for 5 days in experiments with dermatophytes. The compounds were studied in a concentration of 250 μg/ml and lower. It was found that compounds XIa-c, XIIa,c display a weak activity (MIC – 125 μg/ml) Compounds XIa, XIIc with respect to C. aureus, compound XIc with respect to all three types of pathogenic fungi.

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SYNTHESIS 6-FORMYLBENZO(b)THIOPHENE DERIVATIVES AND THEIR ANTIVIRAL ACTIVITY

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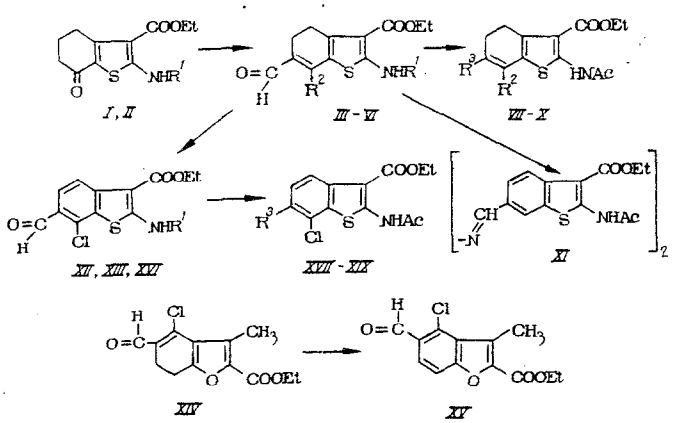
UDC 615.281:547.735].012.1.07

Benzothiophenes containing a formyl group in the benzene ring are of interest as possible key intermediate products in the synthesis of potential biologically active compounds of this series. However, introduction of an aldehyde group (formylation) into the benzene ring of benzothiophene can be accomplished only in the presence of electron-donor substituents, for example the OH group [5, 6]. We found that by the action of the Vilsmeier reagent on the previously obtained 7-oxo-4,5,6,7-tetrahydrobenzo(b)thiophenes (I, II) [1, 4], 6-formyl-7-chloro derivatives III, IV are formed in a yield of 44.2-63.4%. The structure of the compounds obtained was confirmed by means of IR, PMR and mass spectra. In the IR spectra of compounds III,IV, the absorption band of the formyl group appears together with the ethoxycarbonyl group in the form of a broadened band at 1680 cm^{-1}. In the PMR spectrum of aldehyde III the following signals are observed: 2.73 (t, 4-H), 3.08 (t, 5-H), 10.15 ppm (s, CHO), which corresponds to the proposed structure.



R^1=$COCH_3$ (I, III, VI—XII), COC_2H_5 (II, IV, XIII), H (VI, XVI); R^2=Cl (III—V, VII, IX, X), SC_6H_5 (VI, VIII); R^3=CH=$NC_6H_4CH_3$-*o* (VII), CH=NPh (VIII, XIX), CH=NOH (IX, XVII), CH=NNHPh (X), CN (XVIII)

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TABLE 1. Characteristics of Compounds III-XIII, XV-XIX

Compound	Yield, %	Mp, °C	Empirical formula
III	44.2	222—3	$C_{14}H_{14}ClNO_4S$
IV	63.4	129—30	$C_{15}H_{16}ClNO_4S$
V	88.4	200 (dec)	$C_{12}H_{12}ClNO_3S$
VI	82.1	154—5	$C_{20}H_{18}NO_4S_2$
VII	48	173—4	$C_{21}H_{21}ClN_2O_3S$
VIII	67.8	225—6	$C_{26}H_{24}N_2O_3S_2$
IX	93	219—20	$C_{14}H_{15}ClN_2O_4S$
X	54.7	241—2	$C_{20}H_{20}ClN_3O_3S$
XI	61	300	$C_{28}H_{28}Cl_2N_4O_6S_2$
XII	68.8	247—8	$C_{14}H_{12}ClNO_4S$
XIII	48.4	182—3	$C_{16}H_{14}ClNO_4S$
XV	97	131—2	$C_{13}H_{11}ClO_4$
XVI	quant.	224—5	$C_{12}H_{10}ClNO_3S$
XVII	94	261—2	$C_{14}H_{13}ClN_2O_4S$
XVIII	98	234—5	$C_{14}H_{11}ClN_2O_3S$
XIX	41.5	231—2	$C_{20}H_{17}ClN_2O_3S$

Compound III, V, VII-IX, XIII, XVII-XIX were recrystallized from an alcohol—dioxane mixture, IV, VI — from alcohol, X, XII — from dioxane, XV — from hexane, XVI — from a DMFA — dioxane mixture.

In the study of the properties of aldehyde III, we showed that the alcoholysis of the N-acetyl group can be readily carried out by the action of NaOMe with the formation of amine V. In the IR spectrum of amine V there are absorption bands at 3180-3400 cm^{-1} characterizing the unsubstituted amino group. The chlorine atom in the 7-position of compound III is fairly mobile, making it possible to carry out a nucleophilic substitution with the K-salt of thiphenol. Thus, 7-phenylthiobenzo(b)thiophene (VI) is formed.

Aldehyde III undergoes reactions with aromatic amines, hydroxylamine, phenylhydrazine and hydrazine hydrate. Thus derivatives of the formyl group are formed: the arylimonomethylene derivatives VII and VIII, oxime IX, phenylhydrazone X and azine XI. The IR spectrum of a 0.02% solution of oxime IX in CCl_4 contains an absorption band of the OH group at 3580 cm^{-1}.

The synthesis of benzo(b)thiophenes containing an aldehyde group was carried out by the aromatization of dihydro derivatives III, IV by the action of SO_2Cl_2. This method is new and has the advantage that formylbenzo(b)thiophenes with a predetermined position of the aldehyde group can be obtained, which do not contain other electron-acceptor substituents in the benzene ring, but contain a chlorine atom. An attempt to use bromine as the dehydrogenating agent instead of SO_2Cl_2 led to the formation of a mixture of products with molecular masses of M^+ 325 and M^+ 369 (^{79}Br), the chloroderivative XII and the corresponding bromo derivative, 2-acetylamino-3-ethoxycarbonyl-6-formyl-7-bromobenzo(b)thiophene.

The proposed method of aromatization by means of SO_2Cl_2, was used for the synthesis of 4-chloro-5-formylbenzofuran (XV) from the corresponding dihydro derivative XIV. The structure of the compounds obtained was confirmed by means of PMR and mass spectra. The PMR spectrum of aldehyde XII contains the following signals: 7.95 (d, 4-H), 8.23 (d, 5-H), 1053 ppm (s, CHO), molecular mass of compound XII M^+ 325.

The structure of benzofuran XV was confirmed by the PMR spectrum: 7.88 (d,6-H), 8.96 (d, 7-H),10.45 ppm (d, CHO), and by the mass spectrum (M^+ 266).

To synthesize 6-formylbenzo(b)thiophene XVI containing an unsubstituted amino group in the 2-position, alcoholysis of the acetyl group of compound XII was carried out. In the IR spectrum of the compound XVI obtained there are absorption bands of the amino group at 3310-3420 cm^{-1}.

Since cyanothiophenes display antiviral activity [3], we carried out the synthesis of nitrile XVIII via oxime XVII. The structure of compounds XVII and XVIII was confirmed by IR specdtra in which there are: for oxime XVII — an absorption band at 3580 cm^{-1} (a 0.02% solution in CCl_4) and for compound XVIII — a characteristic absorption band of the CN group at 2240 cm^{-1}.

EXPERIMENTAL (CHEMICAL)

The PMR spectra were run on a "Varian XL-200" spectrometer, using TMS as internal standard (Switzerland), the IR spectra – on a Perkin–Elmer 559 spectrophotometer (Great Britian) in mineral oil and in dilute solutions, the molecular masses of the synthesized compounds were determined mass-spectrometrically on a "Varian MAT-112" mass spectrometer (GFR) with a direct introduction of the sample into the ionic source. The energy of the ionizing electrons was 70 eV. The characteristics of the compounds obtained are presented in Table 1. The results of the chemical analyses correspond to the calculated values.

2-Acylamino-3-ethoxycarbonyl-6-formyl-7-chloro-4,5-dihydrobenzo(b)thiophenes (II, IV). A solution of 0.015 mole of compound I or II in 40 ml of dry dichlorethane was added to the Vilsmeier complex prepared from 3.5 ml (0.035 mole) of $POCl_3$ and 2.3 ml (0.03 mole) of DMFA. The reaction mixture was boiled for 10 min, cooled, washed with water, and dichloroethane was distilled off. A 30 ml portion of alcohol was added to the residue, and the mixture was heated to boiling, and then cooled. Yellow crystals of compounds III, IV were filtered off.

2-Amino-3-ethoxycarbonyl-6-formyl-7-chloro-4,5-dihydrobenzo(b)thiophene (V) and 2-amino-3-ethoxycarbonyl-6-formyl-7-chloro-benzo(b)thiophene (XVI). A 5.5 ml portion 0.024 mole) of a 10% solution of MeONa was added to a suspension of 0.009 mole of compounds III or XII in 60 ml of MeOH. The reaction mixture was sitrred for 30 min. Yellow crystals of compounds V, XVI were filtered off, washed with MeOH and dried.

2-Acetylamino-3-ethoxycarbonyl-6-formyl-7-phenylthio-4,5-dihydrobenzo(b)thiophene (VI). A 0.8 g portion (0.007 mole) of thiophene was added to a solution of 0.28 g (0.005 mole) of KOH in 50 ml of a 95% aqueous alcohol, and the mixture was stirred for 15 min. A 20 ml portion of dioxane and 1.7 g (0.005 mole) of compound III were added to the solution obtained. The reaction mixture was boiled for 1 h and poured into water. A yellow precipitate of VI was filtered off, washed with water and dried.

2-Acetylamino-3-ethoxycarbonyl-6-(o-tolyl)iminomethylene-chloro-4,5-dihydrobenzo(b)-thiophene (VII). A reaction mixture consisting of 3.28 g (0.01 mole) of compound III, 3.2 g (0.03 mole) of o-toluidine and 40 ml of dioxane was boiled for 5 min, then was cooled, the precipitate was filtered off, and recrystallized from alcohol.

2-Acetylamino-3-ethoxycarbonyl-6-phenyliminomethylene-7-phenylthio-4,5-dihydrobenzo-(b)thiophene (VIII) and 2-Acetylamino-3-ethoxycarbonyl-6-phenyliminomethylene-7-chlorobenzo-(b)thiophene (XIX). A reaction mixture consisting of 0.01 mole of aldehyde VI or XII, 1 g (0.011 mole) of aniline and dioxane (for compound VI – 40 ml, XII – 90 ml) was boiled for 3 h. To isolate compound VIII, the reaction mixture was cooled, and the precipitate that separated out was filtered off and dried. To isolate compound XIX, the reaction mixture was diluted with alcohol, the precipitate was filtered off, and dried.

Oxime of 2-Acetylamino-3-ethoxycarbonyl-6-formul-7-chloro-4,5-dihydrobenzo(b)thiophene (IX) and Oxime of 2-Acetylamine-3-ethoxycarbonyl-6-formyl-7-chlorobenzo(b)thiophene (XVII). A 0.76 g portion (0.011 mole) of $NH_2OH \cdot HCl$ was added to a solution of 0.01 mole of aldehyde III or XII in 50 ml of pyridine. The reaction mixture was allowed to stand for 24 h at room temperature, then poured into water, the precipitate of IX or XVII that separated out was filtered off, washed with water, and dried.

Phenylhydrazone of 2-Acetylamino-3-ethoxycarbonyl-6-formul-7-chloro-4,5-dihydrobenzo-(b)thiophene (X). A 0.9 g portion (0.0084 mole) of phenylhydrazine was added to a hot solution of 2.3 g (0.007 mole) of aldehyde III in 25 ml of dioxane. The reaction mixture was boiled for 15 min, cooled, and the yellow precipitate was filtered off and washed with dioxane.

Azine of 2-Acetylamino-3-ethoxycarbonyl-6-formul-7-chloro-4,5-dihydrobenzo(b)thiophene (XI). A 0.25 ml portion (0.0051 mole) of hydrazine hydrate was added to a hot solution of 1.7 g (0.005 mole) of aldehyde III in 45 ml of dioxane. The reaction mixture was boiled for 40 min, cooled, and the yellow precipitate was filtered off and washed with dioxane.

2-Acylamino-3-ethoxycarbonyl-6-formyl-7-chlorobenzo(b)thiophenes (XII, XIII) and 3-Methyl-2-ethoxycarbonyl-5-formyl-4-chlorobenzofuran (XV). The reaction mixture consisting of 0.07 mole of aldehyde III, IV or XIV [2], 13.5 g (0.1 mole) of SO_2Cl_2 and 500 ml of dry $CHCl_3$ was boiled for 15 min, then cooled, washed with water and $CHCl_3$, and distilled. The residue was heated with alcohol, cooled, and the precipitate of aldehyde XII, XIII or XV was filtered off.

2-Acetylamino-3-ethoxycarbonyl-6-cyano-7-chlorobenzo(b)thiophene (XVIII). The reaction mixture consisting of 16 g (0.047 mole) of oxime XVII and 60 ml of Ac_2O was boiled for 2 h, then was cooled and poured into water. The precipitate was filterd off and dried.

EXPERIMENTAL (BIOLOGICAL)

The antiviral activity of the compounds was studied with respect to representatives of DNA and RNA reputed viruses – the herpes simplex virus type I, strain L_2 and the influenza virus FPB (H_7N_7), and the virus-inhibiting action – in a culture of chicken embryo fibroblast cells and in model experiments on animals.

It was found that compounds XII and XVIII in concentrations of 2.5 and 5.0 μg/ml inhibit the reproduction of herpes simplex virus in a cell culture, decreasing the infection titer of the virus by 1.0-1.25 log TCD_{50} (50% of tissue cytopathic doses of the virus). The compounds studied did not influence the reproduction of influenza virus in a cell culture and did not display a therapeutic effect on models of influenze related pneumonia and generalized herpes in mice.

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ANTIVIRAL ACTIVITY OF THIOSULFATES AND THIOSULFONATES

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UDC 615.281:547.541.1+547.269.5

It has been previously shown that among the various classes of organosulfur compounds, there is a significant number having activity against different types of viruses. It has been found that introducing sulfur-containing groups into the molecules of known antiviral substances can modulate their activity [8, 9].

In the present work, we have undertaken a study of the antiviral activities in vitro and in vivo, as well as the immunomodulating properties, of some compounds whic contain –S–SO_2–groups – sodium arythiosulfates (I-VI) of general formula RSO_2SNa, where R = C_6H_5 (I), p-$CH_3C_6H_4$ (II), p-iso-$C_4H_9C_6H_4$ (III), p-iso-$C_5H_{11}H_4$ (IV), p-$C_6H_{13}C_6H_4$ (V), $CH_3CONHC_6H_4$ (VI); sodium S-benzoylthiosulfate $C_6H_5COSSO_3Na$ (VII); Benzoylthiosulfonic acid S-ether $(C_6H_5SO_2SCH_2-)_2$ (VIII); sodium s-ethylthiosulfate (a Bunte salt) $C_2H_5SSO_2ONa$ (IX), and inorganic sodium thiosulfate (X).

EXPERIMENTAL (CHEMISTRY)

Synthesis of I-VI were carried out by the method of [4], compound VII by [3], VIII by [2], and IX – [10]; X – sodium thiosulfate – was used as "chemically pure" reagent grade.

EXPERIMENTAL (BIOLOGY)

Antiviral activity of the thiosulfates and thiosulfonates was studied in vitro and in vivo, according to their ability to inhibit the reproduction of influenza virus A/Lenin-

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 25, No. 11, pp. 33-34, November, 1991. Original article submitted December 5, 1990.

0091-150X/91/2511-0792$12.50