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GRAVIMETRIC AND SPECTROPHOTOMETRIC METHODS FOR THE DETERMINATION OF PIPERAZINE. PICROLONIC VS. PICRIC ACID

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In the present work two new analytical methods, a gravimetric and a spectrophotometric, for the assay of piperazine free base and its soluble salts in the anthelmitic preparation "Oxyuran", are described. Both approaches are based on the quantitative reaction between the diprotonated cationic form of piperazine and the 3-methyl-4-nitro-1-*p*-nitrophenyl-5-pyrazolone (picrolonic acid), in sulfuric acid medium, leading to its sparingly soluble canary yellow salt. Both methods exhibit satisfactory levels of mean errors 1.2% and 1.7% respectively. The proposed picrolonate gravimetric method constitutes an improvement of the classical picric acid method regarding the accuracy, sensitivity and selectivity. The two gravimetric methods were compared. Good correlation was achieved, r=0.998. The improvement in sensitivity of the new spectrophotometric method is attributed to the high molar extinction coefficient ε_{max}=18.770 $mol^{-1}lcm^{-1}$ of the picrolonates at the measuring wavelength range λ_{max}=342–345 nm. Triethanolammonium-picrolonate and piperazine-diacetate were synthetized and standardized during this work.

Introduction

Piperazine [1, 2] (Pi) is a hygroscopic crystalline solid base which forms a hexahydrate readily soluble in water. Its dissociation constants in aqeous solution are pK_1=9.8 and pK_2=5.7. It is an anthelmintic drug in human as well as in veterinary medicine.

The anthelmintic preparation "Oxyuran", (Chropei Pharm. Company, Greece) contains piperazine citrate (10% piperazine hexahydrate) with excipients such as citric acid, sugar and flavours. The official method, used for the determination of piperazine in its formulations, is the gravimetric method with 2,4,6-trinitrophenol (picric acid), even in the latest editions of most Pharmacopoeia [3].

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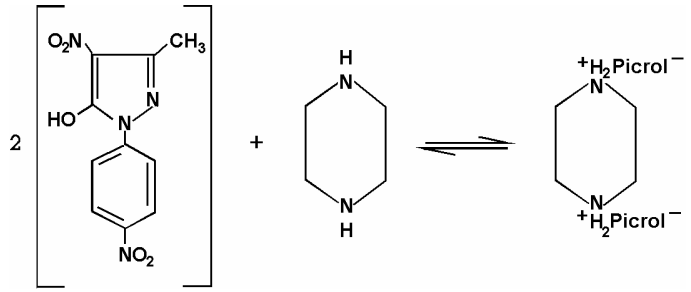
Titrimetric methods with perchloric acid, in the presence of 1-naphthol-benzein [4] or bromocresol green [5] indicators, gravimetric method as diacetylpiperazine [6], complexometric as thiocyanato-chromium complexes [7] or instrumental methods [8, 9] have also been described in the literature for the determination of piperazine.

The aim of the present work was to improve the official method for the determination of piperazine, by replacing picric acid (Pic) by a heavier polynitro reagent, picrolonic acid (Picr) and also to develop a spectrophotometric method, based on the same reagent.

Among the various polynitro organic reagents for the determination of amines, diamines and alkaloids, picrolonic acid is not as widely employed as picric acid. However picric acid is a poorly selective reagent [10]. Not only because it gives crystalline salts with many amines but also because it yields crystalline addition products, mostly of the charge-transfer type, with a variety of organic compounds such as aromatic hydrocarbons, aryl ethers and proteins. On the other hand, picrolonic acid as reagent shows a higher selectivity for piperazine. Although it interacts with some divalent cations of the alkaline earth metals, it is generally regarded as specific reagent for the nitrogenous compounds.

The reaction between piperazine and picrolonic acid is quantitative and yields an insoluble crystalline yellow salt, with a 2:1 stoichiometry, according to the reaction scheme.



Experimental

Apparatus

UV-VIS Spectrophotometer: Perkin Elmer-Lambda 15 UV-VIS.

Preparation of TEA-picrolonate and piperazine-diacetate

Triethanolammonium picrolonate (TEA-picrolonate) and piperazine diacetate were synthetized and standardized during this work because they were not available commercially.

TEA-Picrolonate: 5.64 g TEA (triethanolamine) is dissolved in adequate amount of ether. 10.00 g of picrolonic acid is dissolved in warm alcohol and the solution is filtered. The solutions are mixed and the mixture is allowed to stand for 15 minutes. Then it is filtered through a sintered-glass filter, the precipitate washed with ethanol and ether (6∗20ml), and finally dried at 80 °C for 2 hours.

The molecular weight of the product, $C_{16}H_{23}N_5O_8$, is 413.37 and its melting point 164.5 °C. It is almost insoluble in ether, soluble in ethanol and acetone, and more soluble in methanol. Elemental analysis: C 46.84%, N 16.84% and H 5.70%. The theoretical values are 46.48, 16.94 and 5.61% respectively.

Piperazine diacetate: 0.25 moles glacial acetic acid is dissolved in 250 ml of aceton. 0.125 moles of piperazine hexahydrate is dissolved in 250 ml of aceton. The two solutions are mixed together resulting a white precipitate, which is then filtered and washed with aceton.

The molecular weight of the product, $C_8H_{18}N_2O_4$, is 206.25 and its melting point 216 °C. It is insoluble in ether, soluble in methanol and ethanol and slightly soluble in acetone. Elemental analysis: C 46.88%, N 13.80% and H 8.89%. The theoritical values are 46.59, 13.58 and 8.80%, respectively.

Working solutions

All solutions were prepared in deionized-distilled water from reagent grade materials:

Solution of TEA-picrolonate 0.05 M: Dissolve 5.1674 g TEA-picrolonate in 250 ml of water.

Solution of piperazine-diacetate 2 mg/ml: Dissolve 2.3951 g piperazine diacetate in 250 ml of water.

Piperazine base 8.56 mg/ml: Dissolve 9.7 g (approx.) piperazine hexahydrate in 500 ml glacial acetic acid and standardize with perchloric acid 0.100 N in the presence of 1-naphtholbenzein 2% as indicator.

Standard solution of 'Oxyuran': 10.00 ml solution of the commercial product Oxyuran is transferred to a 250 ml volumetric flask. The solution was standarized gravimetrically with picric acid [3, 11] and was found to contain 1.62 mg/ml piperazine.

Trisma sulfate buffer solution, 1 mol l^{-1}, pH 7.0: Dissolve 30.3 g trisma base (tris(hydroxymethyl)-methylamine) and 6.9 ml concentrated sulfuric acid in distilled water and dilute in 250 ml of water.

Procedure

Gravimetric determination of piperazine with picrolonate. Known weight (10–60 mg) of the piperazine solid or liquid sample, 100 ml distilled water and 10 ml of sulfuric acid 0.16 mol l^{-1} are mixed in a 400 ml beaker. TEA-picrolonate solution is added under stirring to a small excess after the ceasing of the precipitation. This mixture is heated on a water-bath for 15 minutes and allowed to stand for 1 hour. The precipitate with the supernatant liquid are filtered through a sintered glass crucible (BS porosity No. 4) and the precipitate is washed primarily with a solution of TEA-picrolonate, $1.0∗10^{-6}$ mol l^{-1} and then with five successive portions of 10 ml of methanol. The precipitate is dried to constant weight at 150 °C. The gravimetric factor is 0.1402.

Spectrophotometric determination of piperazine. Working curve: Samples ranging between 13 and 20 mg piperazine were placed into volumetric flasks of 50 ml capacity. 10.00 ml of TEA-picrolonate solution $1.0∗10^{-2}$ mol l^{-1} and 10 ml of trisma sulfate buffer $1∗10^{-1}$ mol l^{-1} were added to each flask. 30 μl of the supernatant liquid is diluted with water to 2.6 ml. The absorbance is measured at 343 nm.

Measurements of the unknown: Piperazine in "Oxyuran" was determined spectrophotometrically following the above described procedure. The measurment was performed in a 10.0 ml standard solution of Oxyuran (16.20 mg Pi).

Results and discussion

Gravimetric determination of pirerazine

A big error in our primary experiments was due firstly to the incomplete protonization of piperazine and secondly to the absence of picrolonates in the washing solution. Piperazine is fully diprotonized (PiH_2^{2+}) at pH<3. Therefore, different acidic solutions such as sulfuric acid, hydrochloric acid, perchloric acid and acetic acid were used in order to create the required pH conditions. Sulfuric acid gave the best results. The precipitated salt was washed with a solution of TEA-picrolonate $1.0*10^{-6}$ mol l^{-1} and then with methanol in order to remove the adsorbed picrolonate ions from its surface.

As can be seen from the results of Table I the proposed method of picrolonates gives results which agree with the official picrate method. In addition the picrolonic acid gives a heavy salt of higher molecular weight than picric acid, permiting thus the determination of smaller amounts of piperazine with better accuracy (lower detection limit). The results for the determination of piperazine (10 mg) as illustrated in Table I are the average of five experiments. The lower solubility of the picrolonate salt enhences also the accuracy of the proposed spectrophotometric method (see later).

Statistical analysis was applied in order to compare the proposed gravimetric analytical method with the standard gravimetric method. The correlation curve is described with the equation y=0.660+0.998 x. x and y denote the amount of piperazine in mg determined by the picric- and picrolonic-method, respectively.

Spectrophotometric determination of piperazine

The spectrophotometric determination of piperazine was carried out by measuring the differences between the absorbances of TEA-picrolonate before and after the precipitation of piperazine picrolonate at 343 nm and pH 7.5. Being a strong acid, picrolonic acid exists in its anionic form above pH 3 and for this reason its spectrum is constant between pH 3 and 7.5 (ε=18.770 mol^{-1} l cm^{-1}). The linear range for the spectrophotometric determination of picrolonates is from $1*10^{-6}$ to $7*10^{-5}$ mol l^{-1}. The working curve applied in this investigation was constructed for the concentration range $9.5*10^{-6}$ to $5.2*10^{-5}$ mol l^{-1} picrolonate which is the needed range to cover the concentration levels of piperazine in the examined samples.

Table I

Comparative results for the gravimetric determination of piperazine as the diacetate salt with picric and picrolonic acid

	Picrolonic acid method		Picric acid method	
Taken (mg Pi)	Found (mg Pi)	Error (%)	Found (mg Pi)	Error (%)
10.00	10.04	0.4	9.78	2.2
13.00	13.07	0.5	12.96	0.3
15.41	15.42	0.1	15.40	0.1
16.00	16.04	0.2	16.05	0.3
17.12	17.33	1.2	16.78	0.2
19.00	19.22	1.2	18.75	1.3
21.40	21.73	1.5	21.10	1.4
22.00	22.43	2.0	22.12	0.6
25.00	25.26	1.0	24.87	0.5
28.00	28.49	1.8	28.03	0.1
29.96	30.38	1.4	29.65	1.3
31.00	31.09	0.3	31.08	0.3
34.23	34.77	1.6	33.72	1.5
37.00	37.50	1.4	36.22	2.1
38.52	39.30	2.0	38.16	0.9
40.00	40.73	1.8	41.40	3.5
42.80	42.99	0.4	44.02	2.8
43.00	43.83	1.9	42.40	1.4
46.00	47.00	2.2	47.07	2.3
47.08	47.68	1.3	46.52	1.2
49.00	49.11	0.2	50.20	2.4
51.36	51.70	0.7	52.32	1.9
55.64	56.22	1.0	56.72	1.9
59.92	60.71	1.3	60.59	1.1
	Mean	1.2		1.3

The absorption band of picrolonic ion at pH values of 6.5, 7.5 and 8.5 is shown in Table II. The graph of the relation $A=\varepsilon b[\text{Picr}^-]_r$ is linear. From the stoichiometry of the reaction we have $[\text{Picr}^-]_r = [\text{Picr}^-]_{in}-2\,[\text{Pi}]$, where $[\text{Picr}^-]_{in}$ is the initial and $[\text{Picr}^-]_r$ the remaining concentration of the picrolonate after the precipitation of piperazine picrolonate.

Under the experimental conditions given in the above procedure and after substitution of $\varepsilon_{max}=18770\ \text{mol}^{-1}\ \text{l}\ \text{cm}^{-1}$ and $b=1$ cm, we finally receive,

$$A = -5.275*10^{-3} + 1.92*10^{4}\,[\text{Picr}^-]\ . \qquad (1)$$

Table II

Peak position and intensity in spectra of picrolonic acid in various pH values

pH	λmax	ε(mol^{-1}l cm^{-1})
6.5	342–345	18252
7.5	342–345	18770
8.5	342–345	20582

The amount of piperazine in the sample in mg is calculated applying Eq. (2), which is valid under the experimental conditions given above.

$$mg_{Pi} = 4307\{0.5\ [Picr^-]_{in} - 0.5(A-a)/b\}\ , \qquad (2)$$

where A is the absorbance and a, b are the intercept and slope of the regression Eq. (4) respectively.

In conclusion, the picrolonate gravimetric and spectrophotometric methods developed in this work were applied to real piperazine samples (Oxyuran) with a good accuracy. The relative error was 1.2% and 1.7% for the gravimetric and spectrophotometric method, respectively.

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