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Ring−Chain Tautomerism of 2-Aryl-Substituted *cis*- and *trans*-Decahydroquinazolines

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In $CDCl_3$ at 300 K, 2-aryl-substituted *cis*- and *trans*-3-isopropyldecahydroquinazolines and *trans*-3-phenyldecahydroquinazolines proved to be three-component (r^1-o-r^2) ring−chain tautomeric mixtures, whereas only ring-closed tautomers could be detected for the 3-methyl-substituted analogues. The proportions of the ring−chain tautomeric forms at equilibrium were strongly influenced by the N-substitutents and the cis−trans ring junction and could be described by the equation $\log K_X = \rho\sigma^+ + \log K_{X=H}$. These are the first examples among 2-aryl-1,3-*N*,*N*-heterocycles of a three-component ring−chain tautomeric equilibrium characterized by a Hammett-type equation. The stabilities of the ring-closed forms of *cis*- and *trans*-2-aryldecahydroquinazolines and the corresponding 3,1-benzoxazines were found to increase in the following sequence of the heteroatom at position 3: NPh < N-*i*-Pr < O < NMe.

Introduction

The structures and reactivities of numerous five- and six-membered, saturated, N-unsubstituted 1,3-X,N heterocycles (X = O, S, NR) can be characterized by the ring−chain tautomeric equilibria of the 1,3-*X*,*N* heterocycles and the corresponding Schiff bases.[1] Studies on the ring−chain tautomeric equilibria of 2-aryl-substituted oxazolidines and tetrahydro-1,3-oxazines led to the conclusion that the proportion of the ring-closed forms strongly depends on the electronic character of the substituent on the aromatic ring. For these compounds, a linear correlation was found between the $\log K_X$ values of the equilibria (K_X = [ring]/[chain]) and the Hammett−Brown parameters σ^+ of the substituents X on the 2-aryl group both in solution and in the gas phase.[1,2] The value of ρ in eq 1 was found to be characteristic of the oxazolidine or tetrahydro-1,3-oxazine ring system and dependent on the temperature and the nature of the solvent.[1b] The scope and limitations of eq 1 were extended to multicomponent equilibria involving homologous or regioisomeric 1,3-O,N ring forms in the same tautomeric mixtures.[3]

$$\log K_X = \rho\sigma^+ + \log K_{X=H} \qquad (1)$$

The ring−chain tautomerism of the 1,3-*X*,*N* heterocycles can be advantageously exploited in different areas of organic synthesis. The selectivity of certain transformations can be explained on the basis of the ring−chain tautomeric equilibration of the intermediates, followed by a shift in the equilibrium.[5] Oxazolidines and tetrahydro-1,3-oxazines can be used as aldehyde or ketone sources in the Hantzsch and Pictet−Spengler reactions.[6] Ring−chain tautomeric chiral oxazolidines can be applied for the addition of organometallics or silyl enol ethers in enantioselective syntheses of chiral amines or β-amino acids.[7] Serine- or threonine-derived oxazolidines and cysteine-derived thiazolidines (pseudoprolines) are versatile tools with which to overcome various problems in peptide synthesis and, by virtue of their ring−chain tautomeric character, serve as reversible protecting groups of these amino acids.[8]

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The pharmacological and physicochemical properties of a biologically active compound containing a 1,2- or 1,3-amino alcohol, a diamine, or an amino thiol moiety or an oxo group can be influenced by their transformations to a ring−chain tautomeric prodrug. From the ring−chain equilibrium of this derivative, the open form undergoes continuous hydrolysis to give the bioactive molecule.[9]

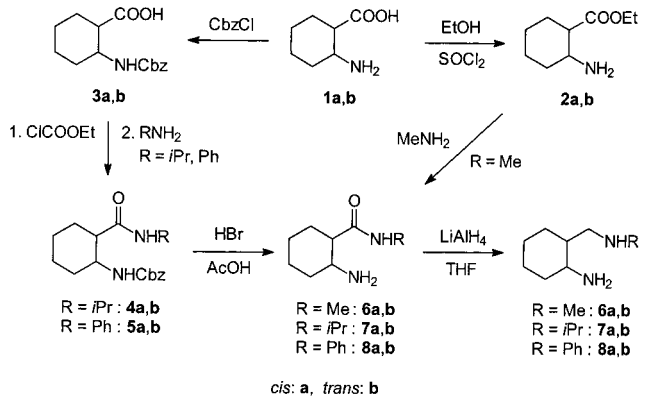
A large number of examples have emerged in recent years that demonstrate that ring−chain tautomerism occurs not only among *N*-unsubstituted saturated 1,3-O,N heterocycles but also among their 1,3-N,N analogues.[1,10,11] On the basis of their ring−chain tautomeric character, 1,2-disubstituted saturated 1,3-N,N heterocycles can be exploited as intermediates in the selective functionalization of N-monosubstituted ethylene- or propylenediamines; the selectivity of the reaction is strongly influenced by the nature of the substituent at position 2.[12] For 2-aryl-substituted imidazolidines, hexahydropyrimidines, and 1,2,3,4-tetrahydroquinazolines, similar to their 1,3-O,N analogues, a Hammett-type linear correlation was found between the ring−chain ratios for the tautomeric equilibria and the electronic character of the substituent on the 2-phenyl ring (eq 1).[11] For N-substituted 2-aryl-1,3-N,N heterocycles, the ring−chain tautomeric process and the values of ρ and log $K_{X=H}$ in eq 1 depend strongly on the steric and electronic characters of the substituent on the nitrogen. In contrast with the 1,3-O,N analogues, the value of ρ proved not to be characteristic of the 1,3-N,N ring system.[11]

As a continuation of previous studies on five- and six-membered 1,3-N,N heterocycles, our present aim was to investigate the effects of the substituents and the stereochemisty of the ring junction on the ring−chain tautomeric character of some 3-substituted 2-aryldecahydroquinazolines for the purpose of refining the scope and limitations of application of eq 1 among six-membered 1,3-N,N heterocycles.

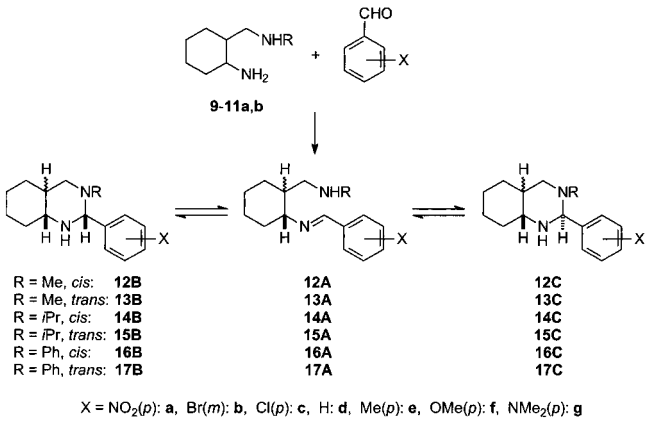
Results and Discussion

The starting materials for the synthesis of decahydroquinazoline model compounds were prepared from *cis*- and *trans*-2-aminocyclohexanecarboxylic acid (**1a**,**b**) by a combination of standard chemical procedures (Scheme 1).[13,14] *cis*- and *trans*-2-(Methyl- or isopropyl or phenylaminomethyl)cyclohexylamines (**9a**,**b**, **10a**,**b**, and **11a**,**b**) were synthesized by $LiAlH_4$ reduction of the corresponding N-substituted amino carboxamides (**6a**,**b**, **7a**,**b**, and **8a**,**b**), which were obtained either by the direct amidation of amino esters **2a**,**b** with methylamine[13] or via the N-protected amino acids **3a**,**b** by using the mixed anhydride method.[14]

SCHEME 1



SCHEME 2



Model compounds **12**−**17** were prepared by the reactions of diamines **9**−**11a**,**b** with equivalent amounts of substituted benzaldehydes (Scheme 2). The ^{1}H NMR spectra of **12**−**17** revealed that, in $CDCl_3$ solution at 300 K, *cis*- and *trans*-3-isopropyl-2-aryldecahydroquinazolines (**14a**−**g** and **15a**−**g**) and *trans*-3-phenyl-substituted 2-aryldecahydroquinazolines (**17a**−**g**) participate in three-component (r^1−o−r^2) ring−chain tautomeric equilibria, having both electron-donating and electron-withdrawing substituents on the 2-phenyl ring. For *cis*-3-phenyl-2-aryldecahydroquinazolines (**16**), ring−chain tautomeric equilibria could be detected only for compounds bearing an electron-withdrawing substituent X (**16a**−**c**); for the 2-phenyl derivative (**16d**) and the compounds with an electron-donating substituent X on the 2-phenyl ring (**16e**−**g**), only the presence of the open-chain tautomer was observed. Similar to other *N*-methyl-substituted six-

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TABLE 1. Proportions (%) of Tautomeric Forms (A−C) in Tautomeric Equilibria for Cis Compounds 12, 14, and 16 ($CDCl_3$, 300 K)

compd	X	σ^+	12A	12B	12C	14A	14B	14C	16A	16B	16C
a	*p*-NO_2	0.79	∼0	91.3	8.7	27.4	66.6	6.0	83.3	11.4	5.3
b	*m*-Br	0.405				39.8	57.2	3.0	98.4	1.6	∼0
c	*p*-Cl	0.114				47.4	48.3	4.3	98.5	1.5	∼0
d	H	0				55.9	42.8	1.3	∼100	∼0	∼0
e	*p*-Me	−0.311				62.5	37.5	∼0	∼100	∼0	∼0
f	*p*-OMe	−0.778				74.3	25.7	∼0	∼100	∼0	∼0
g	*p*-NMe_2	−1.7	∼0	∼100	∼0	88.9	11.1	∼0	∼100	∼0	∼0

TABLE 2. Proportions (%) of Tautomeric Forms (A−C) in Tautomeric Equilibria for Trans Compounds 13, 15, and 17 ($CDCl_3$, 300 K)

compd	X	σ^+	13A	13B	13C	15A	15B[a]	15C[a]	17A	17B[b]	17C[b]
a	*p*NO_2	0.79	∼0	∼100	∼0	5.9	89.5	4.6	32.0	54.0	14.0
b	*m*Br	0.405				15.5	73.7	10.8	64.1	29.3	6.6
c	*p*Cl	0.114				12.2	82.4	5.4	71.9	24.5	3.6
d	H	0				11.0	85.0	4.0	77.9	18.2	3.9
e	*p*Me	−0.311				17.4	77.7	4.9	88.4	10.3	1.3
f	*p*OMe	−0.778				33.6	63.8	2.6	94.5	5.0	0.5
g	*p*NMe_2	−1.7	∼0	∼100	∼0	67.7	32.3	∼0	98.9	1.1	∼0

[a] The proportions of the ring forms were determined by deconvolution because of the overlapping lines. [b] The proportions of the tautomeric forms of **17a**−**f**, measured at 233−273 K, were extrapolated to 300 K by using the van't Hoff equation.

TABLE 3. Proportions (%) of Ring Forms (B and C) in Tautomeric Equilibria for Compounds 17a−f in $CDCl_3$ at 233−273 K

compd	233 K	237 K	241 K	245 K	249 K	253 K	263 K	273 K
17aB	59.3	55.3	55.9	56.0	56.6	57.0	55.6	56.8
17aC	31.9	29.9	28.8	26.4	25.9	24.1	21.8	19.0
17bB	51.2	50.5	50.6	50.6	47.9	47.6	47.3	51.2
17bC	22.0	20.1	18.2	16.7	14.5	12.8	*a*	*a*
17cB	36.3	36.4	36.6	36.6	35.9	35.4	31.6	30.9
17cC	20.6	18.9	17.3	15.9	14.5	12.3	*a*	*a*
17dB	29.1	29.6	29.3	28.9	28.7	28.4	25.7	23.2
17dC	14.4	13.1	11.8	10.0	8.7	6.0	*a*	*a*
17eB	19.2	18.6	19.3	17.7	18.7	17.0	14.1	14.6
17eC	16.4	15.4	13.0	11.6	8.5	7.0	*a*	*a*
17fB	9.1	9.6	9.4	9.2	8.3	8.3	*a*	*a*
17fC	4.4	4.3	4.1	3.7	3.1	2.3	*a*	*a*

[a] Quantitative integration of the NMR signals was not possible due to line broadening.

membered 2-aryl-1,3-N,N heterocycles,[11d] for *cis*- and *trans*-3-methyl-2-aryldecahydroquinazolines (**12a**,**g** and **13a**,**g**), no open-chain tautomeric forms (**A**) could be detected. Despite the presence of the electron-donating *p*-dimethylamino substituent on the 2-phenyl ring, which is favorable for the shift of the equilibrium toward the open tautomer,[1] the NMR spectra of **12g** and **13g** showed exclusively the presence of ring-closed tautomers.

The proportions of the chain (**A**) and diastereomeric ring forms (**B** and **C**) of the tautomeric equilibria (K_X) were determined at 300 K by integration of the well-separated NC*H*ArN (ring) and N=C*H* (chain) proton singlets in the ^{1}H NMR spectra of compounds **12**−**16**. For **15**, the ratios of the ring-closed tautomers were calculated by deconvolution because of their partly overlapping NC*H*ArN singlets (Tables 1 and 2).

For compounds **17**, tautomeric ratios (K_X) could not be determined at 300 K because of the fast interconversion of the tautomeric forms; the signal of the *minor* ring form therefore appeared in the ^{1}H NMR spectrum only at lower temperatures. Values of K_X and the ratios of the ring forms at 300 K for **17** (Tables 2 and 3) were calculated according to the van't Hoff equation (eq 2) on the basis of the tautomeric ratios determined at lower temperatures.[15] The decreasing proportions of the ring-closed tautomers (**17B** and **17C**) with increasing temperature are in good accord with the significant loss of conformational entropy due to ring formation, which is indicative of ring−chain tautomerism.

$$\ln K_X = -\Delta H°/RT + \Delta S°/R \qquad (2)$$

As a consequence of the very similar NMR spectroscopic characteristics of these 2-aryldecahydroquinazolines, with the same N-substituent and stereochemistry of the ring junction, determination of the relative configuration of the *major* and *minor* ring-closed tautomers and conformational analysis were performed only for the *p*-nitrophenyl derivatives **12a**−**17a** (Table 4). Data on **12aB** and **16aA** were chosen to illustrate the ^{1}H NMR spectra of the prepared tautomeric compounds (see the Experimental Section). 2-Aryl substituents did not change the sequence of the chemical shifts of the characteristic NC*H*ArN and N=C*H*Ar protons.

In the EXSY spectra[16] of **14a** and **15a**, there is a negative cross-peak between the N=C*H*Ar singlet of the open form and both NC*H*ArN signals of the *major* and *minor* ring forms, while there is no negative cross-peak between the NC*H*ArN signals of the cyclic tautomers. This proves the interconversion of the ring-closed tautomers (**B** and **C**) through the open-chain form (**A**). The relative configurations of the *major* ring-closed tautomers of **12a**−**17a** were deduced from the NOESY spectra, in which the cross-peak for the protons at positions 2 and 8a proves their cis arrangement (**B**) (Scheme 2). The same relative configuration of H-2 and H-8a for the *major* ring-closed tautomer was found for all the remaining 2-(*p*-nitrophenyl)decahydroquinazolines (**12a**, **13a**, **16a,** and **17a**). In the ring−chain tautomeric equilibria of the corresponding 2-aryldecahydro-3,1-benzoxazines (**18**, **19**),

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TABLE 4. Selected Characteristic ^{1}H Chemical Shifts (ppm, δ_{TMS} = 0 Ppm) and Coupling Constants (Hz) for Compounds 12a−17a

compd	H-2	H-4$_{eq}$	H-4$_{ax}$	H-4a	H-8a	^3J(4$_{eq}$,4a)	^3J(4$_{ax}$,4a)
12aB	3.81	2.87	2.42	1.60	3.05	2.01	3.53
12aC	4.07	2.70	2.63	1.67	2.80	5.29	<1
13aB	3.88	2.97	2.02	1.45	2.27	3.53	11.08
14aA[a]	8.39	2.46	2.36	1.79	3.61	*b*	*b*
14aB	4.39	2.81	2.59	1.67	3.02	2.27	3.27
14aC	4.58	3.16	2.62	1.66	2.96	*b*	*b*
15aA[a]	8.39	2.40	2.54	1.33	3.10	*b*	*b*
15aB	4.44	2.97	2.18	1.39	2.28	3.53	9.06
15aC	5.04	2.85	2.54	1.32	3.08	3.02	11.58
16aA[a]	8.35	3.06	2.92	1.98	3.66	7.55	5.79
16aB	5.90	3.32	3.20	1.70	3.20	*b*	*b*
16aC	5.03	3.67	3.35	2.22	3.72	<1	5.38
17aA[a,c]	8.38	2.98	2.87	2.05	3.07	*b*	*b*
17aB[c]	5.94	3.63	2.81	1.45	2.28	3.27	11.58
17aC[c]	5.06	3.51	2.75	1.63	2.47	3.02	11.33

[a] The protons of the open form (**A**) are numbered according to the corresponding protons of the quinazoline ring forms (**B** and **C**). [b] Coupling constants were not available due to overlapping of the lines and the low proportion of the tautomeric form at equilibrium. [c] Data from the spectra run at 253 K.

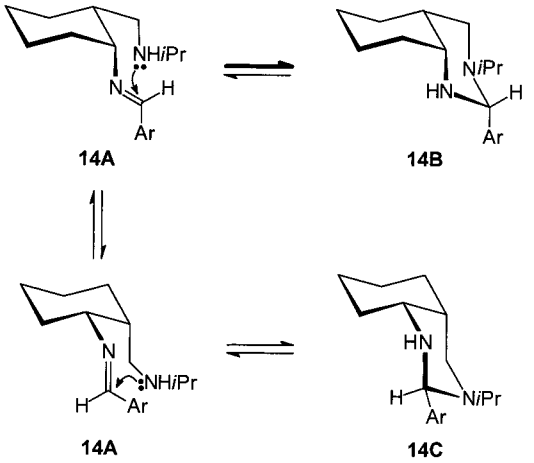
the *major* ring-closed tautomeric form also had cis-arranged H-2 and H-8a.[2b]

The configuration of the azomethine double bond was determined by observing the intensity of the NOE interaction between H-2 and H-8a in model compounds that contain the open tautomeric form in a higher proportion (**16a** and **17a**). A high-intensity NOESY cross-peak could be detected for both compounds, which suggests the *E* configuration of the C=N double bond and shows that the H(8a)−C(8a)−N(1)−C(2) torsion angle is within the region of ±60°.

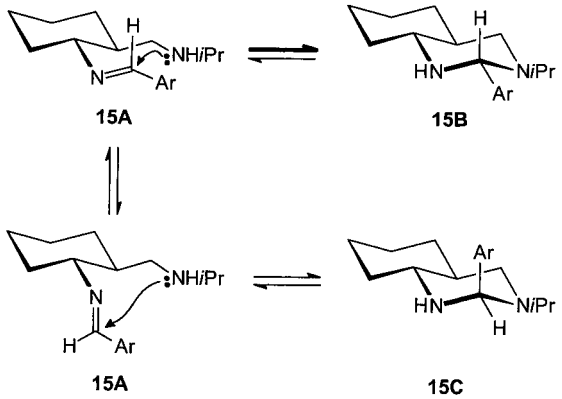
The data in Tables 1 and 2 indicate that the proportions of the diastereomeric ring-closed tautomers in the equilibria, which are proportional to the relative stabilities of these ring forms, are greatly influenced by the relative configurations of the chiral centers. In an attempt to find a relationship between the relative stability and the predominant conformation of the ring epimers, a conformational analyis of *cis*- and *trans*-3-isopropyl-2-(*p*-nitrophenyl)decahydroquinazolines (**14a** and **15a**) was performed by using NMR and modeling methods. An earlier conformational analysis on decahydroquinazoline derivatives led to the conclusion that cis-fused derivatives could exist in two interconvertible chair−chair conformations (*N-in* or *N-out*), the equilibrium of which was strongly dependent on the substitution of the nitrogen at position 1. For 1-unsubstituted *cis*-decahydroquinazolines, the conformational equilibrium is shifted predominantly toward the *N-in* conformer, while the 1-methyl cis derivative can be characterized by a predominant *N-out* conformation.[13c,17]

The conformation for **14aB** (*major* ring form) can readily be determined by analysis of the crucial NMR spectral parameters. The coupling constants of the signals of the protons at positions 4a and 4 are similar, ^3J (H-4$_{eq}$, H-4a) = 2.27 Hz and ^3J (H-4$_{ax}$, H-4a) = 3.27 Hz, and low, which suggests an *equatorial* orientation of H-4a relative to the heterocyclic ring. NOE interactions

SCHEME 3



SCHEME 4



can be detected from H-2 to H-4$_{ax}$ and H-8a, which is evidence of a predominantly *equatorial* aryl group, in accordance with its steric demand. On the basis of these results, it can be concluded that the *major* ring-closed tautomer **14aB** predominantly occupies an *N-in* conformation (Scheme 3). The low relative concentration of the *minor* ring-closed tautomer **14aC** did not facilitate the extraction of useful NMR data and therefore a standard conformational search procedure[18] was carried out to find the lowest energy conformation. The resulting structure (Scheme 3) of **14aC** shows an *N-out* conformation with the sterically demanding aryl group in the *equatorial* position. The energy difference between **14aB** and **14aC**, estimated from the average ring−ring tautomeric ratio, is approximately 6.6 kJ/mol. The steric repulsion between H-4$_{ax}$ and H-5$_{ax}$ and between H-2 and H-7$_{ax}$ in **14C** may account for the observed stability difference.

The *major* trans ring-annelated diastereomer **15aB** exhibits a vicinal coupling constant (^3J(H-4a, H-4$_{eq}$) = 3.53 Hz and ^3J(H-4a, H-4$_{ax}$) = 9.06 Hz) and NOE interaction (H-2−H-4$_{ax}$, H-2−H-8a) pattern, which is in accordance with the expected conformation with the aryl group in an *equatorial* position (Scheme 4). The residual amount of the *minor* component in the sample made molecular modeling necessary. The conformational search for the *minor* epimer **15aC** indicated a chair−chair conformation in which the aryl group has an *axial*

(17) (a) Armarego, W. L. F.; Reece, P. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2313. (b) Fülöp, F.; Bernáth, G.; Pihlaja, K. *Adv. Heterocycl. Chem.* **1998**, *69*, 349.

(18) Martinek, T.; Riddell, F. G.; Wilson, C. F. *J. Chem Soc., Perkin Trans. 2* **2000**, 2192.

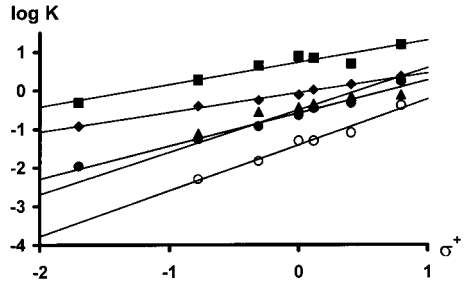


FIGURE 1. Plots of log *K* (in $CDCl_3$) for **14B** (◆), **15B** (■), **15C** (▲), **17B** (●), and **17C** (○) vs Hammett−Brown parameter σ^+.

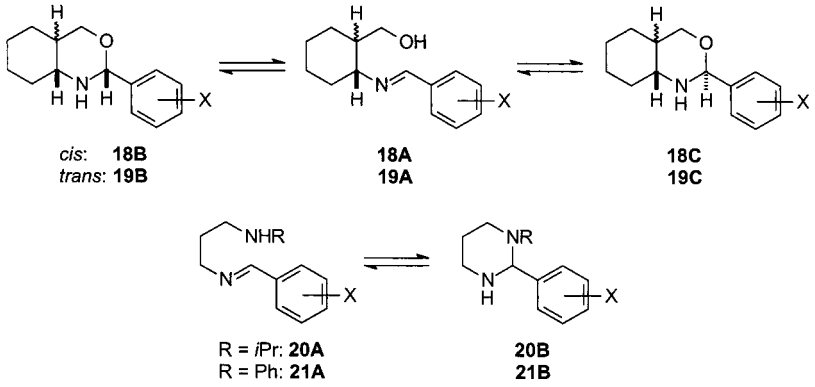
orientation (Scheme 4). The *axial* position of the 2-aryl group explains the lower stability (ΔG = 2.9 kJ/mol) of **15aC** as compared with **15aB**.

When eq 1 was applied to the log K_X values, good linear correlations were obtained vs the Hammett−Brown parameter σ^+ of the substituent X on the 2-phenyl group for compounds **14**, **15,** and **17** (Figure 1 and Table 5), which are the first examples among 2-aryl-1,3-N,N heterocycles of three-component ring−chain tautomeric processes characterized by a Hammett-type correlation. The shift in the tautomeric equilibrium toward the open-chain tautomer meant that a linear correlation could not be calculated for the few plots for compounds **16**.

The linear regression analysis data in Table 5 show that, as customary among 2-aryl-1,3-X,N heterocycles,[1,11] the value of ρ is positive in each case; i.e. electron-withdrawing substituents on the 2-phenyl ring favor the ring-closed tautomer. The slopes for 3-substituted 2-aryldecahydroquinazolines (**14**, **15,** and **17**) lie within a wider range (0.51−1.21) than those for the corresponding 2-aryldecahydro-3,1-benzoxazines (**18** and **19**: 0.55−0.64) and, similarly as for other 2-aryl-1,3-N,N heterocycles exhibiting ring−chain tautomerism, the value of ρ is not characteristic of the ring system. The stereochemistry of the ring junction does not seem to influence the value of ρ: *cis*- and *trans*-3-isopropyl-2-aryldecahydroquinazolines have very similar values of ρ (0.51 and 0.57). The considerable differences in the values of ρ for equilibria containing C-2 epimeric ring forms (**17B**−**17A** and **17C**−**17A**) indicate that the rates of the alternative ring-closures (**A** → **B** or **A** → **C**) of the open form are also influenced by the aromatic substituent. The substituent on the nitrogen exerted a similar effect on the value of ρ to that found for 3-isopropyl- and 3-phenyl-substituted 2-aryl-1,2,3,4-tetrahydroquinazolines:[11d] the value of ρ was somewhat higher for the 3-phenyl derivatives for the equilibria involving either the *major* (**15B**−**17B**) or the *minor* (**15C**−**17C**) ring forms.

Both the substituent on the nitrogen and the cis−trans ring junction gave rise to marked effects on the value of the intercept. To characterize the effects of the annelated ring on the stability of the ring form, a substitution effect parameter (c_s) was calculated as the difference in the intercepts for the given 2-aryldecahydroquinazolines and the corresponding 2-arylhexahydropyrimidines (**20** and **21**) bearing the same substituent on the nitrogen. This

TABLE 5. Linear Regression Data on Compounds 14, 15, 17, *cis*- and *trans*-2-Aryldecahydro-3,1-benzoxazines (18 and 19) and 3-Substituted 2-Arylhexahydropyrimidines (20 and 21)



equilibrium	no. of points	slope[a] (ρ)	intercept[a]	correlation coefficient	substitution effect (c_s)[b]	heteroatom effect (c_h)[b]
14A ⇌ **14B**	7	0.51(2)	−0.06(4)	0.994	0.98	−0.72
15A ⇌ **15B**	7	0.57(8)	0.72(16)	0.957	2.00	−0.40
15A ⇌ **15C**	6	0.71(10)	−0.43(12)	0.952	0.85	0.26
17A ⇌ **17B**	7	0.85(5)	−0.59(10)	0.985	0.69	−1.71
17A ⇌ **17C**	6	1.21(9)	−1.39(11)	0.988	−0.11	−0.70
18A ⇌ **18B**[c]	7	0.60(2)	0.66(3)	0.998	0.81	0
18A ⇌ **18C**[c]	7	0.60(6)	−0.45(12)	0.978	−0.30	0
19A ⇌ **19B**[c]	7	0.55(6)	1.12(12)	0.973	1.27	0
19A ⇌ **19C**[c]	7	0.64(3)	−0.69(6)	0.995	−0.54	0
20A ⇌ **20B**[d]	6	0.77(3)	−1.04(4)	0.997	0	−0.89
21A ⇌ **21B**[d]	7	0.42(3)	−1.28(6)	0.988	0	−1.13

[a] Standard deviations are given in parentheses. [b] Relative ring stability constant: see the text. [c] For compounds **18** and **19** (ref 2b), tautomeric ratios were remeasured and the linear regression analysis was performed separately for the equilibria involving C-2 epimeric ring forms. [d] Data from ref 11d.

kind of relative ring stability constant was introduced earlier for the saturated 2-aryl-1,3-O,N heterocycles bearing substituents at positions 4−6.[1b,2b] Positive values of c_s mean a more stable ring form relative to the corresponding 2-arylhexahydropyrimidine. The values of c_s indicate that the annelated ring had a considerable stabilizing effect on the ring form for **14B**, **15B**, **15C**, and **17B**, but not for **17C**. This effect is entropy-driven, since the annelated ring decreases the flexibility of the C(4a)−C(8a) bond and preorganizes the Schiff base to form the heterocyclic ring; however, the stabilization is compensated by the N-substituents. The destabilization may be due to 1,3 steric interactions; it was more pronounced for the *N*-isopropyl-substituted derivatives (**14** and **15**) than for the *N*-phenyl compounds (**17**). For 3-isopropyl- and 3-phenyldecahydroquinazolines, the trans-annelated cyclohexane ring (**15B**: $c_s = 2.00$) had a higher stabilizing effect than that of the cis ring junction (**14B**: $c_s = 0.98$). The lack of a stabilizing substituent effect in the *cis*-3-phenyldecahydroquinazolines (**16**) led to a nearly quantitative shift in the equilibria toward the open-chain tautomers (**16A**).

The effect of the substituted nitrogen atom at position 3 on the stability of the ring-closed tautomeric form can be expressed by a heteroatom effect parameter (c_h), which is calculated as the difference in intercept for the given 2-aryldecahydroquinazoline and the corresponding 2-aryldecahydro-3,1-benzoxazine (**18B**,**C** and **19B**,**C**).[11b−d] The value of c_h refers to the stability difference of the given 1,3-O,N and 1,3-N,N heterocycles. Earlier studies on the 2-aryl-substituted six-membered 1,3-N,N and 1,3-O,N heterocycles concluded that replacement of the heterocyclic oxygen with nitrogen leads to a significant stabilization of the ring form.[11a,d] However, the data in Table 5 demonstrate that the ring form for compounds **14B**, **15B**, **17B**, and **17C** is less stable than that for the corresponding decahydrobenzoxazine. Since the ring−chain tautomeric equilibria of *cis*- and *trans*-3-methyl-substituted decahydroquinazolines (**12** and **13**) are appreciably shifted toward the ring-closed tautomer, the stabilities of the ring-closed forms of *cis*- and *trans*-2-aryldecahydroquinazolines and the corresponding 3,1-benzoxazines increase in the following sequence of the heteroatom at position 3: NPh < N*i*Pr < O < NMe. This trend suggests that the destabilization effect of the N-substituents is related to their steric demand influencing the conformational energy.

Conclusions

In conclusion, the ring−chain tautomerism of cis- and trans-3-substituted-2-aryldecahydroquinazolines is strongly dependent on the substituents on the nitrogen and on the cis−trans ring junction. Compounds with a small N-substituent (Me) exist exclusively in the ring-closed form, independent of the stereochemistry of the ring junction. Compounds with larger N-substituents (*i*Pr or Ph) participate in three-component ring−chain tautomeric mixtures involving diastereomeric ring-closed forms besides the open-chain tautomer. In all cases, H-2 and H-8a of the *major* ring form (**B**) are cis-arranged. The ratios of the ring-closed tautomers were higher for the trans compounds. For the *cis*- and *trans*-3-isopropyl-2-aryldecahydroquinazolines (**14** and **15**) and *trans*-3-phenyl-2-aryldecahydroquinazolines (**17**), three-component ring−chain tautomeric equilibria characterized by a Hammett-type equation have been detected for the first time among 2-aryl-1,3-N,N heterocyles.

Experimental Section

^{1}H NMR spectra (400 MHz) were recorded at 300 K. Chemical shifts are given in δ (ppm) relative to TMS ($CDCl_3$) or to TSP (D_2O) as internal standards; multiplicities were recorded as s (singlet), d (doublet), dd (double doublet), ddd (double double doublet), dt (double triplet), t (triplet), m (multiplet), or om (overlapping multiplet). For the equilibria to be established in tautomeric compounds,[2,11] the samples were dissolved in $CDCl_3$ and the solutions were allowed to stand at ambient temperature for 1 day before the ^{1}H NMR spectra were run. The number of scans was usually 64.

The conformational search protocol was performed by using the INSIGHTII environment and the CDISCOVER molecular mechanics program. For the calculations, the cvff force field was utilized.

Compounds **3a**,**b**[14] and **6a**,**b**[13b] were prepared according to known procedures.

General Method for the Preparation of *cis*- and *trans*-*N*-Isopropyl- and *N*-Phenyl-2-(benzyloxycarbonylamino)cyclohexanecarboxamides (4a,b and 5a,b). To a stirred and cooled (ice−salt bath) suspension of *cis*- or *trans*-2-(benzyloxycarbonylamino)cyclohexanecarboxylic acid (**3a**,**b**) (2.77 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in dry toluene (100 mL) was added dropwise ethyl choroformate (1.08 g, 0.01 mol) at a rate low enough to keep the internal temperature below −10 °C. After 15 min, a solution of isopropylamine or freshly distilled aniline (0.01 mol) in dry CH_2Cl_2 (10 mL) was added dropwise to the mixture, the internal temperature being kept below −10 °C. Stirring was continued for 30 min with cooling and for 30 min without, and the mixture was then heated slowly to reflux and refluxed for 5 min. The mixture was allowed to cool and washed with saturated aqueous $NaHCO_3$ solution (2 × 50 mL) and water (80 mL) after the addition of $CHCl_3$ (200 mL). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give a white crystalline residue, which was filtered off, washed with Et_2O, and recrystallized from *i*-Pr_2O−EtOAc.

4a: yield 2.75 g (86%); mp 129−130 °C; ^{1}H NMR ($CDCl_3$) δ 1.08 (d, 3H, $J = 6.6$ Hz, CH_3), 1.08 (d, 3H, $J = 6.6$ Hz, CH_3), 1.40 (m, 2H, (CH_2)$_4$), 1.50−1.78 (om, 5H, (CH_2)$_4$), 2.01 (m, 1H, (CH_2)$_4$), 2.53 (m, 1H, COC*H*), 3.87 (m, 1H, NC*H*), 4.04 (m, 1H, NC*H*(CH$_3$)$_2$), 5.08 (s, 2H, OCH_2), 5.44 (br s, 1H, N*H*), 5.68 (br s, 1H, N*H*), 7.27−7.37 (om, 5H, C$_6H_5$). Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.72; H, 8.15; N, 8.69.

4b: yield 1.20 g (38%); mp 201−202 °C; ^{1}H NMR ($CDCl_3$) δ 1.03 (d, 3H, $J = 6.6$ Hz, CH_3), 1.06 (d, 3H, $J = 6.6$ Hz, CH_3), 1.13−1.51 (om, 4H, (CH_2)$_4$), 1.75 (m, 2H, (CH_2)$_4$), 1.98 (m, 2H, (CH_2)$_4$), 2.27 (m, 1H, COC*H*), 3.51 (m, 1H, NC*H*), 4.02 (m, 1H, NC*H*(CH$_3$)$_2$), 5.02 (d, 1H, N*H*, $J = 8.6$ Hz), 5.08(s, 2H, OCH_2), 5.78 (br s, 1H, N*H*), 7.33 (m, 5H, C$_6H_5$). Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.69, H, 8.08; N, 8.68.

5a: yield 2.86 g (81%); mp 169−172 °C (lit.[14] mp 172−173 °C); ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 2H, (CH_2)$_4$), 1.57−1.70 (om, 3H, (CH_2)$_4$), 1.84 (m, 2H, (CH_2)$_4$), 2.07 (m, 1H, (CH_2)$_4$), 2.80 (m, 1H, COC*H*), 3.99 (m, 1H, NC*H*), 5.08 (s, 2H, OCH_2), 5.55 (d, 1H, $J = 6.7$ Hz, N*H*), 7.10 (t, 1 H, $J = 7.4$ Hz, C$_6H_5$), 7.28−7.32 (om, 7H, C$_6H_5$), 7.46 (d, 2H, $J = 7.9$ Hz, C$_6H_5$), 7.55 (br s, 1H, N*H*).

5b: yield 1.17 g (33%); mp 217−218 °C; ^{1}H NMR ($CDCl_3$) δ 1.15−1.85 (om, 6H, (CH_2)$_4$), 1.99 (m, 1H, (CH_2)$_4$), 2.10 (m, 1H, (CH_2)$_4$), 2.52 (m, 1 H, COC*H*), 3.66 (m, 1 H, NC*H*), 4.98−5.13 (om, 3H, OCH_2, N*H*), 7.08 (t, 1H, $J = 7.4$ Hz, C$_6H_5$), 7.18−7.32 (om, 7H, 2 × C$_6H_5$), 7.48 (d, 2H, $J = 7.7$ Hz, C$_6H_5$). Anal.

TABLE 6. Physical Data on Decahydroquinazolines 12−17

compd	mp (°C)	formula	MW	δ N=C*H*Ar chain (**A**)	δ NC*H*ArN ring (**B**)	δ NC*H*ArN ring (**C**)
12a	50−53[a]	$C_{15}H_{21}N_3O_2$	275.35		3.81	4.06
12g	55−57[a]	$C_{17}H_{27}N_3$	273.43		3.59	
13a	oil	$C_{15}H_{21}N_3O_2$	275.35		3.88	
13g	78−81[a]	$C_{17}H_{27}N_3$	273.43		3.67	
14a	oil	$C_{17}H_{25}N_3O_2$	303.41	8.39	4.39	4.58
14b	oil	$C_{17}H_{25}BrN_2$	337.31	8.22	4.23	4.39
14c	oil	$C_{17}H_{25}ClN_2$	292.86	8.25	4.25	4.43
14d	oil	$C_{17}H_{26}N_2$	258.41	8.29	4.26	4.42
14e	oil	$C_{18}H_{28}N_2$	272.44	8.25	4.23	
14f	oil	$C_{18}H_{28}N_2O$	288.44	8.22	4.22	
14g	58−60[a]	$C_{19}H_{31}N_3$	301.48	8.16	4.25	
15a	100−103[a]	$C_{17}H_{25}N_3O_2$	303.41	8.39	4.44	5.04
15b	oil	$C_{17}H_{25}BrN_2$	337.31	8.18	4.24	4.31
15c	oil	$C_{17}H_{25}ClN_2$	292.86	8.24	4.26	4.32
15d	oil	$C_{17}H_{26}N_2$	258.41	8.28	4.27	4.37
15e	oil	$C_{18}H_{28}N_2$	272.44	8.18	4.25	4.29
15f	oil	$C_{18}H_{28}N_2O$	288.44	8.20	4.23	4.27
15g	oil	$C_{19}H_{31}N_3$	301.48	8.13	4.19	
16a	oil	$C_{20}H_{23}N_3O_2$	337.43	8.35	5.90	5.03
16b	oil	$C_{20}H_{23}BrN_2$	371.33	8.21	5.89	
16c	oil	$C_{20}H_{23}ClN_2$	326.87	8.19	5.89	
16d	oil	$C_{20}H_{24}N_2$	292.43	8.30	5.88	
16e	62−63[a]	$C_{21}H_{26}N_2$	306.46	8.24	5.87	
16f	oil	$C_{21}H_{26}N_2O$	322.46	8.22	5.88	
16g	oil	$C_{22}H_{29}N_3$	335.50	8.16		
17a	oil	$C_{20}H_{23}N_3O_2$	337.43	8.38[b]	5.94[b]	5.06[b]
17b	oil	$C_{20}H_{23}BrN_2$	371.33	8.21[b]	5.85[b]	4.88[b]
17c	83−85[a]	$C_{20}H_{23}ClN_2$	326.87	8.24[b]	5.86[b]	4.89[b]
17d	77−80[a]	$C_{20}H_{24}N_2$	292.43	8.30[b]	5.93[b]	4.90[b]
17e	68−70[a]	$C_{21}H_{26}N_2$	306.46	8.26[b]	5.91[b]	4.89[b]
17f	92−93[a]	$C_{21}H_{26}N_2O$	322.46	8.21[b]	5.89[b]	4.84[b]
17g	83−85[a]	$C_{22}H_{29}N_3$	335.50	8.14	5.88	

[a] Recrystallized from *n*-hexane. [b] From the spectra run at 253 K.

Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.34; H, 6.63; N, 7.82.

General Method for the Preparation of *cis*- and *trans*-*N*-Isopropyl- and *N*-Phenyl-2-aminocyclohexanecarboxamides (7a,b and 8a,b). The appropriate N-substituted *cis*- or *trans*-2-(benzyloxycarbonylamino)cyclohexanecarboxamide (**4a**,**b** or **5a**,**b**) (0.01 mol) was suspended in 33% hydrobromic acid in acetic acid (12 mL), and the mixture was allowed to stand at room temperature for 1 h with occasional shaking. The crystalline hydrobromide salt of **7a**,**b** or **8a**,**b** that was formed was filtered off and dissolved in ice-cold water (75 mL). The solution was made alkaline with 10% NaOH and extracted with EtOAc (5 × 50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The crystalline residue was recrystallized from EtOH.

7a: yield 1.44 g (78%); mp 83−86 °C; ^{1}H NMR ($CDCl_3$) δ 1.14 (d, 6H, J = 6.5 Hz, CH(CH_3)$_2$), 1.29−1.68 (om, 7H, (CH_2)$_4$), 1.74 (br s, 2H, NH_2) 1.83 (m, 1H, (CH_2)$_4$), 2.31 (m, 1H, COC*H*), 3.28 (m, 1H, NC*H*), 4.06 (m, 1H, NC*H*(CH_3)$_2$), 7.80 (br s, 1H, CON*H*). Anal. Calcd for $C_{10}H_{20}N_2O$: C, 65.18; H, 10.94; N, 15.20. Found: C, 64.92; H, 10.73; N, 14.96.

7b: yield 1.56 g (85%); mp 105−108 °C; ^{1}H NMR ($CDCl_3$) δ 1.08−1.52 (om, 12H, CH(CH_3)$_2$, (CH_2)$_4$, NH_2) 1.73 (m, 3H, (CH_2)$_4$), 1.80−1.90 (om, 2H, (CH_2)$_4$, COC*H*), 2.92 (ddd, 1H, J = 7.32, 11.58, 4.03 Hz, NC*H*), 4.09 (m, 1H, NC*H*(CH_3)$_2$) 5.92 (br s, 1H, CON*H*). Anal. Calcd for $C_{10}H_{20}N_2O$: C, 65.18; H, 10.94; N, 15.20. Found: C, 64.95; H, 10.72; N, 15.01.

8a: yield 1.84 g (84%); mp 122−124 °C (lit.[14] mp 143−144 °C); ^{1}H NMR ($CDCl_3$) : 1.36−1.73 (om, 7H, (CH_2)$_4$), 1.84 (br s, 2H, NH_2), 1.98 (m, 1H, (CH_2)$_4$), 2.50 (m, 1H, COC*H*), 3.36 (m, 1H, NC*H*), 7.05 (t, 1H, J = 7.4 Hz, C_6H_5), 7.29 (t, 2H, J = 8.36 Hz, C_6H_5), 7.58 (d, 2H, J = 8.44 Hz, C_6H_5), 11.31 (br s, 1H, CON*H*).

8b: yield 1.90 g (87%); mp 108−110 °C; ^{1}H NMR ($CDCl_3$) δ 1.13−1.55 (om, 6H, (CH_2)$_4$, NH_2), 1.77 (m, 2H, (CH_2)$_4$), 2.15 (m, 1H, COC*H*), 2.91 (ddd, 1H, J = 10.58, 10.83, 4.28 Hz, NC*H*), 7.06 (t, 1 H, J = 7.40 Hz, C_6H_5), 7.29 (t, J = 7.9 Hz, 2H, C_6H_5), 7.55 (d, 2H, J = 7.9 Hz, C_6H_5), 9.55 (br s, 1H, CON*H*). Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.29; H, 8.08; N, 12.60.

General Method for the Preparation of *cis*- and *trans*-2-(Methyl-, Isopropyl-, or Phenylaminomethyl)cyclohexylamines (9a,b, 10a,b, and 11a,b). To a stirred suspension of $LiAlH_4$ (2.28 g, 0.06 mol) in dry THF (50 mL) was added dropwise a solution of the appropriate amide (**6a**,**b**, **7a**,**b**, or **8a**,**b**) (0.02 mol) in dry THF (20 mL). The mixture was stirred and refluxed for 4 h and then cooled, and the excess of $LiAlH_4$ was decomposed by addition of a mixture of water (4.5 mL) and dry THF (30 mL). The inorganic salts were filtered off and washed with EtOAc (3 × 75 mL). The combined organic filtrate and washings were dried over Na_2SO_4 and evaporated under reduced pressure to give crude diamines as oily (**9a**,**b** and **10a**,**b**) or crystalline (**11a**,**b**) products.

The crude diamines were purified by distillation (**9a**,**b** and **10a**), by column chromatography on silica by using a mixture of $CHCl_3$ and MeOH (1:1) as eluent (**11a**), or as hydrochloride salts (**10b** and **11b**).

9a: yield 1.55 g (54%); bp 82−90 °C (6 mmHg). The ^{1}H NMR data on the product correspond to the literature[13c] data.

9b: yield 2.30 g (81%); bp 80−85 °C (4 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.92−1.30 (om, 5H, (CH_2)$_4$), 1.62−1.84 (om, 4H, (CH_2)$_4$, CC*H*), 2.38−2.60 (om, 4H, NC*H*, CH_3), 2.50 (dd, 1H, J = 5.9, 11.6 Hz, NCH_2), 2.71 (dd, 1H, J = 5.6, 11.6 Hz, NCH_2). Anal. Calcd for $C_8H_{18}N_2$: C, 67.55; H, 12.76; N, 19.69. Found: C, 67.36; H, 12.95; N, 19.48.

10a: yield 2.56 g (75%); bp 85−89 °C (2−3 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 6H, J = 6.3 Hz, CH(CH_3)$_2$), 1.20−1.68 (om, 12H, (CH_2)$_4$, CC*H*C, NH_2, N*H*), 2.47 (dd, 1H, J = 6.6, 11.5 Hz, NCH_2), 2.62 (dd, 1 H, J = 7.4, 11.5 Hz, NCH_2), 2.75 (m, 1 H,

C*H*(CH_3)$_2$), 3.11 (m, 1 H, NC*H*). Anal. Calcd for $C_{10}H_{22}N_2$: C, 70.53; H, 13.02; N, 16.45. Found: C, 70.36; H, 12.75; N, 16.19.

11a: yield 2.90 g (71%); mp 44−46 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (m, 1H, (CH_2)$_4$), 1.37−1.71 (om, 7H, (CH_2)$_4$), 1.80 (m, 1H, CC*H*), 3.02 (dd, 1H, J = 6.3, 12.5 Hz, NCH_2), 3.14−3.21 (om, 2 H, NCH_2, NC*H*), 6.61 (d, 2H, J = 7.8 Hz, C_6H_5), 6.67 (t, 1H, J = 7.3 Hz, C_6H_5), 7.16 (m, 2 H, C_6H_5). Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.21; H, 9.65; N, 13.59.

Crude diamines **10b** and **11b** were converted to crystalline dihydrochloride salts by treatment of their ethanolic solutions (10 mL) with an excess of 22% ethanolic HCl and Et_2O. The crystalline dihydrochlorides were filtered off and recrystallized from MeOH−Et_2O.

10b·2HCl: yield 3.84 g (79%); mp 200−203 °C; ^{1}H NMR (D_2O) δ 1.17−1.56 (om, 10 H, CH(CH_3)$_2$, (CH_2)$_4$), 1.80 (m, 2H, (CH_2)$_4$), 1.98 (m, 2H, (CH_2)$_4$), 2.08 (m, 1H, CC*H*), 3.03 (dd, 1H, J = 10.4, 12.6 Hz, NCH_2), 3.14 (ddd, 1H, J = 4.0, 10.3, 10.6 Hz, NC*H*), 3.29 (dd, 1 H, J = 3.3, 12.7 Hz, NCH_2), 3.47 (m, 1 H, C*H*(CH_3)$_2$). Anal. Calcd for $C_{10}H_{24}Cl_2N_2$: C, 49.38; H, 9.95; N, 11.52. Found: C, 49.22; H, 9.78; N, 11.36.

11b·2HCl: yield 4.81 g (87%); mp 193−195 °C; ^{1}H NMR (D_2O) δ 1.14−1.44 (om, 4H, (CH_2)$_4$), 1.71 (m, 2H, (CH_2)$_4$), 1.88−2.05 (om, 3H, (CH_2)$_4$, CC*H*), 3.09 (dt, 1H, J = 3.9, 10.3 Hz, NC*H*), 3.39 (dd, 1H, J = 10.1, 12.8 Hz, NCH_2), 3.57 (dd, 1H, J = 3.7, 12.8 Hz, NCH_2), 7.35−7.53 (om, 5H, C_6H_5). Anal. Calcd for $C_{13}H_{22}Cl_2N_2$: C, 56.32; H, 8.00; N, 10.10. Found: C, 56.06; H, 7.85; N, 9.88.

Pure diamine bases **10b** and **11b** were obtained from the above dihydrochlorides by alkaline treatment (20% NaOH), extraction (CH_2Cl_2), and evaporation under reduced pressure. The free bases were dried in a vacuum desiccator for 24 h before the further transformations.

10b: ^{1}H NMR ($CDCl_3$) δ 0.92−1.32 (om, 6 H, (CH_2)$_4$), 1.04 (d, 3 H, J = 6.3 Hz, CH_3), 1.05 (d, 3 H, J = 6.3 Hz, CH_3), 1.60−1.87 (om, 7H, NH_2, N*H*, (CH_2)$_4$), 2.42 (dt, 3.8, 10.2 Hz, 1H, NC*H*), 2.52 (dd, 1H, J = 5.8, 11.4 Hz, NCH_2), 2.69−2.78 (om, 1H, NCH_2, C*H*(CH_3)$_2$). Anal. Calcd for $C_{10}H_{22}N_2$: C, 70.53; H, 13.02; N, 16.45. Found: C, 70.36; H, 12.84; N, 16.22.

11b: mp 38−39 °C; ^{1}H NMR ($CDCl_3$) δ 0.98−1.39 (om, 5H, (CH_2)$_4$), 1.69 (m, 2H, (CH_2)$_4$), 1.69 (m, 2H, (CH_2)$_4$), 1.75−1.84 (om, 2H, (CH_2)$_4$, CC*H*), 2.44 (dt, 1H, J = 4.0, 10.3 Hz, NC*H*), 3.04 (dd, 1H, J = 5.5, 12.2 Hz, NCH_2), 3.21 (dd, 1H, J = 6.2, 12.2 Hz, NCH_2), 6.61 (d, 2H, J = 7.7 Hz, C_6H_5), 6.66 (t, 1H, J = 7.3 Hz, C_6H_5), 7.15 (m, 2H, C_6H_5). Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.27; H, 9.63; N, 13.48.

General Method for the Synthesis of 3-Substituted 2-Aryldecahydroquinazolines 12−17. To a solution of the appropriate diamine (**9**−**11a**,**b**, 3 mmol) in absolute MeOH (20 mL) was added an equivalent amount of aromatic aldehyde (for liquid aldehydes, a freshly distilled sample was used), and the mixture was allowed to stand at ambient temperature for 1 h. The solvent was evaporated off, and the evaporation was repeated after the addition of toluene (10 mL). The oily products were dried in a vacuum desiccator for 24 h. The NMR spectra proved that the purities of these compounds were greater than 95%. The crystalline products were filtered off and recrystallized. All of the recrystallized new compounds (**12a**,**g**, **13g**, **14g**, **15a**, and **17c**−**g**) gave satisfactory data on elemental analysis (C, H, N ±0.3%). The physical data for compounds **12**−**17** are listed in Table 6.

^{1}H NMR Spectroscopic Data for (4a*r*,2*c*,8a*c*)-3-Methyl-2-(4-nitrophenyl)decahydroquinazoline (12aB) and *cis*-*N*-(4-Nitrobenzylidene)-2-(phenylaminomethyl)cyclohexylamine (16aA) in $CDCl_3$. The protons of the open form (**A**) are numbered according to the corresponding protons of the quinazoline ring form (**B**) (δ in ppm, multiplicity, couplings in Hz, and assignment, respectively, in parentheses).

12aB: 1.31 (m, 1H, (CH_2)$_4$), 1.27 (m, 1H, (CH_2)$_4$), 1.49 (m, 1H, (CH_2)$_4$), 1.55 (m, 1H, (CH_2)$_4$), 1.59 (m, 1H, (CH_2)$_4$), 1.63 (m, 1H, CC*H*), 1.75 (m, 1H, (CH_2)$_4$), 1.78 (m, 1H, (CH_2)$_4$), 1.86 (s, 3H, CH_3), 2.43 (dd, 1H, J = 3.5, 11.6 Hz, NCH_2), 2.88 (dd, 1H, J = 2.0, 11.6 Hz, NCH_2), 3.05 (m, 1H, NC*H*), 3.81 (s, 1H, C*H*), 7.65 (d, 2H, J = 8.5 Hz, C_6H_4), 8.21 (d, 2H, J = 8.7 Hz, C_6H_4).

16aA: 1.47 (m, 1H, (CH_2)$_4$), 1.51 (m, 1H, (CH_2)$_4$), 1.63 (m, 1H, (CH_2)$_4$), 1.73 (m, 2H, (CH_2)$_4$), 1.82 (m, 2H, (CH_2)$_4$), 1.85 (m, 1H, (CH_2)$_4$), 1.99 (m, 1H, CC*H*), 2.93 (dd, 1H, J = 5.8, 12.3 Hz, NCH_2), 3.10 (dd, 1H, J = 7.8, 12.3 Hz, NCH_2), 3.66 (bs, 1H, NC*H*), 6.52 (d, 2H, J = 8.1 Hz, C_6H_5), 6.65 (t, 1H, J = 6.6 Hz, C_6H_5), 7.11 (t, 2H, J = 7.6 Hz, C_6H_5), 7.89 (d, 2H, J = 8.5 Hz, C_6H_4), 8.26 (d, 2H, J = 8.5 Hz, C_6H_4), 8.35 (s, 1H, NH=C*H*).

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Supporting Information Available: Table of $-\Delta H°/R$ and $-\Delta S°/R$ for compounds **17a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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