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Determination of propylthiouracil using 1,3-dibromo-5,5-dimethylhydantoin (DBH) Analytical methods of pharmacopeias with DBH in respect to environmental and economical concern: part 9☆

Manfred Hilp *

Institut für Pharmazeutische Chemie der Philipps-Universität, Marbacher Weg 6, D-35032 Marburg, Germany

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Abstract

USP 2000 [The United States Pharmacopeia, Rockville USA, 24th ed., 2000, pp. 1436] and PH. EUR. 1997 [European Pharmacopoeia, third ed., Council of Europe, Strasbourg, 1997, p. 1401] determine propylthiouracil using neutralization titration, whereby 0.1 M silver nitrate and twice boiling is necessary. With the application of 1,3-dibromo-5,5-dimethylhydantoin (DBH), the assay of propylthiouracil can be performed easily, faster and friendlier to environment. A mean deviation of 0.03% and a relative standard deviation of 0.3% are obtained. 5-Bromo-6-propyluracil is formed, when propylthiouracil is determined with DBH.

Keywords: DBH, dibromantin; 1,3-Dibromo-5,5-dimethylhydantoin, 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione [77-48-5] propylthiouracil [51-52-5]; 5-Bromo-6-propyluracil

1. Introduction

USP 2000 [1] and PH. EUR. 1997 [2] determine propylthiouracil using neutralization titration [3]. Thereby, the sample for analysis has to be dissolved in less than an equivalent amount of standardized 0.1 M NaOH by shaking and boiling. An excess of 0.1 M $AgNO_3$ is added and the solution is boiled again during 5 min. Propylthiouracil is transformed into the insoluble disilver salt, whereby two protons are liberated. After cooling to room temperature, the titration has to be performed with 0.1 M NaOH and potentiometric indication. The content of propylthiouracil is calculated with the applied standard solution for the dissolution of the sample and the consumption arising by the titration. Silver nitrate solutions are not only expensive, but also require costs for disposal [4,5]. Furthermore, assays should be

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* Tel.: +49-6421-2825814; fax: +49-6421-2826652.
E-mail address: hilp@mailer.uni-marburg.de (M. Hilp).

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performed without boiling. Therefore, the assay of USP 2000 and PH. EUR. 1997 is obsolete in respect to environmental and economical concern. The aim of the investigations is to improve the determination of the pharmacopeias for the pure substance of the antithyroid drug propylthiouracil using DBH. DBH is in contrast to elemental bromine a stable and easy to handle crystalline compound [4–11]. DBH has been qualified for the determination of iodide [4–6], iodine values [4,7], phenol, resorcinol [4,8], the iodine content of organic compounds according to Schöniger [4,9] and identification tests of PH. EUR. 1997 [4,10,11].

2. Experimental

2.1. Instrumentation

2.1.1. Elementary analysis

CH, according to F. Salzer, CWH-Labormatic-Wösthoff, N, CHN-Analyzer 185, Hewlett-Packard, S according to Schöniger; MS, Vakuum Generators VG 7070H; NMR, Jeol Eclipse + 500, s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, ^{1}H-NMR, 500 MHz, tetramethyl silane (TMS, 0.00 ppm as internal standard); ^{13}C-NMR, 125.65 MHZ, proton broad band decoupling, applied deuterated solvent as internal standard.

2.2. Materials

Acetic acid [64-19-7] min 99.8% p.a., Riedel-de Haën art. 33209, HAc; 1,3-dibromo-5,5-dimethylhydantoin (DBH), 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione [77-48-5], for synthesis Merck art. 803600, DBH (for analytical purpose qualified); iodine, Iodum PH. EUR. 1997, USP 2000 [7553-56-2], Riedel-deHaën art. 3002; potassium iodate [7758-05-6] p.a., volumetric standard, Merck art. 5053; potassium iodide [7681-11-0] ≥ 99.5%, p.a., Roth, D-76185 Karlsruhe, art. 6750; propylthiouracil [51-52-5], Propylthiouracilum PH. EUR. 1997, USP 2000, Kali-Chemie, $C_7H_{10}N_2OS$ (170.2) calculated C 49.39, H 5.92, N 16.46, S 18.84, found C 49.42, H 5.82, N 16.39, S 18.80; sodium acetate anhydrous [127-09-3], NaAc, p.a., Merck art. 106268; sodium hydroxide, Rotipuran 99% [1310-73-2], Roth, art. 9356; sodium thiosulfate pentahydrate [7772-98-7] > 98.5%, Roth art. 8649; starch soluble [9005-84-9] extra pure, Merck art. 101253; sulfuric acid [7664-93-9], p.a. conc., 95–97%, Riedel-deHaën art. 30743.

2.3. Solutions

0.05 M DBH–HAc—1.43 g (5 mM) of DBH are dissolved with stirring in glacial acetic acid to 100.0 ml; 0.05 M DBH–0.5 M NaOH—1.43 g (5 mM) of DBH are dissolved with stirring in 0.5 M NaOH to 100.0 ml; 1/60 M KIO_3—3.567 g of potassium iodate p.a., volumetric standard, are diluted to 1000.0 ml; 0.25 M NaAc/10 M HAc, pH-buffer about 3.0–20.5 g of anhydrous sodium acetate are dissolved in 570 ml of glacial acetic acid and diluted to 1000.0 ml with water; 0.1 M $Na_2S_2O_3$ is prepared according to PH. EUR. 1997 and standardized with 20.00 ml of 1/60 M KIO_3, 10.0 ml of 0.25 M NaAc/10 M HAc, 5.0 ml of 1 M KI and 0.5 ml of starch solution, iodide-free (PH. EUR. 1997); Starch solution, iodide-free PH. EUR. 1997, without HgI_2, is stable at a temperature of about 4 °C for about 6 weeks. It is necessary to avoid a temperature below 0 °C.

2.4. Assays

2.4.1. Iodometric determination of propylthiouracil

About 68 mg (0.4 mM) of propylthiouracil, accurately weighed, are dissolved in 10 ml of aqueous, 2.5% NaOH. 50.0 ml of 0.05 M iodine are added and allowed to stand at room temperature under light protection for 5 resp. 30 min. The iodine is titrated with 0.1 M $Na_2S_2O_3$ after acidification with 2.5–3 ml of 1 M H_2SO_4 to obtain a pH value of about 4.0, and after addition of 5 ml of 1 M KI. At the end of the titration, 0.5 ml of starch solution and iodide-free PH. EUR. 1997, are added. A blank value has to be determined using 3.0 ml of 1 M H_2SO_4. 1 ml of 0.1 M $Na_2S_2O_3$ [difference of blank value − analytical value] is equivalent to 2.128 mg of $C_7H_{10}N_2OS$.

Weight of sample—68.22–69.41 mg; waiting time, 5 min, found, 42.1; 41.1%; 30 min, 41.5% propylthiouracil.

2.4.2. Determination of propylthiouracil using DBH in alkaline solution

About 68 mg (0.4 mM) of propylthiouracil, accurately weighed, are dissolved in 20.0 ml of 0.05 M DBH/0.5 M NaOH and allowed to stand for a waiting time as below-mentioned. The liberated iodine is titrated with 0.1 M $Na_2S_2O_3$ (starch solution, iodide-free PH. EUR. 1997) after addition of 5 ml of 1 M KI and acidification with 10.0 ml of glacial acetic acid to pH value of 3.2 up to 3.5. A blank value has to be determined.

About 1 ml of 0.1 M $Na_2S_2O_3$ [difference of blank value − analytical value] is equivalent to 2.128 mg of $C_7H_{10}N_2OS$.

Weight of sample—67.69–69.32 mg; waiting time; immediately, 72.7%; 5 min, 73.1%; 15 min, 77.7%; 30 min, 80.9% propylthiouracil; 25 ml instead of 20.0 ml of 0.05 M DBH/0.5 M NaOH (0.5 mol/l), 30 min, 84.7% propylthiouracil.

2.4.2.1. Determination of propylthiouracil using DBH in acidic solution. About 42.5 mg (2.5 mmol) of propylthiouracil, accurately weighed, are dissolved in 10 ml of glacial acetic acid using an iodine flask of 200 ml. Fifty ml of 2 M HCl and 20.0 ml of 0.05 M DBH/HAc are added, and the mixture is allowed to stand for 5 min in the dark. The expelled iodine is titrated with 0.1 M $Na_2S_2O_3$ after addition of 5 ml of 1 M KI. At the end of the titration 0.5 ml of starch solution, iodide-free PH. EUR. 1997, is added.

Determination of blank values. About 25 ml of H_2O and 20.0 ml of 0.05 M DBH/HAc are mixed. The titration is performed immediately after addition of 5 ml of 1 M KI as mentioned above. About 1 ml of 0.1 M $Na_2S_2O_3$ [difference of blank value − analytical value] is equivalent to 1.702 mg of $C_7H_{10}N_2OS$.

Demanded (USP 2000 [1], PH. EUR. 1997 [2]): 98.0–100.5% propylthiouracil.

Waiting time—5 min, weight of sample—40.96–43.50 mg.

Found, 100.4; 100.1; 100.5; 99.9; 100.2; 99.9; 99.6; 99.6% propylthiouracil; $n = 8$; $\bar{x} = 100.0$; bias (%) = 0.03; R.S.D. (%) = 0.34.

Waiting time—30 min, weight of sample—40.30–42.02 mg; found, 100.0; 100.5; 99.8%; $\bar{x} =$ 100.1% propylthiouracil.

2.4.2.2. Determination of propylthiouracil using DBH in acidic solution and varying weights of samples. (Table 1).

Table 1
Determination of propylthiouracil using DBH in acidic solution and varying weights of samples

Weight of sample (mg)	0.05 M DBH/HAc (ml)	Propylthiouracil (%)
8.19	2.450	101.8
9.23	2.730	100.7
15.68	4.695	101.9
17.73	5.285	101.5
24.60	7.235	100.1
25.77	7.615	100.6
32.93	9.665	99.9
36.63	10.69	99.3
42.65	12.38	98.8
42.82	12.52	99.5
49.35	14.29	98.6
50.31	14.73	99.7

2.5. Preparation of 5-bromo-6-propyluracil

Aboout 170 mg (1 mmol) of propylthiouracil are dissolved in 25 ml of glacial acetic acid and mixed with 100 ml of 2 M HCl and 55 ml of 0.05 M DBH/HAc (equivalent to 5.5 mmol of bromine) [12]. 2 ml of 1 M NaOH are added and evaporated to about 5 ml. About 151 mg (65%) of 5-bromo-6-propyluracil is obtained as colorless crystals, if 10 ml of H_2O is slowly added to the yellow colored residue.

M.p., 222 °C (H_2O). The substance is slightly soluble in methanol, ethanol, acetone and dioxan, freely soluble in DMSO and poorly soluble in H_2O or chloroform.

$C_7H_9BrN_2O_2$ (233.1) calculated C 36.07, H 3.89, Br 34.28, N 12.02, found C 36.15, H 3.88, Br 34.35, N 11.82; ^{1}H-NMR (DMSO-d_6, 45 °C, 500 MHz), δ_H (ppm) = 0.94 (t, $^3J = 7.3$ Hz, CH_2–CH_2–CH_3), 1.60 (m, CH_2–CH_2–CH_3), 2.51 (t, $^3J = 7.6$ Hz, CH_2–CH_2–CH_3, partly overlaid from DMSO signals), 11.14 (s, NH) 11.33 (s, NH); ^{13}C-NMR (DMSO-d_6, 45 °C, 500 MHz), δ_C (ppm) = 18.37 (CH_2–CH_2–CH_3), 25.30 (CH_2–CH_2–CH_3), 39.50 (CH_2–CH_2–CH_3), 99.99 (C-5), 155.4 (C-6), 159.4 (C-3) 165.1 (C-1); IR

(KBr), ν (per cm) = 3226m, 3156w, 3074w, 2963m, 2932w, 2872w, 2828w, 1727s, 1700s, 1679s, 1617s, 1494w, 1465w, 1452w, 1426m, 1349w, 1328w, 1294w, 1233w, 1114w, 1080m, 1043w, 995w, 894w, 768m, 750w, 747w, 741w, 735w, 730w, 724m, 721w, 718w, 711w, 703w, 696w, 689w, 681w, 677w, 674w, 671w, 664w, 662w, 653w, 626w, 586w, 537m, 512w, 450w, 434m; MS (EI, 70 eV, 200 °C), m/z (%) = 234 ($^{81}BrM^+$, 83), 232 ($^{79}BrM^+$, 84), 219 (–$^{\bullet}$NH, 4), 217 (–$^{\bullet}$NH, 4.), 207 (6), 206 (–CO, 97), 204 (–CO, 100), 190 (3), 188 (3), 176 (7), 163 (–HNCO [13], 43) 161 (–HNCO [13], 44), 160 (2), 153 (–$^{\bullet}$Br, 4), 148 (2), 146 (2), 126 (6), 125 (7), 122 (9), 120 (10), 118 (2.0) 111 (10), 99 (5), 85 (1), 83[1] ([13], 7), 70 (HN=C^+–C_3H_7 [13], 26), 68 (4), 67 (2), 55, (2), 54 (2), 42 ($C_3H_6^{\bullet+}$, 5).

2.6. Statistical methods

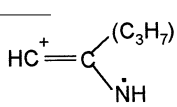
Evaluations and graphics have been performed with EXCEL 97 on an IBM-compatible PC running under WINDOWS 95. The built-in F- and t-test routines of EXCEL 97 have been used.

3. Results and discussion

3.1. Iodometric determination of propylthiouracil

The iodometric determination of propylthiouracil, described by Ebel [14], may be a simple and appropriate procedure for a pharmacopeia assay. According to this literature and the unprecise description in Chem. Zentralblatt [15] methylthiouracil can be determined in an 2.5% aqueous NaOH at room temperature and with a waiting time of only 5 min. According to my investigations, [4] propylthiouracil results only 41–42% of the expected value even after a waiting time of 30 min.

The original literature [16], written in Hungarian language and cited in Chem. Zentralblatt [15], shows, that 30 min heating on a boiling water bath and 10% NaOH are necessary for the quantitative determination of methylthiouracil. These results are confirmed in the extensive investigation from Wojahn and Wempe [17], likewise published in 1952, concerning methyl- and propylthiouracil. These authors describe 45 min heating on a boiling water bath. Thus, due to the heating and the volatility of iodine, the iodometric determination of propylthiouracil is not recommendable as an assay for a pharmacopeia.

[1] 

3.2. Determination using DBH in alkaline medium

Investigations using 0.05 M DBH/0.5 M NaOH instead of a standard iodine solution in alkaline medium have been performed for the quantitative determination of propylthiouracil. About 72.7–84.7% of propylthiouracil [4] is found at room temperature depending on the waiting time and concentration of DBH.

3.3. Determination using DBH in acidic solution

The bromatometric determination of methyl- and propylthiouracil applying $KBrO_3$/KBr in hydrochloric acidic solution consumes bromine not only for the oxidation of the sulfur, but also for the bromination of the formed uracil [18–20]. According to the conditions of the reaction, 5-bromo-6-methyl- [21,22] resp. 5-bromo-6-propyluracil (**1**) [12] and 5,5-dibromo-6-hydroxy-6-methyl- [21,23] resp. 5,5-dibromo-6-hydroxy-6-propyluracil (**2**) are generated. Whereas eight redox equivalents are required for the oxidation of the sulfur, ten equivalents are consumed for the formation of the 5-bromouracils and 12 equivalents for the formation of the 5,5-dibromo-6-hydroxyuracils (Fig. 1).

5,5-Dibromo-6-hydroxyuracil results with potassium iodide the bromouracil 1 and iodine. This reaction proceeds slowly in acetic acid solution and is accelerated in the presence of mineral acids [19]. According to USP 1950 (propylthiouracil tablets in the presence of lactose) [24], the excess of bromine and 5,5-dibromo-6-hydroxyuracil 2 are converted with potassium iodide to iodine, which is titrated with sodium thiosulfate. It is reported in the literature [19] that with this

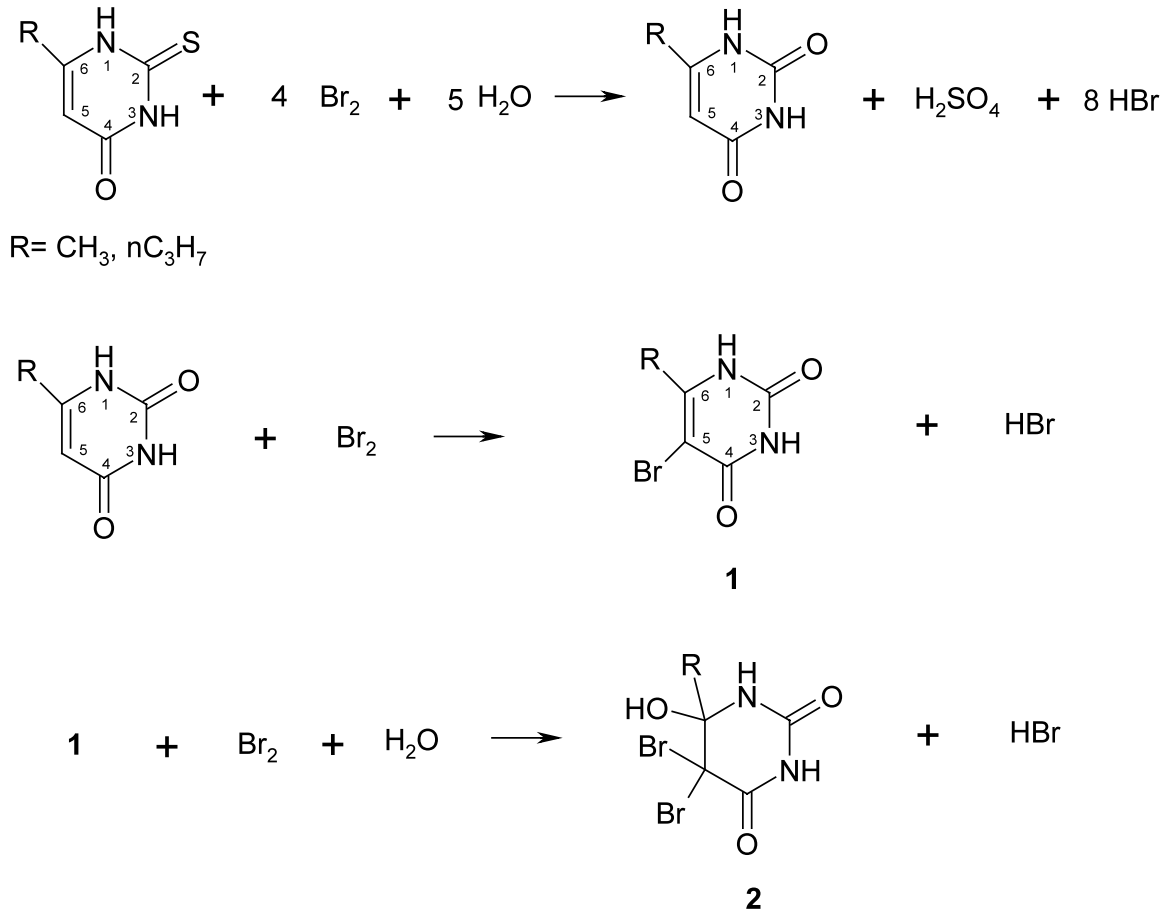


Fig. 1. Reaction of propylthiouracil with bromine.

procedure significantly too high values (108–116%) are obtained. Thus, Wojahn and Wempe [18,19] recommend to remove the excess of bromine with a surplus of 0.05 M sodium arsenite, whereupon the 5,5-dibromo-6-hydroxyuracil (**2**) does not react. The surplus of sodium arsenite is determined afterwards by titration with 0.0167 M $KBrO_3$ and *p*-ethoxychrysoidine hydrochloride as indicator. In my opinion, this assay is too complicated and obsolete in ecological concern due to the application of a toxic and carcinogenic sodium arsenite solution.

Propylthiouracil is slightly soluble in H_2O, ethanol and other solvents. Therefore, the analytical sample is dissolved in sodium hydroxide solution performing the above described assays. However, propylthiouracil is fairly soluble in glacial acetic acid. After a waiting time of only 5 min before the addition of potassium iodide, the liberated iodine can be titrated with sodium thiosulfate, if the acetic acidic solution of propylthiouracil is mixed with diluted hydrochloric acid and DBH/HAc. The values, obtained by this method have been found within the tolerance of USP 2000 [1] and of PH. EUR. 1997 [2]. The consumption amounts ten redox equivalents. The precision and the accuracy are remarkable ($n = 8$; $\bar{x} = 100.0$; bias (%) = 0.03; R.S.D. (%) = 0.34).

Fig. 2 shows, that propylthiouracil can be determined in a broad range.

5-Bromo-6-propyluracil (**1**) [12] can be prepared with DBH as described in the propylthio-

uracil assay. IR-, MS-, ^{1}H- and ^{13}C-data of the compound, so far as I know, not yet described in the literature, are given in the experimental part.

The direct titration with a standard DBH solution and amaranth as indicator or with potentiometric indication is not possible, because the reaction of propylthiouracil with bromine is too slow. The indicator is already partly decolorized before the equivalence point is reached.

4. Conclusions

The determination of the pure antithyroid drug propylthiouracil using neutralization titration and silver nitrate is applied in the pharmacopeias since USP 1950 [24] with bromothymol blue as indicator, since USP 1985 [25] with potentiometric indication, which is also utilized in PH. EUR. 1997 [2]. This method is in respect to environmental and economical concern due to the application of silver nitrate and 2-fold boiling obsolete. When using DBH/HAc as oxidant and brominating agent, the determination can be performed easily, faster and safer to environment. The mean deviation of 0.03% and the R.S.D. of 0.34% are remarkable, and correspond to the demanded content of 98.0–100.5 of USP 2000 and PH. EUR. 1997.

It must be pointed out, that this method is only qualified for pure propylthiouracil corresponding to the pharmacopeias and not practicable for the determination in a complex matrix. The method with chloramine T as standard solution [20–23] is less practicable, because a titration temperature of 30–40 °C is necessary.

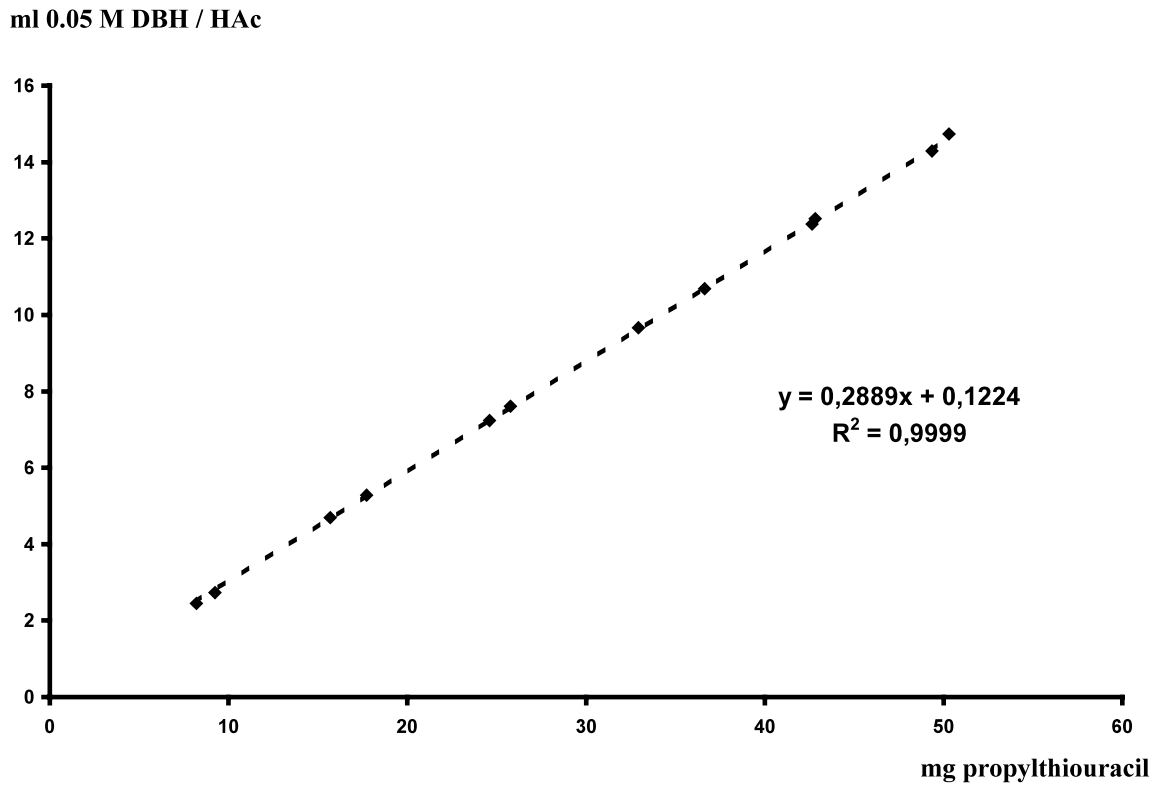


Fig. 2. Determination of propylthiouracil using DBH/HAc in the presence of hydrochloric acid.

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