SYNTHESIS OF THIAMINE MONONITRATE

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Thiamine bromide hydrobromide (II) or thiamine chloride hydrochloride (V) has been used in the synthesis of 3-(2'-methyl-4'-aminopyrimidyl-5'-methyl)-4-methyl-5-(β-hydroxyethyl)triazole nitrate, i.e., thiamine mononitrate (I) by substituting the halide anion in them by the anion of nitric acid directly or via thiamine thiocyanate (VII) [1-4]. In this way the nitric acid salt (VI) is formed which is then converted into thiamine mononitrate. The synthesis of thiamine mononitrate from 3-(2'methyl-4'-aminopyrimidyl-5'-methyl)-4-methyl-5-(β-hydroxyethyl)-2-thiothiazolone, i.e., thiothiamine (III) seemed of interest. Thiamine sulfate (IV) is formed on oxidizing (III) with hydrogen peroxide, and in the presence of hydrochloric, nitric, or hydrobromic acid is converted into (V), (VI), or (II) [4-6].

The synthesis of (I) has been described for the most part in patents and many problems connected with the preparation and purification of this form of thiamine have not been presented fully enough in the literature. We have studied and refined the process of obtaining (I) from (III). A description of the oxidation of (III), isolation, and purification of (I) is presented in this communication. Compound (III) was oxidized with nitric acid or with hydrogen peroxide in the presence of mineral acid. The thiamine formed was isolated from aqueous solution as (I) by the action of a saturated solution of ammonium carbonate or sodium bicarbonate or as (VII) by the action of ammonium thiocyanate and ammonia at pH 9.0. Under the action of nitric acid, (VII) was converted into the nitric acid salt (VIII) an aqueous solution of which was treated with anion exchange resin AV-17 or wofatite L-150. Salt (VI) was obtained as a result, and then (I). Purification of compounds (VII) and (I) was effected by solution in nitric acid (solution pH 3.0), purifying the solution with charcoal, and subsequent isolation by the addition of ammonium carbonate or sodium bicarbonate.

EXPERIMENTAL

Thiamine Thiocyanate (VII). Thiothiamine (14.8 g) was mixed with 75 ml distilled water, hydrochloric or nitric acid was added with stirring to pH 3.0-4.0, 16 ml 28% hydrogen peroxide solution was poured in over 30 min at 25°C, and stirring continued for 1 h at the same temperature. Active charcoal (2 g) was then added to the reaction mixture, which was stirred for 30 min at 25°C, filtered, and the charcoal washed with water. The main filtrate and the aqueous washings were combined, 5 g ammonium thiocyanate added, and then 5% aqueous ammonia solution (35 ml) to pH 9.0. The reaction mixture was stored at 0°C for 3 h for a more complete separation of (VII), which was filtered off, washed with distilled water (3 times with 20 ml), and dried in vacuum at 60°C to constant weight. Yield was 13.3 g (60.01% calculated from thiothiamine).

For purification, 13 g (VIII) was mixed with 100 ml distilled water, 5% nitric acid solution poured into pH 3.0, the solution decolorized with charcoal (1 g), filtered, 5% ammonia solution added to pH 9.0, and (VII) isolated as described above. Mp 180-181°C. Found, %: C 46.82, 46.78; H 5.40, 5.25; N 21.55, 21.60; S 19.29, 19.03. C₁₃H₁₁N₅O₅S₂·½H₂O. Calculated, %: C 46.96; H 5.46; N 21.07; S 19.29.

Similarly, (VII) was obtained by oxidizing thiothiamine with nitric acid. Yield was 62.5%.

Thiamine Mononitrate from Thiamine Thiocyanate (VII). A portion of (VII) (13.3 g) was mixed with 130 ml distilled water, 12% nitric acid solution (16 ml) added to pH 3.0 and then activated charcoal (1.3 g). The mixture was stirred for 30 min and filtered. The main filtrate and water washings were combined.
and passed through ion exchange resin (30 g anionite AV-17 or wofatite L-150 in a column of size 12 × 500 mm) at a rate of 100-120 ml/h. The resin was then washed with distilled water (300-400 ml) for the complete removal of thiamine (checked with thiochrome).

The solution of thiamine nitric acid salt (VI) collected from the column must not contain thiocyanate ions. If it forms a red coloration with silver chloride it is passed through the ion exchange column once again. It was then evaporated from 500-600 ml to 60-65 ml in vacuum at 40-50 °C. Sodium bicarbonate (3.5 g) was added to the concentrate to pH 6.5-6.8. In this way (I) was precipitated as a white solid. The reaction mixture was stored at 0 °C for 4 h. Then (I) was filtered off, washed with distilled water (3 times with 15 ml), and dried in vacuum at 60 °C to constant weight. Yield was 11.4 g, mp 181-182 °C (decomposition). The content of (I) was 99.97% in the dry substance.

The mother liquor and aqueous washings were combined, 0.5-1 g ammonium thiocyanate added, and then aqueous ammonia solution to pH 9.0. In this way (VII) precipitated from the solution and was separated as described above. Yield was 0.8 g. The yield of (I) was 92.7% allowing for recovered (VII) or 74.16% based on thiothiamine.

Compound (I) was isolated analogously with the aid of ammonium carbonate. The yield was 72.24% calculated on thiothiamine.

Preparation and Regeneration of Ion Exchange Resin. The ion exchange resin (30 g), either anionite AV-17 or wofatite L-150, was mixed with water and loaded into a column of size 12 × 500 mm, washed with water, 1 N nitric acid solution, and then distilled water until complete removal of free acid. The spent resin, after complete removal of thiamine was washed with 1 N nitric acid solution (300-400 ml), passing the solution through the column at 80-100 ml/h until complete removal of thiocyanate ion (check with silver chloride), and then washed with distilled water as indicated above.

Thiamine Mononitrate (I) from Thiothiamine (III). Thiothiamine (44.45 g) was oxidized with 28% hydrogen peroxide (52 ml) as described above. After purification with charcoal and addition of nitric acid