INVESTIGATION OF ANTIVIRAL ACTIVITY AMONG DERIVATIVES OF 4-OXYBENZOFURAN

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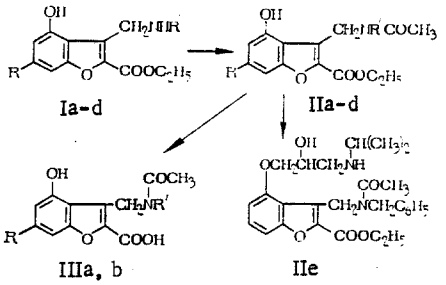
The benzofuran derivatives exhibit a broad spectrum of biological activity [4-6]. No biological activity was exhibited by the aminomethyl derivatives of 4-oxy- [3] and 4,5-dioxybenzofuran [1] which we had synthesized earlier although we did find substances among the aminomethyl derivatives of 5-oxy- and 4,5-dioxyindole which did have antiviral activity [2].

In that connection we obtained derivatives of 4-oxybenzofuran with acetylaminomethyl substituents in position 3 of the benzofuran ring. The starting compounds were Mannich bases Ia-d [3] which were then subjected to acetylation, O-alkylation, and hydrolysis. We obtained the amides IIa-d from the amines Ia-d through the action of acetic anhydride at 20°C. This reaction resulted in a high yield of the target compounds (75-93%) and there was no observed formation of O-acylation products under these conditions.



Ia-d IIa-d IIIa, b IIe

R = H Ia, b, d; II a, b, d, III a, b, Ph (Ic, IIc);
R′ = CH_3 (Ia–IIIa); $CH(CH_3)_2$ (I b, c, II b, c, IIIb); CH_2Ph Id, IId

The course of acylation was determined by comparing the PMR spectra of the starting amines and amides. Thus, the introduction of an acetyl group into amine Id induced a weak polar shift ($\Delta\delta$ 0.91 and 0.69 ppm) of CH_2 group singlet proton signals. In addition, two sets of proton signals of the CH_3 group and one of the methylene group were observed (δ 2.03, 2.38 and 4.58, 4.40 ppm respectively) which was apparently due to the retarded rotation around the N-$COCH_3$ bond.

Our study of the synthesized compounds' antiviral activity showed that compounds IIa and IIIb exhibit virus-inhibiting action against type A influenza virus.

Thus, the introduction of an acetyl residue into an amine group resulted in the appearance of antiviral activity.

EXPERIMENTAL (CHEMICAL)

PMR spectra were recorded on a Varian XL-200 spectrometer in DMSO-d_6. TMS was the internal standard. The reaction was controlled chromatographically on Silufol UV-254 plates in a 9:1 benzene-methanol system. The compounds' characteristics are given in Tables 1 and 2.

2-Ethoxycarbonyl-3-(N-Methyl, N-acetylaminomethyl)-4-oxybenzofuran (IIa). A 0.5 ml portion of acetic anhydride was added to 0.4 g (1.6 mmole) of 2-ethoxycarbonyl-3-methylaminomethyl-4-oxybenzofuran Ia. The resultant solution was left for 30 min at room temperature and then cooled to +5°C. The resultant precipitate was filtered off, washed with water, and

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TABLE 1. Characteristics of Compounds IIa-e, IIIa, b

Compound	mp, °C	Yield, %	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
IIa	180—2	75,4	61,7	5,8	4,9	$C_{15}H_{17}NO_5$	61,8	5,9	4,8
IIb	224—6	93,0	64,0	6,5	4,5	$C_{17}H_{21}NO_5$	63,9	6,6	4,4
IIc	190—3	90,0	69,7	6,3	3,8	$C_{23}H_{25}NO_5$	69,8	6,4	3,5
IId	169—1	85,3	69,1	6,1	3,8	$C_{21}H_{21}NO_5$	68,7	5,8	3,8
IIe	80—3	50,0	66,9	7,1	5,8	$C_{27}H_{34}N_2O_6$	67,2	7,1	5,8
IIIa	218—20 with decomposition	81,2	59,2	5,0	5,5	$C_{13}H_{13}NO_5$	59,3	5,0	5,3
IIIb	221—22 with decomposition	77,5	61,3	5,9	4,7	$C_{15}H_{17}NO_5$	61,8	5,9	4,8

Note. Compounds IIa, c recrystallized from acetone, IIb, d from ethanol, IId from petroleum ether, and IIIa, b from water.

TABLE 2. PMR Spectra of Compounds Id and IId

Compound	Chemical shifts δ ppm (in DMSO-d_6)					
	H^5	H^6	H^7	$-CH_2NRCH_2-$	$COCH_3$	$COOC_2H_5$
Id	6,57 qd	7,31 t	6,96 qd	4,23 s; 3,78 s	—	1,28 t 4,25 q
IId	6,65 qd	7,26 t	6,98 qd	5,14 s; 4,47[a] s 5,15 s; 4,58; 4,40[b]	2,03 2,38[b]	1,26 t 4,28 q

[a]At 70°C.
[b]At 25°C.

dried. The yield of IIa was 0.35 g (75.4%), mp 180-182°C (from acetone).

Compounds IIb-d were obtained in a similar manner.

1-[2-Ethoxycarbonyl-3-(N-benzyl, N-acetylaminomethyl)benzofuran-4-yloxy]-3-isopropylamino-2-propanol (IIe). A 0.44 g (11 mmole) portion of NaOH and 4 ml of epichlorohydrin was added upon stirring to a solution of 3.7 g (10 mmole) of compound IId in 40 ml of acetone. The reaction mixture was boiled and stirred for 5 h and then vacuum evaporated. A 30 ml portion of ethanol and 1.8 g (30 mmole) of isopropylamine was added to the residue which was then boiled for 3 h. The solvent was evaporated and the residue was recrystallized from alcohol. The yield of compound IIe was 2.4 g (50%), mp 80-83°C (from petroleum ether).

2-Carboxy-3-(N-methyl, N-acetylaminomethyl)-4-oxybenzofuran (IIIa). A solutions comprised of 0.48 g (12 mmole) of NaOH in 7 ml of water was added to a solution of 1.65 g (6 mmole) of compound Ia in 10 ml of ethanol which was then boiled for 30 min. The reaction mixture was diluted with 100 ml of water and then acidified to pH 7.0 with conc. HCl. The precipitate was then filtered off, washed with water, and dried. The yield of compound IIIa was 1.2 g (81.2%), mp 218-220°C (with decomposition).

Compound IIIb was obtained in the same manner.

EXPERIMENTAL (BIOLOGICAL)

The antiviral activity of the oxybenzofuran derivatives was tested against influenza virus type A strain A/PR-8/34 (H0N1), A/FPV (H7N7), and A/Bethesda/63 (H2N2) I.

The virus-inhibiting action of the test substances was assayed in a primary trypsinized culture of chick embryo (CE) fibroblast cells inoculated at a 10-100 viral TCD_{50} and evaluated by the substances' suppression of the virus' cytopathic effect on the cells. The substances were used at concentrations that were $^1/_4$ and $^1/_8$ of the maximum tolerated dose for the CE cells.

The therapeutic action of the compounds was studied on a model of mouse influenza pneumonia induced by intranasal inoculation of the influenza virus. The substances were administered at the maximum tolerated and minimum doses 1 h before the mice were inoculated

and once a day thereafter for 4 days. The test results were computed on the 14th day after inoculation and evaluated by the reduction in mortality (in percent) of the treated animals in comparison to the control animals. The results were statistically processed by employing the χ^2 criteria.

We found that among the seven examined derivatives of 4-oxybenzofuran (IIa-e, IIIa, b) compounds IIa and IIIb at a concentration of 5 μg/ml suppress influenza virus reproduction in the cell culture and reduced the virus titer by 1.0 g TCD_{50} in comparison to the control. The other five compounds did not exhibit virus inhibiting activity. In an influenza pneumonia model compound IIIb had a slight therapeutic effect at doses of 250 and 500 mg/kg in which case it reliably reduced mouse mortality by 30-40% ($P < 0.05$) in comparison to the control. The chemotherapeutic index of compound IIIb was 2 since it was inactive at lower doses.

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 5-HYDROXYNAPHTHO[1,2-b] THIOPHENES AND 4-HYDROXYBENZO[2,1-b:3,4-b']DITHIOPHENES

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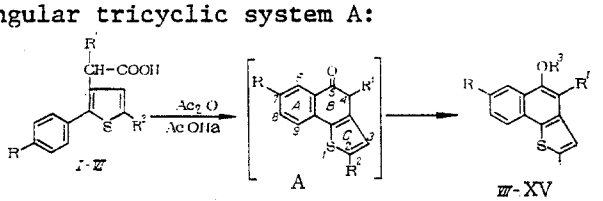
The search for new, effective antitubercular drugs is an important task in public health, as a result of the appearance of strains of mycobacteria which are resistant to current antitubercular drugs.

Antitubercular activity is known to be present in derivatives of 5-hydroxyindole, 5-hydroxybenzindole, 5-hydroxybenzofuran, and 5-hydroxynapthofuran [2]. Continuing work on condensed heterocycles containing the thiophene moiety [5], we have obtained and examined the antimicrobial activity of some 5-hydroxynaphtho[1,2-b]thiophenes and 4-hydroxybenzo[2,1-b:3,4-b']-dithiophenes. The naptho[1,2-b] thiophene and benzo[2,1-b:3,4-b']dithiophene heterocyclic systems have been described previously [6, 7], but we have found no literature reports of the preparation of hydroxy derivatives.

It was decided to prepare 5-hydroxy[1,2-b]thiophenes from 2-arylthienyl-3-acetic acids (I-VI), previously prepared by us from aliphatic precursors [1]. We have found that boiling (I-VI) in acetic anhydride in the presence of sodium acetate results in facile intramolecular acylation to give the angular tricyclic system A:



I-VI VII-XV

R = H(I, V—VII, XI—XIII, XVII, XVIII), Me(II, VIII, XIV), OMe (III, IV, IX, X, XV, XVI); R^1 = H (I—III, VII—IX, XIII—XV), Me (IV—VI, X—XII, XVI—XVIII); R^2 = H (I—IV, VII—X, XIII—XVI), COPh (V, XI, XVII), COC_6H_4OMe-p (VI, XII, XVIII); R^3 = H (XIII—XVIII), Ac (VII—XII).

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