(F-Test $\alpha = 2.3 \cdot$ E-10; t-Test, one-sided, $\alpha = 3.9 \cdot$ E-3).
15 min: $n = 8$; $\overline{X} = 100.5\%$ phenol; mean error $= -0.77\%$; $s_{rel} = 0.18\%$.
(5 zu 15 min: F-Test $\alpha = 0.44$; t-Test, two-sided, $\alpha = 5.2 \cdot$ E-3;
5 min zu 3.3.1.4: F-Test $\alpha = 0.19$; t-Test, two-sided, $\alpha = 0.35$).

3.3.1.6. 2,4,4,6-Tetrabromo-2,5-cyclohexadiene-1-one [20244-61-5]

2,4,4,6-Tetrabromo-2,5-cyclohexadiene-1-one is seperated after about 5 min as pale yellow coloured needles (170 mg, 83%), when mixing 25 ml of the analytical solution (0.02 M phenol) and 20 ml of 0.05 M DBH/HAc.
$C_6H_2Br_4O$ (409.7) calcd. C 17.59, H 0.49, Br 78.01, active Br 39.01; found C 17.55, H 0.55, Br 78.18, active Br 39.03 (freshly prepared substance, the content of bromine is diminished when stored).

3.3.1.7. Determination of active bromine

About 41 mg (10^{-3} mol) of 2,4,4,6-tetrabromo-2,5-cyclohexadiene-1-one are dissolved in 10 ml of glacial acetic acid. After addition of 5.0 ml of 0.2 M KI the expelled iodine is titrated with 0.02 M $Na_2S_2O_3$/starch solution, iodide-free. 1 ml of 0.02 M $Na_2S_2O_3$ is equivalent to 1.598 mg of active bromine.

3.3.2. Determination of resorcinol

3.3.2.1. Determination of resorcinol mit DBH/glacial acetic acid

About 551 mg (5×10^{-3} mol) of resorcinol, accurately weighed, are diluted with H_2O to 250.0 ml. 25.00 ml the solution (5×10^{-4} mol) are mixed with 20.00 ml of 0.05 M DBH/HAc in a ground-glass-stoppered Erlenmeyer flask and allowed to stand in the dark for 15 min. After addition of 5 ml of 1 M KI the expelled iodine is titrated with 0.1 M $Na_2S_2O_3$/starch solution, iodide-free. A blind value is determined with 25 ml of H_2O, and 20.00 ml 0.05 M DBH/HAc without a waiting time. 1 ml of 0.1 M $Na_2S_2O_3$ (difference of blind value and analytical value) is equivalent to 1.835 mg of $C_6H_6O_2$.
Waiting time after addition of DBH:
5 min: $n = 7$; $\bar{x} = 98.7\%$ resorcinol; mean error $= -1.3\%$; $s_{rel} = 0.25\%$.
15 min: $n = 7$; $\bar{x} = 99.7\%$ resorcinol; mean error $= -0.27\%$; $s_{rel} = 0.18\%$.
(5 to 15 min: F-Test $\alpha = 0.30$; t-Test, two-sided, $\alpha = 9.5 \cdot$ E-5).

3.3.2.2. Determination of resorcinol according to PH. EUR. 1997

Found: $n = 7$; $\bar{x} = 100.9\%$ resorcinol; mean error $= +0.89\%$; $s_{rel} = 0.19\%$.
(3.3.2.1., 15 min to 3.3.2.2. F-Test $\alpha = 0.85$; t-Test, two-sided, $\alpha = 7.5 \cdot$ E-6).

3.4. Statistical methods

Evaluations were performed with Excel 97 on an IBM-compatible PC running under Windows 95. The built-in F- and t-test routine of Excel 97 has been used.

[1] Part 5 see [1]

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References

1 Hilp, M.: Pharmeuropa, in print
2 Koppeschaar, W. F.: Fresenius' Z. Anal. Chem. **15**, 233 (1876)
3 Ebel, S.; Roth, H. J.: Lexikon der Pharmazie, p. 380, G. Thieme, Stuttgart, New York 1987
4 Hilp, M.: Habil. thesis, Marburg (2000)
5 Hilp, M.: Fresenius' J. Anal. Chem. **360**, 184 (1998)
6 Hilp, M.: Pharmazie **53**, 321 (1998)
7 Hilp, M.; Senjuk, S.: J. Pharm. Biomed. Anal. in print
8 Hilp, M.: Pharmazie **56**, 548 (2001)
9 Kolthoff, I. M.; Sandell, E. B.; Meehan, E. J.; Bruckenstein, St.: Quantitative Chemical Analysis, 4. Ed., p. 844, Collier-Macmillan, London 1969
10 Radhamma, M. P.; Indrasenan, P.: Indian J. Chem. Sect. A **23**, 794 (1984)
11 Hartke, K.; Hartke, H.; Mutschler, E.; Rücker, G.; Wichtl, M.: Arzneibuch- Kommentar, Wissenschaftliche Erläuterungen zum Europäischen Arzneibuch, 1. suppl., P36 p. 2., Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, Govi- Verlag – Pharmazeutischer Verlag GmbH, Eschborn 1993
12 Benedikt, R.: Justus Liebigs Ann. Chem. **199**, 130 (1879)
13 Sørensen, A. M.; Jerslev; B.: Acta Chem. Scand. **22**, 319 (1968)
14 Salvi, Y. E.: Rev. fac. cienc. quim. (Univ. nacl. La Plata) **25**, 49 (1950), C. A. **49**, 923c (1955)
15 Lit. 13: 5. suppl. R8 p. 2 (1995)
16 Stenhouse, J.: Justus Liebigs Ann. Chem. **163**, 174 (1872)
17 Liebermann, C.; Dittler, A.: Justus Liebigs Ann. Chem. **169**, 252 (1873)
18 Usaevich, Y. Y.; Vekshina, L. I.: Pharm. Chem. J. (Engl. Transl.), **11**, 1612 (1977); Khim. Farm. Zh. **11**, 30 (1977), C.A. **88**, 104828j (1978)

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