Spiro[cyclobutane-2-thiobarbituric] Acid (Ia). A solution of 1.62 g (0.07 g-atom) of sodium in 30 ml of methanol was treated with 50 ml of DMSO. The excess alcohol was distilled from the reaction flask under vacuum. The resulting solution was treated with 4.2 g (0.0535 mole) of thiourea. The reaction mixture was cooled, treated dropwise over 1 h with a solution of 7 g (0.035 mole) of IIa in 20 ml of DMSO, and kept in a refrigerator overnight. The precipitate formed was filtered off to give 4 g (63%) of Ia, mp 365° (decomp., from isopropyl alcohol). Found, %: C 45.59; H 4.45; N 15.42; S 17.41. Calculated, %: C 45.63; H 4.32; N 15.21; S 17.40. R_f 0.85 (ethanol–chloroform, 1 : 5), 0.44 (acetone–cyclohexane, 1 : 1) on silica gel.

Spiro[cyclopentane-2-thiobarbituric] Acid (Ib). This was prepared by the above method from 1.15 g of sodium, 2.85 g (0.0375 mole) of thiourea and 5.35 g of IIb, giving 2.73 g (55%) of the hydrate of Ib, mp 162-163° (from isopropyl alcohol). Found, %: C 44.6; H 5.63. Calculated, %: C 44.42; H 5.60. R_f 0.85 (ethanol–chloroform, 1 : 5) on silica gel.

Spiro[cyclohexane-2-thiobarbituric] Acid (Ic). This was prepared by the above method from 0.92 g of sodium, 2.28 g of thiourea and 4.56 g of IIc, giving 2.15 g (50.5%) of the hydrate of Ic, mp 191-192° (from isopropyl alcohol). Found, %: C 46.91; H 6.11; N 12.00; S 13.89. Calculated, %: C 46.93; H 6.14; N 12.17; S 13.97. R_f 0.55 (chloroform–ethanol, 9 : 1) on silica gel.

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SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF 5-ARYLPYROMUCIC ACID DERIVATIVES

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Continuing our investigations into the synthesis and biological activity of arylfuran derivatives [1], we have synthesized 5-arylpyromusic acids and a number of their derivatives (acid chlorides, esters, and hydrazides), and have studied their bacteriostatic activity against Mycobacterium tuberculosis.

Several works in the recent literature have been devoted to the synthesis of arylpyromucic acids [2-4]. In these works, the said acids were prepared either by Meerwein arylation of pyromucic acid [2, 3] or by oxidation of the corresponding 5-arylfurfurals [4]. In spite of the fact that the Meerwein arylation of pyromucic acid gives low yields, this method is more convenient than other methods since it allows the arylpyromucic acids to be prepared in one step.

In studying the Meerwein arylation of pyromucic acid, we discovered that 2,5-bisarylfurans (IIa-IIc) are formed as byproducts when diazonium salts with electron-acceptor substituents in the benzene ring are used,

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TABLE 1. Pyromucic Acid Chlorides (III), Ethyl Esters (IV) and Hydrazides (V)

Compound No.	Yield (%)	Melting point (deg)[*]	Found (%)				Empirical formula	Calculated (%)				Tuberculostatic activity (μg/ml), H-37 strain, So-tone medium	
			C	H	Cl (Br)	N		C	H	Cl (Br)	N	without serum	with serum
IIIa	56	76	46,3	2,2	—	—	$C_{11}H_6BrClO_2$	46,2	2,1	—	—	500	—
IIIb	69	81	54,5	2,6	29,3	—	$C_{11}H_6Cl_2O_2$	54,8	2,5	29,5	—	60	—
IIIc	73	144,5—5	52,5	2,5	13,7	—	$C_{11}H_6ClNO_4$	52,5	2,4	14,1	—	500	—
IIId	69	53	63,8	3,3	17,1	—	$C_{11}H_7ClO_2$	63,9	3,4	17,2	—	500	—
IIIe	73	71,5—72,5	65,2	4,1	15,8	—	$C_{12}H_9ClO_2$	65,3	4,1	16,1	—	125	—
IIIf	66	98	60,7	3,7	15,0	—	$C_{12}H_9ClO_3$	60,9	3,8	15,0	—	1000	—
IVa	65	84,5	52,7	3,8	27,0	—	$C_{13}H_{11}BrO_3$	52,9	3,7	27,1	—	1	1000
IVb	43	71	62,2	4,4	14,0	—	$C_{13}H_{11}ClO_3$	62,3	4,4	14,2	—	2	30
IVc[†]	57	123	59,3	4,2	—	—	$C_{13}H_{11}NO_5$	59,8	4,2	—	—	—	—
IVd	39	—[‡]	72,2	5,7	—	—	$C_{13}H_{12}O_3$	72,2	5,6	—	—	1,6	200
IVe	42	—[‡]	72,9	6,0	—	—	$C_{14}H_{14}O_3$	73,0	6,0	—	—	0,06	125
IVf	24	—[‡]	68,0	5,6	—	—	$C_{14}H_{14}O_4$	68,3	5,7	—	—	—	—
Va	59	171	46,9	3,3	28,3	9,9	$C_{11}H_9BrN_2O_2$	47,0	3,2	28,5	10,0	0,12	60
Vb	70	160	55,7	3,8	14,8	—	$C_{11}H_9ClN_2O_2$	55,8	3,8	15,0	—	0,06	125
Vc[**]	46	220	53,4	3,7	—	16,8	$C_{11}H_9N_3O_4$	53,4	3,6	—	17,0	2	500
Vd	41	135	65,3	4,8	—	13,8	$C_{11}H_{10}N_2O_2$	65,3	4,9	—	13,9	4	60
Ve	43	151—	66,7	5,4	—	12,9	$C_{12}H_{12}N_2O_2$	66,7	5,5	—	13,0	0,25	60
Vf	51	145,5—47	61,8	5,1	—	12,1	$C_{12}H_{12}N_2O_3$	62,1	5,2	—	12,1	1	30

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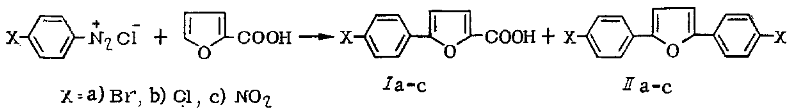
[*] Compounds IIIa, IIId, IIIe, and IVb were recrystallized from petroleum ether; IIIb, IIIc IIIf, Va, Ve, and Vf from benzene; IVa, IVb, and IVc from alcohol; and Vc and Vd from ethyl acetate.

[†] Prepared via 5-(p-nitrophenyl)pyromucic acid chloride, yield 37%, mp 126-127° (from alcohol) [6].

[‡] Boiling point in °/mm (n_D^{20}): IVd 169-170/1 (1.5947); IVe 145-146/2 (1.5926); IVf 188/3.

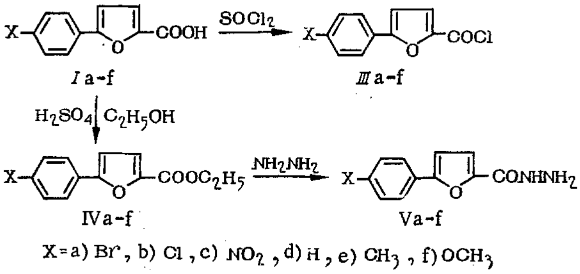
[**] Literature data [6]: yield 50%, mp 208-210° (from water).

as in the case of the arylation of acylfurans [5].



Reaction of the acids Ia-If with thionyl chloride gave good yields of the corresponding arylpyromucic acid chlorides (IIIa-IIIf).

By boiling alcoholic solutions of the arylpyromucic acids I with a catalytic amount of sulfuric acid, we obtained the ethyl esters of the corresponding furancarboxylic acids (IVa-IVf). The latter, when treated with hydrazine hydrate, formed the arylpyromucic acid hydrozides (Va-Vf).



A study of the tuberculostatic activity of the 5-arylfuran-2-carboxylic acids and derivatives synthesized by us showed that the acids themselves and their acid chlorides have low activity, whereas the 5-arylfuran-2-carboxylic acid hydrazides and esters possess high bacteriostatic activity against the tuberculosis bacillus (see Table 1). The presence of 10% normal equine blood serum in the medium sharply reduces the activity of the compounds.

EXPERIMENTAL

5-(p-Bromophenyl)pyromucic Acid (Ia). The hydrochloride of p-bromoaniline, prepared from 43 g (250 mmole) of p-bromoaniline, 50 ml of water and 113 ml of concentrated hydrochloric acid, was diazotized with a solution of 17.5 g (250 mmole) of sodium nitrite in 75 ml of water. The reaction mixture was stirred at 5° for 30 min and then treated with 28 g (250 mmole) of pyromucic acid in 125 ml of acetone and with a solution of 5 g of copper chloride in 10 ml of water. The reaction mixture was stirred at 25-30° for 4 h, and the precipitate filtered off and washed with water and 50 ml of hot benzene, to give 20 g (30%) of 5-(p-bromophenyl)pyromucic acid (Ia), mp 203-204°.* The precipitate formed on cooling the benzene wash liquor was separated and treated with 30 ml of chloroform. The chloroform solution was evaporated in vacuo to precipitate 0.66 g of 2,5-bis-(bromophenyl)furan (IIa), mp 200.5-202.5° (from alcohol). Literature data [5]: mp 202-203°, R_f 0.39 (Silufol UV= 254, petroleum ether, fluorescence in UV light). The acids Ib and Ic were prepared analogously to Ia.

5-(p-Bromophenyl)pyromucic Acid Chloride (IIIa). A solution of 4.4 g (37 mmole) of thionyl chloride in 4 ml of dry benzene was added to a solution of 8.4 g (31 mmole) of 5-(p-bromophenyl)pyromucic acid (Ia) in 12 ml of dry benzene. The mixture was boiled for 3 h and then evaporated down to half volume. The precipitate was filtered off. Acid chlorides IIIb-IIIf were prepared analogously. The yields, constants, and analysis data of acid chlorides IIIa-IIIf are given in Table 1.

Ethyl 5-(p-Bromophenyl)pyromucate (IVa). A solution of 8.5 g (31 mmole) of 5-(p-bromophenyl)pyromucic acid in 70 ml of absolute ethyl alcohol was treated with 2 ml of concentrated sulfuric acid. The mixture was boiled for 4 h. After cooling, the solution was poured into 100 ml of water, and the precipitate filtered off and washed with water. Esters IVb and IVc were prepared analogously to IVa. In the case of the liquid esters IVd-IVf, the reaction mixture after treating with water was extracted with ether, and the extract dried with magnesium sulfate, evaporated in vacuo and distilled. The yields, constants and analysis data of esters IVa-IVf are given in Table 1.

5-(p-Bromophenyl)pyromucic Acid Hydrazide (Va). A solution of 3 g (10 mmole) of IVa in 20 ml of absolute ethyl alcohol was treated with 2 ml of hydrazine hydrate. The reaction mixture was boiled for 1 h, cooled, and poured into 100 ml of water. The precipitate was filtered off. Hydrazides Vb-Vf were prepared analogously to Va. The yields, constants and analysis data of hydrazides Va-Vf are given in Table 1.

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*Literature data [2]: yield 18%, mp 198-200°.