21. W. Kwapiszewski, J. Iliaszenko, and M. Sokolowska-Muszynska, Arch. Immunol. Ther. Exp., 26, 917-919 (1978).
22. N. J. Lewis, R. L. Inloes, J. Hes et al., J. Med. Chem., 21, 1070-1073 (1978).
23. I. Litchfield and F. Wilcoxon, J. Pharmacol. Exp. Ther., 96, 99 (1949).
24. I. R. Neher, A. Wettstein, and K. Miescher, Helv. Chim. Acta, 29, 1815-1829 (1946).
25. R. F. Nutt, F. W. Holly, C. Homnick et al., J. Med. Chem., 24, 692-698 (1981).
26. C. G. Overberger, H. Ringsdorf, and B. Avchen, ibid., 8, 862-864 (1965).
27. J. C. Schwartz, Trends Neurosci., 6, 45-48 (1983).

SYNTHESIS AND ANTIVIRAL ACTIVITY OF 7-OXO- AND 7-HYDROXY-4,5,6,7-TETRAHYDROBENZO[b]THIOPHENE DERIVATIVES

M. V. Kapustina, I. A. Kharizomenova,
V. I. Shvedov, A. N. Fomina,
I. S. Nikolaeva, E. A. Golovanova,
G. A. Bogdanova, and L. M. Alekseeva

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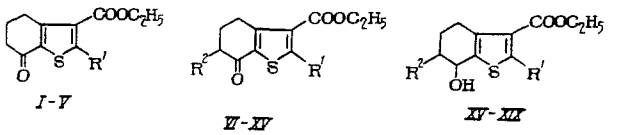
Continuing our research [1, 2] in series of benzo[b]thiophene derivatives in order to search for substances that have biological activity we have synthesized 6-substituted 7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes. Compounds that have antiviral activity have been previously detected among carbinols of the thiophene series [4]. The introduction of a phenylthiomethyl group into the 2 position of the indole molecule also leads to the development of antiviral activity [3]. In this connection we obtained 4,5,6,7-tetrahydrobenzo[b]thiophene derivatives that contain a phenylthio group and a hydroxy group.

In the bromination of I-IV we isolated the corresponding 6-bromo-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes VI-IX, the structures of which were confirmed by means of the PMR spectra. In the case of bromo derivative VI the protons of two methylene groups in the 4 and 5 positions are manifested by a multiplet at 2.48-3.16 ppm, and the signal of the proton in the 6 position shows up in the form of a triplet at 4.6 ppm.



I-V V-XV XV-XIX

R^1=NHAc (I, VI, X, XI, XII, XIII, XIV, XVI, XIX), NHCOEt (II, VII), $NHCOCH_2Cl$ (III, VIII), NHCOPh (IV, XI, XV, XVII), H (V, XVIII); R^2= N-piperidyl·HCl (XII), SCN (XIII), N-morpholyl·HCl (XI), SPh (XIV, XV, XIX), H (XVI, XVII, XVIII), Br (VI, VII, VIII, IX), I (X).

The synthesis of 2-acetamido-6-iodo derivative X was accomplished by iodinating of I with iodine chloride.

Compounds VI and IX, which contain a bromine atom in the 6 position, readily undergo nucleophilic substitution with reagents such as secondary amines, potassium thiocyanate, and thiophenol to give the corresponding 6-substituted 7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes XI-XV. An absorption band that is characteristic for the thiocyanato group at 2165 cm^{-1} appears in the IR spectrum of derivative XIII.

7-Hydroxy derivatives XVI-XIX are formed in high yields in the reduction of 7-oxo-derivatives I, IV, V, and XIV with sodium borohydride. An absorption band of a hydroxy group at 3620 cm^{-1} appears in the IR spectra of XVI-XIX recorded from solutions in CCl_4.

The PMR spectrum of XIX confirms the proposed structure. Signals of substituents in the 2 and 3 positions are present in the spectrum: a $COCH_3$ singlet at δ 2.24 ppm, a triplet and

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 24, No. 4, pp. 39-40, April, 1990. Original article submitted June 29, 1989.

TABLE 1. 7-Oxo- and 7-Hydroxy-4,5,6,7-tetrahydrobenzo[b]thiophene Derivatives

Compound	Yield, %	mp, °C	Empirical formula
VI	68,0	184—185	$C_{13}H_{14}BrNO_4S$
VII	62,4	154—155	$C_{14}H_{16}BrNO_4S$
VIII	91,0	106—107	$C_{13}H_{13}BrClNO_4S$
IX	77,0	178—179	$C_{18}H_{16}BrNO_4S$
X	34,4	145—146	$C_{13}H_{14}INO_4S$
XI	42,5	213—214	$C_{17}H_{23}ClN_2O_5S$
XII	41,6	221—222	$C_{18}H_{25}ClN_2O_4S$
XIII	65,0	133—134	$C_{14}H_4N_2O_4S_2$
XIV	54,6	115—116	$C_{19}H_{19}NO_4S$
XV	82,0	183—184	$C_{24}H_{21}NO_4S_2$
XVI	80,0	119—120	$C_{13}H_{17}NO_4S$
XVII	94,0	145—146	$C_{18}H_{19}NO_4S$
XVIII	70,0	56—57	$C_{11}H_{14}O_3S$
XIX	56,0	137—138	$C_{19}H_{21}NO_4S_2$

a quartet of methyl and methylene groups in an ethoxycarbonyl group (δ 1.30 and 4.30 ppm), and a multiplet of a phenyl radical (7.21-7.46 ppm). Signals of protons in the 4-7 positions are observed at 1.96-5.73 ppm; doubling is characteristic for the individual signals. Since, according to the mass spectrum, the m/z value of the molecular-ion peak corresponds to the molecular mass of this compound and impurities were not detected, it may be assumed that the compound is a mixture of isomers with cis and trans orientations of the substituents in the 6 and 7 positions of the molecule in which the percentage of the minor isomer does not exceed 10%. The following signals, which belong to the predominant isomer, can be isolated in the spectrum: doublet, δ 5.73 ppm, J ≅ 6.8 Hz (7-H); quartet, δ 4.79 ppm, J_1 ≅ 3.5 Hz, J_2 = 2 Hz (6-H); multiplets, δ 3.0 ppm, J_1 = 18 Hz, J_2 ≅ 4 Hz, and δ 3.67 ppm, J_1 = 8 Hz, J_2 = 4 Hz (equatorial protons in the 4 and 5 positions). For the minor isomer the following signals are isolated from the general group of signals: doublet of the 7-H proton (δ 5.95 ppm, J = 7 Hz) and triplet of the 6-H proton (δ 4.50 ppm, $J_1 = J_2$ ≅ 3 Hz).

EXPERIMENTAL (CHEMICAL)

The PMR spectra of the compounds were recorded with a Varian XL-200 spectrometer (Switzerland) with tetramethylsilane as the internal standard. The IR spectra were recorded with a Perkin—Elmer 559 spectrometer (Great Britain).

The characteristics of the compounds obtained are presented in Table 1. The results of the elementary analyses were in agreement with the calculated values.

2-Acylamino-6-bromo-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes VI-IX. A solution of 0.02 mole of bromine in 50 ml of $CHCl_3$ was added gradually to a refluxing solution of 0.02 mole of 7-oxo derivative I-IV in 50 ml of $CHCl_3$, and the mixture was refluxed for 2 h. It was then cooled and washed with water until the wash water was neutral, and the $CHCl_3$ was removed by vacuum distillation. Alcohol was added to the residue, and the precipitate was removed by filtration, washed with alcohol, and dried.

3-Acetamido-6-iodo-3-ethoxycarbonyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (X). A solution of 3.24 g (0.02 mole) of CII in 20 ml of $CHCl_3$ was added dropwise at 20-25°C in the course of 1 h to a solution of 5.62 g (0.02 mole) of I in 50 ml of $CHCl_3$ containing 0.2 g of benzoyl peroxide, after which the mixture was maintained at room temperature for 48 h. It was then washed with water until the wash water was neutral, and the $CHCl_3$ was removed by distillation. Alcohol was added to the residue, and the precipitate was removed by filtration, washed with alcohol, and dried.

2-Acetamido-6-morpholino-3-ethoxycarbonyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene Hydrochloride (XI) and 2-Acetamido-6-piperidino-3-ethoxycarbonyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene Hydrochloride (XII). A reaction mixture consisting of 2.81 g (0.01 mole) of VI, 0.025 mole of the amine, and 25 ml of dry dichloroethane was refluxed for 2 h, after which the mixture was cooled and washed with water, and the dichloroethane was removed by vacuum distillation. The residual oil was dissolved in acetone—ether (1:1), the solution was acidified with an ether solution of HCl, and the precipitated XI or XII was removed by filtration and dried.

2-Acetamido-6-thiocyanato-3-ethoxycarbonyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (XIII). A reaction mixture consisting of 3.6 g (0.01 mole) of VI, 1.07 g (0.011 mole) of KCNS, and 30 ml of alcohol was refluxed for 2 h, after which it was cooled, and the precipitate was removed by filtration, washed with water, recrystallized from alcohol–dioxane (1:1), and dried.

2-Acylamino-6-phenylthio-3-ethoxycarbonyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes XIV and XV. A solution of 0.033 mole of KOH in 6 ml of water was added to a solution of 0.033 mole of thiophenol in 100 ml of alcohol, and the mixture was stirred for 15 min at 20°C. A 0.03-mole sample of VI or IX was then added, and the mixture was stirred for 2.5 h at 20°C. The precipitate was removed by filtration and recrystallized from alcohol.

7-Hydroxy-3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thiophene Derivatives XVI, XVII, XVIII, and XIX. A 1.5-g sample of $NaBH_4$ was added in portions with stirring to a suspension of 0.02 mole of I, IV, V, or XiV in 80 ml of dioxane and 30 ml of MeOH in the course of 1 h at 40-50°C, after which the mixture was stirred for another 30 min. It was then poured into water, and the precipitate was removed by filtration, recrystallized from alcohol, and dried.

EXPERIMENTAL (BIOLOGICAL)

The antiviral activity of the compounds was studied with respect to influenza A/FPV (H7N7) virus and herpes simplex I virus of the antigen type (L_2 strains).

The virus inhibiting activity of the substances was studied in an initially trypsinized culture of chicken embryo fibroblasts (CEF) infected with 10-100 TCD_{50} of the virus. The maximally tolerable concentrations (MTC) of the compounds for the CEF were determined beforehand. The antiviral activity of the compounds was studied using concentrations amounting to 1/4 to 1/8 of the MTC. The evaluation of the virus-inhibiting activity of the compounds was carried out with allowance for the warding off (by them) of the cytopathic effect (CPE) of the virus on the cells and the decrease in its infection titer as compared with the control.

It was established that XVII and XIX had a virus-inhibiting effect on the reproduction of the influenza virus in the CEF cell culture; in concentrations of 2.5 and 5 μg/ml XVII and XIX decreased the infection titer of the virus by 1.1.25 TCD_{50}. Compound VII was slightly active with respect to this virus: in a concnetration of 0.6 μg/ml it decreased the infection titer of the virus by 0.75 log TCD_{50}.

It should be noted that the introduction of a halogen atom (Br, I) into the molecules of the 7-oxotetrahydrobenzo[b]thiophene derivatives increased the cytotoxicity of the compounds significantly, and the MTC for the culture of CEF cells decreased from 10 μg/ml to 2.5 μg/ml.

Substances that have antiherpes activity were not found among the investigated compounds.

LITERATURE CITED

1. A. N. Grinev, I. A. Kharizomenova, M. V. Kapustina, et al., Khim. Geterotsikl. Soedin., No. 9, 1178-1180 (1986).
2. A. N. Grinvev, I. A. Kharizomenova, M. V. Kapustina, et al., ibid., No. 4, 460-462 (1987).
3. E. K. Panisheva, A. N. Fomina, I. S. Nikolaeva, et al., Khim.-farm. Zh., No. 5, 565-569 (1988).
4. I. A. Kharizomenova, A. N. Grinev, N. V. Kaplina, et al., ibid., No. 9, 1079-1080 (1985).