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Dedicated to Full Member of the Russian Academy of Sciences I. P. Beletskaya on occasion of her jubilee

Synthesis and Properties of *N*-Alkyl-6-hydroxy-5-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)-1*H*-pyrimidine-2,4-diones and Their 2-Thioanalogs

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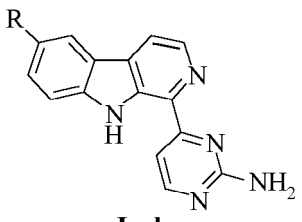
Abstract—Addition of N-substituted barbituric and 2-thiobarbituric acids to 3,4-dihydro-β-carboline results in formation of *N*-alkyl-6-hydroxy-5-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)-1*H*-pyrimidine-2,4-diones and their 2-thioanalogs, which are structural analogs of alkaloids from annomontin group. Acylation of 1,3-dimethyl-substituted adduct is accompanied by opening of the tetrahydropyridine ring furnishing *N*-{2-[2-(1,3-dimethyl-2,4,6-trioxotetrahydropyrimidin-5-ylidenomethyl)-1*H*-indol-3-yl]ethyl}acetamide. The structure of compounds synthesized was studied by means of ^{1}H NMR spectroscopy.

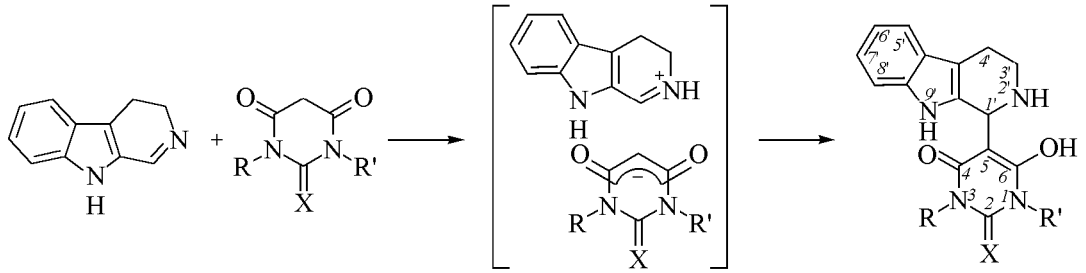
Development of new ways of chemical modification for β-carbolin compounds attracts a considerable interest due to the search for promising synthetic approach to preparation of various groups of substances of biogenic origin or analogs thereof [1]. In particular, introduction into the β-carboline fragment of a pyrimidine substituent also may provide is natural heterocyclic system. For instance, alkaloids annomontin (**Ia**) and its methoxy derivative (**Ib**) isolated from *Annona Montana* (the preparations obtained from the bark and shoots of this tree are known to be widely used in the traditional oriental medicine as sedative and tranquillizing drugs) are 1-(2-amino-4-pyrimidinyl)-β-carbolines [2].



Ia, b

R = H (**a**), R = OMe (**b**).

Synthesis of these unusual alkaloids described in [3] is fairly labor-consuming. Therefore the development of new approaches to the synthesis of such heterocyclic systems is undoubtedly interesting.



II **IIIa–h** **IVa–h**

R = Me (**a, d**), H (**b, c, d–h**); **R = Me (a, d)**, Bu (**b, e**), *p*-EtC6H4 (**c**), Et (**e**), *p*-EtOC6H4 (**g**), p–FC6H4 (**h**); X = O (**a–c**), S (**d–h**).

We report here on the investigation of direct introduction of a pyrimidine substituent into the β-carboline system based on reaction of 3,4-dihydro-β-carboline (**II**) with derivatives of perhydropyrimidine-

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Yields and elemental analyses of compounds **IVa**–**h**

Compd no.	X	R	R'	Yield, %	Found, %				Formula	Calculated, %			
					C	H	N	S		C	H	N	S
IVa	O	Me	Me	92	62.42	5.62	17.11	–	$C_{17}H_{18}N_4O_3$	62.57	5.56	17.17	–
IVb	O	H	Bu	78	64.15	6.33	15.70	–	$C_{19}H_{22}N_4O_3$	64.39	6.26	15.81	–
IVc	O	H	*p*-EtC_6H_4	84	68.79	5.57	13.85	–	$C_{23}H_{22}N_4O_3$	68.64	5.51	13.92	–
IVd	S	Me	Me	94	59.69	5.34	16.33	9.32	$C_{17}H_{18}N_4O_2S$	59.63	5.30	16.36	9.36
IVe	S	H	Et	88	59.44	5.25	16.24	9.30	$C_{17}H_{18}N_4O_2S$	59.63	5.30	16.36	9.36
IVf	S	H	Bu	88	61.52	5.90	15.10	8.54	$C_{19}H_{22}N_4O_2S$	61.60	5.99	15.12	8.65
IVg	S	H	*p*-$EtOC_6H_4$	85	63.55	5.19	12.68	7.31	$C_{23}H_{22}N_4O_3S$	63.28	5.10	12.89	7.38
IVh	S	H	p-FC_6H_4	87	61.51	4.16	13.62	7.80	$C_{21}H_{17}FN_4O_2S$	61.75	4.20	13.72	7.85

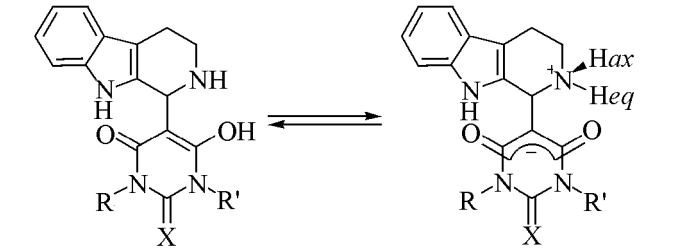
2,4,6-trione (barbituric acid) **IIIa–c** and with their 2-thioanalogs **IIId–g** that has not been previously described in the literature.

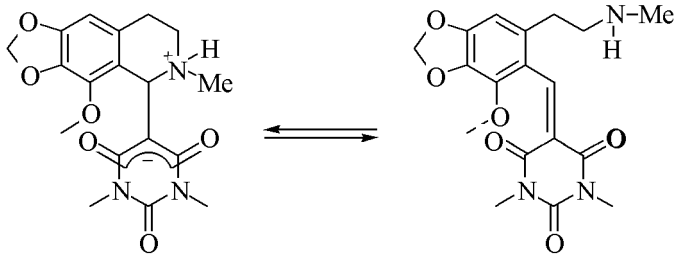
It was found that 3,4-dihydro-β-carboline (**II**) in alcoholic solution quickly reacted with 1,3-dimethylbarbituric acid (**IIIa**) affording in high yield (see table) a colorless crystalline substance, very poorly soluble in organic solvents save DMF and DMSO. The structure of the adduct obtained was unambiguously established from its ^{1}H NMR spectrum: It was 6-hydroxy-1,3-dimethyl-5-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)-1*H*-pyrimidine-2,4-dione (**IVa**).

Thus under the given conditions occurred addition of the nucleophilic carbon C^5 of acid **IIIa** to the electrophilic carbon atom of the C=N bond of compound **II**. The high rate of the process, untypical for barbituric acids which relatively reluctantly enter Michael addition reaction [4], may be rationalized by assuming that intermediately arises a salt or ion pair where the electrophilic and nucleophilic sites are brought together.

The observed reaction may be regarded as a special case of interaction between cyclic azomethines (e.g, dihydroisoquinoline and its analogs) and β-diketones leading to formation of labile C,C-adducts [5, 7] or salts [8]. Therewith unlike the systems described before compound **IVa** we obtained was stable in crystalline state (up to 200°C and higher), was subjected to chromatography on Silufol plates and did not suffer decomposition, and was not hydrolyzed in water solutions.

It is presumable that the properties of compound **IVa** and in particular its chemical stability are due to significant extent to its existence in a stable zwitter-ionic form **V**. The specific features of structure of the latter are worth special discussion.





Since in the structure of compound **IVa** are present simultaneously an acidic trioxopyrimidine fragment (pK_a of a free 1,3-dimethylbarbituric acid is 4.70 [9], and of a basic tetrahydropyridine moiety it should be expected that the equilibrium between the neutral **IVa** and zwitter-ionic **V** forms is considerably shifted to the latter. Actually, in the ^{1}H NMR spectrum in DMSO-d_6 are present signals from the protonated group $+NH_2$ (8.50 and 9.11 ppm, 1H + 1H) unambiguously evidencing the prevalence of form **V**. The appearance of two strongly differing in chemical shifts proton signals belonging to $+NH_2$ group may be explained by existence in the system **V** of a strong intramolecular hydrogen bond that ensures stable equatorial position for the proton of $+NH_2$ group coordinated to O^6 oxygen while the second proton is located in an axial position.

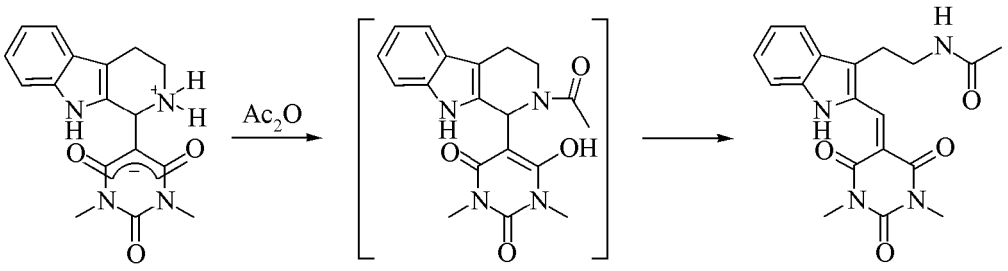
Elimination of free rotation in the zwitter-ionic system **V** results in appearance in the proton spectrum

of spin-spin couplings between the protons of $+NH_2$ group and vicinal CH-protons. Under ordinary conditions this phenomenon is seldom observed. Thus the C^1H proton signal is split into a doublet with a coupling constant *J* 9.5 Hz due to interaction with the axial +NH-proton whereas the coupling of the C^1H proton with an equatorial +NH-proton has a considerably smaller constant (~1.5 Hz) due to the angle close to 90 and thus only a broadening of the signal is observed. On the other hand, the splitting into a quartet (or a doublet of doublets) of the equatorial NH^+-proton signal with a constant of 6.0 Hz is caused by interaction with protons of C^3H_2 group having respectively *ax*- and *eq*-orientation.

Addition of 1-butyl (**IIIb**) and 1-(*p*-ethylphenyl)-barbituric (**IIIc**) acids to 3,4-dihydro-β-carboline (**II**) occurred in a similar way. The spectral and physicochemical characteristics of compounds **IVb, c** obtained are similar to those presented for **IVa** derivative.

Analogous reaction with compound **II** was also carried out with 2-thiobarbituric acids **IIId–h**. The N-akyl(N-aryl) derivatives of 6-hydroxy-5-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one **IVd–g** obtained are distinguished from their oxygen-containing analogs **IVa–c** by lower solubility in organic solvents and higher hydrolytic stability caused apparently by still higher energy of stabilization of the zwitter-ion system due to the greater (by about two orders of magnitude) acidity of the 2-thiobarbituric acid fragment [10].

An interesting structural similarity exists between compounds **IVa–h** and zwitter-ionic 5-dihydrocotarnylbarbituric acids, such as compound **VI** and its analogs, whose synthesis and structure are described in [11, 12]. The latter are somewhat more chemically labile and can take part in ring-chain transformations [13].



IVa **XII**

We also were able to demonstrate that compounds **IV** also are prone to opening of the tetrahydropyridine ring. At treating the 1,3-dimethyl derivative **IVa** with acetic anhydride under mild conditions formed *N*-{2-[2-(1,3-dimethyl-2,4,6-trioxotetrahydropyrimidin-5-ylidenomethyl)-1*H*-indol-3-yl]ethyl}acetamide (**VII**), whose structure was unambiguously established from ^1H NMR, UV, and mass spectra. We presume that in the first stage of reaction acylation occurs at the tetrahydropyridine nitrogen N^2 followed by ring opening caused by the disturbance of the zwitter-ion system. Simultaneously arises $C^1=C^5$ double bond and a conjugated arylidene system **VII**. The rearrangement observed may be used in synthesis of hard-to-prepare 2-substituted derivatives from tryptamine series. Thus in this study a convenient one-stage synthetic route was developed providing 2,4,6-trioxopyrimidinyl-2,3,4,9-tetrahydro-1*H*-β-carbolines, structural analogs of alkaloids of annomontin group, and an interesting possibility was found permitting transformation of these compounds into 2-substituted tryptamine derivatives.

EXPERIMENTAL

^1H NMR spectra were registered on spectrometer Bruker AM-500 at operating frequency 500 MHz in DMSO-d_6, mass spectra were measured on MKh-1303 instrument with direct admission of the sample into the ion source at 150°C, ionizing electrons energy 70eV. The purity of compounds obtained was checked by TLC on Silufol plates, eluents chloroform–ethyl acetate, 1:1, 2-propanol water, 4:1, or DMF 25% aqueous NH_4OH, 4:1, by ^1H NMR spectra, and data of elemental analysis.

3,4-Dyhydro-β-carboline (II) was prepared from tryptamine as described in [1]. N-Substituted barbituric **IIIb, c** and 2-thiobarbituric **IIIe–g** acids were obtained along general procedure [14] from diethyl

malonate and the corresponding derivatives of urea and thiourea.

6-Hydroxy-1,3-dimethyl-5-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)-1*H*-pyrimidine-2,4-dione (IVa). To a solution of 0.01 mol of 3,4-dihydro-β-carboline (**II**) in 20 ml of alcohol at 40°C was added while stirring a hot solution of 0.01 mol of acid **IIIa** in 25 ml of alcohol. The reaction mixture was kept for 1 h at room temperature. The separated precipitate was filtered off, washed with alcohol, and dried at 40°C in a vacuum-desiccator. We obtained 2.96 g (91%) of compound **IVa** as colorless crystals, decomposition temperature 260°C. ^{1}H NMR spectrum, δ, ppm: 2.88±3.06 d.d+d.d (1H+ 1H, $C^{4'}H_2$, AB-system, ^1J 16.0, ^2J 4.5 Hz), 3.11 s (6H, 2Me), 3.33+ 3.62 m+ m (1H+ 1H, $C^{3'}H_2$, AB-system, ^1J 11.0, ^2J 4.5 Hz), 5.71 d (1H, $C^{1'}H$, *J* 9.5 Hz), 6.94 t (1H, $H^{6'}$, J 7.5 Hz), 6.96 t (1H, $H^{7'}$, *J* 7.5 Hz), 7.25 d (1H, $H^{5'}$, *J* 7.5 Hz), 7.37 d (1H, $H^{8'}$, *J* 7.5 Hz), 8.50 br.m (1H, $N^{2'}H$-*ax*, ^1J 9.5 Hz), 9.10 br.m (^{1}H, $N^{2'}H$-*eq*, ^1J 6.0 Hz), 10.46 s (1H, $N^{9'}H$).

Compounds **IVb–h** were prepared similarly from 3,4-dihydro-β-carboline and the corresponding derivatives of barbituric **IIIb, c** and 2-thiobarbituric **IIId–h** acids. The yields are given in the table.

6-Hydroxy-1-butyl-5-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)-1*H*-pyrimidine-2,4-dione (IVb). 1H, δ, ppm: 1.07 t (3H, Me, *J* 7.0 Hz), 1.20–1.45 m (4H, CH_2CH_2), 2.86+ 3.05 d.d+ d.d (1H+ 1H, $C^{4'}H_2$, AB-system, ^1J 15.5, ^2J 4.0 Hz), 3.25+ 3.60 m+ m (1H+ 1H, $C^{3'}H_2$, AB-system, ^1J 11.0, ^2J 4.0 Hz), 3.64 m (2H, N^1CH_2) 5.65 br.s* (1H, $C^{1'}H$, *J* 10.0 Hz), 6.91 t (1H, $H^{6'}$, *J* 7.5 Hz), 6.96 t (1H, $H^{7'}$, J 7.5), 7.25 d (1H, $H^{5'}$, *J* 7.5 Hz), 7.31 d (1H, $H^{8'}$, *J* 7.5 Hz), 8.75 br.s (1H, $N^{2'}H$-*ax*), 9.18 br.s* (1H, $N^{2'}H$-*eq*), 9.46 s* (1H, N^3H), 10.31 s (1H, N9 H).

6-Hydroxy-1-(*p*-ethylphenyl)-5-yl(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)-1*H*-pyrimidine-2,4-dion (IVc). 1H, δ, ppm: 1.07 t (3H, Me, *J* 7.0 Hz), 2.64 q (2H, CH_2, *J* 7.0 Hz), 2.87+ 3.01 d.d+ d.d (1H+ 1H, $C^{4'}H_2$, AB-system, 1*J* 16.0, 2*J* 4.5 Hz), 3.29+ 3.64 m+ m (1H+ 1H, $C^{3'}H_2$, AB-system, 1*J* 11.0, 2*J* 4.0 Hz), 5.67 br.s* (1H, $C^{1'}H$), 6.93–7.33 m (8H, Harom), 8.55 br.s (1H, $N^{2'}H$-*ax*), 9.28 br.s* (1H, $N^{2'}H$-*eq*), 9.46 s (1H, N^3H), 10.31 s (1H, $N^{9'}H$).

6-Hydroxy-1,3-dimethyl-5-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (IVd). ^{1}H, δ, ppm: 2.89+ 3.13 m+ m (1H+ 1H, $C^{4'}H_2$, AB-system, 1*J* 15.0 Hz), 3.33+ 3.62 m+ m (1H+ 1H, $C^{3'}H_2$, AB-system, 1*J* 9.5), 5.76 d (1H, $C^{1'}H$, *J* 5.6 Hz), 6.92 t (1H, $H^{6'}$, *J* 7.2 Hz), 6.95 t (1H, $H^{7'}$, *J* 7.7 Hz), 7.24 d (1H, $H^{5'}$, *J* 7.9 Hz , 7.37 d (1H, $H^{8'}$, *J* 7.5 Hz), 8.62 m (1H, $N^{2'}H$-*ax*, 1*J* 10.5, 2*J* 5.6 Hz), 9.16 m (1H, $N^{2'}H$-*eq*, 1*J* 6.8 Hz), 10.42 s (1H, $N^{9'}H$).

6-Hydroxy-1-ethyl-5-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (IVe). 1H, δ, ppm: 0.94 t (3H, Me, *J* 7.0 Hz), 2.80+ 3.06 m+ m (1H+ 1H, $C^{4'}H_2$, AB-system, 1*J* 15.0 Hz), 3.24+ 3.63 m+ m (1H+ 1H, $C^{3'}H_2$, AB-system, 1*J* 10.0 Hz), 5.66 d (1H, $C^{1'}H$, *J* 8.5 Hz), 6.91 t (1H, $H^{6'}$, *J* 7.3 Hz), 6.97 t (1H, $H^{7'}$, *J* 7.5 Hz), 7.26 d (1H, $H^{5'}$, *J* 7.3 Hz), 7.29 d (1H, $H^{8'}$, *J* 7.5 Hz), 8.52 m (1H, $N^{2'}H$-*ax*, 1*J* 8.5 Hz), 9.26 m (1H, $N^{2'}H$-*eq*, 1*J* 6.5 Hz), 10.46 s (1H, $N^{9'}H$), 10.60 s (1H, N^3H).

6-Hydroxy-1-butyl-5-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (IVf). 1H, δ, ppm: 0.86 t (3H, Me, *J* 7.5 Hz), 1.25–1.45 m (4H, CH_2CH_2), 2.84+ 3.03 m+ m (1H+ 1H, $C^{4'}H_2$, AB-system, 1*J* 15.0 Hz), 3.28+ 3.64 m+ m (1H+ 1H, $C^{3'}H_2$, AB-system, 1*J* 9.5 Hz), 3.68 t (2H, N^1CH_2, *J* 7.0 Hz) 5.66 d (1H, $C^{1'}H$, *J* 8.0 Hz), 6.92 t (1H, $H^{6'}$, *J* 7.5 Hz), 6.95 t (1H, $H^{7'}$, *J* 7.5 Hz), 7.25 d (1H, $H^{5'}$, *J* 7.5 Hz), 7.31 d (1H, $H^{8'}$, *J* 7.5 Hz), 8.55 d (1H, $N^{2'}H$-*ax*, 1*J* 8.0 Hz), 9.23 d (1H, $N^{2'}H$-*eq*, 1*J* 6.0 Hz), 9.48 s (1H, N^3H), 10.31 s (1H, $N^{9'}H$).

6-Hydroxy-1-(*p*-ethoxyphenyl)-5-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (IVg). 1H, δ, ppm: 1.38 t (3H, Me, *J* 7.0 Hz), 2.87+ 3.02 m+ m (1H+ 1H, $C^{4'}H_2$, AB-system, 1*J* 15.0 Hz), 3.32+ 3.64 m+ m (1H+ 1H, $C^{3'}H_2$, AB-system, 1*J* 10.0 Hz), 4.02 q (2H, OCH_2 , *J* 7.0 Hz), 5.67 br.s* (1H, $C^{1'}H$), 6.83–7.06 m (6H, Harom), 7.29 d (1H, $H^{5'}$, *J* 7.5 Hz), 7.33 d (1H, $H^{8'}$, *J* 7.5 Hz), 8.46 br.s* (1H, $N^{2'}H$-*ax*), 9.30 br.s* (1H, $N^{2'}H$-*eq*), 10.84 br.s (2H, N^3H+ $N^{9'}H$).

6-Hydroxy-1-(*p*-fluorophenyl)-5-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (IVh). 1H, δ, ppm: 2.87+ 3.07 m+ m (1H+ 1H, $C^{4'}H_2$, AB-system, 1*J* 15.0 Hz), 3.32+ 3.66 m+ m (1H+ 1H, $C^{3'}H_2$, AB-system, ^1J 10.0 Hz), 5.66 br.s* (1H, $C^{1'}H$), 6.93–7.32 m (8H, Harom), 8.43 br.s* (1H, $N^{2'}H$-*ax*), 9.33 br.s (1H, $N^{2'}H$-*eq*), 10.59 s (1H, N9 H), 10.90 s (1H, N_3H).

* No splitting of signals was observed because of exchange.

***N*-{2-[2-(1,3-Dimethyl-2,4,6-trioxotetrahydropyrimidin-5-ylidenomethyl)-1*H*-indol-3-yl]ethyl}acetamide (VII).** To 0.005 mol of powdered compound **IVa** was added 5 ml of acetic anhydride, and the mixture was stirred for 1 h at 40°C. Then the mixture was left standing for 6 h at room temperature, the separated precipitate was isolated, washed with small amount of 50% alcohol, and dried at 40°C in a vacuum-desiccator. We obtained 1.55 g (84%) of compound **VII** as bright red-orange crystals, mp 234–235°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.78 s (3H, MeCO), 3.22 t (2H, CH_2Ar, *J* 7.1 Hz), 3.31 t (2H, CH_2N, *J* 7.1 Hz), 3.32 + 3.38 s + s (3H + 3H, MeN1 + MeN3), 7.11 t (1H, H$^{6'}$), 7.38 t (1H, H$^{5'}$, *J* 7.5 Hz), 7.53 d (1H, H$^{7'}$, *J* 7.5 Hz), 7.78 t (1H, H4 , *J* 7.5 Hz), 7.80 s (1H, HNC=O), 8.46 s (1H, =CH), 12.50 s (1H, HN^{1}). Found, %: C 61.90; H 5.51; N 15.14. $C_{19}H_{20}N_4O_4$. Calculated, %: C 61.95; H 5.47; N 15.21.

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