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Quantitative Determination of Pentetrazol

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A method for quantitative determination of pentetrazol has been worked out based on the precipitation of the cadmium chloride complex and subsequent complexometric titration of the cadmium content in the precipitate.

Pentetrazol [Cardiazol ®, Leptazol (Belg. 30, Suppl. 51, B.P. 58), Pentylenetetrazol (U.S.P. 55)] has usually been determined with the help of its more or less insoluble complexes with different inorganic salts [1–8]. Several authors [1,4,5,7] have found the complex with cuprous chloride to be the most convenient for this purpose. Ph. Helv. 33, Add. 55 has admitted the cuprous chloride method of Dister [4], and the British Pharmacopoeia of 1958 a modification of it, worked out by Sharp [5]. We have examined both methods and found none of them to be accurate enough despite rigorous precautions. Since the accuracy of other methods, cited in literature, was judged not to be greater, we have on the suggestion of Dr. T. Canbäck * investigated the possibilities of using the complex proposed by Warren [2] for identification purposes, *i.e.* with cadmium chloride even for quantitative determination. The solubility of the cadmium chloride complex of pentetrazol in water is reported by several authors to be too great for quantitative precipitation. Warren [2] found it to be about 1:95 and Paulsen [7] reports the solubility in 0.1 M cadmium chloride to be 0.25 %. Paulsen [7] moreover reports that there are two different complexes with cadmium chloride, one with a composition of $CdCl_2 \cdot 2C_6H_{10}N_4$, obtained by mixing about equimolecular quantities of pentetrazol and cadmium chloride, and the other with a composition of $CdCl_2 \cdot C_6H_{10}N_4$, obtained by adding cadmium chloride in excess to a solution of pentetrazol, both compositions being determined after drying at 150°C.

As a result of this we have tried to find a suitable medium, where the solubility of the cadmium chloride complex, obtained by excess of the reagent, is small enough for quantitative precipitation. We have found that a mixture of *iso*propanol and water complies with this requirement and have worked out a method for quantitative determination of pentetrazol based on the precipi-

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tation of the cadmium chloride complex and subsequent complexometric titration of the cadmium content in the precipitate.

EXPERIMENTAL

The cadmium chloride complex, $C_6H_{10}N_4 \cdot CdCl_2 \cdot 3H_2O$ was precipitated with an excess of the reagent and isolated. The solubility of the complex was determined in different solutions of alkaline salts, hydrochloric acid and in some organic solvents. The complex was found to be more or less soluble in the solutions of alkaline salts and hydrochloric acid but almost insoluble in *iso*propanol. Cadmium chloride was found to have a solubility of about 1:1 000 in *iso*propanol and by using a mixture of *iso*propanol and water, it is possible to get a relatively strong reagent solution, without any risk of precipitation of the reagent. After some preliminary work we have found the following method suitable.

Mix 0.1500 g, dissolved in 2 ml of a mixture of 3 volume parts of *iso*propanol and 2 volume parts of water, with 10 ml of cadmium chloride-*iso*propanol-R. Filtrate the mixture after 10 min, during which time the bottle from time to time is swirled, through a glass crucible (3 G 4). Transfer the precipitate completely with the aid of the filtrate. Wash the filter twice with 5 ml of a mixture of 9 volume parts of *iso*propanol and 1 volume part of water, and finally 3 times with *iso*propanol, each time with 10 ml. Transfer the filter to another suction flask and dissolve the precipitate in 100 ml of water, heated to boiling-point. Cool the solution, add 10 ml of ammonium chloride-ammonia-R and 5 drops of eriochrome black-I and titrate immediately with 0.1 N tetracemindisodium to a blue colour. Each ml of 0.1 N tetracemindisodium is equivalent to 0.006909 g of $C_6H_{10}N_4$.

Reagents

Iso*propanol*, purum min. 99 %. B.p. 81–83°C.

Cadmium chloride-iso*propanol-R.* Dissolve 15.0 g of cadmium chloride ($CdCl_2 \cdot 2\frac{1}{2} H_2O$) in 40 ml of water by warming. Filter the solution and dilute with *iso*propanol to 100 ml after cooling. The solution must be freshly prepared.

Ammonium chloride-ammonia-R *. Dissolve 6.75 g of ammonium chloride (NH_4Cl) in 57 ml of strong ammonia solution and dilute with water to 100 ml.

Eriochrome black-I *. Dissolve 0.50 g of eriochrome black T and 4.5 g of hydroxylamine hydrochloride in 100 ml of methanol.

*0.1 N Tetracemindisodium 0.05 M**. Tetracemindisodium (EDTA, Komplexon, Titriplex) dissolved in water to contain in 1 000 ml 18.61 g of $C_{10}H_{14}O_8N_2Na_2 \cdot 2H_2O$.

DISCUSSION

The content of cadmium in the precipitate was determined after repeated washings and drying in the air and found to be 34.96 % (calculated for

Table 1. The solubility of $C_6H_{10}N_4 \cdot CdCl_2$ in different solvents, g/100 g.

Ammonium chloride 2 M	0.80	Ether	0
Sodium chloride 10 %	0.55	*Iso*propanol 50 % v/v	0.79
Hydrochloric acid 0.1 M	0.97	*Iso*propanol 60 % v/v	0.61
Hydrochloric acid 0.5 M	0.78	*Iso*propanol 70 % v/v	0.53
Hydrochloric acid 1 M	0.68	*Iso*propanol 80 % v/v	0.24
Hydrochloric acid 2 M	0.76	*Iso*propanol 90 % v/v	0.10
Hydrochloric acid 3 M	1.02	*Iso*propanol 95 % v/v	0.06
Hydrochloric acid 4 M	1.20	*Iso*propanol	0
Acetone	0		

* From prescriptions accepted by the Scandinavian Pharmacopoeia Council for the Nordic Pharmacopoeia.

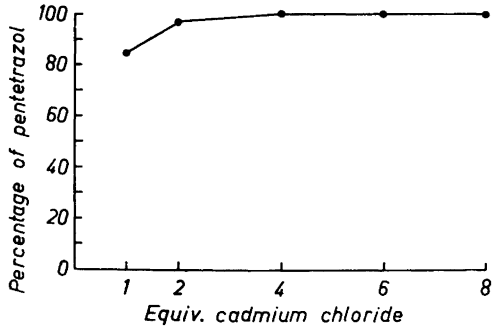

Fig. 1. Relation between results in percentage of pentetrazol and equivalents of cadmium chloride.

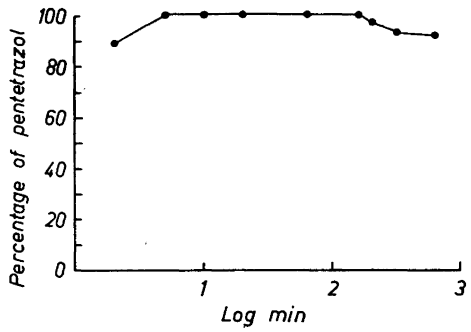

Fig. 2. Relation between results in percentage of pentetrazol and time of precipitation.

$C_6H_{10}N_4 \cdot CdCl_2$: 34.96 %). By heating at 105°C and 150°C for about 20 h it did not lose appreciably in weight. According to Zwikker [1] and Paulsen [7] the complex hydrate $C_6H_{10}N_4 \cdot CdCl_2 \cdot 3H_2O$ (= 29.93 % Cd) loses its water by drying at 150°C and becomes anhydrous. The precipitate obtained in the mixture of *iso*propanol and water is therefore obviously anhydrous and has a composition of $C_6H_{10}N_4 \cdot CdCl_2$.

The solubility of the complex is 0.61 g/100 g (Table 1) in a mixture of 3 parts of *iso*propanol and 2 parts of water but in the presence of cadmium chloride, the solubility decreases so that a quantitative precipitation is possible. The solubility in the wash liquid, 9 parts of *iso*propanol and 1 part of water is 0.10 g/100 ml but the loss in the washing is unnoticeable, owing to the excess of cadmium chloride in the precipitate, which is only gradually washed out, and to the short time of the washing. For that reason correction for solubility is not necessary.

To obtain quantitative precipitation a certain excess of the precipitant is necessary. We have found that under the present conditions a quantity of cadmium chloride is required which is about 4 times that calculated (Fig. 1). We have chosen a somewhat greater excess, about 6 times the quantity calculated.

The precipitate does not appear until about half a minute after the addition of the reagent and it takes some minutes until the precipitation is complete. If the precipitate stands in contact with the mother liquid for a longer time than about 2.5 h, the precipitate is changed and passes easily through the filter, perhaps owing to hydrolysis to basic complexes (Fig. 2).

Table 2. The importance of swirling the bottle during the precipitation. Sample C.

Swirled	Not swirled
99.9—99.8 %	97.4—98.3 %

Table 3. The cadmium content of the precipitate after washing with the number of *iso*propanol-water mixture 9 + 1 noted, followed by 3 × 10 ml of *iso*propanol.

1 × 2 ml	2 × 2 ml	3 × 2 ml	1 × 5 ml	2 × 5 ml	3 × 5 ml	4 × 5 ml
36.47 %	35.60 %	34.82 %	35.25 %	34.96 %	34.98 %	34.98 %

Table 4. Results obtained with commercial samples: I, In original state; II, After one recrystallization from water.

	Sample A	Sample B	Sample C
I.	99.1—99.2—99.3— —99.1—99.2 %	100.2—100.2—100.0— —100.0—100.2—99.9— —100.2—100.0— —100.0—100.1 %	99.9—100.2—99.9— —100.1—99.9—99.8— —99.8—99.9—99.9— —99.8—99.6 %
II.	99.5—99.6 %	— — — — —	100.0—99.8 %

During the precipitation the bottle must be swirled from time to time, as otherwise low results are obtained (Table 2) and the precipitate sometimes becomes fine-grained and passes easily through the filter.

To wash out the great excess of cadmium chloride it is necessary to use a mixture of *iso*propanol and water. The water content of the wash liquid can however be decreased considerably compared with the mixture that is used in the reagent solution, since the precipitation of cadmium chloride of the reagent solution on the addition of more *iso*propanol is markedly delayed. When washed with 2×5 ml of a mixture of 9 volume parts of *iso*propanol and 1 volume part of water, the excess of cadmium chloride is removed from the precipitate (Table 3).

The results obtained with commercial samples are tabulated in Table 4.

The method can also be used for the determination of pentetrazol in plain aqueous solutions by adding *iso*propanol to the solution in the amount required to get the same proportion of *iso*propanol and water as is used for the substance.

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