SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF ADDUCTS OF ARYL- AND ARYLOXYFURANS WITH ACETYLENEDICARBOXYLIC ESTER, MALEIC ANHYDRIDE, AND N-PHENYLMALEIMIDE

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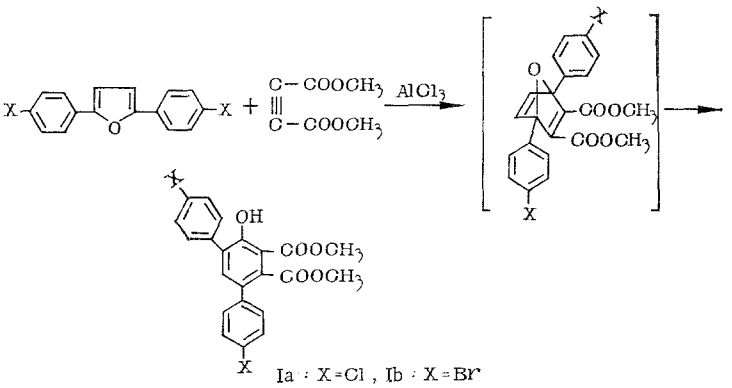
Continuing our investigations in the series of aryl- and aryloxyfurans [1], we have studied the reactions of these compounds with acetylenedicarboxylic ester, maleic anhydride, and N-phenylmaleimide.

We have previously shown [1] that 2-aryloxyfurans and 2-arylfurans with electron-donor substituents in the benzene ring enter easily into reaction with acetylenedicarboxylic ester, forming the corresponding adducts, which, after aromatization, were converted into esters of 3-aryl- and 3-aryloxy-6-hydroxyphthalic acids.

In the present work we have shown that 2,5-diarylsurans enter into reaction with acetylenedicarboxylic ester only in the presence of a catalyst—aluminum chloride. The reaction products were dimethyl esters of 3,5-diaryl-6-hydroxyphthalic acids (Ia, b).



Ia : X=Cl , Ib : X=Br

The migration of the substituent which takes place in this transformation was first described in [2], which concerned the formation of benzene derivatives from Diels—Alder adducts.

The structure of the compounds obtained (Ia and Ib) was confirmed by the use of IR and NMR spectra. In the IR spectra of these compounds there were absorption bands characteristic of free and bonded carbomethoxy groups.

In the NMR spectra of compounds Ia and Ib, a narrow singlet was observed in the 11.47 ppm region (Ia) and the 11.49 ppm region (Ib) for a hydroxyl group (the 6-OH) which is involved in the formation of an intramolecular hydrogen bond with the CO fragment of the neighboring ester group (the 1-$COOCH_3$) [1, 3, 4]. The marked high-field shift of the 2-$COOCH_3$ group as compared with the second ester group (1-$COOCH_3$) ($\Delta\delta_{COOCH_3}$ 3.87-3.61 = 0.36 ppm (Ia); $\Delta\delta_{COOCH_3}$ 3.91-3.64 = 0.36 ppm (Ib)) is brought about by the shielding effect of the ring currents of the benzene ring which has an ortho-disposition to the 2-$COOCH_3$ group [2-4].

The 2-aryloxyfurans entered easily into reaction with maleic anhydride or N-phenylmaleimide, forming the corresponding adducts, IIa-d, in high yields. The structures of the compounds obtained were confirmed by their NMR spectra, and also by their further conversion into derivatives of 3-aryloxyphthalic acid, IIIa-d,

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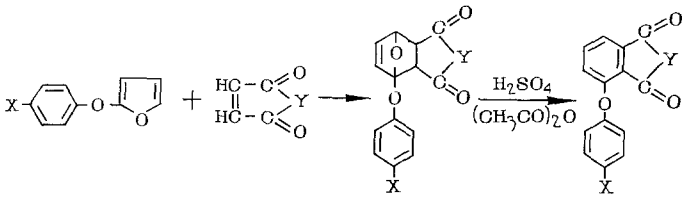
TABLE 1. NMR Spectral Data, Compounds IIa-d

Compound	Configuration	($\Delta\delta_{23}$), ppm						Aromatic protons	J, Hz		
		H_1	H_2	H_4	H_5	H_6	CH_3		12	16	46—56
IIa	Exo		3,39* (0,025)	6,38	6,62	5,34	—	7,00 7,35	7,0	~0	2,0
IIb	Exo		3,38* (0,025)	6,39	6,62	5,35	2,28	7,02— 7,38	7,5	~0	2,0
IIc	Endo	3,68	3,90	6,41	6,54	5,34	—	7,06— 7,60	7,2	5,5	2,0
	Exo		3,19* (0,04)	6,30	~6,54	5,34	—	7,06— 7,60	6,5	~0	†
	Endo	3,65	3,81	6,39	6,52	5,30	2,29	7,00— 7,60	7,6	5,5	2,0
IId	Exo		3,18* (0,04)	6,34	~6,52	5,30	2,27	7,00— 7,60	6,5	~0	2,0

Notes. *The H_1 and H_2 protons form a quartet of the AB system.
†It was not possible to determine $\Sigma J_{46} + J_{56}$ because of overlap of the H_5 and H_6 signals of the endo- and exo-isomers.

by the scheme:



IIa-d IIIa-d

I, IIIa: X=H, Y=O; b: X=CH_3, Y=O; c: X=H, Y=N-C_6H_5
d: X=CH_3, Y=NC_6H_5

Examination of molecular models of the series II compounds made it possible to establish that for the endo-isomer the value of the spin—spin coupling constant JH_1H_6 is about 6 Hz, while for the exo-form this constant should be close to zero. From an analysis of the values of the spin—spin JH_1H_6 coupling constants for the compounds IIa-d (Table 1), it follows that the adducts with maleic anhydride, IIa, b, were formed in the exo-isomer form ($JH_1H_6 \sim 0$).* The adduct of phenoxyfuran with N-phenylmaleimide was formed in the form of the endo-isomer ($JH_1H_6 = 5.5$Hz). The adduct of N-phenylmaleimide with p-tolyloxyfuran was isolated from the reaction mixture in the form of a mixture of approximately equal amounts of the endo-form ($JH_1H_6 = 5.5$ Hz) and the exo-form ($JH_1H_6 \sim 0$).

The 2-arylfurans, being less active dienes as compared with the 2-aryloxyfurans, did not enter into the Diels—Alder reaction when maleic acid derivatives (maleic anhydride or N-phenylmaleimide) were used as the dienophiles.

Tuberculostatic activity of the type II adducts synthesized in the present work, and of their aromatization products, III, as well as of the adducts of acetylenedicarboxylic ester with p-tolylfuran, IVa, and of p-(acetaminphenyl)-furan, IVb, with respect to a tuberculosis mycobacterium of the human type (strain H-37R_V) and to atypical mycobacteria (strain ATSS-608) was investigated by the method of deep implantation into Soton medium. Results are given in Table 2.

As is evident from Table 2, the adducts of the arylfurans with acetylene-dicarboxylic ester, IVa and b, have the greatest activity.

The adducts of the aryloxyfurans with maleic anhydride, IIa and b, and with N-phenylmaleimide, IIc and d, and also the 3-aryloxyphthalic acid derivatives, IIIa, b, and d, have weak tuberculostatic activity.

*The value of the JH_1H_6 spin—spin coupling constants for the exo-isomers of IIa-d corresponds to the literature data of [5] relative to the adduct of maleic anhydride with furan.

TABLE 2. Tuberculostatic Activity and Action on Enzyme Activity of the Adducts of Aryl- and Aryloxyfurans with Derivatives of Acetylenedicarboxylic and Maleic Acid and Their Aromatization Products

Compound	Minimum mycobacteriostatic concentration μg/ml			Inhibition of enzyme activity, %
	H-37 R_V		ATCC-608	DNase, %
	without blood serum	with blood serum		
IIa	250	—	1000	—
IIb	62,5	—	500	—
IIc	>7,8	—	>1000	52
IId	125	—	>1000	22
IIIa	125	—	>1000	—
IIIb	62,5	—	>1000	—
IIId	250	—	>1000	—
IVa	7,8	250	>250	66
IVb	1	31,2	62,5	27

*Concentration of preparations, 10 γ/ml.

TABLE 3. Anhydrides and N-Phenylimides of 3-Aryloxy-3,6-endoxo-3,6-dihydrophthalic Acids (IIa-d)

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calc., %			R_f (chloroform)
			C	H	N		C	H	N	
IIa	89	112,5—4,0	65,4	3,8	—	$C_{14}H_{10}O_5$	65,1	3,9	—	0,27
IIb	82	128—29	66,1	4,4	—	$C_{15}H_{12}O_5$	66,2	4,4	—	
IIc	89	152—53	72,1	4,5	4,2	$C_{20}H_{13}NO_3$	72,1	4,5	4,2	0,64
IId	86	140—200	72,7	4,7	3,8	$C_{21}H_{17}NO_4$	72,6	4,9	4,0	0,70

TABLE 4. Anhydrides and N-Phenylimides of 3-Aryloxyphthalic Acids (IIIa-d)

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calc., %			R_f (chloroform)
			C	H	N		C	H	N	
IIIa	46	107—9 [10]	70,1	3,3		$C_{14}H_8O_4$	70,0	3,4	—	0,7
IIIb	75	118—20 [10]	70,7	4,0		$C_{15}H_{10}O_4$	70,9	4,0	—	—
IIIc	80	140—41 [10]	75,7	4,5	4,2	$C_{20}H_{13}NO_3$	76,2	4,2	4,4	0,99
IIId	90	163—4*	77,3	4,5	4,3	$C_{21}H_{15}NO_3$	76,6	4,6	4,3	—

*Purified on an Al_2O_3 column in ethyl acetate.

We also studied the inhibiting action of the compounds synthesized on the activity of DNase (KF 3.1.4.7) and of pyridoxal enzymes – aspartate-aminotransferase (KF 2.6.1.1) and alanine-aminotransferase (KF 2.6.1.2). We have previously described the procedure for determining the activity of enzymes and for studying the inhibiting action of preparations [6, 7].

As is evident from Table 2, the compounds studied exert an inhibiting action on DNase: In concentrations of 10 γ/ml preparations Ia, b and IIc, d suppress the activity of the enzyme by 66-22%. Compound Ia, which also displayed tuberculostatic activity, exerted the greatest inhibiting action. In high concentrations (100 γ/ml) the compounds examined (types II-IV) did not suppress the activity of aspartate- and alanine-aminotransferases, that is, they did not cause a breakdown in the biosynthesis of the amino acids.

On the basis of the data obtained, it may be suggested that the biological activity and mechanism of action of the class of compounds that has been examined are connected with a breakdown of the biosynthesis process

of nucleic acids, apparently the process of DNA reparation [8], in connection with which a further search for biologically active compounds in this series is promising.

EXPERIMENTAL CHEMICAL PART

IR spectra were taken on a Perkin-Elmer 457 spectrophotometer in vaseline oil. Thin-layer chromatography was carried out on Silufol UV-254 plates, development in UV-light. The NMR spectra were taken on LX-100 and C-60-HL spectrometers; the solvent was deuterochloroform; the internal standard was tetramethylsilane.

Dimethyl 3,5-bis-(p-chlorophenyl)-6-hydroxyphthalate (Ia). To a suspension of 0.7 g (6 mmole) of aluminum chloride in 25 ml of dry methylene chloride was added, with stirring, 1.7 g (6 mmole) of 2,5-bis-(p-chlorophenyl)-furan [9] in 25 ml of methylene chloride plus a saturated solution of 0.9 g (6 mmole) of acetylene-dicarboxylic ester in methylene chloride. The reaction mixture was boiled for 2 h, and was cooled; the solution was washed with water until a neutral reaction was obtained, dried over magnesium sulfate, and evaporated; the remaining oil was recrystallized from acetone. Compound Ia (1.5 g, 58%) was obtained, m.p. 163-165°C. Found, %: C 61.5; H 4.0; Cl 16.3. $C_{16}H_{10}Cl_2O$. Calculated, %: C 61.3; H 3.7; Cl 16.4. Infrared frequencies (ν, in cm^{-1}): 1718, 1670 (CO). UV spectrum, λ_{max} (in nm) and log ε (in parentheses): 241, 334 (4.46; 3.79).

Dimethyl 3,5-bis-(p-bromophenyl)-6-hydroxyphthalate (Ib). This compound was prepared analogously to the preceding one. Yield, 42%; m.p. 195-197°C (from alcohol). C 50.8; H 3.1; Br 30.7. $C_{15}H_{10}Br_2O$. Calculated, %: C 50.8; H 3.1; Br 30.9.

Infrared frequencies (ν, cm^{-1}): 1730, 1672 (CO). UV spectrum: λ_{max}, nm; log ε (in parentheses): 241, 335 335 (4.60; 3.91).

3-Phenoxy-3,6-endoxo-3,6-dihydrophthalic anhydride (IIa). A solution of 1.6 g (10 mmole) of phenoxyfuran and 0.98 g (10 mmole) of maleic anhydride in 10 ml of benzene was kept at room temperature for 2 days. The crystals which separated were filtered off and washed with benzene. Adducts IIb-d were prepared similarly to IIa. The physicochemical constants of the compounds obtained are given in Table 3.

3-Phenoxyphthalic Anhydride, IIIa. A solution of 1 g of IIa in 20 ml of acetic anhydride containing 0.5 ml of concentrated sulfuric acid was heated for 1 h at 120°C. The acetic anhydride was distilled off under vacuum; the residue was dissolved in benzene; the solution was boiled with charcoal, filtered, and evaporated. The oil remaining crystallized; the crystals were filtered off, washed with ether, and recrystallized from an ether-benzene mixture (1:1). The anhydrides and N-phenylimides of phthalic acids IIIb-d were prepared similarly to IIIa. The physicochemical constants of the compounds obtained are given in Table 4.

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