mixed mechanism of action, laudolissin and cyclomethon [2]. The largest sensitivity is found in pigeons, rabbits, and dogs, then follow cats, and considerably less sensitive are mice. The muscle-relaxant effect is developed on intravenous administration after 15-30 sec and lasts, depending on the kind of animal, for 7-9 min. Consequently, IVc can be placed in the group of myorelaxants with moderate time of action.

Thus, among the derivatives of isocyanuric acid that were prepared for the first time is found a compound that with regard to muscle-relaxant properties is not inferior to the imported peripheral myorelaxant tubocurarine chloride and, in contrast to the latter, is prepared from well available and cheap starting materials.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF SUBSTITUTED PIPERIDINES AND PERHYDROQUINOLINES

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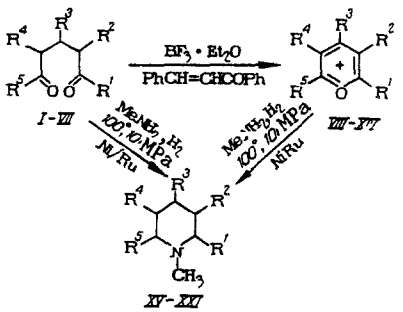
In order to discover new antiviral preparations of high activity, a synthesis was carried out of a series of phenyl- and alkyl-substituted piperidines and perhydroquinolines and their antiviral activity was studied. The compounds of this type were obtained by liquid phase catalytic hydromethylamination of 1,5-diketones and their heterocyclization products – the pyrylium salts (Table 1).



R^1=Ph (I—XVII, XIX—XXI), R^2=Me (III, V, X, XII, XVII, XIX), R^3=Me (II, IX, XVI), Ph (IV, V, VII, XI, XII, XIV, XIX, XXI), R^4=Me (III, X, XVII), R^5=Ph (I—V, VIII—XII, XV—XVII, XIX), R^4+R^5=—$(CH_2)_4$— (VI, VII, XIII, XIV, XX, XXI), nonindicated R = H

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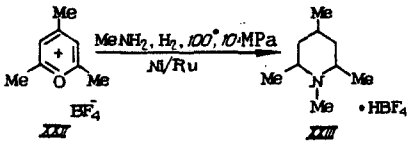
The hydromethylamination reaction was carried out in an alcoholic solution at 100°C under a hydrogen pressure of 10 mPa in the presence of nickel modified by ruthenium. Under these conditions 1,5-diketones convert into piperidine bases XV-XXI in a yield of 17-72%. The use of pyrylium salts as highly active substrates with respect to nucleophilic reagents leads to a considerable increase in the yield of the desired end products XV-XXI (55-83%).

Moreover, not only 2-aryl-, but also 2-alkyl-substituted piperidines, which are difficult to prepare from 1,5-diketones because of the ready intramolecular aldolization of the latter, can be obtained in this way.

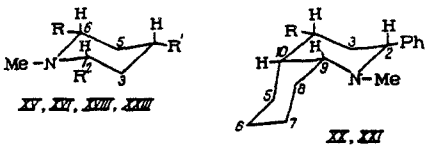
The structure of the azaheterocycles obtained was confirmed by means of elemental analysis and spectral methods. Analysis of



XXII XXIII

the ^{13}C NMR spectra (Table 2) showed that the stereochemical composition of the hydroamination products of 1,5-diketones I, II, IV, VI, VII and the corresponding pyrylium salts VIII, IX, XI, XIII, XIV was identical. The isomers obtained have a cis-configuration.

The number of signals in the spectrum of the piperidine bases XV, XVI, XVIII, XXIII indicates that the molecules are symmetrical. The signals of the methyl groups in the 2,6-posi-



XV, XVI, XVIII, XXIII XX, XXI

tions at 18.13 ppm and in the 4-position at 21-21.04 ppm (XXIII) are similar in value to the signal of the equatorial methyl groups of the 1,2,6-trimethylpiperidinium hydrochloride [3] (18.30 ppm) and strongly differ from the signals of the axially-oriented methyl groups [2] (13.7 ppm). The signal of the methyl substituent at the nitrogen atom at 38.43 ppm confirms its equatorial position (the axial methyl group appears in a stronger field at 31.86 ppm). Moreover, the axial N-CH_3 group causes a shift of the C(3), C(5) signals to the stronger field (24.34 ppm), which is not observed in the present case. Similar conclusions can be made in considering the spectra of compounds XV, XVI, XVIII, assuming that they have a structure with an equatorial disposition of all the substituent groups.

The presence in decahydroquinolines XX, XXI of a strong field signal of the C atom at 19.97 and 20.18 ppm, respectively, indicates a cis-coupling of the carbo- and heterocyclic

TABLE 1. Substituted Piperidines

Compound	Yield, %		Mp, °C (from methanol)	Empirical formula
	from a 1,5-diketone	from a pyrylium salt		
XV	63	71	108—109	$C_{18}H_{21}N$
XVI	51	83	72—73	$C_{19}H_{23}N$
XVII	0	75	85—86	$C_{20}H_{25}N$
XVIII	17	54	83—85	$C_{24}H_{25}N$
XIX*	18	55	261—263 (acetone)	$C_{25}H_{28}NCl$
XX	72	72	62—64	$C_{16}H_{23}N$
XXI	62	48	117—118	$C_{22}H_{27}N$
XXIII**	—	72	199—201	$C_9H_{20}NI$

*Isolated and characterized in the form of a hydrochloride.
**Isolated and characterized in the form of an iodide.

TABLE 2. ^{13}C NMR Chemical Shifts of Azaheterocycles

Compound	C(2)	C(3)	C(4)	C(5)	C(6)	N—CH_3	Note
XV	70,93	36,98	25,17	36,98	70,93	42,17	
XVI	70,61	45,49	31,37	45,49	70,61	42,87	21,77 C(4)—CH_3
XVIII	70,80	44,85	42,52	44,85	70,80	41,89	
XX	70,58	40,76	31,16	26,60	27,30	39,89	19,97 C(7) 31,14 C(8) 63,38 C(9) 37,68 C(10)
XXI	71,15	35,82	45,76	21,03	26,82	39,50	20,18 C(7) 30,84 C(8) 64,53 C(9) 44,50 C(10)
XXII	62,64	40,52	29,38	40,52	62,64	38,43	18,13 C(2)—CH_3, C(6)—CH_3 21,04 C(4)—CH_3

TABLE 3. Characteristics of the Antiviral Action of Piperidine and Perhydroquinoline Derivatives

Compound	Virus	Antiviral action					
		screening test		the plaque reduction method			
		toxicity zone, mm	inhibition zone of plaque formation, mm	concentration of compound, μg/ml	titer of the virus, log PFU/ml	decrease in the titer of the virus compared with control, log PFU/ml	CTI
XVIII	Smallpox vaccines	0	12	800	⩽2,0	⩾1,6	1
				400	3,34	0,26	
				200	3,41	0,19	
				0	3,6	—	
XV	»	0	22	400	⩽3,2	⩾1,72	
				200	⩽3,2	⩾1,72	
				100	⩽3,2	⩾1,72	⩾8
				50	⩽3,2	⩾1,72	
				0	4,92	—	
XXI	Respiratory syncytial	0	18	800	⩽3,0	⩾1,45	
				400	⩽3,0	⩾1,45	
				200	3,78	0,67	2
				100	4,34	0,11	
				0	4,45	—	

rings, while the resonance signal of the C(8) atom (30.78 and 31.4 ppm) indicates the predominance of conformation A (in conformation B, this signal is present at 15.65 ppm) [6].

The antiviral properties were studied (Table 3) of the synthesized mono- and bicyclic azaheterocyclic compounds, differing in number, nature (alkyl, phenyl) and position of the substituent groups.

In the above series, two compounds were discovered: 2,4,6-triphenyl-N-methylpiperidine (XVIII) and 2,6-diphenyl-N-methylpiperidine (XV) which display activity with respect to the smallpox vaccine virus. Compound XVIII is effective in only a single concentration, corresponding to that maximally tolerated by the cell culture, whereas compound XV has a pronounced antiviral activity and is able to inhibit the multiplication of the virus over a wide range of concentrations which are not toxic for the cells.

A weak activity of compound XXI (2,4-diphenyl-N-methylperhydroquinoline) was also revealed with respect to the respiratory syncytial virus.

The tests that were carried out show the expediency of carrying out further search for potential antiviral compounds in the series of similarly structured azaheterocycles.

EXPERIMENTAL (CHEMICAL)

The IR spectra were recorded on a UV-20 spectrophotometer in mineral oil and the ^{13}C NMR spectra on a Varian FT-80A spectrometer in $CDCl_3$, using TMS as internal standard. The synthesis of the pyrylium salts was carried out by the method described in [5]. The elemental analysis data correspond to the calculated values.

Hydroamination of 1,5-diketones I-VII. A 0.01 mole portion of a 1,5-diketone, 80 ml of alcohol containing 0.02 mole of methylamine and 0.5-1 g of a ruthenium-modified nickel catalyst were placed in a 150 ml autoclave. The initial hydrogen pressure was 10.1 MPa and the reaction temperature 100°C. After 5-7 h, the catalyst was filtered off, and the alcohol was

evaporated. Bases XV-XXI were separated from nitrogen-free impurities by extraction with hexane. Compound XIV was converted into the hydrochloride by the action of dilute HCl.

Hydromethylamination of pyrylium tetrafluoroborates VIII-XIV, XXII was carried out under conditions similar to the hydroamination of the 1,5-diketones. Compound XXIII was isolated in the form of a tetrafluoroborate, which was converted into an iodide by the action of KI.

EXPERIMENTAL (BIOLOGICAL)

The antiviral properties were determined in experiments on tissue cultures, infected with smallpox vaccine, herpes simplex type I, the classical fowl plague, vesicular stomatitis, the equine Venezuela encephalomyelitis, respiratory syncytial, and "ECHO-6" viruses by the "screening test" method [4], with subsequent determination of the antiviral action by the plaque reduction method under agar coating, as described previously in [1].

With the ECHO virus, the investigations were carried out on single layer cultures of passivated skin-muscular cells of a human embryo, with respiratory-syncytial virus on a grafted culture of rabbit lung cells, and with the remaining cultures on primarily trypsinized chicken embryo fibroblasts.

The determination of the quantitative characteristics of the antiviral action was preceded by finding the maximally tolerated concentration of the compounds studied for noninfected tissue cultures after a 96 h incubation in their presence. The chemotherapeutic index (CTI) was calculated as the ratio of the maximally tolerated concentration to the minimal concentration, decreasing the titer of the virus by the value of 1.25 log PFU/ml.

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ANTIANDROGENIC ACTIVITY OF CERTAIN STEROID SPIROLACTONES

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Cyprosterone acetate (CPA) is widely used in clinical practice for treating androgen-dependent diseases, either by itself (the androur preparation), or in combination with estrogens (the dian preparation) [1]. However, the variety of pathological states for which use of antiandrogens has been indicated demands considerable extension of the arsenal of these agents.

Several authors [7, 8, 11, 16, 17] have studied the antiandrogenic properties of spironolactone Ia and the possibilities of its use in clinical practice for treating certain androgen-dependent diseases. In experiments with a tissue culture it was found that Ia has a greater affinity to androgenic receptors than CPA [10]. At the same time, in a systemic administration, CPA displays a more pronounced antiandrogenic action than Ia [6, 7].

The last fact is attributed to the possible transformation of spironolactone in the organism into the slightly active antiandrogen canrenone (II) [6]. This indicates that derivatives of spironolactone which do not undergo a rapid metabolic deactivation and which retain a fairly high affinity to androgen receptors may be of a considerable practical interest.

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