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SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF 5-ARYL-2-(2-HYDROXYETHYL)FURANS AND THEIR CARBAMOYL DERIVATIVES

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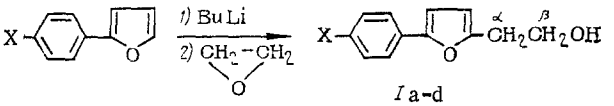
Our earlier publications [1, 2] showed that 5-arylfuryl-2-carbinols and their esters and ethers possess high tuberculostatic activity *in vitro*.

In the present work, we synthesized the 5-aryl-2-(2-hydroxyethyl)furans Ia-d and their N-methyl carbamates IIa-f, and studied their tuberculostatic activity. In addition, we have now synthesized the carbamoyl derivatives of 5-aryl-2-hydroxymethylfurans described earlier [3, 4] and studied their tuberculostatic activity.

The 5-aryl-2-hydroxyethylfurans Ia-d were prepared by condensation of 5-aryl-2-lithiofurans with ethylene oxide:

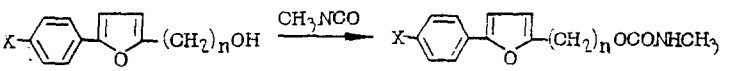


I a-d

a: X=Cl; b: X=H; c: X=CH_3; d: X=CH_3O.

Arylfuryllithium, formed by the interaction of arylfurans with butyl lithium, was treated *in situ* with ethylene oxide to give the hydroxyethyl derivatives Ia-d. The structure of the compounds obtained was confirmed by the presence of absorption bands in the 3350-3500 and 1028-1055 cm^{-1} regions of the IR, and of proton signals for the OH at 2.19 ppm (s),* and for the methylene group at 2.85 ppm (β-CH_2, t) and 3.82 ppm (α-CH_2, t) in the NMR spectrum.

The interaction of the 5-aryl-2-hydroxyethylfurans with methyl isocyanate gave the N-methyl carbamoyl derivative of the 2-hydroxyalkylarylfurans in high yield.



II a-d (n=2)
III a-f (n=1)

a) X=Cl, b) X=H, c) X=CH_3, d) X=OCH_3, e) X=Br, f) X=NO_2

Study of the tuberculostatic activity of the 5-aryl-2-(2-hydroxyethyl)furans and of the carbamoyl derivatives of 5-aryl-2-hydroxyethyl and hydroxymethylfurans against human tuberculosis mycobacteria (Stamm H-37Rv) showed that the carbamoyl derivatives of the 5-aryl-2-hydroxymethylfurans IIIa, c, and e possess high tuberculostatic activity, inhibiting the growth of the tuberculosis bacterium at a concentration of 0.25-1 μg/ml (see Table 1). The presence of blood serum in the nutrient medium lowered the activity of these compounds. Substitution of halogen and other groups on the benzene ring of these compounds by a nitro group leads to a decrease of tuberculostatic activity (see Table 1), which agrees with our earlier data [1, 2] on the influence of benzene ring substituents on biological activity.

We also studied the influence of these compounds on bacterial nuclease (E.C. 3.1.4.7) activity.

*Abbreviations used here and below: s = singlet; t = triplet.

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TABLE 1. 5-Aryl-2-(N-methylcarbamoyloxy)alkylfurans (IIa-d, IIIa-f)

Compound	Yield, %	Melting point, °C*	Found, %				Empirical formula	Calculated, %				IR spectrum, cm^{-1}	Tuberculostatic activity (μg/ml), Stamm H-37 Sauton Medium		Inhibition of nuclease activity	
			C	H	Hal	N		C	H	Hal	N		without serum	with serum (10%)	10 μg/ml	100 μg/ml
IIa	93	114—5	59,9	5,2	12,8	4,8	$C_{14}H_{14}ClNO_3$	60,1	5,0	12,7	5,0	1689—1691	32	—	—	—
IIb	88	81—2	68,6	6,0	—	5,9	$C_{14}H_{15}NO_3$	68,6	6,1	—	5,7	1687—1690	4	32	0	19
IIc	76	102—3	69,8	6,9	—	5,2	$C_{15}H_{17}NO_3$	69,5	6,6	—	5,4	1690—1692	16	—	—	—
IId	82	105—6	65,5	5,9	—	5,0	$C_{15}H_{17}NO_4$	65,5	6,2	—	5,1	1690—1697	8	—	19	55
IIIa	68	122—3	58,6	4,3	13,1	5,3	$C_{13}H_{12}ClNO_3$	58,8	4,5	13,4	5,3	1689—1692	0,25	16	53	58
IIIb	81	95—7	67,7	5,7	—	6,2	$C_{13}H_{13}NO_3$	67,5	5,6		6,1	1680—1690	16	—	0	16
IIIc	89	111—2	68,6	6,2	—	5,7	$C_{14}H_{15}NO_3$	68,6	6,1	—	5,7	1685—1695	1	125	10	55
IIId	92	126—8	64,5	5,5	—	5,3	$C_{14}H_{15}NO_4$	64,4	5,7	—	5,4	1685—1695	32	—	—	—
IIIe	87	126—7	50,3	3,9	26,2	4,5	$C_{13}H_{12}BrNO_3$	50,3	3,9	25,8	4,5	1680—1700	1	250	10	55
IIIf	76	158—60	56,2	4,5	—	10,1	$C_{13}H_{12}N_2O_5$	56,5	4,4	—	10,1	1683—1692	1000	—	0	32

*Compounds IIa-c crystallized from hexane; IId from benzene; IIIa-f from alcohol.

TABLE 2. 5-Aryl-2-(2-hydroxyethyl)furans Ia-d

Compound	Yield, %	Melting (boiling) point, °C	Found, %			Empirical formula	Calculated, %			IR spectrum, (OH), cm^{-1}	Tuberculostatic activity (μg/ml), Stamm H-37 Sauton Medium	Inhibition of nuclease activity, %	
			C	H	Cl		C	H	Cl		without serum	10 μg/ml	100 μg/ml
Ia	55	88—9	64,7	4,8	15,9	$C_{12}H_{11}ClO_2$	64,7	4,9	15,9	3380—3440 1035	1000	10	23
Ib	51	137—8	76,6	6,2	—	$C_{12}H_{12}O_2$	76,6	6,4	—	330—3380 1022—1055		—	—
Ic	45	62—3	77,2	7,0	—	$C_{13}H_{14}O_2$	77,2	6,9	—	3350—3430 1035	62,5	—	—
Id	41	61—2	71,6	6,6	—	$C_{13}H_{14}O_3$	71,6	6,4	—	3460—3500 1028—1050	8	—	26

The strongest inhibitory activity was shown by the 5-aryl-2-hydroxymethylfuran N-methylcarbamates IIIa, c, and e, which suppressed the enzyme activity at a concentration of 100 μg/ml by 55% (see Table 1). The most inhibition was observed for 5-(p-chlorophenyl)-2-[(N-methylcarbamoyloxy)methyl]furan (IIIa), which produced a 50% suspension of enzyme activity even at 10 μg/ml. This compound also showed the highest tuberculostatic activity. The studied compounds did not depress the activity of the pyridoxal enzymes, i.e., did not depress the biosynthesis of the essential amino acids.

EXPERIMENTAL METHOD

IR spectra were recorded on a UR-10 instrument on plates in mineral oil.

5-(p-Chlorophenyl)-2-(2-hydroxyethyl)furan (Ia). To a solution of butyl lithium, prepared from 0.4 g (0.050 mole) of lithium and 2.9 g (0.029 mole) of butyl bromide in 30 ml of absolute ether, at −10°C was added a solution of 3.1 g (0.018 mole) of 2-(p-chlorophenyl)-furan [5] in 20 ml of absolute ether. The reaction mixture was stirred under reflux for 4 h, cooled to −10°C, and 3.4 g of ethylene oxide were added. The mixture was maintained at this temperature for 1 h, decomposed with 15% aqueous ammonium chloride and extracted with ether. The ether extract was dried with sodium sulfate, and after removal of the ether, the residue was recrystallized from hexane. Compounds Ib-d were prepared analogously. Yields, constants, analytical data, and IR spectra for the hydroxyethylfurans are given in Table 2.

5-(p-Chlorophenyl)-2-[2-(N-methylcarbamoyloxy)ethyl]furan (IIa). To a solution of 2 g (0.004 mole) of Ia in 7 ml of pyridine was added 0.8 g (0.007 mole) of methyl isocyanate. The reaction mixture was stirred at room temperature for 20 h, then heated on a boiling water bath for 1 h and poured into 20 ml of water. The resulting precipitate was filtered off, washed with water, and recrystallized. Compounds IIb-d and IIIa-f were prepared in the same manner. Yields, constants, analytical data, and IR spectra for the N-methyl carbamates IIa-d and IIIa-f are given in Table 1.

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