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Specific features of the reactions of quinazoline and its 4-hydroxy and 4-chloro substituted derivatives with C-nucleophiles

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ABSTRACT

Reactions of quinazoline **1** with indole, pyrogallol and 1-phenyl-3-methylpyrazol-5-one in the presence of acid led to C-4 adducts **2**, **3** and **5**. Adduct **4** is formed by heating **1** with 1,3-dimethylbarbituric acid without acid catalysis. 1-Phenyl-3-methylpyrazol-5-one reacts with **1** without acid catalysis to form dipyrazolylmethane **6**. 4-Chloroquinazoline **8** reacts with 1-phenyl-3-methylpyrazol-5-one to form 4-(1-phenyl-3-methyl-5-oxopyrazol-4-yl) quinazoline **9** and dipyrazolylmethane **6**. Heating **8** with 2-methylindole leads to the formation of 4-(2-methylindol-3-yl) quinazoline **10** and tris(2-methylindol-3-yl)methane **11**.

The quinazoline moiety is an important part of many natural alkaloids.[1] Compounds with diverse biological activities (hypotonic, antiallergenic, antibacterial and anthelminthic) have been found among quinazoline derivatives.[2] The search for antagonists of folic and isofolic acids as cellular mitosis inhibitors has received significant attention recently.[3,4] Antitumour[2] and radioprotective[5,6] quinazoline derivatives have also been synthesized.

In acidic medium, unsubstituted quinazoline was found to form a covalent hydrate at the N3=C4 bond.[7] Similarly, 3-methylquinazolinium iodide undergoes addition of alkyl- and arylamines and indoles to form 4-substituted-3,4-dihydroquinazolines.[8]

In this work, we found that unsubstituted quinazoline **1**, on heating with indole in boiling butanol for 2 h in the presence of trifluoroacetic acid, afforded the stable salt 4-(indol-3-yl)-3,4-dihydroquinazoline **2** (Scheme 1). 4-(2,3,4-Trihydroxyphenyl)-3,4-dihydroquinazoline **3** was obtained on heating quinazoline with pyrogallol in boiling ethanol for 2 h in the presence of hydrochloric acid. Products **2** and **3** precipitated after the reaction mixture had been cooled and were isolated in pure state by filtration.

We observed quantitative formation of 4-(1,2,3,4,-tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)-3,4-dihydroquinazoline **4** when recording the ^{1}H NMR spectrum of a solution of the reaction of an equimolar mixture of quinazoline **1** and 1,3-dimethylbarbituric acid in dimethyl sulfoxide at room temperature. We also isolated adduct **4** in crystalline state after heating the starting components in *n*-butanol for a short time.

Heating quinazoline **1** with 1-phenyl-3-methylpyrazol-5-one in boiling *n*-butanol in the presence of trifluoroacetic acid for 2 h produced 4-(1-phenyl-3-methyl-3-oxopyrazol-4-yl)-3,4-dihydroquinazoline trifluoroacetate **5**. At the same time, the known 4,4-methylidene-bis(1-phenyl-3-methylpyrazol-5-one) **6**[9] was obtained by heating quinazoline **1** for 10 h with a threefold excess of 1-phenyl-3-methylpyrazol-5-one in boiling *n*-butanol without acidic catalysis. After cooling the reaction mixture, product **6** was filtered off and recrystallized from *n*-butanol (35% yield).

Dipyrazolylmethane **6** may be formed via nucleophilic attack of 1-phenyl-3-methylpyrazol-5-one at the C-2 atom of **1** followed by pyrimidine ring-opening and attack of a second pyrazolone followed by elimination (Scheme 2).

4-Chloroquinazoline **8** (Scheme 3) reacts with a threefold molar excess of 1-phenyl-3-methylpyrazol-5-one in dimethylsulfoxide in the presence of triethylamine to form the substitution product, namely, 4-(1-phenyl-3-methyl-5-oxopyrazol-4-yl)-quinazoline **9** (45% yield) along with dipyrazolylmethane **6** (6% yield).

Product **9** was isolated by recrystallization of the precipitate obtained from the cooled reaction mixture from ethanol. Treatment of the mother liquor from the recrystallization of **9** with water gave dipyrazolylmethane **6**. The formation of product **6** indicates that, in this case, competitive nucleophilic attack at the C-2 atom of quinazoline occurs along with nucleophilic substitution of the halogen.

The halogen substitution product 4-(2-methylindol-3-yl)-quinazoline **10**, and the known tris(2-methylindol-3-yl)-methane

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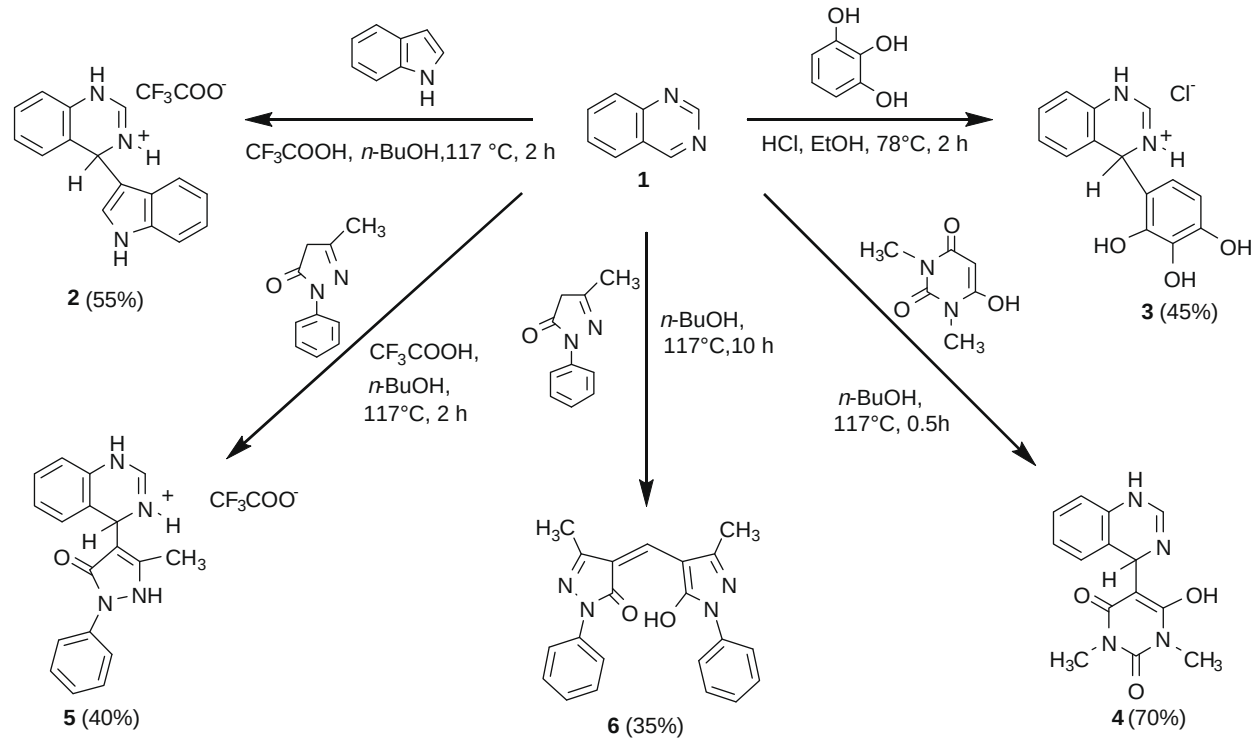
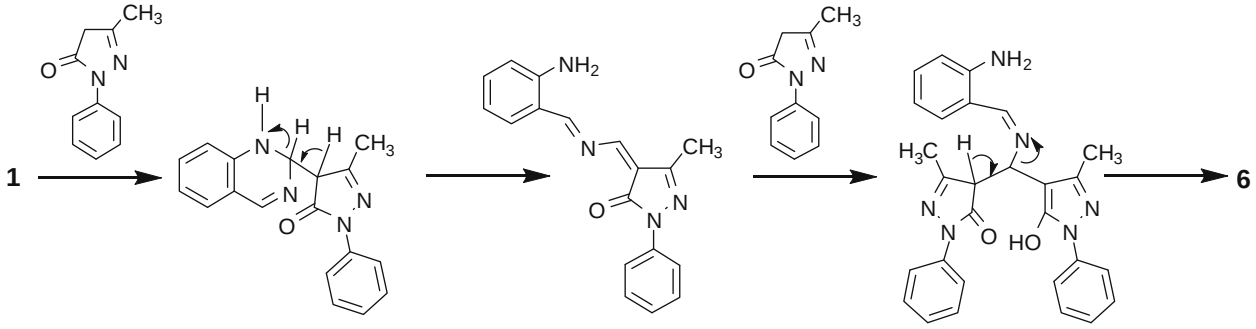


Scheme 1.



Scheme 2.

11[10] were obtained by heating 4-chloroquinazoline **8** with a threefold molar excess of 2-methylindole in boiling ethanol for 1 h. Tris(indolylmethane) **11** was filtered off from the cooled reaction mixture (10% yield). The mother liquor was dried and **10** was isolated from the solid residue by thin layer chromatography on silica (R_f = 0, chloroform).

The formation of tris(indolylmethane) **11** results from nucleophilic attack of indole on the C-2 atom of 4-chloroquinazoline **8** followed by further transformation via Scheme 4.

The high reactivity of 4-chloroquinazoline towards C-nucleophiles is due, most likely, to the autocatalytic effect of the hydrogen chloride evolved upon substitution.

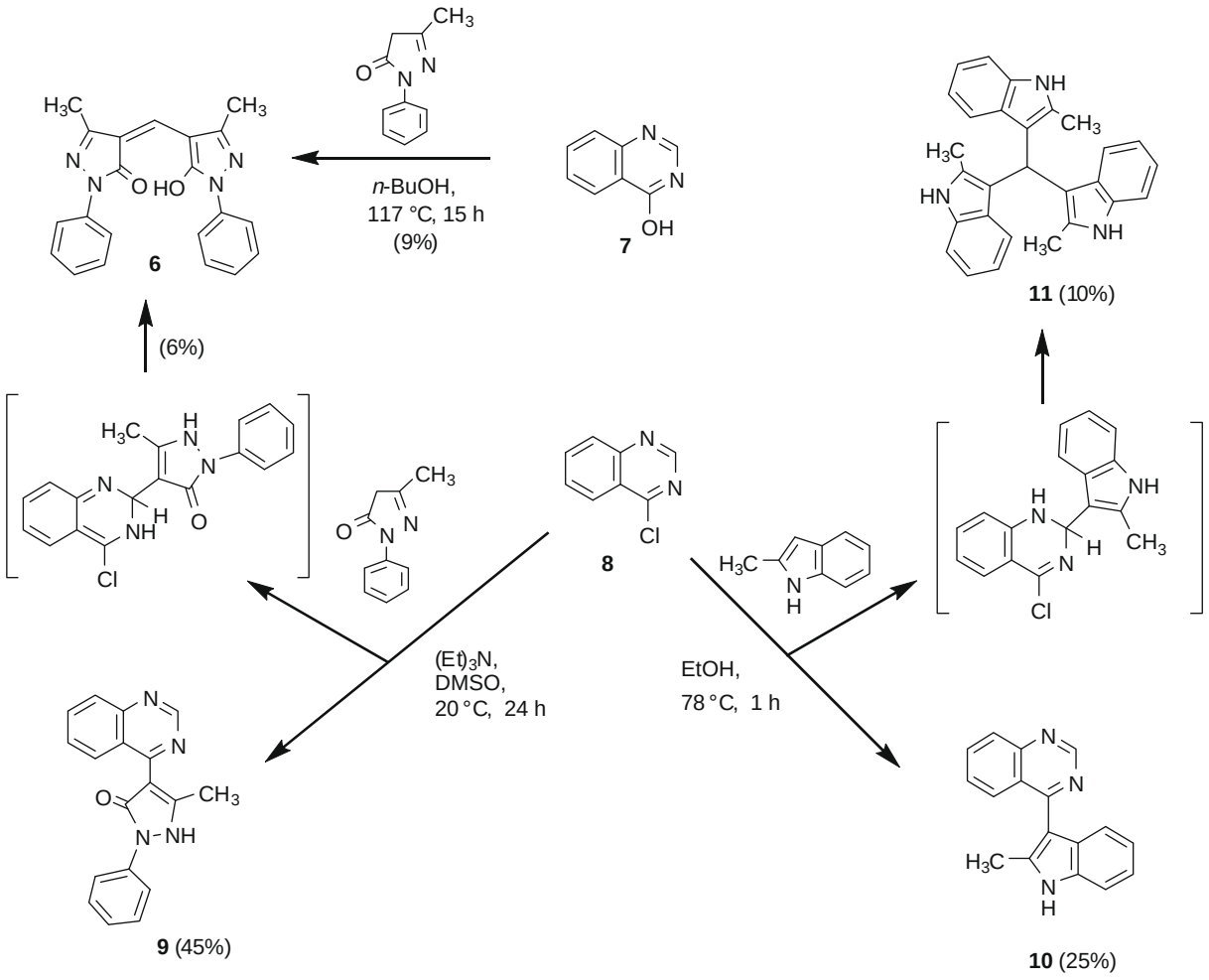
Heating of product **9** in boiling *n*-butanol in the presence of water also affords dipyrazolylmethane **6** in 14% yield. Product **6** was isolated by filtration after cooling the reaction mixture. The formation of dipyrazolylmethane **6** is preceded, most likely, by nucleophilic substitution of the pyrazole residue for the hydroxy group.

Initially formed pyrazolone attacks 4-hydroxyquinazoline at the C-2 atom. Next, the heterocycle is cleaved, and a second attack of pyrazolone occurs, leading eventually to product **6** (Scheme 5).

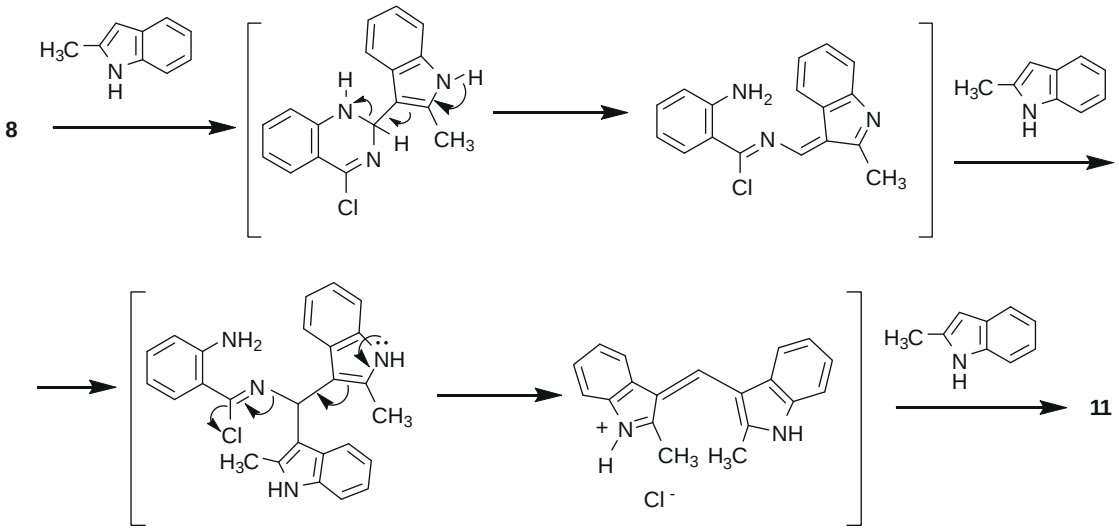
The validity of this assumption is confirmed by the formation of dipyrazolylmethane **6** (9% yield) on heating an authentic sample of 4-hydroxyquinoline **7** with 1-phenyl-3-methylpyrazol-5-one in boiling *n*-butanol for 15 h.

Characteristic properties for adducts **2-5** are signals for the H-4 proton in the range 6.0–6.5 ppm.[11] Note that in the 2D-NOESY spectrum of compounds **4**, detection of the cross-peak connecting the proton nucleus at C-4 (heterocyclic fragment) with the proton at C-5 (aromatic cycle) that unequivocally confirms the structures of these C-4 adducts (Fig. 1).

The electron impact mass spectrum of adduct **2** exhibited an intense peak due the molecular ion at *m/z* 247. At the same time, only molecular ions of the starting components and products of their decomposition were detected in the EI spectra of adducts **3**, **4** and **5**.

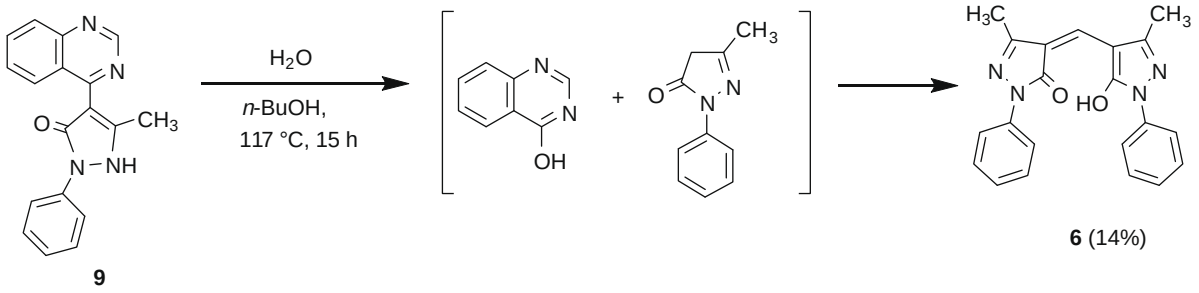


Scheme 3.



Scheme 4.

It is noteworthy that these unusual transformations result from nucleophilic attack on the C-2 atom of quinazoline without external activation (catalysis). The described transformations open opportunities for the synthesis of new, potentially biologically active products and have fundamental value in quinazoline chemistry.



Scheme 5.

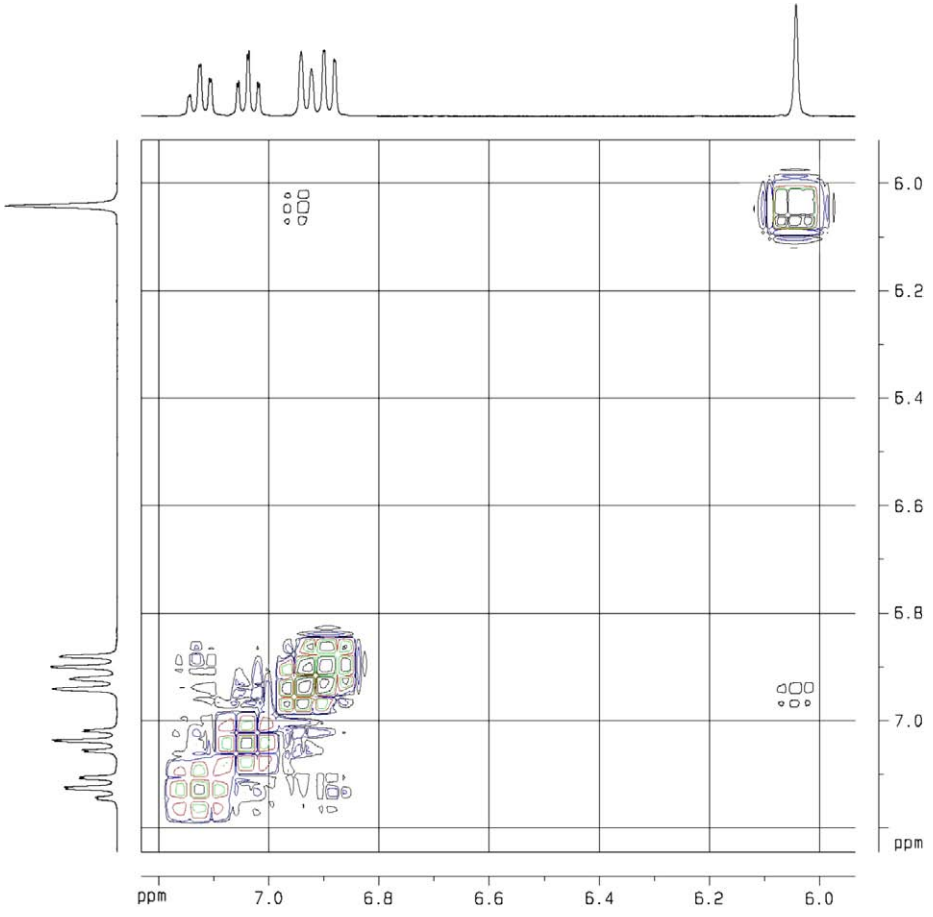


Figure 1. 2D-NOESY NMR spectrum of compound **4**.

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11. *Compound* **2**: mp 215–218 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.35 (s, 1H, H-4), 6.85–7.15 (m, 4H, CH_{arom}), 7.15–7.45 (m, 4H, CH_{arom}), 8.43 (s, 1H, H-2), 11.28 (s, 1H, NH_{indole}). MS: *m/z* 247 (M^+). Anal. Calcd for $C_{18}H_{14}F_3N_3O_2$: C, 59.8; H, 3.9; N, 11.6. Found: C, 60.2; H, 4.0; N, 11.3.*Compound* **3**: mp 227–228 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.08 (s, 1H, H-4), 6.32 (d, 1H, J = 8.4 Hz, CH_{arom}), 6.48 (d, 1H, J = 8.4 Hz, CH_{arom}), 6.90–7.00 (m, 1H, CH_{arom}), 7.00–7.20 (m, 2H, CH_{arom}), 7.22–7.30 (m, 1H, CH_{arom}), 8.39 (s, 1H, H-2), 8.62 (s, 1H, OH), 8.90 (s, 1H, OH), 9.32 (s, 1H, OH), 10.65 (br s, 1H, NH), 12.15 (br s, 1H, NH). Anal. Calcd for $C_{14}H_{13}ClN_2O_3$: C, 57.4; H, 4.5; N, 9.6. Found: C, 57.0; H, 4.4; N, 9.4.*Compound* **4**: mp>250 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.11 (s, 6H, 2 × NCH_3), 6.04 (s, 1H, H-4), 6.89 (dd, 1H, J = 7.8 Hz, J = 0.9 Hz, H-8), 6.93 (d, 1H, J = 7.5 Hz, H-5), 7.04 (ddd, 1H, J = 7.6, J = 7.5 Hz, J = 1.1 Hz, H-6), 7.13 (ddd, 1H, J = 7.8 Hz, J = 7.6 Hz, J = 1.2 Hz, H-7), 8.17 (d, 1H, J = 4.5 Hz, H-2), 9.96 (d, 1H, J = 4.5, $N_{(1)}H$), 11.48 (br s, 1H, OH). Anal. Calcd for $C_{14}H_{14}N_4O_3{\cdot}H_2O$: C, 55.3; H, 5.3; N, 18.4. Found: C, 55.6; H, 5.6; N, 18.2.*Compound* **5**: mp 128–130 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.02 (s, 3H, CH_3), 6.11 (s, 1H, H-4), 7.00–7.80 (m, 9H, CH_{arom}), 8.38 (s, 1H, H-2), 10.50 (br s, 1H, NH), 13.20 (br s, 1H, NH). Anal. Calcd for $C_{20}H_{17}$ $F_3N_4O_3$: C, 57.4; H, 4.1; N, 13.4. Found: C, 57.8; H, 4.4; N, 13.7.*Compound* **9**: mp 98-99 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, CH_3), 6.27 (s, 1H, H-4), 7.20–8.27 (m, 9H, CH_{arom}), 8.73 (s, 1H, H-2). MS: *m/z*

302 (M^+). Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.5; H, 4.7; N, 18.5. Found: C, 71.2; H, 4.4; N, 18.2.*Compound* **10**: mp 225–227 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 2.61 (s, 3H, CH_3), 6.60–8.10 (m, 8H, CH_{arom}), 9.20 (s, 1H, H-2), 11.54 (s, 1H, NH). MS: *m/z* 259 (M^+). Anal. Calcd for $C_{17}H_{13}N_3$: C, 78.7; H, 5.1; N, 16.2. Found: C, 78.5; H, 4.8; N, 16.0.