SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF AMINO AND HYDROXY DERIVATIVES OF FURAN AND PYRROLIDINE

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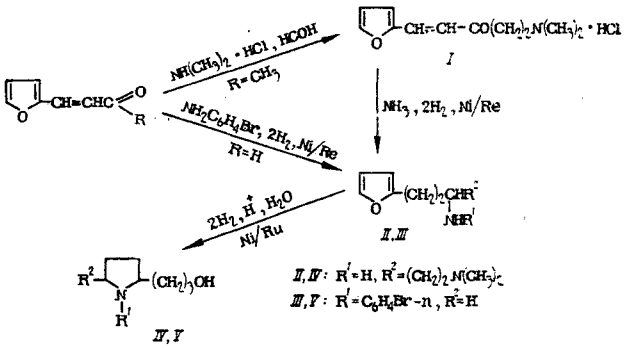
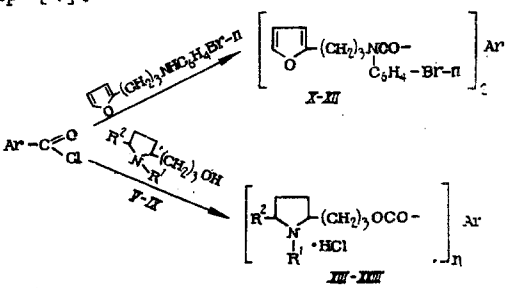
In a recent paper [1, 2], we reported the preparation of some alkyl and arylpyrrolidine alcohols from furan amines; these compounds are intended for use in the synthesis of biologically active preparations.

In a continuation of this work, we have now prepared some new furan amines, containing aminoalkyl and bromoaryl substituents in the side chain, and converted these to the corresponding 3-(1-R'-5-R^2-2-pyrrolidyl)-propan-1-ol derivatives by catalytic intramolecular hydroamination [1, 3]:



For a study of antimicrobial activity, the amides X-XII and the hydrochlorides of the esters XIII-XXIII were prepared from compounds III and V-IX; the acid chlorides of nitroaromatic acids were used as acylating agents. The acyl chlorides were chosen on the basis of literature data, suggesting that antimicrobial action increases with the introduction of a nitro group into the acid group [4].



V: $R' = C_6H_4Br$-*n*, $R^2 = H$; VI: $R' = CH_3$, $R^2 = CH_3$-*cis*;
VII: $R' = CH_3$, $R^2 = CH_3$-*trans*; VIII: $R' = CH_3$, $R^2 =$ *iso*-C_4H_9-*cis*;
IX: $R' = CH_3$, $R^2 =$ *iso*-C_4H_9 *trans*; X: Ar = *p-phenylene*,
XI: Ar = 2,3-*dinitro-p-phenylene*; XII: Ar = 2,4-*dinitro-m-phenylene*;
XIII: $R^1 = C_6H_4Br$-*p*, $R^2 = H$, Ar = 4-*nitrophenyl*, $n = 1$; XIV: $R^1 = CH_3$, $R^2 = CH_3$-*cis*,
Ar = 4-*nitrophenyl*, $n = 1$; XV: $R^1 = CH_3$, $R^2 = CH_3$-*cis*, Ar = 3,5-*nitrophenyl*, $n = 1$;
XVI: $R^1 = CH_3$, $R^2 = CH_3$-*trans*, Ar = 4-*nitrophenyl*, $n = 1$; XVII: $R^1 = CH_3$,
$R^2 = CH_3$-*trans*, Ar = 3,5-*dinitrophenyl*, $n = 1$; XVIII: $R^1 = CH_3$, R^2-*iso*-C_4H_9-*cis*,
Ar = 4-*nitrophenyl*, $n = 1$; XIX: $R^1 = CH_3$, R^2-*iso*-C_4H_9-*cis*, Ar = 3,5-*dinitrophenyl*,
$n = 1$ XX: $R^1 = CH_3$, R^2-*iso*-C_4H_9-*trans*, Ar = 4-*nitrophenyl*, $n = 1$, XXI: $R^1 = CH_3$,
R^2-*iso*-C_4H_9-*trans*, Ar = 3,5-*dinitrophenyl*, $n = 1$; XXII: $R^1 = CH_3$,
R^2-*iso*-C_4H_9-*cis*, Ar = 2,3-*dinitro-p-phenylene*, $n = 2$; XXIII: $R^1 = CH_3$,
R^2-*iso*-C_4H_9-*trans*, Ar = 2,3-*dinitro-p-phenylene*, $n = 2$.

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TABLE 1. Antimicrobial Activity of Compounds

Compound	Minimum bacteriostatic concentration, μg/ml				
	Staph. aureus 209P	E. coli 675	Proteus vulgaris 38	Pseudomonas aeruginosa 165	Candida albicans 45
II	50	50	50	100	50
III	100	50	100	50	50
IV	50	100	50	100	50
V	50	50	50	50	50
X	100	50	100	50	25
XI	100	50	50	50	25
XII	100	50	100	50	50
XIII	50	50	50	50	50
XIV	100	50	100	100	50
XV	100	50	100	50	25
XVI	100	50	100	100	50
XVII	100	50	100	50	25
XVIII	100	100	100	100	50
XIX	100	100	100	50	25
XX	100	100	100	50	50
XXI	100	100	100	50	25
XXII	100	100	100	50	50
XXIII	100	50	100	50	50

The structure of the compounds were confirmed by elemental analysis and IR spectroscopy. Compounds I-III, V, and X-XXIII absorb at 3160-3140 cm^{-1} (furan ring) and 3060-3030 cm^{-1} (aromatic ring); the IR spectrum of III contains sharp bands at 3400 and 1630 cm^{-1} (stretching and bending vibrations of the secondary amino group). The hydrochloride of I, the diperchlorate of II, and the hexachlorostannate of IV absorb at 2700-2250 cm^{-1} (ν^{+}_{NH}). The stretching vibrations from the associated OH group in compounds IV and V gave rise to broad, strong bands at 3380-3390 cm^{-1}. The amines X-XII absorb at 1660-1630 cm^{-1} (amide carbonyl). Compounds XIII-XXIII absorb at 1740-1730 cm^{-1} (ester C=O).

Results of the investigation of the antimicrobial and antiphage activity of these compounds are given in Tables 1 and 2. Analysis of the data shows that the furylpropylamines (II and III) and the pyrrolidylpropanols (IV and V) with aminoalkyl and bromoaryl substituents, and also the acyl derivatives possess moderate antimicrobial activity and an even more marked fungicidal action.

The most effective antiphage agents are the esters of the isomeric 5-alkyl-2-pyrrolidylpropanols and nitrobenzoic acids. The antiphage activity of these esters is independent of their geometry. The presence of a second nitro group in the acid group increases the activity of the esters towards RNA-containing phages (compounds XV, XVII, XIX, and XXI).

As some of these compounds exhibit antimicrobial activity and inhibit the propagation of phages, it would be appropriate to study these compounds further with a view to finding chemotherapeutic agents.

EXPERIMENTAL CHEMISTRY

IR spectra of the compounds in mineral oil or hexachlorobutadiene were obtained on a VR-20 (GDR) spectrophotometer. Data are given in Table 3.

5-Dimethylamino-1-furyl-1-penten-3-one Hydrochloride (I). This compound was obtained by the Mannich reaction using furfurylideneacetone, dimethylamine hydrochloride, and paraform (1:1.1:1.3) in dilute alcohol in the presence of a catalytic amount of hydrochloric acid.

1-Dimethylamino-3-amino-5-furylpentane Diperchlorate (II). This was prepared by the hydroamination of the ketone I with ammonia at 80°C in the presence of Raney nickel with subsequent treatment of the hydrogenated product with 70% perchloric acid.

N-(p-Bromophenyl)-3-(2-furyl)-1-propylamine (III). A mixture of equimolar quantities of furylacrolein and p-bromoaniline in ethyl alcohol was hydrogenated in an autoclave under

TABLE 2. Antiphage Activity of the Nitro and Dinitrobenzoates of the 3-(1-Methyl-5-R^2-2-pyrrolidyl)propanols XIV-XXI

Compound	Inactivation, %			
	phage T_6		phage MS-2	
	dose, μg/ml			
	1000	100	1000	100
XIV	30	28	10	0
XV	59	27	63	52
XVI	44	34	26	3
XVII	48	29	35	30
XVIII	35	28	20	10
XIX	41	35	40	20
XX	32	21	7	0
XXI	43	30	27	17

TABLE 3. Physical Properties of the Compounds

Compound	Yield, %	mp, °C	Found, %		Empirical formula	Calculated, %	
			N	Cl(Br)		N	Cl(Br)
I	66	161—2	6,13	15,35	$C_{11}H_{15}NO_2 \cdot HCl$	6,10	15,47
II*	46	260—1	6,98	17,90	$C_{11}H_{20}N_2O \cdot 2HClO_4$	7,06	17,90
III	50	152—3	5,00	(28,63)	$C_{13}H_{14}BrNO$	5,02	(28,57)
IV†	49	270	7,43	28,94	$C_{22}H_{48}N_4O_2 \cdot H_2SnCl_6$	7,60	29,10
V ‡	40	211—2	4,78	(27,98)	$C_{13}H_{18}BrNO$	4,93	(28,17)
X	30	172—3	4,30	(26,60)	$C_{34}H_{30}Br_2N_2O_2$	4,13	(26,55)
XI	45	248—9	7,34	(23,28)	$C_{34}H_{28}Br_2N_4O_6$	7,29	(23,44)
XII	30	293—4	7,27	(23,20)	$C_{34}H_{26}Br_2N_4O_6$	7,29	(23,44)
XIII	40	254—5	5,82	7,38	$C_{20}H_{21}BrN_2O_4 \cdot HCl$	5,96	7,56
XIV	50	165—6	8,40	10,02	$C_{16}H_{22}N_2O_4 \cdot HCl$	8,17	10,22
XV	55	124—5	10,64	9,26	$C_{16}H_{21}N_3O_6 \cdot HCl$	10,84	9,16
XVI	60	98—0	8,34	10,31	$C_{16}H_{22}N_2O_4 \cdot HCl$	8,17	10,22
XVII	58	81—2	10,60	9,02	$C_{16}H_{21}N_3O_6 \cdot HCl$	10,84	9,16
XVIII	64	126—7	7,43	9,18	$C_{19}H_{28}N_2O_4 \cdot HCl$	7,28	9,23
XIX	52	118—9	9,75	8,20	$C_{19}H_{27}N_3O_6 \cdot HCl$	9,78	8,27
XX	56	112—3	7,20	9,06	$C_{19}H_{28}N_2O_4 \cdot HCl$	7,28	9,23
XXI	60	105—6	9,65	8,08	$C_{19}H_{27}N_3O_6 \cdot HCl$	9,78	8,27
XXII	58	177—8	8,34	10,16	$C_{32}H_{50}N_4O_8 \cdot 2HCl$	8,13	10,30
XXIII	56	169—70	8,42	10,16	$C_{32}H_{50}N_4O_8 \cdot 2HCl$	8,13	10,30

*Isolated as the diperchlorate.
†Isolated as the hexachlorostannate.
‡Amino alcohols VI-IX are described in [1, 5].

100 atmospheres of hydrogen at 80°C in the presence of Raney nickel (10% of the weight of the starting amine). At the end of the reaction, the amine III was isolated from the hydrogenate by freezing out and recrystallization from ethanol.

3-(5-Dimethylaminoethyl-2-pyrrolidyl)propan-1-ol (IV). This compound was obtained by hydrogenating an aqueous solution of the amine II (pH 4.0) at 90°C in the presence of Raney nickel containing 0.5% of mercury, followed by treatment with an excess of a hydrochloric acid solution of tin tetrachloride; the product was recrystallized from DMFA.

3-(N-p-Bromophenyl-2-pyrrolidyl)propan-1-ol (V). A mixture of 15 g of the amine III, 120 ml of dioxane, 15 ml of hydrochloric acid (1:3), and 2 g of Raney nickel containing 1% of mercury was hydrogenated in an autoclave under 50 atmospheres of hydrogen at 120°C. When the reaction was complete, the solvent was evaporated, and the residue treated with isooctane to give V, which was recrystallized from ethanol.

The amides X-XIII and esters XIII-XXIII were obtained by the method given in [2].

EXPERIMENTAL BIOLOGY

The antimicrobial activity of the compounds was determined by the method of double serial dilution in meat-peptone broth (pH 7.2-7.4); *Staph. aureus* 209P, *E. coli* 675, *Pro-*

teus vulgaris 38, *Pseudomonas aeruginosa* 165, and *Candida albicans* 45 were tested (see Table 2). The antiphage activity of the compounds against DNA-containing (T_6) and RNA-containing (MS-2) phages was also studied (see Table 3). Cultures of *E. coli* B and HfrC were used as indicators. The number of surviving phage particles was determined by the agar-layer method. The antiphage activity was expressed as percentage inactivation, according to the formula $(1 - C_0/C_K) \cdot 100$, where C_0 is the number of surviving phage particles in the test, and C_K is the number of phage particles in the control.

The substances were dissolved in DMFA and the solutions diluted with sterile distilled water.

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