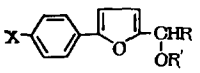
SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF 5-ARYLFURYL-2-CARBINOLS

A. F. Oleinik, K. Yu. Novitskii,
G. A. Modnikova, G. N. Pershin,
O. O. Makeeva, and T. N. Zykova

UDC 615.281.221.1:547.724

In previous communications we described the synthesis of a number of arylfuran derivatives and pointed out the tuberculostatic activity of some of them [1, 2]. References to bacteriostatic activity of some derivatives of 5-(p-nitrophenyl)-furfural with respect to tubercular mycobacteria are available in the literature [3]. The present work concerns the synthesis of 5-arylfuryl-2-carbinols and their ethers; the tuberculostatic activity of these compounds was also studied in order to establish the relation between their biological properties and structure.

TABLE 1. Bacteriostatic Activity of 5-Arylfuryl-2-carbinols with Respect to Tubercular Mycobacteria (strain H-37 R_V)



Compound	X	R	R'	Minimum bacteriostatic concn. (in μg/ml in Sutton's medium)	
				without serum	with 10% serum
I	H	H	H	31,2	125
II	H	H	C_2H_5	60,0	
III	H	H	$COCH_3$	125	500
IV	CH_3	H	H	31,2	
V	CH_3	H	C_2H_5	0,125	15,6
VI	CH_3	H	$COCH_3$	250	
VII	OCH_3	H	H	15,6	
VIII	OCH_3	H	C_2H_5	125	
IX	OCH_3	H	$COCH_3$	>1000	
X	Cl	H	H	15,6	
XI	Cl	H	C_2H_5	2	7,8
XII	Cl	H	C_4H_9	1,6	10
XIII	Cl	H	$COCH_3$	15,6	
XIV	Br	H	H	<0,015	125
XV	Br	H	C_2H_5	15,6	
XVI	Br	H	$COCH_3$	1,0	125
XVII	NO_2	H	H	500	
XVIII	NO_2	H	$COCH_3$	60	
XIX	NH_2	H	H	2	60
XX	$NHCOCH_3$	H	$COCH_3$	15	>15
XXI	Cl	C_2H_5	H	30	125
XXII	Cl	C_2H_5	$COCH_3$	125	250
XXIII	Cl	C_3H_7	H	0,03	60
XXIV	Br	C_2H_5	H	8	500
XXV	Br	C_2H_5	$COCH_3$	30	250
XXVI	Br	C_3H_7	H	8	60
XXVII	NO_2	C_2H_5	H	30	250
XXVIII	NO_2	C_2H_5	$COCH_3$	60	250

S. Ordzhanikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow.
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 8, No. 8, pp. 13-16, August, 1974. Original article submitted August 6, 1973.

TABLE 2. 5-Arylfuryl-2-carbinols

Compound	Yield, %	mp (deg)[b]	(on Rf Selufol)[c]	Found, %			Empirical formula	Calc., %			IR spectrum (OH, cm^{-1})	UV spectrum[a]	
				C	H	halogen or N		C	H	halogen or N		λ_{max}	lg ε
XXI	71,7	76—7	0,63	66,0	5,5	14,8	$C_{13}H_{13}ClO_2$	65,9	5,5	15,0	3350—3200, 1108—1098	293; 224	4,42; 3,89
XXII	67,0	59—61	0,66	64,8	5,6	—	$C_{15}H_{15}ClO_3$	64,6	5,4	—			
XXIII	81,2	38—9,5	0,76	66,9	6,0	14,2	$C_{14}H_{15}ClO_2$	67,0	6,0	14,1	3310—3150, 1102—1096	293; 223	4,40; 3,86
XXIV	70,3	89—90	0,23	55,4	4,6	28,4	$C_{13}H_{13}BrO_2$	55,5	4,6	28,4	3340—3240, 1107—1101	294; 225	4,43; 3,81
XXV	61,7	73—5	0,49	55,8	4,7	—	$C_{15}H_{15}BrO_3$	55,7	4,7				
XXVI	67,0	62,5—64	0,27	56,9	5,2	27,0	$C_{14}H_{15}BrO_2$	57,0	5,1	27,2	3320—3180, 1106—1075	295; 226	4,43; 3,90
XXVII	81,0	84,5—8	0,22	63,0	5,2	—	$C_{13}H_{13}NO_4$	63,1	5,3	—	3380—3260, 1107—1104	363; 245	4,28; 3,99
XXVIII	63,6	70—2	0,43	62,4	5,2	4,6	$C_{15}H_{15}NO_5$	62,3	5,2	4,8			

[a] In ethanol.
[b] Compounds XXI, XXII-XXVI were crystallized from petroleum ether; XXII, from ethanol; XXVII, XXVIII, from 50% ethanol.
[c] Compound XXI was chromatographed in the chloroform–petroleum ether (2:3) system, XXIII, in the chloroform–ethyl acetate (5:2) system, and the remaining compounds in chloroform.

The hydroxy derivatives of arylfurans described in this work can be presented in the form of two groups of substances: compounds with a primary hydroxyl group, namely, 5-aryl-2-hydroxymethylfurans, their ethyl ethers and acetates (Table 1, compounds I-XX); and compounds with a secondary hydroxyl grouping, namely (5-arylfural-2)-alkylcarbinols and their acetates (see Table 1), compounds XX-XXVIII. The synthesis of the first group of compounds was described by us earlier [1, 4], except 5-(p-aminophenyl)-2-hydroxymethylfuran (XIX), obtained in the present work by reducing the corresponding nitro compounds, and also compounds XII and XX, the synthesis of which is described in the experimental part. The second group of compounds was synthesized by us by reducing 5-aryl-2-acylfurans with sodium borohydride in aqueous dioxane solution (Table 2). The structure of the obtained carbinols, apart from elementary analysis, was also verified by the data on IR spectra – by the disappearance of the carbonyl group band of the starting acylfurans and by the appearance of absorption bands characteristic of the hydroxy group: in the 3380-3150 and 1107-1096 cm^{-1} regions (vibrations of secondary hydroxyl group). A confirmation of the structure of the obtained compounds was also provided by the formation of acetates when acted upon by acetic anhydride and sodium acetate.

A study of bacteriostatic activity of both groups of compounds with respect to tubercular mycobacteria of the human type (strain H-37R_V) showed that seven compounds (V, XI, XII, XIV, XVI, XIX, XXIII) possessed high tuberculostatic activity and inhibited the growth of tubercular bacillus in a concentration of 0.015-2 μg/ml (see Table 1). The presence of a protein load in the nutrient medium sharply decreased the activity of these compounds. However, the decrease in the activity was much less expressed in ethers (compounds V, XI, XII, see Table 1) than in carbinols themselves and their acetates. The substitution of halides and other substituents in the benzene ring by a nitro group, as a rule, leads to a decrease in the tuberculostatic activity (see Table 1).

One of the highly active compounds, 5-(p-bromophenyl)-2-hydromethylfuran (XIV), was used to treat experimental tuberculosis in white mice, and it was found to be inactive.

EXPERIMENTAL

5-(p-Chlorophenyl)-2-(n-butoxymethylfuran) (XII). A mixture of 2 g of (p-chlorophenyl-2-hydroxymethylfuran (X) [1], 7 ml of butyl bromide, and 1 g of potassium hydroxide was heated on a boiling bath for 2.5 h and after cooling poured

into 200 ml of water. The aqueous solution was extracted with ether. The ether extracts were dried over magnesium sulfate, evaporated, and the residue distilled. Yield of XII, 1.4 g (56%), bp 140° (7 mm), n_D^{20} 1.5618. Found, %: C 67.9; H 6.3, $C_{15}H_7ClO_2$. Calculated, %: C 68, H 6.4.

5-(p-Aminophenyl)-2-hydroxymethylfuran (XIX). To a mixture of 3 g of 5-(p-nitrophenyl)-2-hydroxymethylfuran (XVIII) [1] in 20 ml of absolute alcohol and 3.7 g of hydrazine hydrate was added in four portions a suspension of 0.15 g of Raney nickel in 20 ml of absolute alcohol. On the completion of gas evolution the mixture was boiled for 1.5 h on a water bath. After cooling, the reaction mixture was filtered and the solution evaporated to dryness. Yield, 2.4 g (91%) of XIX, mp 102.5-104.5 (from ethyl acetate). Found, %: C 69.7; H 5.8; N 7.5. $C_{11}H_{11}NO_2$. Calculated, %: C 69.8; H 5.8; N 7.4.

5-(p-Acetylaminophenyl)-2-acetoxymethylfuran (XX). A mixture of 2 g of XIX, 16 ml of benzene, 19 ml of acetic anhydride, and 7.1 g of sodium acetate was heated for 4 h on a boiling water bath. After cooling, 72 ml of water was added to the reaction mixture, and the organic layer separated. Sodium carbonate (5%, 19 ml) was added to the organic layer and stirred for 2 h at room temperature. The precipitate XX was filtered off and washed with water. The benzene solution was separated, washed with water, and dried over potassium carbonate. After distilling off benzene, the residue was washed with ether and combined precipitates of XX recrystallized from benzene. Yield, 1.3 g (46%) of XX, mp 139-141°. Found, %: C 66; H 5.5. $C_{15}H_{15}NO_4$. Calculated, %: C 65.9; H 5.5%.

[5-(p-Chlorophenyl)-2]-ethylcarbinol (XXI). To 1.4 g of 5-(p-chlorophenyl)-2-propionylfuran in 20 ml of dioxane was added dropwise a solution of 0.4 g of sodium borohydride in 5 ml of water. The mixture was boiled for 1 h, cooled, 20 ml of 10% sulfuric acid added, and poured into 100 ml of water. The precipitate was filtered off. Carbinols XXIII, XXIV, XXVI, XXVII were prepared similarly to XXI. The yields, constants, and data on the analysis of carbinols XXI, XXIII, XXIV, XXVI, XXVII are given in Table 2. The reaction of carbinols XXI, XXIV, XXVII with acetic anhydride in the presence of sodium acetate yielded the corresponding acetates. Their constants are also given in Table 2.

LITERATURE CITED

1. A. F. Oleinik, T. I. Vozyakova, and K. Yu. Novitskii, Khim. Farm. Zh., No. 7, 19 (1971).
2. A. F. Oleinik, T. I. Vozyakova, G. A. Modnikova, et al., Khim i Geterotsikl. Soed., 1448 (1972).
3. R. Frimm and J. Kovac, Cbornik pràci chem., fak SVST, 29 (1968); C. A., 73, 33595h (1970).
4. A. F. Oleinik, T. I. Vozyakova, and K. Yu. Novitskii, Khim. Geterotsikl. Soed., 1011 (1971).