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Complex tauto- and rotamerism of 2-(R-phenyl)-1,2,3,4-tetrahydroquinazolines†

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ABSTRACT: Detailed NMR spectral analysis of $CDCl_3$ solutions of 2-(R-phenyl)-1,2,3,4-tetrahydroquinazolines reveals three or four tautomeric forms. Apart from 2-[(benzylideneamino)methyl]aniline, the other chain tautomeric forms are present only in minor quantities. In general, electron-donating substituents increase the contribution of all chain forms. Lowering the temperature of the $CDCl_3$ solution of 2-(R-phenyl)-1,2,3,4-tetrahydroquinazolines decreases the content of the 2-[(benzylideneamino)methyl]aniline form. At the same time, the amount of the ring form increases. Opening of the tetrahydropyrimidine ring in 2-(R-phenyl)-1,2,3,4-tetrahydroquinazolines was found to be an endothermic process especially for less electron-donating substituents. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: ring–chain tautomerism; Schiff bases; hydrogen bond; multinuclear magnetic resonance; conjugation; temperature effect; rotamers

INTRODUCTION

Tautomeric equilibria in *N*-unsubstituted 1,3-*N*,*N*-heterocycles derived from asymmetric diamines may involve two distinct chain forms.[1,2] Such chain–ring–chain tautomerism was observed recently for 2-aryl-4-methylhexahydropyrimidines.[1] Theoretical calculations suggest that the reaction enthalpies for the formation of Schiff bases being derivatives of benzylic amines and aromatic amines (anilines) are close to each other.[3] However, only one type of the chain form was detected in solutions of the condensation products of 2-aminobenzylamine with carbonyl compounds (these are imines involving the benzylic amino nitrogen atom, see **C1** in Scheme 1).[4] On the other hand, NMR spectra of unsymmetrically substituted 2-aryl-4-methylhexahydro-pyrimidines in $CDCl_3$ solution exhibited two chain forms and two epimeric ring forms.[1]

In addition to the ring form, a mixture of the condensation products of 2-amino-*N*-R′-benzylamines with benzaldehydes contains evidently only one chain form, $\mathbf{C^F2}$ (Scheme 2).[5] Electron-donating ring substituents were found to increase amount of this chain form.[5]

Hence, the question of the presence of the other tautomeric form **C2** in solutions of 2-(R-phenyl)-1,2,3,4-tetrahydroquinazolines is still open. Since the other tautomers (labile species) may appear in only minute quantities, their identification may not be easy and definitive.

RESULTS AND DISCUSSION

Sinkkonen *et al.*[4] and Lázár and Fülöp[5] studied the effect of substituents on the percentages of different tautomeric forms in DMSO and $CDCl_3$ solutions of 2-(R-phenyl)-1,2,3,4-tetrahydroquinazolines and showed that electron-donating substituents shift these equilibria towards the chain form(s). This is why the compounds studied (Scheme 1) contain mostly strong electron-donating *para* substituents on the 2-phenyl. It should be mentioned, however, that substitution at the *ortho* carbon of *N*,*N*-dimethylaniline makes the NMe_2 group twist out of the ring plane, and as a consequence the nitrogen valences become more pyramidal (steric inhibition to resonance).[6,7] Hence the dimethylamino groups in compounds **8** and **9** are much less electron-donating than in **5**.

At least eight chain tautomers and their rotamers (Scheme 3) have to be considered when studying tautomerism of 2-(R-phenyl)-1,2,3,4-tetrahydroquinazolines. These forms are expected to be revealed with multinuclear NMR spectroscopy (Fig. 1). Both 2-[(benzylideneamino)methyl]aniline (**C1**) and 2-(benzylideneamino) benzylamine (**C2**) may appear in four different planar conformations, two with and two without intramolecular

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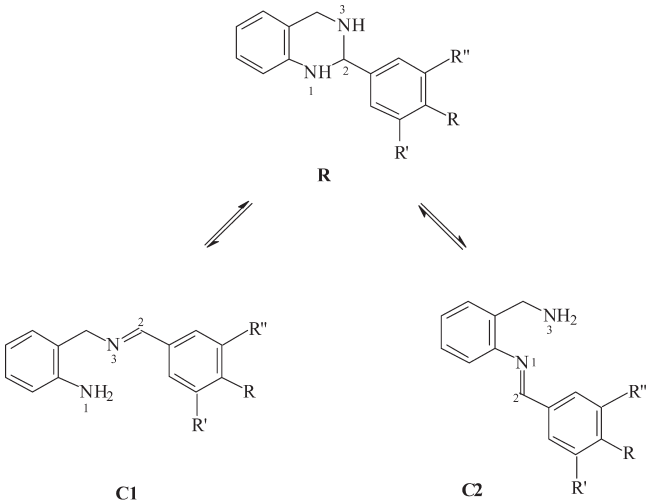
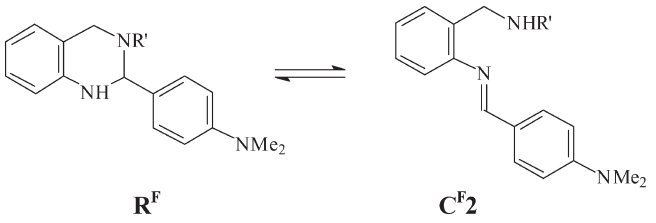
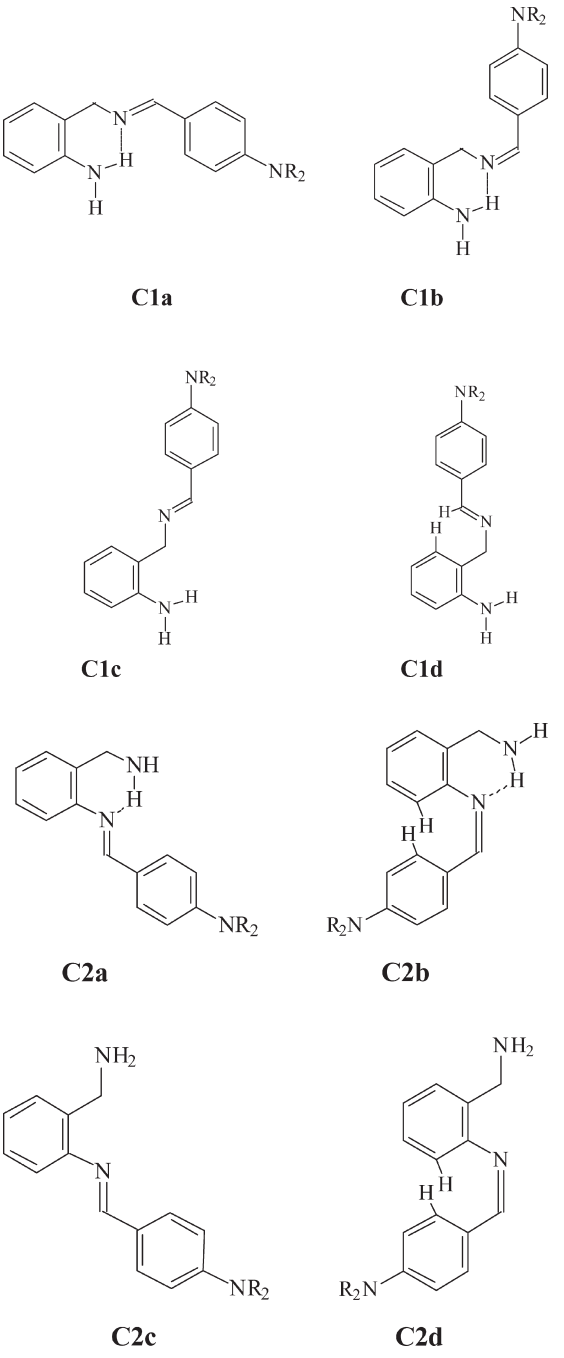


Compound	R	R'	R"
1	$N(CH_2)_4$	H	H
2	NEt_2	H	H
3	NMeEt	H	H
4	$N(CH_2)_6$	H	H
5	NMe_2	H	H
6	$N(CH_2)_5$	H	H
7	H	H	H
8	NMe_2	Me	H
9	NMe_2	Me	Me

Scheme 1



Scheme 2



Scheme 3

hydrogen bonds. In **C1d**, **C2b** and **C2d**, serious steric interactions should appear. Since aliphatic amines are known to be weaker acids than anilines,[4] the CH_2—$NH_2\cdots N$ hydrogen bonds are expected to be weaker than Ar—$NH_2\cdots$N—CH_2 hydrogen bonds. As a consequence, intramolecular hydrogen bonds in **C1a** and **C1b** will be much stronger than those in **C2a** and **C2b**.

NMR signals of the **R** tautomeric form (Scheme 1) can be clearly seen in the spectra. Thus, H-2 resonates at 5.13–5.23 ppm (Table 1), in accordance with results published earlier for the same type of compounds[4] and their *N*-alkylated derivatives.[5] Although we, like others,[4] could not observe all ^{15}N NMR signals (Table 1), the chemical shifts of C-2 (from 69.1 to 69.5 ppm), N-1 (from −303.8 to −301.7 ppm) and N-3 (from −334.3 to −332.6 ppm) are also comparable to those obtained earlier for the ring tautomer.[4]

Unfortunately, the N-1 NMR signals of **C1** form could not be seen in the ^{1}H,^{15}N HMBC spectra. The chemical shifts of H-2 (8.25–8.38 ppm), C-2 (160.8–162.0 ppm) and N-3 (from −79.2 to −59.5 ppm) for this tautomer (Table 1) are comparable to those obtained earlier.[4] It should be mentioned that there are cross peaks in the ^{1}H,^{13}C HMQC and ^{1}H,^{13}C and ^{1}H,^{15}N HMBC spectra of the compounds studied that confirm the respective short- and long-distance ^{1}H-^{13}C and ^{1}H-^{15}N interactions, e.g. that of the H-2 signal (8.24–8.38 ppm) versus the N-3 signal (from −59.5 to −79.2 ppm) for **C1** (^{1}H,^{15}N HMBC).

The NMR spectra also contain signals which suggest the presence or three or four other components (Table 2). Although some ^{1}H,^{15}N cross peaks are missing, these

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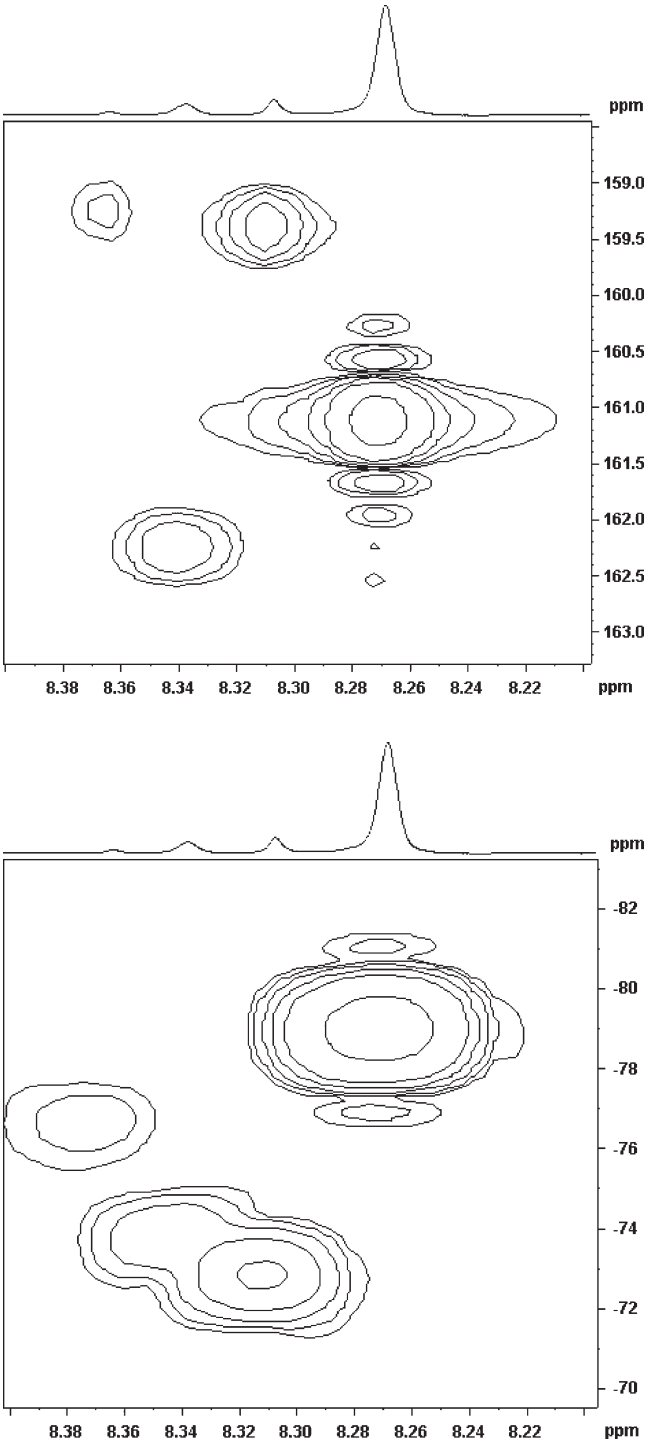

Figure 1. PFG ^{1}H–^{13}C HMQC (top) and PFG ^{1}H–^{15}N HMBC (bottom) partial spectra of **1**, both showing four heteronuclear chemical shift correlation peaks. For their assignments and exact chemical shift values, see Tables 1 and 2

additional signals probably refer to other tautomeric forms, e.g. there are typical signals of the azomethine protons, CH═N, (Table 2). Since they appear in the range 8.26–8.41 ppm (Table 2) and are comparable to those found for *N*-alkylated derivatives of **C2**,[5] they seem to refer to **C2**.

Resonance structures of the ring and chain tautomers in question are shown in Scheme 4. Inspection of the ^{15}N chemical shifts of 2-[(benzylideneamino)methyl]aniline (**C1**) shows that electron-donating substituents increase the charge density at the imino nitrogen.[4] This is expected to happen also in the other chain form (Scheme 4).

The extended conjugation in 2-(benzylideneamino)-benzylamine (**C2**) seems to be the main driving force for the stabilization of this form. Electron-withdrawing substituents in *para* and *ortho* positions of the phenyl in question would additionally extend this conjugation (Scheme 5); nevertheless, *N*-(*p*-dimethylaminobenzylidene)-*p*-nitroaniline is known to be non-planar (the two phenyl rings are considerably twisted with respect to the plane of the —CH═N— fragment).[8] Although this refers to the solid (crystal) state, the non-planarity is expected to be conserved, at least to some extent, in solution. Electron spectroscopic parameters for *N*-(*p*-dimethylaminobenzylidene)amines show that the quinoid resonance structure (Scheme 6; R = phenyl or alkyl) makes a significant contribution.[9,10] This requires that the two phenyl rings in the *N*-(*p*-dimethylaminobenzylidene)aniline in question are not coplanar.

Although the dihedral angle between the —CH═N— plane and the phenyl bound to nitrogen in *N*-(*p*-dimethylaminobenzylidene)anilines (Scheme 7) is presumably fairly large,[11] resonance interactions between the Me_2N—C_6H_4—CH═N and N—Ar moieties are still possible, although considerably diminished.[11] The nitro group in the *N*-bound phenyl of the *N*-benzylidene-*p*-nitroaniline (R′, R″ = H, Scheme 8) is responsible for the twisting of this ring out of the plane of the other phenyl substituent in this molecule.[9] Methyl group(s) in *ortho* position(s) (R′, R″ = H and/or Me) do not affect the parameters of absorption bands in the electronic spectra of these compounds.[12,13] This observation additionally confirms that the azomethine nitrogen in these compounds is sp hybridized.

The data in Table 3 indicate that the ring substituent alters mainly the amounts of the **R** and **C1**(major) tautomers [contents of the respective forms are based on integral intensities of the signal of (azo)methine protons in the ^{1}H NMR spectra]. In general, electron-donating ring substituents increase the amount of the chain form **C1**(major). The other forms, i.e. **C1**(minor) and **C2**, appear in only small or even minute quantities.

Table 4 shows that lowering the temperature of the $CDCl_3$ solution decreases the content of **C1**(major) tautomers of 2-(R-phenyl)-1,2,3,4-tetrahydroquinazolines. On the other hand, the amount of the **R** form increases simultaneously.

Relative experimental enthalpies and entropies of tautomers based on the linear dependence $\ln K = f(1/T)$ are shown in Table 5 (the procedure for the calculations was described previously).[14,15] It can be seen that transformation **R** → **C1** is an endothermic process, especially for less electron-donating substituents.

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Table 1. Selected ^{1}H, ^{13}C and ^{15}N NMR chemical shifts (δ, ppm) of the **R** and major **C1** tautomeric forms in $CDCl_3$ solutions at 303 K

	R				**C1**			
Compound	H-2	C-2	N-1	N-3	H-2	C-2	N-1	N-3
1	5.16	69.25	−301.4	−332.9	8.27	161.05	—[a]	−79.2
2	5.16	69.31	—[a]	−332.6	8.24	160.96	—[a]	−79.1
	4.95[b]	67.37[b]	−300.4[b]	−336.5[b]	8.22[b]	160.72[b]	−307.6[b]	−72.6[b]
3	5.16	69.14	−301.7	−333.1	8.27	160.86	—[a]	−77.2
4	5.14	69.33	−301.7	−333.0	—[a]	161.05	—[a]	−78.9
5	5.16	69.38	−301.8	−332.9	8.23	161.05	—[a]	−78.1
	4.98[b]	67.93[b]	−300.8[b]	—[a]	8.25[b]	160.78[b]	—[d]	−70.5[b]
	5.14[c]							
6	5.15	69.12	−302.4	−333.5	8.25	160.77	—[a]	−73.5
7	5.23	69.46	−303.8	−334.3	8.38	161.12	—[a]	−59.5
	5.10[b]	68.08[b]	−302.3[b]	−337.5[b]	8.46[b]	161.28[b]	−322.1[b]	−52.4[b]
8	5.16	69.28	−302.5	−333.3	8.29	161.00	—[a]	−67.8
9	5.13	69.37	−302.4	−333.1	8.26	161.19	—[a]	−65.0

[a] Signal not detected.[4]
[b] According to Ref. 4 in DMSO-d_6.
[c] For the $\mathbf{R^F}$ form, R′ = *i*-Pr (see Scheme 2) in $CDCl_3$.[5]
[d] Signal not detected in DMSO-d_6.[4]

Table 2. Selected ^{1}H, ^{13}C and ^{15}N NMR Chemical Shifts (δ/ppm) of the minor **C1**, and **C2** tautomeric forms in $CDCl_3$-solutions at 303 K

	Minor **C1**			**C2**[a]					
Compound	H-2	C-2[b]	N-3	H-2	C-2[b]	N-1	H-2	C-2[b]	N-1
1	8.34	162.32	—	8.31	159.45	—	8.36	159.34	—
			−74.2			−73.1			—
									77.3
2	8.31	162.2	−74.9	8.28	159.3	−72.4	8.34	159.1	—
									76.5
3	8.33	162.0	−72.0	8.31	159.2	−71.2	—[c]	159.0	—
									75.0
4	—[c]	162.2	−74.4	—[c]	159.3	−72.5	—[c]	—[c]	—
									76.5
5	8.29	162.2	—[c]	8.26	159.4	−71.0	8.33	159.3	—[c]
				8.38[d]					
6	8.30	162.0	−68.4	8.27	159.2	−67.9	—[c]	—[c]	—
									71.8
7	8.42	162.3	—[c]	8.41	159.8	−54.1	—[c]	—[c]	—[c]
8	8.33	162.18	−63.4	8.30	159.54	−62.1	8.37	—[c]	—[c]
9	8.35	161.19	−61.2	8.31	—[c]	−59.1	—[c]	—[c]	—[c]

[a] Signal of N-3 was not detected.
[b] For the one decimal accuracy of ^{13}C chemical shifts, see Experimental.
[c] Signal not detected.
[d] For the $\mathbf{R^F}$ form, R′ = *i*-Pr (see Scheme 2) in $CDCl_3$.[5]

It is worth mentioning that the situation in the compounds studied here resembles somewhat the complex molecular rearrangements found earlier in 2,2-disubstituted-1,3,4-benzotriazepinones involving (i) ring to open-chain tautomerization, (ii) pseudorotation of the ring forms and ring (N-3)-inversion processes and (iii) interconversion of the open-chain forms via *cis–trans*-amide bond and/or *Z*/*E* C═N bond isomerizations.[16]

CONCLUSIONS

2-(R-Phenyl)-1,2,3,4-tetrahydroquinazolines, the condensation products of 2-aminobenzylamine with substituted benzaldehydes, are in equilibrium with 2-[(benzylideneamino)methyl]aniline (**C1**) and 2-(benzylideneamino)benzylamine (**C2**) in deuteriochloroform solution. The former is the major and the latter the minor

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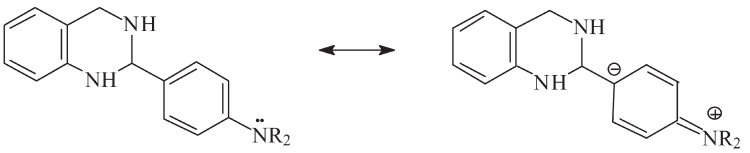
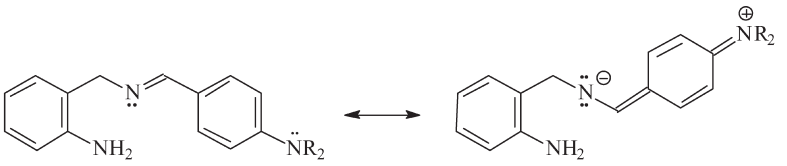
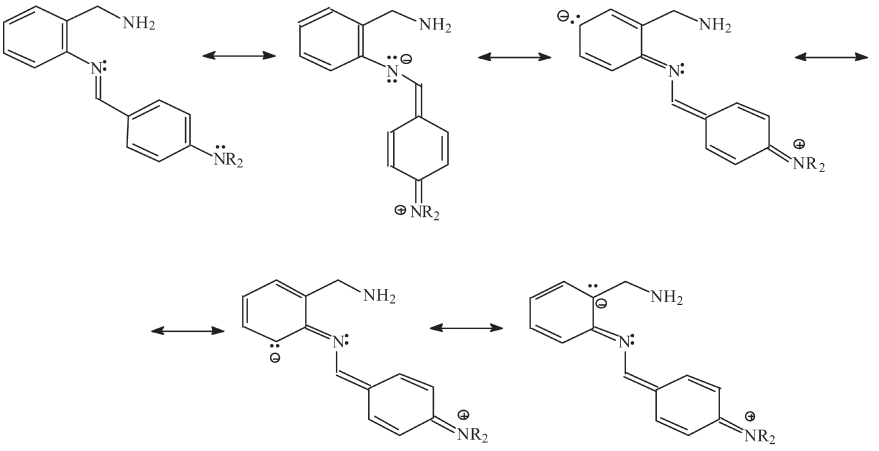


R

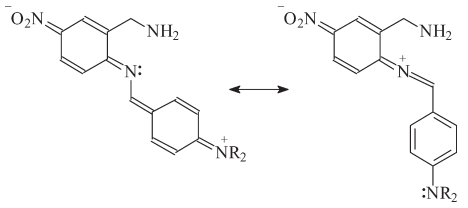


C1



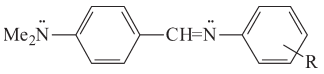
C2

Scheme 4

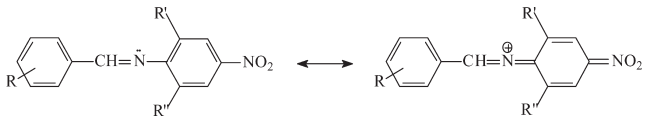


Scheme 5

Scheme 6



Scheme 7



Scheme 8

chain tautomer. Traces of **C2** were detected even when no electron-donating substituents were present in the molecule. The two chain forms may appear in different conformations. In some of them the free amino groups (NH_2) act as proton donors to form intramolecular hydrogen bonds with the imine nitrogen atom. Lowering

Table 3. Percentages of different tauto/rotameric forms in $CDCl_3$ at 30 °C

Compound	**R**	Major **C1**	Minor **C1**	**C2**[a]	
1	53.9	37.9	3.4	3.6	1.2
2	58.0 69.4[b]	36.0	2.6	2.7	0.7
3	63.0	32.6	2.0	2.2	0.2
4	56.9 64.5[b]	37.2	2.8	3.2	0
5	63.9	29.1	2.9	3.4	0.8
6	72.5	22.0	2.3	2.7	0.5
7	92.6 94.3[b]	6.3	0.5	0.6	0
8	85.4	12.0	1.0	1.4	0.2
9	92.9	6.3	0.1	0.7	0

[a] Probably two different rotamers.
[b] According to Ref. 4 in the same solvent at 30 °C.

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Table 4. Percentages of **R/C1**(major) tautomeric forms in $CDCl_3$ at different temperatures

Compound	Temperature (°C)			
	50	40	30	20
1	45.2/42.5	49.5/40.3	53.9/37.9	58.9/33.1
2	—	52.6/37.1	58.0/36.0	62.7/32.1
3	54.7/39.2	57.9/36.8	63.0/32.6	68.3/28.7
4	48.1/43.4	52.9/40.5	56.9/37.2	63.6/32.5
5	—	57.4/34.2	63.9/29.1	70.7/26.9
7	88.7/11.3	91.7/8.3	92.6/6.3	94.9/4.5
8	77.5/17.9	81.5/14.8	85.4/12.0	—

Table 5. Relative (with respect to form **R**) experimental enthalpies and entropies of the **C1** (major) chain form

Compound	Enthalpy (kJ mol^{-1})	Entropy (kJ mol^{-1} K^{-1})
1	13.3	40.9
2	12.2	36.3
3	14.3	41.5
4	14.7	44.7
5	17.1	50.0
7	25.6	61.9
8	20.2	50.4

the temperature of the solution of 2-(R-phenyl)-1,2,3,4-tetrahydroquinazolines resulted in a decreasing content of the 2-[(benzylideneamino)methyl]aniline form. On the other hand, the mole fraction of the ring form increases on lowering the temperature. Opening of the tetrahydropyrimidine ring in 2-(R-phenyl)-1,2,3,4-tetrahydroquinazolines was found to be an endothermic process, especially for less electron-donating substituents.

EXPERIMENTAL

The synthetic procedure has been described previously.[4] The solid products were recrystallized from methanol (reaction yields were 55–82%). Satisfactory analytical data ($\pm 0.3\%$ for C, H and N) were obtained for all new compounds. The m.p.s (°C) are 95–97 (102–105)[4] for **1**, 97–99 (96–98)[4] for **2**, 71–73 for **3**, 107–109 (122–124)[4] for **4**, 98–100 for **5**, 111–113 for **6**, 88–90 for **7**, 89–90 for **8** and 108–110 for **9**.

All NMR spectra were recorded in dilute deuteriochloroform solution. One-dimensional ^{1}H and composite pulse proton decoupled (waltz-16) ^{13}C NMR spectra and two-dimensional homonuclear PFG (pulsed field gradient) DQF (double quantum filtered) ^{1}H–^{1}H COSY, PFG ^{1}H–^{13}C HMQC (heteronuclear multiple quantum coherence), PFG ^{1}H–^{13}C HMBC (heteronuclear multiple bond correlation) and PFG ^{1}H–^{15}N HMBC chemical shift correlation maps were recorded with a Bruker Avance DRX 500 NMR spectrometer equipped with an inverse detection 5 mm diameter probehead and z-gradient accessory working at 500.13 MHz (^{1}H), 125.77 MHz (^{13}C) and 50.69 MHz (^{15}N). In the PFG ^{1}H–^{13}C HMBC experiment the evolution delay was set to 50 ms, which is optimal for 10 Hz proton–carbon-13 spin–spin coupling, whereas in the PFG ^{1}H–^{15}N HMBC experiment that delay was set to 100 ms, corresponding a 5 Hz proton–nitrogen-15 coupling. The ^{1}H chemical shifts are referenced to the trace signal of chloroform (7.26 ppm from internal TMS), ^{13}C chemical shifts are referenced to the center peak of the triplet of deuteriochloroform (77.0 ppm from internal TMS) and ^{15}N chemical shifts are referenced to the signal of external CH_3NO_2 (0.0 ppm) in a 1 mm diameter capillary tube inserted coaxially inside the 5 mm diameter NMR tube.

Because the ^{13}C NMR signals originated from the minor contributors and ^{15} N NMR signals could not be detected directly, their chemical shifts are taken from 1D projections of inversely (and much more sensitively) detected 2D spectra. The accuracy of the chemical shift values are therefore limited in one decimal although 1K (^{1}H) $\times$ 4K (^{13}C) in PFG ^{1}H–^{13}C HMQC and 1K (^{1}H) $\times$ 4K (^{15}N) in PFG ^{1}H–^{15}N HMBC processing matrix sizes were used. Detailed acquisition and processing parameters are available from E.K. on request. Variable-temperature ^{1}H NMR spectra were recorded in the range +40 to −10 °C in 10 °C steps.

Acknowledgments

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REFERENCES

1. Maloshitskaya O, Sinkkonen J, Ovcharenko VV, Zelenin KZ, Pihlaja K. *Tetrahedron* 2004; **60**: 6913–6921.
2. Lázár L, Fülöp F. *Eur. J. Org. Chem.* 2003; 3025–3042.
3. Lessel J. *Pharm. Acta Helv.* 1996; **71**: 109–119.
4. Sinkkonen J, Zelenin KN, Potapov A-KA, Lagoda IV, Alekseyev VV, Pihlaja K. *Tetrahedron.* 2003; **59**: 1939–1950.
5. Göblyös A, Lázár L, Fülöp F. *Tetrahedron.* 2002; **58**: 1011–1016.
6. Taft RW, Price E, Fox IR, Lewis IC, Andersen KK, Davis GT. *J. Am. Chem. Soc.* 1963; **85**: 3146–3156.
7. Taft RW, Evans HD. *J. Chem. Phys.* 1957; **27**: 1427–1428.
8. Nakai H, Shiro M, Ezumi K, Sakata S, Kubota T. *Acta Crystallogr., Sect. B* 1976; **32**: 1827–1833.
9. Gawinecki R. *Pol. J. Chem.* 1986; **60**: 831–836.
10. Ebara N. *Bull. Chem. Soc. Jpn.* 1961; **34**: 1151–1158.
11. Gawinecki R. *Pol. J. Chem.* 1988; **62**: 799–806.
12. Akaba R, Tokumaru K, Kobayashi T. *Bull. Chem. Soc. Jpn.* 1980; **53**: 1993–2001.
13. Akaba R, Tokumaru K, Kobayashi T, Utsunomiya C. *Bull. Chem. Soc. Jpn.* 1980; **53**: 2002–2006.
14. Kolehmainen E, Ośmiałowski B, Nissinen M, Kauppinen R, Gawinecki R. *J. Chem. Soc., Perkin Trans. 2* 2000; 2185–2191.
15. Kolehmainen E, Ośmiałowski B, Krygowski TM, Kauppinen R, Nissinen M, Gawinecki R. *J. Chem. Soc., Perkin Trans. 2* 2000; 1259–1266.
16. Pihlaja K, Simeonov MF, Fülöp F. *J. Org. Chem.* 1997; **62**: 5080–5088.

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