ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
25 (2001) 363–377

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

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Determination of iodide with 1,3-dibromo-5,5-dimethylhydantoin (DBH) in comparison with the ICl-method☆,☆☆ Analytical methods of pharmacopeias with DBH in respect to environmental and economical concern. Part 3

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Received 17 August 2000; accepted 29 August 2000

Abstract

USP 1995 (The United States Pharmacopeia, 23rd Edit., (1995), potassium iodide p. 1265, sodium iodide p. 1424), PH. EUR. 1997 (European Pharmacopoeia, third ed., Council of Europe, Strasbourg, (1997), potassium iodide p. 1367, sodium iodide p. 1493) and JAP 1996 (The Japanes Pharmacopoeia, 13th ed. (1996), potassium iodide p. 578, sodium iodide p. 630) determine iodide with the ICl-method (J. Am. Chem. Soc. 25 (1903) 756–761; Z. Anorg. Chem. 36 (1903) 76–83; Fresenius Z. Anal. Chem. 106 (1936) 12–23; Arzneibuch-Kommentar, Wissenschaftliche Erläuterungen zum Europäischen Arzneibuch, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, Govi-Verlag — Pharmazeutischer Verlag GmbH, Eschborn, 12th suppl. (1999), K10 p. 2), using chloroform, which is toxic and hazardous to environment. Without the application of chlorinated hydrocarbons USP 2000 (The United State Pharmacopeia, 24th ed. (2000), potassium iodide p. 1368, sodium iodide p. 1535) and Brit 1999 (British Pharmacopoeia London, (1999), Appendix VIII C, p. A162) titrate iodide with the redox indicator amaranth. A titration with potentiometric indication giving two end-points at the step of I_2 and $[ICl_2]^-$ is described. Due to the high concentration of hydrochloric acid required for the ICl-method, the determination with DBH (1,3-dibromo-5,5-dimethylhydantoin; 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione) can be recommended and is performed easily. Similarly, the iodide content of gallamine triethiodide may be analyzed with DBH by application of a visual two-phase titration in water and ethyl acetate or with potentiometric indication in a mixture of 2-propanol and water. During the removal of the excess of DBH 4-bromo-triethylgallamine (2,2′,2″-[1-bromo-benzene-2,3,4-triyltris(oxy)]*N*,*N*,*N*-triethylethanium) is formed.

☆ Cooperation between the Setchenov Academy of Moscow and the Philipps-University of Marburg.
☆☆ (Professorial dissertation (2000) Marburg; Fresenius J. Anal. Chem., 360 (1998) 184–191; Pharmazie 531 (1998) 321–323)
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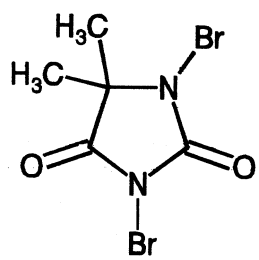
0731-7085/01/$ - see front matter
PII: S0731-7085(00)00505-7

Keywords: Iodide determination; DBH, Dibromantin; 1,3-dibromo-5,5-dimethylhydantoin, 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (77-48-5); Gallamine triethiodide (65-29-2)

1. Introduction

In contrast to elemental bromine, DBH is a stable and easy to handle crystalline compound [1–3]. The iodine determination of organic compounds by oxygen flask combustion [1,2] according to USP 2000 and Brit. 1999 could be improved by using an alkaline solution of DBH as absorbing liquid. Neither elemental bromine nor addition of sodium bisulfite to the absorbing liquid (USP 2000) is necessary. For the removal of the excess of DBH resp. arising bromine 5-sulfosalicylic acid (SSS) [1–3,6,7] is more suitable than formic acid, because it reacts faster. When acidifying the alkaline solution with SSS and acetic acid (HAc), no bromine is liberated in contrast to formic acid. Blank values with usual weights of sample are not necessary. The blowing out of the combustion flask with a current of air (Brit. 1999) or nitrogen (USP 2000) is not required.



The determination of iodide underlies the following reaction equations (Fig. 1).

DBH oxidizes iodide in alkaline medium quantitative to iodate. After acidifying with a mixture of SSS and HAc to an optimal pH value of about 3.0, the excess of DBH is destroyed immediately. The liberated iodine can be titrated with sodium thiosulfate and starch solution visually or by potentiometric indication after adding potassium iodide.

Iodide is titrated directly with potassium iodate according to the ICl-method corresponding to the following equation,

$$2\ I^- + IO_3^- + 6H_3O^+ + 6Cl^- \rightarrow\ 3[ICl_2]^- + 9H_2O$$

Iodide is oxidized to the colorless anion of $[ICl_2]^-$ at high concentration of hydrochloric acid. PH. EUR. 1997 applies a concentration of about 25% (about 8.0 M), USP 2000 of about 29% (about 9.4 M) at the beginning of the titration. When a two-phase titration is used, the recognition of the end-point due to very slow decolorization of the chloroform phase is complicated and tedious [4]. The use of the redox indicator amaranth according USP 2000 and Brit 1999 improves the method.

Due to environmental reasons [8], the titration of iodide with silver nitrate [9] according to Volhard (USP 1926 [10], Pharmacopoea Helvetica 1971 [11]), to Fajans (Pharmacopoea Nordica 1963 [12]), with ethanolic iodine solution as indicator (PH. EUR. 1 [13]) or determining the endpoint with potentiometric indication (USP 2000 potassium iodide and sodium iodide as used in oral solution and tablets) should not be employed. Silver ions have a less human toxicity. However, smallest concentrations (100 ppb) are bactericide and, therefore, disturb the purification of waste water by sewage treatment plants. Moreover, the high price for silver salts, their light sensitivity and the production of blackish pigmentation on skin, clothing and apparatuses argue against argentimetry. Determinations with silver nitrate and visual indicators are nonspecific for iodide in contrast to the ICl- and DBH-method, because bromides, chlorides, cyanates etc. interfere.

2. Experimental

2.1. Instrumentation

2.1.1. Elementary analysis

CH, according to F. Salzer, CWH-Labormatic-Wösthoff, N, CHN-Analyzer 185, Hewlett–Packard, Br, I [2] according to Schöniger.

2.1.2. MS

ESI^+-MS, Finnigan LCQ DUO, the electrospray needle was hold at +4.5 kV, N_2, methanol–water (50:50 v/v) 5 μl min^{-1}.

2.1.3. 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.

2.1.4. Potentiometry

Metrohm potentiograph E 536 with Metrohm dosimat 665, 20 and 50 ml exchange unit, pla-

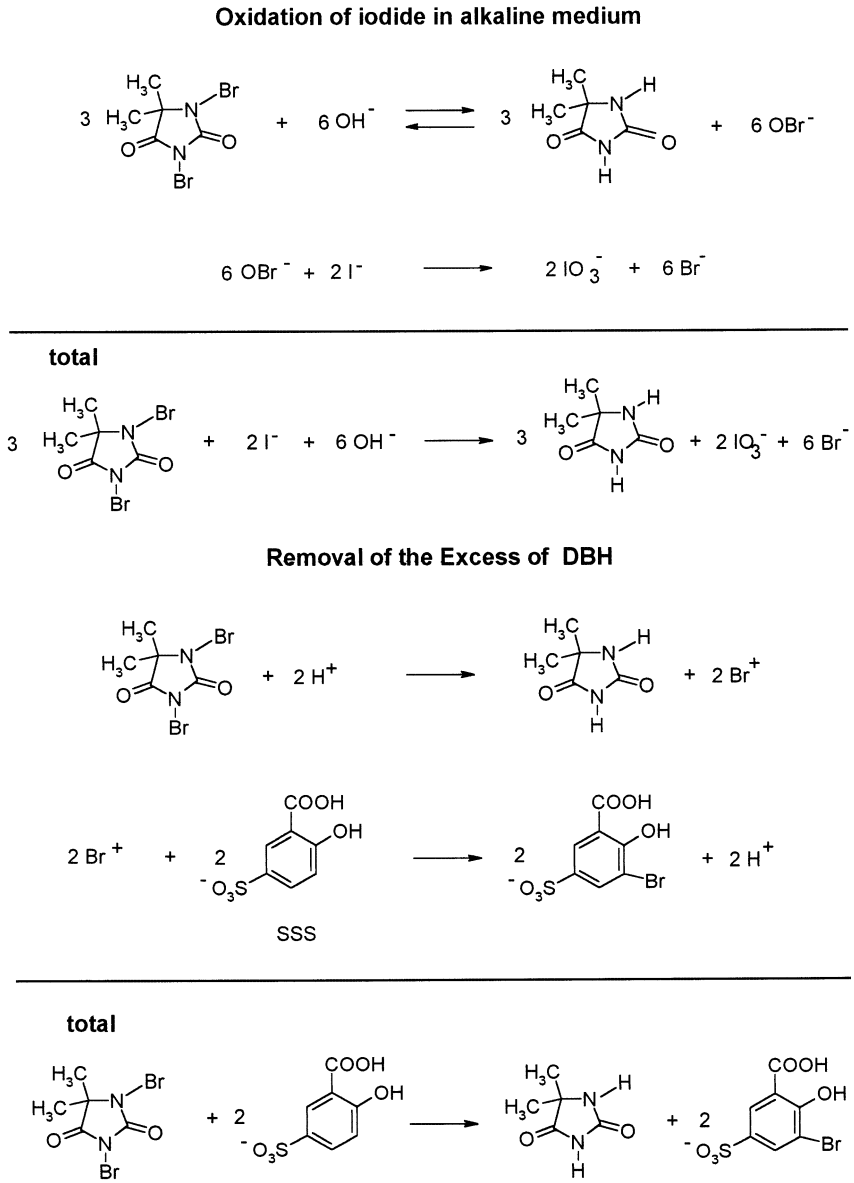


Fig. 1. Determination of iodide with DBH.

tinum electrode (Pt/Ag/AgCl) Metrohm AG No. 9100, parameters, stop % U, off; adjustment of dosing time depending on dU/dV, ten, time of dosing for burette volume (min/100% vol.), 5/200; counter voltage, 600 mV, measuring margin ΔU per 250 mm width of recording page, 1 V; counter voltage-U-for zero point calibration, 8.65, temperature, 20.0°C, stirrer, 7–10, damp, on.

2.2. Chemicals

Acetic acid (64-19-7) min. 99.8% p.a., Riedel-de Haën Art. 33209 = HAc; amaranth (915-67-3), azorubin S for microscopy, Riedel-de Haën Art. 32618; bromine (7726-95-6), extra pure DAB 6, Merck Art. 1945; chloroform, trichloromethane (67-66-3) extra pure, DAB 9, Merck Art.159129; 1,3-dibromo-5,5-dimethylhydantoin=1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (77-48-5), for synthesis Merck Art. 803 600 = DBH (for analytical purpose qualified); ethyl acetate (141-78-6) extra pure, Riedel-de Haën Art. 27 227; gallamine triethiodide, Gallamini triethiodidum PH. EUR. 1997, USP 2000 (65-29-2) Rhône-Poulenc Rorer, $C_{30}H_{60}I_3N_3O_3$ (891,5) calculated C 40.42, H 6.78, N 4.71, I 42.70; found C 40.17, H 6.90, N 4.80, I 42.64 [2]; gallamine triethiodide, Sigma (approximately 95%) Art. G-8134, found C 40.02, H 6.92, N 6,04, I 42.24 [2]; hydrobromic acid, not less than 47% HBr (10 035-10-6), Merck Art. 304; hydrochloric acid (7647-01-0), fuming, 37%, extra pure Merck, Art. 100 314; iodine, Iodum PH. EUR. 1997, USP 2000 (7553-56-2), Riedel-de Haën Art. 3002; ion exchanger III (strong basic anion exchanger) Merck Art. 102 404 (approximately 5 mmol/g exchange capacity); 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; 2-propanol (67-63-0), extra pure, PH. EUR., Merck Art. 100 995; sodium acetate anhydrous (127-09-3) p.a., Merck Art. 106 268 = NaAc; sodium chloride, Natrii chloridum PH. EUR. 1997, USP 2000 (7647-14-5), extra pure, Merck Art. 106 400; sodium hydroxide (1310-73-2) Rotipuran, 99%, Roth Art. 9356; sodium iodide, Natrii iodidum PH. EUR. 1997 (7681-82-5), extra pure, Riedel-de Haën Art. 03129, sodium sulfate, (7757-82-6) anhydrous, finely powdered, extra pure, DAB, Merck Art. 6645; sodium tetraphenylborate, Kalignost® (143-66-8) p. A., Riedel-de Haën, Art. 33322; sodium thiosulfate pentahydrate (7772-98-7) > 98.5%, Roth Art. 8649; starch soluble (9005-84-9) extra pure Erg. B. 6, Merck Art. 101253; 5-sulfosalicylic acid dihydrate (5965-83-3), extra pure, Merck Art. 689 = SSS.

2.3. Solutions

Amaranth (3.3×10^{-4} M; 0.02%) — 20 mg of amaranth is dissolved in water to 100.0 ml; 0.05 M bromine — about 250 μl of bromine is dissolved in 100.0 ml of water and standardized by iodimetry; 0.02 M DBH/0.5 M NaOH — 0.57 g (0.002 mol) of DBH is dissolved with stirring in 0.5 M NaOH to 100.0 ml; 0.02 M DBH/1 M NaOH — 0.57 g (0.002 mol) of DBH is dissolved with stirring in 1 M NaOH to 100.0 ml; 0.05 M DBH/0.5 M NaOH — 1.43 g (0.005 mol) of DBH is dissolved with stirring in 0.5 M NaOH to 100.0 ml; 10 M HAc — 573 ml of acetic acid is diluted with water to 1000.0 ml; 1 M HBr — 11.5 ml of hydrobromic acid (47% HBr) is diluted to 100.0 ml; 0.05 M iodine is prepared according to PH. EUR. 1997; 0.2 M KI — 3.32 g (0.02 mol) of potassium iodide is dissolved with water to 100.0 ml; 1 M KI — 16.6 g (0.1 mol) of potassium iodide is dissolved with water to 100.0 ml; 0.05 M KIO_3 is prepared according to PH. EUR. 1997; 1/60 M KIO_3 — 3.567 g of potassium iodate p.a., volumetric standard, is diluted to 1000.0 ml; 1/300 M KIO_3 — 200.0 ml of 1/60 M KIO_3 is diluted to 1000.0 ml; 0.25 M NaAc–10 M HAc, pH-buffer about 3.0: 20.5 g of anhydrous sodium acetate is dissolved in 570 ml acetic acid and water to 1000.0 ml; 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); 0.02 M $Na_2S_2O_3$ is prepared by dilution of 0.1 M and standardized with 20.00 ml of 1/300 M KIO_3, 10.0 ml of 0.25 M NaAc/10 M HAc, 5.0 ml of 0.2 M KI and 0.5 ml of starch solution, iodide-free (PH. EUR. 1997); 0.05 M sodium tetraphenylborate — 856 mg of sodium tetraphenylborate (5×10^{-4}

mol) is dissolved with water to 50.0 ml. 0.2 M SSS–2.5 M Hac — 50.8 g (0.2 mol) of 5-sulfosalicylic acid dihydrate is dissolved in 145 ml of acetic acid and water to 1000 ml; 0.2 M SSS/5 M HAc — 50.8 g (0.2 mol) of 5-sulfosalicylic acid dihydrate is dissolved in 290 ml of acetic acid and water to 1000.0 ml; 0.5 M SSS/5 M HAc — 127 g (0.5 mol) of 5-sulfosalicylic acid dihydrate are dissolved in 290 ml of acetic acid and water to 1000.0 ml; 0.5 M SSS–10 M HAc — 127 g (0.5 mol) of 5-sulfosalicylic acid dihydrate is dissolved in 580 ml of acetic acid and water to 1000.0 ml; 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. ICl-method according to PH. EUR. 1997 with amaranth as indicator

Dissolve about 1.300 g of sodium iodide, accurately weighed with water to 100.0 ml. To 20.00 ml of the solution add 40.0 ml of hydrochloric acid (37%) and 1.0 ml of 3.3×10^{-4} M amaranth (0.02%). Titrate until the red violet color just changes to pale yellow. Loss on drying at 100–105°C for 3 h is regarded. Weigh of sample — 259.9 mg sodium iodide per 20.00 ml.

2.4.2. ICl-method with potentiometric end-point determination to I_2 (first end-point) and to $[ICl_2]^-$ (second end-point)

2.4.2.1. According to PH. EUR. 1997 at about 8.0 M HCl. Test solution (20.00 ml) are mixed with 40.0 ml of hydrochloric acid (37%). See Table 2 for further concentrations of acid.

KIO_3 (0.05 M; 1 ml) is equivalent to 37.47 mg sodium iodide resp. 31.73 mg iodide (first equivalent point) and 14.99 mg sodium iodide resp. 12.69 mg iodide (second equivalent point).

2.4.3. DBH-method

2.4.3.1. Semimicro analysis (range, about 50 mg). About 249 mg of potassium iodide resp. 225 mg sodium iodide (corresponding to 1.5×10^{-3} mol) is dissolved with water to 100.0 ml. To 20.00 ml of the solution (3×10^{-4} mol) add 10.00 ml 0.05 M DBH/0.5 M NaOH. After 5 min, acidify with 5.00 ml of 0.5 M SSS/10 M HAc and, after further 5 min, pipette 5.00 ml of 1 M KI. Titrate with 0.1 M $Na_2S_2O_3$ determining the end-point with starch as indicator or by potentiometry.

Weight of sample — 50.05 mg of potassium iodide per 20.00 ml resp. 45.23 mg of sodium iodide per 20.00 ml.

2.4.3.2. Micro analysis (range, about 8 mg). About 8.3 mg of potassium iodide resp. 7.5 mg sodium iodide (corresponding to 5×10^{-5} mol) is dissolved with water to 20.00 ml. Add 5.00 ml 0.02 M DBH/0.5 M NaOH. Wait for 5 min and then acidify with 5.00 ml of 0.2 M SSS/5 M HAc and after further 5 min pipette 5.00 ml of 0.2 M KI. Titrate with 0.02 M $Na_2S_2O_3$ determining the end-point with starch as indicator or by potentiometry.

Weight of sample — 8.608 mg of potassium iodide per 20 ml resp. 7.606 mg of sodium iodide per 20 ml.

2.4.3.3. Micro analysis (range, about 8 mg) with high concentration of SSS. Analogous to 2.4.3.2. 5.00 ml of 0.02 M DBH/1 M NaOH instead of 5.00 ml 0.02 DBH/0.5 M NaOH and 5.00 ml of 0.5 M SSS/5 M HAc instead of 5.00 ml of 0.2 M SSS/5 M HAc are employed.

Weight of sample — 8.608 mg of potassium iodide per 20.00 ml.

2.4.3.4. Gallamine triethiodide, semimicro analysis (range, about 20 mg) and potentiometric indication. About 19.6 mg (2.2×10^{-5} mol) of gallamine triethiodide, accurately weighed, are dissolved in 20.00 ml of water. Mix with 2.50 ml of 0.05 M DBH/0.5 M NaOH. After 5 min, acidify with 5.00 ml of 0.2 M SSS/2.5 M HAc to a pH value of about 3.0. Wait 5 min and then add 30.0 ml of 2-propanol and 5.00 ml of 0.2 M KI. The expelled iodine is titrated with 0.02 M $Na_2S_2O_3$ and potentiometric indication.

Weight of sample — 19.83 mg of gallamine triethiodide per 20.00 ml.

2.4.3.5. Gallamine triethiodide, semimicro analysis (range, about 20 mg) and visual indication. About 19.6 mg (2.2×10^{-5} mol) of gallamine triethiodide, accurately weighed, is dissolved in 20.00 ml of water. Mix with 2.50 ml of 0.05 M DBH/0.5 M NaOH. After 5 min, acidify with 5.00 ml of 0.2 M SSS/2.5 M HAc to a pH value of about 3.0. Wait 5 min and then add with stirring 25.0 ml of ethyl acetate and 5.00 ml of 0.2 M KI. Two phases are formed. The expelled iodine is titrated with rapid stirring and 0.02 M $Na_2S_2O_3$ until the ethyl acetate layer is decolorized.

Weight of sample — 20.02 mg of gallamine triethiodide per 20.00 ml.

2.4.3.6. Gallamine triethiodide, semimicro analysis (range, about 90 mg) and visual indication. About 89.2 mg (10^{-4} mol) of gallamine triethiodide, accurately weighed, is dissolved in 20.00 ml of water. Mix with 10.00 ml of 0.05 M DBH/0.5 M NaOH. After 5 min, acidify with 5.00 ml of 0.5 M SSS/10 M Hac to a pH value of about 3.0. Wait 5 min, and then add with stirring 25.0 ml of ethyl acetate and 5.00 ml of 1 M KI. Two phases are formed. The expelled iodine is titrated with rapid stirring and 0.1 M $Na_2S_2O_3$ until the ethyl acetate layer is decolorized.

Weight of sample — 90.31 mg of gallamine triethiodide per 20.00 ml.

2.4.3.7. Gallamine triethiodide, semimicro analysis (range, about 20 mg) without using SSS and potentiometric indication. About 19.6 mg (2.2×10^{-5} mol) of gallamine triethiodide, accurately weighed, is dissolved in 20.00 ml of water. Mix with 2.50 ml of 0.05 M DBH/0.5 M NaOH. After 5 min, acidify with 25.00 ml of 10 M HAc to a pH value of about 3.0. Wait 5 min and then add 30.0 ml of 2-propanol and 5.00 ml of 0.2 M KI. The expelled iodine is titrated with 0.02 M $Na_2S_2O_3$ using potentiometric indication.

Weight of sample — 20.00 mg of gallamine triethiodide per 20.00 ml.

2.4.3.8. Gallamine triethiodide, semimicro analysis (range, about 90 mg) without using SSS and visual indication. About 89.2 mg (10^{-4} mol) of gallamine triethiodide, accurately weighed, is dissolved in 20.00 ml of water. Mix with 10.00 ml of 0.05 M DBH/0.5 M NaOH. After 5 min, acidify with 25.00 ml of 10 M HAc to a pH value of about 3.0. Wait 5 resp. 10 min and then add with stirring 25.0 ml of ethyl acetate and 5.00 ml of 1 M KI. Two phases are formed. The expelled iodine is transferred as gallamine triethtriodide to the ethylacetate phase. Titrate with rapid stirring and 0.1 M $Na_2S_2O_3$ until the ethyl acetate layer is decolorized.

Weight of sample — 96.09 mg of gallamine triethiodide per 20.00 ml.

2.5. Preparation of gallamine triethtriodide — 2,2′,2″-[1,2,3-benzenetriyltris(oxy)]-tris[N,N,N-tri-ethylethanaminium] tritriiodide

Gallamine (5×10^{-4} M; 446 mg) triethiodide is dissolved in 25 ml of water and 25.0 ml of 0.05 M iodine is added. A tawny clouding is arising. After about 5 min a reddish-brown, viscous oil is formed. The substance is extracted three times each with 25 ml of ethyl acetate. Sodium chloride (5 g) is solved in the aqueous layer for a better phase separation. Then the organic layer is dried over glowed sodium sulfate. After removal of the ethyl acetate by rotary evaporation in vacuo 593 mg (86%) of a dark brown, solid compound is obtained. The substance is freely soluble in methanol, acetone and ethyl acetate and less soluble in diethyl ether resp. dioxane. By addition of heptane resp. toluene resp. dioxane to a solution of the substance an oil is obtained. No crystals can be gained from ethyl acetate/dioxane (1:1). $C_{30}H_{60}I_9N_3O_3$, $C_{30}H_{60}N_3O_3 + 3I_3^-$(1653), calculated C 21.80, H 3.66, N 2.54, total I 69.1 I_2 46.1; found C 22.04, H 3.76, N 2.99, total I 70,1 I_2 47.0.

I_2 — about 50 mg (3×10^{-5} mol) of gallamine triethtriiodide, accurately weighed, is dissolved in 25.0 ml of ethyl acetate. Titration is performed with 0.02 M $Na_2S_2O_3$ under rapid stirring until decolorization of the ethyl acetate layer. $Na_2S_2O_3$ (0.02 M; 1 ml) is equivalent to 5.510 mg gallamine triethtriiodide corresponding to 2.538 mg of iodine.

I_3^-, total iodine — about 11.6 mg (7×10^{-6} mol) of gallamine triethtriiodide, accurately weighed, is dissolved in 25.0 ml of ethyl acetate

and shaked with 2.50 ml of 0.05 M DBH/0.5 M NaOH for 5 min. Add to the colorless solution 5.00 ml 0.2 M SSS/2.5 M HAc and after further 5 min 5.00 ml of 0.2 M KI. The expelled iodine is titrated with rapid stirring and 0.02 M $Na_2S_2O_3$ until the ethyl acetate layer is decolorized.

One milliliter of 0.02 M $Na_2S_2O_3$ is equivalent to 0.6122 mg gallamine triethtriiodide corresponding to 0.4230 mg of I_3^- resp. iodine.

2.6. Preparation of 4-bromogallamine triethbromide-2,2′,2″-[1-bromo, 2,3,4-benzene-triyltris (oxy)] tris [N,N,N-triethylethanaminium] tribromide

Gallamine triethiodide (5×10^{-4} M; 446 mg) is dissolved in 5 ml of water and loaded on a glass tube of about 1 cm diameter, about 20 cm in length with a stop-cock and filled with 5 g of strong basic anion exchanger. Eluate with 25 ml of water at a flow rate of 2–3 ml per min. After acidifying the eluate with 2.5 ml of 1 M HBr 10 ml of 0.05 M bromine are dropped to the solution. At first, a yellow precipitate arises, which is solved by shaking over about 2 min. An excess of bromine results a yellow-up-to-orange precipitate of bromogallamine triethtribromide. Heating the solution to boiling the precipitate can be decomposed and the excess of bromine be removed. Rotary evaporation in vacuo gives 399 mg (96%) of a colorless, crystalline, very hygroscopic compound. According to ^{1}H-, ^{13}C-NMR und ESI$^+$-MS the raw product contains small amounts of not brominated galamine triethbromide. Elementary analysis shows a major portion of hydrobromic acid. The salt is freely soluble in water, methanol, 2-propanol and nitromethane, sparingly soluble in dioxan even if boiled. Recrystallization with acetonitrile or addition of toluene to a solution in nitromethane does not succeed in getting a crystalline product. $C_{30}H_{59}Br_4N_3O_3$, $C_{30}H_{59}BrN_3O_3^+$ $3Br^-$(829,4) calculated C 43.44, H 7.17, Br 38.5, N 5.07, found C 35.37, H 6.53, Br 44.6, N 4.42; ^{1}H-NMR (methanol-d_4, 21°C, 500 MHz), δ_H (ppm) = 1.36–1.40 (m, $N^\oplus$–CH_2–C***H***$_3$); 3.53–3.62 (m from 3 × q, $N^\oplus$–C***H***$_2$–CH_3); 3.86–3.88 (m from 2 q, O–CH_2–C***H***$_2$–$N^\oplus$ at the arom. C-1 and the arom. C-2); 3.95 (t, ^3J = 4.8 Hz, O–CH_2–C***H***$_2$–$N^\oplus$ at the arom. C-3); 4.42 (t, ^3J = 4.7 Hz, O–C***H***$_2$–CH_2–$N^\oplus$ at the arom. C-1); 4.46 (t, ^3J = 5.3 Hz, O–C***H***$_2$–CH_2–$N^\oplus$ at the arom. C-2); 4.59 (t, ^3J = 5.7 Hz, O–C***H***$_2$–CH_2–$N^\oplus$ at the arom. C-3); 7.09 (d, ^3J = 9.2 Hz, at the arom. C-6); 7.44 (d, ^3J = 9.2 Hz, at the arom. C-5); ^{13}C-NMR (methanol-d_4, 24°C, 125.8 MHz). The assignment of the signals is obtained by means of the calculated ^{13}C-NMR-spectrum [14] of 1-bromo-2,3,4-trimethoxybenzene (10385-36-1). δ_C (ppm) = 7.71; 7.75; ($N^\oplus$–CH_2–***C***H_3); 54.81 ($N^\oplus$–***C***H_2–CH_3); 56.27; 57.25; 57.47 (O–CH_2–***C***H_2–$N^\oplus$) 62.92; 67.53; 67.68 (O–***C***H_2–CH_2–$N^\oplus$); 109.56; (arom. C-4); 112.76 (arom. C-6); 129.22 (arom. C-5); 142.31 (arom. C-2); 149.87 (arom. C-1); 152.19 (arom. C-3). The assignment of the signals of the aromatic carbon atoms C-4, C-5 and C-6 is obtained by means of ^{13}C-DEPT-spectrum (CH-groups) of the compound. ESI$^+$-MS, *m*/*z* (rel. intensity) 753 (7.5), 752 (32), 751 (28), 750 (97), 749 (31), 748 (100), 747 (14), 746 (33) (M–$^{79}Br^-$, $C_{30}H_{59}$ $^{79}Br_3N_3O_3$), 672 (7.5), 671 (5), 670 (15), 668 (8.5) (gallamine triethbromide–$^{79}Br^-$, starting material), 651 (5), 650 (4), 649 (19), 648 (5), 647 (18), 645 (5.5), 643 (5.5), 642 (26), 641 (14), 640 (51), 639 (7.5), 638 (27) (M–$^{79}Br^-$–C_2H_5 ^{79}Br), 562 (8), 541 (5), 539 (12), 537 (5.5), 532 (8.5), 530 (9) [M–$^{79}Br^-$–$2C_2H_5$ ^{79}Br], 360 (8), 358 (8) [M–$^{79}Br^-$–$2C_2H_5$ ^{79}Br–$2CH_2$–$N(C_2H_5)_2$], 359 (9), 336 (12), 335 (21), 334 (13), 285 (4), 284 (7.5), 281 (8) 280 (12).

2.6.1. Spectra of gallamine triethiodide as comparison

^{1}H-NMR (methanol-d_4, 21°C, 500 MHz), δ_H (ppm) = 1.38 (t, ^3J = 7.2 Hz, $N^\oplus$–CH_2–C***H***$_3$); 3.54 (q, ^3J = 7.3 Hz, O–CH_2–CH_2–$N^\oplus$–C***H***$_2$–CH_3 at the arom. C-1 and at the arom. C-3); 3.61 (q, ^3J = 7.3 Hz, O–CH_2–CH_2–$N^\oplus$–C***H***$_2$–CH_3 at the arom. C-2); 3.77 (t, ^3J = 4.9 Hz, O–CH_2–C***H***$_2$–$N^\oplus$ at the arom. C-2); 3.85 (t, ^3J = 5.4 Hz, O–CH_2–C***H***$_2$–$N^\oplus$ at the arom. C-1 and at the arom. C-3); 4.37 (t, ^3J = 4.9 Hz, O–C***H***$_2$–CH_2–$N^\oplus$ at the arom. C-2); 4.56 (t, ^3J = 5.38 Hz, O–C***H***$_2$–CH_2-$N^\oplus$ at the arom. C-1 and C-3); 6.92 (d, ^3J = 8.5 Hz, at the arom. C-4 and at the arom. C-6); 7.17 (t, ^3J = 8.5 Hz, at the arom.

Table 1
Determination of iodide content of sodium iodide (calculated 84.67% I) according to the ICl-method

Prescription	*n*	Mean (%)	Bias (%)	R.S.D. (%)	*F*-test *p*	*t*-test two-sided *p*
PH. EUR. 1997	7	84.47	−0.24	0.13		
PH. EUR. 1997 with amaranth as indicator	7	84.51	−0.19	0.15	0.782	0.560

C-5); ^{13}C-NMR (methanol-d_4, 24°C, 125.8 MHz). The assignment of the signals is obtained by means of the calculated [14] and in the literature described [15] ^{13}C-NMR-spectrum of 1,2,3-trimethoxybenzene (pyrogallol trimethylether) (634-36-6), δ_C (ppm) = 7.85; 7.97; 8.02 ($N^{\oplus}$–CH_2–***C***H_3); 54.85 ($N^{\oplus}$–***C***H_2–CH_3); 56.63 (O–CH_2–***C***H_2–$N^{\oplus}$ at the arom. C-1 and the arom. C-3); 57.54 (O–CH_2–***C***H_2–$N^{\oplus}$ at the arom. C-2); 62.79; 62.86 (O–***C***H_2–CH_2–$N^{\oplus}$ at the arom. C-1 and the arom. C-3); 66.92 (O–***C***H_2–CH_2–$N^{\oplus}$ at the arom. C-2); 108.48; 108.57 (arom. C-4 and arom. C-6) 126.05 (arom. C-5); 136.92 (arom. C-2); 152.35 (arom. C-1 and arom. C-3). ESI$^+$-MS — *m*/*z* (rel. intensity) 766 (4), 765 (20), 764 (100) [M–I$^-$], 663 (6), 608 (10) [M–I$^-$–C_2H_5I], 320 (18), 319 (54), 280 (4) [M–I$^-$–2C_2H_5I–2H_2C–N(C_2H_5)$_2$], 242 (3), 241 (4) 171 (12).

2.7. Preparation of gallamine triethtetraphenylborate–2,2′,2″-[1,2,3-benzenetriyltris(oxy)] tris [N,N,N-triethylethanaminium] tritetraphenylborate

Sodium tetraphenylborate (0.05 M; 40 ml) are slowly dropped to the solution of 446 mg (5×10^{-4} mol) of gallamine triethiodide in 25 ml of water. The white, voluminous precipitate is difficult to filtrate or to centrifugate. After washing with water and drying at 60°C, 735 mg (99.9%) of raw product is gained. The compound is freely soluble in acetone, methyl ethyl ketone, nitromethane, acetonitrile and dimethyl formamide. By addition of water or 2-propanol or toluene to a solution of the compound, the substance can be precipitated in solid but not crystalline form. For crystallization, a suitable solvent has not been found. $C_{102}H_{120}B_3N_3O_3$, $C_{30}H_{60}N_3O_3^+3C_{24}H_{20}B^-$(1469) calculated C 83.43, H 8.24, I 0.00, N 2.86 found C 83.32, H 8.07, I 0.60, N 3.18.

2.8. Preparation of 4-bromogallamine triethtetraphenylborate–2,2′,2″-[1-bromo, 2,3,4-benzenetriyltris(oxy)] tris [N,N,N-triethylethanaminium] tri-tetraphenylborate)

According to 2.6. 446 mg (5×10^{-4} mol) of gallamine triethiodide are transferred to 4-bromogallamine triethbromide by means of anion exchange, acidifying with hydrobromic acid and bromination. To the obtained solution 40 ml of 0.05 M sodium tetraphenylborate are slowly dropped. The white, voluminous difficult to filtrate or to centrifugate precipitate is washed with water and dried at 60°C to give 758 mg (98%) of raw product. The substance shows the same solubility behavior as gallamine triethtetraphenylborate. $C_{102}H_{119}B_3BrN_3O_3$, $C_{30}H_{59}BrN_3O_3^+$ $3C_{24}H_{20}B^-$, (1547) calculated C 79.17, H 7.75, Br 5.16, N 2.72, found C 78.77, H 7.42; Br 5.79, N 3.15.

2.9. 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.

3. Results and discussion

3.1. Determination of iodide according to the ICl-method

As shown in Table 1, the analytical values according to PH. EUR. 1997 do not differ from those with amaranth as indicator. The indicator

change from red violet to pale yellow is well to recognize. Using potentiometric indication, two end-points are obtained by the ICl-method. The first step corresponds to elemental iodine according to the following reaction equation.

$$5I^- + IO_3^- + 6H_3O^+ \rightarrow 3I_2 + 9H_2O$$

The second equivalent point correlates to the visual indication forming the anion complex $[ICl_2]^-$. On the basis of the redox equivalents, the consumption of 0.05 M KIO_3 to the first and the second end-point has the ratio 1:2.5. This agrees with the results in Fig. 2.

Reducing the concentration to 3.8 M HCl (3.5 at the first, 3.2 at the second equivalent point) the potential jump from iodide to iodine improves (see Fig. 2.). With a concentration of 1.4 M HCl only the first potential jump is recognizable (see Fig. 2). Elemental iodine partly precipitates and dissolves again in the course of the further titration. Up to a concentration of 6 M HCl at the starting of the titration acceptable analytical results are gained not only on the basis of the first but also of the second potential jump (see Table 2). Calculating the consumption of the second potential jump with lower concentrations as 6 M HCl at the starting of the analysis leads definitively to too high values (2.9 M HCl, bias (%) = + 10%).

By the addition of non-volatile acids such as sulfuric and perchloric acid elemental iodine is also precipitated. A definite first potential jump is seen and can be taken into calculation. As iodine deposits on the diaphragma and on the platinum rod of the electrode, this is no alternative to acidification with hydrochloric acid. No definitive potential jump is received, if 2-propanol is added to avoid the precipitation of iodine.

3.2. Determination of iodide according to the DBH-method

The DBH-method [1–3] corresponds to the iodide determination according to Winkler [16–19] of DAB 7 (1986) [20] and of 2 (Table 3). AB/DDR [21] as well as the potassium iodide determination from ethanolic iodine solution of DAB 1999 [22]. Since elemental bromine, formic acid and sodium salicylate are replaced by easy to handle DBH and SSS [1–3], this iodide specific method is simply to perform.

Certainly, the DBH concentration is to adapt to the iodide content. An 10% excess in relation to the theoretical consumption is recommended. A prescription as well for an analytical semimicro concentration of 3×10^{-4} mol (50 mg potassium iodide resp. 45 mg sodium iodide) as for a micro concentration of 5×10^{-5} mol (8.3 mg potassium iodide resp. 7.5 mg sodium iodide) is given.

The indication can be performed by addition of starch solution visually or by potentiometry. Results according to the DBH-method do not differ significantly from those according to PH. EUR. 1997 and according to the ICl-method with amaranth as redox indicator (DBH, semimicro, visual/ICl-amaranth, F-test, $p = 0.99$ and t-test, two-sided, $p = 0.41$).

As shown for iodine determination according to Schöniger [1,2] SSS reacts so fast with bromine, that no bromine vapor is released. Blind values are so low, that they can be neglected. The determination of blind values for the iodide analysis, however, is critical, because a large excess of DBH and only traces of hydrobromic acid in contrast to the analysis are present. Hydrobromic acid is required for the reaction of DBH to

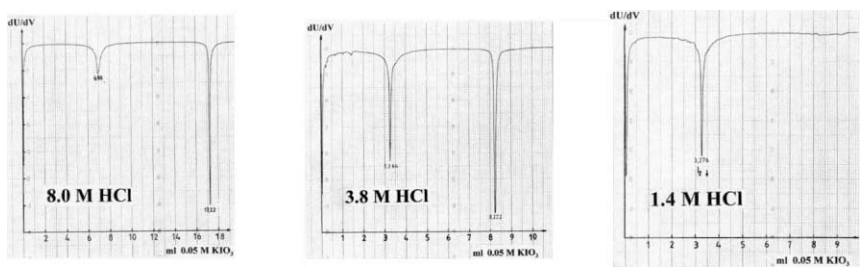


Fig. 2. Determination of iodide with the ICl-method and potentiometric indication at various concentration of hydrochloric acid.

Table 2
Determination of iodide content of sodium iodide (calculated 84.67% I) according to the ICl — method with potentiometric indication, various addition of acid and various sample weight

$H^{\oplus}$ (mol l^{-1})			Addition of acid to 20.00 ml of test solution	Weight (mg)	n	1. Equivalence point			2. Equivalence point		
Start	1. Equivalence point	2. Equivalence point				Mean (%)	Bias (%)	R.S.D. (%)	Mean (%)	Bias (%)	R.S.D. (%)
8.0	7.2	6.2	40 ml 37%HCl	259.5	4	85.18	+0.60	0.46	83.89	−0.92	0.18
8.0	7.2	6.9	40 ml 37%HCl	150.0	7	84.94	+0.32	0.45	84.44	−0.27	0.19
8.0	7.6	7.1	40 ml 37%HCl	120.0	5	85.26	+0.69	0.34	83.89	−0.92	0.22
7.0	6.6	6.2	45 ml 32%HCl	130.2	1	85.04	+0.44	–	84.80	+0.15	–
6.7	6.4	5.9	40 ml 32%HCl	130.2	1	85.29	+0.73	–	84.99	+0.38	–
6.1	5.7	5.2	30 ml 32%HCl	130.2	1	85.53	+1.02	–	85.09	+0.50	–
6.0	5.5	4.8	20 ml 37%HCl	150.0	5	84.59	−0.10	0.35	84.01	−0.78	0.20
6.0	5.5	4.9	20 ml 37%HCl	130.0	1	85.17	+0.59	–	84.17	+0.59	–
5.6	5.2	4.7	25 ml 32%HCl	130.2	2	85.29	+0.73	–	85.72	+1.24	–
5.0	4.6	4.1	20 ml 32%HCl	130.2	1	85.29	+0.73	–	85.68	+1.19	–
4.0	3.8	3.4	20 ml 37%HCl + 20 ml H_2O	150.0	4	84.65	−0.02	0.51	85.48	+0.95	0.33
3.8	3.5	3.2	20 ml 25%HCl	120.3	5	85.28	+0.72	0.29	86.28	+1.91	$n=1$
3.4	3.2	2.9	20 ml 32%HCl +20 ml H_2O	130.2	1	85.04	+0.44	–	93.18	+10.0	–
1.4	1.3	1.2	20 ml 10%HCl	120.3	1	86.40	+2.04	–	Precipitation of iodine		
7.1	6.7	6.2	40 ml 40%H_2SO_4	120.3	1	85.09	+0.50	–	Precipitation of iodine		
7.8	7.4	6.9	40 ml 70%$HClO_4$	120.3	1	85.11	+0.52	–	Precipitation of iodine		

Table 3
Determination of iodide content of potassium iodide (calculated 76.45% I) and sodium iodide (calculated 84.67% I) according to the DBH-method

Prescription	Compound	Concentration (mg/20 ml)	*n*	Indication					
				Visual			Potentiometric		
				Mean (%)	Bias (%)	R.S.D. (%)	Mean (%)	Bias (%)	R.S.D. (%)
Semimicro analysis (range, about 50 mg)	KI	50.05	7	76.44	−0.01	0.07	76.49	+0.05	0.03
	NaI	45.23	7	84.56	−0.12	0.14	84.57	−0.12	0.15
Micro analysis (range, about 8 mg)	KI	8.608	7	76.29	−0.19	0.14	76.32	−0.17	0.28
	NaI	7.606	7	84.37	−0.35	0.21	84.44	−0.27	0.23
Micro analysis (range, about 8 mg) with high concentration of SSS	KI	8.608	7	76.34	−0.13	0.14	76.32	−0.17	0.15

Table 4
Determination of iodide content of gallamine triethiodide (calculated 42.70% I) according to the DBH-method

Prescription	Concentration (mg/20 ml)	*n*	Mean (%)	Bias (%)	R.S.D. (%)
Gallamine trieth-iodide, semimicro analysis (range, about 20 mg) potentiometric indication	19.83	7	42.79	+0.22	0.13
Gallamine trieth-iodide, semimicro analysis (range, about 20 mg) visual indication	20.02	7	42.48	−0.52	0.05
Gallamine trieth-iodide, semimicro analysis (range, about 90 mg) and visual indication	90.31	7	42.67	−0.07	0.05
Gallamine trieth-iodide, semimicro analysis (range, about 20 mg) without using SSS and potentiometric indication	20.00	1	47.23	+10.6	–
Gallamine trieth-iodide, semimicro analysis (range, about 90 mg) without using SSS and visual indication waiting time 5 min	96.09	3	43.47	+1.80	0.07
Gallamine trieth-iodide, semimicro analysis (range, about 90 mg) without using SSS and visual indication waiting time 10 min	96.09	4	42.68	−0.05	0.31

bromine. Apparently, an excess of DBH only can be removed by an interim development of bromine, which is bound to SSS. Therefore, the determination of blind values should not be performed. Even a high application of SSS (0.5 instead of 0.2 M) for micro determination of potassium iodide has no influence (visual/potentiometric, F-test, $p = 0.98/0.74$ and t-test, two-sided, $p = 0.74/0.97$). This demonstrates that under the conditions of the analysis the complete excess of DBH is removed.

3.3. Determination of iodide content of gallamine triethiodide according to the DBH-method

According to USP 1995 and PH. EUR. 1997 the content of gallamine triethiodide is determined by non-aqueous titration applying perchloric acid and toxic and strong environmental hazardous mercuric acetate Table 4. Thereby, the iodide content is determined non-specific by complexation of the halogenid. Nowadays, the application of mercuric salts is considered to be obsolete. Thus PH. EUR. Suppl. 1999 [23] performs the titration in a mixture of acetic anhydride and formic acid, whereby the application of mercuric acetate is not necessary. USP 2000 uses liquid chromatography and demands a R.S.D. (%) not exceeding 2.

Also the iodide content of gallamine triethiodide can be determined with the DBH-method [1–3]. Problems arise after acidification with SSS/HAc and addition of potassium iodide, because the liberated iodine forms with gallamine triethiodide a sparingly soluble gallamine triethtriiodide [24,25]. By elementary analysis and details on solubility the triiodide existing as an ion pair [26] is characterized (see Section 2.5). Trying to determine the end-point with potentiometric indication in aqueous solutions failed, because the diaphragma and the platinum rod is overlayed with the precipitated gallamine triethtriiodide. This reddish brown, oily precipitate retains iodine and dissolves very slowly, when the equivalent point is exceeded, so a visual titration is impossible too.

2-Propanol proves suitable for the dissolution of the troublesome precipitated gallamine triethtriiodide. A titration in aqueous propanolic solution with potentiometric indication can be realized (see Fig. 3). The addition of sodium lauryl sulfate, ceteareth-30 (macrogol cetostearyl ether PH. EUR. 1997) and tartaric acid (cp. the iodine determination of gallamine triethiodide PH. EUR. 1 [27,28]) is improper. Iodine does not yield a blue inclusion complex in aqueous propanolic medium. Using a visual indication, the color change from yellow brown to colorless at the end of the titration is difficult to recognize. So, for the visual titration, a method with the addition of ethyl acetate is explored, using the decolorization of the organic layer. Ethyl acetate is more suitable than the toxic chloroform applied

from the ICl-method [4,5]. If stirring, ethyl acetate distributes significantly better in the aqueous layer than chloroform. Also, the exchange of iodine between the two phases is faster with ethyl acetate than with chloroform.

A prescription for an analytical half micro concentration of 20 mg (2.2×10^{-5} mol, potentiometric resp. visual indication) as well as for a concentration of 90 mg of gallamine triethiodide (10^{-4} mol, visual indication) is given.

The excess of employed DBH determining with a sample weight of about 90 mg is bound quantitative to gallamine triethiodide, a 1,2,3-trihydroxybenzene derivative. However, after acidification, a waiting time of 10 min is required, so that the addition of SSS for binding of the not consumed DBH is not needed. Analytical results after a waiting time of 5 resp. 10 min differ high significantly (F-test, $p = 0.003$, t-test, two-sided, $p = 0.003$). Determinations in the range of 20 mg without the addition of SSS result too high values. These findings clearly indicate, that the application of SSS for removal of the excess of DBH can be recommended. The ruggedness of the analytical method is improved.

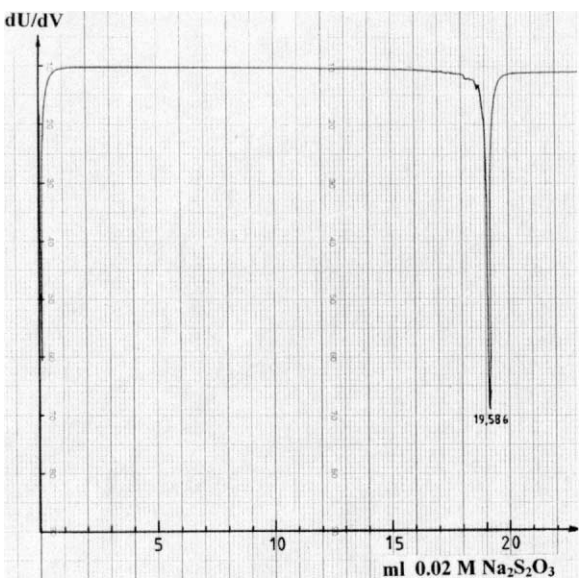


Fig. 3. Determination of iodide content of gallamine triethiodide with the DBH-method and potentiometric indication in water–propanol.

To elucidate the structure of the brominated derivative arising from the bromination of triethylgallamin triethiodide, the compound is converted using anion exchange, acidifying with hydrobromic acid and bromination to bromogallamine triethbromide (see Section 2.6). Due to the ^{1}H-NMR-spectrum, the very hygroscopic substance refers explicitly to 4-bromogallamine triethbromide with a doublet at δ 7.44 ppm, $^3J = 9.2$ Hz and δ 7.09 ppm, $^3J = 9.2$ Hz (integral = 1:1) in the field of the aromatic protons. In comparison, gallamine triethiodide shows a triplet at δ 7.17 ppm, $^3J = 8.5$ Hz and a doublet at δ 6.92 ppm, $^3J = 8.5$ Hz (integral = 1:2). Characteristic for bromine substitution are the isotopic peaks at 746, 748, 750 and 752 (rel. intensity, 1:3:3:1) for the $C_{30}H_{59}Br_3N_3O_3$-cation in the ESI$^+$-MS, which are absent in the spectrum of gallamine triethiodide ($C_{30}H_{30}I_2N_3O_3^+$, $m/z = 764$). So far as we know, 4-bromogallamine triethbromide is not yet described in the literature.

Gallamine triethiodide as well as 4-bromogallamin triethbromide form in aqueous solution with sodium tetraphenylborate (Kalignost®) a white, voluminous precipitate (see Sections 2.7 and 2.8).

4. Conclusions

With the application of the non-reversible redox indicator amaranth (USP 2000 and Brit. 1999), also with now described potentiometric indication the ICl-method can be improved with respect to environmental concern avoiding the use of chloroform as solvent. Nevertheless, the high concentration of hydrochloric acid, which can be reduced by the potentiometric determination, is disadvantageous. Because of the high concentration of hydrochloric acid working in an exhaust hood is required. Furthermore, vapors of hydrochloric acid lead to corrosion and damage of instrumental apparatus. Thus, the iodide determination according to the DBH-method [1–3] with visual or potentiometric indication is in our opinion, the much better and the more practicable analytical method.

Due to the application of mercuric acetate also the DBH determination of iodide content of gallamine triethiodide [1] mainly with potentiometric indication in propanol–water must be preferred to the methods according to PH. EUR. 1997 and USP 1995. Working with glacial acetic acid resp. dioxane requires an exhaust hood. Aqueous standard solutions such as sodium thiosulfate solutions are less problematic than those in glacial acetic acid or dioxane, especially using autotitrators.

According to PH. EUR. Suppl. 1999 [23] with the application of acetic anhydride, formic acid and potentiometric indication without using mercuric acetate also an exhaust hood is required. In order to avoid overheating, the reaction medium has thoroughly and throughout to be stirred during the titration and stopped immediately after the end-point is reached. The waste solutions of perchloric acid, acetic anhydride and formic acid arising during the titration can form carbon monoxide. Therefore, the storage can lead to an excess pressure and bursting of the waste jar [29]. Therefore, titrations in aqueous and aqueous alcoholic solution as the DBH-method are preferable. Also the R.S.D. (%) receiving with the iodometric DBH determination of gallamine triethiodide are better than those, demanded of USP 2000 using liquid chromatography.

With respect to environmental concern, the identification test C of gallamine triethiodide according to der PH. EUR. 1997 with potassium tetraiodomercurate solution (Mayer reagent) should be replaced with a test using the less toxic and easier to dispose sodium tetraphenylborate.

Acknowledgements

The authors acknowledge the former president of the University of Marburg Professor Dr. h.c.W. Schaal and Mr. T. Komm, international office of the Philipps-University, financing the stay of Swetlana Senjuk at Marburg, the company Rhône-Poulenc Rorer (Aventis) for delivery of gallamine triethiodide.

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