SYNTHESIS OF NITRONICOTINES

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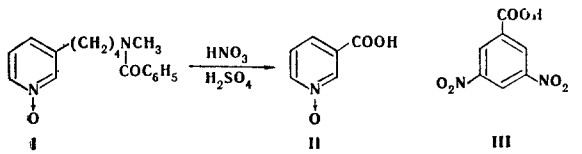
A number of nitro- and bromonitronicotines have been synthesized by the oxidation of the corresponding aminonicotines with Caro's acid. A nitro group in the α position of the pyridine ring of a nitronicotine is capable of being replaced by an ethoxy group under the action of sodium ethoxide, but in this process the reduction of the nitro group is also observed. The halogen in the bromonitronicotines readily undergoes nucleophilic replacement by a phenylthio group under the action of sodium thiophenoxide.

In a broad study of the pharmacology of nicotine and its derivatives, the extremely interesting fact was established that the introduction of an amino group into the pyridine ring of the molecule of this compound leads to a sharp fall in toxicity (see, for example, [1]) although in some other respects its pharmacological features are retained, at least qualitatively in its amino derivatives. The significance of this fact appears still more clearly if it is considered that α-aminopyridine, of which the aminonicotines are derivatives, is more toxic than pyridine [2], and aniline is more toxic than benzene. It may be assumed that the reduction in toxicity as the result of the conversion of nicotine into its amino derivative is connected to some extent with the racemization that takes place on amination, but it is fairly obvious that it is impossible to exclude the influence of other factors from consideration. In this connection, we may mention that another type of process – the oxidation of the pyridine moiety of the nicotine molecule to the N-oxide – also leads to a very pronounced fall in toxicity [3].

In the light of what has been said, it was of interest to obtain nitro derivatives of nicotine and substitution products of these derivatives and to study their pharmacological properties. This would create the possibility of the broader comparison in pharmacological respects of compounds of the pyridine and aromatic series bearing similar substituents. Furthermore, it appeared desirable to investigate the antibacterial spectrum of the nitronicotines, since, as is well known, the products of the nitration of some heterocyclic systems are characterized by bactericidal properties. In addition to this, the introduction of a nitro group into the pyridine ring of the nicotine molecule would to some extent facilitate nucleophilic substitution reactions and thereby broaden the possibilities of obtaining substances with potential biological activity.

Of the nitro derivatives of nicotine, only 2- and 6-amino-5-nitronicotines have been described [4]. Attempts to introduce a nitro group into the pyridinic N-oxide of nicotine by nitration were unsuccessful [5], although the nitration of pyridine N-oxide itself and its derivatives takes place fairly readily [6-9]. It might be thought that these difficulties were connected with the closeness to the ring of a strong basic center – the pyrrolidine nitrogen atom – which, under the conditions of electrophilic reactions, is protonated and acquires a positive charge. However, when the Py-N-oxide of benzoyldihydrometanicotine (I) that we had obtained, in which the nitrogen atom belonging to the pyrrolidine part of the molecule is absent, was subjected to treatment with nitrating mixture, only the N-oxide of nicotinic acid (II) (11%) and 3,5-dinitrobenzoic acid (III) (57%) were isolated.

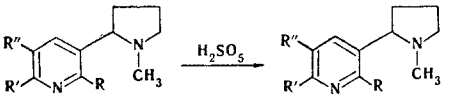


I II III

N. D. Zelinskii Institute of Organic Chemistry of the Academy of Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1062-1066, August, 1973. Original article submitted July 6, 1972.

Thus, in this case, as well, no nitration of the pyridine ring takes place. Consequently, another method for obtaining the derivatives of interest to us was selected – the oxidation of the amino group in the readily accessible aminonicotines [10] by means of Caro's acid. Various nitropyridines have been synthesized by this method with fairly good yields [11-13].

The oxidation with Caro's acid of 2- and 6-aminonicotines (IV and V) gave 2- and 6-nitronicotines (VI and VII) with yields of 53 and 70%, respectively. The presence of bromine in the pyridine ring in the case of 5-bromo-2-aminonicotine and 5-bromo-6-aminonicotine (VII and IX) considerably decreased the yields of the corresponding nitro derivatives (X and XI), apparently because of a reduction in the basicity of the amino group [14].



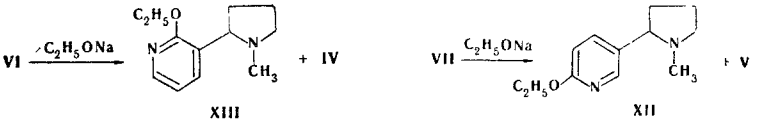
IV, V, VIII, IX — VI, VII, X, XI

IV R=NH_2, R′=R″=H
V R=R″=H, R′=NH_2
VIII R=NH_2, R′=H, R″=Br
IX R=H, R′=NH_2, R″=Br

VI R=NO_2, R′=H
VII R=R″=H, R′=NO_2
X R=NO_2, R′=H, R″=Br
XI R=H, R′=NO_2, R″=Br

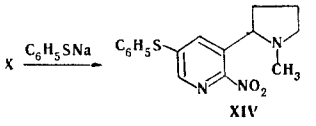
The structures of the nitronicotines obtained were confirmed by spectroscopy and also by chemical reactions. The IR spectra of compounds (VI, VII, X, and XI) have strong bands in the region of the stretching vibrations of the NO_2 group (1540 and 1360-1380 cm^{-1}) and lack absorption in the 3100-3400-cm^{-1} region that is characteristic for the stretching vibrations of an NH_2 group. In the PMR spectra of compounds (VI, VII, X, and XI) there are the multiplet signals of the protons of an N-methylpyrrolidine ring, among which are isolated the signals of four protons not directly attached to a nitrogen atom (2.1-2.2 ppm) and those of an N-methyl group (3.20-3.30 ppm), while the signal of the protons of an NH_2 group is absent. In 2-nitronicotine (VI), for the β proton a doublet of doublets is observed ($\delta \approx 7.45$ ppm) with $J_{4,5} = 7.5$ Hz and $J_{5,6} = 4.8$ Hz, which coincide with the known values of the spin–spin coupling constants [15]. The α and β protons of the pyridine ring appear in the form of a multiplet (δ 8.1-8.3 ppm). In the case of 6-nitronicotine (VII), the signals of the β and γ protons ($\delta \approx 8.05$ ppm) overlap, which complicates the interpretation of the spectrum. The signal of the α proton appears in the form of a broadened singlet with $\delta \approx 9.17$ ppm. Similar positions of the signals of the α and γ protons are observed in the spectrum of 5-bromo-2-nitronicotine (X) ($\delta \approx 8.32$ ppm), while in the case of 5-bromo-6-nitronicotine (XI) two distinct doublets are found (δ 8.08 and 8.28) with $J_{2,4} = 2.0$ Hz.

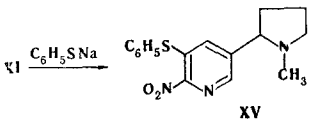
We have studied some reactions of the nitronicotines with nucleophilic agents. The action of sodium ethoxide on 6-nitronicotine (VII) leads to the replacement of the nitro group and the formation of 6-ethoxynicotine (XII) with a yield of 56%. Together with the replacement of the nitro group, its partial reduction to an amino group is also found. The molar ratio of the (V) to (XII) in the reaction products, determined by the GLC method, is 1 : 6. In the reaction of sodium ethoxide with 2-nitronicotine (VI), the amount of reduction product increases and the amount of 2-ethoxynicotine (XIII) decreases [molar ratio of (IV) to (XIII) of 1 : 3.5].



The replacement of a nitro group by an ethoxy group is a chemical confirmation of the structures of the nitronicotines (VI) and (VII).

In the bromonitronicotines (X) and (XI), the bromine, being activated by a nitro group, readily undergoes direct nucleophilic exchange with the thiophenoxide anion.





XV

The PMR spectrum of (XI) contains a multiplet of the protons of the pyrrolidine ring with the distinguishable signals of four protons not attached to the nitrogen ($\delta \approx 2.08$ ppm) and the three protons of the N-methyl group ($\delta \approx 3.05$ ppm), a broadened singlet of the five protons of the benzene ring (δ 7.44 ppm) and two doublets and the α and γ protons of the pyridine ring (δ 8.28 and 8.08 ppm), $J_{2,4} = 2$ Hz.

Some aspects of the biological activity of the nitro derivatives of nicotine that have been synthesized have been studied. 5-Bromo-6-nitronicotine (XI) and 6-nitronicotine (VII) possess weak germistatic activities with respect to the majority of the microorganisms tested. The neurotropic, antispasmodic, antiserotonin, and antireserpine activities of the nitronicotines (VI, VII, X, and XI) have been investigated.* All the compounds studied caused hypothermia in mice and interfered with the coordination of motion in the rotating rod test. The highest activity was found in 5-bromo-6-nitronicotine (XI). Only this compound has an influence on the threshold of electrical pain and the duration of chloral hydrate sleep; it potentiates sleep almost twofold. In addition to this, compound (XI) possesses a pronounced central and peripheral activity. It is interesting to observe that this substance is the least toxic for warm-blooded animals (LD_{50} = 600 mg/kg), while the LD_{50} values for (VII, VI, and X) are, respectively, 30, 300, and 500 mg/kg.

EXPERIMENTAL

The IR spectra were taken on a UR-10 spectrometer, and the PMR spectra on a Varian DA-60JL instrument (in CCl_4 with HMDS as internal standard). GLC was performed on a "Tsvet 2-65" chromatograph with a flame-ionization detector on a column 130 cm long filled with Chromaton bearing 5% of SE-30 silicone elastomer with nitrogen as the carrier gas at a temperature of 170°C. The melting points were determined on a "Boetius" microscope stage.

Nitration of N'-Benzoyldihydrometanicotine N-Oxide (I). A solution of 15.2 g (0.06 mole) of N-benzoyldihydrometanicotine [16] in 46 ml of 30% H_2O_2 and 198 ml of glacial acetic acid was heated at 68-70° for 3 h. The solution was evaporated to half its original volume in a film evaporator, diluted with water, and evaporated completely, and the last traces of water were removed by azeotropic distillation with benzene. This gave 12.1 g of (I) in the form of a light-colored oil (containing the starting material as impurity). A solution of 2.6 g (0.009 mole) of (I) in 9 ml of concentrated H_2SO_4 was carefully poured into a nitrating mixture obtained by the addition of 5.5 ml of 60% oleum and 4 ml of concentrated H_2SO_4 to 15 ml of nitric acid (d 1.51). The liquid was heated at 100°C for 1 h and was then cooled and poured onto ice. The green solution was diluted twofold with water and was neutralized with sodium carbonate to a weakly acid reaction. The yellow-brown precipitate was filtered off and washed with water. After recrystallization from water with activated carbon, 0.94 g (49%) of 3,5-dinitrobenzoic acid (III), mp 203.5-206.5°C, was obtained. Ethyl ester mp 90.5-92°C (see [17]). The filtrates after the separation of (III) were evaporated and the residue was extracted with nitromethane. After the elimination of the solvent and recrystallization of the residue from methanol, 0.14 g (11%) of nicotinic acid N-oxide (II) with mp 256-258°C was obtained [18]. Found: C 51.7; H 3.6%. $C_6H_5NO_3$. Calculated: C 51.8; H 3.6%.

2-Nitronicotine (VI). With ice–salt cooling and vigorous stirring, 70 ml of 95% sulfuric acid and 130 ml of 60% oleum were added dropwise to 80 ml of 36% H_2O_2, the temperature of the flask being kept below 20°C. With stirring and at a temperature below 10°C, over 15 min a solution of 17.7 g (0.1 mole) of 2-aminonicotine [10] in 60 ml of 95% sulfuric acid was added to the Caro's acid so obtained, and the mixture was left at room temperature for three days. During this time, the color of the liquid changed from a faint brown through dark blue to faint yellow. The reaction mixture was poured onto ice and neutralized with concentrated aqueous ammonia (temperature not above 25°C). The alkaline liquid was extracted several times with ether. The extract was dried with anhydrous Na_2SO_4. The residue after the elimination of the solvent was dissolved in hexane and the solution was cooled to 0°C. The crystals that deposited were separated off, giving 10.1 g (59%) of 2-nitronicotine (VI), bp 95-100°C (0.02 mm); mp 42-43°C. Found, %: C 57.9; H 6.4; N 19.9. $C_{10}H_{13}N_3O_2$. Calculated, %: C 58.0; H 6.3; N 20.3. Picrate, mp 208.5-210.5°C (from ethanol). Found,%: C 44.1; H 3.8; N 19.4. $C_{10}H_{13}N_3O_2 \cdot C_6H_3N_3O_7$. Calculated,%: C 44.0; H 3.7; N 19.3.

*The study of the pharmacological properties of the compounds was performed in the pharmacology laboratory of the Novokuznetsk Scientific-Research Institute of Pharmaceutical Chemistry under the direction of V. M. Kurilenko. The authors consider it their pleasant duty to express their gratitude to V. M. Kurilenko.

6-Nitronicotine (VII). At a temperature of 5°C, a solution of 25 g (0.1 mole) of 6-aminonicotine hydrochloride [10] in 50 ml of concentrated sulfuric acid was added over 10 min to one mole of Caro's acid prepared as described above. The mixture was kept at room temperature for nine days. Then the acid solution was poured onto ice and neutralized with an excess of aqueous ammonia (pH 9-10). The precipitate that deposited was separated off and dried. This gave 7.6 g of a substance with mp 77.5-79°C. From the alkaline liquid, ether extracted an additional 7.6 g of material with mp 76.5-78.5°C. The total yield of 6-nitronicotine (VII) was 70%, mp 78.5-79°C (from hexane). Found,%: C 58.0; H 6.3. $C_{10}H_{13}N_3O_2$. Calculated,%: C 58.0; H 6.3. Picrate, mp 142.5-144.5°C (from ethanol). Found, %: C 44.5; H 3.8; $C_{10}H_{13}N_3O_2 \cdot C_6H_3N_3O_7$. Calculated, %: C 44.0; H 3.7. Methiodide: obtained by boiling (2 h 30 min) 4.1 g (0.02 mole) of (VII) with 3 ml (0.05 mole) of CH_3I in 30 ml of CH_3OH. Yield 72%, mp 205-207°C (from methanol). Found,%: C 38.1; H 4.8; N 12.1. $C_{11}H_{16}IN_3O_2$. Calculated, %: C 37.8; H 4.6; N 12.0.

5-Bromo-2-nitronicotine (X). Over 20 min, a solution of 25.6 g (0.1 mole) of 2-amino-5-bromonicotine in 100 ml of concentrated H_2SO_4 was added to one mole of Caro's acid at 5°C. The temperature of the mixture was kept at about 0°C for 6 h (the reaction is highly exothermic), and then it was left for five days in a water bath at room temperature. The brown liquid was poured onto ice, neutralized with ammonia, and extracted with ether. This gave 10 g (35%) of the bromonitronicotine (X), mp 55-56.5°C (from hexane and 80% ethanol). Found, %: C 42.4; H 4.5; Br 28.4. $C_{10}H_{12}BrN_3O_2$. Calculated,%: C 42.0; H 4.2; Br 27.9. Picrate, mp 222.5-223°C (from ethanol). Found,%: C 37.3; H 2.7; Br 15.6, $C_{10}H_{12}BrN_3O_2 \cdot C_6H_3N_3O_7$. Calculated, %: C 37.3; H 2.9; Br 15.5.

5-Bromo-6-nitronicotine (XI) was obtained in a similar way to (X). Yield 41%, mp 41.5-43°C. Found, %: C 42.3; H 4.4; Br 27.8; N 15.0. $C_{10}H_{12}BrN_3O_2$. Calculated,%: C 42.0; H 4.2; Br 27.9; N 14.7. Picrate, mp 195.2-196.2°C (from ethanol). Found,%: C 37.3; H 2.7; Br 15.1. $C_{10}H_{12}BrN_3O_2 \cdot C_6H_3N_3O_7$. Calculated, %: C 37.3; H 2.9; Br 15.5.

6-Ethoxynicotine (XII). A hot solution of 4.14 g (0.02 mole) of 6-nitronicotine (VII) in 50 ml of ethanol was added to a hot solution of 0.04 mole of sodium ethoxide (from 0.92 g of sodium) in 50 ml of ethanol. The darkening liquid was boiled for 6 h. Then the ethanol was driven off, the residue was treated with ether, the solution was filtered, and the ether was evaporated off. This gave 2.3 g (56%) of 6-ethoxynicotine (XII), bp 82-83°C (0.1 mm); n_D^{20} 1.5175. Found,%: C 69.8; H 8.8; N 13.8. $C_{12}H_{18}N_2O$. Calculated,%: C 69.9; H 8.8; N 13.6. Picrate, mp 173-173.5°C (from water). Found,%: C 49.6; H 4.7; N 15.8. $C_{12}H_{18}N_2O \cdot C_6H_3N_3O_7$. Calculated,%: C 49.7; H 4.7; N 16.1. In addition to (XII), 6-aminonicotine (V) was found in the reaction mixture by TLC and GLC. According to GLC, the reaction mixture contained the (V) and (XII) in a ratio of 1 : 6.

2-Ethoxynicotine (XIII). A mixture of 2.07 g (0.01 mole) of 2-nitronicotine (VI) in 50 ml of ethanol and 0.02 mole of sodium ethoxide in 50 ml of ethanol was boiled for 7 h. By GLC, the reaction mixture was found to contain 2-ethoxynicotine (XIII) and 2-aminonicotine (IV) in a molar ratio of 1 : 3.5. The ethanol was evaporated off, the residue was extracted with ether, the ether was driven off, the residue was treated with cold hexane, and the insoluble (IV) was filtered off, mp 122°C (from hexane). Evaporation of the hexane filtrate and two distillations of the residue gave 2-ethoxynicotine (XIII) with bp 72°C (1.5 mm), n_D^{20} 1.5155. Picrate, mp 135-135.5°C (from ethanol). Found,%: C 49.8; H 5.0; N 15.7. $C_{12}H_{18}N_2O \cdot C_6H_3N_3O_7$. Calculated,%: C 49.7; H 4.7; N 16.1.

5-Phenylthio-6-nitronicotine (XV). In an atmosphere of nitrogen, a solution of 2.25 ml (0.022 mole) of thiophenol and, after 5 min, a solution of 5.72 g (0.02 mole) of 5-bromo-6-nitronicotine (XI) in 50 ml of ethanol were added to a solution of 0.8 g (0.02 mole) of caustic soda in 100 ml of 96% ethanol, and the mixture was boiled for 2 h and was then evaporated to dryness. The residue was recrystallized from 80% ethanol with the addition of activated carbon, giving 3.85 g (61%) of 5-phenylthio-6-nitronicotine (XV) with mp 79-80°C. Found,%: C 61.1; H 5.1; N 13.5; S 9.8. $C_{16}H_{17}N_3O_2S$. Calculated,%: C 60.9; H 5.4; N 13.3; S 10.2. Picrate, mp 195-196°C (from ethanol). Found,%: C 48.1; H 3.9; N 15.2; S 5.8. $C_{16}H_{17}N_3O_2S \cdot C_6H_3N_3O_7$. Calculated,%: C 48.5; H 3.7; N 15.4; S 5.9.

5-Phenylthio-2-nitronicotine (XIV). In an atmosphere of nitrogen, 0.245 ml (2.4 mmoles) of thiophenol was added to a solution of 0.08 g (2 mmoles) of caustic soda in 30 ml of 96% ethanol and, after the mixture had been stirred, a solution of 0.57 g (2 mmoles) of 5-bromo-2-nitronicotine (X) in 20 ml of ethanol was added. The resulting solution was boiled for 7 h, and then the solvent was evaporated off and the residue was dissolved in dilute hydrochloric acid. The acid solution was washed with ether, made alkaline, saturated with potassium carbonate, and extracted with ether. The extract was dried with magnesium sulfate, and evaporation of the solvent yielded 0.53 g of compound (XIV in the form of a colored oil. Picrate, mp 181.5-182.5°C (from ethanol). Found,%: C 48.8; H 3.8; N 15.3; S 5.8. $C_{16}H_{17}N_3O_2S \cdot C_6H_3N_3O_7$. Calculated,%: C 48.5; H 3.8; N 15.4; S 5.9.

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