The effects on chronic proliferative inflammation, along with the systemic effects of the synthesized compounds and the reference preparation, are given in Table 1. It is evident that with daily injection in a dose of 5 mg/kg for 7 days, all compounds studied inhibited the formation of granulomatous tissue by 25-30%. Prednisolone hemisuccinate and Vb were found to have the greatest thymolytic activity (35 and 27%, respectively); Va decreased the mass of the thymus by 19%. Compounds Va and Vb and the reference preparation caused the animals to gain weight to a similar degree, but did not decrease the weight of the adrenals. At the same time, it was found that the compounds synthesized did not change the content of corticosterone in blood plasma, in contrast to prednisolone hemisuccinate, subcutaneous administration of which changed the hormone's concentration by 26%.

in terms of antishock activity, both compounds and the reference preparation did not differ; at a subcutaneous dose of 5 mg/kg, they resulted in a survival rate of 50-70%, while in the control group, all the animals died.

Thus, the incorporation of amino acid residues into a molecule of prednisolone hemisuccinate enables one to obtain soluble compounds which, in their spectrum of phrmacological activity (reduction in exudative and proliferative inflammatory reactions and antishock activity), do not differ from prednisolone hemisuccinate; at the same time, they cause less pronounced systemic side effects when given by subcutaneous injection for 7 days.

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SYNTHESIS AND ANTIVIRAL ACTIVITIES OF 5-(PYRIDYL-2)-OXYINDOLE DERIVATIVES

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Among the derivatives of phenoxybenzoles and phenoxypyridines are found compounds which exhibit antiviral activities [7]. During their studies of structure-activity relationships, the authors of the referenced work concluded that one or more electron-accepting substituents must be present on the aromatic or heteroaromatic (pyridine) ring for the compound to be biologically active. Although the biochemical causes for the antiviral activity of this class of compound are not fully understood, the authors proposed that the inhibition of nucleic acid synthesis plays a role, and that the activities of these electron-deficient aromatic (and heteroaromatic) ethers may be due to their possible capabilities to form σ-complexes with nucleophilic regions of virus proteins [7].

With the above as a starting point, we sought to synthesize heteroatomic ethers with pyridine and indole rings, especially since 5-oxyindole derivatives have been found which

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TABLE 1. Characteristics of Compounds V-XX

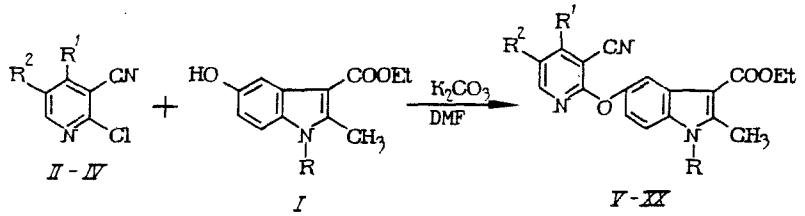
Compound	mp, °C	Yield, %	Chemical formula
V	144—5	60,9	$C_{24}H_{19}N_3O_3$
VI	158—9	73,2	$C_{25}H_{21}N_3O_3$
VII	157—8	79,6	$C_{25}H_{21}N_3O_4$
VIII	192—4	89,7	$C_{30}H_{24}N_4O_3$
IX	208—9	62,5	$C_{31}H_{26}N_4O_3$
X	249—50	87,5	$C_{30}H_{23}ClN_4O_3$
XI	179—80	89,4	$C_{31}H_{26}N_4O_4$
XII	191—2	100	$C_{32}H_{28}N_4O_4$
XIII	193—4	74,0	$C_{32}H_{28}N_4O_5$
XIV	234—5	81,9	$C_{31}H_{25}BrN_4O_4$
XV	206—7	91,1	$C_{32}H_{28}N_4O_3$
XVI	164—6	67,3	$C_{32}H_{25}N_5O_4$
XVII	160—2	61,3	$C_{32}H_{25}N_5O_3$
XVIII	142—3	60,7	$C_{31}H_{22}BrN_5O_3$
XIX	203—4	79,4	$C_{26}H_{24}N_4O_4$
XX	203—4	90,0	$C_{26}H_{24}N_4O_4$

Notes. The following solvents were used for recrystallization: compounds V-VII, XI, XVI, XVII, i-PrOH; VIII, ethyl acetate; IX, XII, XX, acetone; X, a mixture of ethyl acetate and dioxane; XIII, XIV, XVIII, a mixture of ethanol and dioxane; XV, XIX, acetone—dioxane.

have pronounced antiviral activities [3-5]. N-methyl- and N-aryl-2-methyl-3-ethoxycarbonyl-5-oxyindole (I) [2] were chosen as indole starting materials; for the pyridine derivatives, 2-chloro-3-cyanopyridine (II) [8], 2-chloro-3-cyano-4-arylaminopyridine (III), and 2-chloro-3,5-dicyano-4-anilinopyridine (IV) [1, 6] were selected. Thus, in all cases there is one or two strongly electron-accepting cyano groups in the pyridine ring.

In detailed studies of the pyridylation of I at the 5-oxy group by the indicated 2-chloropyridine derivatives, it was established that carrying out these reactions in the presence of potash in acetonitrile (MeCN) is inconvenient: even with lengthy heating of the indole (I, R=Ph) and chloropyridine (III, R^1=NHPh and R^2=H) solution in the presence of a large excess of anhydrous potash, a large quantity of unreacted compounds remains in the reaction mixture. The process takes place significantly faster in DMSO under boiling conditions (both in the presence of potash and during the use of either NaOH or NaH the reaction is complete in 2 h), however, in this case the reaction mixture becomes very tar-like, and the desired product can only be isolated in low yield and poor quality.

The best synthesis conditions were shown to be heating of the solutions of the chloropyridines II-IV and the indole I in DMF in the presence of anhydrous potash. Satisfactory yields of the 5-(pyridyl-2)oxyindoles (V-XX) were produced in this manner.



R=Ph (V, VIII, XI), $C_6H_4CH_3$-p (VI, IX, XII, XV, XVII, XX), C_6H_4OMe-p (VII, XIII, XVI, XIX), C_6H_4Br-p (XIV, XVIII), C_6H_4Cl-p (X); R^1=H (V—VII), NHPh (VIII—X, XVI—XVIII), $NHC_6H_4CH_3$-p (XV, XX), NHC_6H_4OMe-p (XI—XIV, XIX); R^2=H (V—XV, XIX, XX), CN (XVI—XVIII).

EXPERIMENTAL (CHEMICAL)

Characteristics of the compounds synthesized are presented in Table 1. The values found by elemental analyses correlate with theoretical calculated values.

1-Phenyl-2-methyl-3-ethoxycarbonyl-5-(3-cyanopyridyl-2)oxyindole (V). A mixture containing 3.92 g (0.028 mole) of 2-chloro-3-cyanopyridine (II), 9.52 g (0.032 mole) of 1-phenyl-2-methyl-3-ethoxycarbonyl-5-oxyindole, 31.5 g (0.23 mole) of anhydrous potash, and 175 ml DMF

was boiled for 5 h (the end of the reaction was determined by chromatography). After filtering off the potash, the mother liquor was evaporated to dryness, and the residue recrystallized from water. This produced 7.8 g compound V.

Compounds VI-XX were synthesized in an analogous manner.

EXPERIMENTAL (BIOLOGICAL)

The antiviral activities of these compounds were studied against the herpes simplex virus (HSV) Type I, strain L_2, in a primary culture of chicken embryo fibroblasts (CEF), as well as in experiments with cases of generalized herpes in mice produced by intranasal inoculation of the animals.

It was determined that compounds VI, VII, X-XII, and XVI-XVIII, XIX inhibit the reproduction of the HSV in the CEF cell culture. Compounds VI and XI at 10 μg/ml reduce the infection titer of the virus by 1.5 log TCD_{50} relative to a control culture: the remaining compounds reduce the infection titer by 1.0-1.25 log TCD_{50} at concentrations from 5 to 10 μg/ml. For compound XI only the chemotherapeutic index was equal to 4; for the other active compounds, it did not exceed 2.

The activities of compounds VI and XI were studied against the generalized herpes cases in mice. Medicinal properties were not established.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF BENZOYLMETHYLTHIO DERIVATIVES OF PYRIDINE, QUINOLINE, AND ACRIDINE

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A wide range of pharmacological effects has been documented for thio derivatives of pyridine, quinoline, and acridine [6, 8, 9]. In this paper, we continue the search for biologically active compounds among the 2-thiopyridines, 2- and 4-thioquinolines, and 9-thioacridines through the synthesis and biological study of benzoylmethylthio derivatives of these heterocycles.

Hydrobromide salts of the 2-benzoylmethylthio derivatives of pyridine (X-XII) and quinoline (XIII-XV) were produced by alkylation of 2-mercaptopyridine or 2-mercaptoquinoline by substituted α-bromacetophenones in an organic solvent in the presence of alkali, followed by workup of the reaction products in hydrobromic acid. 2-Methyl-4-benzoylmethylthio-6-methoxyquinoline (XVI) was produced as the free base by alkylation of 2-methyl-4-mercapto-6-methoxyquinoline by α-bromacetophenone in DMF in the presence of alkali. The syntheses of methyl-, chloro-, dichloro-, and nitrochloro-9-benzoylmethylthioacridines (XVII-XXVII) were carried out by reacting 9-mercaptoacridines with phenacylbromides in acetone in the presence

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