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SYNTHESIS AND PSYCHOPHARMACOLOGICAL AND ANTIHYPOXIC ACTIVITY OF SOME β-SUBSTITUTED PYRIDINECARBOXYLIC ACIDS

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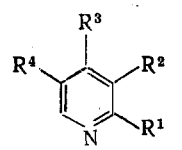
UDC 615.272.2.014.425.012.1

A study was recently proposed to test pyridine carboxylic acid derivatives for biological activity, in particular antiinflammatory activity and hypolipodynamic activity. The compounds selected for study were the β-hydroxypyridine carboxylic acids [3, 5, 6], which have a phenolic hydroxyl group in the β-position, characteristic of vitamin B_6 group compounds; in addition, unsubstituted pyrididinecarboxylic acids constitute part of a number of drugs and vitamins.

As a part of the study, we have synthesized some derivatives of 5-hydroxynicotinic acid (II, III), 3-hydroxyisonicotinic acid (IV, V), and 5-bromo- and 5-aminonicotinic acid (VI-IX). The psychopharmacological and antihypoxic activities of these compounds have been studied and compared with those of related compounds — nicotinamide (X), 3-hydroxypyridine (I), and others.



I: $R^1 = R^3 = R^4 = H$, $R^2 = OH$; II: $R^1 = R^3 = H$, $R^2 = OH$, $R^4 = CONH_2$;
III: $R^1 = R^2 = OH$, $R^3 = H$, $R^4 = COOH$; IV: $R^1 = R^4 = H$, $R^2 = OH$, $R^3 = COOH$;
V: $R^1 = R^4 = H$, $R^2 = OH$, $R^3 = COONa$; VI: $R^1 = R^3 = H$, $R^2 = Br$, $R^4 = CONH_2$;
VII: $R^1 = R^3 = H$, $R^2 = Br$, $R^4 = COOH$; VIII: $R^1 = R^3 = H$, $R^2 = COOC_2H_5$, $R^4 = NHCOC_6H_5$;
IX: $R^1 = R^3 = H$, $R^2 = COOC_2H_5$, $R^4 = NHCOC_6H_2(OCH_3)_2$; X: $R^1 = R^2 = R^3 = H$, $R^4 = CONH_2$

The amide of 5-hydroxynicotinic acid (II) was obtained by the action of aqueous ammonia on the ethyl ester of 5-hydroxynicotinic acid. The acyl derivatives of 5-aminonicotinic acid (VIII, IX) were synthesized by condensation of an ester of 5-aminonicotinic acid with an arylcarboxylic acid chloride in the presence of pyridine. Synthesis of 5,6-dihydroxynicotinic acid (III) was carried out by the replacement of an iodine atom by a hydroxyl group in 6-iodo-5-hydroxynicotinic acid. The starting compounds, 5-hydroxynicotinic acid, 5-bromonicotinic acid, 5-aminonicotinic acid, and 3-hydroxyisonicotonic acid, and also compounds V-VII were obtained by standard methods [7-10]. The purity of the compounds was checked by TLC.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 20, No. 1, pp. 45-47, January, 1986. Original article submitted September 20, 1985.

0091-150X/86/2001-0029$12.50

TABLE 1. Relative Activities of Some β-Substituted Pyridinecarboxylic Acids

Compound	Hypobaric hypoxia (pressure chamber, dose 100 mg/kg), %	Disturbance of orienting reflex	Corazol antagonism*	Disturbance of motor coordination*	Toxicity (loss of animals) LD_{50}
I	320	500—50	600—50	600—50	900
II	344	100—0	300—16	100—0	800
III	104	100—50	300—16	100—0	800
IV	125	100—0	400—16	100—0	1000
V	245	100—0	400—0	100—0	1000
VI	210	100—0	100—0	100—0	900
VII	190	100—33	100—0	100—0	800
VIII	128	100—0	300—0	100—0	800
IX	180	100—83	400—16	100—16	1000
X	230	500—50	1250—50	1600—50	2500

*First figure, dose, mg/kg; second, % effect.

EXPERIMENTAL (CHEMICAL)

Amide of 5-Hydroxynicotinic Acid (II). A solution of 1 g (0.0062 mole) of ethyl 4-hydroxynicotinate in 12 ml of 25% NH_4OH was maintained at room temperature for 24 h, then neutralized with dilute H_2SO_4, and the precipitated material recrystallized from water to give the amide of 5-hydroxynicotinic acid (II) in 83% yield, mp 222-224°C. Found, %: C 51.95, H 4.98. $C_6H_6O_2N_2$. Calculated, %: C 52.19, H 4.35.

5,6-Dihydroxynicotinic Acid (III). A mixture of 1 g (0.0037 mole) of 6-iodo-5-hydroxynicotinic acid [9], 0.3 g of copper sulfate, and 0.1 g of powdered activated copper in 20 ml of 10% NaOH solution was heated for 12 h at 120-140°C. On completion of the reaction, the solution was cooled, filtered, and 0.8 g of sodium sulfide added to the filtrate to remove excess copper. The precipitated copper sulfide was filtered off, and the filtrate neutralized to pH 3-4 with concentrated HCl. Filtration and recrystallization from water gave III in 75% yield, mp >300°C. Found, %: C 46.48, H 3.23. $C_6H_5O_4N$. Calculated, %: C 46.47, H 3.22.

N-Substituted Amines of Ethyl 5-Aminonicotinate. A mixture of 2 g (0.0012 mole) of ethyl 5-aminonicotinate, 20 ml of anhydrous pyridine, and 1.8 g (0.0013 mole) of benzoyl chloride were heated on a boiling water bath for 2 h. The reaction mixture was poured into water, the precipitated material separated, washed with aqueous ammonia, and dried. Recrystallization from benzene gave a 78% yield of ethyl-5-benzoylaminonicotinate (VIII), mp 132-133°C. Found, %: C 66.81, H 5.19. $C_{15}H_{14}O_3N_2$. Calculated, %: C 60.67, H 5.18.

The same method was used for the preparation of ethyl 5-(3,4,5-trimethoxybenzoylamino)-nicotinate (IX), in 81% yield, mp 174-175°C. Found, %: C 60.04, H 5.58. $C_{18}H_{20}O_6N_2$. Calculated, %: C 60.00, H 5.56.

EXPERIMENTAL (PHARMACOLOGICAL)

White mice (18-20 g) and rats (180-220 g) were used to study the effect of the β-substituted pyridinecarboxylic acids on the orientation reflex, avoidance reflex, efficiency (swimming with a load of 7% of body weight), aggressive behavior, corazol-induced spasms, and soporific action of sodium barbiturate; antihypoxic effects were evaluated from the animals surviving acute hypoxia in a pressure chamber. The methods used are described in [1, 2]. Compounds were injected intraperitoneally 30 min before the test. Compounds I and X, sodium hydroxybutyrate, and γ-hydroxyaminobutyric acid were used for comparison.

The results of this study showed that compound I was pharmacologically active in several of the tests, causing a decrease in the orientation reflex, a disturbance of motor coordination, and protection from destruction from acute hypoxia. Comparison of the pharmacological action of I and II confirms that the presence of an OH or $CONH_2$ at the β-position of the pyridine ring increases the antihypoxic action (compound II) in comparison with the unsubstituted 3-hydroxypyridine and nicotinamide (I and X), whereas in the remaining tests compound II was less active. Going from X to 5-bromonicotinamide (VI) there is also a decrease in activity in all the tests, particularly in corazole antagonism, and an increase in toxicity (see Table 1).

One feature of the activity of compound III is its ability to increase the physical efficiency of the animals. Thus, in the control experiments, the swimming time for mice was 4.5 (3.4-5.6) min, while under the action of compound III it was increased to 7.3 (5.2-9.4) min.

In going from 5-hydroxynicotinic acid to derivatives of 3-hydroxyisonicotinic acid (IV-V) there was a decrease in antihypoxic activity and toxicity. On the other hand, substitution of a hydroxy group at position 5 by a bromine atom (VI, VII) or an amino group (VIII, IX) was accompanied by a decrease in the protection of the animals from hypoxia, and an increase in the sedative action.

In the spectrum of pharmacological activity of derivatives of 5-hydroxynicotinic acid, the foremost component was their antihypoxic effect. The activity of the most active compound was similar to that of known antihypoxic agents — sodium hydroxybutyrate, γ-hydroxyaminobutyric acid, and also isonicotinamide. Use of these substances in equivalent doses (100 mg/kg) showed that the life span of mice in a pressure chamber under the influence of compounds I and II increased by 330% compared with a control, under the action of nicotinamide by 230%, γ-hydroxyaminobutyric acid by 130%, and sodium hydroxybutyrate by 704%.

Since substituted 3-hydroxypyridines exhibit antihypoxic activity, it is possible that this type of activity is determined not only by the substituent at the 3-position, but also by the 3-hydroxypyridine molecule itself, which has a phenolic hydroxyl group and can exhibit antioxidant properties.

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