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Ring-chain tautomerism of 2-aryl-substituted-hexahydropyrimidines and tetrahydroquinazolines

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Dedicated to Professor András Messmer on the occasion of his 80th birthday.

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Abstract—2-Aryl-substituted-1-isopropyl- and 1-phenylhexahydropyrimidines and 3-isopropyl- and 3-phenyl-1,2,3,4-tetrahydroquinazolines proved to be ring-chain tautomeric mixtures in $CDCl_3$ at 300 K, whereas only ring-closed tautomers could be detected for the 1- or 3-methyl-substituted analogues. The ratios of the ring-chain tautomeric forms at equilibrium could be described by the equation $\log K_X = \rho\sigma^+ + \log K_{X=H}$.

1. Introduction

The ring-chain tautomerism of five- and six-membered 1,3-*X*,*Y*-heterocycles (X,Y=O, S, NR) has been studied thoroughly in recent years.[1] This phenomenon allows 1,3-*O*,*N*-heterocycles to be exploited as intermediates in the synthesis of *N*-substituted-amino alcohols[2] or as aldehyde sources in carbon transfer reactions.[3] Depending on the nature of the substituent at position 2 selective functionalizations of *N*-monosubstituted-ethylene- or propylene-diamines can be achieved on the basis of the ring-chain tautomeric character of their 2-substituted 1,3-*N*,*N*-heterocyclic derivatives.[4]

For the ring-chain tautomerism of 2-(X-phenyl)-substituted-oxazolidines and tetrahydro-1,3-oxazines, a linear correlation was earlier found between the equilibrium ring-chain ratio (K=[ring]/[open]) and the electronic character (σ^+) of the substituent X on the 2-phenyl ring (Eq. (1)):[1]

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

The ring-chain tautomerism of 1,3-*N*,*N*-heterocycles has been observed in only a few cases[1a,4,5] and, in contrast with the five- and six-membered 2-aryl-1,3-*O*,*N*-heterocycles, merely a limited number of examples of the application of Eq. (1)[6,7] are known among the analogous 1,3-*N*,*N*-heterocyclic compounds.

Previous studies on 1-substituted-2-arylimidazolidines showed that these five-membered 1,3-*N*,*N*-heterocyclic compounds participate in ring-chain tautomerism, the equilibria of which can be described by Eq. (1).[7] Substituents at position 1 caused a significant effect on the ring-chain tautomeric ratios. However, less is known about the ring-chain tautomerism of the corresponding six-membered analogues. Of these types of compounds, only *N*-unsubstituted-2-arylhexahydropyrimidines (**1**) were investigated earlier; they proved to be the first example of 2-aryl-1,3-*N*,*N*-heterocycles that participate in a ring-chain tautomeric equilibrium ($CDCl_3$) characterized by Eq. (1).[6] It is noteworthy that the benzologues of **1**, 1,3-unsubstituted-2-aryltetrahydroquinazolines, were described as ring-closed tautomers in DMSO-d_6, without detectable amounts of the open forms.[8]

As a continuation of our previous studies on 1,2-disubstituted-imidazolidines,[7] our present aim was to investigate the substituent effects on the ring-chain tautomeric character of some 1-substituted-2-arylhexahydropyrimidines and 3-substituted-2-aryl-1,2,3,4-tetrahydroquinazolines for the purpose of refining the scope and limitations of application of Eq. (1) among six-membered 1,3-*N*,*N*-heterocycles.

2. Results and discussion

The condensation of *N*-monosubstituted-1,2- or 1,3-diamines with the appropriate aromatic aldehydes provides a convenient method for the synthesis of saturated 2-aryl-1-substituted-*N*,*N*-heterocycles.[6,7] Of the 1,3-diamines required for the synthesis of hexahydropyrimidines, *N*-methyl- (**12**) and *N*-isopropylpropylenediamine (**13**) were commercial products, while *N*-phenylpropylene-diamine (**4**) was prepared by the reduction of β-alanine

Keywords: diamines; tautomerism; pyrimidines; quinazolines.

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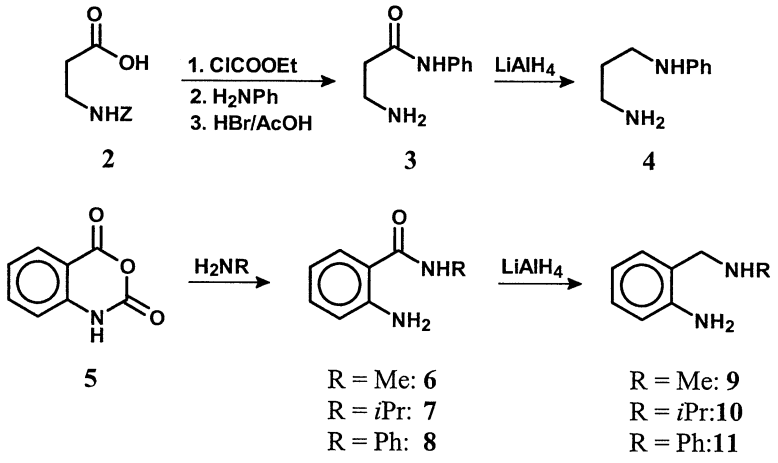
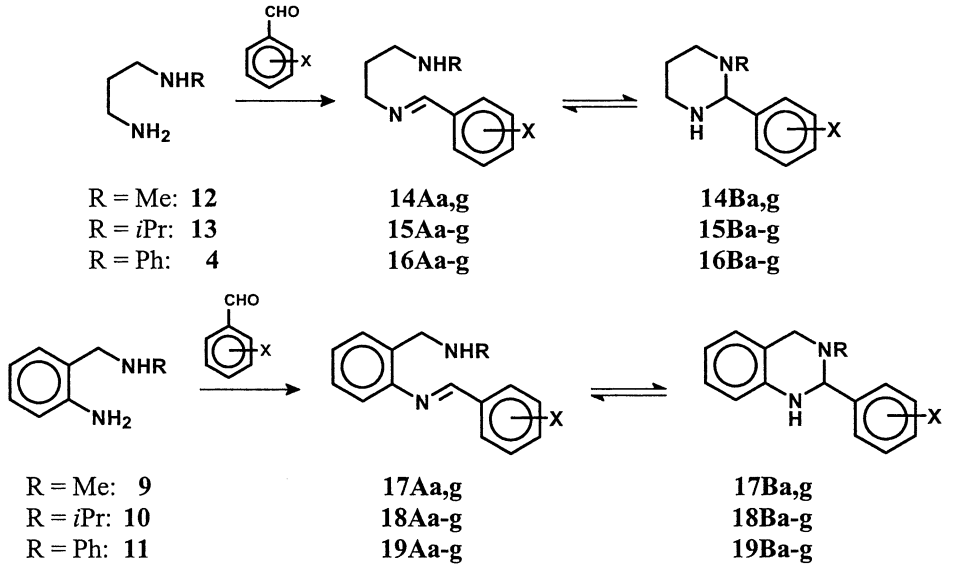


Scheme 1.



Scheme 2. X=pNO$_2$: **a**; mNO$_2$: **b**; pBr: **c**; H: **d**; pMe: **e**; pOMe: **f**; pNMe$_2$: **g**.

anilide (**3**) with $LiAlH_4$. The starting materials for the tetrahydroquinazolines, 2-(methyl-, isopropyl- or phenyl-aminomethyl)anilines (**9**–**11**), were synthesized by similar reductions of the appropriate *N*-substituted-aminocarboxamides (**6**–**8**), obtained by the ring-opening reactions of isatoic anhydride (**5**) with the appropriate amines (Scheme 1).[9]

Model compounds **14**–**16** and **17**–**19** were prepared by the condensation of propylenediamines (**4**, **12**, **13**) or *o*-aminobenzylamines (**9**–**11**) with equivalent amounts of the appropriate substituted benzaldehydes under mild conditions (ambient temperature, 1 h) (Scheme 2).

The ^{1}H NMR spectra of **15**, **16**, **18**, and **19** (in $CDCl_3$ solution at 300 K) revealed that these compounds participate in ring-chain tautomeric equilibria of the 1,3-*N*,*N*-heterocycles (**B**) and the corresponding Schiff bases (**A**), while in the spectra of the *N*-methyl-substituted-hexahydropyrimidines (**14a**,**g**) and tetrahydroquinazolines (**17a**,**g**) no open-chain form could be detected. Despite the electron-donating *p*-dimethylamino substituent on the 2-phenyl ring, which is favourable for the shift of the equilibrium towards the open tautomer, **14g** and **17g** proved to be exclusively ring-closed tautomers. The predominance of the ring-closed forms in the case of the *N*-methyl-substituted-hexahydropyrimidines (**14a**,**g**) is in accordance with the literature data on 2-phenyl and 2-(*p*-nitrophenyl) derivatives.[4a,c]

The equilibrium ratios were determined by integration of

Table 1. Proportions (%) of ring forms (**A**) in tautomeric equilibria ($CDCl_3$, 300 K) for compounds **14**–**19**

Compound	X	σ^+	14	15	16	17	18	19
a	pNO$_2$	0.79	~100	26.2	11.2	~100	99.2	97.5
b	mNO$_2$	0.73	–	24.4	9.2	–	99.2	96.4
c	pBr	0.15	–	12.3	5.5	–	97.9	83.1
d	H	0	–	7.6	5.9	–	95.9	75.2
e	pMe	−0.311	–	4.9	3.0	–	92.1	64.1
f	pOMe	−0.778	–	2.2	2.3	–	87.3	46.8
g	pNMe$_2$	−1.7	~100	~0	1.1	~100	72.6	16.5

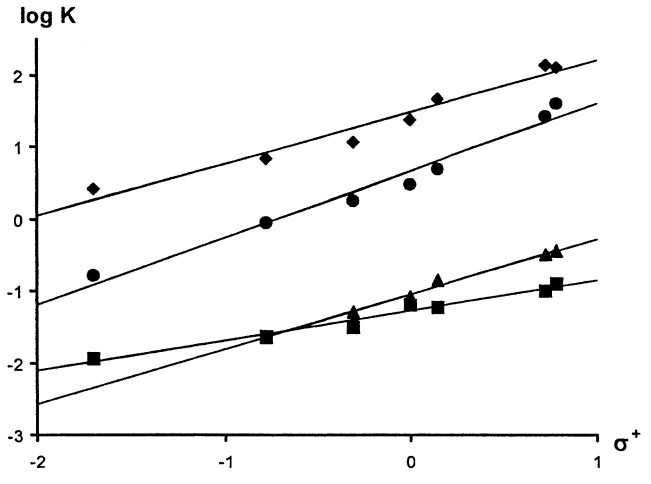


Figure 1. Plots of log K (in $CDCl_3$) for **15** (▲), **16** (■), **18** (◆), **19** (●) vs Hammett–Brown parameter σ^+.

the well-separated N–C*H*–N (ring, **B**) and N=C*H* (chain, **A**) singlets (Tables 1 and 3). The selected data on **15c** and **18f** reflect the ^{1}H NMR spectra of the prepared hexahydropyrimidines and tetrahydroquinazolines exhibiting a tautomeric character (see Section 4).

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 **15**, **16**, **18** and **19** (Fig. 1, Table 2).

The linear regression analysis data in Table 2 show that the slope ρ for 1-isopropylhexahydropyrimidines (**15**: 0.77) has approximately the same value as that for the corresponding six-membered 1,3-*O*,*N*-heterocycle[1a,10] (**20**: 0.74), while ρ for 1-phenylhexahydropyrimidines (**16**: 0.42) is considerably smaller. The 3-phenyl-substituted-tetrahydroquinazolines (**19**) have a markedly higher ρ value (0.93) than those for the 3-isopropyl-tetrahydroquinazolines (**18**) and 2-aryl-3,1-benzoxazines (**21**). The significant differences in ρ for **1**, **15** and **16** or for **18** and **19** suggest that for the six-membered 1,3-*N*,*N*-heterocycles, in contrast with the 1,3-*O*,*N*-heterocycles[1a] and similarly to the imidazolidines,[7] the value of ρ is not characteristic of the ring system, and depends strongly on the *N*-substituent. While *N*-isopropyl-heterocycles **15** and **18** have very similar ρ values, the ρ values for *N*-phenyl derivatives **16** and **19** are very different.

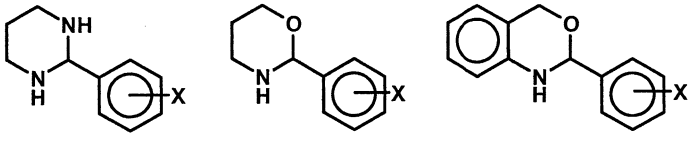
The nitrogen substituent causes a marked effect not only on the value of ρ, but also on the intercept. The effects of the substituents on the stability of the ring form relative to the analogous 1,3-*O*,*N*-heterocycle can be expressed by a value *c*, which is the difference in intercept for the given 2-aryl-1,3-*N*,*N*-heterocycle and the corresponding unsubstituted saturated 2-aryl-1,3-*O*,*N*-heterocycle. A positive *c* value means a more stable ring form than that of the corresponding 2-aryl-1,3-*O*,*N*-heterocycle.[7a,10] For the six-membered 1,3-*Y*,*N*-heterocycles **1**, **14**–**16** and **20**, the value of *c* is minimal for the *N*-phenyl substituent, and the stability of the ring-closed form increases in the following sequence of Y: NPh<N*i*Pr<O<NH<NMe.

Similarly as with the analogous 1,3-*O*,*N*-heterocycles,[10] a condensed benzene ring increases the stability of the ring form (cf. **15** and **18** or **16** and **19**). For the tetrahydroquinazolines **17**–**19** and the related 3,1-benzoxazine **21**, the *N*-phenyl substituent again causes the strongest destabilizing effect and the stability of the ring-closed form increases in the following sequence of Y: NPh<O<N*i*Pr<NMe.

3. Conclusion

In conclusion, the ring-chain tautomerism of six-membered saturated 1-substituted-2-aryl-1,3-*N*,*N*-heterocycles is strongly dependent on the substituents on the nitrogen and on the presence of a condensed benzene ring. Compounds with a small *N*-substituent (Me) exist exclusively in ring-closed form. Compounds with larger substituents (*i*Pr or Ph) participate in ring-chain tautomeric equilibria that can be characterized by the Hammett-type Eq. (1).

Table 2. Linear regression analysis data on compounds **15**, **16**, **18** and **19**, 2-arylhexahydropyrimidines (**1**),[6] 2-aryl-1,3-oxazines (**20**)[10] and 2-aryl-3,1-benzoxazines (**21**)[10]



1 **20** **21**

Compound	Number of points	Slope (ρ)[a]	Intercept[a]	Correlation coefficient	c[b]
15 (N*i*Pr)	6	0.77(3)	−1.04(4)	0.997	−0.89
16 (NPh)	7	0.42(3)	−1.28(6)	0.988	−1.13
1 (NH)	7	0.84(1)	0.93(1)	0.99	1.08
20 (O)	7	0.74(6)	−0.15(5)	0.984	0
18 (N*i*Pr)	7	0.72(7)	1.49(14)	0.978	0.38
19 (NPh)	7	0.93(8)	0.67(16)	0.984	−0.44
21 (O)	7	0.78(3)	1.11(2)	0.997	0

[a] Standard deviations are given in parentheses.
[b] Relative ring stability constant, see the text.

Table 3. Physical data on compounds **14–19**

Compound	Mp (°C)	Yield (%)	MS *m/z* $[M+1]^+$	IR ν_{max} (cm^{-1})	δ N=C*H* chain (**A**)	δ N–C*H*–N ring (**B**)
14a	88–90[a,b]	85	222	1517, 1346, 1101, 972, 838	–	3.82
14g	Oil	[c]	220	2941, 1608, 1525, 1352, 815	–	3.58
15a	Oil	[c]	250	2965, 1645, 1602, 1520, 1346	8.38	4.35
15b	Oil	[c]	250	2965, 1648, 1529, 1349, 720	8.36	4.36
15c	Oil	[c]	283/285	2965, 1645, 1486, 1011, 819	8.19	4.14
15d	Oil	[c]	205	2964, 1645, 1451, 755, 694	8.28	4.19
15e	Oil	[c]	219	2965, 1647, 1379, 1174, 813	8.24	4.16
15f	Oil	[c]	235	2962, 1645, 1607, 1513, 1251	8.21	4.16
15g	Oil	[c]	248	2962, 1608, 1526, 1361, 1179	8.14	–
16a	Oil	[c]	284	1602, 1519, 1345, 749, 693	8.37	5.32
16b	Oil	[c]	284	1603, 1529, 1506, 1350, 751	8.57	5.33
16c	Oil	[c]	317/319	1602, 1504, 1486, 1010, 749	8.23	5.21
16d	Oil	[c]	239	1645, 1603, 1505, 750, 693	8.28	5.29
16e	Oil	[c]	253	1645, 1603, 1507, 749, 693	8.24	5.27
16f	Oil	[c]	269	1605, 1510, 1252, 1167, 750	8.21	5.20
16g	Oil	[c]	282	1604, 1526, 1365, 745, 694	8.15	5.24
17a	101–103[d]	67	270	3393, 1519, 1489, 1345, 749	–	4.31
17g	Oil	[c]	268	1607, 1523, 1490, 1346, 749	–	4.63
18a	58–61[a]	83	298	1518, 1499, 1348, 1267, 743	5.41	8.58
18b	132–134[e]	72	298	3429, 1528, 1348, 1266, 747	5.42	8.57
18c	103–105[a]	75	331/333	1497, 1484, 1268, 1008, 749	5.21	8.39
18d	92–94[a]	75	253	3412, 1607, 1486, 1267, 747	5.25	8.46
18e	85–88[a]	82	267	3410, 1607, 1502, 1486, 745	5.19	8.42
18f	104–106[a]	69	283	3410, 1607, 1510, 1245, 749	5.17	8.38
18g	58–60[a]	70	296	1661, 1598, 1370, 1164, 813	5.14	8.38
19a	103–107[a]	87	332	1592, 1519, 1499, 1344, 753	6.05	8.52
19b	55–57[a]	89	332	1526, 1493, 1347, 749, 694	6.04	8.58
19c	79–82[e]	92	365/367	3397, 1596, 1500, 1010, 756	5.88	8.30
19d	94–95[a]	73	287	3413, 1596, 1494, 1445, 746	6.05	8.46
19e	80–82[a]	84	301	3401, 1494, 1264, 755, 743	6.02	8.42
19f	73–75[a]	87	317	1605, 1508, 1495, 1247, 753	5.89	8.27
19g	Oil	[c]	330	1603, 1588, 1527, 1166, 749	4.95	8.28

[a] Recrystallized from *n*-hexane.
[b] Lit.[4a] mp 90–91°C.
[c] The conversion was quantitative according to the ^{1}H NMR spectra.
[d] Recrystallized from *i*Pr_2O.
[e] Recrystallized from *n*-hexane–*i*Pr_2O.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer. 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), t (triplet), m (multiplet) and om (overlapping multiplet). For the equilibria of tautomeric compounds to be established,[6,7,11] the samples were dissolved in $CDCl_3$ and the solutions were left to stand at ambient temperature for 1 day before the ^{1}H NMR spectra were run. The number of scans was usually 64.

IR spectra were run in KBr discs on a Perkin–Elmer Paragon 1000 PC FT-IR spectrometer controlled by GRAMS Analyst for PE 1000 3.01A software. Mass spectra were recorded on a Shimadzu QP 8000 instrument using electrospray ionization. Melting points were determined on a Kofler micro melting point apparatus and are not corrected. The physical data on compounds **14–19** are listed in Table 3.

Compounds **6**,[9a] **7**[9b] and **8**[9c] were prepared according to known procedures.

4.1.1. β-Alanine anilide (3). To a stirred and cooled (ice–salt bath) solution of *N*-benzyloxycarbonyl-β-alanine (**2**, 22.32 g, 0.10 mol) and triethylamine (10.12 g, 0.10 mol) in dry toluene (150 mL), ethyl chloroformate (10.85 g, 0.10 mol) was added dropwise at a rate to keep the internal temperature below −10°C. After 15 min, a solution of aniline (9.31 g, 0.10 mol) in dry $CHCl_3$ (20 mL) was dropped into 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 down and washed with saturated aqueous $NaHCO_3$ solution (2×100 mL) and water (100 mL) after the addition of $CHCl_3$ (250 mL). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give *N*-benzyloxycarbonyl-β-alanine anilide as a white crystalline residue, which was filtered off, washed with Et_2O and recrystallized from EtOAc. Yield 21.96 g (75%), mp 135–136°C (lit.[12] mp 137–138°C); ^{1}H NMR ($CDCl_3$) δ: 2.59 (m, 2H, CH_2CO), 3.55 (m, 2H, CH_2N), 5.10 (s, 2H, OCH_2), 5.45 (br s, 1H, N*H*), 7.11 (m, 1H, NC_6H_5), 7.26–7.38 (om, 7H, $CH_2C_6H_5$, NC_6H_5) 7.49 (d, 2H, *J*=7.8 Hz, NC_6H_5), 7.55 (br s, 1H, N*H*); IR ν_{max} 3329, 3293, 1686, 1657, 1533, 1247 cm^{-1}; MS *m/z* 299 $[M+1]^+$. Analysis: calculated for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39; found: C, 68.24; H, 5.85; N, 9.12.

N-Benzyloxycarbonyl-β-alanine anilide (21.96 g, 0.07 mol) was suspended in 33% HBr in AcOH (90 mL) and the mixture was left to stand at room temperature for an hour with occasional shaking. The crystals of **3** hydrobromide that were formed were filtered off and dissolved in ice-cold water (75 mL). The solution was made alkaline with 20% NaOH and extracted with $CHCl_3$ (5×100 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The crystalline residue was purified by column chromatography on silica gel (eluent: toluene–MeOH=1:1). Yield 9.10 g (74%), mp 190–192°C, ^{1}H NMR ($CDCl_3$) δ: 2.47 (m, 2H, CH_2CO), 3.12 (m, 2H, NCH_2), 7.07 (m, 1H, C_6H_5), 7.31 (m, 2H, C_6H_5), 7.54 (d, 2H, J=7.8 Hz, C_6H_5), 9.92 (br s, 1H, N*H*); IR ν_{max} 1659, 1599, 1556, 1498, 1445, 751 cm^{-1}; MS *m*/*z* 165 $[M+1]^+$. Analysis: calculated for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06; found: C, 65.71; H, 7.12; N, 16.87.

4.1.2. General method for the synthesis of *N*-phenylpropylenediamine (4) and 2-(methyl-, isopropyl- or phenylaminomethyl)anilines (9–11). To a stirred suspension of $LiAlH_4$ (11.39 g, 0.30 mol) in dry THF (350 mL), a solution of β-alanine anilide (**3**) or the appropriate 2-amino-*N*-substituted-benzamide (**6**–**8**) (0.10 mol) in dry THF (**3**: 200 mL, **6**–**8**: 50 mL) was added dropwise. The mixture was stirred and refluxed for 7.5 h and then cooled and the excess of $LiAlH_4$ was decomposed by addition of a mixture of water (20 mL) and THF (50 mL). The inorganic salts were filtered off and washed with EtOAc (3×200 mL). The combined organic filtrates and washings were dried over Na_2SO_4 and evaporated under reduced pressure to give the crude diamines as oily (**4**, **9**, **10**) or crystalline products (**11**, mp 80–81°C, lit.[9c] mp 81–83°C).

Crude diamine **4** was distilled in vacuo. Yield 14.08 g (93%). Bp 100–105°C/1–2 mm. The ^{1}H NMR data on the product correspond to the literature[13] data.

For purification, crude diamines **9**–**11** were converted to the crystalline dihydrochlorides by treatment of their ethanolic (10 mL) solutions with an excess of 22% ethanolic HCl and Et_2O. The crystalline dihydrochlorides were filtered off and recrystallized from MeOH–Et_2O.

Compound **9**: yield 16.35 g (78%), mp 210–212°C (lit.[14] mp 236–238°C), ^{1}H NMR (D_2O) δ: 2.84 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 7.46 (m, 1H, C_6H_4), 7.50–7.61 (om, 3H, C_6H_4); IR ν_{max} 2773, 2565, 1538, 1496, 1454, 766, 754 cm^{-1}; MS *m*/*z* 137 $[M+1]^+$. Analysis: calculated for $C_8H_{14}Cl_2N_2$: C, 45.95; H, 6.75; N, 13.40; found: C, 45.68; H, 6.57; N, 13.26.

Compound **10**: yield 18.65 g (79%), mp 193–195°C (lit.[15] mp 191°C), ^{1}H NMR (D_2O) δ: 1.42 (d, 6H, J=6.6 Hz, 2×CH_3), 3.62 (m, 1H, C*H*), 4.36 (s, 2H, CH_2), 7.46 (m, 1H, C_6H_4), 7.50–7.63 (om, 3H, C_6H_4); IR ν_{max} 2800, 1561, 1502, 1444, 1392, 1145, 763, 754 cm^{-1}; MS *m*/*z* 165 $[M+1]^+$. Analysis: calculated for $C_{10}H_{18}Cl_2N_2$: C, 50.64; H, 7.65; N, 11.81; found: C, 50.38; H, 7.41; N, 11.73.

Compound **11**: yield 23.79 g (88%), mp 165–167°C, ^{1}H NMR (D_2O) δ: 4.76 (s, 2H, CH_2), 7.34 (m, 2H, C_6H_4, C_6H_5), 7.40–7.60 (om, 7H, C_6H_4, C_6H_5); IR ν_{max} 2727, 2583, 1497, 1478, 1430, 760, 690 cm^{-1}; MS *m*/*z* 199 $[M+1]^+$. Analysis: calculated for $C_{13}H_{16}Cl_2N_2$: C, 57.58; H, 5.95; N, 10.33; found: C, 57.33; H, 5.67; N, 10.21.

Pure diamine bases **9**–**11** 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 further transformations.

4.2. General method for the synthesis of 2-arylhexahydropyrimidines (14–16) and 2-aryl-1,2,3,4-tetrahydroquinazolines (17–19)

To a solution of the appropriate diamine (**4**, **9**–**13**, 3 mmol) in absolute MeOH (20 mL), an equivalent amount of aromatic aldehyde was added (in the case of liquid aldehydes, a freshly distilled sample was used), and the mixture was left 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%. Crystalline products were filtered off and recrystallized. All of the recrystallized new compounds (**17a**, **18a**–**g**, **19a**–**f**) gave satisfactory data on elemental analysis (C, H, N±0.3%).

4.2.1. ^{1}H NMR spectroscopic data on 1-isopropyl-2-(4-bromophenyl)hexahydropyrimidine (15c) and 3-isopropyl-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinazoline (18f) in $CDCl_3$. The protons of the open form (**A**) are numbered according to the corresponding protons of the ring form (**B**) (δ in ppm, in brackets the multiplicity, couplings in Hz and assignment, respectively).

Compound **15cA**: 1.00 (d, 6H, J=6.3 Hz, 2×CH_3), 1.80–1.87 (m, 2H, 5-CH_2), 2.66 (*t*, 2H, J=7.0 Hz, 6-CH_2), 2.68–2.80 (m, 1H, C*H*), 3.63 (*t*, 2H, J=6.5 Hz, 4-CH_2), 7.52 (dd, 4H, J=20.3, 8.5 Hz, C_6H_4), 8.19 (s, 1H, N=C*H*); Compound **15cB**: 0.75 (d, 3H, J=6.5 Hz, CH_3), 0.85 (d, 3H, J=6.8 Hz, CH_3), 1.59–1.71 (m, 2H, 5-CH_2), 2.39–2.45 (m, 1H, 6-CH_2), 2.62–2.74 (m, 1H, C*H*), 2.63–2.72 (m, 1H, 4-CH_2), 3.01–3.05 (m, 1H, 6-CH_2), 3.13 (*t*, 1H, J=6.96 Hz, 4-CH_2), 4.14 (s, 1H, NC*H*N), 7.29 (d, 2H, J=8.1 Hz, C_6H_4), 7.42 (d, 2H, J=8.1 Hz, C_6H_4).

Compound **18fA**: 1.06 (d, 6H, J=6.2 Hz, 2×CH_3), 2.77–2.80 (m, 1H, C*H*), 3.87 (s, 3H, OCH_3), 3.90 (s, 2H, CH_2), 6.96–7.05 (om, 3H, C_6H_4), 7.14–7.18 (m, 1H, C_6H_4), 7.26–7.28 (m, 1H, C_6H_4), 7.31–7.32 (m, 1H, C_6H_4), 7.85 (d, 2H, J=8.7 Hz, C_6H_4), 8.38 (s, 1H, N=C*H*); Compound **18fB**: 1.01 (d, 3H, J=6.4 Hz, CH_3), 1.17 (d, 3H, J=6.5 Hz, CH_3), 2.89–2.80 (m, 1H, C*H*), 3.76 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 4.14 (br s, 1H, N*H*), 5.14 (s, 1H, NC*H*N), 6.54 (d, 1H, J=7.9 Hz, C_6H_4), 6.63–6.66 (m, 1H, C_6H_4), 6.83–6.90 (om, 3H, C_6H_4), 6.96–7.04 (m, 1H, C_6H_4), 7.37–7.40 (m, 2H, C_6H_4).

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