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FIRST CASE OF RING–CHAIN TAUTOMERISM OF N-UNSUBSTITUTED 1,2,3,4-TETRAHYDROQUINAZOLINES

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Göblyös et al. [1] have shown that ring–chain tautomerism is a characteristic feature of arylidene derivatives of 2-methylaminophenylamine with a substituent at the benzylic nitrogen atom. 1,2,3,4-Tetrahydroquinazoline structure has been assigned to the products of the reaction of aldehydes and ketones with 2-methylaminophenylamine [2, 3]. In previous work [4], we reported the tendency of imines of β-dicarbonyl compounds such as diketones, keto esters, and keto amides to exist as enamines. This suggested ring–chain tautomerism among the corresponding 2-methylaminophenylamine derivatives.

In the present communication, we report the first example of such tautomerism **A'**⇌**B** for 3-(2-aminobenzylimino)-1-morpholin-4-yl-1-butanone (**1**), which is the product of the condensation of 2-methylaminophenylamine with acetoacetic acid morpholide.

NMR spectral data indicate the instantaneous establishment of the **A'**⇌**B** equilibrium. The signal for sp^3-hybrid atom $C_{(2)}$ at 66.75 ppm serves as a characteristic feature for cyclic form **B**. Structure **A** should be eliminated due to the lack of a signal for the corresponding methylene group in the ^{1}H NMR spectrum. All the signals of the linear form are in complete accord with structure **A'**, which represents a *cis* isomer as indicated by NOE spectra. The nuclear Overhauser effect is observed for the signal of the C=C–H proton upon irradiation of the methyl protons, which indicates their *cis* orientation. Intramolecular hydrogen bonding between the NH proton and carbonyl group oxygen atom stabilizes the *cis* form. The nature of the solvent has a significant effect on the ratio of the tautomeric forms. The linear form predominates in DMSO-d_6, while the ring form predominates in $CDCl_3$. This phenomenon is well known for many tautomeric systems involving 1,3-dicarbonyl derivatives [4] (Scheme 1).

We should note that the **A'**⇌**B** equilibrium differs fundamentally from the tautomerism of 1-substituted 2-methylaminophenylamines [1], in which the imine form participates at the anilinic nitrogen atom rather than the benzylic nitrogen atom.

The NMR spectra were taken on a JEOL JNM-A-500 spectrometer. The ^{1}H NMR spectra were taken at 500 MHz and the ^{13}C NMR spectra were taken at 125 MHz, in DMSO-d_6 at 30°C and in $CDCl_3$ at 25°C. The 1D measurements involved NOE and determination of the major parameters of these spectra. The homonuclear ^{1}H–^{1}H correlations involved the phase-sensitive DQF-COSY method, while the ^{1}H–^{13}C heteronuclear correlations were determined by the HMQC method (for correlations through one bond, J_1 = 145 MHz) and HMBC method (for correlations through two bonds, $J_{2,3}$ = 8 Hz) with gradient selection. All the spectra were taken using standard pulse sequence sets.

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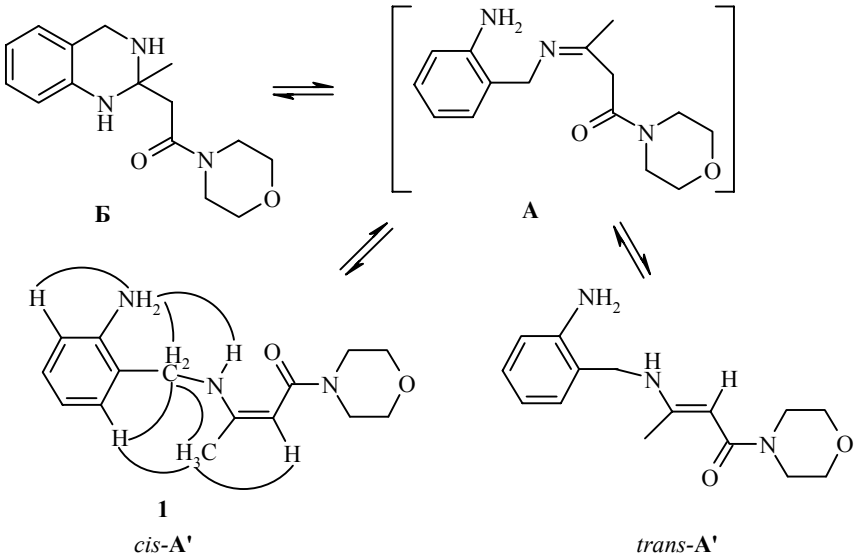
Scheme 1



3-(2-Aminobenzylimino)-1-morpholin-4-yl-1-butanone (1) was obtained by the reaction of 2-aminomethylphenylamine (0.36 g, 3 mmol) with 1-morpholin-4-yl-1,3-butanedione (0.78 g, 3 mmol) in methanol (10 ml). The reaction mixture was maintained for 24 h at ~20°C. The solvent was removed in vacuum without heating and the residue was recrystallized from 1:1 hexane–benzene to give compound **1** in 72% yield; mp 146-148°C (1:1 hexane–benzene), R_f 0.37 on Silufol UV-254 plate with methanol as eluent. Form **A'**: ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 1.90 (3H, s, CH_3); 3.35 (4H, m, N–CH_2); 3.51 (4H, m, O–CH_2); 4.21 (2H, d, *J* = 5.8, 4-H); 4.73 (1H, s, =CH); 4.94 (2H, br. s, 1-NH_2); 6.53 (1H, t, 6-H); 6.64 (1H, d, 8-H); 6.96 (1H, t, 7-H); 9.61 (1H, t, *J* = 5.8, 3-NH). ^{13}C NMR spectrum (DMSO-d_6); δ, ppm: 19.38 (CH_3); 42.52 ($C_{(4)}$); 42.99 (2C, N–CH_2); 66.18 (2C, O–CH_2); 80.99 (=CH); 114.84 ($C_{(8)}$); 116.09 ($C_{(6)}$); 122.16 ($C_{(4a)}$); 127.49 ($C_{(7)}$); 127.68 ($C_{(5)}$); 145.82 ($C_{(8a)}$); 159.88 ($C_{(2)}$); 169.22 (C=O). Form **B**: ^{1}H NMR spectrum in DMSO-d_6, δ, ppm: 1.29 (3H, s, CH_3); 2.58 (2H, s, CH_2); 3.43 and 3.46 (4H, m, N–CH_2); 3.51 (4H, m, O–CH_2); 3.80 (2H, s, 4-H); 5.70 (1H, br. s, 1-NH); 6.44 (1H, d, 8-H); 6.47 (1H, t, 6-H); 6.81 (1H, d, 5-H); 6.87 (1H, t, 7-H). The signal for 3-NH proton was not observed. ^{13}C NMR spectrum in DMSO-d_6, δ, ppm: 26.03 (CH_3); 41.23 ($C_{(4)}$ or CH_2); 41.26 ($C_{(4)}$ or CH_2); 45.94 (2C, N–CH_2); 65.38 ($C_{(2)}$); 66.01 (2C, O–CH_2); 114.22 ($C_{(8)}$); 115.63 ($C_{(6)}$); 119.44 ($C_{(4a)}$); 125.59 ($C_{(5)}$); 126.56 ($C_{(7)}$); 143.01 ($C_{(8a)}$); 168.95 (C=O). Found, %: C 68.81; H 8.96; N 16.11. $C_{15}H_{23}N_3O$. Calculated, %: C 68.93; H 8.87; N 16.08.

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