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PECULIARITIES OF TRANSFORMATIONS OF UNSUBSTITUTED QUINAZOLINE WITH C-NUCLEOPHILES

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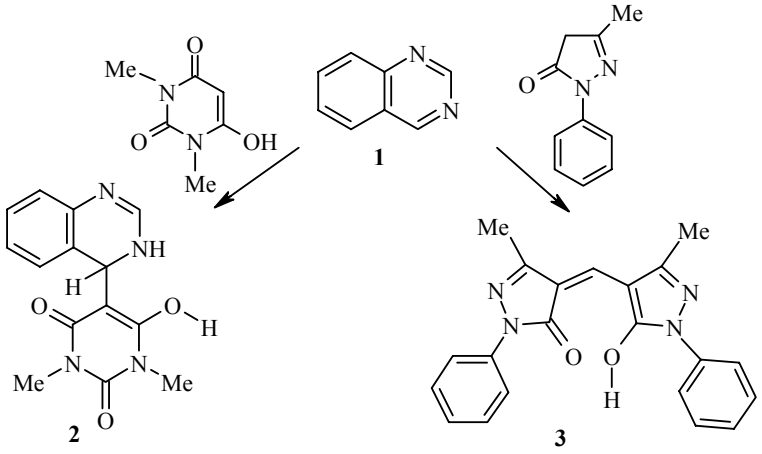
In acidic media, quinazoline forms a covalent hydrate with water at the N(3)=C(4) bond [1]. Analogously, 3-methylquinazolinium iodide adds alkylamines, arylamines, and indoles to give 4-substituted 3,4-dihydroquinazolines [2].

We have found that unsubstituted quinazoline **1** reacts with 1,3-dimethylbarbituric acid upon heating in butanol to give C(4)-substituted adduct **2**.



The quantitative formation of adduct **2** was indicated from an examination of the ^{1}H NMR spectrum of a solution of an equimolar mixture of the starting components in DMSO-d_6 at room temperature. The signal for H-4 at 6.0 ppm is diagnostic for adduct **2**. The ^{1}H NMR signal for sp^3-hybridized C-4 in dihydroquinazoline **2** is found at 48.3 ppm. The discovery of cross peaks in the 2D-NOESY correlation spectrum between quinazoline protons H-4 (in the heterocyclic fragment) and H-5 (6.93 ppm, in the aromatic ring) unequivocally confirms the C-4 adduct structure for dihydroquinazoline **2**.

Heating quinazoline **1** in butanol with 3-methyl-1-phenyl-5-pyrazolone gave 4,4'-methylidenebis-(3-methyl-1-phenyl-5-pyrazolone) **3**, which we described in our earlier work [3].

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The formation of bispyrazolone **3** probably proceeds through nucleophilic attack at C-2 with subsequent opening of the pyrimidine ring, a second attack by 3-methyl-1-phenyl-5-pyrazolone, and elimination of the quinazoline C-2 atom.

The unusually facile addition of dimethylbarbituric acid is likely a consequence of protonation of the quinazoline system by the nucleophile itself. This is the first observation of a neutral pyrazolone molecule attacking unsubstituted quinazoline at C-2.

The ^{1}H NMR, ^{31}C NMR, and 2D-NOESY spectra were taken on a Bruker DRX-400 spectrometer at 400 and 100 MHz, respectively, in DMSO-d_6 with the signal of the residual protons of the deuterated solvent as the standard (δ 2.50 ppm). The sample of quinazoline was acquired from Acros Organics.

4-(1,2,3,4-Tetrahydro-6-hydroxy-1,3-dimethyl-2,4-dioxa-5-pyrimidinyl)-3,4-dihydroquinazoline (2). A mixture of quinazoline **1** (0.039 g, 0.3 mmol) and 1,3-dimethylbarbituric acid (0.047 g, 0.3 mmol) in butanol (2 ml) was heated at reflux for 2-3 min. The precipitate was filtered off, washed with 1 ml butanol, and dried to give compound **2**, yield 0.55 g (64%); mp >250°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.11 (6H, s, $2NCH_3$); 6.04 (1H, s, H-4); 6.89 (1H, dd, $J_1 = 7.8$, $J_2 = 0.9$, H-8); 6.93 (1H, d, $J = 7.5$, H-5); 7.04 (1H, ddd, $J_1 = 7.6$, $J_2 = 7.5$, $J_3 = 1.1$, H-6); 7.13 (1H, ddd, $J_1 = 7.8$, $J_2 = 7.6$, $J_3 = 1.2$, H-7); 8.17 (1H, d, $J = 4.5$, H-2); 9.96 (1H, d, $J = 4.5$, $N_{(3)}H$); 11.48 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm: 26.7, 48.3, 91.7, 115.2, 125.0, 126.0, 126.5, 127.2, 131.1, 147.3, 152.8, 161.7. Found, %: C 58.5; H 5.0; N 9.4. $C_{14}H_{14}N_4O_3$. Calculated, %: C 58.7; H 4.9; N 19.6.

Reaction of Quinazoline 1 with 3-Methyl-1-phenyl-5-pyrazolone. A mixture of quinazoline **1** (0.039 g, 0.3 mmol) and 3-methyl-1-phenyl-5-pyrazolone (0.157 g, 0.9 mmol) in butanol (3 ml) was heated at reflux for 8 h. The reaction mixture was cooled. Filtration gave **3** in 35% yield. Product **3** was identical to a sample of 4,4'-methylidenebis(3-methyl-1-phenyl-5-pyrazolone) obtained according to our previous procedure [3].

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