BIOLOGICALLY ACTIVE THIOPHENE DERIVATIVES. IV. SYNTHESIS AND ANTIVIRAL ACTIVITY OF UNSATURATED KETONES OF THE THIOPHENE SERIES

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Thiophene ketones and thiophene analogs of chalcones possess antimicrobial activity [1-3]. However, the literature contains comparatively few references to the antiviral activity of compounds containing the thiophene ring. In particular, the thiosemicarbazones of 2- and 3-thiophene aldehydes, and the bromo-, chloro-, and cyanosubstituted thiophene aldehydes are active antiviral agents [4, 5].

Continuing the search for substances with antiviral properties [6], we have synthesized some new α,β-unsaturated ketones of the dithiophene series Ia-o and studied their biological action.

$$RCHO + CH_3COR' \rightarrow \underset{Ia-o}{RCH=CHCOR'}$$

a: R = C_6H_5; R' = 5'-methyl-2,2'-dithienyl-5-yl; b: R = 2-furyl; R' = 2,2'-dithienyl-5-yl; c: R = 2-furyl; R' = 5'-methyl-2,2'-dithienyl-5-yl; d: R = 2-thienyl; R' = 5'-methyl-2,2'-dithienyl-5-yl; e: R = 2-thienyl; R' = 2,2'-dithienyl-5-yl; f: R = 2,2'-dithienyl; R' = 2-thienyl; g: R = 2,2'-dithienyl-5-yl; R' = 5'-methyl-2,2'-dithienyl-5-yl; h: R = 5'-methyl-2,2'-dithienyl-5-yl;* i: R = 5'-methyl-2,2'-dithienyl-5-yl; R' = 2-furyl; j: R = 5'-methyl-2,2'-dithienyl-5-yl; R'=2-thienyl; k: R = 5'-methyl-2,2'-dithienyl-5-yl; R' = 2,2'-diethienyl-5-yl; l: R = R' = 5'-methyl-2,2'-diethienyl-5-yl; m: R = 2,2'-diethienyl-5-yl; R' = CH_3; n: R = 5'-methyl-2,2'-dithienyl-5-yl; R' = CH_3; o: R = 5'-ethyl-2,2'-dithienyl-5-yl; R' = CH_3.

EXPERIMENTAL CHEMICAL PART

The IR spectra of the compounds as KBr pellets were taken on a UR-20 (GDR) instrument. The purity of the compounds was checked by thin-layer chromatography on Silufol UV-254 plates (Czechoslovakia). The starting aldehydes were synthesized by the method given in [7] and the ketones by that given in [8].

1-(5"-Methyl-2',2"-dithienyl-5'-yl)-3-(2'-thienyl)propen-2-al-1 (1d). To a solution of 0.22 g (0.001 mole) of 5'-methyl-5-acetyl-2,2'-dithienyl in 50 ml of alcohol at room temperature was added 1 ml of 10% NaOH followed by 0.11 g (0.001 mole) of 2-thiophene aldehyde in 20 ml of alcohol.

The mixture was heated to boiling and left overnight. The crystalline material which separated was filtered off, washed with a small quantity of alcohol, dried, and recrystallized from alcohol.

The dithiophene analogs of chalcone Ia, c, e, and g-l were obtained from the corresponding aromatic or heterocyclic aldehydes and ketones using the same method [9, 10].

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TABLE 1. Physicochemical Properties of Compounds Ia-o

Compound*	Yield, %	mp, °C	Found, %			Empirical formula	Calculated %			IR spectra, cm^{-1}	
			C	H	S		C	H	S	$\nu_{C=O}$	$\nu_{C=C}$
Ia	96	154—154,5	69,9	4,7	20,9	$C_{18}H_{14}OS_2$	69,7	4,6	20,7	1651	1621
Ib	96	151—152†	62,4	3,6	22,1	$C_{15}H_{10}O_2S_2$	62,9	3,3	22,4	1650	1595
Ic	83	142—143	63,8	3,9	21,1	$C_{16}H_{12}O_2S_2$	64,0	4,0	21,4	1650	1620
Id	98	165—166	60,6	3,9	30,6	$C_{16}H_{12}OS_3$	60,7	3,8	30,4	1641	1619
Ie	96	143—144†	59,2	3,4	31,4	$C_{15}H_{10}OS_3$	59,6	3,3	31,8	1630	1570
If	97	125—126†	60,0	3,9	31,4	$C_{15}H_{10}OS_3$	59,3	3,5	31,8	1638	1578
Ig	90	228—229	60,5	3,7	32,1	$C_{20}H_{14}OS_4$	60,3	3,5	32,2	1642	1620
Ih	99	135—136	69,9	4,7	20,6	$C_{18}H_{14}OS_2$	69,7	4,6	20,7	1652	1622
Ii	70	119—120	64,2	4,3	21,4	$C_{16}H_{12}O_2S_2$	64,0	4,0	21,4	1652	1621
Ij	94	152—152,5	60,9	3,6	30,5	$C_{16}H_{12}OS_3$	60,7	3,8	30,4	1640	1618
Ik	93	205—206	60,1	3,7	32,4	$C_{20}H_{14}OS_4$	60,3	3,5	32,2	1636	1614
Il	98	213—213,5	61,4	3,3	30,9	$C_{21}H_{16}OS_4$	61,1	3,9	31,1	1640	1620
Im	74	130	61,4	4,3	27,5	$C_{12}H_{10}OS_2$	61,5	4,3	27,4	1658	1600
In	81	96—97	62,5	5,0	26,0	$C_{13}H_{12}OS_2$	62,9	4,9	25,8	1670	1615
Io	62	71—72	64,3	5,7	24,9	$C_{14}H_{14}OS_2$	64,1	5,4	24,4	1670	1618

*Compounds Ia-f and h-j were recrystallized from alcohol; Ie, g, k, and l from a mixture of dioxane and water (1:1); Im-o from hexane.

†Literature values [9, 10]; Ib, mp 130-132°C; Ie, mp 116-118°C; If, mp 105-108°C.

TABLE 2. Antiviral Activities of Compounds

Compound	Maximum tolerable conc., μg/ml	Test virus						
		Influenza	Parain-fluenza	VEE	ECHO 6	Adeno-virus 3	Herpes	Vaccinia
Ia	100	—	—	—	—	—	—	—
Ib	100	—	—	—	—	—	—	—
Ic	10	—	—	—	++	—	—	—
Id	100	—	—	—	—	—	—	—
Ie	50	—	+++	—	++	—	—	—
If	5	—	—	—	+++	—	—	—
Ig	100	—	—	—	—	—	—	—
Ih	400	—	—	—	—	—	—	—
Ii	10	—	—	—	+++	—	—	—
Ij	10	—	—	—	++	—	—	—
Ik	0,5	—	—	—	—	—	—	—
Il	10	—	—	—	—	—	—	—
Im	100	—	—	—	—	—	—	—
In	25	—	—	—	—	—	—	—
Io	0,5	—	—	—	—	—	—	—

1-(2',2"-dithienyl-5'-yl)-3-(2'-furyl)propen-2-al-1 (Ib). To a stirred mixture of 0.96 g (0.01 mole) of freshly distilled furfural and 2.08 g (0.01 mole) of 5-acetyl-2,2'-dithienyl in 10 ml of alcohol at room temperature was added dropwise 3 ml of 20% NaOH. After 5-7 h the crystalline material which separated was filtered off, washed with a small quantity of dilute HCl, and with water, dried, and recrystallized from alcohol. The ketone If was synthesized in the same way.

Synthesis of 5-R-2,2'-dithienylideneacetones (Im-o). A mixture of the corresponding aldehyde, 10 ml of acetone, and 15 ml of alcohol was cooled to 0°C and with mixing was added dropwise 1.5 ml of 10% aqueous NaOH. After stirring for 2-3 h, the crystals which separated were filtered off, washed with water, dried, and recrystallized from alcohol.

The physicochemical characteristics of Ia-o are given in Table 1.

EXPERIMENTAL BIOLOGICAL PART

The compounds were tested for antiviral activity against influenza (FPV), parainfluenza type 3, Venezuelan equine encephalomyelitis (VEE), vaccinia, and herpes simplex subtype 1 using tissue cultures. Screening tests were used [11] initially and the results were

confirmed by determining the relationship between dose and effect [12, 13]. The effectiveness of the compounds against ECHOvirus 6 and adenovirus 3 was also tested using the same methods.

FPV, VEE, vaccinia, and herpes viruses were propagated in trypsinized chick embryo fibroblasts, parainfluenza in transplanted HEP-2 cells, and ECHOvirus 6 in human embryonic epithelial cells.

RESULTS AND DISCUSSION

The antiviral properties of Ia-ℓ and Im-o are listed in Table 2; it can be seen that only the first group of compounds possesses the desired properties. A number of the dithiophene analogs of chalcone (41.7%) exhibited moderate activity against ECHOvirus 6 (Ic, e, d, i, and j); Ie was also active against the parainfluenza virus.

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