FUNCTIONAL DERIVATIVES OF THIOPHENE.

XXI.* SYNTHESIS AND ANTIVIRAL ACTIVITY OF 2-BENZOYLAMINO-3-α-HYDROXYALKYL-4,5-DIALKYLTHIOPHENES

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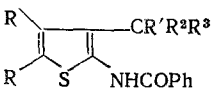
We accomplished the synthesis of 3-α-hydroxyalkylthiophenes (IIIa-c) for the study of their antiviral activity. The 4,5-dimethyl- and 4,5-tetramethylene-2-benzoylaminothiophenes (Ia, b) were utilized as the initial compounds [2]. These compounds were acylated at the position 3 by the action of Ac_2O or acid chlorides in the presence of H_3PO_4. As a result, the 2-benzoylamino-3-acylthiophenes (IIa-f) were obtained. The structure of the compounds (IIa-f) was confirmed by the PMR and IR spectra. The singlet in the region of the aromatic protons of the thiophene ring is absent from the PMR spectrum of compound (IIa). Consequently, the acyl group is inserted at the position 3 of the thiophene derivative (Ia). The absorption band of carbonyl appears at 1655-1670 cm^{-1}, and characterizes the acyl substituent in the IR spectra of (IIa-f).

The α-hydroxyalkylthiophenes (IIIa-c) were obtained with a yield of 53-98% by the reduction of the 3-acylthiophenes (IIa, IIb, IIe) with sodium borohydride. The presence of the hydroxyl groups in the compounds (IIIa-c) is shown by the fact that the absorption band of the OH group is observed at 3350 cm^{-1} in the spectra of the last compounds.



IIa-f, IIIa-c

II a, c, b; III a, c: R = Me; II b, d, f, III b: R + R = $(CH_2)_4$; II a, b, III a, b: R^3 = Me; IIc, d: R^3 = CH_2Cl; II e, f, III c: R^3 = Et; IIa = f: $R^1 + R^2$ = O=; III a = c: R^1 = H, R^2 = OH.

EXPERIMENTAL (CHEMICAL)

The IR spectra of the compounds were taken in a paste with mineral oil on a UR-10 spectrophotometer (GDR). The PMR spectra were taken on an XL-100 instrument of the firm "Varian" (USA).

Derivatives of 2-Benzoylamino-3-acetylthiophene (IIa, IIb). The reaction mixture consisting of 0.03 moles of (Ia) or (IIb), 10 ml of Ac_2O, and 1 ml of 85% H_3PO_4 is heated for 30 min in a water bath. After cooling, the residue is filtered off. Recrystallization is performed from a 2:1 mixture of alcohol–dioxane. The data on the compounds (IIa, IIb) are presented in Table 1.

Derivatives of 2-Benzoylamino-3-acylthiophene (IIa, IIc-f). The reaction mixture consisting of 0.01 moles of (Ia) or (IIb), 0.04 moles of the corresponding acid chloride, 0.5 ml of 85% H_3PO_4, and 5 ml of dioxane is boiled for 1 h. After cooling, the mixture is poured into water and ice. The residue is filtered off and recrystallized. The data on the compounds (IIa, IIc-f) are presented in Table 1.

Derivatives of 2-Benzoylamino-3-α-hydroxyalkylthiophene (IIIa-c). To a solution of 0.0256 moles of (IIa, IIb, IIe) in 180 ml of dioxane and 80 ml of alcohol at 20°C is added 6.8 g (0.18 mole) of $NaBH_4$ in portions for 30 min. After the complete addition, the reaction mixture is stirred for a further 1 h and poured into water and ice. The residue is filtered off and dried. The data on the compounds (IIIa-c) are presented in Table 1.

* Communication XX, see [1].

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TABLE 1. Physicochemical Properties of the Synthesized Compounds

Compound	Yield, %	mp,* °C	Found, %				Empirical formula	Calculated, %			
			C	H	N	S		C	H	N	S
IIa	33,3†										
	37‡	158–9	65,8	5,5	5,1	11,9	$C_{15}H_{15}NO_2S$	65,9	5,5	5,1	11,7
IIb	43	180–1	68,0	5,8	4,5	10,8	$C_{17}H_{17}NO_2S$	68,2	5,7	4,7	10,7
IIc	29,3	148–50	58,5	4,6	4,5	10,4	$C_{15}H_{14}NO_2SCl$	58,5	4,6	4,5	10,4
IId	13,5	227–8	60,8	4,6	4,2	9,4	$C_{17}H_{14}NO_2SCl$	61,1	4,8	4,2	9,6
IIe	34,8	134–5	66,7	6,0	4,8	11,0	$C_{16}H_{17}NO_2S$	66,9	6,0	4,9	11,1
IIf	38,3	129–30	69,1	6,4	4,6	10,0	$C_{18}H_{19}NO_2S$	69,0	6,1	4,5	10,2
IIIa	53	169–70	65,5	6,0	5,3	11,5	$C_{15}H_{17}NO_2S$	65,5	6,2	5,1	11,6
IIIb	98	141–2	67,9	6,6	4,6	10,5	$C_{17}H_{19}NO_2S$	67,7	6,4	4,5	10,6
IIIc	89,5	170–1	66,2	6,6	4,9	11,1	$C_{16}H_{19}NO_2S$	66,4	6,6	4,5	11,1

*Substances were recrystallized as follows: (IIa, IIc, IIe) from alcohol, (IIb, IId, IIf) from a 2:1 mixture of alcohol–dioxane, and (IIIa-c) from 50% aqueous MeOH.

†Obtained by the action of AcCl.

‡Obtained by the action of Ac_2O.

EXPERIMENTAL (BIOLOGICAL)

The antiviral action of the compounds (IIIa-c) was studied in chick embryo cell culture (CEF) in regard to examples of DNA viruses (viruses of herpes simplex types I and II) as well as RNA viruses: the influenza virus A/F PV (Hav I No. 1), the virus of Venezuelan equine encephalitis (VEE), and the virus of vesicular stomatitis (VVS).

The compounds were introduced in the maximal bearable and lower concentrations at 1 h after the infection of the cell monolayer by the virus. The results were taken into consideration according to the ability of an investigated compound to prevent the cytopathic action of the virus on the cells. In studying the virus-inhibiting activity of the compounds toward influenza virus, we also took into consideration the decrease in the titer of hemagglutinins in the culture fluid by the hemagglutination reaction. As a result of the conducted study, it was established that compound (IIIb) shows weak virus-inhibiting action on the reproduction of the herpes simplex virus, both of type I and type II, lowering the infectious titer of the virus relative to the control by 1.0 and 1.8 log TCD_{50} respectively. Compound (IIIb) does not influence the reproduction of the influenza virus. In contrast, compound (IIIa) suppresses the propagation of the influenza virus, lowering the infectious titer of the virus relative to the control by 1.0 log TCD_{50} (the mean geometric titer of viral hemagglutinins in the culture fluid was thereby equal to zero, and the titer in the control was 1:64); but it does not show influence on the reproduction of both types of the herpes virus. The chemotherapeutic indexes of activity were equal to 2. The compounds (IIIa, IIIb) were not active toward the virus of VEE and VVS. Compound (IIIc), which contains an α-hydroxypropyl group at position 3, was inactive in regard to all the viruses studied.

LITERATURE CITED

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