α,β-Unsaturated Ketones Derived from Acetylpyridines. VI.* Preparation of Some Pyridyl-Substituted Pyrazoles

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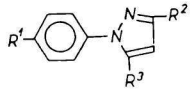
A group of 28 pyridyl-substituted pyrazoles was prepared by dehydrogenation of pyridine analogs of 1,3,5-triphenyl-2-pyrazoline. The structure of the synthesized compounds was determined by nuclear magnetic resonance spectroscopy.

In our previous work [1], we described the preparation of pyridine analogs of 1,3,5-triphenyl-2-pyrazoline (TPP) and showed the possibility of their utilization mainly as optical brightening agents.

Because the dehydrogenation of 2-pyrazolines leads to the appropriate pyrazoles [2], the described analogs of TPP [1] can represent suitable starting compounds for the preparation of 1,3,5-trisubstituted pyrazoles, where R^1 is phenyl, *p*-tolyl, *p*-chlorophenyl, *p*-nitrophenyl, and *p*-carbethoxyphenyl radical, respectively. In the type *I* R^2 is pyridyl, R^3 phenyl, while in the type *II*, pyridyl is in the position 5 and R^2 is phenyl (Table 1).



In the present work we focused our attention on the preparation of the above-mentioned types of pyrazoles. For dehydrogenation of the starting pyridine analogs of TPP [1], we applied methods [8—10] from all the methods worked out up to now [3—11] because they gave positive results in a great number of different (mainly 1,3,5-trisubstituted) 2-pyrazolines.

We were interested in pyrazoles of the types *I* and *II* from the standpoint of their possible antibacterial properties as some substituted pyrazoles had been shown to have such properties [2]. The second reason for our interest was the possibility of their utilization as multifunctional molecular ligands in the region of coordinated compounds [12, 13].

Experimental

The initial pyridine analogs of 1,3,5-triphenylpyrazoline were prepared from the appropriate azachalcones and phenylhydrazines by the procedure described in [1].

The purity of the synthesized pyrazoles was checked by thin-layer chromatography (Silufol, Lachema) in the system benzene—ethanol 9 : 1. The detection was carried out in ultraviolet light.

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Characterization of the compounds prepared

No.	R^1	R^2	R^3	Formula	M	Calculated/found % C	% H	% N	Method	Yield [%]	M.p. [°C] (Kofler) Solvent	R_F values	Chemical shift τ
I	H	phenyl	phenyl	$C_{21}H_{16}N_2$	296.50	85.10 84.89	5.44 5.72	9.45 9.31	*A*, *B*, *C*	86, 87, 68	138–140[a] ethanol		3.33
II	H	phenyl	2-pyridyl	$C_{20}H_{15}N_3$	297.34	80.78 80.38	5.08 5.30	14.13 14.42	*A*, *B*	85, 85	110–112 ethanol	0.57	3.01
III	H	phenyl	3-pyridyl	$C_{20}H_{15}N_3$	297.34	80.78 80.25	5.08 5.08	14.13 14.12	*A*, *B*	82, 80	114–116 ethanol	0.47	3.25
IV	H	phenyl	4-pyridyl	$C_{20}H_{15}N_3$	297.34	80.78 81.00	5.08 5.25	14.13 14.19	*A*, *B*	89, 85	153–155 ethanol	0.43	3.21
V	H	2-pyridyl	phenyl	$C_{20}H_{15}N_3$	297.34	80.78 80.90	5.08 5.01	14.13 13.89	*A*, *B*	83, –	122.5–124 ethanol	0.55	2.93
VI	H	3-pyridyl	phenyl	$C_{20}H_{15}N_3$	297.34	80.78 80.89	5.08 5.06	14.13 14.32	*A*, *B*	78, 85	106–108 ethanol	0.37	3.29
VII	H	4-pyridyl	phenyl	$C_{20}H_{15}N_3$	297.34	80.78 80.60	5.08 5,18	14.13 14.30	*A*, *B*	42, –	118–120 ethanol	0.33	3.23
VIII	CH_3	phenyl	2-pyridyl	$C_{21}H_{17}N_3$	311.39	81.00 81.29	5.56 5.50	13.49 13.51	*A*	74	97–99 ethanol	0.74	2.30
IX	CH_3	phenyl	3-pyridyl	$C_{21}H_{17}N_3$	311.39	81.00 81.28	5.56 5.80	13.49 13.44	*A*	51	104–105.5 ethanol	0.46	3.28
X	CH_3	phenyl	4-pyridyl	$C_{21}H_{17}N_3$	311.39	81.00 80.96	5.56 5.80	13.49 13.36	*A*	68	155–156.5 ethanol	0.30	3.21
XI	CH_3	2-pyridyl	phenyl	$C_{21}H_{17}N_3$	311.39	81.00 81.73	5.56 5.46	13.49 13.41	*A*	67	108–109 ethanol	0.65	2.01
XII	CH_3	3-pyridyl	phenyl	$C_{21}H_{17}N_3$	311.39	81.00 81.05	5.56 5.60	13.49 13.44	*A*	78	137–138 ethanol	0.47	3.28
XIII	Cl	phenyl	2-pyridyl	$C_{20}H_{14}ClN_3$	331.81	72.40 72.57	4.25 4.47	12.66 12.46	*A*	51	117–119 ethanol	0.87	3.07
XIV	Cl	phenyl	3-pyridyl	$C_{20}H_{14}ClN_3$	331.81	72.40 71.98	4.25 4.31	12.66 12.72	*A*	65	90–93 ethanol	0.69	3.24
XV	Cl	phenyl	4-pyridyl	$C_{20}H_{14}ClN_3$	331.81	72.40 72.70	4.25 4.26	12.66 12.54	*A*	71	139–140 ethanol	0.61	3.25
XVI	Cl	2-pyridyl	phenyl	$C_{20}H_{14}ClN_3$	331.81	72.40 72.58	4.25 4.41	12.66 12.76	*A*	70	123–124 ethanol	0.67	2.95

Table 1 (Continued)

No.	R^1	R^2	R^3	Formula	M	Calculated/found % C	% H	% N	Method	Yield [%]	M.p. [°C] (Kofler) Solvent	R_F values	Chemical shift τ
XVII	Cl	3-pyridyl	phenyl	$C_{20}H_{14}ClN_3$	331.81	72.40	4.25	12.66	*A*	60	123—125	0.48	3.24
						72.59	4.33	12.54			ethanol		
XVIII	Cl	4-pyridyl	phenyl	$C_{20}H_{14}ClN_3$	331.81	72.40	4.25	12.66	*A*	50	142—143	0.40	3.24
						72.39	4.55	12.72			ethanol		
XIX	$CO_2C_2H_5$	phenyl	2-pyridyl	$C_{23}H_{19}N_3O_2$	369.43	74.78	5.18	11.37	*A*	81	105—107	0.58	3.08
						74.48	5.36	11.22			ethanol		
XX	$CO_2C_2H_5$	phenyl	3-pyridyl	$C_{23}H_{19}N_3O_2$	369.43	74.78	5.18	11.37	*A*	86	99—101	0.45	3.24
						74.37	5.48	11.64			ethanol		
XXI	$CO_2C_2H_5$	phenyl	4-pyridyl	$C_{23}H_{19}N_3O_2$	369.43	74.78	5.18	11.37	*A*	85	122—123.5	0.39	3.25
						75.00	5.40	11.56			ethanol		
XXII	$CO_2C_2H_5$	2-pyridyl	phenyl	$C_{23}H_{19}N_3O_2$	369.43	74.78	5.18	11.37	*A*	83	121—123	0.48	2.87
						75.08	5.30	11.34			ethanol		
XXIII	$CO_2C_2H_5$	3-pyridyl	phenyl	$C_{23}H_{19}N_3O_2$	369.43	74.78	5.18	11.37	*A*	87	115—116.5	0.33	3.26
						74.44	4.90	11.41			ethanol		
XXIV	$CO_2C_2H_5$	4-pyridyl	phenyl	$C_{23}H_{19}N_3O_2$	369.43	74.78	5.18	11.37	*A*	90	171—173	0.26	3.24
						75.06	5.08	11.62			ethanol		
XXV	NO_2	phenyl	2-pyridyl	$C_{20}H_{14}N_4O_2$	342.36	70.16	4.12	16.36	*A*	80	180—182.5	0.79	3.04
						70.43	4.42	16.53			ethanol		
XXVI	NO_2	phenyl	3-pyridyl	$C_{20}H_{14}N_4O_2$	342.36	70.16	4.12	16.36	*A*	75	138—139.5	0.49	3.19
						69.89	4.60	16.12			ethanol		
XXVII	NO_2	phenyl	4-pyridyl	$C_{20}H_{14}N_4O_2$	342.36	70.16	4.12	16.36	*A*	61	184—185	0.44	3.15
						70.21	4.20	16.58			ethanol		
XXVIII	NO_2	2-pyridyl	phenyl	$C_{20}H_{14}N_4O_2$	342.36	70.16	4.12	16.36	*A*	65	169—170.5	0.60	
						69.82	4.40	16.23			ethanol		
XXIX	NO_2	4-pyridyl	phenyl	$C_{20}H_{14}N_4O_2$	342.36	70.16	4.12	16.36	*A*	45	159—161	0.27	3.19
						69.79	4.14	16.29			ethanol		

a) References [8—10] give m.p. 140, 139—140, and 137°C, respectively.

The n.m.r. spectra of pyrazoles in $CDCl_3$ were taken on a Tesla BS 487 A spectrometer of the operating frequency 80 MHz. Hexamethyldisiloxane was used as a standard and the results were calculated with regard to tetramethylsilane.

1,3,5-Trisubstituted pyrazoles

Method A

Pyrazoline (0.018 mole) was dissolved in dry, freshly redistilled dichloromethane (160 ml) and mixed with the solution of lead tetraacetate (0.022 mole) [14] in dichloromethane (80 ml). The mixture was allowed to react for 24 hours in an enclosed vessel. Then diluted acetic acid was added until dissolution of the solid compound formed during reaction and finally several drops of hydrazine hydrate were added to remove brown turbidity caused by lead compounds. The dichloromethane layer was separated and dried with anhydrous potassium carbonate. Dichloromethane was distilled off under reduced pressure and the solid residue recrystallized from ethanol. Compounds *VIII*—*XII*, *XXV*—*XXIX* were first precipitated with water from their acetone solutions and then recrystallized from ethanol.

Method B

Pyrazoline (0.006 mole) was dissolved in anhydrous benzene (60 ml) and activated manganese dioxide (10 g) [15] was added into the solution. The mixture was stirred at laboratory temperature for 5 hours and then filtered. The evaporation of benzene under reduced pressure left an oil which upon standing for several hours yielded a solid compound which was recrystallized from ethanol.

Method C

Pyrazoline (0.02 mole) was heated on an oil bath to 150°C and sulfur (0.64 g; 0.02 mole) was added. The mixture was then heated to 180—200°C for 3 hours, or until liberation of hydrogen sulfide, and then poured into methanol (40 ml). In a short time, a solid substance was precipitated and recrystallized from ethanol.

Results and Discussion

Pyridyl-substituted pyrazoles of the types *I* and *II* were synthesized by oxidation of the appropriate pyridine analogs of TPP [1] with lead tetraacetate according to the procedure worked out by *Gladstone* and *Norman* [9] (method *A*). The same method was used to prepare also 1,3,5-triphenylpyrazole (compound *I*) which was used as standard for structural determination of the synthesized compounds. This method was very advantageous and enabled to prepare all of the proposed compounds in good yields (Table 1). We failed only to prepare 1-*p*-tolyl-3-(4-pyridyl)-5-phenylpyrazole and 1-*p*-nitrophenyl-3-(3-pyridyl)-5-phenylpyrazole by this method but could not explain the reason of this failure yet.

In our early experiments, when preparing the standard substance and its six pyridine analogs (compounds *II*—*VII*), we examined besides the presented method also oxidation of the initial 2-pyrazolines by activated manganese dioxide [10] (method *B*) and their dehydrogenation by sulfur [8] (method *C*). Although these methods, similarly as method *A*, enabled to prepare the standard (compound *I*), synthesis of pyridyl-substituted pyrazoles *II*—*VII* was only partly successful in the method *B* and gave no positive results in the method *C* (Table 1). Therefore, we applied only method *A* in our further experiments.

The obtained white or slightly yellow, well crystallizing compounds were soluble in usual organic solvents.

Checking the purity of these compounds by thin-layer chromatography, we found that some of them showed fluorescence of low intensity. In this connection, it is also noticeable that in the series of isomeric compounds (for instance *II*—*IV*, *V*—*VII*) the R_F values decreased according to the position of nitrogen atom in pyridyl radical ($2 > 3 > 4$; Table 1) similarly as we found for the initial 2-pyrazolines [1]. Results of thin-layer chromatography also showed that the fluorescence of the synthesized pyrazoles was not due to the present trace amounts of the initial 2-pyrazolines (which showed intensive fluorescence [1]) as we assumed, but it was a characteristic of the prepared compounds. This conclusion was proved indirectly by the detailed study of *Grandberg* and co-workers [16] which showed that some substituted pyrazoles had fluorescent properties.

The structures of the synthesized compounds were determined by interpretation of their n.m.r. spectra. We started from the fact that the molecule of 1,3,5-triphenylpyrazole (the standard) and that of the other synthesized compounds had only one hydrogen atom in the five-membered heterocyclic ring. Its presence would appear on the spectrum of these compounds as a singlet not overlapped by signals of other hydrogen atoms present in the molecule [17]. On the contrary, five-membered heterocyclic ring of the initial 2-pyrazolines has three hydrogen atoms forming ABC system so that three quadruplets at $\tau = 6.5-6.9$ (H_A), $6.1-6.3$ (H_B), and $4.6-4.8$ (H_C) with the coupling constants at about 7 (J_{AC}), 12 (J_{BC}), and 17 (J_{AB}) (Fig. 1) can be noticed in the n.m.r. spectra of these compounds [18—20].

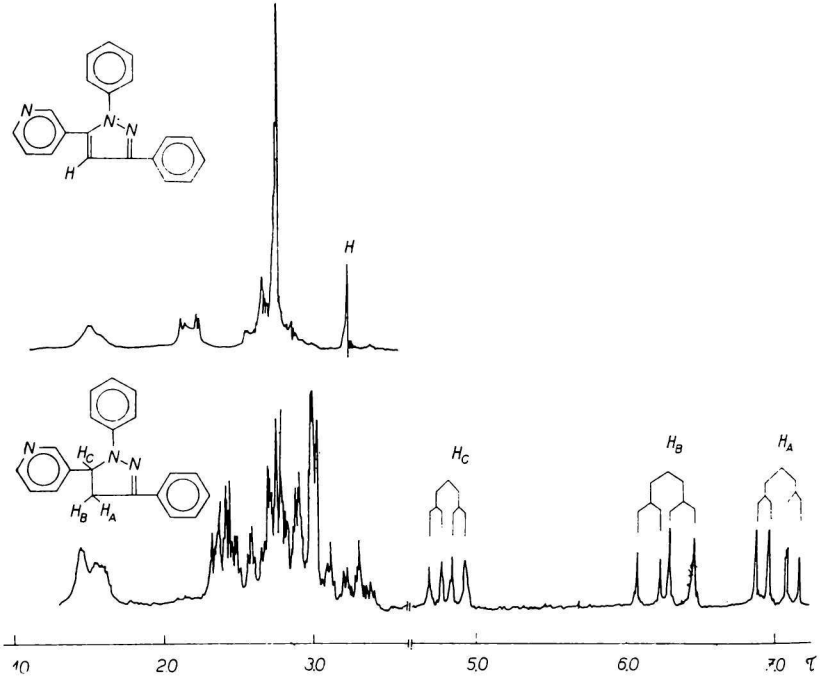

Fig. 1. The n.m.r. spectra of pyrazole and pyrazoline.

From the obtained results (Table 1) it is clear that the standard as well as the synthesized compounds have shown singlets in the region of $\tau = 3$ and that is in agreement with the above-mentioned fact. We assume therefore that the synthesized compounds have the supposed pyrazole structure.

Results of the study of antibacterial and complexing properties of the prepared compounds will be published separately.

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