Preparation, structure, and antibacterial activity of some 1,5-diphenyl-3-pyrazinyl-2-pyrazoline derivatives

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Thirteen new 1,5-diphenyl-3-pyrazinyl-2-pyrazolines were prepared by the reaction of halogen, alkoxy, and hydroxy derivatives of 2′,5′-diazachalcones with phenylhydrazine under the catalytic action of 10% aqueous solution of tetramethylammonium hydroxide. The structures of the synthesized compounds were proved by their i.r. and ^{1}H-n.m.r. spectra. The prepared compounds (1% solutions in ethylene glycol dimethyl ether) were found to be active against *Staphylococcus aureus* OXFORD and *Escherichia coli.*

Реакцией галоген-, алкокси- и гидроксипроизводных 2′,5′-диазахалконов с фенилгидразином при каталитическом воздействии 10%-ного водного раствора тетраметиламмонийгидроксида было приготовлено 13 новых 1,5-дифенил-3-пиразинил-2-пиразолинов. Структура синтезированных соединений была подтверждена на основании ИК спектров и ^{1}Н-ЯМР. 1%-ные растворы в этиленгликольдиметиловом эфире оказались эффективными по отношению к *Staphylococcus aureus* OXFORD и *Escherichia coli.*

Some types of substituted pyrazolines show biological activity, *e.g.* antibacterial activity including tuberculostatic [1, 2], hypotension [3], insecticidal [4], *etc.* At present, 1,3,5-triphenyl-2-pyrazoline (TPP) and its derivatives are in foreground of interest. Some authors [5] studied the replacement of phenyls in TPP by pyridyl.

In the present work we focused our attention to the replacement of phenyl by pyrazine in the position 3. We prepared 1,5-diphenyl-3-pyrazinyl-2-pyrazolines and proved their structures by spectral methods. We applied the most frequently used method for the preparation of 2-pyrazolines based on the reaction of α,β-unsaturated ketones or aldehydes with the appropriate hydrazines [6, 7].

Experimental

All the prepared heterocyclic analogues of TPP were recrystallized from anhydrous ethanol. Elemental analysis, yields, and melting points are presented in Table 1.

Table 1

Characterization of the prepared 2-pyrazoline derivatives

Compound	R^1	R^2	Formula	*M*	Calculated/found % C	% H	% N	Yield %	M.p., °C Kofler
I	H	H	$C_{19}H_{16}N_4$	300.36	75.97	5.36	18.65	86	157—158
					75.87	5.67	18.60		
II	2-Br	H	$C_{19}H_{15}N_4Br$	379.26	60.21	3.99	14.78	90	178—180
					60.40	4.30	14.24		
III	2-Cl	H	$C_{19}H_{15}N_4Cl$	334.81	68.12	4.51	16.73	81	150—153
					67.95	4.90	16.93		
IV	4-Cl	H	$C_{19}H_{15}N_4Cl$	334.81	68.12	4.51	16.73	80	140—142
					68.47	4.55	16.81		
V	2-F	H	$C_{19}H_{15}N_4F$	318.35	71.67	4.75	17.62	96	143—145
					71.39	4.95	17.80		
VI	2-OH	H	$C_{19}H_{16}N_4O$	316.36	72.14	5.10	17.71	55	266—269
					72.51	5.38	17.32		
VII	3-OH	H	$C_{19}H_{16}N_4O$	316.36	72.14	5.10	17.71	88	234—236
					71.83	5.40	17.82		
VIII	4-OH	H	$C_{19}H_{16}N_4O$	316.36	72.14	5.10	17.71	64	266—268
					72.52	5.34	17.39		
IX	4-OCH_3	H	$C_{20}H_{18}N_4O$	330.39	72.79	5.50	16.98	83	140—142
					72.56	5.94	16.57		
X	3-OC_2H_5	2-OH	$C_{21}H_{20}N_4O_2$	360.42	69.97	5.59	15.54	79	204—206
					70.30	5,81	15.25		
XI	3-OC_2H_5	4-OH	$C_{21}H_{20}N_4O_2$	360.42	69.97	5.59	15.54	81	207—209
					69.84	5.60	15.43		
XII	2-OH	3-OCH_3	$C_{20}H_{18}N_4O_2$	346.39	69.35	5.24	16.18	91	194—196
					69.35	5.40	16.16		
XIII	4-OH	3-OCH_3	$C_{20}H_{18}N_4O_2$	346.39	69.35	5.24	16.18	60	218—221
					69.69	5.53	15.86		

Table 2

Infrared and ^{1}H-n.m.r. data of 2-pyrazoline derivatives

Compound	$\tilde{\nu}$/cm^{-1}					δ/p.p.m.			J/Hz		
	ν(C=N)^a	δ(CH$_2$)	ν(Ar—N)	ν(CH—N)	γ(C—H)	H$_A$	H$_B$	H$_X$	J_{AX}	J_{BX}	J_{AB}
I	1596	1375 d 1381	1323	1132 d 1136	693 d 704	3.18	3.81	5.37	7.0	12.4	18.0
II	1597	1380	1320	1138	688 d 677	3.11	3.97	5.64	6.9	12.6	18.3
III	1597	1380	1322	1138	688 d 673	3.13	3.97	5.69	6.7	12.6	18.3
IV	1596	1378	1322	1133	688 d 673	3.16	3.85	5.30	7.3	12.4	18.0
V	1597	1376	1319	1133	687 d 671	3.21	3.89	5.62	6.7	12.6	18.1
VI	1598	1377 d 1382	1323	1142	690 d 676	3.37	3.99	5.98	6.7	12.5	18.0
VII	1601	1367	1315	1118	688	3.31	3.85	5.67	6.8	12.5	18.0
VIII	1597	1381	1323	1131 d 1136	686 d 674	3.24	3.80	5.35	6.9	12.4	18.0
IX	1596	1374	1324	1127	688 d 672	3.18	3.83	5.29	7.4	12.4	17.8
X	1602	1382	1327	1150	694	3.20	3.87	5.67	6.7	12.7	18.0
XI	1600	1375	1318	1130	687	3.29	3.84	5.36	7.5	12.7	18.0
XII	1601	1382	1329	1149	693	3.20	3.88	5.67	6.7	12.5	18.1
XIII	1596	1370	1319	1118 d 1126	692	3.29	3.84	5.36	7.5	12.7	18.1

a) The band overlapped by the band ν(C=C); d — doublet.

Infrared spectra were measured on a Perkin—Elmer 377 instrument in the region of 4000—400 cm^{-1}. KBr pellets containing 3.0—3.5 mg compound per 400 mg KBr were measured.

^{1}H-N.m.r. spectra were taken on a Tesla BS 487 B spectrometer at 80 MHz in deuterated chloroform. Infrared and ^{1}H-n.m.r. spectral data are presented in Table 2.

The antibacterial activity of the prepared compounds was determined by the modified method after Vincent [8]. Paper discs were dipped into 1% ethylene glycol dimethyl ether solutions of the compounds tested. As standard 1% solution of ajatin (dimethyllauryl-benzylammonium bromide) was used. Standard microbial strains *Staphylococcus aureus* OXFORD and *Escherichia coli* were used for tests. Meat-peptone agar (2.5% concentration), prepared from products of Imuna, Šarišské Michaľany, was used as cultivation medium. Antibacterial activity was evaluated after 24 h incubation at 37°C in a thermostat. At the end of incubation the diameter of the growth inhibition zone was measured around 5 discs with all compounds. The inhibition zone is given in mm. From the measured values, arithmetic mean ($\bar{y}$), standard deviation (s), and confidence interval ($s\bar{y}$) were calculated after *CsL 3*. The results are presented in Table 3.

Table 3

Antibacterial activity (arithmetic mean ($\bar{y}$) of the inhibition zone in mm) of some 2-pyrazoline derivatives

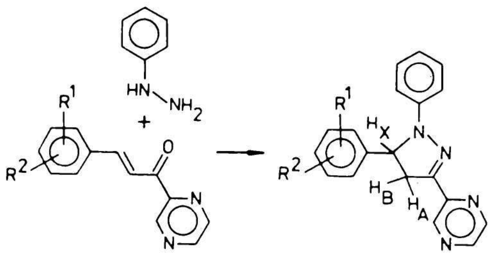
Compound	*Staphylococcus aureus* OXFORD	*Escherichia coli*
I	10.0	10.0
II	16.7	16.0
III	14.2	11.9
V	16.0	13.3
VII	14.0	13.0
VIII	14.5	13.5
IX	14.8	12.8
X	14.0	11.9
XI	14.1	14.6
XII	13.6	14.8
Standard	20.0	18.0

1,5-Diphenyl-3-pyrazinyl-2-pyrazolines (I—XIII)

The appropriate 2′,5′-diazachalcone (2.10 g; 0.01 mol) was dissolved in anhydrous ethanol (5 ml). Phenylhydrazine (1.08 g; 0.01 mol) in anhydrous ethanol (5 ml) was added into the reaction mixture. As catalyst, 10% aqueous solution of tetramethylammonium hydroxide (TMAH) (5 drops) was used. The reaction mixture was refluxed for 1 h. After cooling a lemon-coloured compound precipitated which was filtered and crystallized from anhydrous ethanol.

Results and discussion

The heterocyclic analogues of TPP were prepared from the appropriate diazachalcones [9] synthesized earlier by the modifield Claisen—Schmidt condensation of methyl pyrazinyl ketone with aromatic aldehydes under the catalytic action of diethylamine. 1,3,5-Trisubstituted 2-pyrazolines (Scheme 1) were prepared by the reaction of 2′,5′-diazachalcones with phenylhydrazine in equimolar ratio at elevated temperature under the catalytic action of 10% aqueous solution of TMAH. The used method enabled to prepare all probable pyrazolines in good yields. Under relatively simple reaction conditions yellow crystalline compounds insoluble in water were formed. In alcoholic solution they exhibited intensive blue fluorescence.



Scheme 1

The structures of the prepared compounds were proved by infrared and ^{1}H-n.m.r. spectra. The i.r. spectra of all prepared 2-pyrazoline derivatives showed strong absorption bands attributed to deformation vibrations of CH_2 groups of the pyrazoline ring in the region of 1382—1367 cm^{-1}. Moreover, absorption bands belonging to the vibration of C=N group (1602—1596 cm^{-1}) were observed. These bands cannot be unambiguously assigned to the C=N bond itself because, in some cases, overlapping and interaction with other conjugated double C=C bonds may occur [10, 11]. The absorption bands belonging to the vibrations of Ar—N (1329—1315 cm^{-1}), CH—N (1150—1118 cm^{-1}), and C—H (704—671 cm^{-1}) groups also proved the pyrazoline structure [11—13].

The most convincing proof of the CH_2 group can be obtained by ^{1}H-n.m.r. spectroscopy. The molecules of 2-pyrazoline derivatives contain 3 protons belonging to CH_2 and CH groups of the pyrazoline ring (ABX system). The proton in the position 5 is marked H_X, the proton in the position 4, which is in *trans* position to H_X is marked H_A, and the one in *cis* position to H_X is marked H_B. Table 2 presents the chemical shifts of the protons H_A, H_B, H_X and the coupling constants J_{AB}, J_{AX}, J_{BX}, which are in agreement with the so far published values for the compounds of pyrazoline structure (TPP) [14, 15].

The antibacterial activity obtained with all compounds tested was influenced by the fact that, since the prepared compounds were insoluble in water, measurements were carried out in ethylene glycol dimethyl ether (itself not exhibiting antibacterial activity) which is not the most suitable medium for these measurements [8].

References

1. Belzecki, C. and Urbánski, T., *Rocz. Chem. 32,* 769 (1958); *Chem. Abstr. 53,* 10187 (1959).
2. Kost, A. N., Grandberg, I. I., Terenťev, A. P., and Milanovova, S. N., *Zh. Obshch. Khim. 29,* 93 (1959).
3. Traverso, J. J., Whitehead, C. W., Bell, J. F., Boaz, H. E., and Willard, P. W., *J. Med. Chem. 10,* 840 (1967).
4. Mooser, H., *Angew. Chem. 68,* 717 (1956).
5. Szücs, L., *Chem. Zvesti 23,* 677 (1969).
6. Szücs, L., Ďurinda, J., Krasnec, Ľ., and Heger, J., *Chem. Zvesti 20,* 817 (1966).
7. Ďurinda, J., Kolena, J., Szücs, L., Krasnec, Ľ., and Heger, J., *Česk. Farm. 16,* 14 (1967).
8. *Mikrobiologické vyšetřovací methody.* (Microbiological Investigation Methods.) P. 152. Státní zdravotnické nakladatelství. (State Publishing House of Health.) Prague, 1958.
9. Zámocká, J., Dvořáčková, D., and Heger, J., *Z. Chem.,* in press.
10. Rao, C. N. R., *Chemical Applications of Infrared Spectroscopy,* p. 267. Academic Press, New York, 1963.
11. Toi, Y., Kawai, M., Isagawa, K., and Fushizaki, Y., *Nippon Kagaku Zasshi 88,* 1095 (1967).
12. Tsukerman, S. V., Buryakovskaya, E. G., Rozum, Y. S., and Lavrushin, V. F., *Zh. Prikl. Spektrosk. 8,* 453 (1968).
13. Sandler, S. R., Loshaek, S., Broderick, E., and Tsou, K. C., *J. Phys. Chem. 66,* 404 (1962).
14. Szmant, H. H. and Basso, A. J., *J. Amer. Chem. Soc. 74,* 4397 (1959).
15. Ioffe, B. V., *Khim. Geterotsikl. Soedin. 1968,* 1089.

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