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Formation, Structure and Heterocyclization of Aminoguanidine and Ethyl Acetoacetate Condensation Products

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Abstract—Condensation of aminoguanidine hydrochloride and ethyl acetoacetate results in 2,3-diamino-6-methylpyrimidin-4(3*H*)-one, 5-hydroxy-1-carboxamidino-3-methylpyrazole or ethyl *N*-[(5-hydroxy-3-methylpyrazol-1-yl)imidoyl]aminocrotonoate depending on the type of the base. Formation of pyrazole derivatives occurs in the case of dequaternized substrate imine-group protonating by the acids formed as a result of ion exchange reaction. Chelate fragment of amidinohydroxypyrazole structure provides stabilization of this compound and stipulates its inertness towared the heterocycle closure.

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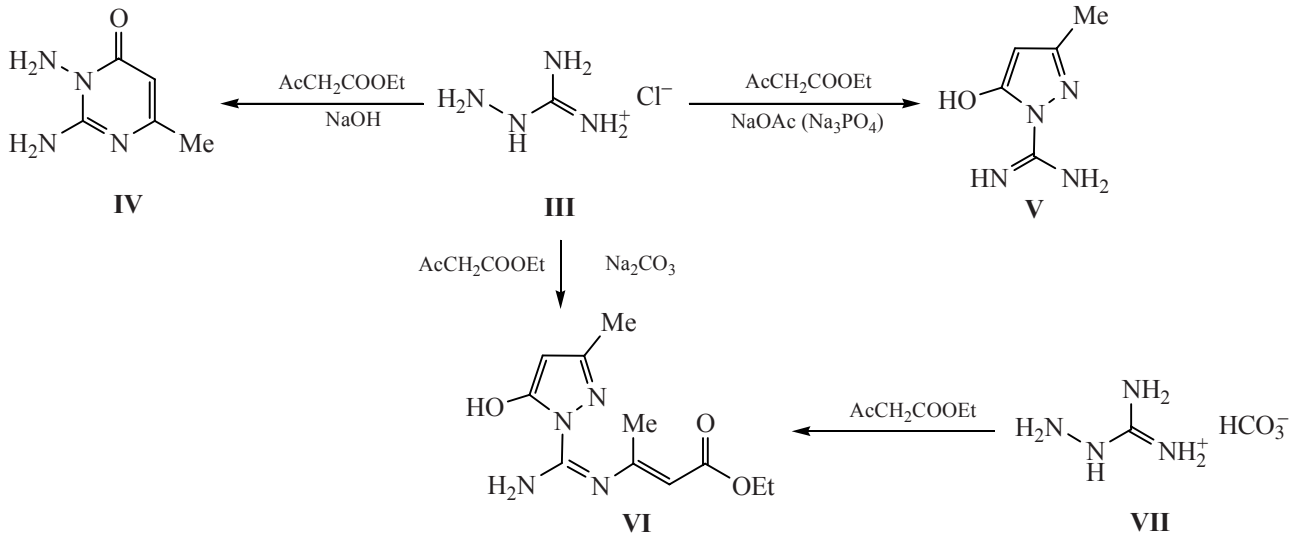
Condensation of aminoguanidine and β-ketocarboxylates as bifunctional reagents gives rise to 2,3-diaminopyrimidin-4(3*H*)-ones (**I**) and 1-carboxamidinopyrazol-5(4*H*)-ones (**II**) mainly. Reaction of aminoguanidine salts with β-ketocarboxylates in the presence of organic base yields diaminopyridines **I** [1] and in the absence of neutralizing agent forms amidinopyrazolones **II** [2, 3].

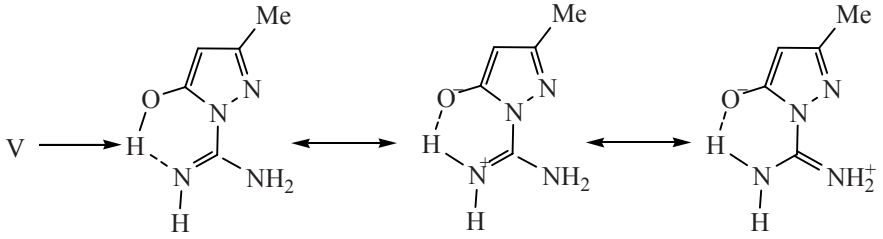
The aim of this work is to establish the direction of the condensation of aminoguanidine hydrochloride **III** with ethyl acetoacetate in the water–alkali solutions and to study heterocyclization of the products formed.

The studied reaction direction is appreciably determined by the base reagent type. 2,3-Diamino-6-methylpyrimidin-4(3*H*)-one **IV** is formed as a result of the subsequent action of sodium hydroxide and ethyl acetoacetate on the compound **III**. The structure of diamine **IV** obtained is confirmed by ^{1}H NMR spectrum, where signals of the exocyclic amino group protons are observed at 5.2 and 6.9 ppm. The IR and



UV spectra analysis of compound **IV** allows to exclude alternative structure of 1,2-diamino-6-methylpyrimidin-4-(1*H*)-one from the consideration. In the IR spectrum there is intensive absorption band at 1679 cm^{-1} belonging to the carbonyl group stretching vibrations and characteristic of aminopyrimidines having 4-oxo-3,4-dihydro-configuration [4]. The UV spectrum contains the absorption bands with the maxima at 222 (log ε = 3.89) and 280 (log ε = 3.99) nm, which are close by location and intensity with the absorption bands of 2-amino-3-methylpyrimidin-4(3*H*)-one [5].

When sodium hydroxide is replaced by the less strong base sodium acetate (pathway *a*), other condensation product, 5-hydroxy-1-carboxamidino-3-methylpyrazole **V**, is formed. The latter is identified by the presence of the imino group proton singlet at 4.4 ppm in the ^{1}H NMR spectrum. The absence of the methylene protons signals and the appearance of a broad singlet at 7.7 ppm with integral intensity corresponding to four protons indicate that the compound **V** exists predominantly in the lactime form **Va** with an intramolecular hydrogen bond. This is confirmed by its IR spectrum, which is characterized by the presence of broad overlapped intensive absorption bands with maxima at 3237 and 2967 cm^{-1} belonging to stretching vibrations of the bonded amino (imino) and hydroxyl groups. In the spectrum the low intensity absorption band partially masked by these bands was also observed at 2738 cm^{-1}. Appearance of the two latter bands, which are absent in the spectrum of amidine **V** sodium salt, is conditioned by the strong association of hydroxyl group proton with π- and *n*-electrons of the imino group nitrogen atom. It leads to the electron density redistribution in the initial molecule and to formation of resonance structures **Vb** and **Vc** hybrid.



Intramolecular hydrogen bond provides the amidine **V** structure stabilization. Similar conclusion follows from comparison of the UV spectra of compound **V** neutral (pH 7) and anionic (pH 12) forms. In these spectra, apart from coincidence of the absorption bands with maximum at 227 nm, occur hypsochromic shifts of the long-wave absorption band maximum of nonionized form, corresponding to the process of charge transfer, and the accompanying its low hyperchromic effect (Δε ~500) on increasing of medium pH (Fig. 1).

Change in direction of the reaction of hydrochloride **III** with ethyl acetoacetate in the presence of sodium acetate to amidine **V** formation forces us to suppose that acetic acid (pK_a 4.75), obtaining as a result of ion exchange, protonates the more basic imino group of substrate dequaternizated *in situ* and thus it prevents reaction involving this reaction centre. The proof of this is obtaining of compound **V** at the sequential reaction of hydrochloride **III** with sodium phosphate and ethyl acetoacetate (pathway *b*), which results in the appearance of phosphoric acid (pK_a 2.12) in the reaction mixture. Phosphoric acid is a more pronounced proton-donor than acetic acid.

At the treatment of hydrochloride **III** with sodium carbonate (pathway *a*), the unexpected direction of condensation of **III** and ethyl acetoacetate is realized. In this case the amidine **V** functional derivative, ethyl

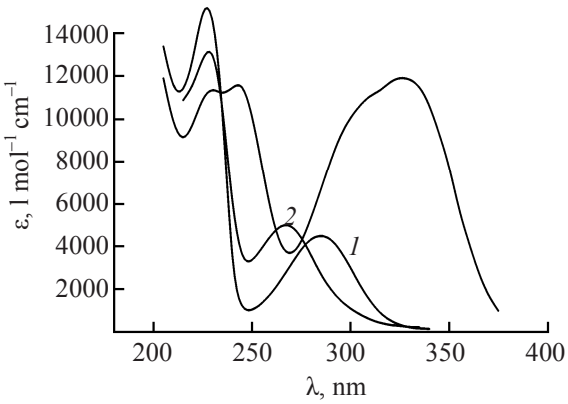
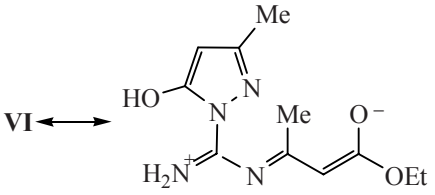


Fig. 1. UV spectra of (*1*) neutral and (*2*) anionic forms of amidine **V** and ethyl crotonoate **VI**.

3-[(5-hydroxy-3-methylpyrazol-1-yl)imidoyl]aminocrotonoate **VI** is formed. In the ^{1}H NMR spectra of the latter is absent a singlet of imino group proton at 4.4 ppm, but there are signals of ester group protons at 1.2 and 4.0 ppm and also singlet of exocyclic methyne group protons at 6.2 ppm. The IR spectrum contains a low-frequency shift at 1672 cm^{-1} originating from stretching vibrations of the carbonyl group. It is anomalous for aliphatic unsaturated acids and their esters [7], but it is inherent in the structurally close ethyl 3-(5-hydroxypyrazol-4-yl)-3-methyl-2-propenoate [8]. From this fact one can conclude that the resonance component **VIa** brings some contribution into the electron structure of ethyl crotonoate **VI**.

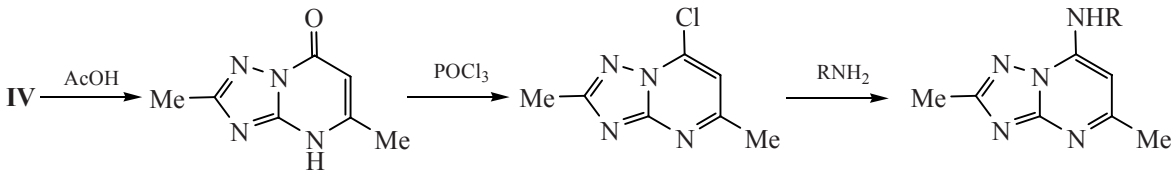


VIa

The unsaturated character of ethyl crotonate **VI** is illustrated by absorption bands at 325 nm in the UV spectrum. The heterocycle lactime form involving into the general conjugation system is proved by the presence in this spectrum of a broad band of $\pi \rightarrow \pi^*$ transition with the maxima at 230 and 242 nm, which un-dergoes bathochromic shifting relative to the analogous band in the spectrum of amidine **V** (Fig. 1).

Ethyl crotonoate **VI** formation becomes explainable, if we take into account the hydrochloride **III** tendency of decomposing in the presence of sodium carbonate [9]. Owing to this, the amount of free aminoguanidine undergoing further protonation with carbon acid involving imino group decrease considerably. Therefore excess of ethyl acetoacetate arises in the reaction mixture. Carbon dioxide dilutetd in water is transformed partially into carboxylic acid [10], which couples with aminoguanididne to form aminoguanidine carbonate **VII**. The latter reacts sequentially with ketoester excess resulting in ethyl crotonoate **VI**. In order to confirm this hypothesis we carried out condensation of carbonate **VII** and ethyl acetoacetate in the molar ratio 1:2 (pathway *b*) and obtain product similar by physico-chemical characteristics to compound **VI** obtained by way *a*.

Compound **IV** undergoes heterocyclization by reaction with the lower carboxylic acids. We established that formation of 2,5-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine **VIII** occurs actually on heating of diamine **IV** with excess of acetic acid. This reaction requires longer contact of reagents in comparison with the outlined in literature [11]. The reaction time decrease results in the incomplete conversion of compound **IV**. Therefore the target product **VIII** is impossible to isolate from the unreacted diamine **IV** admixture even by the repeated crystallization. In the ^{1}H NMR spectrum of bicycle **VIII** there are signals of methyl group protons in the region 2.3 ppm as well as a signal of one of the ring imine centers near 13 ppm. The correctness of description of compound **VIII** structure by the respective formula is dictated by the work [12] attesting its stabilization through proton localization on the atom N^4 of the annelated system.



VIII **IX** **Xa, Xb**

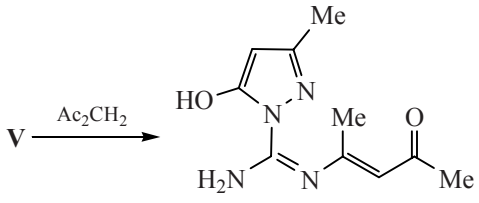
R = $PhCH_2$ (**a**), 4-MeC_6H_4 (**b**).

The exchange chlorination of bicycle **VIII** with phosphorus oxotrichloride results in 2,5-dimethyl-7-chloro[1,2,4]triazolo[1,5-*a*]pyrimidine **IX**. We emphasize that the crystallization of chloride **IX** from chloroform by procedure [13] fails to realize due to high product solubility in this solvent. Replacing chloroform by cyclohexanone, we obtain compound **IX** with the yield 33% only. We attained the almost twofold increase in chloride **IX** yield by the continual extraction of the uncrystallized product with minimal amount of solvent in the Soxhlet apparatus.

The compound **IX** have a halogen atom capable of substitution with amino-group. Its reaction with the

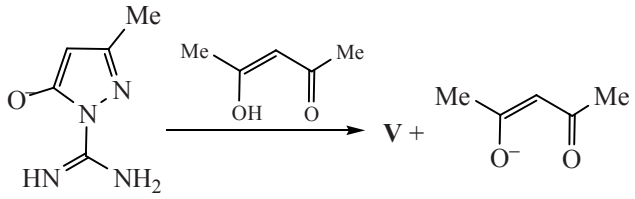
equimolar amounts of some aralkyl- and arylamines under rigid conditions produces 7-amino-2,5-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidines hydrochlorides **Xa** and **Xb**. The latter compounds transform into the free bases by workup with aqueous ammonia solution. The ^{1}H NMR spectra of aminotriazolopyrimidines **Xa** and **Xb** contain signals of the aromatic fragments protons at 7 ppm and signals of the second amino group in the region of 8–10 ppm.

The amidine chelate structure determines its inertness toward heterocycle closure. We could not obtain 5-hydroxy-3-methyl-1-[*N*-(4-oxopent-2-en-2-yl) carboxamidino]pyrazole **XI** or 2-(5-hydroxy-3-methylpyrazol-1-yl)-4,6-dimethylpyrimidine by heating of substrate **V** with 2,4-pentadione under various conditions: in toluene using a water separator or in the presence of phosphorus pentaoxide as dehydrating agent. In the first case the initial compound **V** regenerated, and in the second the reaction mixture tarring occurs. Oxopentene **XI** is formed only at reflux of amidine with the diketone excess. In the ^{1}H NMR spectrum of compound **XI** there are singlets of methyl groups in the region 2.0–2.5 ppm and of exocyclic fragment methyne group at 6.7 ppm. The UV spectrm contains high-intensive absorption band with the maximum at 367 nm (log ε = 4.19) belonging to electron transitions in the conjugatied bond system involving heterocycle.



XI

The low yield of oxopentene **XI** is indicative of high strength of the intramolecular hydrogen bond in amidine **V**. To prevent chelation influence on the reactivity of the amidine group in this compound, we carried out reaction of amidine **V** sodium salt with 2,4-pentanedione in absolute ethanol. This allows to localize anionic center on the oxygen atom through hydrogen bonds formation and thus to exclude imine group from potential process of proton transfer. In spite of the reasonable choice of solvent the similar pathway of heterocycle closure also did not give rise to the expected result: we isolated compound **V** from the reaction mixture not undergone preliminary neutralization. This circumstance attests clearly the deprotonation of diketone molecule with amidine **V** anion acting as a base.



Just diketone serves as a proton source since the compound **V** sodium salt is the only product chromatographically detected under conditions of its producing by addition of substrate to solution of sodium ethoxide in absolute ethanol.

EXPERIMENTAL

The ^{1}H NMR spectra were registered on a Bruker WM-400 spectrometer (400.13 MHz) in DMSO-d_6 relatively to the signals of residual DMSO protons as internal reference. The IR spectra were taken on a Shimadzu FTIR-8400S spectrophotometer from KBr pellets. The UV spectra were recorded on a SF-26 spectrophotometer at the substances concentration ~1×10^{-4} M in water except for the spectrum of **XI** registered in ethanol. The individuality of compound obtained was monitored by TLC method on Silufol UV-254 plates in the systems 1-butanol–acetic acid–water, 1:1:1 (A), 2-propanol–25% aqueous ammonia, 3:1 (B), acetone–heptane, 3:1 (C) and 2-propanol–25% aqueous ammonia, 3:2 (D); UV detection. The elemental analysis was performed on a Leco CHNS-932 analyser.

2,3-Diamino-6-methylpyrimidine-4(3*H*)-one (IV). To a solution of 11.05 g of hydrochloride **III** in 40 ml of water were sequentially added dropwise a solution of 4 g of sodium hydrochloride in 10 ml of water and 13 g of ethyl acetoacetate in 15 ml of ethanol, under vigorous stirring. The mixture was stirred for 3 h; then precipitate was filtered off, washed with water, recrystalled from water and dried at 80°C during 8 h. Yield 3 g (21%), mp 280°C (decomp.) (published data: mp 283–285°C [1], 283°C [11]), R_f 0.50 (A). ^{1}H NMR spectrum, δ, ppm: 1.99 s (3H, Me), 5.24 s (2H, NH_2), 5.48 s (1H, CH), 6.96 br.s (2H, NH_2).

5-Hydroxy-1-carboxamidino-3-methylpyrazole (V). *a*. To a solution of 5.53 g of hydrochloride **III** in 25 ml of water was sequentially added 4.1 g of sodium acetate, and then dropwise added 6.5 g of ethyl acetoacetate under vigorous stirring. The mixture was

stirred for 3 h and kept for 15 h at room temperature. The precipitate formed was filtered off, washed with water, recrystalled from water and then from 50% ethanol and dried at 80°C for 8 h. Yield 2.35 g (34%), mp 235°C (decomp.) (published data: mp 235°C [2]), R_f 0.61 (B). ^{1}H NMR spectrum, δ, ppm: 1.95 s (3H, Me), 4.39 s (1H, NH), 7.69 br.s (4H, NH_2, CH, OH).

b. To a solution of 5.53 g of hydrochloride **III** in 25 ml of water were sequentially added 6.34 g of sodium phosphate and dropwise 6.5 g of ethyl acetoacetate, under vigorous stirring. The mixture was stirred for 3 h and kept for 15 h at room temperature. The precipitate formed was filtered off, washed with water, recrystalled from water and dried at 80°C for 8 h. Yield 2.34 g (34%).

Ethyl *N*-[(5-hydroxy-3-methylpyrazol-1-yl)imidoyl]aminocrotonoate (VI). *a*. A mixture of 5.53 g of hydrochloride **III** and 2.65 g of sodium carbonate was dissolved in 25 ml of water. To the filtered solution was dropwise added 6.5 g of ethyl acetoacetate at vigorous stirring. The reaction mixture was stirred for 2 h and kept for 3 days at room temperature. The precipitate formed was filtered off, recrystalled from 10% ethanol, and dried at 80°C for 8 h. Yield 1.52 g (12%), mp 180°C (decomp.) (published data: mp 180°C [2]), R_f 0.67 (B). ^{1}H NMR spectrum, δ, ppm: 1.19 t (3H, OCH_2*Me*), 2.22 s (3H, Me), 2.44 s (3H, Me), 3.99 q (2H, OCH_2Me), 6.22 s (1H, CH), 7.90 br.s (2H, NH_2), 8.86 br.s (2H, CH, OH).

b. To a suspension of 6.8 g of carbonate **VII** in 40 ml of water was dropwise added 13 g of ethyl acetoacetate ander vigorous stirring. The mixture was stirred for 2 h and kept at room temperature for 2 days. Then precipitate was separated and filtrate was kept to full crystallization of the oil released from them. The precipitate formed was filtered off, twice recrystalled from water and then from 30% ethanol and dried at 80°C for 8 h. Yield 0.4 g (3.2%).

2,5-Dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-7(4*H*)-one (VIII). A mixture of 1 g of diamine **IV** and 12 ml of glacial acetic acid was refluxed for 16 h. The precipitate formed was filtered off, recrystalled from nitromethane-DMFA (1:1) mixture, washed with diethyl ether and dried under vacuum. Yield 0.62 g (53%), mp > 280°C (decomp.) (literary data: mp 310–313°C [13]), R_f 0.70 (A). ^{1}H NMR spectrum, δ, ppm: 2.28 s (3H, Me), 2.33 s (3H, Me), 5.68 s (1H, CH), 12.93 br.s (1H, NH).

2,5-Dimethyl-7-chloro[1,2,4]triazolo[1,5-*a*]pyrimidine (IX). A mixture of 2.41 g of bicycle **VIII** and 15 ml of the freshly distilled phosphorus oxotrichloride was refluxed for 1 h. The excess of $POCl_3$ was distilled off in vacuum. To the reaction residue were added ground ice and then 25% aqueous ammonia to appearance of the stable alkalescent reaction. The precipitate formed was filtered off, washed with water and dried under vacuum over phosphorus pentaoxide. The dry product was extracted with 35 ml of cyclohexane and dried in vacuum. Yield 1.69 g (63%), mp 149°C (published data: mp 149–150°C [13]), R_f 0.59 (C). ^{1}H NMR spectrum, δ, ppm: 2.48 s (3H, Me), 2.61 s (3H, Me), 7.47 s (1H, CH).

7-Benzylamino-2,5-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine (Xa). A mixture of 0.5 g of chloride **IX** and 0.29 g benzylamine freshly distilled was refluxed at 130–140°C for 30 min. On cooling to room temperature, the caked reaction residue was mechanically crushed, suspended in 10 ml of water and alkalified with 25% aqueous ammonia to appearance of the stable alkaline reaction. After 30 min the precipitate was filtered off, washed with water and dried in vacuum over phosphorus pentaoxide. The dry product was crystalled from benzene and the suspension formed was diluted with equal volume of heptane to precipitating completeness. Yield 0.32 g (46%), mp 165°C, R_f 0.24 (C). ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, Me), 2.43 s (3H, Me), 4.55 d (2H, CH_2), 6.06 s (1H, CH), 7.32 m (5H, Ph), 8.61 t (1H, NH). Found, %: C 66.05; H 5.68; N 27.52. $C_{14}H_{15}N_5$. Calculated, %: C 66.38; H 5.97; N 27.65.

2,5-Dimethyl-7-(4-methylphenyl)amino[1,2,4]triazolo[1,5-*a*]pyrimidine (Xb). A mixture of 0.5 g of chloride **IX** and 0.293 g of 4-methylphenylamine was held at 130–140°C for 1 h. On cooling to room temperature, the caked reaction residue was mechanically crushed, suspended in 10 ml of water and alkalified with 25% aqueous ammonia to appearance of the stable alkaline reaction. The precipitate was filtered off, washed with water and dried in vacuum over phosphorus pentaoxide. The dry product was recrystalled from benzene:cyclohexene (3:7) mixture and dried under vacuum. Yield 0.29 g (42%), mp 160°C, R_f 0.22 (C). ^{1}H NMR spectrum, δ, ppm: 2.35 s (3H, Me), 2.37 s (3H, Me), 2.48 s (3H, Me), 6.19 s (1H, CH), 7.25 m (4H, Ar), 9.92 s (1H, NH). Found, %: C 66.12; H 5.81; N 27.47. $C_{14}H_{15}N_5$. Calculated, %: C 66.38; H 5.97; N 27.65.

5-Hydroxy-3-methyl-1-[*N*-(4-oxopent-2-en-2-yl)-carboxamidino]pyrazole (XI). A mixture of 0.6 g of amididne **V** and 5 ml of 2,4-pentandione was refluxed at 150–160°C to homogenizing. The excess of diketone was distilled off under vacuum, and the residue was crystalled by grinding with 5 ml of acetone. The precipitate formed was filtered off, washed with water and dried in vacuum over phosphorus pentaoxide. The dry product was recrystalled from acetonitrile and dried under vacuum over phosphorus pentaoxide. Yield 95 mg (10%), mp 156°C (comp.), R_f 0.68 (D). ^{1}H NMR spectrum, δ, ppm: 2.03 s (3H, Me), 2.24 s (3H, Me), 2.43 s (3H, Me), 6.73 s (1H, CH), 7.92 br.s (2H, NH_2), 8.84 br.s (2H, CH, OH). Found, %: C 53.45; H 5.81; N 24.72. $C_{10}H_{14}N_4O_2$. Calculated, %: C 54.04; H 6.35; N 25.21.

REFERENCES

1. Hlavka, J.J., Bitha, P., Yang-I Lin, and Strohmeyer, T., *J. Heterocyclic Chem*., 1984, vol. 21, no. 5, p. 1537.
2. Vystrčil, A., and Prokeš, R., *Chem. Listy*, 1952, vol. 46, no. 11, p. 670.
3. Japan Patent 7466686, 1974, *C.A*., 1975, vol. 82, P57727 q.
4. Short, L.N. and Thompson, H.W., *J. Chem. Soc*., 1952, no. 1, p. 168.
5. Brown, D.J. and Teitei, T., *Austral. J. Chem*., 1965, vol. 18, no. 4, p. 559.
6. Keiko, N.A., Mamashvili, T.N., Rassolova, G.V., Kashik, T.V., Kalikhman, I.D., and Voronkov, M.G., *Izv. Akad. Nauk SSSR Ser. Khim*., 1984, no. 3, p. 608.
7. Bellami, L., *Infrakrasnye spektry slozhnykh molekul* (Complex Molecules IR Spectra), Moscow: Inostrannaya Literatura, 1963, p. 590.
8. Evans, N.A., Whelan, D.J., and Johns, R.B., *Tetrahedron*, 1965, vol. 21, no. 12, p. 3351.
9. Lieber, E. and Smith, G.B.L., *Chem. Rev*., 1939, vol. 25, no. 2, p. 213.
10. Cotton, F.A. and Wilkinson, G., *Sovremennaya neorganicheskaya khimiya* (Advanced Inorganic Chemistry), Moscow: Mir, 1969, vol. 1, p. 223.
11. Tsuji, T. and Ueda, T., *Chem. Pharm. Bull*., 1971, vol. 19, no. 12, p. 2530.
12. Glier, C., Dietz, F., Scholz, M., and Fischer, G., *Tetrahedron*, 1972, vol. 28, no. 23, p. 5779.
13. Allen, C.F.H., Beilfuss, H.R., Burness, D.M., Reynolds, G.A., Tinker, J.F., and Van Allan, J.A., *J. Org. Chem*., 1959, vol. 24, no. 6, p. 793.