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SYNTHESIS AND BIOLOGICAL ACTIVITY OF N-ARYLAMIDINES OF NICOTINIC AND 2-METHOXY-6-METHYLNICOTINIC ACIDS AND THEIR DERIVATIVES

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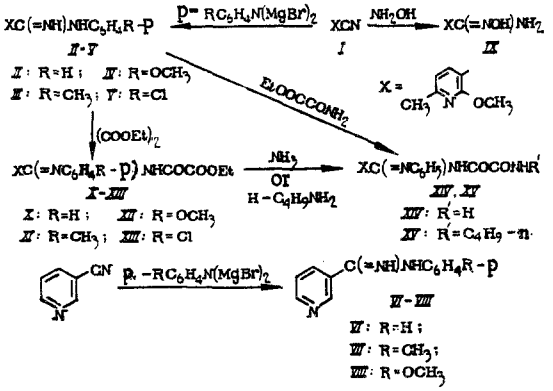
In continuation of studies on the search for antispasmodic compounds among the amides of substituted nicotinic acids [1], we synthesized N-arylamidines of 2-methoxy-6-methylnicotinic acid (II-V) (Table 1).

N-Arylamidines II-V were obtained in yields of 55-72% by the reaction of 2-methoxy-6-methylnicotinonitrile (I) with dimagnesylamines. Under similar conditions, we synthesized N-phenyl-, N-p-tolyl-, and N-p-anisylamidines of nicotinic acid (VI-VIII). When I is boiled with hydroxylamine in an alcoholic solution, the amidoxime of 2-methoxy-6-methylnicotinic acid (IX) is formed.



Compounds II-IX are colorless crystalline substances. Bands at 1630 (C=N), 3410, and 3520 cm^{-1} (NH of secondary amino and imino groups) were observed in their IR spectra.

In [2, 3] it was shown that hydrazides and amides of oxalic acid have different types of biological activity. It was therefore interesting to introduce the ethoxalyl and oxamoyl radicals into the molecule of amidines II-V. It was found that with short boiling of the alcoholic solutions of compounds II-V with diethyl oxalate, they are converted into N-aryl-N'-ethoxalylamidines of 2-methoxy-6-methylnicotinic acid (X-XIII). It was shown in the case of compound X that it reacts with ammonia or n-butylamine to give the corresponding oxamoyl derivatives (XIV, XV). Compound XIV was also obtained by reacting ethyl oxamate with N-arylamidine II.

EXPERIMENTAL CHEMICAL SECTION

The IR spectra were run on the UR-20 spectrometer (GDR) in CCl_4.

N-Aryl-2-methoxy-6-methylnicotinamidines (II-V). A 4.44 g portion (0.03 g-mole) of

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TABLE 1. Characteristics of Compounds Synthesized

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
II	55	67—68	69,89	6,33	17,25	$C_{14}H_{15}N_3O$	69,67	6,28	17,41
III	66	89—90	70,62	6,45	16,75	$C_{15}H_7N_3O$	70,55	6,72	16,46
IV	60	140—141	66,13	5,98	15,33	$C_{15}H_{17}N_3O_2$	66,39	6,33	15,49
V	72	103—104			15,22*	$C_{14}H_{14}ClN_3O$			15,24*
VI	82	136—137	74,80	5,44	21,65	$C_{19}H_{11}N_3$	73,07	5,62	21,30
VII	87	157—158	74,27	6,23	20,06	$C_{19}H_{13}N_3$	73,90	6,20	19,89
VIII	78	144—145	68,50	5,57	18,60	$C_{19}H_{13}N_3O$	68,70	5,77	18,49
IX	61	133—134	52,81	5,92	22,96	$C_8H_{11}N_3O_2$	53,00	6,07	23,20
X	71	159—160			12,17	$C_{18}H_{19}N_3O_4$			12,30
XI	65	184—185			11,71	$C_{19}H_{21}N_3O_4$			11,82
XII	85	152—153			11,28	$C_{19}H_{21}N_3O_5$			11,31
XIII	48	159—160			11,26	$C_{18}H_{18}ClN_3O_4$			11,17
XIV	75	220—221			17,63	$C_{16}H_{16}N_4O_3$			17,93
XV	45	68—69			16,83	$C_{20}H_{24}N_4O_3$			17,02

*Found, %: Cl 12.96. Calculated, %: Cl 12.85.

TABLE 2. Antispasmodic Activity and Acute Toxicity of Nicotinamidines during Intraperitoneal Administration to White Mice

Compound	ED_{50} according to MEST, in mg/kg	Peak of action, min	LD_{50}, mg/kg	Conditional latitude of pharmacological effect
II	35 (27—44)	5	80 (74—86)	2,3
V	73 (68—79)	5	285 (237—342)	3,9
VI	146 (129—165)	5	320 (305—336)	2,2
Hexamidine	90 (79—103)	240	340 (288—401)	3,8

Note. Fluctuation limits are shown in parentheses.

2-methoxy-6-methylnicotinonitrile in absolute ether is added to an ether solution of aryldimagnesylamine, obtained from 0.06 g-atom of magnesium, 0.06 g-mole of ethyl bromide, and 0.03 g-mole of arylamine. The reaction mixture is heated for 3 h, and when cool, a saturated solution of ammonium chloride is added. The ether layer is separated, washed with water to neutral reaction, and dried over magnesium sulfate, The ether is evaporated, and the residue is crystallized from benzene. In a similar way, N-arylnicotinamidines (VI-VIII) are obtained from nicotinonitrile and aryldimagnesylamines.

6-Methyl-2-methoxynicotinamidoxime (IX). A 2.96 g portion of 2-methoxy-6-methylnicotinonitrile is added to a mixture of 4.2 g of hydroxylamine hydrochloride and 6.4 g of anhydrous sodium carbonate in 60 ml of ethanol. The mixture is stirred at 50°C for another 20 h. The hot solution is filtered and evaporated, and the residue is washed with water, and crystallized from a mixture of benzene and alcohol (see Table 1).

N-Aryl-N'ethoxalyl-2-methoxy-6-methylnicotinamidines (X-XIII). A 1 g portion of II-V and 1 g of diethyl oxalate in 10 ml of ethanol are heated for 10 h. The alcohol is distilled, and the residue crystallized.

N-Phenyl-N'-oxamoyl-2-methoxy-6-methylnicotinamidine (XIV). Method A. A solution of 1 g of II and 0.7 g of ethyl oxamate in 5 ml of ethanol is heated for 13 h. The precipitate is filtered, washed with water, and crystallized from alcohol.

Method B. Gaseous ammonia is passed for 1 1/2 h, with snow cooling, into a solution of 0.4 g of X in 10 ml of alcohol. The mixture is left to stand for 2 days, then alcohol is evaporated, and the residue is crystallized.

N-Phenyl-N'-(N"-n-butyloxamoyl)-6-methyl-2-methoxynicotinamidine (XV). A mixture of 2 g of X and 0.9 g of n-butylamine in 10 ml of alcohol is heated for 22 h. The alcohol is evaporated, and the noncrystallizable residue is dissolved in benzene and chromatographed on Al_2O_3. After evaporation of benzene, the residue is recrystallized from hexane.

EXPERIMENTAL PHARMACOLOGICAL PART

Compounds II-XV were studied on 710 mice of both sexes weighing 18-22 g each. The compounds were introduced intraperitoneally in 2% starch mucilage. The experimental data were processed statistically according to Leachfield and Wilkoxon and by variation series analysis at $P = 0.05$ [4].

The antispasmodic activity of compounds II-XV was studied according to the maximal electric shock test (MEST) [5] and Corazole test [6], the analgetic action of compounds IX, XIV, XV in doses of 1/5 LD_{50} and LD_{50} by the Eddy and Leimbach method [7], and the acute toxicity, according to G. N. Pershin [8]. The depressant and stimulant action was determined visually. From the maximal electric shock test we calculated the conditional latitude of the pharmacological effect, i.e., the LD_{50}/ED_{50} ratio. The time during which the smallest ED_{50} values was observed was taken as the peak of the effect.

The antispasmodic activity according to the maximal electric shock test was shown by compounds II, V, VI (Table 2), compound II being more active than V, and V twice as active as VI. Compound II is more active than hexamidine by a factor of 2.3, V is equal to it in activity, and VI is less active by a factor of 1.6. The compounds studied differ from hexamidine in the rapid occurrence of the antispasmodic effect, but their action is short-term (up to 1 h).

None of the compounds studied in doses of 1/5 LD_{50} protected the animals from Corazole-induced spasms.

Amidoxime IX in doses of 50 mg/kg (1/5 LD_{50}) and 155 mg/kg (LD_{50}) increased the latent time of defense reflex in mice according to the "hot plate" test from 12 ± 1.1 min in the control to 20.9 ± 5.6 and 23.4 ± 7.8 min, respectively, and was inferior to amidopyrine, whose latent time of the defensive reflex at a dose of 147 mg/kg (LD_{50}) was 33.7 ± 8.6 min. Compounds XIV and XV did not have analgetic activity.

The LD_{50} of the compounds studied is within 61-320 mg/kg. The most active compound II, according to the maximal electric shock test, is 4.2 times more toxic than hexamidine (see Table 2), V is 1.2 times more toxic, and VI has an activity equal to that of hexamidine. The conditional latitude of the pharmacological effect compounds II and VI is smaller than that for hexamidine, and for V it is the same as for hexamidine. All the compounds studied in doses close to toxic induced clonical spasms.

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