SYNTHESIS AND PHARMACOLOGICAL STUDY OF PIMADIN HOMOLOGS*

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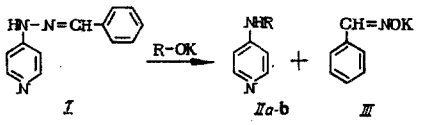
UDC 615.214.21.012.1

The hydrochloride of 4-aminopyridine is a curare antagonist with analeptic properties and this drug is used abroad under the name "pimadin" [1]. The mechanism of the action of pimadin is still not clear, and is the subject of conflicting opinions [1-3]. In spite of the difference between pimadin and anticholinesterase preparations such as proserine and galanthamine, pimadin possesses a similar mode of action for the restoration of synaptic transmission in skeletal muscles [4]. Intravenous injection of therapeutic doses of the preparation eliminates or lowers the narcotic action of diazepam and causes a fourfold reduction in the length of time for recovery from narcosis caused by a mixture of diazepam and nitrous oxide; it also acts as an antagonist to nonpolarizing myorelaxants [5].

Because of the high toxicity of pimadin [13], we are continuing to look for amino pyridines which are curare antagonists. A number of substituted 4-aminopyridines have been studied [6], and, among these, pimadin homologs with alkyl amino substituents seemed to be of particular interest.

Cleavage of the pyridyl hydrazones of benzaldehyde (I) under the action of alkali metal alcoholates [7], gave 4-monoalkylamino pyridines (II), from which were synthesized the homologous 4-methyl, 4-ethyl-, 4-n-butylaminopyridines (IIa-c):



I IIa-b III

IIa: R = CH_3; IIb: R = C_2H_5; IIc: R = n-C_4H_9.

Substances IIa-c were obtained in 72-86% yields and were converted to the water-soluble hydrochlorides for pharmacological testing.

An electromyographic study of the synthesized compounds was carried out; their action on tubocurarine in narcotized cats compared with that of pimadin when used in equimolar doses, showed that all the tested compounds possess the ability to accelerate the restoration of nerve-muscle transmission. Additionally, the duration of the anticurare effect (T_{75}) in pimadin, and its N-methyl (IIa) and N-ethyl (IIb) analogs are approximately the same and are, respectively, 5(4.1-5.9), 6(4.8-7.2), and 7 (5-9) min, while for the N-butyl derivative (IIc), the ability to accelerate the blocking effect of tubocurarine is considerably weaker: T_{75} = 11(8-14) min. The spontaneous restoration of nerve-muscle transmission after the use of tubocurarine took 45 min.

Thus, the introduction of a small alkyl substituent into the pimadin amino group did not alter the anticurare effect: The introduction of a larger alkyl group decreased the pharmacological action.

EXPERIMENTAL CHEMISTRY

Methods of Preparation of the Homologous 4-Monoalkylpyridines (II). To 20 mmoles of freshly prepared potassium alkoxide was added 2 g (10.1 mmoles) of the pyridyl-4-hydrazone of

*The authors wish to thank D. A. Kharkevich, associate member of the Academy of Medical Sciences of the USSR, director of the pharmacology department of the I. M. Sechenova Moscow Medical Institute, where the biological testing of the pimadin homologs was carried out, for valuable discussions.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 8, pp. 934-936, August, 1983. Original article submitted January 21, 1983.

0091-150X/83/1708-0557$07.50

TABLE 1. Properties of the 4-Monoalkylamino Derivatives

Compound	Yield, %	mp, °C	Calculated, %				Empirical formula	Found, %			
			C	H	N	Cl		C	H	N	Cl
IIa	72	187—88	49,79	6,22	19,36	24,55	$C_6H_9N_2Cl$	49,89	6,28	19,26	24,35
IIb	86	210—11	52,96	6,93	17,65	22,38	$C_7H_{10}N_2Cl$	53,04	7,01	17,29	22,36
IIc	84	164—65	57,90	8,03	14,99	19,01	$C_9H_{14}N_2Cl$	57,98	8,09	14,86	18,67

benzaldehyde (I). The reaction mixture was heated for 25 min at 230-235°C. After cooling to room temperature, the reaction products were dissolved in 150 ml of water and extracted with chloroform. The chloroform extract was dried over magnesium sulfate, evaporated, the residue dissolved in 50 ml of acetone, and ethanolic hydrogen chloride added until an acid reaction to congo red was obtained. The precipitated material was filtered off and washed with acetone. Yields, analysis, and physical constants are given in Table 1.

EXPERIMENTAL BIOLOGY

Evaluation of the anticurare activity of 4-aminopyridine homologs was carried out using cats narcotized with urethane (600 mg/kg) or chlorazole (70 mg/kg). The ability of these compounds to restore gastrocnemius muscle contractions inhibited by the injection of tubocurarine was studied electromyographically. The gastrocnemius muscle was contracted electrically at a 5 Hz frequency by the supramaximal stimulation of the peripheral section of the sciatic nerve.

The extent to which the neuromuscular transmission was restored was obtained by taking the arithmetic mean of the 6th, 7th, and 8th potentials and expressing this as a percentage of the magnitude of the starting potential. In addition, the duration of the anticurare effect (T_{75}) on the gastrocnemius muscle — the time from the moment of injection of the 4-aminopyridine derivative until the potential peak height is restored to 75% of the background level — was measured. The tubocurarine was used in doses exceeding the myoparalytic dose by a factor of 1.5 to 2. Test substances were used in equimolar doses and were administered when the electromyogram indicated the beginning of spontaneous recovery of neuromuscular transmission; their effect was evaluated every 30 sec after the injection until full restoration of the action of the gastrocnemius muscle. Tubocurarine and test compounds were administered intravenously. Dosages were: pimadin, 0.5 mg/kg; IIa, 0.6 mg/kg; IIb, 0.7 mg/kg; and IIc, 0.85 mg/kg.

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