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Reaction of Aromatic Aldehydes with Ammonium Acetate*

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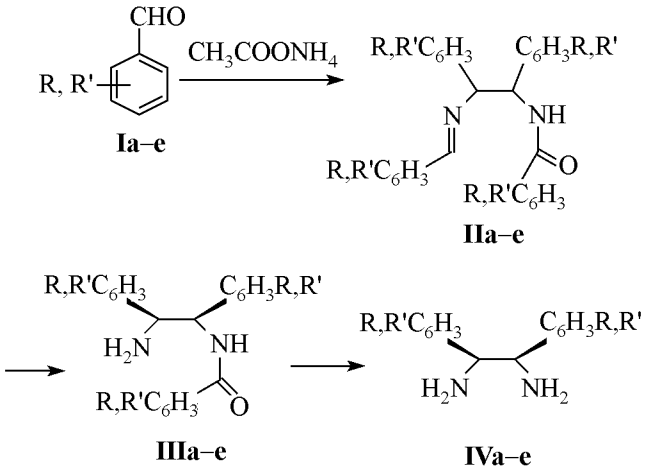
Abstract—By reaction of aromatic aldehydes with ammonium acetate a series of 1,2-diaryl-1,2-diaminoethanes and their derivatives was obtained. The mechanism of reaction was suggested and its principal stages were proved. Reactions with ammonium acetate of aromatic aldehydes containing ortho-substituents resulted in the corresponding 2,4,5-triaryl-4,5-dihydroimidazoles.

1,2-Diaryl-1,2-diaminoethanes are important building blocks in designing enantioselective catalysts [1–8]. Moreover, these diamines are interesting as models for preparation of "twin-drug" analogs [9] of benzylamine derivatives. The synthesis of diamines from this series is based on intermediate formation of hydrobenzamide in reaction between benzaldehydes and ammonia [4–7]. Although the study of this reaction was described in an enormous number of reports, the structure of all intermediates of the process including hydrobenzamide and amarine was unambiguously proved only in 1997 [6].

We believed that from the synthetic viewpoint the statement on ready reaction between three aromatic aldehydes and ammoium acetate [2, 8] was very interesting. With benzaldehyde (**Ia**) the reaction afforded benzylbenzoyl derivative **IIa** that by acid hydrolysis was converted into *meso*-1,2-diphenyl-1,2-diaminoethane (**IVa**) [2].

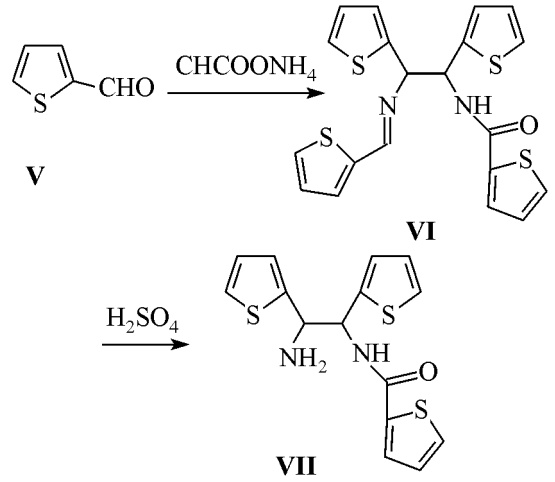


R = R' = H (**a**); R = 4-F, R' = H (**b**); R = 4-Br, R' = H (**c**); R = 3-Cl, R' = 4-Cl (**d**); R = 4-MeO, R' = H (**e**).

A possibility to perform the reaction yielding compound **IIa** under the action of microwave irradiation was further demonstrated by this single example [8]. Although the reaction was obviously attractive for its synthetic promise and easy performance it was not further investigated. The target of the present study is the extension of possibilities of this synthetic procedure.

We found that benzaldehyde (**Ia**) proper, and also *p*-fluorobenzaldehyde (**Ib**), *p*-bromobenzaldehyde (**Ic**), 3,4-dichlorobenzaldehyde (**Id**), and 4-methoxybenzaldehyde (**Ie**) at heating with ammonium acetate furnished the corresponding benzylidenebenzoyl derivatives **IIa–e**. The hydrolysis with sulfuric acid resulted in the *meso*-diamines **IVa–c**. In each case the hydrolysis can be stopped at the stage of monobenzoyl derivatives **IIIa–e**; this is very important because therefore a formation of intermediates is ensured already having benzoyl protection of one amino group.

It was reported in [2] by the example of anisaldehyde that the donor substituents in the aromatic



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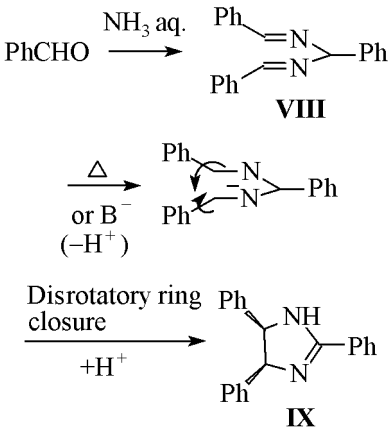
ring prevented formation of compound of type **II** in reaction with ammonium acetate. It was assumed from this result that this reaction was impossible with aldehydes having donor substituents in the aromatic ring. However we demonstrated that the anisaldehyde reacted with ammonium acetate to yield compound **IIe** but it took more time. A similar reaction sequence was also performed with 2-thiophenecarbaldehyde (**V**) (compounds **V** → **VI** → **VII**).

Thus the reaction of aromatic aldehydes with ammonium acetate can be used to synthesize symmetrical vicinal diamines and simple derivatives thereof.

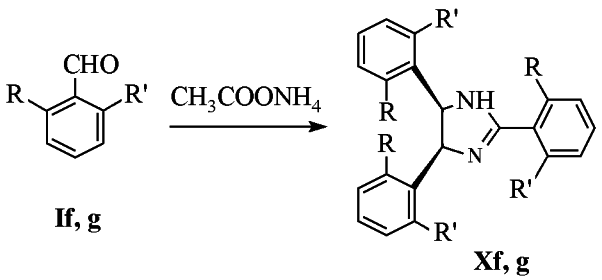
It is known that the reaction between aromatic aldehydes and ammonia provides hydrobenzamide **VIII** that in its turn can transform into amarine **IX** [6].



The mechanism of reaction we were studying apparently should also involve intermediate formation of compounds of **VIII** and **IX** types, and thus ammonium acetate should be a source of ammonia. To prove this assumption we added to the reaction mixture of ammonium acetate with a little benzaldehyde[**] the compounds that may arise in the intermediate stages, namely, hydrobenzamide (**VIII**) and amarine **IX** prepared by independent procedure. Therewith in both cases we obtained benzylidenebenzoyl derivative **IIa** in good yield.

However an attempt to prepare the corresponding *threo*-derivative **II** by reaction of *trans*-2,4,5-triphenylimidazoline with ammonium acetate and equimolar amount of benzaldehyde was unsuccessful. After three days of maintaining the reaction mixture the unreacted initial compound and a small amount of erythro-product **II** originating from benzaldehyde used were isolated.

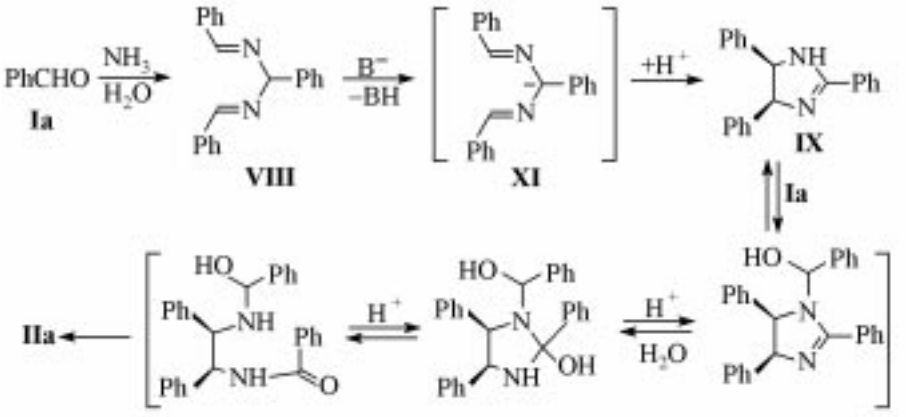
We also found that *ortho*-substituted benzaldehydes, namely, 2-nitro- (**If**) and 2,6-dichlorobenzaldehyde (**Ig**) react with ammonium acetate under the same conditions furnishing the corresponding *cis*-2,4,5-triaryl-4,5-dihydroimidazolines **X**.



R = NO_2, R' = H (**f**); R = R' = Cl (**g**).

The *cis*-configuration of the aryl substituents in compound **Xg** was proved by X-ray diffraction study (Fig. 1).[***]

This result suggests that the reaction between aldehydes and ammonium acetate initially follows the



[**] The X-ray diffraction analysis has been carried out by K. A. Potekhin (Vladimir State Pedagogical University) and will be completely published elsewhere.

[***] To preserve the stoichiometry of the process requiring four benaldehyde molecules.

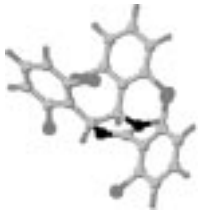


Fig. 1. Structure of compound **Xg** according to the X-ray diffraction analysis.

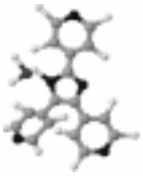


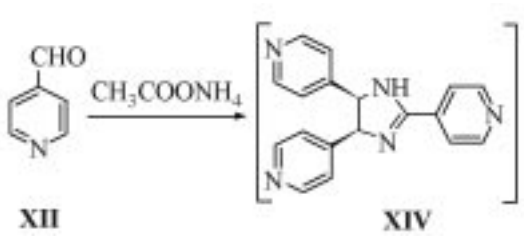
Fig. 2. Structure of compound **XIII** according to the X-ray diffraction analysis.

scheme similar to that previously assumed [6] for the reaction of aldehydes with ammonia solutions.

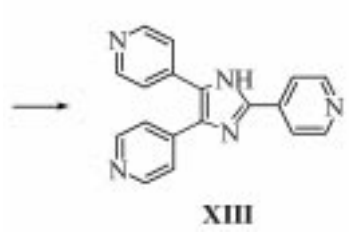
In the first stage formed hydrobenzamide **VIII** that under the base action was converted into anion **XI**. The latter underwent a stereospecific disrotatory ring closure resulting in *cis*-triphenylimidazoline **IX**. The compound further reacted with benzaldehyde and through a series of intermediates formed benzylidenebenzoyl derivative **IIa**.

The presence of *ortho*-substituents hampers the subsequent reaction of 2,4,5-triaryl-4,5-dihydroimidazole of **IX** type with a new aldehyde molecule, and the reaction stops at this stage (see the above conversion of 2,6-dichlorobenzaldehyde into *cis*-2,4,5-triaryl-4,5-dihydroimidazoles). An uncommon result was also obtained in reaction of ammonium acetate with 4-pyridinecarbaldehyde **XII**. The main reaction product was the corresponding 2,4,5-tris(4-pyridinyl)imidazole **XIII** crystallized as a hydrate as was confirmed by X-ray diffraction study (Fig. 2).

In this case the prevailing process was oxidation of dihydroimidazole **XIV** into imidazole **XIII** (apparently with the air oxygen) and not the opening of the five-membered ring in keeping with the above-described general scheme of the reaction:



XII **XIV**



XIII

Thus we demonstrated that the reaction with ammonium acetate of aromatic aldehydes, especially those containing electron-withdrawing substituents, was a convenient and simple preparation procedure for vicinal 1,2-diaryldiamines and their derivatives. Amine fragments in the reaction product obtained are differently substituted, providing a possibility to selective deprotection of one of amino groups in order to carry out further modification of the other one. Besides convenient approach to the synthesis of difficultly accessible 2,4,5-triaryl-substituted imidazolines was developed.

EXPERIMENTAL

IR spectra of compounds under investigation were recorded on spectrphotometer Specord UR-20 from solutions in chloroform in thin film or from mulls in mineral oil. ^{1}H and ^{13}C NMR spectra were registered on spectrometers Bruker AC-300 and Bruker AC-200. The chemical shifts are listed in δ scale measured from the signal of the corresponding solvent or from TMS as internal reference.

General procedure for the synthesis of 1,2-diaryl-*N*-arylmethylene-*N*'-aroyl-1,2-diaminoethanes IIa–e. The mixture of aldehyde and ammonium acetate was heated to 120°C and stirred at this temperature for 3 h. The reaction mixture was cooled, the precipitate was filtered off, and washed with water, 5% solution of NaOH, and hot alcohol. A sample for analysis was recrystallized from 95% ethanol.

1,2-Diphenyl-*N*-phenylmethylene-*N*'-benzoyl-1,2-diaminoethane IIa. From 41.2 g (0.38 mol) of benzaldehyde and 83 g (1.08 mol) of ammonium acetate was prepared 25 g (65%) of compound **IIa**, mp 257°C. IR spectrum, cm^{-1}: 3400 (NH), 2900–3100, 1640 (doublet). ^{1}H NMR spectrum (DMSO-d_6): 4.8 d (1H, CH–N=), 5.65 t (1H, CH–NHCO) 7.05–7.7 m (20H, C_6H_5), 8.0 s (1H, CH=N), 8.8 d. (1H, NH). Found, %: C 83.01; H 5.91; N 6.72. $C_{28}H_{24}N_2O$. Calculated %: 83.14; H 5.98; N 6.93.

1,2-Di(4-fluorophenyl)-*N*-(4-fluorophenyl)-methylene-*N*'-(4-fluorobenzoyl)-1,2-diaminoethane

(IIb). From 5 g (0.04 mol) of 4-fluorobenzaldehyde (**Ib**) and 10 g (0.13 mol) of ammonium acetate we obtained 4.2 g (89%) of compound **IIb**, mp 240–242°C. ^{1}H NMR spectrum (DMSO-d_6): 4.75 d (1H, CH–N=), 5.55 t (1H, CH–NHCO), 6.9–7.15 m (8H, C_6H_4F), 7.45 t (2.5H, C_6H_4F), 7.55 t (2.5H, C_6H_4F), 7.7 q (3H, C_6H_4F), 8.0 s (1H, CH=N), 8.65 d (1H, NH). Found, %: C 70.57; H 4.23; N 5.90. $C_{28}H_{20}F_4N_2O$. Calculated, %: C 70.58; H 4.23; N 5.88.

1,2-Di(4-bromophenyl)-*N*-(4-bromophenyl)-methylene-*N*′-(4-bromobenzoyl)-1,2-diaminoethane IIc. From 10 g (0.054 mol) of 4-bromobenzaldehyde (**Ic**) and 13 g (0.168 mol) of ammonium acetate we obtained 7 g (72%) of compound **IIc**, mp 265°C. ^{1}H NMR spectrum (DMSOd_6)): 4.35 d (1H, CH–N=), 5.15 t (1H, CH–NHCO), 7.35–7.7 m (16H, C_6H_4Br), 8.0 s (1H, CH=N), 8.7 d (1H, NH). Found, %: C 46.78; H 2.83; N 3.98. $C_{28}H_{20}Br_4N_2O$. Calculated, %: C 46.70; H 2.80; N 3.89.

1,2-Di(3,4-dichlorophenyl)-*N*-(3,4-dichlorophenyl)methylene-*N*′-(3,4-dichlorobenzoyl)-1,2-diaminoethane (IId). From 3.2 g (0.018 mol) of 3,4-dichlorobenzaldehyde (**Id**) and 8 g (0.108 mol) of ammonium acetate we obtained 1.7 g (53%) of compound **IId**, mp 248–250°C. ^{1}H NMR spectrum (DMSO-d_6)): 4.8 d (1H, CH–N=), 5.55 t (1H, CH–NHCO), 7.3–7.55 m (4.5H, $C_6H_3Cl_2$), 7.56–7.65 m (4H, $C_6H_3Cl_2$), 7.75 s (2H, $C_6H_3Cl_2$), 7.85 s (2H, $C_6H_3Cl_2$), 8,1 s (1H,CH=N), 8.9 d (1H, NH). Found, %: C 49.48; H 2.38; N 4.20. $C_{28}H_{16}Cl_8N_2O$. Calculated, %: C 49.45; H 2.37; N 4.12.

1,2-Di(4-methoxyphenyl)-*N*-(4-methoxyphenyl)-methylene-*N*′-(4-methoxybenzoyl)-1,2-diaminoethane IIe. From 7 g (0.013 mol) of 4-methoxybenzaldehyde **Ie** and 13 g (0.168 mol) of ammonium acetate we obtained within 24 h 2.9 g (22%) of compound **IIe**, mp 218°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4: 3.69 s (3H, OMe), 3.70 s (3H, OMe), 3.8 s (6H, OMe), 4.66 d (1H, CH–N=), 5.45 t (1H, CH–NHCO), 6.7–6.9 m (8H, C_6H_4OMe), 7,35 d (2H, C_6H_4OMe), 7.45 d (2H, C_6H_4OMe), 7.55 d (2H, C_6H_4OMe), 7.65 d (2H, C_6H_4OMe), 7.9 s (1H, CH=N), 8.19 d (1H, NH). Found, %: C 73.30; H 5.99; N 5.28. $C_{32}H_{32}N_2O_5$. Calculated, %: C 73.26; H 6.15; N 5.34.

1,2-Di(2-thienyl)-*N*-(2-thienylmethylene)-*N*′-(2-thenoyl)-1,2-diaminoethane (VI). From 5 g (0.05 mol) of 2-thiophenecarbaldehyde (**V**) and 10 g (0.13 mol) of ammonium acetate we obtained 3.1 g (58%) of compound **VIc**, mp 207°C. IR spectrum, cm^{-1}: 3400 (NH), 2900–3100, 1640 (doublet). ^{1}H NMR spectrum (DMSO-d_6): 5.1 d (1H, CH–N=), 5.65 t (1H, CH–NHCO), 6.9 m (2H, C_4H_3S), 7.1 m (4H, C_4H_3S), 7.3–7.45 m (3H, C_4H_3S), 7.65–7.8 m (3H, C_4H_3S), 8.35 s (1H, CH=N), 9.0 d (1H, NH). Found, %: C 56.18; H 3.73; N 6.35. $C_{20}H_{16}N_2OS_4$. Calculated,%: C 56.05; H 3.76; N 6.54.

General procedure for hydrolysis of 1,2-diaryl-*N*-arylmethylene-*N*′-aroyl-1,2-diaminoethanes IIa–e. Compound **II** was boiled with 60–75% sulfuric acid, the reaction mixture was cooled, the precipitate of monoaroylamine **III** was filtered off, washed with water and 5% solution of NaOH, and recrystallized from ethanol. Initial compound that did not dissolve in hot alcohol could be repeatedly hydrolyzed. Alkalizing the filtrate to strongly alkaline reaction we separated *meso*-1,2-diaryl-1,2-ethylenediamines **IV**. The relative yield of aroyl derivative **III** and diamine **IV** is controlled by sulfuric acid concentration and by time of boiling. The definite conditions are given separately for each compound. The prevailing diamine formation is seen from nearly complete dissolution of the precipitate.

***N*-Benzoyl-*meso*-1,2-diphenyl-1,2-diaminoethane (IIIa).** From 25 g (0.061 mol) of compound **IIa**, 55 ml of concn. H_2SO_4, and 200 ml of water after boiling for 12 h we obtained 12 g (63%) of compound **IIIa**, mp 204°C. IR spectrum, cm^{-1}: 3400 (NH), 2900–3100, 1640. ^{1}H NMR spectrum (DMSO-d_6–CCl_4): 4.55 d (1H, CH–NH_2), 5.45 t (1H, CH–NHCO), 7.05–7.7 m (15H,C_6H_5), 8.5 d (1H, NHCO). Found, %: C 79.68; H 6.21; N 8.79. $C_{22}H_{20}N_2O$. Calculated, %: C 79.72; H 6.37; N 8.85.

On alkalizing the filtrate to strongly alkaline reaction 1.2 g of *meso*-1,2-diphenyl-1,2-ethylenediamine (**IVa**) was separated.

***meso*-1,2-Diphenyl-1,2-diaminoethane IVa.** From 25 g (0.061 mol) of compound **IIa**, 65 ml of concn. H_2SO_4, and 200 ml of water after boiling for 24 h we isolated 1.3 g of compound **IIIa** and on alkalizing the reaction mixture 7 g (85%) of diamine **IVa**, mp 123°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4): 3.95 s, (2H, CH), 7.15–7.3 m (10H, C_6H_5). Found, %: C 79.12; H 7.85; N 12.92. $C_{14}H_{16}N_2$. Calculated,%: C 79.21; H 7.60; N 13.20.

***N*-(4-Bromobenzoyl)-*meso*-1,2-di(4-bromophenyl)-1,2-diaminoethane IIIc.** From 7 g (0.061 mol) of compound **IIc**, 33 ml of concn. H_2SO_4, and 100 ml of water after boiling for 24 h we obtained 3 g (56%) of compound **IIIc**, mp 201°C.

^{1}H NMR spectrum (DMSO-d_6–CCl4): 4.50 d (1H, CH–NH_2), 5.35 t (1H, CH–NH), 7.35– 7.65 d.d (12H, C_6H_4Br), 8.65 d (1H, NHCO). Found, %: C 45.58; H 3.08; N 4.95. $C_{21}H_{17}Br_3N_2O$. Calculated, %: C 45.60; H 3.10; N 5.06.

On alkalizing the filtrate to strongly alkaline reaction 0.2 g of *meso*-1,2-di(4-bromophenyl)-1,2-diaminoethane (**IVc**), mp 123–124°C, was separated.

***N*-(4-Methoxybenzoyl)-*meso*-1,2-di(4-methoxyphenyl)-1,2-diaminoethane IIIe.** From 0.9 g (1.7 mmol) of compound **IIe**, 3 ml of concn. H_2SO_4, and 12 ml of water after boiling for 24 h we obtained 0.4 g (0.98 mmol) of diaminoethane **IIIe** (58%), mp 192°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4): 3.71 s (3H, OMe), 3.76 s (3H, OMe), 3.82 s (3H, OMe), 4.23 d (1H, CH–NH_2), 4.55 t (1H, CH–N=), 6.75–6.9 m (6H, C_6H_4OMe), 7.3 d (4H, C_6H_4OMe), 7.55 d (2H, C_6H_4OMe), 8.1 d (1H, NH). Found, %: C 70.91; H 6.43; N 6.83. $C_{24}H_{26}N_2O_4$. Calculated, %: C 70.92; H 6.45; N 6.89.

***N*-Thenoyl-*meso*-1,2-di(2-thienyl)-1,2-diaminoethane VII.** From 3.1 g (0.0072 mol) of compound **VI**, 10 ml of concn. H_2SO_4, and 100 ml of water after boiling for 12 h we obtained 1.4 g (58%) of thenoyldiaminoethane **VII**, mp 137–149°C. ^{1}H NMR spectrum (DMSO-d_6–CCl4): 4.75 d (1H, CH–NH_2), 5.45 t (1H, CH–NHCO), 6.9–7.05 m (2H, C_4H_3S), 7.05–7.2 m (3H, C_4H_3S), 7.35–7.5 m (2H, C_4H_3S), 7.65–7.8 m (2H, C_4H_3S), 8.85 d (1H, NH). Found, %: C 53.91; H 4.25; N 8.40. $C_{15}H_{14}N_2S_3O$. Calculated,%: C 53.86; H 4.22; N 8.38.

2,4,5-Tris(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazole Xg. A mixture of 4.7 g (0.027 mol) of 2,6-dichlorobenzaldehyde and 8 g (0.10 mol) of ammonium acetate was heated to 120°C with stirring for 3 h. The reaction mixture was cooled, the precipitate was filtered off, washed with water, 5% solution of NaOH, and recrystallized from ethanol. Yield 2.72 g (60%), mp 138–143°C. ^{1}H NMR spectrum (DMSO-d_6): 6.05 br. s (1H, CH), 6.45 br.s (1H, CH), 7.05–7.2 m (5.5 H, $C_6H_3Cl_2$), 7.43–7.6 m (3.5H, $C_6H_3Cl_2$), 8.5 d (1H, NH). Found, %: C 50.06; H 3.60; N 4.64. $C_{21}H_{12}Cl_6N_2$. Calculated, %: C 49.94; H 2.39; N 5.55.

2,4,5-Tris(2-nitrophenyl)-4,5-dihydro-1*H*-imidazole Xf. A mixture of 1.5 g (0.01 mol) of 2-nitrobenzaldehyde and 3 g (0.039 mol) of ammonium acetate was heated to 120°C with stirring for 3 h. The reaction mixture was cooled, the precipitate was filtered off, washed with water, 5% solution of NaOH, and recrystallized from ethanol. Yield 0.71 g (50%), mp 244–246°C. ^{1}H NMR spectrum (DMSO-d_6): 5.98 d (1H, CH), 6.18 d (1H, CH), 7.25–7.56 m (6H, $C_6H_4NO_2$), 7.65 d (1H, $C_6H_4NO_2$), 7.73 d (1H, $C_6H_4NO_2$), 7.8 d (1H, $C_6H_4NO_2$), 7.88 t (1H, $C_6H_4NO_2$), 8.0 d (1H, $C_6H_4NO_2$), 8.5 d (1H, $C_6H_4NO_2$) 8.3 s (1H, NH). Found,%: C 58.26; H 3.39; N 16.42. $C_{21}H_{15}N_5O_6$. Calculated,%: C 58.20; H 3.49; N 16.16.

2,4,5-Tris(4-pyridinyl)-imidazole XIII. A mixture of 2 g (0.018 mol) of 4-pyridinecarbaldehyde **XII** and 8 g (0.1 mol) of ammonium acetate was heated to 120°C with stirring for 3 h. The reaction mixture was cooled, the precipitate was filtered off, washed with water, 5% solution of NaOH, and recrystallized from ethanol. Yield 1.2 g (67%), mp 333°C (the compound crystallized as monohydrate). ^{1}H NMR spectrum (DMSO-d_6): 7.5 s (4H, C_5H_4N), 8.0 s (2H, C_5H_4N), 8.6 d (5,5H, C_5H_4N), 13.2 br. s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6): 120 (C^4 of imidazole ring), 122.9 (C^5 of imidazole ring), 136.8 (C^2 of imidazole ring), 145.1 (C_5H_4N), 149.9 (C_5H_4N), 150 (C_5H_4N), 163.8 (C_5H_4N). Found, %: C 68.28; H 4.83; N 23.12. $C_{18}H_{13}N_5 \cdot H_2O$. Calculated,%: C 68.13; H 4.76; N 22.07.

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