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RING-CHAIN TAUTOMERISM OF 1,2,3,4-TETRAHYDROQUINAZOLINES. THE PRODUCTS OF REACTION OF 1,3-DICARBONYL COMPOUNDS WITH 2-AMINOMETHYLANILINE

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The reaction of 2-aminomethylaniline with 1,3-dicarbonyl compounds gives a series of 1,2,3,4-tetrahydroquinazoline derivatives. A ring-chain tautomeric equilibrium of the type enamine-1,2,3,4-tetrahydroquinazoline is observed in solutions of these compounds and its position depends of the structure of the starting dicarbonyl component and the solvent polarity.

Keywords: 1,2,3,4-tetrahydroquinazolines, ring-chain tautomerism.

The condensation products of 2-aminomethylaniline **1** with aliphatic aldehydes and ketones exist in solvents of different polarity totally in the cyclic 1,2,3,4-tetrahydroquinazoline form [1-4]. However, a change to the N-(2-aminobenzyl)imines of substituted aromatic aldehydes leads to the appearance of a 1,2,3,4-tetrahydroquinazoline-imine ring-chain type tautomeric equilibrium [5].

In this tautomeric equilibrium the cyclic form generally predominates. With this in mind we have found a single example (the derivative of 2-aminomethylaniline **1** with acetoacetic acid morpholide) in which the linear imine form **A** can be stabilized via a prototropic transition to the enamine **A'** [6]. On the basis of reported data [7-9] there might be expected here the appearance of a three component tautomeric equilibrium which includes the cyclic form **B** and the two geometric isomers of the enamine form **A'**$_{E,Z}$. However, only the two tautomers **A'**$_Z$ and **B** were in fact discovered.

In our work we have turned to other derivatives of 1,3-dicarbonyl compounds. Assuming that the imine-enamine equilibrium will be characterized by similar dependencies as for the keto-enol equilibrium in the starting 1,3-dioxo compounds [7-9] we have selected three groups of 1,3-dicarbonyl compounds, *viz*. 1,3-dioxo compounds **2a-c**, 1,3-keto esters **2d,e**, and the 1,3-keto amides **2f-h**, since the fraction of the enol form decreases systematically in this series of starting 1,3-dioxo compounds [7-9].

The series of the condensation products **3a-h** (yields 35-75%, Table 1) of 2-aminomethylaniline **1** with the selected 1,3-dicarbonyl compounds were obtained by us and their structure investigated using the ^{1}H NMR method (Tables 2 and 3).

Proof of the presence of the 1,2,3,4-tetrahydroquinazoline tautomer **B** was based on the presence in the ^{13}C NMR spectra of $C_{(2)}$ atom signals of the tetrahydropyrimidine ring which appeared in the region 63-65 ppm and are typical of an sp^3-hybridized carbon atom in an N–C–N environment [5, 6].

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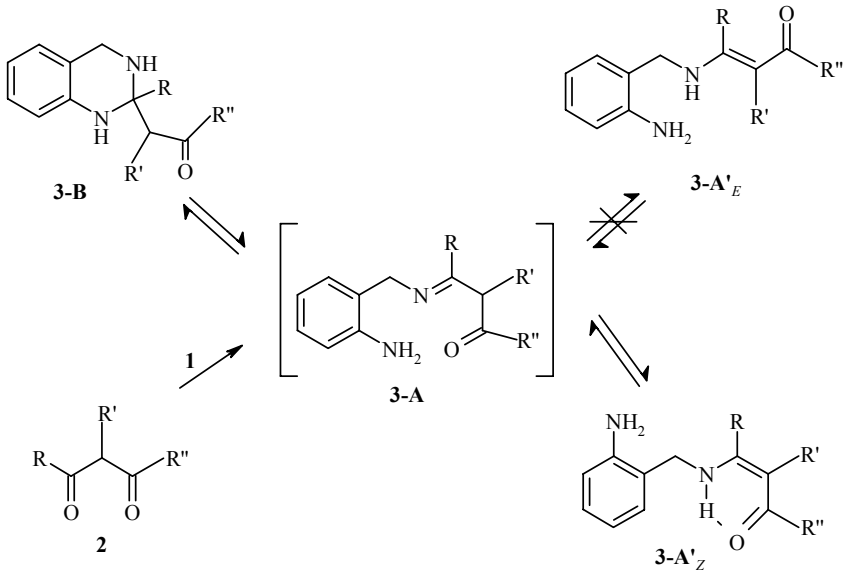

2, **3 a** R = H, **b-d, f-h** R = Me; **a-d**, **f-h** R' = H; **e** R–R' = –$(CH_2)_5$–; **a**, **c** R" = Ph, **b** R" = Me, **d**, **e** R" = OEt, **f** R" = NEt_2, **g** R" = $NHC_6H_3(OMe)_2$-2,4; **h** R" = $N(CH_2CH_2)_2O$

The enamine form **A'** in the NMR spectra presents as the "olefine" proton signals in the region 4.45-5.76 ppm and the NH signal at 9.21-11.52 ppm as well as the sp^2-hybridized "olefine" carbon atoms at 82-96 and 154-167 ppm respectively (Tables 2 and 3). These data agree with the spectra of many enamines, as referred to in the reviews [7, 8].

TABLE 1. Parameters for Compounds **3a-h**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	R_f (eluent)	Yield, %
		C	H	N			
3a	$C_{16}H_{16}N_2O$	76.22 / 76.16	6.50 / 6.39	11.03 / 11.10	133-134	0.43 (heptane–ether, 1:1)	67
3b	$C_{12}H_{16}N_2O$	70.50 / 70.56	7.71 / 7.90	13.53 / 13.71	72-74	0.71 (ethyl acetate)	74
3c	$C_{17}H_{18}N_2O$	76.75 / 76.66	6.94 / 6.81	10.37 / 10.52	170-171	0.61 (ethanol–benzene, 1:1)	75
3d	$C_{13}H_{18}N_2O_2$	66.46 / 66.64	7.88 / 7.74	11.79 / 11.96	63-65	0.53 (ethyl acetate–benzene, 1:1)	45
3e	$C_{17}H_{24}N_2O_2$	70.73 / 70.80	8.51 / 8.39	9.59 / 9.71	80-81	0.71 (ethyl acetate–benzene, 1:1)	53
3f	$C_{15}H_{23}N_3O$	68.77 / 68.93	8.68 / 8.87	16.22 / 16.08	Oil	0.53 (methanol)	35
3g	$C_{19}H_{23}N_3O_3$	66.55 / 66.84	6.77 / 6.79	12.53 / 12.31	64-65	0.51 (ethyl acetate–benzene, 1:1)	47
3h	$C_{15}H_{21}N_3O_2$	65.14 / 65.43	7.45 / 7.69	15.03 / 15.26	146-148	0.37 (methanol)	50

* Solvent hexane–benzene, 1:1.

TABLE 2. ^{1}H NMR Spectra of Compounds **3a-h**

Compound	Chemical shift ($CDCl_3$), δ, ppm (*J*, Hz)						
	Form (%)	CH_3 (3H, s)	$C\underline{H}_2NH$	CH_2 or C=CH	1-NH br. s (1H)	$CH_2N\underline{H}$ br. s (1H)	Other group
1	2	3	4	5	6	7	8
3a	**A'**$_Z$	1.97	4.22 (2H, d, *J* = 4.85)	4.45 (1H, s)	3.76	10.89	1.99 (3H, s, $COCH_3$); 6.60-7.00 (4H, m, H arom.)
3b	**A'**$_Z$	—	4.33 (2H, d, *J* = 4.73)	5.76 (1H, d, *J* = 7.36)	3.66	10.47	6.70-8.00 (9H, m, H arom.)
3c	**A'**$_Z$	2.11	4.38 (2H, d, *J* = 4.88)	5.76 (1H, s)	3.75	11.52	6.70-8.00 (9H, m, H arom.)
3d	**A'**$_Z$ (45)	1.95	4.28 (2H, d, *J* = 5.04)	4.53 (1H, s)	3.72	8.61	1.24 (3H, t, *J* = 7.40, $CH_2C\underline{H}_3$); 4.12 (2H, q, *J* = 7.40, $C\underline{H}_2CH_3$); 6.60-7.10 (4H, m, H arom.)
	B (55)	1.41	3.97 (2H, s)	2.63 (1H, d, *J* = 5.14); 2.67 (1H, d, *J* = 5.14)	4.68	—*	1.21 (3H, t, *J* = 7.40, $CH_2C\underline{H}_3$); 4.03 (2H, q, *J* = 7.40, $C\underline{H}_2CH_3$); 6.60-7.10 (4H, m, H arom.)
3e	**A'**$_Z$ (89)	—	4.29 (2H, d, *J* = 4.93)	—	3.78	9.33	1.13 (3H, t, *J* = 7.33, $CH_2C\underline{H}_3$); 1.18-1.23 (4H, m, $2CH_2$); 1.52-1.59 (2H, m, CH_2); 2.03-2.20 (4H, m, $2CH_2$); 4.10 (2H, q, *J* = 7.33, $C\underline{H}_2CH_3$); 6.60-7.00 (4H, m, H arom.)
	B (11)	—	3.86 (1H, d, *J* = 7.36); 3.92 (1H, d, *J* = 7.36)	—	4.47	—*	1.24 (3H, t, *J* = 7.33, $CH_2C\underline{H}_3$); 1.41-1.52 (4H, m, $2CH_2$); 1.65-1.75 (2H, m, CH_2); 2.46-2.57 (4H, m, $2CH_2$); 4.13 (2H, q, *J* = 7.33, $C\underline{H}_2CH_3$); 6.40-7.10 (4H, m, H arom.)

TABLE 2 (continued)

1	2	3	4	5	6	7	8
3f	**A'$_Z$** (10)	2.03	4.22 (2H, d, J = 4.83)	4.58 (1H, s)	3.78	9.52	1.02, 1.27 (6H, t, J = 7.48, $N(CH_2C\underline{H}_3)_2$); 2.91-3.24 (4H, m, J = 7.48, $N(C\underline{H}_2CH_3)_2$); 6.50-8.10 (4H, m, H arom.)
	B (90)	1.40	3.91 (1H, d, J = 7.01); 3.98 (1H, d, J = 7.01)	2.50 (1H, d, J = 5.89); 2.65 (1H, d, J = 5.89)	4.59	—*	1.08, 1.12 (6H, t, J = 7.48, $N(CH_2C\underline{H}_3)_2$); 3.25-3.45 (4H, m, J = 7.48, $N(C\underline{H}_2CH_3)_2$); 6.50-8.00 (4H, m, H arom.)
3g	**A'$_Z$** (9)	1.93	4.25 (2H, d, J = 6.28)	4.55 (1H, s)	3.77	9.86	3.72 (3H, s, OCH_3); 3.79 (3H, s, OCH_3); 6.40-8.20 (7H, m, H arom.)
	B (91)	1.44	4.02 (1H, d, J = 7.14); 4.05 (1H, d, J = 7.14)	2.50 (1H, d, J = 15.74); 2.83 (1H, d, J = 15.74)	4.44	—*	3.75 (3H, s, OCH_3); 3.77 (3H, s, OCH_3); 6.40-8.20 (7H, m, H arom.)
3h	**A'$_Z$** (32)	1.99	4.29 (2H, d, J = 4.87)	4.64 (1H, s)	5.37	9.21	3.42-3.49 (8H, m, $[N(CH_2CH_2)_2O]$); 6.60-7.10 (4H, m, H arom.)
	B (68)	1.46	3.96 (1H, d, J = 7.09); 4.03 (1H, d, J = 7.09)	2.59 (1H, d, J = 5.68); 2.65 (1H, d, J = 5.68)	—*	—*	3.59-3.69 (8H, m, $N(CH_2CH_2)_2O$]); 6.50-7.00 (4H, m, H arom.)

* Signal not observed.

TABLE 3. ^{13}C NMR Spectra of Compound **3a-h**

Compound	Chemical shift ($CDCl_3$), δ, ppm						
	Form (%)	CH_2NH	C=CH or CH_2	C arom.	$C_{(8a)}$	C=O	other groups
3a	**A'**$_Z$	49.48	91.24	116.41-139.53 (11 signals)	144.70	190.19	153.30 (C=CH)
3b	**A'**$_Z$	44.21	96.02	116.29-140.16 (5 signals)	144.33	195.22	21.50 (CH_3), 28.72 ($COCH_3$), 163.46 (C=CH)
3c	**A'**$_Z$	44.44	92.82	116.54-140.17 (11 signals)	144.44	188.09	19.62 (CH_3), 165.13 (C=CH)
3d	**A'**$_Z$ (45)	44.46	83.66	115.44-128.82 (10 signals)	144.50	170.47	14.57 (CH_2CH_3), 19.55 (CH_3), 58.39 (CH_2CH_3), 161.88 (C=CH)
	B (55)	44.00	42.01		142.17	171.24	14.15 (CH_2CH_3), 26.10 (CH_3), 60.56 (CH_2CH_3), 65.16 ($C_{(2)}$)
3e	**A'**$_Z$ (89)	44.60	95.93	114.83-128.91 (10 signals)	144.45	170.66	14.25 (CH_2CH_3), 25.02, 25.82, 28.28, 28.80, 31.79 ((CH_2)$_5$), 60.37 (CH_2CH_3), 167.32 (C=CH)
	B (11)	41.72	41.60		142.57	174.08	14.15 (CH_2CH_3), 24.48, 25.22, 26.49, 26.96, 27.11 ((CH_2)$_5$), 60.50 (CH_2CH_3), 70.57 ($C_{(2)}$)
3f	**A'**$_Z$ (10)	49.89	83.16	115.79-132.67 (10 signals)	144.70	170.31	12.99, 13.97 (NCH_2CH_3)$_2$, 20.15 (CH_3), 40.14, 41.98 (NCH_2CH_3)$_2$, 154.88 (C=CH)
	B (90)	42.17	41.39		142.50	169.82	12.63, 14.23 (NCH_2CH_3)$_2$, 24.78 (CH_3), 40.30, 42.24 (NCH_2CH_3)$_2$, 65.75 ($C_{(2)}$)
3g	**A'**$_Z$ (9)	44.36	86.92	98.52-156.48 (22 signals)	144.64	168.74	19.58 (CH_3), 55.57 (OCH_3), 55.61 (OCH_3), 159.67 (C=CH)
	B (91)	46.59	41.77		141.83	168.02	26.06 (CH_3), 55.48 (OCH_3), 55.73 (OCH_3), 65.30 ($C_{(2)}$)
3h	**A'**$_Z$ (32)	44.51	82.01	115.82-128.62 (10 signals)	144.58	170.01	25.63 (CH_3), 46.13 (N(CH_2CH_2)$_2$O), 66.90 (N(CH_2CH_2)$_2$O), 160.38 (C=CH)
	B (68)	42.17	41.74		142.54	169.34	20.18 (CH_3), 41.54 (N(CH_2CH_2)$_2$O), 66.19 (N(CH_2CH_2)$_2$O), 65.73 ($C_{(2)}$)

In addition to this, the presence of these forms in solution is unambiguously indicated by the ^{13}C NMR spectroscopic signals for the C_{8a} atoms at 141-142 corresponding to the cyclic form **B** and 144-145 ppm for the linear form **A'** [5].

With regard to the specifics, the condensation products with benzoylacetaldehyde (**3a**), acetylacetone (**3b**), and benzoylacetone (**3c**) exist in solutions of different polarity* in the single enamine form.

We consider this to be the *Z*-isomer form since it is known [7-11] to be stabilized by intramolecular hydrogen bonding. Important support for this structure is, in fact, found in the anomalously high field position of the signals of the NH protons involved in this bond and this is, moreover, weakly sensitive to temperature and concentration effects. Further evidence for this structure is the spin spin coupling between the CH=CH protons in the ^1H NMR spectrum of the derivative **3a**. Its value of J = 7.36 Hz corresponds to a cis relationship of these protons in the multiple bond.

The condensation product **3d** of the 2-aminomethylaniline **1** with acetoacetic ester (**2d**) exists in solutions as a 1:1 mixture of the cyclic **B** and enamine **A'**$_Z$ forms.

In compound **3e**, prepared from the cyclic β-keto ester **2e**, the fraction of the enamine form is 89%. This agrees with data [7, 8], according to which the conjugated enamine tautomer **A'**$_Z$ is favored by the introduction of a cyclic element into a series of nitrogen containing 1,3-keto ester derivatives.

In the tautomeric equilibrium for the condensation products **3f-h** of 2-aminomethylaniline **1** with the 1,3-keto amides **2f-h** the cyclic form **B** predominates. The content of the linear form in solution does not exceed 32%. The linear form consists of the cis- isomer and this is confirmed by the NOE spectra of compound **3h**. The Overhauser effect is observed for the C=C–H proton signal when the methyl protons are irradiated thus pointing to this cis orientation.

The effect of the solvent on the position of the tautomeric equilibrium is very marked. Changing from solution in $CDCl_3$ to DMSO-d_6 causes an increase in the fraction of the enamine tautomer **A'**, which increases consecutively in the series of derivatives of 1,3-diketones, 1,3-keto esters, and 1,3-keto amides.

It can be seen that our results agree with known literature data regarding the tendency for the fraction of the enamine tautomer to increase within the series of nitrogenous derivatives of β-diketones, β-keto esters, and β-keto amides [7-11].

It was of interest that the ring-chain tautomer effect in the series of functionally substituted imines of 1,3-dicarbonyl compounds has remained virtually unreported [10]. It was only known that the β- and γ-hydroxyalkylimines of β-dicarbonyl compounds demonstrate such a property; however its dependence has not been investigated [7].

Hence the data obtained by us for the series chosen can help reveal the mechanism of the ring-chain tautomerism in the series of nitrogenous derivatives of 1,3-dicarbonyl compounds as a whole.

EXPERIMENTAL

The NMR spectra of solutions in DMSO-d_6 and $CDCl_3$ were taken on JEOL JNM-A-500 (500 and 125 MHz for ^1H and ^{13}C respectively) and Bruker AM-300 (300 and 75 MHz for ^1H and ^{13}C respectively) under conditions of complete suppression of spin spin coupling with the carbon atoms and with HMDS internal standard. Elemental analysis was carried out for the first time using a Carlo Erba Strumentazione analyzer (model 1106). Monitoring of the course of the reaction and the purity of the compounds obtained was carried out by TLC on Silufol UV-254 plates. Chromatographic separation was carried out on column and using flash chromatography with Merck Silicagel 60 with a specific choice of solvent system.

* The spectra recorded in DMSO solutions are similar and therefore not reported here.

Parameters for the synthesized compounds **3** are given in Table 1.

3-[(2-Aminobenzyl)amino]-1-phenylprop-2-en-1-one (3a). A solution of the 2-aminomethylaniline **1** (0.33 g, 2.7 mmol) in methanol (20 ml) was stirred with a solution of freshly prepared benzoylacetaldehyde (**2a**) (0.39 g, 2.7 mmol) in methanol (10 ml). The mixture was allowed to stand at room temperature for 1 day. At the end of the reaction (monitoring by TLC) the solvent was removed in vacuo and the residue was purified by flash chromatography using diethyl ether as eluent.

3-[(2-Aminobenzyl)amino]-1-phenylbut-2-en-1-one (3c) was prepared under the same conditions from freshly prepared benzoylacetone (**2c**) and 2-aminomethylaniline **1**.

4-[(2-Aminobenzyl)amino]pent-3-en-2-one (3b). 2-Aminomethylaniline **1** (0.33 g, 2.7 mmol) was dissolved in anhydrous benzene (20 ml). A solution of acetylacetone (**2b**) (0.28 g, 2.7 mmol) in anhydrous benzene (5 ml) and a catalytic amount of trifluoroacetic acid were added. The reaction mixture was held for 1 day at ~20°C while the reaction was followed by the TLC method. At the end of the reaction the mixture was dried over anhydrous sodium sulfate, the mother liquor decanted, and the solvent was evaporated in vacuo. The residue was recrystallized from hexane, filtered, washed with pentane, and dried in vacuo using an oil pump.

Ethyl 3-[(2-Aminobenzyl)amino]but-2-enoate (3d). A solution of ethyl acetoacetate (**2d**) (0.35 g, 2.7 mmol) in benzene (5 ml) and a catalytic amount of trifluoroacetic acid were added to a solution of the 2-aminomethylaniline **1** (0.33 g, 2.7 mmol) in benzene (20 ml). The reaction mixture was held for 1 day at ~20°C while the reaction was followed by the TLC method. At the end of the reaction the solvent was evaporated in vacuo and the remaining oil was crystallized from a mixture of pentane and ether (1:1). The crystalline precipitate was separated by filtration, washed with pentane, and dried in vacuo using an oil pump.

Ethyl 2-[(-2-Aminobenzyl)amino]cyclopent-1-en-1-carboxylate (3e) was prepared similarly to compound **3d** from the 2-aminomethylaniline **1** and ethyl 2-oxocycloheptanoate (**2e**).

N,N-Diethyl-2-(2-methyl-1,2,3,4-tetrahydroquinazolin-2-yl)acetamide (3f). A solution of acetoacetic acid N,N-diethylamide (**2f**) (0.45 g, 2.7 mmol) in methanol (10 ml) was added to a solution of the 2-aminomethylaniline **1** (0.33 g, 2.7 mmol) in methanol (10 ml). The mixture was held for 1 day at ~20°C. At the end of the reaction (TLC monitoring) the solvent was evaporated in vacuo. The remaining viscous oil could not be crystallized but appeared to be spectroscopically pure N,N-diethyl-2-(2-methyl-1,2,3,4-tetrahydroquinazolin-2-yl)acetamide (**3f**).

N-(2,4-Dimethoxyphenyl)-2-(2-methyl-1,2,3,4-tetrahydroquinazolin-2-yl)acetamide (3g) and 2-Methyl-2-(2-morpholin-4-yl-2-oxoethyl)-1,2,3,4-tetrahydroquinazoline (3h) were prepared similarly to compound **3f** from the 2-aminomethylaniline **1** and N-(2,4-dimethoxyphenyl)-3-oxobutanamide (**2g**) and 4-morpholin-4-yl-4-oxobutan-2-one (**2h**) respectively.

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