Pharmaceutical Chemistry Journal *Vol. 36, No. 1, 2002*

DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

CATALYTIC CONVERSION OF NICOTINE INTO NICOTINONITRILE – A PHARMACEUTICAL INTERMEDIATE PRODUCT

A. D. Kagarlitskii,[1] M. K. Iskakova,[2] and A. Zh. Turmukhambetov[2]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 36, No. 1, pp. 26 – 27, January, 2002.

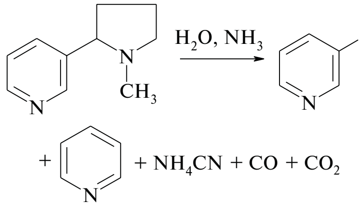
Original article submitted August 30, 2001.

An important problem of the tobacco industry is related to the utilization of wastes. The amount of such products is quite large: for example, the Alma-Ata Tobacco Plant (Philip Morris – Kazakhstan Company) alone puts into storage more than one thousand tons of wastes a year. As is known, until the middle 1960s tobacco wastes were reprocessed into nicotinic acid by extracting the alkaloid nicotine, followed by oxidation with nitric acid or potassium permanganate. However, this technology turned out to be economically ineffective and went out of use.

We believe that a promising course of action is to convert nicotine, as well as the accompanying alkaloids (anabasine, nornicotine, nicotyrine, myosmine, anatabine) extracted from tobacco, into nicotinic acid nitrile by means of oxidative ammonolysis – an effective pathway for the synthesis of pyridinecarboxylic acid nitriles from alkylpyridines [1]. The possibility of such transformation is confirmed by the results of our experiments on the oxidative ammonolysis of anabasine, a nicotine isomer [2]. Nicotinonitrile synthesized in this way can be used for the synthesis of vitamin PP (nicotinic acid and nicotinamide) and a series of drugs such as cordiamine, nicodine, coamide, feramide, etc.

The process of oxidative ammonolysis was effected with three oxide catalysts that proved to be most effective in the synthesis of nicotinonitrile from 3-methylpyridine [3]. Two of these catalysts, representing vanadium pentoxide (catalyst K1) and a mixture of vanadium pentoxide with titanium dioxide ($V_2O_5 - TiO_2$) in a molar ratio of 1 : 0.5 (catalyst K2), were prepared by melting. The third catalyst was prepared by pelletizing a mixture of the same initial components V_2O_5–TiO_2 taken in the ratio 1 : 16 (catalyst K_3), followed by calcining the pellets at 850 – 900°C.

The results of our experiments showed that the compositions of reaction mixtures obtained in the presence of catalysts K1 – K3 are qualitatively the same. The main reaction mixture components are nicotinonitrile and deeper oxidation products – ammonium cyanide and carbon and nitrogen oxides. The overall process of nicotine transformation can be described by the following scheme:



As the reaction temperature is increased from 380 to 460°C, the target product yield initially grows to reach a maximum at about 420°C and then drops as a result of the increasing proportion of deeper oxidation products (Table 1).

Approximately the same pattern is observed on increasing the reaction duration on catalysts K1 and K2 (Table 2), for which the optimum contact time is 0.5 sec. A somewhat

TABLE 1. Dependence of Nicotinonitrile Yield on Process Temperature for Catalysts K1 – K3 (Reagent Ratio: Nicotine–NH_3–H_2O, 1 : 16 : 100; Contact Time: τ = 0.76 sec)

T, °C	Yield, %		
	K1	K2	K3
380	30.0	25.0	42.0
400	48.0	39.0	44.0
420	50.0	60.0	46.5
440	48.0	45.0	44.0
460	45.0	37.0	42.0

---

[1] Kazakh State Medical University, Alma-Ata, Kazakhstan.
[2] Institute of Phytochemistry, Ministry of Education and Science of the Republic of Kazakhstan, Karaganda, Kazakhstan.

TABLE 2. Dependence of Nicotinonitrile Yield on the Contact Time for Catalysts K1 – K3 (Nicotine–NH_3–H_2O, 1 : 16 : 100; Process Temperature $T = 420°C$)

τ, sec	Yield, %		
	K1	K2	K3
0.3	42.0	48.0	43.0
0.4	45.0	52.0	43.0
0.5	50.0	65.0	44.0
0.6	49.0	58.0	45.0
0.76	48.0	58.0	46.5
1.0	45.0	43.0	46.5

TABLE 3. Dependence of Nicotinonitrile Yield on Ammonia Concentration for Catalysts K1 – K3 (Nicotine – H_2O, 1 : (110 – 130); τ = 0.5 sec; $T = 420°C$)

Nicotine : NH_3, mole/mole	Yield, %		
	K1	K2	K3
1 : 8	40.0	36.3	29.0
1 : 12	44.0	52.6	29.0
1 : 16	50.0	68.0	45.0
1 : 20	70.0	59.0	50.0
1 : 25	58.0	56.0	50.0

TABLE 4. Dependence of Nicotinonitrile Yield on Amount of Water for Catalysts K1 – K3 (Nicotine – NH_3, 1 : (16 – 20); τ = 0.5 sec; $T = 420°C$)

Nicotine : H_2O, mole/mole	Yield, %		
	K1	K2	K3
1 : 85	28.0	51.0	30.0
1 : 105	48.0	60.0	40.0
1 : 120	40.0	65.0	45.0
1 : 140	65.0	70.0	48.0
1 : 155	56.0	70.0	50.0
1 : 175	52.0	55.0	50.0

different behavior is observed for catalyst K3, on which the yield of nicotinonitrile continuously grows as the contact time increases from 0.3 to 1.0 sec.

The effect of the concentration of ammonia and water in the contact zone on the selectivity of conversion of nicotine into nicotinonitrile is illustrated by the data in Tables 3 and 4. By varying the supply of these reagents from 8 to 25 and 85 to 175 moles per mole of the initial reagent, respectively, we established that the optimum reaction conditions are provided by the molar ratios of nicotine to ammonia 1 : (16 – 20) and nicotine to water 1 : (140 – 155).

A comparison of the results of the oxidative ammonolysis of nicotine showed that the three catalysts can be arranged in the following order with respect to selectivity: K1 = K2 > K3. Using the first two systems, it is possible to convert nicotine into nicotinic acid nitrile with a sufficiently high yield reaching (provided that the other process parameters are optimized as well) up to 65 – 70%.

Our experiments on the oxidative ammonolysis of nicotine were studied in a single-tube reactor representing the element of a commercial reactor [4]. The experimental setup consists of three main parts: reagent supply system, flow contact reactor, and reaction product collector. The initial substance was nicotine, extracted with benzene from wastes of the Alma-Ata Tobacco Plant, representing a liquid with b.p. = 238 – 242°C and $n_D^{20} = 1.5250$.

The products of the oxidative ammonolysis of nicotine were analyzed on a Chrome-5 chromatograph equipped with a 2.5 m × 3 mm column containing a 5% SE-30 immobile phase on inerton AW – HMDS (0.2 – 0.25 mm fraction). The chromatography conditions were as follows: column temperature, 160°C; evaporator temperature, 200°C; detector temperature, 190°C; carrier gas (argon) flow rate: 30 ml/min (argon); air flow rate, 300 ml/min. Sometimes, parallel analyses were conducted by methods of bulk chemical analysis and gravimetry, with isolation and identification of the target reaction product. Nicotinonitrile isolated from the catalytic reaction mixtures was characterized by m.p. = 49°C and b.p. = 240°C; the data of elemental analyses corresponded to the results of analytical calculation according to the empirical formula.

Thus, the results of our investigation showed that the alkaloid nicotine can be effectively converted into nicotinonitrile, which paves the way for utilizing large-scale tobacco industry wastes for obtaining valuable pharmaceuticals.

REFERENCES

1. B. V. Suvorov, S. R. Rafikov, and A. D. Kagarlitskii, *Usp. Khim.*, **34**(9), 1526 – 1548 (1965).
2. M. K. Iskakova and A. D. Kagarlitskii, *Khim. Prirod. Soedin.*, No. 6, 771 – 773 (1999).
3. USSR Inventor’s Certificate No. 298163 (1970); *Ref. Zh. Khim.*, 11L162P (1974).
4. A. D. Kagarlitskii, V. R. Kudinova, S. R. Rafikov, et al., *Izv. Akad. Nauk KazSSR*, *Ser. Khim.*, No. 2, 23 – 29 (1966).