# SYNTHESIS OF ISONIAZID FROM 4-CYANOPYRIDINE

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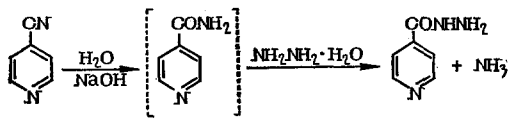
UDC 615.281.221.1(ISONIAZIDUM).012.1

Isoniazid, the hydrazide of isonicotinic acid, is a highly active tuberculostatic compound which is widely used for the medical treatment of all forms of tuberculosis of the lungs in both children and adults. In the Soviet Union isoniazid is derived from the $\beta$-picoline fraction containing $\gamma$-picoline or from pure $\gamma$-picoline which is converted to a mixture of its methylol derivatives, which are in turn oxidized with nitric acid to isonicotinic acid; the latter is converted to the ethyl ester through its acid chloride, and by reacting the ester with hydrazine hydrate, the hydrazide is obtained. This method consists of five steps and is associated with the use of such reagents as nitric acid, thionyl chloride, etc.

Lately, work on the search for new, more ideal methods of synthesizing isoniazid is being carried out in a number of countries. One of them is based on the employment of 4-cyanopyridine, which can be prepared by the oxidative ammoniolysis of $\gamma$-picoline with a 90% yield* [1] as the starting raw material.

The method of synthesizing isonicotinic acid hydrazide from 4-cyanopyridine has been described in the patent literature [2-4]. According to these patents, 4-cyanopyridine is reacted with hydrazine hydrate in an aqueous alkaline medium, and the hydrazide is obtained with a yield of 50 to 62% of theoretical. A similar method of synthesizing isoniazid has also been described which differs by the fact that the isonicotinamide formed during the alkaline hydrolysis of 4-cyanopyridine is isolated and then reacted with hydrazine hydrate; the isoniazid yield based on the amide is about 55% [5].

Later, it was shown that when the alkaline hydrolysis of 4-cyanopyridine is carried out in the presence of hydrazine hydrate, a difficultly soluble by-product is formed consisting chiefly of 3,5-bis-(pyridyl-4)-4-amino-1,2,4-triazole; freeing the isoniazid from the latter has been completely unsuccessful [6]. Therefore, it was proposed that the alkaline hydrolysis of 4-cyanopyridine to the amide be carried out first, and then, without isolating the latter, react it with hydrazine hydrate. The hydrazide formed is crystallized from water and 60 to 65% of the pure isoniazid based on the nitrile is obtained (the product obtained from the mother liquors was accounted for) [6, 7].




During the development of a laboratory procedure for preparing isoniazid from 4-cyanopyridine, we used the latter method [6, 7], whereby the temperature regulation, ratio of reagents, and their rate of addition were defined more accurately. In addition, the treatment of the reaction mixture was changed; instead of partially concentrating the aqueous mother liquors and crystallizing the technical hydrazide from water, the aqueous mother liquors were evaporated to dryness and the crystallization was carried out from methanol. This method of treatment provides a higher isoniazid yield (65-69%) and better quality; when we crystallized the isoniazid from water, the maximum yield in our experiments amounted to 58%, and the prep-

*The 4-cyanopyridine obtained by this method was kindly submitted to us by B. V. Suvorov and co-workers at the Institute of Chemical Sciences, Academy of Sciences of the Kazakh SSR in order to carry out this work.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 6, No. 11, pp. 6-8, November, 1972. Original article submitted August 26, 1971.

aration did not always meet the color requirements of the 10th Edition of the State Pharmacopoeia because of the presence of a slight yellow color.

The residue left after evaporating the methanolic mother liquors was saponified with an aqueous alkaline solution, and isonicotinic acid was isolated in a 15 to 20% yield based on the original 4-cyanopyridine. We carried out experiments on the conversion of this isonicotinic acid through its methyl ester (without additionally purifying it) to isoniazid. Isoniazid which met all the requirements of the 10th Edition of the State Pharmacopoeia was thereby obtained; its yield was about 60% based on the isonicotinic acid.

Thus, the overall isoniazid yield, upon taking into account the nicotinic acid that was isolated, amounts to about 80% (without taking into consideration the mother liquors which remain after synthesizing the isoniazid through the methyl ester, from which an additional amount of isonicotinic acid can be obtained after saponification).

## EXPERIMENTAL

### Synthesis of Isoniazid

Synthesis of Technical Isonicotinic Acid Hydrazide. Into a 500-ml three-necked flask equipped with a stirrer, thermometer, and reflux condenser was charged 104.11 g (1 mole) of 4-cyanopyridine (mp 79-81°C) and 112 ml of distilled water. The mixture was heated to 40°C, and 25 ml of 8% aqueous sodium hydroxide was added at this temperature over a 30 min period; the sediment quickly dissolved at this time. The reaction mixture was boiled for 1 h, then slightly cooled, and 152.6 ml (1.5 mole) of a 49.2% aqueous hydrazine hydrate solution was added dropwise at 95°C and with agitation over a 20 min period.* The reaction is accompanied by the rather energetic evolution of ammonia. After the addition of the hydrazine hydrate, the temperature within the flask was raised to 100-104°C, and the solution was stirred at this temperature for 3 h; then the reaction mixture was maintained for 12 h at 0°C. The precipitate of isonicotinic acid hydrazide was filtered off, washed first with 25 ml of distilled ice water, then with 31 ml of methanol cooled to −5°C, and air dried for 3-4 h. A total of 83 g of the technical hydrazide was obtained.

The aqueous mother liquor was evaporated in vacuo at 20-25 mm and at a temperature not higher than 60°C until the liquid had ceased distilling off; the remaining moist mass was recrystallized from 100 ml of methanol containing 3.5 g of carbon. After maintaining it for 12 h at 0°C, the isoniazid residue was filtered off, washed with 25 ml of methanol cooled to −5°C, and air dried. A total of 20.23 g of technical isonicotinic acid hydrazide was obtained. The methanolic mother liquor (A) was evaporated and the remainder was saponified to isonicotinic acid (see below).

Synthesis of Pharmacopoeia-Grade Isonicotinic Acid Hydrazide (Isoniazid). In a 1500 ml flask equipped with a reflux condenser was dissolved with heating in 760 ml of methyl alcohol 83 g of the technical grade isonicotinic acid hydrazide isolated from the reaction mixture. The hot solution was treated with 7.5 g of carbon and after filtering and cooling to 4-6°C for 12 h, the isoniazid precipitate was filtered off, washed with cold methanol, and dried at a temperature not higher than 50°C. A total of 69 g of isoniazid was isolated as a white crystalline substance with a mp of 170-174°C, which meets the requirements of the 10th edition of the State Pharmacopoeia.

The methanolic mother liquor (containing about 14 g of isoniazid) was combined with the wash methanol, evaporated in vacuo (20-25 mm) to a volume of about 270 ml, and was used to recrystallize the hydrazide obtained from the aqueous mother liquors (20.23 g). After the usual treatment and drying, an additional 26 g of pharmacopoeia grade isoniazid was obtained. The overall isoniazid yield was 95 g, which amounts to 69.27% of theoretical based on the 4-cyanopyridine. The methanolic mother liquor (B) was evaporated, and the residue was saponified to isonicotinic acid.

Treatment of the Mother Liquors from the Isoniazid and the Isolation of the Isonicotinic Acid. The combined methanolic mother liquors A and B (after the first and second crystallization of the isonicotinic acid hydrazide obtained from the evaporated, aqueous mother liquors) were evaporated to dryness in vacuo at 20-25 mm; to the residue was added 62 ml of 10% aqueous sodium hydroxide, and the mixture was re-

*We used 47-49% hydrazine hydrate solutions in all the experiments; an accurate assay was obtained by titration. The use of a large excess of hydrazine hydrate is expedient, as our experiments demonstrated.

fluxed for 3 h. To the yellow, slightly turbid solution was added 62 ml of water; it was again heated to boiling. Three g of carbon was added, and it was boiled 2-3 min and filtered while hot. After cooling the filtrate, concentrated hydrochloric acid (d 1.178) was added to it dropwise to pH 3.0 while stirring.

The light-yellow crystalline residue of isonicotinic acid that separated out was filtered off, washed with water, and dried at 50°C. A total of 25.35 g of 92% isonicotinic acid was obtained (23.32 g calculated on the 100% acid basis) with decomp. point 307-309°C. The isonicotinic acid yield (calculated on the 100% basis) amounts to 19% of theoretical based on the amount of 4-cyanopyridine used in the reaction.

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