Ring–Chain Tautomerism of 4-Hydroximino-hexahydropyrimidines Substituted in Position 2

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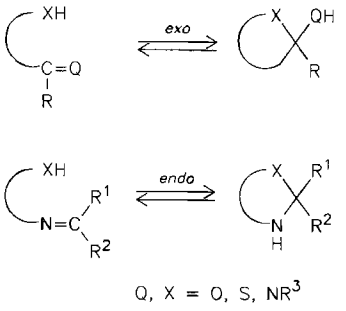
As shown by NMR spectroscopy, the reaction of 3-aminopropionamide oxime (**9**) with benzaldehyde or benzaldehyde derivatives **2a–d** substituted with electron-attracting substituents affords products which exist as an equilibrium mixture of tautomers involving the open-chain 3-(benzylideneamino)-propionamide oximes **11a–d** and the cyclic 4-hydroximino-hexahydropyrimidines **12a–d**. Tautomers **11** and **12**, isolated also in crystalline form, can be interconverted by using an appropiate solvent. In contrast, in the reaction of benzaldehydes substituted with electron-releasing groups (**2e,f**) and cinnamaldehyde (**2g**) with **9** only the open-chain imines are formed, and in aprotic solvents no tautomerism can be observed.

Recently, we have reported on a ring–chain tautomerism of pyrimidines which is characteristic of pseudobases[1] and belongs to the *exo*[2] type as shown in Scheme 1.

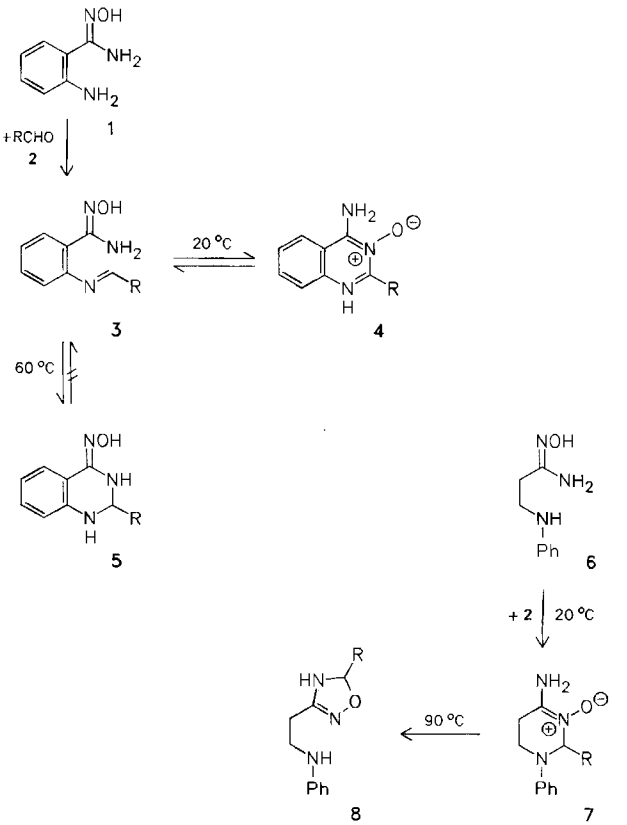
Scheme 1



In the present paper another example of a pyrimidine ring–chain tautomerism, corresponding to the *endo*[2] type in Scheme 1, will be described. Similar reversible intramolecular additions to the C=N bond are well-known in the case of various azoles and azines[3]. Although in the reaction of 1,3-diaminopropanes and their condensed derivatives with carbonyl compounds the formation of both pyrimidines and the isomeric open-chain compounds and the possibility of a tautomeric equilibrium have been reported[3a,4], tautomerism has only been unambiguously proved for the protonated forms in trifluoroacetic acid solution[5]. It seems that it is the first time that direct evidence is presented for an *endo*[2] type ring–chain tautomerism of pyrimidines in aprotic solution by the NMR method. Both tautomers have been isolated in crystalline form and can be interconverted.

Earlier we have described that the reaction of 2-aminobenzamide oxime (**1**) and aldehydes **2** at room temperature yields the 4-aminoquinazoline 3-oxides **4** which isomerize above 60°C via the imine **3** to the 4-quinazolone oximes **5**[6]. The reaction is irreversible, no tautomerism has been detected. 3-Anilinopropionamide oxime (**6**), structurally similar to **1**, forms with aldehydes also primarily pyrimidine *N*-

Scheme 2



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oxides[7a] (7), which isomerize irreversibly on heating, not to pyrimidines in analogy to **5** but to the oxadiazolines **8**[7b] (Scheme 2).

In connection with the reaction of aromatic aldehydes with 3-aminopropionamide oxime (**9**) which can be regarded as the parent compound of the amide oximes **1** and **6**, Gonçalves and Barrans have mentioned the possibility of a ring–chain tautomerism involving the imine **11** and the pyrimidine **12**[8], but later on, based on solution IR and ^{1}H-NMR spectra, they have definitely assigned the open-chain structure **11** to their product[9] (Scheme 3).

Scheme 3

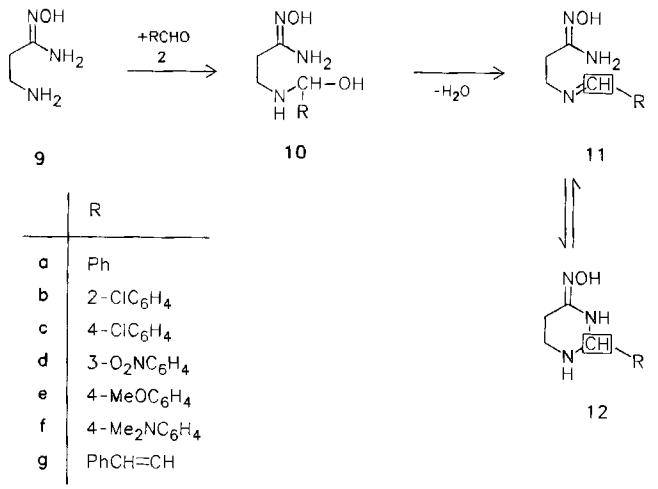

Table 1. Characteristic ^{1}H-NMR and ^{13}C-NMR data and ratios of **11** and **12** in the equilibrium solutions ([D$_6$]DMSO, 20°C)

No.	R	11		12		11	12
		δ(^{1}H)	δ(^{13}C)	δ(^{1}H)	δ(^{13}C)	%	
a	Ph	8.33	161.33	5.01	69.62	92	8
b	2-ClC$_6$H$_4$	8.66	157.44	5.86	66.46	85	15
c	4-ClC$_6$H$_4$	8.32	161.01	5.00	62.24	89	11
d	3-O$_2$NC$_6$H$_4$	8.47	159.60	5.14	68.51	75	25
e	4-MeOC$_6$H$_4$	8.26	160.60	–	–	100	–
f	4-Me$_2$NC$_6$H$_4$	8.15	160.77	–	–	100	–
g	PhCH=CH	8.08[a]	163.02	–	–	100	–

[a] J = 7.5 Hz.

Since in the reaction of the derivatives of **9** with the aldehydes **1** and **6** a strong tendency for cyclization has been observed[6,7], we have reinvestigated the reaction of **9**, which can be regarded as a 1,3-diaminopropane, with the aldehydes **2a–g**.

Following the reported method[9], i.e. heating of **9** with benzaldehyde at 80–90°C for 10 min, provides a crystalline product which is different from the expected imine **11a** and proves to be 4-hydroximino-2-phenyl-hexahydropyrimidine (**12a**). The same compound can be obtained more readily and in higher yield when an equimolar amount of **2a** is added to a suspension of **9** in methanol or ethanol at room temperature. Within a short time **12a** spontaneously crystallizes or can be precipitated by the addition of diethyl ether. When, however, the solution of the components is immediately mixed with *n*-hexane, first as an oil, then, on trituration, as crystals, it is indeed the open-chain imine **11a** (m.p. 84–86°C) which can be isolated. **11a** and **12a** can be interconverted by dissolution in methanol or ethanol and precipitation, after cooling, by the addition of either diethyl ether or *n*-hexane. The structures of **11a**, **12a** and the existence of their tautomeric equilibrium has unambiguously been proved by analytical and spectroscopic data. Most information can be gained from ^{1}H- and ^{13}C-NMR studies carried out in different solvents. When the ^{1}H-NMR spectra are recorded within 2 min by use of freshly prepared solutions of **11a** or **12a** in [D$_6$]DMSO and $CDCl_3$, the most characteristic differences are observed in the signals for azomethine CH of the Schiff's base and 2-CH of the pyrimidine ring (Table 1). It has to be noted that starting from either of the two compounds (**11a** or **12a**), signals of the other tautomer gradually appear on standing, also in the corresponding ^{13}C-NMR spectra, until an equilibrium is reached. In [D$_6$]DMSO this takes about 48 h, and finally the mixture contains 92% of **11a** and 8% of **12a**.

On heating the equilibrated solution in [D$_6$]DMSO from 20°C to 100°C only signals for the open-chain form (**11a**) can be observed, but the change is reversible.

In $CDCl_3$, equilibration also takes about two days and the observed composition is 68% of **11a** and 32% of **12a**.

Slow equilibration permits to follow the formation of the tautomeric pair **11a** and **12a** by ^{1}H-NMR spectroscopy. When equimolar amounts of **9** and **2a** are mixed in [D$_6$]DMSO at 20°C, after 1 min a clear solution is obtained. The characteristic signals of the starting material are completely replaced by the signals of the adduct of the components, i.e. of the geminal amino alcohol **10a** (60%) and of the imine **11a** derived from the adduct by elimination of water (Scheme 3). Characteristic of **10a** are the following ^{1}H-NMR signals: δ = 2.10 (t, 2H, CH_2), 2.75 (t, 2H, CH_2), 5.45 (br. s, 3H, CH + NH_2), 10.0 (br., 1H, CHO*H*). With advancing time, signals for **10a** gradually disappear and after about 10 min only the imine **11a** can be detected. On combining solutions of **9** and **2a**, in about 25 min the signals for the cyclic tautomer **12a** emerge, but the final equilibrium is established under such conditions also only after 2 days. The composition of the equilibrium mixture is the same as that observed for isolated samples of **11a** or **12a**, i.e. 92% and 8%.

The surprisingly high tendency for crystallization of the **11a** and **12a** tautomers is probably due mainly to the presence of the oxime groups.

Based on the above results, the erroneous assignment of the **11a** to the crystalline product (m.p. 127–128°C) arising from the reaction of **9** with **2a**[9] is due to the fact that the NMR spectrum has been recorded in an aprotic solvent after standing of **12a**. Under such conditions only signals for the dominant imine form **11a** have been identified.

The structures of **11a** and **12a** and their tautomeric equilibrium in solution are also supported by IR spectral studies. The most characteristic difference in the spectra of the cry-

stalline products, when recorded in KBr pellets, is in the 1700–1600 cm^{-1} and 900–800 cm^{-1} regions. While for the cyclic compounds **12a** only one C=N band appears at 1630 cm^{-1}, the imine **11a** shows a second one at 1660 cm^{-1}. With **12a** a very strong band can be seen at 875 cm^{-1}, which is characteristic of the N–O bond of cyclic amide oximes[6,10] and missing in the spectrum of **11a**. One or two bands also appear in the 1700–1600 cm^{-1} range for freshly prepared 5% solutions of **12a** and **11a**, respectively, in acetonitrile. In an acetonitrile solution of **12a** the second C=N band typical of **11a** appears already after 15 min. According to the literature, IR spectra of the product resulting from the reaction of **9** with **2a** have been recorded in carbon tetrachloride, acetonitrile and bromoform. The C=N bands appear between 1700 and 1600 cm^{-1}, from which structure **11a** has been deduced[9]. Since we have been able to show that in fact the cyclic product **12a** is isolated, misassignment can again be explained by equilibration prior to recording the spectra. The reaction of amide oxime **9** with aldehydes **2b–d** containing electron-attracting groups proceeds quite similarly as that with benzaldehyde. Imines **11b,d** and pyrimidines **12b–d** are also crystalline and the existence of their tautomeric equilibria in solution has been proved. At elevated temperature again complete ring opening results. The imine **11c** cannot be crystallized, but its solution NMR spectra permit its identification. Characteristic NMR data and equilibrium ratios in [D_6]DMSO are compiled in Table 1. Note that increasing electron attraction by the phenyl group diminishes the contribution of the open-chain form to the equilibrium in conformity with earlier observations[3]. This effect is, however, not strong enough to induce the profound differences experienced in the reaction of **9** with benzaldehydes bearing electron-releasing substituents such as **2e,f**, as well as with cinnamic aldehyde **2g**. In these cases, the imines **11e–g** crystallize spontaneously and this cannot be influenced by solvent treatment. The IR spectra of the crystalline product indicate an open-chain structure and according to the NMR spectra recorded in [D_6]DMSO and $CDCl_3$ these compounds practically do not equilibrate with other tautomeric forms in solution.

Conclusions

The existence of an *endo*-type[2] ring-chain tautomerism of non-protonated hexahydropyrimidines of a novel type has been proved and both tautomeric forms have been isolated as crystals. Substituents have been found to play a decisive role in the formation of this tautomeric system. The present work is closely related to our earlier studies on aminoamide oximes and their derivatives[1,6,7b,10,11].

Recording of the IR spectra is gratefully acknowledged to Dr. *L. Pusztay*, for microanalyses we thank Dr. *I. Remport*.

Experimental

IR: Zeiss Specord M-80. – ^1H and ^{13}C NMR: Jeol FX-100 (100 and 25 MHz).

3-(Benzylideneamino)propionamide Oxime (**11a**): a) To a suspension of **9**[8a] (5.16 g, 50 mmol) in ethanol (30 ml) at 20–25°C **2a** (5.41 g, 51 mmol) was given within 30 s. After stirring for about 2 min a clear solution resulted to which *n*-hexane (150 ml) was added with vigorous stirring. An oil precipitated from which the solvent was decanted. With fresh hexane (75 ml) this operation was repeated and finally the product crystallized by trituration with diethyl ether; yield 7.25 g (76%), m. p. 84–86°C (ref.[9] 128–130°C).

b) **12a** (0.95 g, 5 mmol) was dissolved by gentle heating in methanol (8 ml). After cooling to 20°C and standing for 5 min, *n*-hexane (100 ml) was added with vigorous stirring, the solvent decanted from the precipitated oil and the oil processed as described under a) to give **11a** (0.65 g, 68%) which was identical with the above product. – IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1}, 3260, 1660, 1630. – ^1H NMR ([D_6]DMSO): δ = 2.32 (t, *J* = 7 Hz, 2H, CH_2), 3.74 (t, *J* = 7 Hz, 2H, CH_2N), 5.43 (br. s, 2H, NH_2), 7.2–7.5 (m, 3H, 3′,4′,5′-H), 7.6–7.8 (m, 2H, 2′,6′-H), 8.33 (s, 1H, CH=N), 8.87 (br. s, 1H, OH). – ^{13}C NMR ([D_6]DMSO): δ = 32.68 (C-2), 57.98 (C-3), 128.01 (C-2′,6′), 128.77 (C-3′,5′), 130.73 (C-4′), 136.23 (C-1′), 151.50 (C-1), 161.33 (CH=N).

$C_{10}H_{13}N_3O$ (191.2) Calcd. C 62.81 H 6.85 N 21.97
Found C 62.50 H 6.74 N 22.27

Substituted 3-(Benzylideneamino)propionamide Oximes **11b–d**: The title compounds were prepared either by reaction of **9** with

Table 2. Yields (method), melting points, IR spectral and analytical data of compounds **11b–g** and **12b–d**

No.	Yield % (method)	M.p. [°C]	$\tilde{\nu}$ (KBr) [cm^{-1}]	Empirical formula (mol. mass)	Calcd. Found C	H	N
11b	53 (a) 50 (b)	113–116[a]	3410, 3300, 1660, 1630	$C_{10}H_{12}ClN_3O$ (225.7)	53.22 53.18	5.36 5.34	18.62 18.54
11c	61 (a) 66 (b)	oil[b]	3400[c], 3305, 1660, 1640	$C_{10}H_{12}ClN_3O$ (225.7)	53.22 53.50	5.36 5.51	18.62 18.40
11d	84 (a) 90 (b)	128–131[d]	3470, 3320, 1665, 1650	$C_{10}H_{12}N_4O_3$ (236.2)	50.84 50.96	5.12 4.88	23.72 23.66
11e	88	119–120	3425, 3280, 1660, 1640	$C_{11}H_{15}N_3O_2$ (221.3)	59.71 59.50	6.83 6.80	18.99 18.60
11f	83	157–160	3400, 3250, 1660, 1642	$C_{12}H_{18}N_4O$ (234.3)	61.51 61.32	7.74 7.86	23.91 23.62
11g	66	127–130[e]	3405, 3320, 1663, 1640, 1620	$C_{12}H_{15}N_3O$ (217.3)	66.34 66.18	6.96 6.86	19.34 19.00
12b	56 (a)	91–94	3400, 3245, 1636, 876	$C_{10}H_{12}ClN_3O$ (225.7)	53.22 53.29	5.36 5.35	18.62 18.77
12c	52 (a) 50 (b)	99–102	3398, 3250, 1631, 875	$C_{10}H_{12}ClN_3O$ (225.7)	53.22 53.32	5.36 5.54	18.62 18.91
12d	93 (a) 91 (b)	162–164	3380, 3210, 1640, 872	$C_{10}H_{12}N_4O_3$ (236.2)	50.84 50.93	5.12 4.93	23.72 23.79

[a] Ref.[9] 113–115°C. – [b] Ref.[9] 110–112°C. – [c] In nujol. – [d] Ref.[9] 160–164°C. – [e] Ref.[9] 128–130°C.

2b–d or from the pyrimidines **12b–d** as described above. Characteristic NMR data are given in Table 1, melting points, yields, IR and analytical data in Table 2. **11c** was obtained as an oil and dried over paraffin chips.

Substituted 3-(Benzylideneamino)propionamide Oximes **11e,f** *and 3-(Cinnamylideneamino)propionamide Oxime* (**11g**). – *General Method:* To a suspension of **9** (5.16 g, 50 mmol) in ethanol (50 ml) aldehydes **2e–g** (51 mmol) were added with stirring within 30 s. On cooling after 2–3 min the imines **11e–g** crystallized and were recrystallized from ethanol. Characteristic NMR data are given in Table 1, melting points, yields, IR and analytical data in Table 2.

4-Hydroximino-2-phenyl-hexahydropyrimidine (**12a**): a) To a suspension of **9** (5.16 g, 50 mmol) in ethanol (30 ml) **2a** (5.41 g, 51 mmol) was added with stirring within 30 s. A clear solution was obtained from which after 15 min crystals separated on scratching. After standing at about 1–2 °C for 24 h the product was filtered off and washed with ether to give **12a** (7.8 g, 82%), m.p. 127–128 °C (ethanol). Dilution of the reaction mixture after a few minutes with diethyl ether (150 ml) gave the same result.

b) **11a** (0.95 g, 5 mmol) was dissolved in methanol (6 ml) with gentle heating. After cooling to 20 °C diethyl ether (100 ml) was added and 0.4 g of a slowly crystallizing product was obtained. An additional 0.3 g of this product was isolated from the mother liquor (combined yield 79%). The product was identical with that obtained under a).

c) According to the literature[9] equimolar amounts of **9** and **2a** were heated without solvent at 80–90 °C for 10 min. On cooling and trituration with dicthyl ether, **12a** was isolated in 40% yield; it was identical with the samples obtained according to methods a) and b), m.p. 127–128 °C (ref.[9] m.p. given for structure **11a** 128–130 °C). – IR (KBr): $\tilde{\nu}$ = 3260 cm^{-1}, 3120, 1630, 875. – ^1H NMR ([D_6]DMSO): δ = 2.15 (m, 2H, CH_2), 2.92 (m, 2H, CH_2N), 5.01 (s, 1H, CH), 5.73 (s, 1H, NH), 7.41 (m, 5H, Ph), 9.06 (s, 1H, OH). – ^{13}C NMR ([D_6]DMSO): δ = 26.39 (C-5), 41.63 (C-6), 69.62 (C-2), 126.90 (C-2′,6′), 127.95 (C-4′), 128.21 (C-3′,5′), 142.72 (C-1′), 150.07 (C-4).

$C_{10}H_{13}N_3O$ (191.2) Calcd. C 62.81 H 6.85 N 21.97
Found C 62.70 H 6.74 N 21.66

Phenyl-Substituted 4-Hydroximino-2-phenyl-hexahydropyrimidines **12b–d**: The title compounds were obtained by reaction of **9** with **2b–d** or by transformation of **11b–d** as described for **12a** under a) and b). Characteristic NMR data are given in Table 1, melting points, yields, IR and analytical data in Table 2.

CAS Registry Numbers

2a: 100-52-7 / **2b**: 89-98-5 / **2c**: 104-88-1 / **2d**: 99-61-6 / **2e**: 123-11-5 / **2f**: 100-10-7 / **2g**: 104-55-2 / **9**: 16750-43-9 / **11a**: 17883-88-4 / **11b**: 17883-89-5 / **11c**: 17883-90-8 / **11d**: 17883-91-9 / **11e**: 131636-87-8 / **11f**: 131636-88-9 / **11g**: 17883-92-0 / **12a**: 90871-68-4 / **12b**: 131636-89-0 / **12c**: 131636-90-3 / **12d**: 131636-91-4

[1] D. Korbonits, G. Horváth, P. Kiss, K. Simon, P. Kolonits, *Chem. Ber.* **123** (1990) 493.
[2] The terms *exo* and *endo* have been used as understood by: J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734.
[3] [3a] R. E. Valters, W. Flitsch, *Ring-Chain Tautomerism*, (A. R. Katritzky, Ed.), Plenum Press, New York 1985. – [3b] F. Fülöp, K. Pihlaja, J. Mattinen, G. Bernáth, *J. Org. Chem.* **52** (1987) 3821. – [3c] F. Fülöp, J. Mattinen, K. Pihlaja, *Tetrahedron Lett.* **29** (1988) 5427.
[4] [4a] R. E. Harmon, J. L. Parson, S. K. Gupta, *J. Org. Chem.* **34** (1969) 2760. – [4b] L. A. Ignatova, M. G. Zaitseva, M. M. Donskaya, *Khim. Geterosikl. Soedin.* **1965**, 586 [*Chem. Abstr.* **64** (1966) 560[d]].
[5] [5a] H. Piotrowska, W. Sas, T. Urbanski, *Tetrahedron* **33** (1977) 1979. – [5b] J. B. Lambert, M. W. Majchrzak, *J. Am. Chem. Soc.* **102** (1980) 3588.
[6] D. Korbonits, P. Kolonits, *J. Chem. Soc. Perkin Trans. 1*, **1986**, 2163.
[7] [7a] H. Gonçalves, M. Bon, *C. R. Acad, Sci., Ser. C*, **280** (1975) 141. – [7b] D. Korbonits, K. Simon, P. Kolonits, *Tetrahedron Lett.* **24** (1983) 5763.
[8] [8a] H. Gonçalves, J. Barrans, *C. R. Acad. Sci.* **258** (1964) 3507. – [8b] D. J. Brown, *The Pyrimidines, Suppl. 1*, in *The Chemistry of Heterocyclic Compounds* (A. Weissberger, E. C. Taylor, Eds.), p. 357, Wiley-Interscience, 1970.
[9] H. Gonçalves, F. Mathis, J. Barrans, *Bull. Soc. Chim. Fr.* **1967**, 2321.
[10] D. Korbonits, I. Kanzel-Szvoboda, Cs. Gönczi, K. Simon, P. Kolonits, *Chem. Ber.* **122** (1989) 1107.
[11] D. Korbonits, K. Simon, P. Kolonits, *Chem. Ber.* **124** (1991) 111, and references cited therein.

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