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Dedicated to Academician M.G.Voronkov on occasion of his 80th birthday

Assembling of Complex Heterocyclic Ensembles, Schiff Bases, from 5-Amino-3-[2-(4,5,6,7-tetrahydroindolyl)]pyrazoles and 1-Vinyl(ethyl)-2-formylimidazoles

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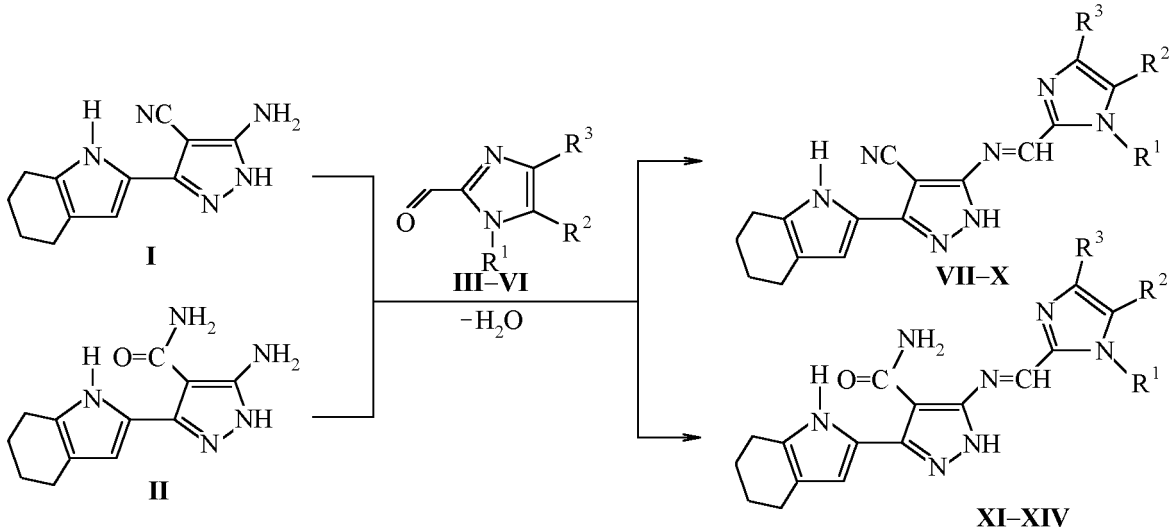
Abstract—Condensation of 5-amino-3-(2-pyrrolyl)pyrazoles with 1-vinyl(ethyl)-2-formylimidazoles afforded complex heterocyclic ensembles: Schiff bases containing pyrrole, pyrazole, and imidazole rings. The *cis*,*trans*-orientation of CH=N and CH_2=CH groups and E-isomeric structure of the Schiff bases under study with respect to the imine fragment, and also the presence of intra- and intermolecular hydrogen bonds were established.

The analysis of publications shows that although investigations on synthesis and chemistry of Schiff bases are widely developed [1–4], azomethines containing ensembles of heterocycles remain poorly understood. In continuation of our studies on the synthesis of polyfunctional heterocyclic structures [5–9] we report here on new azomethines containing in the structure functionalized pyrrole, pyrazole, imidazole rings. The compounds obtained are polydental ligands for designing metal complex catalysts, models for investigation of conformational isomerism and of new types of intramolecular and intermolecular effects, potential photochrome compounds (molecular switches), and also initial material for the synthesis of promising pharmaceuticals. Aiming at elucidation of the role of the heteroring nature and its substituents in the amine component on the condensation with imidazolecarboxaldehydes in comparison with the previously published data [5, 6] we studied for the first time the reaction between 5-amino-4-R-3-[2-(4,5,6,7-tetrahydroindolyl)]pyrazoles (**I, II**) and 1-vinyl- and 1-ethylimidazole(benzimidazole)carboxaldehydes (**III–VI**). It was established that the corresponding azomethines **VII–XIV** cleanly form in a reaction without catalyst.



R^2 = R^3 = H: R^1 = CH=CH_2 (**III, VII, XI**), Et (**IV, VIII, XII**); R^2, R^3 = benzo: R^1 = CH=CH_2 (**V, IX, XIII**), Et (**VI, X, XIV**).

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Condensation conditions and the nature of initial reagents significantly affect the yield of reaction products. The reaction between 1-vinyl- and 1-ethyl-2-formylimidazoles (**III, IV**) with 5-amino-3-[2-(4,5,6,7-tetrahydroindolyl)]-4-cyanopyrazole (**I**) in ethanol at 70°C proceeded for 5–6 h affording bases **VII, VIII** in 53 and 65% yield respectively. Under similar conditions the yields of azomethines from benzimidazolecarboxaldehydes **V, VI** and the same aminopyrazole **I** did not exceed 25%. In the latter case the synthesis of Schiff bases is performed under more rigid conditions: fusion of the initial reagents at 90–95°C for 4 h, and then the yield of reaction products **IX, X** amounts to 89–95%. In reaction carried out in this fashion with imidazolecarboxaldehydes **III, IV** the yield of compounds **VII**, **VIII** increases insignificantly (by 5–7%). 2-Aminobenzimidazoles in reactions with aldehydes *III–VI* are more reactive than 5-aminopyrazoles **I, II** under study: the yields of the corresponding azomethines [5, 6] are on the average by 10–20% higher.

The condensation of azole **II** with imidazolecarboxaldehydes **III–VI** is to a large degree reversible if the reaction is carried out in ethanol or benzene (an intractable mixture arises containing azomethines and the initial reagents). Such reversible reaction we previously observed [6] only with 2-aminobenzimidazole and 1-vinylimidazolecarboxaldehyde (**V**). The equilibrium shifts considerably to the right at fusion (90–95°C) of equimolar amounts of aminopyrazole **II** and aldehyde **III–VI** with simultaneous removal from the reaction mixture of the formed water; in this case the yield of Schiff bases **XI** and **XIII** originating from imidazolecarboxaldehydes **III, V** reaches 65 and 47% respectively. With 1-ethyl-2-formylimidazoles **IV, VI** amine **II** affords azomethines **XII** and **XIV** in high yield (79–90%).

Azomethines **VII–XIV** synthesized are high-melting crystalline compounds of yellow color, sparingly soluble in the most organic solvents. The structure of the products was established with the use of ^{1}H NMR and IR spectroscopy. Therewith the data obtained were compared with the parameters of the original compounds and of the azomethines obtained earlier from aminobenzimidazoles and aminophenols [5, 6, 10].

In the ^{1}H NMR spectra of bases **VII–XIII** are lacking the proton signals from NH_2 group observed in the spectra of original pyrazoles **I** (6.09 ppm) and **II** (6.96 ppm) [7], and appears a proton signal from the azomethine group in 8.81–9.20 ppm region (see table). Due to the electron-withdrawing effect of CN and $CONH_2$ substituents in the *4*-position of the pyrazole moiety in bases **VII–XIII** the signal of the azomethine proton =CH is shifted downfield as compared to the similar signal in the spectra of vinyloxyphenyloxyazomethines (δ 8.4 ppm) [10]. Note that in the ^{1}H NMR spectra of azomethines **XI–XIII** (see table) appear two signals from NH of the amide group unlike the singlet in the spectrum of azole **II** (δ_{CONH_2} 5.08 ppm) [7]; apparently the rotation of the substituent NH_2CO in azomethines is hindered.

Same as with the corresponding azomethines originating from 2-aminobenzimidazoles [5, 6], in the spectra of 1-vinyl derivatives **VII, IX, XI, XIII** the proton H_X of substituent $CH_2{=}CH_X$ suffers a considerable downfield shift (δ 7.65–8.17 ppm, see table) as compared to the corresponding signal in 2-substituted 1-vinylimidazoles (δ 6.6–7.0 ppm) [11–13]. This fact indicates that the proton H_X takes part in the intramolecular specific interaction with the nitrogen from the azomethine group suggesting prevailing *cis,trans*-orientation of CH=N and CH_2=CH groups in the bases under study and their occurrence in the *E*-form with respect to the imine bond.

The assignment of the characteristic absorption bands in the IR spectra of azomethines synthesized **VII–XIII** with accounting for the presumable for these molecules inter- and intramolecular interactions was performed by comparative analysis of the spectra recorded from KBr pellets, mulls in mineral oil, and solutions in $CHCl_3$ of the initial pyrazoles **I, II** and unsubstituted tetrahydroindole and pyrazole.

In the IR spectra of bases **VII–X** prepared from azole **I** the stretching vibrations of the azomethine bond (νN=CH) appear as a strong absorption band in 1602–1598 cm^{-1} region, same as in the spectra of the azomethines originating from 2-aminobenzimidazoles [5, 6]. In the spectra of azomethines **VII** and **VIII** obtained with the use of imidazolecarboxaldehydes **III, IV** in this region is observed a single band of the CH=N group. A doublet band with the maxima at 1600 and 1598 cm^{-1} in the spectra of benzimidazole derivatives **IX, X** corresponds to vibrations of the aromatic ring and the azomethine group. The vinyl substituent in the spectra of azomethines **VII, IX** appears as a band at 1640–1635 cm^{-1} (ν$CH{=}CH_2$). In all azomethine spectra is lacking the absorption band at 1624 cm^{-1} that in the initial 5-aminopyrazole (**I**) corresponds to the bending vibrations of NH_2 group; the position of the absorption band from N≡C substituent (~2220 cm^{-1}) is conserved in the spectra of azomethines.

^{1}H NMR spectra of azomethines **VII**–**XIV** (DMSO-d_6), δ, ppm

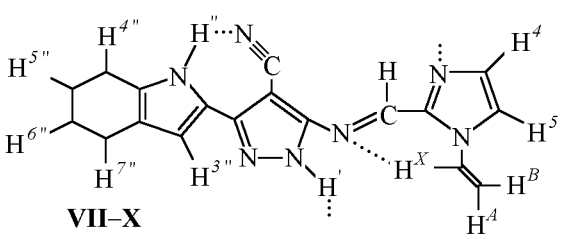
Compd. no.	H_X, d.d	H_A, d.d	H_B, d.d	CH_2, q	CH_3, t	H^4, [a] m	H^5, [a] m	H^6, m	H^7, m	= CH, s	NH", s	NH', s	$H^{3"}$, m	$H^{4"}$, m	$H^{5"}$, m	$H^{6"}$, m	$H^{7"}$, m	$CONH_2$, s
VII	8.17	5.92	5.63			7.97	7.30			8.87	10.80	13.35	6.45	2.57	1.72	1.72	2.57	
VIII				4.49	1.37	7.58	7.27			8.81	10.81	12.41	6.43	2.56	1.72	1.72	2.56	
IX	8.00	5.45	5.76			7.89	7.47	7.47	7.89	9.13	10.87	13.00	6.48	2.59	1.71	1.71	2.59	
X				4.79	1.39	7.75	7.42	7.31	7.75	9.06	10.82	13.10	6.45	2.56	1.69	1.69	2.56	
XI	7.80	5.18	5.63			7.91	7.33			8.96	12.50	13.26	6.57	2.58	1.70	1.70	2.58	8.02, 7.68
XII				4.45	1.37	7.59	7.25			8.97	12.53	13.24	6.57	2.41	1.68	1.68	2.41	8.16, 7.71
XIII	7.65	5.32	5.76			7.80	7.41	7.41	7.80	9.20	12.59	13.41	6.61	2.61	1.70	1.70	2.61	8.25, 7.75
XIV				4.78	1.43	7.82	7.39	7.39	7.82	9.20	12.54	13.39	6.61	2.42	1.70	1.70	2.42	8.10, 7.90

[a] In the spectra of imidazole derivatives **VII, VIII, XI, XII** the signal appears as a doublet.

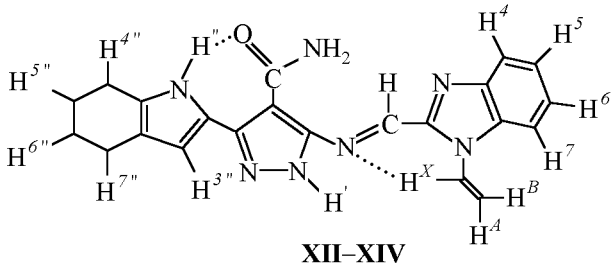
The bands of stretching vibrations of the NH group in the IR spectrum of solid azole **I** (in mineral oil), ν, cm^{-1}: 3390 w, 3340 s, 3290 s, 3240 w, 3190 m have virtually the same values as in the spectrum of compound **I** taken from pellets with KBr [7]. These low frequency values are due to hydrogen bonds formation between various parts of molecule **I** [for comparison: self-association of tetrahydroindole molecule (KBr) is characterized by an absorption band at 3370 cm^{-1}, that of pyrazole by strong absorption in the range 3300–2500 cm^{-1}, and the corresponding bands in the spectra of these compounds recorded from solutions in $CHCl_3$ (c ~0.1 mol l^{-1}) are located respectively at 3480 and 3474 cm^{-1}]. In the spectrum of a solution of 5-aminopyrazole (**I**) in $CHCl_3$ ($c < 10^{-2}$ mol l^{-1}) the two observed high-frequency bands at 3450 and 3374 cm^{-1} belong to vibrations ν_{as} and ν_s of the free NH_2 group, and the bands at 3334 and 3286 cm^{-1} correspond to strong hydrogen bonds obviously with participation of indole and pyrazole fragments of molecule **I**.

In azomethines **VII**–**X** exist two main types of H-bonds. One of them is intermolecular bond N–H···N with participation of the "pyridine" nitrogen of the imidazole fragment; to this bond in the IR spectrum corresponds a broad absorption band in the 3000–2500 cm^{-1} range that is characteristic of the previously studied azomethines [5, 6]. On the other hand, the narrow strong band at 3320–3290 cm^{-1} is apparently due to internal hydrogen bonds in the indolo-pyrazole fragment of molecules **VII**–**X**. The invariable vibration frequency of the azomethine group (νCH=N ~1600 cm^{-1}) in the spectra of compounds **VII**–**X** in contrast to the spectra of azomethines lacking the NH group [5, 6] evidences its inertness with respect to hydrogen bonds formation.

The analysis of IR spectra of 5-aminopyrazole **II** and its condensation products **XI**–**XIV** is complicated by overlapping of absorption bands from vibrations of functional groups and heterorings in the regions 1650–1500, 3500–3000 cm^{-1} and by low solubility of these compounds. For instance, the doublet band in the spectrum of azole **II** at 1650–1600 cm^{-1} we assigned to the bending vibrations of amine substituent (δNH_2 1625 cm^{-1}) and stretching vibrations of amide substituent ($\nu_{max}CO$ 1640 cm^{-1}) for in the



VII–**X**



XII–**XIV**

condensation products is retained a single band at 1640 cm^{-1} and appear absorption bands in the region 1602–1598 cm^{-1} belonging to vibrations of the azomethine group, similar to the spectra of bases **VII**–**X**. The absorption band of $CH_2{=}CH$ group in compounds **XI, XIII** is observed at 1655 cm^{-1}. A broad multiplet absorption band in the region 3200–3100 cm^{-1} in the spectrum of pyrazole **II** is apparently a combination of stretching vibration bands of NH groups in heterocycles and amide substituent, and the band at 3370 cm^{-1} is a similar combination of νNH_2 bands from amino and amido groups. All the spectra of condensation products **XI**–**XIV** possess in this region relatively narrow strong absorption bands at 3200–3180 and 3400–3370 cm^{-1} that may be prevailingly assigned to the stretching vibrations of NH_2 in the amide moiety of the molecules. Obviously in azomethines **XI**–**XIV** does not occur intermolecular association with the N^3 atom, and in their spectra the corresponding absorption in the range 3000–2500 cm^{-1} is lacking.

EXPERIMENTAL

IR spectra of compounds obtained were recorded on spectrometer Bruker IFS 25 from pellets with KBr, mulls in mineral oil, or solutions in $CHCl_3$. ^1H NMR spectra were registered from solutions in DMSO-d_6 on spectrometer Bruker DPX-400 at 20–25°C, internal reference HMDS.

Initial compounds **I**–**VI** were prepared by known procedures [5–7, 14].

5-[2-(1-Vinylimidazolyl)methylenamino]-3-[2-(4,5,6,7-tetrahydroindolyl)]-4-cyanopyrazole (VII). To a solution of 0.14 g (1.15 mmol) of aldehyde **III** in 10 ml of ethanol was added by portions while stirring 0.3 g (1.32 mmol) of 5-amino-[2-(4,5,6,7-tetrahydroindolyl)]-4-cyanopyrazole (**I**). The reaction mixture was boiled for 6 h, then the solvent was removed till the volume was 5 ml. The separated yellow precipitate was filtered off, washed with benzene and ether. Yield 0.2 g (53%), mp 249–252°C. Found, %: C 64.17; H 5.70; N 31.15. $C_{18}H_{17}N_7$. Calculated, %: C 63.95; H 5.33; N 30.72.

5-[2-(1-Ethylimidazolyl)methylenamino]-3-[2-(4,5,6,7-tetrahydroindolyl)]-4-cyanopyrazole (VIII). To a solution of 0.2 g (1.6 mmol) of aldehyde **IV** in 10 ml of ethanol was added by portions while stirring 0.36 g (1.6 mmol) of pyrazole **I**. The reaction mixture was boiled for 5 h, then the solvent was removed till the volume was 5 ml. The separated yellow precipitate was filtered off, washed with benzene and ether. Yield 0.35 g (65%), mp 250–253°C. Found, %: C 64.61; H 6.01; N 29.01. $C_{18}H_{19}N_7$. Calculated, %: C 64.86; H 5.71; N 29.43.

5-[2-(1-Vinylbenzimidazolyl)methylenamino]-3-[2-(4,5,6,7-tetrahydroindolyl)]-4-cyanopyrazole. To a melt of 0.23 g (1.32 mmol) of aldehyde **V** was added by portions 0.3 g (1.32 mmol) of pyrazole **I** and 3 ml of ethanol. The reaction mixture was heated for 6 h to 90–95°C. The formed yellow precipitate was ground with 5 ml of ethanol, filtered off, washed with benzene and ether. Yield 0.48 g (95%), mp 271–274°C. Found, %: C 69.33; H 5.16; N 25.67. $C_{22}H_{19}N_7$. Calculated, %: C 69.29; H 4.99; N 25.72.

5-[2-(1-Ethylbenzimidazolyl)methylenamino]-3-[2-(4,5,6,7-tetrahydroindolyl)]-4-cyanopyrazole (X) was prepared in a similar way. Yield 0.35 g (89%), mp 267–269°C. Found, %: C 68.77; H 5.46; N 25.35. $C_{22}H_{21}N_7$. Calculated, %: C 68.93; H 5.48; N 25.59.

5-[2-(1-Vinylimidazolyl)methylenamino]-3-[2-(4,5,6,7-tetrahydroindolyl)]pyrazole-4-carboxamide (XI). To a melt of 0.07 g (0.61 mmol) of aldehyde **III** was added by portions 0.15 g (0.61 mmol) of azole **II** and 3 ml of ethanol. The reaction mixture was heated for 9 h to 90–95°C with simultaneous removing of ethanol and the forming water at 10–15 mm Hg into a cooled trap. The obtained yellow solid was ground with 5 ml of ethanol, filtered off, washed with benzene and ether. Yield 0.13 g (65%), mp >350°C. Found, %: C 61.91; H 5.10; N 27.85. $C_{18}H_{19}N_7O$. Calculated, %: C 61.89; H 5.44; N 28.08.

5-[2-(1-Ethylimidazolyl)methylenamino]-3-[2-(4,5,6,7-tetrahydroindolyl)]pyrazole-4-carboxamide (XII). To a melt of 0.08 g (0.61 mmol) of aldehyde **IV** was added by portions 0.15 g (0.61 mmol) of azole **II** and 3 ml of ethanol. The reaction mixture was heated for 7 h to 90–95°C with simultaneous removing of ethanol and the forming water at 10–15 mm Hg into a cooled trap. The obtained yellow solid was ground with 5 ml of ethanol, filtered off, washed with benzene and ether. Yield 0.18 g (79%), mp >350°C. Found, %: C 61.98; H 5.68; N 27.53. $C_{18}H_{21}N_7O$. Calculated, %: C 61.54; H 5.98; N 27.92.

5-[2-(1-Vinylbenzimidazolyl)methylenamino]-3-[2-(4,5,6,7-tetrahydroindolyl)]pyrazole-4-carboxamide (XIII). To a melt of 0.11 g (0.61 mmol) of aldehyde **V** was added by portions 0.15 g (0.61 mmol) of azole **II** and 3 ml of ethanol. The reaction mixture was heated for 6 h to 90–95°C with simultaneous removing of ethanol and the forming water at 10–15 mm Hg into a cooled trap. The

obtained yellow solid was ground with 5 ml of ethanol, filtered off, washed with benzene and ether. Yield 0.11 g (47%), mp 274–275°C. Found, %: C 66.55; H 5.57; N 24.48. $C_{22}H_{21}N_7O$. Calculated, %: C 66.17; H 5.26; N 24.56.

5-[2-(1-Ethylbenzimidazolyl)methylenamino]-3-[2-(4,5,6,7-tetrahydroindolyl)]pyrazole-4-carboxamide (XIV) was synthesized in a similar way from aldehyde **VI** and azole **II**. Yield 0.2 g (90%), mp 267–270°C. Found, %: C 65.51; H 5.91; N 24.27. $C_{22}H_{23}N_7O$. Calculated, %: C 65.84; H 5.74; N 24.44.

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