SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF FURAN-CONTAINING PYRAZOLINES

M. K. Bratenko, S. E. Deineka,
N. G. Prodanchuk, I. N. Chernyuk,
V. K. Patratii, and V. G. Sinchenko

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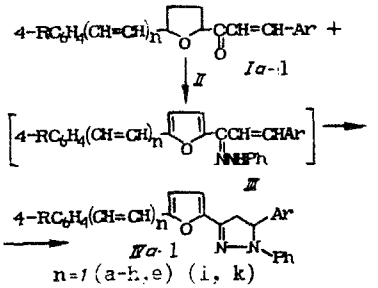
Earlier [2] we showed that triphenylphosphonium salts based on 5-styryl-2-acetylfuran, their phosphonium-ylides, and also α,β-unsaturated ketones obtained by the Wittig reaction, exhibit antimicrobial activity. In a continuation of this investigation, new derivatives of furan – Δ^2-pyrazolines, containing styryl and phenylbutadienyl substituents in the 5-position of the furan ring, have been synthesized and their antimicrobial activity has been studied.

The synthesis of Δ^2-pyrazolines (IVa-k) was carried out by the condensation of furan analogs of chalcone (Ia-k) [2] with phenylhydrazine (II) and followed by heterocyclization of the unstable intermediate hydrazones (III) formed in the first stage of the reaction.



Compounds IVa-k were prepared by a base-catalyzed reaction and compound IVl was obtained using acetic acid as catalyst.

The compositions of the synthesized compounds were confirmed by elemental analysis, and the structures by UV spectroscopy. In the UV spectra of pyrazolines IVa-l are three absorption bands: a short-wave band at 250-258 nm, due to the absorption of the phenyl radical, a second short-wave band at 308-317 nm – due to the furylazomethine group, resulting from the reaction with the phenylimine group $-\overset{|}{N}C_6H_5$, and finally, a long-wave band at 400-423 nm, reflecting the absorption of the 1,3 conjugated system as a whole [3].

EXPERIMENTAL

UV and visible spectra were recorded on a Specord M-40 spectrometer (Germany) using alcoholic solutions with concentrations of $1 \cdot 10^{-5}$ mole/liter. Data for the synthesized compounds are given in Table 1.

Values obtained for the elemental analysis agreed well with calculated values.

1-Phenyl-3-[5-(4-R-styryl)-2-furyl]-5-arylpyrazolines (IVa-h), 1-phenyl-3-[5-(1-phenyl-4-buta-1,3-dienyl)-2-furyl]-5-arylpyrazolines (IVi and k). To a solution of the ketone Ia-k (0.01 mole) and II (0.012 mole) in a mininum quantity of ethanol was added 30% NaOH (0.5 ml) and the mixture heated for 4 hours under reflux. After cooling, the precipitate formed was filtered off, washed with ethanol, diluted with a solution of acetic acid and water, and recrystallized from glacial acetic acid.

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TABLE 1. 1-Phenyl-3-[5-(4-R-styryl)-2-furyl]-5-arylpyrazolines (IVa-h, l), 1-phenyl-3-[5-(1-phenyl-4-buta-1,3-dienyl)-2-furyl-[5-arylpyrazolines (IVi and j)

Compound	Ar	R	Yield, %	MP	Empirical formula
IVa	Furyl-2	H	42	138—9	$C_{25}H_{15}N_2O_2$
IVb	Ph	Br	40	180—1	$C_{27}H_{21}BrN_2O$
IVc	Furyl-2	Br	35	176—8	$C_{25}H_{18}BrN_2O_2$
IVd	Ph	Cl	46	170—1	$C_{27}H_{21}ClN_2O$
IVe	Furyl-2	Cl	38	173—4	$C_{25}H_{18}ClN_2O_2$
IVf	$_nClC_6H_4$	Me	32	181—3	$C_{28}H_{23}ClN_2O_2$
IVg	Ph	Me	60	157—8	$C_{28}H_{24}N_2O_2$
IVh	Furyl-2	Me	56	156—8	$C_{26}H_{21}N_2O_3$
IVi	Ph	—	41	173—4	$C_{29}H_{24}N_2O$
IVk	Furyl-2	—	37	148—50	$C_{27}H_{21}N_2O_2$
IVl	Ph	Me_2N	37	225—6	$C_{29}H_{27}N_3O$

1-Phenyl-3-[5-(4-dimethylaminostyryl)-2-furyl]-5-phenylpyrazoline (IVl). To a solution of the ketone I1 (0.68 g, 0.002 mole) in glacial acetic acid (5 ml) was added II (0.22 g, 0.0021 mole) and the mixture heated on the water bath for 5 h. After cooling, the precipitated material was filtered off, and recrystallized from acetic acid.

EXPERIMENTAL (BIOLOGICAL)

The antimicrobial activity of the compounds was studied by the standard method of double serial dilution in agar broth pH 7.2-7.4 [1, 5]. Thirteen standard microbes belonging to 11 species were selected for testing: Staphylococcus aureus 209, Staphylococcus aureus ATCC 25923, Escherichia coli K-12, Bacillus subtilis F-800, Pseudomonas aeruginosa 136, Serratia marcescens 1266, Proteus vulgaris 410, and others.

The microbial loading was $1 \cdot 10^6$-$5 \cdot 10^6$ microbe bodies in 1 ml of daily broth culture [4]. The minimum suppressing concentration and the minimum bactericidal concentration were determined. The test compounds were dissolved in dimethyl sulfoxide and 0.87% solution of NaCl to give a final concentration of 1000 μg/ml.

Study of biological activity showed that the test compounds exhibited antimicrobial activity against Gram-positive and Gram-negative bacteria. The substitution of the furan ring in the 5 position of the pyrazoline (compounds IVe, IVk, IVh, IVc) by a phenyl group, led to an increase in the antimicrobial action against Staphylococcus aureus (IVd, IVi, IVg, IVb) but a decrease in activity towards Bacillus subtilis (compounds IVd and IVb). Substituents H, Br, Cl, MeO, Me_2N in position 4 of the styryl group did not affect the antimicrobial activity of the test compounds.

The data obtained indicate that further study of the compounds of this series is worthwhile, and the results obtained here will provide a basis for attempts to synthesis new furan-containing pyrazolines with antimicrobial properties.

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