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**STUDIES IN THE FIELD OF CHEMISTRY OF NITRO COMPOUNDS (TO 100TH BIRTHDAY ANNIVERSARY OF S. S. NOVIKOV)**

# Development of Improved Laboratory Technique for Nicorandil Synthesis

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**Abstract**—Results of a study of a two-stage laboratory technique for nicorandil synthesis from nicotinic acid ethyl ester are presented. The process for nicorandil synthesis is fundamentally improved.

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The research team headed by S.S. Novikov, for the most part aimed to solve applied problems, has devoted a considerable attention to synthesis and analysis of properties of nitrates of organic polyfunctional alcohols. Historically, nitrates are double-purpose compounds. For example, manufacture of nitroglycerine is known to specialists as a basis for development of dynamites and powders. At the same time, nitroglycerine is a means for curing heart pains. Nicorandil, a compound containing a nitrate group, is presently regarded as the most effective basis of anti-stenocardia medicinal preparations.

According to published evidence, nicorandil was first obtained in Japan in 1976. Several patents for nicorandil synthesis were issued in other countries [1–5]. Also known are later publications about nicorandil synthesis in China [6], Poland [7], Romania [8], India [9], and other countries. Nicorandil is not manufactured in Russia.

## EXPERIMENTAL

The total number of publications devoted to nicorandil has exceeded a thousand, whereas the chemistry and synthesis technology of this compound have been reflected in not more than one-and-a-half tens of communications. For the most part, these are the already mentioned patents and published data with a minimum amount of technological information. At the same time, analysis of these data reveals a number of shortcomings in the existing technological processes for nicorandil synthesis.

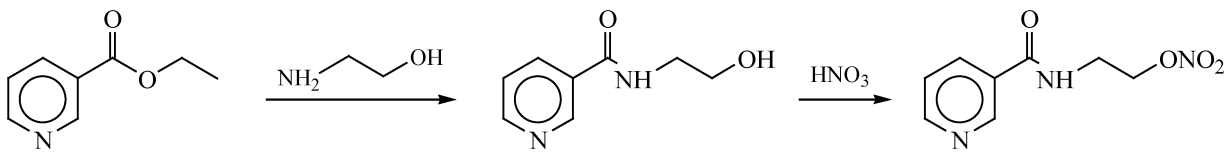
We used as the starting product for synthesis the industrially manufactured ethyl nicotinate (**I**), which reacts with 2-amino alcohol to give *N*-(2-hydroxyethyl)ni cotinamide (**II**). Nitration of **II** yields the target nicorandil (**III**) (see the Scheme).

The scheme is not novel. However, the above analysis of published data suggests several improvements of the laboratory technique for nicorandil synthesis. The aim of our study was the following.

(i) To improve the stage in which **II** is obtained from **I** with the excess components regenerated.

(ii) To modify the process of nitration of **I** to exclude detonable combinations of the components.

**Scheme.**




**I** **II** **III**

(iii) To introduce, in the stage of purification of nicorandil, its crystallization from water, with the aqueous mother liquor recycled.

In addition, it was necessary to make nicorandil less expensive by lowering the cost of the starting raw materials, creating more favorable technological conditions, and pursuing the goal of developing a nonwaste production process.

**Improvement of the stage of synthesis of *N*-(2-hydroxyethyl)nicotinamide (II).** The above process for nicorandil synthesis was fully reproduced by Chinese researchers [9]. Heating of **I** with an excess amount of amino alcohol produced **II** in 87% yield, nitration of **II** with fuming nitric acid gave **III** in 80% yield.

Conditions have been found in which boiling of **I** with a 50% excess of amino alcohol in ethanol produced **II** in nearly quantitative yield [10]. This provides complete utilization of **I**, which is the most expensive component among those necessary for obtaining **II**. A method has been developed for regeneration of ethanol and the excess amino alcohol by fractional distillations with the use of rectification units (reflux condenser with a full-condensation head) [10]. In this case, up to 95% of ethanol present in the reaction mass (including ethanol formed in the interaction of **I** with amino alcohol) and up to 85% of the excess amino alcohol can be recycled. The regenerated components can be used in further cycles of **II** synthesis. With account taken of the amount of ethanol released in the reaction, the achieved degree of its regeneration does not require addition of fresh ethanol in subsequent cycles. Only a new portion of **I** and the necessary amount of amino alcohol are consumed, which, combined with the regenerated product, provides its 50% excess. The residue obtained upon the regeneration is a colored oil with embedded crystals. The amount of the residue is 1–2% relative to the mass of **II** obtained. This residue was eliminated by burning [10]. Particular attention was paid to the purity of the starting products in the stage of synthesis of **II**, compound **I**, amino alcohol, and ethanol. These should be colorless liquids with refractive indices and densities corresponding to reference data. At room temperature, **II** crystallizes into a glassy mass which is difficult to grind to obtain a product with a suitable size and shape of particles. Compound **II** is hygroscopic, and becomes colored in storage. The coloration is imparted to nicorandil upon nitration. No methods for purification of **II** were found. Therefore, after vacuum evaporation of ethanol and amino alcohol, melted **II** was directly batched into the nitrating mixture. This is a characteristic feature of the suggested technological process [10] and technologically combines the reactions by which nicorandil is obtained from ethyl nicotinate into a single chain.

**Modification of the process of nitration of II to give nonrecrystallized nicorandil.** It has been recommended to use, in the stage of nitration of *N*-(2-hydroxyethyl)nic otinamide **II**, concentrated (fuming) nitric acid at as low temperature as possible to preclude side reactions with other reactive centers of the molecule of **II** [1, 2, 4, 7, 11]. The effect of the acid concentration on the formation of nicorandil was demonstrated in the patent [11].

When assessing the safety of nitration, it is necessary to keep in mind the ability of concentrated nitric acid to form explosive mixtures with organic compounds. Equally dangerous are solutions produced by addition of **II** to concentrated nitric acid. A test of the detonation properties of such solutions by the method recommended by GOST (State Standard) 5984–80 demonstrated that a solution of **II** in 94% nitric acid has an explosion power comparable to that of the known explosive, TNT, and a solution in 100% acid exceeds TNT in explosion power by approximately 6%.

Methods for lowering the detonation capacity of nitro masses containing nitric acid have been, in principle, developed. For this purpose, nitric acid can be diluted with energetically inert compounds, e.g., methylene chloride or chloroform [1, 2, 4]. However, there is no published evidence about the absence of detonation capacity for nitro masses based on nitric acid diluted in this way. The most attractive diluent is concentrated sulfuric acid; however, by no means all alcohols can be successfully nitrated with sulfuric-nitric mixtures. It has been found that mixtures of this kind can be used to sufficiently selectively perform nitration of compound **II** at oxygen [12]. This opportunity opens up certain prospects for improving the technology of nicorandil synthesis.

Sulfuric acid and its mixtures with most of organic compounds are explosion-proof. It should be noted that alcohol (II) is nearly insoluble in sulfuric acid and the nitration process occurs more effectively if the nitrating mixture contains, in addition to nitric and sulfuric acids, 10–15% water. In addition to having a phlegmatizing effect, water improves the economical parameters of the process. It can, e.g., be introduced into the sulfuric-nitric mixture together with the comparatively inexpensive self-produced nitric acid containing 65–70% main substance.

Results of nitration of N-(2-hydroxyethyl)nicotinamide (III) with mixtures of nitric and sulfuric acids

| Content of components in nitrating mixture, wt % | | | Mass fractions of mixture per mass fraction of (II) | Temperature of nitration and keeping, °C | Keeping time, h | Yield of nicorandil, % | Melting point of nicorandil, °C |
|---|---|---|---|---|---|---|---|
| $HNO_3$ | $H_2SO_4$ | $H_2O$ | | | | | |
| 33.5 | 52.9 | 13.6 | 3.48 | 8–12 | 0.5 | 83 | 91–92 |
| 34.5 | 54.5 | 11.0 | 4.31 | 15–18 | 1.0 | 84 | 91–92 |
| 34.5 | 54.5 | 11.0 | 4.31 | 20–25 | 0.5 | 83 | 91–92 |
| 24.2 | 65.5 | 10.3 | 4.83 | 8–12 | 0.5 | 88 | 91–92 |
| 23.1 | 62.9 | 14.0 | 5.02 | 8–12 | 0.5 | 83 | 91–92 |
| 44.4 | 42.2 | 14.4 | 4.46 | 0–5 | 1.0 | 84 | 91–92 |

Such an acid has its own GOST, is manufactured in a rather pure state, and is well stored without changes in its characteristics.

Our study included an extensive set of experiments devoted to a search for nitrating mixtures based on nitric and sulfuric acids, which would exhibit no detonation properties when being tested in conformity with GOST 5984–80 and, at the same time, would provide satisfactory results in the yield and quality of nicorandil formed. The table lists selected results obtained in nitration of **II** with mixtures of various compositions at various mass ratios between **II** and a mixture. The introduction of **II** and the subsequent keeping of the nitro mass until a transparent solution was formed were carried out under vigorous agitation.

As a result of the experiments, we introduced a limitation on the content of nitric acid in nitrating mixtures. It should not exceed 45% [12]. At a higher content of nitric acid, nitro masses acquire a detonation capacity upon nitration. The nitro mass was neutralized upon completion of the nitration with a concentrated aqueous solution of ammonia, instead of alkali metal carbonates recommended in [1, 2, 4, 7, 11]. This was done to diminish the reaction volume in neutralization by precluding formation of a foamed solution, whose thermal conductivity is lower, compared with the homogeneous solution, in cooling in the course of neutralization.

Because a study of nicorandil revealed its lowered thermal stability, compared with the known nitrates (nitroglycerine, nitrosorbitol) [14], we made efforts to keep the temperature of crystalline nicorandil below 50°C. In doing so, we paid particular attention to drying. As for the general result of experiments on nitration of **II** with sulfuric-nitric mixtures, it can be seen from the table that the yield and quality of unpurified nicorandil are not strongly dependent on other characteristics of the nitration process, included in the table. Possibly more important here are the agitation and cooling modes, which were not strictly specified. The most significant advantage of this improvement is the considerable decrease in the expenditure of nitric acid and the possibility of stable nitration at higher temperatures, up to room temperature.

Crystallization of nicorandil from water and recycling of the aqueous mother liquor. A significant distinction of the suggested process is that water used as a solvent for nicorandil purification by crystallization and the aqueous mother liquor remaining after the crystallization is recycled [10, 12].

A number of solvents for nicorandil purification by recrystallization have been suggested in the literature. Most frequently, mixtures of diethyl ether with ethanol or isopropanol are mentioned [1–5]. Their use makes the whole process more fire-hazardous and contributes to the final cost of the process. The crystallization loss is not specified. After a purification of this kind, nicorandil has mp 92–93.5°C.

It has been found that nicorandil can be purified by recrystallization from distilled water [12]. It is believed that water is the best suitable for additional purification of the product obtained by nitration of **II** with a sulfuric-nitric mixture. After a recrystallization of this kind and vacuum drying, the melting point of nicorandil also increases to 92–93.5°C. However, the decision to use water for purification requires special explanation because there are several contraindications to use of water in nicorandil synthesis.

It is known [13] that nicorandil decomposes in aqueous solutions. When dissolving nicorandil at 60°C, we isolated four decomposition products whose predominant formation strongly depends on the acidity of the medium. Also rather complicated and unconventional for nitrates is the previously described [14] conversion of nicorandil at temperatures lower than its melting point. An increase in the relative humidity of air substantially affects the preservation of the product. Possibly, this is the reason why medicinal preparations based on nicorandil require special protection from atmospheric moisture.

In the given case, a high-quality product was isolated in a ~80% yield in nicorandil recrystallization from water at a temperature of 50°C. Thus, the overall yield of nicorandil in nitration of **II** with a sulfuric-nitric mixture (see table) was, with the yield of raw nicorandil taken into account, about 70%. According to [7], the yield of nicorandil in nitration of **II** with concentrated nitric acid at lowered temperature was 85–86%.

An additional economical substantiation of the given method for nicorandil synthesis is utilization of the aqueous mother liquor remaining after recrystallization of raw nicorandil at 50°C (see table), which was evaporated to dryness in a vacuum at room temperature. The residue was a substance with mp ~90°C and exhibited no melting point depression on being mixed with purified nicorandil. Its amount was about 17% relative to the mass of nicorandil taken for recrystallization. To utilize nicorandil remaining in the mother liquor, this solution was used instead of water for dilution of the nitro mass before its neutralization with ammonia. As a result, the yield of nicorandil released in neutralization could be raised to 94% and made nearly quantitative. This product was, as before, purified by recrystallization from water and the mother liquor was again used to dilute the nitro mass.

Thus, with the exception of a small amount of waste burnt after the regeneration of ethanol and monoethanolamine, nearly the only production waste was the aqueous solution of ammonium nitrate and sulfate, with admixture of a small amount of water-soluble products of nicorandil conversion. Taking into account the possible use of ammonium salts as mineral fertilizers, we can conclude that prerequisites are created for development of almost nonwaste nicorandil production technique.

## CONCLUSIONS

(1) An improved method for nicorandil production from the industrially manufactured ethyl nicotinate was developed. Two stages of the process are technologically combined.

(2) The explosion- and fire-hazard of nicorandil production are significantly lowered by exclusion of detonable mixtures of components from the process and by substantial decrease in the necessary amounts of combustible fluids, for which regeneration procedures were developed.

(3) The cost of the components is lowered and a number of technological parameters in the stages of nitration and neutralization of the nitro mass and product purification by crystallization are improved.

(4) Introduction of an ammonia solution in the stage of nitro mass neutralization and water in the purification stage creates prerequisites for development of a nearly nonwaste nicorandil production process.

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## REFERENCES

1. US Patent 4200640.
2. Brevet d·invention 853144.
3. FRG Patent 2.714.713.
4. USSR Patent 942593.
5. USSR Patent 999965.
6. Jiao, J., Huang, Q., Cao, X., Li, Q., and Zhang, D., *Chin. J. Med. Chem*., 1990, no. 1(1), pp. 75–76.
7. Rzeczpospolita Polska Patent 162496.
8. Nr. brevet 114613.
9. Patil, V.D. and Viswanatban, C.L., *Indian J. Pharm. Sci*., 1999, vol. 61, no. 5, pp. 304–305.
10. RF Patent 2341517.
11. RF Patent 2147577.
12. Japan Patent H.2-207072.
13. Nagai, H., Kikuchi, M., Nagano, H., and Shiba, M., *Chem. Pharm. Bull*., 1984, vol. 32, no. 3, pp. 1063–1071.
14. Dubikhin, V.V., Eremenko, L.T., Eremenko, I.L., et al., *Dokl. Akad. Nauk*, 2000, vol. 374, no. 6, pp. 790–791.