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MAIN METHODS OF SYNTHESIZING ISONIAZID IN LABORATORY

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ABSTRACT

Isonicotin hydrazine (INH) known as isoniazid is a first-line anti-tuberculosis drug. The main methods to synthesize this compound in the lab are: the reaction of isonicotinic acid and hydrazine and the reaction of isonicotinic acid ester and hydrazine. The recommended method for obtaining isoniazid is isonicotinic acid with hydrazine because the reaction temperature is low and the purification is done easily. In the laboratory syntheses were conducted to determine the best reaction conditions for the synthesis of isoniazid. In terms of duration synthesis is observed that with increasing reaction time the yield increases but the most convenient time interval is two hours.

KEYWORDS: Tuberculosis, isonicotinic acid, hydrazine, isonicotinic acid ethyl ester, air oxidation, oxidation with ozone, electrolysis method.

INTRODUCTION

Tuberculosis is one of the most common infections caused by Mycobacterium tuberculosis. According to the World Health Organization, nearly one third of the world population is exposed to the tuberculosis pathogen.

There are a number of factors that make people more susceptible to infection with tuberculosis, the most important is the human immunodeficiency virus (HIV). Also, smoking increases the risk of tuberculosis.

Isoniazid is an organic compound which is part of what makes the first-line drugs used in the prevention and treatment of tuberculosis.

This organic compound although it was discovered in 1912, was introduced in therapeutics since 1951, as a result of the discovery of tuberculosis antimycobacterium action Has also been shown efficient against tuberculosis by inhibiting mycolic acid.

Together isoniazid and rifampicin are the most active drugs to combat tuberculosis. Used in all forms of tuberculosis, combination with other synergists. It has very low toxicity and good tolerance. Isoniazid is never used alone to treat active tuberculosis because resistance quickly is developing.

Isoniazid also has an antidepressant effect. Isoniazid is a prodrug and must be activated by a bacterial enzyme catalaseperoxidase, which in M. tuberculosis KatG is called. It is bactericidal and bacteriostatic and inhibits P450.

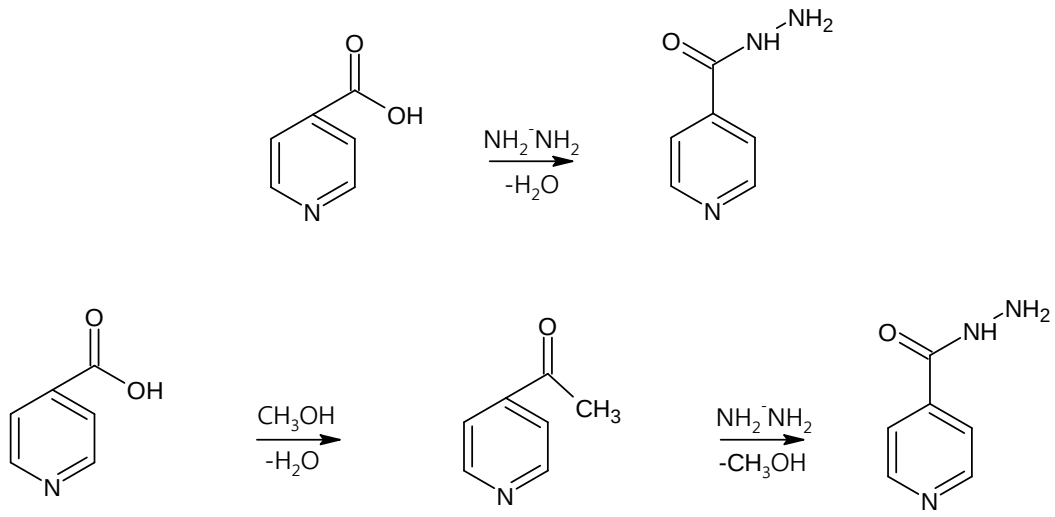
Isoniazid inhibits also the development stages of the malaria parasites (Plasmodium gallinaceum) produced by mosquitoes. Increasing drug resistance (such as rifampicin and isoniazid antimycobacterial) against strains of M. tuberculosis leads to the necessity of finding more effective drugs for the effective management of tuberculosis. New hydrazone have been prepared by the reaction of isoniazid (HIN) with benzaldehyde, o-chlorobenzaldehyde and vanilla. The compounds show activity in mice that were infected with different strains of M. tuberculosis, and indicates a lower toxicity than hydrazine, isonicotinic acid.

Isoniazid can be prepared by reaction of isonicotinic acid and methanesulfonyl chloride, followed by reaction with hydrazine. Using the acid chloride method may not be used industrially because it is uneconomical.

Isonicotin acetate was used for the enzymatic synthesis of isoniazid by transesterification in non-aqueous medium.

Isoniazid can be made in several chemical methods: The potassium permanganate oxidation, air oxidation, oxidation with ozone, electrolysis method.

Methods to synthesize isoniazid are: the reaction of hydrazine and isonicotinic acid, and reacting the ester isonicotinic acid and hydrazine. The reaction to produce the izonicotin hydrazide confrom the first embodiment is:



MATERIALS AND METHODS

Reagents and materials

Reagent used were isonicotinic acid (Sigma, Aldrich), hydrazine (Sigma, Aldrich), ethyl ester Reagents of isonicotinic acid

In this work reagents are analytical purity and used as such without further purification. Toluene (Sigma, Aldrich) and ethanol using other materials are used without special treatment.

Melting points were determined using a Melting Point Meter KRS-P1 capillary apparatus from the company Kruss Optronic GmbH.

The IR spectrum was carried out using a Perkin Elmer FTIR spectrophotometer - Spectrum 100.

Summaries

The first version is used to obtain isonicotinic hydrazide from ethyl ester isonicotinic acid. In a flask was introduced ethyl ester of isonicotinic acid, ethanol, and hydrazine hydrate. The reaction mixture was heated at 70^0C for 2 hours. The reaction was cooled izonicotin hydrazide precipitated, which was filtered and washed with water. The product is purified by recrystallization from water.

The second method consists in directly reacting isonicotinic acid with hydrazine. The reagents are placed in a flask and heat the mixture. After 2-3 hours it stops heating. Isoniazid crystallizes on cooling, is filtered under vacuum, purified by recrystallization and dried.

RESULTS AND DISCUSSION

Two variants were studied to obtain isoniazid. The syntheses were carried out in order to find the optimal reaction conditions to obtain the best yields possible

Thus, synthesis was carried out starting isoniazid from ethyl ester of isonicotinic acid and hydrazine (variant I), and the second method is a direct condensation of the isonicotinc acid with hydrazine (variant II).

In the variant I temperature is 70-75^{0}C, while in the case of the variant II, the synthesis is carried out at 129-130^{0}C. Duration of both variants is for 2 hours and 4 hours respectively.

The experimental data obtained are shown in Table I.

Table I: The experimental data obtained are shown.

Nr. Crt.	Synthesis variant	Time (Hours)	Yield (%)
1	Variant 1	2	70.8
		4	78.6
2	Variant 2	2	66.9
		4	70.1

It is noted that yields are higher in the synthesis of the first version, even when the reaction time increase from 2:00 to 4:00. In these circumstances it is preferred to work with version I, starting from isonicoticnic acid ethyl ester it is more economical because the reaction temperature is 70^{0}C. In this variant were varied the reaction parameters to obtain the best conditions for achieving a higher yield in isoniazid.

Variant 1 is used for the synthesis of isoniazid, by reacting isonicotinic acid ethyl ester and hydrazine. Were used the molar ratios isonicotinic acid ethyl ester: hydrazine of 1:1 to 1:3. It works in the presence of a solvent. In our case we used ethanol. The solvent was used at a rate of 15% compared to quantity of ester of isonicotinic acid used in the reaction.

The duration of the synthesis is 2 hours and a temperature of 70-75^{0}C. Results do obtained are shown in Table II.

Table II: Results do obtained are shown.

Nr. Crt	The molar ratio Ethyl ester of isonicotinic acid : hydrazine	Yield (%)
1	1:1	40.1
2	1:1:5	70.8
3	1:2	71.4
4	1:3	72.9

One can see an increase in yield with increasing molar ratio of ethyl ester of isonicotinic acid : hydrazine. Since the molar ratio of ethyl ester of isonicotinic acid : hydrazine is 1:1.5 where we obtain a yield of 70.8%, the yield increases, but this In this variant were varied the reaction parameters to obtain the best conditions for achieving a higher yield in isoniazid. increase is not spectacular. It is therefore not necessary to use greater amounts of hydrazine.

The influence of the reaction time

To determine the best reaction time, track the yield variation after 1, 2, 4 and 6 hours of reaction. Operating temperature is from 70-75^{0}C. The molar ratio of the reactants ethyl ester of isonicotinic acid: hydrazine used is 1:1.5. Solvent at a rate of 15% compared to the amount of ethyl ester of isonicotinic acid used.

In Table III are shown the experimental data obtained in the synthesis conditions.

Table 3: Experimental Data.

Nr. Crt	Time (Hours)	Yield (%)
1	1	30
2	2	70.9
3	4	78.6
4	6	79.1

With increasing the reaction time the yield increases in the isoniazid. The optimal time is 4 hours. After that increasing the the yield is too small to justify increasing the duration of the synthesis, which requires energy.

Isoniazid obtained was processed and purified by crystallization. After hot filtration, the filtrate was cooled and the crystals of isoniazid solution was filtrate in vacuum and dried in an oven.

Isoniazid crystallized was analyzed for properties physico-chemical. Melting point determined was 170-171^{0}C, which indicates that the managed purification by recrystallization

of isoniazid. From IR spectrum measured with a spectrophotometer FT-IR Perkin Elmer can observe some characteristic absorption bands of isoniazid. Very intense peak at 1668 cm-1 were assigned to the characteristic stretching vibration group C=O of amide υC=O. In around 1638 cm-1 appears a little intense which is characteristic of specific asymmetric stretching vibration group C=N υc=N. Absorption bands assigned to the pyridine ring appear at 1557 cm-1 (i) corresponding to stretching vibrations υC=N and 1493 cm-1 (i) corresponding to stretching vibrations of υC-N-H. Other peaks occur at 1336 cm-1 (i) corresponding to the characteristic bands υC-N stretching vibration and 1222 cm-1 (vi) of the vibration characteristic δC-CH asymmetric deformation. Also appears absorption band at 1143 cm-1 (s) is specific vibration δN-NH2 stretch. Absorption bands appearing below 1000 cm-1 are at 889 cm-1 characteristic δC-CN bending vibrations (characteristic cycle) at 846 cm-1 characteristic of symmetrical bending vibrations δC-C-H and 677 cm-1 corresponding bending vibrations δCC=O.

CONCLUSION

Through research conducted and presented in the paper were determined reaction conditions best if isoniazid synthesis by reaction of ethyl isonocotinic and hydrazine. Thus it was found that the variant starting from isonicotinic acid ethyl ester. It was determined the molar ratio of ester and hydrazine and reaction time best, such as how to obtain higher yields in isoniazid.

The obtained compound was purified by recrystallization and characterized from the point of view of physico-chemical properties.

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