SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-METHOXY- AND 2-OXO-3-AROYLPYRIDINE DERIVATIVES

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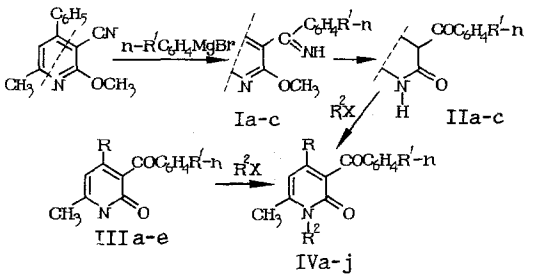
In the continuing search for biologically-active compounds among the pyridyl ketones [3, 4] substituted 2-methoxy- and 2-oxo-aroylpyridines were synthesized by reacting 6-methyl-2-methoxy-4-phenylnicotinonitrile [1] with aryl magnesium halides.



R=H(IIIa,b, VIa,b,i), CH_3(IIIc-e IVc-e,j), C_6H_5(IVf-h); R^1=H(Ia, IIa, IIIa, IIIc IVa,c,f,i,j), CH_3(Ib IIb, IIIb,d IVb,d,g), Cl(I , II c IVh); Br(IIIe, IVej; R^2=C_2H_5(IVa-e), CH_3(IVf-h; CH_2CONH_2(IVa), CH_2COOCH_3(IVj)

Investigations showed that the reaction produces the aryl-(6-methyl-2-methoxy-4-phenyl-3-pyridyl)ketimines Ia-c (Table 1), whose IR spectra reveal bands at 3250-3270 cm^{-1} (NH) and 1600-1610 cm^{-1} (C=N), but unlike the spectrum of the starting compound, show no nitrile group band at 2230 cm^{-1}.

Heating of compounds Ia-c with 20% hydrochloric acid in ethanol leads to hydrolysis of the ketimine and methoxy groups, yielding 3-aroyl-6-methyl-4-phenylpyridones-2 (IIa-c), which exhibit IR spectra absorption bands at 1630-1640 cm^{-1} and 1660-1670 cm^{-1} (CO), and at 3270-3290 cm^{-1} (NH).

Ketones IIa-c and the compounds IIIa-e described in a previous work [5] react with alkyl halides and chloroacetamide in the presence of a water-alcohol potassium hydroxide solution and with methyl chloroacetate in alcoholic sodium alcoholate to produce the 1,4-disubstituted 3-aroyl-6-methylpyridones-2 (IVa-j).

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Yield, %	mp, °C	Empirical formula
Ia	42	92—94	$C_{20}H_{18}N_2O$
Ib	50	87—89	$C_{21}H_{20}N_2O$
Ic	40	81—83	$C_{21}H_{17}ClN_2O$
IIa	34	232—234	$C_{19}H_{15}NO_2$
IIb	52	241—243	$C_{20}H_{17}NO_2$
IIc	58	212—215	$C_{19}H_{14}ClNO_2$
IVa	54	155—157	$C_{15}H_{15}NO_2$
IVb	60	165—167	$C_{16}H_{17}NO_2$
IVc	63	125—127	$C_{16}H_{18}NO_2$
IVd	61	167—169	$C_{16}H_{20}NO_2$
IVe	51	145—147	$C_{16}H_{19}BrNO_2$
IVf	70	174—176	$C_{20}H_{17}NO_2$
IVg	69	133—135	$C_{21}H_{19}NO_2$
IVh	42	121—123	$C_{20}H_{16}ClNO_2$
IVi	48	183—185	$C_{15}H_{14}N_2O$
IVj	50	163—165	$C_{16}H_{15}NO_4$

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TABLE 2. Anticonvulsant Activity and Toxicity of Synthesized

Compound	Maximum electric shock, ED_{50}, mg/kg	LD_{50}, mg/kg	RBPA LD_{50}/ED_{50}
IVa	170,0 (146,5—197,2)	890,0 (559,6—1291,2)	5,23
IVg	190,0 (154,4—233,7)	1030 (676,0—1384,0)	5,42
IVh	52,0 (42,6—63,4)	355,0 (148,8—461,2)	6,82
Hexamidine*	90,0 (79,0—103,0)	340,0 (288,0—401,0)	3,77

*From the data compiled by V. K. Danilova [2].

In the IR spectra ketones IVa-h reveal bands at 1630-1670 cm^{-1} (CO), compound IVi has bands at 1640, 1670, and 1710 cm^{-1} (CO) and at 3190 and 3320 cm^{-1} (NH_2), and compound IVj has bands at 1650, 1680, and 1740 cm^{-1} (CO).

Compounds Ia-c, IIa-c, and IVa-j are colorless, crystalline substances that are soluble in the usual organic solvents, but insoluble in water.

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded in Vaseline on a UR-20 instrument. Elemental analysis data were in line with calculated values.

(6-Methyl-2-methoxy-4-phenylpyridyl-3)arylketimines (Ia-c). To the aryl magnesium halide obtained from 9.4 g (0.06 moles) of the aryl halide and 1.4 g (0.06 gram-atom) of magnesium was added 4.5 g (0.02 moles) of 6-methyl-2-methoxy-4-phenyl-3-cyanopyridine in 100 ml of dry ether. The mixture was heated for 8 h and decomposed with a saturated ammonium chloride solution. The ethereal layer was separated off and treated with steam. The residue was crystallized from ethanol.

3-Aroyl-6-methyl-4-phenylpyridones-2 (IIa-c). A sample of 0.01 moles of the appropriate (6-methyl-2-methoxy-4-phenylpyridyl-3) arylketimine Ia-c was boiled for 1 h with 5g of 20% hydrochloric acid in 20 ml of ethanol. This was diluted with water and the resulting precipitate was crystallized from ethanol.

4-Substituted 3-Aroyl-6-methyl-2-oxo-1-ethylpyridines (IVa-e). To a solution of 0.01 moles of the corresponding IIIa-e in 30 ml of ethanol were added 0.014 moles of potassium hydroxide in 8 ml of water and 5 g of ethyl bromide. After the mixture had ben boiled for 3 h, the solvent was evaporated off, and the residue was washed with water and crystallized from ethanol.

Ketones IIa-c were reacted in a similar way with methyl iodide to obtain 3-aroyl-1,6-dimethyl-2-oxo-4-phenylpyridines (IVf-h).

3-Benzoyl-1-carbamylmethyl-6-methylpyridone-2 (Vi). To 1 g (0.004 moles) of 3-benzoyl-6-methylpyridone-2 in 20 ml of ethanol were added 0.4 g of potassium hydroxide in 4 ml of water and 4 g of chloroacetamide. The mixture was heated for 5 h, then cooled; the resulting precipitate was crystallized from methanol.

3-Benzoyl-1-carbomethoxymethyl-6-methylpyridone-2 (IVj). To a solution of 0.5 g of sodium in 15 ml of dry ethanol were added 1 g (0.004 moles) of 3-benzoyl-6-methylpyridone-2 in dry benzene and 2 g of methyl monochloroacetate. The mixture was heated for 3 h. It was then evaporated, washed with water and crystallized from ethanol.

EXPERIMENTAL (BIOLOGICAL)

Experiments were carried out with outbred white mice weighing 18-22 g to study the anticonvulsant activity of compounds Ia-c, IIa-c, and IVa-j using the maximum electric shock test with the parameters elaborated by K. S. Raevskii [7]. All the compounds were admin-

istered as suspensions in 2% starch mucilage by intraperitoneal injection in doses of 300 mg/kg. ED_{50} and median lethal dose LD_{50} values in mg/kg [6] were determined for those compounds that exhibited anticonvulsant activity at that particular dosage, and from their ratio (LD_{50}/ED_{50}) the relative breadth of pharmacological activity (RBPA) was calculated.

The study was performed using the well-known anticonvulsant hexamidine as the reference preparation.

Pronounced anticonvulsant activity was displayed by the three compounds IVa, IVg, and IVh. The assessment of toxicity and anticonvulsant effect given in Table 2 indicates that compound IVh is positively superior to hexamidine in terms of anticonvulsant activity, while compounds IVa and IVg demonstrate about half its activity. Compound IVh has approximately the same toxicity as the reference compound, while IVa and IVg are less toxic by a factor of 2.6 and 3.0 respectively.

All three compounds have a greater RBPA than hexamidine, i.e., they are safer than the reference preparation.

The investigation have shown that the search to find anticonvulsant preparations among the pyridyl ketones may prove fruitful.

LITERATURE CITED

1. Z. A. Bomika, M. B. Andaburgskaya, Yu. E. Pelcher, et al., Khim. Geterotsikl. Soedin., No. 10, 1085 (1976).
2. V. K. Danilova, Investigation of the Anticonvulsant Activity of Substituted Amides of 2-Amino-, 2-Anilino-, and 2-Chloronicotinic Acids [in Russian], Author's abstract, Dis. Cand. Biol. Sciences, Kupavna (1984).
3. V. A. Lepikhin, E. M. Chukichev, M. L. Suslina, et al., The Search for Pharmacological Preparations among Organic Synthesis Products and Natural Substances [in Russian], Perm (1982), pp. 23-25.
4. V. A. Lepikhin, A. S. Zaks, M. L. Suslina, et al. Deposited at the All-Union Scientific and Technical Information Institute, (1984) No. 7592.
5. V. A. Lepikhin, V. M. Petrichenko, and M. E. Konshin, Khim. Geterotsikl. Soedin., No. 10, 1354-1356 (1986).
6. V. P. Prozorovskii, M. P. Prozorovskaya, and V. M. Demchenko, Farmakol. Toksikol., No. 4, 497-502 (1978).
7. K. S. Raevskii, Farmakol. Toksikol., No. 4, 495-497 (1961).