Assisted hydrolysis of *cis*-2-(3-phenylthioureido)cyclopentane-carbonitrile in alkaline solution. Solvent dependent switch from hydrolysis to rearrangement of the iminothiooxopyrimidine intermediate

Ergun Atay, Iva B. Blagoeva, Francis L. Chubb, John T. Edward, Ivan G. Pojarlieff, and Maria M. Toteva

Abstract: The *cis* and *trans* isomers of 2-(3-phenylthioureido)cyclopentanecarbonitrile, **1**, and the respective carboxamides, **3**, and acids, **4**, have been prepared. Acid cyclization of both nitriles, faster with the *cis* isomer, gave the more stable *cis*-2-thiooxo-cyclopenta[*d*]pyrimidin-4-one, **7**. In base *cis*-**1** formed the *cis* 4-imino-2-thiooxopyrimidine **2** which in aqueous alkali broke down via **3** to the acid **4**; while in the presence of 66% acetonitrile **2** rearranged to the 4-phenyliminopyrimidine **5** to give as final product the thioureido acid **6** carrying no phenyl group. The ^{1}H NMR data for imino and phenylimino derivatives **2** and **5** showed strong bias for conformation **A** with 1-N pseudoaxial in the cyclopentane ring. Spectra of the *E* and *Z* isomers of the iminopyrimidine **2** under slow exchange could be recorded in DMSO-d_6. The phenylimino tautomer of **5** is observed in CD_3OD and in $CDCl_3$ with the *E* and *Z* isomers in a 1:1 ratio. In DMSO-d_6 the phenylamino tautomer **5a** is also detected. The first process in aqueous KOH, the conversion of nitrile *cis*-**1** into the imino intermediate **2**, reaches an equilibrium which shifts towards the nitrile at higher alkalinities because of ionization of the phenylthioureido group (K_e = [**2**]/[**1**] = 2.43 and pK_{AH} = 12.74). The cyclization of **1** to **2** is first order in [OH^-] while the slower breakdown of **2** is pH independent. The latter is 10^4 times faster than the hydrolysis of acetonitrile evidencing substantial anchimeric assistance. The change in the reaction route towards the rearranged phenyliminopyrimidine **5** upon addition of acetonitrile can be caused by the lower dielectric constant favouring the elimination step leading to the intermediate isothiocyanate, and by increased activity of OH^- accelerating the (presumably) second order elimination step as opposed to the pH-independent hydrolysis of the imino derivative **2**.

Key words: anchimeric assistance, phenylthioureido nitriles, iminothiooxopyrimidine tautomers, alkaline hydrolysis, solvent effects.

Résumé : On a préparé les isomères *cis* et *trans* du 2-(3-phénylthiouréido)cyclopentanecarbonitrile (**1**) et des carboxamides (**3**) et acides (**4**) correspondants. La cyclisation des deux nitriles, plus rapide pour l'isomère *cis*, conduit dans chaque cas à la *cis*-2-thiooxocyclopenta[*d*]pyrimidin-4-one (**7**), l'isomère le plus stable. En milieu basique, l'isomère **1**-*cis* conduit à la formation de la *cis*-4-imino-2-thiooxopyrimidine (**2**) qui, dans ces conditions, se décompose en acide **4** par le biais de **3**; toutefois, dans un milieu contenant 66% d'acétonitrile, le produit **2** se réarrange en 4-phényliminopyrimidine (**5**) qui se transforme pour fournir comme produit final l'acide thiouréido **6** où la groupe phenyle est absent. Les données de RMN du ^{1}H pour les dérivés imino et phénylimino **2** et **5** montrent que la conformation **A** est fortement favorisée, avec le 1-N en position axiale par rapport au cyclopentane. En opérant dans le DMSO-d_6, on a pu enregistrer les spectres des isomères *E* et *Z* de l'iminopyrimidine dans des conditions d'échange lent. Dans le CD_3OD et dans le $CDCl_3$, on peut observer le tautomère phénylamino de **5**; les isomères *E* et *Z* se trouvent dans un rapport de 1:1. On a aussi détecté le tautomère phénylamino **5a** dans le DMSO-d_6. Le premier processus réactionnel observé dans le KOH aqueux, la conversion du nitrile 1-*cis* en intermédiaire imino **2** atteint un équilibre qui, en raison de l'ionisation du groupe phénylthiouréido (K_e = [**2**]/[**1**] = 2,43 et pK_{AH} = 12,74), se déplace vers le nitrile à des niveaux d'alcalinité élevés. La cyclisation de **1** et **2** est du premier ordre en [OH^-] alors que la décomposition plus lente de **2** est indépendante du pH. Cette dernière réaction est 10^4 fois plus rapide que l'hydrolyse de l'acétonitrile; ceci confirme l'importance de l'assistance anchimérique. Le changement de la voie réactionnelle

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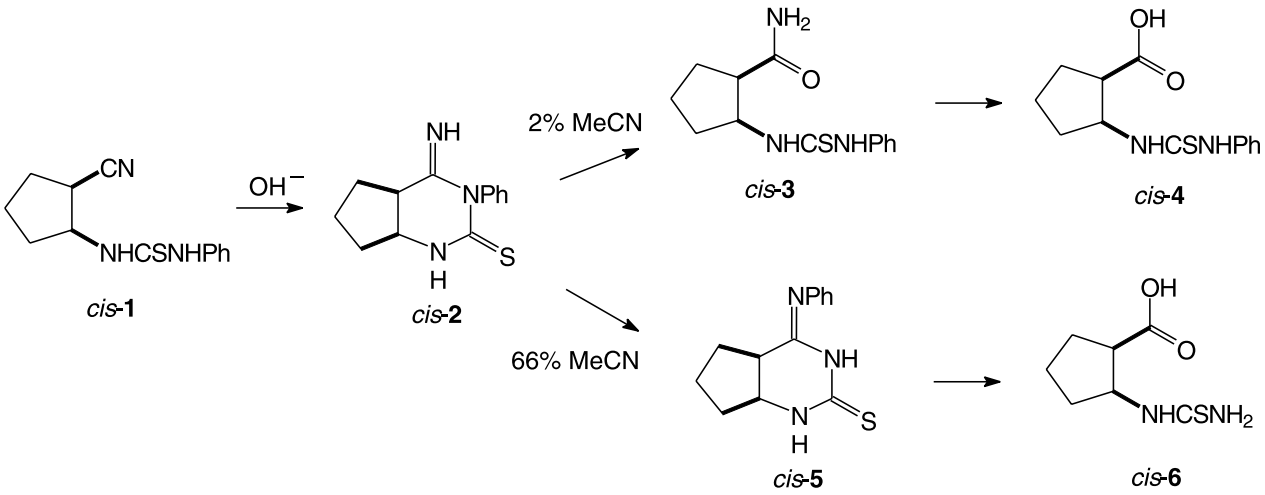
conduisant à plus de phényliminopyrimidine réarrangée **5** par addition d'acétonitrile peut être provoqué par une baisse de constante diélectrique favorisant l'étape d'élimination qui conduit à l'intermédiaire isothiocyanate et par une activité accrue des ions OH^- qui augmente la vitesse de l'étape d'élimination que l'on croit être du deuxième ordre par opposition à l'hydrolyse du dérivé imino **2**, qui est indépendante du pH.

Mots clés : assistance anchimérique, nitriles phénylthiouréido, tautomères des iminothiooxopyrimides, hydrolyse alcaline, effets de solvant.

[Traduit par la Rédaction]

Scheme 1.



Introduction

Ureido or thioureido nitriles, readily available from amino nitriles, have been widely used (1) in the synthesis of aminopyrimidines, aminoimidazoles, or thiazoles. On a preparative level the ring-closure was found to be base catalyzed (2). The products of attack of the ω-nitrogen of the ureido group are formed from thioureido nitriles in neutral and basic media (3).

We now report that the hydrolysis of a nitrile group is anchimerically assisted by a suitably orientated β-phenylureido group as in *cis*-**1**. The latter compound, in 0.01 M aqueous alkali, converts into the amide **3** 10^4 times faster than acetonitrile (4). The hydrolysis is facilitated by the formation of the iminopyrimidine **2** as shown in Scheme 1.

However, hydrolysis of aminopyrimidine **2** to **3** and further to the phenylthiouredo acid **4** was observed in aqueous alkali with a low (1–2%) content of acetonitrile. When the concentration of MeCN was increased to 66% (v/v) the major products were the rearranged pyrimidine **5**, hydrolyzing ultimately to the thioureido acid **6** without the phenyl group.

Results and discussion

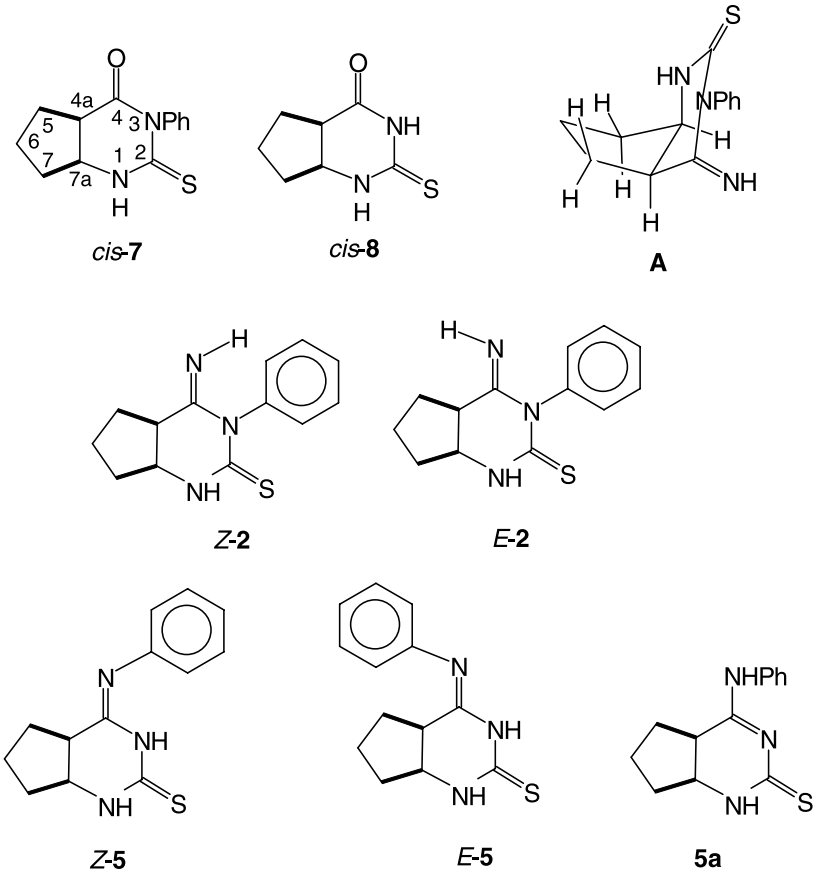
Preparation and configuration of 2-phenylthioureidocyclopentanecarboxylic acid and 4-oxo-2-thioxooctahydrocyclopenta[*d*]pyrimidine derivatives

2-Aminocyclopentanecarbonitrile is obtained as a mixture of *cis* and *trans* isomers which have not yet been separated, but the phenylthioureido derivatives **1** are readily separated by column chromatography.

The configurations of the thioureido nitriles **1** were assigned from their behaviour in 1:2 HCl. Upon refluxing, the two isomers both cyclized in high yield to produce the single product *cis* 2-thiodihydrouracil **7** (Scheme 2). The latter has recently been obtained by cyclization of the respective *cis* thioureido ethyl ester in hydrochloric acid solution (5) and assigned as *cis* from bandwidths of the signals for 4a-H (ca. 25 Hz) and 7a-H (ca. 12 Hz) in the ^{1}H NMR (6). We proved this independently by double resonance experiments[2] which showed $J_{4a,7a}$ to be 6.5 Hz, which fell within the usual range for *cis* coupling in dihydrouracils (7). The 7a-H signal splittings due to the neighbouring methylene hydrogens were considerably smaller than those for 4a-H, indicating that the NH group is pseudoaxial in the presumably half-chair conformation of the cyclopentane ring. Cyclization of *cis* and *trans* **1** under milder conditions (2 h in 1 M HCl at 50°C) gave 86% and 15% *cis*-**7**, respectively. Whatever the reaction path from *cis*- or *trans*-**1** to *cis*-**7**, it can be safely assumed that the more readily cyclizing isomer has the same configuration as the ring product. Isomerization most likely occurs by acid catalyzed enolization which requires prior protonation of the carbonyl or imino function. It has been previously shown (8) that upon cyclization of ureido acids to dihydrouracils, isomerization occurs with the more basic ring compounds. Under the conditions used for obtaining the amides **3** on a

[2] Irradiation of H-6 of thiodihydrouracil decreased the 4a-H band by 6.5 Hz. Irradiation of 1-H sharpened the signal for 7a-H to a multiplet of 8 lines with couplings 6.6, 5.3, and 4.2 Hz. In the multiplet for 4a-H these couplings are 6.6, 7.8, and 9.0 Hz.

Scheme 2.



preparative scale (hydrolysis of the nitriles **1** in 60% sulfuric acid) the *cis* nitrile gave *cis* amide, shown by TLC to be free of the *trans* amide, while the *trans* nitrile hydrolyzed to a mixture of *cis* and *trans* isomers. Since the *trans* nitrile **1** and amide **3** are certainly more stable than *cis*-**1** and **3**, the isomerization must occur after the formation of a bicyclic derivative more stable in the *cis* configuration.

Greater stability of the *cis* isomer of dihydrouracil **7** can be understood by reference to the hydrindane system (bicyclo[4,3,0]nonane) (9). The *trans* hydrindane is more stable (ΔH) by 1.1 kcal mol^{-1} as the result of two conflicting forces: the unavoidable axial interactions in the *cis* isomer and the mismatch of torsion angles between the five and six membered rings. In a *trans* junction these can be accommodated by unfavourable greater puckering. Because dihydrouracils are considerably planar (10) with the torsion angles between the *trans* diequatorial bonds ca. 90°, *trans* fusion to a cyclopentane with an endocyclic torsion angle of ca. 45° would require considerable strain, which is apparently the main factor in determining the relative stability of the two isomers. Exclusive preference for *cis*-annelation has also been observed in the formation of 3-aryl-2,4-dioxo-octahydrocyclopenta[*d*]pyrimidines in a ring expansion reaction (6).

Acid *cis*-**4** was readily available by means of alkaline hydrolysis of *cis* dihydrouracil **7** while *trans* acid **4** was obtained under milder acid hydrolysis of *trans* nitrile **1** along with some *cis* dihydrouracil **7**. Acid *trans*-**4** has been isolated in high yield from the ethyl ester in an attempt to cyclize the latter under reflux in hydrochloric acid (5).

Preparation of 4-imino and 4-phenylimino-2-thiooxooctahydrocyclopenta[*d*]pyrimidine

When the hydrolysis of *cis* thioureido nitrile **1** was monitored by UV in aqueous alkaline media containing only 1–2% acetonitrile, a decrease of absorption at 245 nm due to NHCSNHPh and an accompanying increase in absorption at 267 nm were observed. The latter reached a maximum after which the absorption at 245 nm was restored in a slower process. Detailed product analysis (*vide infra*) showed that the intermediate formed broke down to amide *cis*-**3** and this in turn to *cis*-acid **4** with both compounds having the same UV absorption as the initial nitrile. The intermediate, expected to be the iminopyrimidine **2**, however, proved elusive. The usual work up gave the rearranged product, the phenyliminopyrimidine **5**. Its structure was deduced from the products of hydrolysis: in base the thioureido acid **6**, while in acid the known thiodihydrouracil **8** (11) without the phenyl group. Compounds **6** and **8** could be readily interconverted in acid or base as appropriate. Under the conditions described in the experimental section no isomerization was observed because ^{1}H NMR evidence demonstrated retention of *cis* configuration.

Under conditions where imines similar to **2** have been obtained from ureido nitriles our starting nitrile *cis*-**1** either remained unchanged (refluxing in benzene (3a,b)) or yielded the rearranged phenylimino product **5** directly (refluxing in methanol (3a) or in EtOH–EtONa (3c)). As the behaviour of *cis*-**1** in aqueous alkali could only be explained by the participation of imine **2** as depicted in Scheme 1, an attempt was

Table 1. ^{13}C NMR chemical shifts (in ppm) from TMS, in DMSO-d_6 solution

(a) Derivatives of cyclopentanecarboxylic acid											
Compound	COOH	CS	1-C	2-C	3-C	4-C	5-C	i-C	*o*-C	*m*-C	*p*-C
cis-**4**	175.1	179.9	45.8	56.6	31.0	21.4	27.4	139.2	124.0	128.5	122.7
cis-**6**	174.8	182.8	46.0	57.1	31.1	21.4	27.1	—	—	—	—
(b) Derivatives of 2-thio-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]pyrimidines											
	4-C	2-C	4a-C	7a-C	5-C	6-C	7-C	i-C	*o*-C	*m*-C	*p*-C
cis-**7**	169.2	179.6	43.0	54.5	27.9	21.5	32.0	139.3	128.2	129.5	127.4
cis-**5**[a]	153.4	176.6	36.6	55.5	29.7	21.5	31.4	148.3	120.4	128.8	122.7
cis-**8**	169.3	177.2	41.6	55.4	27.7	21.6	32.2	—	—	—	—

[a]Resonances of the major isomer.

made to obtain it in this medium. To avoid the inconvenience of the limited solubility of *cis*-**1** in water, the experiment was carried out with 0.01 M KOH in a water–acetonitrile 1:2 mixture. Unexpectedly the reaction proceeded by the completely different course shown in Scheme 2. This meant that the rate of isomerization became faster than the rate of hydrolysis of the imine **2** to amide **3**. The procedure for obtaining the non-rearranged imine *cis*-**2** described in the experimental was based on the kinetic study of the hydrolysis of the nitrile **1**. Conditions were chosen where formation of *cis*-**2** was rapid and, at the moment of its maximum formation, the mixture was quenched in acid. The reaction is reversible and in acid unconverted nitrile was extracted from the aqueous solution. The water layer could be used as a stock solution of *cis*-**2**. The latter was isolated as a solid by rapid alkalization of the acid solution from which the nitrile has been removed, extraction with methylene chloride, and evaporation in vacuo. The ^1H NMR of the solid showed small admixtures of *cis*-**1** and the rearranged product *cis*-**5**, both most likely formed during the work up. In solution the imino compound converted into the phenylimino one with a rate dependant on the solvent. Rough estimates of the half lives (in min) were: 16 in DMSO, 130 in CD_3OD, and 400 in $CDCl_3$ (monitored by NMR at room temperature).

The structure of *cis*-**2** followed from the chemical transformations discussed above. The other possible structure, that of a iminothiazinone resulting from sulfur attack on the nitrile group can be refuted from the ^{13}C spectra of the final product of the transformations in Scheme 2. As shown in Table 1 the thioureido acid *cis*-**6** shows resonances for CS and COOH at 182.8 and 174.8 ppm respectively. It can be readily shown that the thiazine would ultimately afford an ureido thioacid for which resonances are expected at ca. 160 and 195 ppm for CO and CSOH (12). In DMSO the structurally similar R^*,R^*-2-methyl-3-ureidobutanoic acid showed resonances at 176.2 (COOH) and 158.5 ($NHCONH_2$).[3]

Tautomers and configurations of the imines.

The amidine moiety in iminopyrimidine *cis*-**2** is fixed and allows no tautomers. However, two geometrical isomers around the C=N bond are possible. According to Perrin (13) it is especially unusual to see separate forms such as *Z*-**2** and *E*-**2** (Scheme 2), since proton exchange interconverts them. Accordingly in CD_3OD and $CDCl_3$ the ^1H NMR spectrum showed only one, apparently time averaged, set of signals. In DMSO, however, spectra under fast and slow exchange were observed with various samples. Under fast exchange 1-H resonated at 9.26 ppm while =N*H* was hidden under the multiplet for the *m*-H and *p*-H at ca. 7.35 ppm, integrating for 4 protons. Under slow exchange 1-H gave rise to two signals: 9.38 (0.4H) and 9.15 (0.6H) ppm. The signals for =NH were at 8.59 (0.6H) and 6.58 (0.4H) ppm respectively. The 2 ppm upfield shift can be attributed to the ring current effect of the 3-phenyl group in the *Z*-isomer because the benzene ring is not in the plane of the heterocyclic ring in similar systems (14). Other samples showed intermediate exchange. On standing all of them converted cleanly into the phenyliminopyrimidine **5**, indicating that the initial spectra dealt with the same compound. In view of the rapid conversion in DMSO of **2** into **5** and the difficulty in controlling chemical exchange, further investigation was discontinued.

With compound **5** two tautomers are possible: the phenylimino and phenylamino isomers shown. Similar cyclic acylated phenylamidines such as 3-aryliminoisoindolinones have been found to be only in the phenylimino tautomeric form (15). This is also the predominant form with phenyliminopyrimidine **5**. An IR band at 1664 cm^{-1} is observed in $CHCl_3$ which is within the characteristic range for exocyclic C–N double bonds non-conjugated to an acyl group (16). Another feature is the upfield chemical shifts of the *o*- and *p*-protons and carbons of the phenyl ring which is due to better conjugation with the electron pair on nitrogen than is the case when interaction with an acyl group (C=S) is possible, as in **5a** (15) (see Tables 1 and 2). However, in DMSO a third set of signals could be detected which was assigned to the amino form **5a**. The assignment was supported by variable temperature measurements. Notably a doublet of the **5a** set at 7.89 ppm did not exchange with D_2O and coalesced with the *ortho* protons upon heating. That this belongs to the interchanging system is supported by the fact that at 383 K the *m*- and *p*-protons had already coalesced to sharp triplets while the signal for the *o*-protons at ca. 6.8 ppm was still broad due to the greater chemical shift difference (>1 ppm between the imino and amino forms). The greater significance of the amino form compared to the above mentioned isoindolinones can be attributed to the greater acidity of thioamides compared to ordinary amides. The isomer ratio is *E*-**5**:*Z*-**5**:**5a** = 7.5:1.5:1.

[3]Unpublished.

Table 2. ^{1}H NMR data for compounds in DMSO-d_6, chemical shifts from TMS (ppm), band widths, and couplings (Hz).[a]

(a) Derivatives of 2-phenylthioureidocyclopentanecarboxylic acid

Compound	1-H	2-H	*o*-H[c]	*m*-H[c]	*p*-H[d]	1′-NH	3′-NH
nitrile *cis*-**1**	3.53 quart bw 20.5	4.74 m[b]	7.50 d	7.32 t	7.11 t	8.06 d *J* ca. 7	9.60 s
in $CDCl_3$	3.62 bw 18.2	4.902 bw 33.1	[e]	7.47 t	[e]	6.19 d *J* 7.5	7.87 s
nitrile *trans*-**1**	3.060 quart bw 22.9	4.871 quin bw 29.7	7.397 d	7.303 t	7.117 t	7.99 d *J* 7.3	9.59 s
amide *cis*-**3**[f]	2.879 quart bw 22.2?	4.804 m[b]	7.432 d	7.303 t	7.087 t	7.64 d *J* 7.9	9.80 s
amide *trans*-**3**[g]	2.614 quart bw 22.8	4.66[b]	7.452 d	7.297 t	7.075 t	7.80[b]	9.41 s
acid *cis*-**4**[h]	2.993 quart bw 21.2	4.891[b] m	7.469 d	7.305 t	7.09 t	7.625 d *J* 8.3	9.696 s
acid trans-**4**[i]	2.709 quart bw 23	4.748[b]	7.423 d	7.297 t	7.076 t	7.93 d *J* ca. 6	9.44 s
cis-**6**[j]	2.924 quart bw 21.3	4.71[b]	—	—	—	7.47 d *J* 7	7.05 s 2H

(b) Derivatives of 2-thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]pyrimidines

Compound	4a-H	7a-H	*o*-H[c]	*m*-H[c]	*p*-H[d]	1-NH	3-NH
4-oxo[k] *cis*-**7**	3.045 quart bw 23.3[l]	4.052 quart bw 15.9[m]	7.1 d	[n]	[n]	9.84	
4-oxo *cis*-**8**	2.770 quart bw 23.2	3.833 quart bw 19.0				9.49	10.93
4-imino[k] *cis*-**2**	3.039 sext bw 22.2	3.945[b] hw 11.5	7.088 d	7.37 t	7.317 t	9.26 s[o]	[p]
in CD_3OD	3.100 sext bw 24	4.042 hw 12.0	7.18 d	7.456 t	7.35 t		
in $CDCl_3$	3.118 sext bw 22.5	4.042 hw 12	7.295 d	[q]	[q]	7.21 s[r]	r
4-phenylimino *cis*-**5**-*E*[s]	2.584 bw 21	3.799[b] hw 10	6.752 d 7.7	7.299 t	7.029 t	8.87 s	10.51s
4-phenylimino cis-**5**-*Z*[s]	2.74	3.85	6.83 d	7.378	7.109	8.9 7s	9.99s
5a[s]	2.95	3.97	7.89 d	[t]	[t]	7.77 s	9.43 s
in CD_3OD **5a**-*E*[u]	2.760 sext bw 24	3.858 t bw 8	6.811 d	7.315 t	7.078 t		
5a-*Z*[u]		2.98[v]	4.02[v]	6.92[v]	7.404[v]	7.171[v]	
in $CDCl_3$ **5a**-*E*[u]	2.728 sext bw 22	3.912 bw 8.4	6.789 d	7.322 t	7.105 t	8.5 v.br.	7.239 7.1
5a-*Z*[u]		3.007 bw 22.3	4.052 bw 9.0	6.907 d	7.371 t	7.136 t	7.79 br

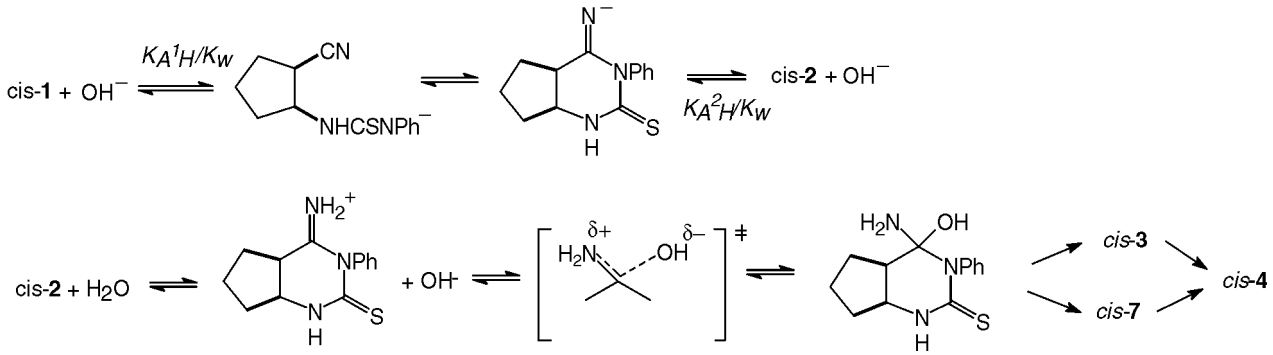
[a]The three methylene group gave complex peaks in the 1.4–2.2 ppm region.
[b]Unresolved.
[c]2H.
[d]1H.
[e]Part of multiplet 7.32–7.37 ppm.
[f]6.961 s, 7.448 s ppm $CONH_2$.
[g]6.87 s, 7.3 s ppm $CONH_2$.
[h]12.30 ppm COOH.
[i]12.22 ppm COOH.
[j]12.15 ppm COOH.
[k]3-phenyl, similar to data of ref. 9 except for $\delta_{1\text{-NH}}$ reported as 7.80 ppm.
[l]*J* = 6.6, 7.8 and 9.0 Hz.
[m]After removal of NH coupling by double resonance: *J* = 6.6, 5.3, and 4.2 Hz.
[n]Part of m 7.27–7.38 ppm.
[o]1H under fast exchange; under slow exchange 9.377 ppm 0.4H *Z*-isomer and 9.146 ppm 0.6H *E*-isomer.
[p]Imino group proton: under fast exchange 7.40 ppm; under slow exchange 8.59 ppm 0.6H *E*-isomer, 6.58 ppm 0.4H *Z*-isomer.
[q]Part of multiplet 7.39–7.55 ppm.
[r]2H, common signal for 1-H and the imino proton.
[s]*E*:*Z*:**5a** = 7.5:1.5:1.
[t]Could not be assigned.
[u]*E*:*Z* = 1:1.
[v]Broadened.

In CD_3OD only, a 1:1 ratio of the imino *Z* and *E* isomers was observed. The signals of one of the isomers were broadened, which is most likely due to exchange with the amino form. In $CDCl_3$ only two sets of signals, both sharp, in 1:1 ratio were observed. This could be due either to fast exchange with the amino isomer or to its absence in significant amounts.[4]

The assignment of *Z* or *E* configurations was based on the expected upfield shift of 4a-H and 7a-H caused by the ring current effect of the phenyl group, because in the *E*-isomer

[4]One of the referees has suggested that the doubling of the NMR resonances could be due to dimer-polymer equilibria. We believe that the amidines studied in ca. 0.04 M solutions are unlikely to give associates, particularly in DMSO and MeOH.

Scheme 3.



allylic strain will force it into a perpendicular position. Such an assignment readily explains the favouring of the *E*-isomer in DMSO: solvation at 3-NH will hinder the phenyl group in the *Z*-isomer. The conformation, *syn* or *anti,* of the **5a** isomer could not be assigned.

Noteworthy is the strong bias of *cis*-**2** for conformation **A** (Scheme 2) suggested by the bandwidths of the signals for protons 4a and 7a in DMSO: 22.2 and 11.5 Hz respectively. 7a-H is axial in the pyrimidine ring thus J_{HNH} will be 0–1 Hz (7) and pseudoequatorial in the cyclopentane ring so that the sum of 11.5 Hz has to be made up of three gauche couplings. The signals for the 4a- and 7a-protons in the imino tautomers of compound **5** were better resolved than those for the iminopyrimidine **2**. Again the bandwidths for the 7a-H signals are very small: 8.4–9.0 Hz in CD_3OD and $CDCl_3$. The signals are triplets which can be due to two couplings of ca. 4 Hz. This is the value of a *cis*-coupling in dihydrouracils in cases of a directed electronegativity effect (7), i.e., when an electronegative atom is *anti* to one of the coupled protons. In conformation **A,** shown on Scheme 2 for compound **2,** the ring nitrogen is *anti* to 4a-H and to the neighbouring *cis* cyclopentane ring proton which accounts for the low couplings. The coupling with the *trans* proton of the pentane ring with a torsion angle of ca. 90° can be close to zero and thus not seen. The sextets observed for 4a-H can be accommodated by two couplings of 9–10 Hz and one of ca. 4 Hz. The latter is of course $J_{4a,7a}$ while the large couplings are the expected ones with torsions of ca. 30 and 150° with the *cis* and *trans* cyclopentane ring protons, respectively.

Kinetics of alkaline hydrolysis of nitrile *cis*-1

The equilibrium nitrile cis-*1*-*imine* cis-*2*

As described above when the hydrolysis of *cis*-**1** in aqueous hydroxide is monitored by UV, the peak at 245 nm decreases while a new absorption at 267 nm appears due to *cis*-**2**. The latter then breaks down by a much slower process and the absorption at 245 nm is restored. Quantitative estimates showed that the conversion of *cis*-**1** into *cis*-**2** is incomplete and an equilibrium is established (Scheme 3). At an [OH^-] higher than 0.01 M the amount of *cis*-**2** at equilibrium decreased. This can be explained by considerable ionization of the phenylthioureido group.

Table 3. Absorbance ratios in 0.1 M HCl for determining K_e = [*cis*-**2**]/[*cis*-**1**] and pK_{AH} of the phenylthioureido group of nitrile *cis*-**2** (25.0°C and ionic strength of 1 M (KCl)).

[OH^-] (mol/dm^{-3})	$A_{295}{}^{a}/A_{265}{}^{b,c}$
0.00200	1.42
0.00400	1.43
0.00600	1.39
0.00800	1.38
0.0140	1.32
0.0160	1.29
0.0200	1.24
0.0400	1.05
0.100	0.785
0.160	0.68
0.200	0.634
0.320	0.538
0.400	0.511
0.520	0.502
1.00	0.474

[a] $A^\circ_{1,294}$ = 1 870, $A^\circ_{2,294}$ = 11 200.
[b] $A^\circ_{1,265}$ = 9810, $A^\circ_{2,265}$ = 4260.
[c] Ratios are averages from several experiments.

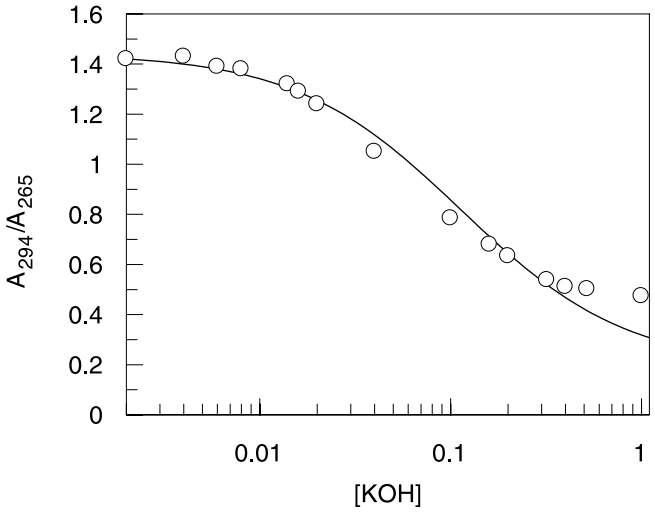
Defining K_e = [*cis*-**2**]/[*cis*-**1**] as the equilibrium constant between the neutral species, then upon considerable ionization of the thioureido group the apparent equilibrium between the stoichiometric concentrations is given by eq. [1]:

$$[1] \qquad K_{app} = \frac{[cis\text{-}\mathbf{2}]_{st}}{[cis\text{-}\mathbf{1}]_{st}} = \frac{K_e}{1 + [OH^-]K^N_{AH}/K_w}$$

The equilibrium mixture was analyzed by quenching the reaction mixture with hydrochloric acid at the moment of reaching the maximum of absorption at 267 nm, when the final products could still be neglected. HCl was added to a final concentration of ca. 0.1 M. Under these conditions the imine *cis*-**2** was fully protonated (pK_{BH^+} was determined spectrophotometrically to be 6.40 ± 0.11)[5] and hydrolysis is relatively slow. To avoid errors due to dilution, the equilibrium constant (K_e) and the dissociation constant for the CSNHPh group (K^N_{AH}) was determined from the ratio of the absorbances at two wave lengths:

[5] p*K* values for 4-imino-3-phenylhydantoins ranging from 6.1 to 6.5 have been reported in ref. 17.

Fig. 1. Semilogarithmic plot of A_{294}/A_{265} against [OH^-]. Curve is drawn by means of eq. [2] and parameters in text.

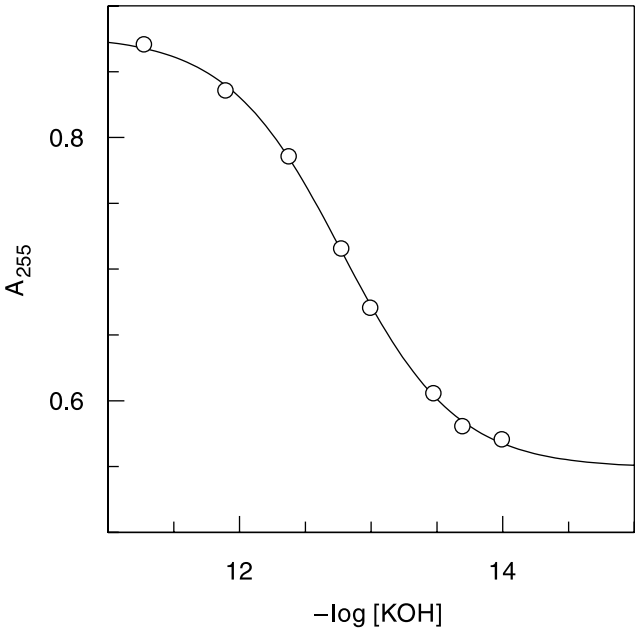


$$[2] \qquad \frac{A_{l1}}{A_{l2}} = \frac{A^{\circ}_{l1} + A^{\circ}_{21}K_e/(1 + K^N_{AH}[OH]/K_w)}{A^{\circ}_{l2} + A^{\circ}_{22}K_e/(1 + K^N_{AH}[OH]/K_w)}$$

where A^0_{ii} are the molar absorbances, the first subscript denoting the compound and the second one the wave length. A curve fit of the ratios A_{294}/A_{265} (Table 3) to eq. [2] in the interval 0.002 to 1 M KOH gave $K_e = 2.43 \pm 0.11$ and $K^N_{AH}/K_w = 18.0 \pm 2.1$ (I = 1 M (KCl)). Taking $K_w = 1 \times 10^{-14}$ and [OH^-] = a_{OH} gave a pK^N_{AH} of 12.74. These parameters resulted the fit shown in Fig. 1. The positive deviation of the points in 0.5 and 1 M KOH could be due to deprotonation of the amidine **2** (18) but attempts to include such an ionization in eq. [2] were unsuccessful.

Due to the rapid conversion of the nitrile *cis*-**1** in the region of ionization its p*K* could not be determined independently by spectroscopy. To check whether the value was reasonable, the p*K* for the ionization of the phenylthioureido group of the related amide *cis*-**3** was determined in KOH solutions (I = 1 M (KCl)). Again using –log [KOH] as the acidity function and $pK_w = 14$, a pK_{AH} of 12.78 ± 0.02 was obtained (Fig. 2).

Fig. 2. Determination of pK_{AH} for ionization of the phenylthioureido group in carboxamide *cis*-**3**.



$$[3] \qquad k_{obs} = k_f[OH^-]/(1 + K^N_{AH}[OH^-]/K_w) + k_f[OH^-]/K_e$$

The experimental data were fitted eq. [3] using the ionization and equilibrium constants found above as fixed parameters. This afforded $k_f = 4.24 \pm 0.08$ dm^3 mol^{-1} s^{-1} (Fig. 3). A $k_r$value of 1.74 dm^3 mol^{-1} s^{-1} was calculated from the equilibrium constant.

The kinetics observed indicate that the reactive form of *cis*-**2** is the ureide anion. According to the principle of microscopic reversibility the return path will involve the amidine anion.

The breakdown of the iminopyrimidine *cis*-**2** to products was found to be independent of the concentration of OH^- between 0.001 and 0.012 M KOH, where the observed first-order rates averaged to 2.21×10^{-4} s^{-1}. The somewhat higher rate observed in 0.1 M KOH indicates that a first order in [OH^-] process sets in. Actually, taking into account the lower fraction of *cis*-**2** at equilibrium in 0.1 M KOH, a lower pseudo-first-order constant should have been observed if only the pH-independent reaction took place. pH-independent rates are often encountered in the hydrolysis of amidines (18) in the alkaline region. The reaction can be formulated as attack of water on neutral iminopyrimidine, however, attack of OH^- on the protonated form as shown in Scheme 3 appears more appealing. The tetrahedral intermediate could either lose ammonia to give the pyrimidine **7** which would rapidly hydrolyze[6] to the acid **4**, or open the cycle to form the amide **3** which would then hydrolyze to the same acid **4**.[7] ^{1}H NMR of extracts of the acidified reaction mixture leaving *cis*-**2** as salt in the acid solution showed that the second route through the amide is preferred. After 110 min in 0.01 M KOH at room temperature (around two half-lives of *cis*-**2**) nitrile *cis*-**1** gave a mixture of *cis*-**3**:*cis*-

Rates of formation of imine *cis*-2 and its breakdown

The large difference in the rates of formation of *cis*-**2** from *cis*-**1** and the breakdown of the former allowed these to be measured as two separate first-order processes. The formation and breakdown were measured only up to 0.04 M KOH because of the considerable drop (due to the ionization of the ureido group at the higher alkalinities) in the amount of intermediate **2** formed at equilibrium. Furthermore, the rate of formation became too fast to measure by conventional means.

The cyclization of ureido nitrile **1** was found to be first order in [OH^-] at lower alkalinities. Taking into account the equilibria in Scheme 3, the following expression for the dependence of k_{obs} on [OH^-] can be derived:

[6] At pH 9.18 *cis*-**7** hydrolyzes with an observed rate of 0.0015 s^{-1}.
[7] Thin layer chromatography showed general retention of configuration. Only trace *trans* isomers of the products were found.

Scheme 4.

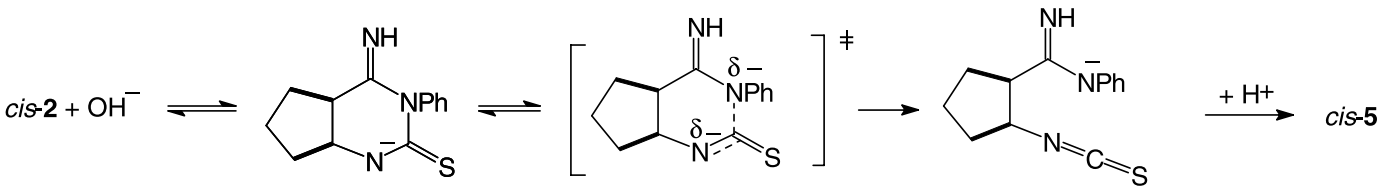
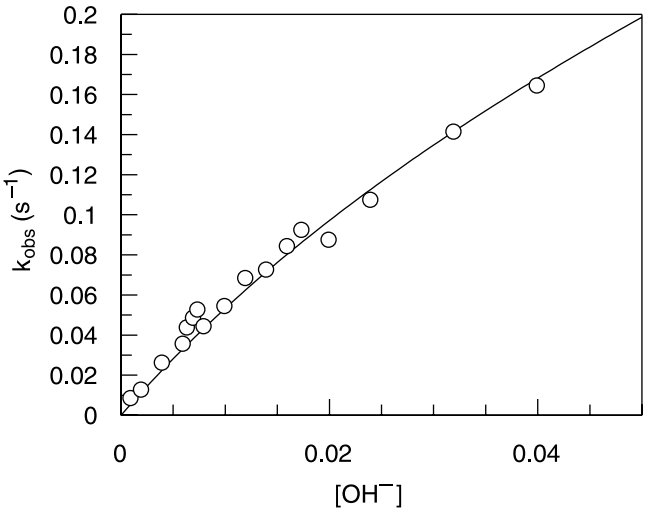


Fig. 3. Pseudo first order rate constants for the cyclization of nitrile **1**. Curve calculated by means of eq. [3] with parameters in text.



4:*cis*-**1** in a ratio of 57:30:13. After 7 h [*cis*-**3**]:[*cis*-**4**] = 19:81 and in 24 h the extract was pure acid *cis*-**4**.

In the introduction the magnitude of the anchimeric assistance to the alkaline hydrolysis of the nitrile group by the neighbouring phenylthioureido one is quoted as 1×10^4. This is estimated by comparing the rate of breakdown of *cis*-**2** with the second order rate constant of alkaline hydrolysis of acetonitrile. Another comparison could be provided by the hydrolysis of the nitrile group in *trans*-**1** which has a closer similarity with respect to steric and electronic influences. For 18 days at room temperature in aqueous 0.01 M KOH *trans*-**1** degraded only around 50%, the products were not, however, the amide *trans*-**3** or the acid *trans*-**4** (^{1}H NMR), and probably result from transformations of the thioureido group. If that time is compared with the half-life of *cis*-**2** of 50 min, the *trans* nitrile is at least 500 times more stable towards alkali.

Solvent effect on the breakdown of imine *cis*-2

The most likely transition states for the reaction of *cis*-**2** in water and in a mixture of water:acetonitrile (1:2 v/v) are shown on Schemes 3 and 4. The zero order in [OH^-] hydrolysis of **2** proceeds as suggested above as an attack by OH^- on the protonated form of the imine. On the other hand, the slow step in the isomerization is usually (19) a base catalyzed elimination giving the thioisocyanate shown on Scheme 4. The first reaction involves charge separation in the transition state while the second one dispersal of charge. Decreasing the dielectric constant by addition of acetonitrile will favour the second and disfavour the former reaction. Addition of a polar aprotic solvent will raise specifically the activity of the ground state of the elimination reaction (OH^-) and thus further accelerate elimination over hydrolysis.

Experimental

Unless otherwise stated IR-spectra are in nujol mulls on a Bruker IFS instrument, frequencies are in cm^{-1}, wavelengths are in nm. Instruments included a Bruker Spectrospin WM 250 NMR spectrometer (chemical shifts in ppm against TMS, couplings in Hz), a Jeol-D 300 mass spectrometer and a Unicam SP 800 UV spectrophotometer. Uncorrected melting points were determined in capillaries.

Inorganic reagents for kinetic measurements were of analytical grade and were used without further purification.

cis- *and* trans-*2-(-3-Phenylthioureido)cyclopentanecarbonitrile (**1**)*: The parent 2-aminocyclopentanecarbonitrile was prepared as a crude oil as follows. A solution of 2-amino-1-cyanocyclopentene (20) (7.3 g, 68 mmol) in methanol (100 mL) was made acid to bromocresol green with 1 N methanolic HCl. Sodium cyanoborohydride (4.9 g) was added by portions while the solution was kept acidic by the addition of more methanolic HCl. After stirring for 3 h the reaction mixture was concentrated. The residue was treated with 10% aqueous NaOH (68 mL) and NaCl (14 g), and taken up in dichloromethane (4 × 50 mL). It was removed from dichloromethane with 10% HCl (4 × 50 mL). The aqueous extract was made basic with 20% aqueous NaOH and extracted with dichloromethane (4 × 50 mL). The dichloromethane solution was dried (Na_2SO_4) and concentrated under reduced pressure to yield 2-aminocyclopentanecarbonitrile (6.53 g, 88%) as a colourless oil. IR (Nujol) ν_{max}: 3370, 3305 (NH), 2220 (CN) 1600 (NH_2).

A solution of phenylisothiocyanate (2.80 g, 21 mmol) in ether (5 mL) was slowly added to a solution of the above 2-aminocyclopentanecarbonitrile (2.2 g, 20 mmol) in ether (5 mL). A crystalline precipitate formed which was filtered and washed with petroleum ether to give the crude *cis* and *trans* isomers of **1** (4.4 g, 88%). The crude mixture (2 g) was chromatographed on 60 g "Florosil" with chloroform as the eluent. 50 mL fractions were taken and fractions 4 to 7 yielded the more mobile *cis* isomer while 9 to 25 yielded the

trans isomer. Crystallization from ethanol-water (2:1) yielded 0.67 g solid *cis*-**1** (mp 163–164°C). λ_{max} (H_2O): 245; IR (KBr disk) ν_{max}: 3230 (NH), 2232 (CN) 1546 (NHCSNHPh); MS *m/z*: 245. Anal. calcd. for $C_{13}H_{15}N_3S$: C 63.6, H 6.2; found: C 63.3, H 6.15. *trans*-**1** (1.07 g) had a mp 156–157°C. λ_{max} (H_2O): 244; IR (KBr disk) ν_{max}: 3295, 3181 (NH), 2240 (CN); MS *m/z*: 245. Anal. calcd. for $C_{13}H_{15}N_3S$: as above; found: C 63.25; H 6.5.

cis-*2-(3-Phenylthioureido)cyclopentanecarboxamide (*cis-***3***)*: The *cis* nitrile **1** (0.30 g, 1.2 mmol) was stirred in 60% sulfuric acid (5 mL). When solution was complete (1 h) it was diluted with water (15 mL) under cooling. The mixture was extracted with chloroform and the chloroform layer washed with 5% sodium carbonate and water, dried, and evaporated to dryness. TLC of the solid residue of *cis* amide **3** showed no appreciable admixture of the *trans* amide. Recrystallization from $CHCl_3$–petroleum ether yielded 0.15 g, 47% (mp 160–161°C after second crystallization). λ_{max} (H_2O): 245. IR (KBr disk) ν_{max}: 3388, 3356, 3277, 3165 (NH), 1662 ($CONH_2$), 1541 (NHCSNHPh). MS *m/z*: 263. Anal. calcd. for $C_{13}H_{17}N_3OS$: N 15.96; found N 15.54.

trans-*2-(3-Phenylthioureido)cyclopentanecarboxamide (*trans-***3***)*: The same procedure with *trans* nitrile **1** (0.30 g, 1.2 mmol) in which the dilution with water followed 5 min of stirring afforded, after two recrystallizations from chloroform-petroleum ether, 0.16 g (50%) of *trans*-**3** (mp 155–156°C, the crude product contained considerable amounts of the *cis* amide-**3** (determined by TLC)). λ_{max} (H_2O): 245. IR (KBr disk) ν_{max}: 3346, 3209 (NH), 1660, 1633 ($CONH_2$), 1541 (NHCSNHPh). Anal. calcd. for $C_{13}H_{17}N_3OS$: N 15.96; found N 15.95.

cis-*4-Oxo-1,2,3,4a,5,6,7,7a-octahydro-3-phenyl-2-thiooxocyclopenta[*d*]pyrimidine (*cis-***7***)*: (a) *cis* Nitrile **1** (0.305 g, 1.24 mmol) in 1:2 HCl (30 mL) was refluxed for 30 min. Cooling and filtering afforded 0.289 g (94%) of the crude thiouracil **7** (mp 267–269°C, ethanol, lit. mp 285–287°C (5)). λ_{max} (H_2O): 278; IR (Nujol) ν_{max}: 3171 (NH), 1711 (CO), 1564 (NHCSNPh); MS *m/z*: 246. Anal. calcd. for $C_{13}H_{14}N_2OS$: C 63.4; H 5.7; found: C 63.6; H 5.8. (b) Refluxing the *trans* nitrile **1** (60 mg, 0.24 mmol) in 1:2 HCl (30 mL) for 1 h, cooling, and standing overnight gave as precipitate 47 mg (78%) of pure (determined by ^{1}H NMR) *cis* pyrimidine **7**.

trans-*2-(3-Phenylthioureido)cyclopentanecarboxylic acid (*trans-***4***)*: Refluxing the nitrile *trans*-**1** (52 mg, 0.21 mmol) in 1:2 HCl for 30 min after cooling and standing overnight afforded 30 mg of a 4:1 mixture (^{1}H NMR) of the *cis* pyrimidine **7** and the *trans* acid **4**. Evaporating the mother liquor with a rotary evaporator yielded 19 mg, 34% of pure *trans* acid (mp 146–147°C, lit. mp 142–144°C(5)); λ_{max} (H_2O): 245; IR (KBr disk) ν_{max}: 3346, 3169 (NH), 1701, 1687 (CO), 1549 (NHCSNHPh). Anal. calcd. for $C_{13}H_{16}N_2O_2S$: C 59.1; H 6.1; N 10.6; found: C 59.0; H 6.32; N 10.8.

cis-*2-(3-Phenylthioureido)cyclopentanecarboxylic acid (*cis-***4***)*: The *cis* pyrimidine **7** (0.5 g, 2.03 mmol) dissolved easily in warm 0.5 M NaOH (20 mL). After acidifying the cooled solution with conc. HCl (2 mL) the *cis* acid **4** separated as a gum which crystallized rapidly to give 0.53 g. 99% of solid (mp 152–153°C, (chloroform-petroleum ether), resolidifies and melts again at 230°C). λ_{max} (H_2O): 245; IR (Nujol) ν_{max}: 3344, 3167 (NH), 1686 (CO), 1536 (NHCSNHPh). MS *m/z*: 264. Anal. calcd. for $C_{13}H_{16}N_2O_2S$: C 59.1; H 6.1; found: C 58.9; H 6.3.

cis-*4-Imino-1,2,3,4a,5,6,7,7a-octahydro-3-phenyl-2-thiooxocyclopenta[*d*]pyrimidine (*cis-***2***)*: The *cis* nitrile **1** (36 mg, 0.146 mmol) was dissolved by warming in acetonitrile (2 mL) and subsequently mixed with 0.01 M KOH (100 mL) at room temperature. After 3 min the mixture was transferred to a cooled separatory funnel containing ice and HCl, the amount of the latter dependant on the desired final acid concentration. The solution was extracted rapidly with dichloromethane (3 × 40 mL) in the course of five to eight min and passed through a fluted filter. The dry residues of the extracts amounted to 30–35% (by weight) of the starting material and consisted of (according to ^{1}H NMR) mixtures of the initial nitrile and the *cis* amide, the amount of the latter varying from trace to 30%). The aqueous layer was made alkaline (ca. 0.01 M in [OH^-]) and extracted twice rapidly with chloroform (ca. 12 min from the start of the experiment). The organic layer was filtered, dried with $MgSO_4$, and evaporated to give a solid, the iminopyrimidine *cis*-**2** (25 mg, containing up to ca. 15% the *cis* nitrile according to ^{1}H NMR). λ_{max} (H_2O): 267, (0.1 M HCl 295); IR ($CHCl_3$) ν_{max}: 3409, 3288, 3199b (NH), 1647 (C=N), 1528 (NCSNH).

cis-*4-Phenylimino-1,2,3,4a,5,6,7,7a-octahydro-3-phenyl-2-thiooxocyclopenta[*d*]pyrimidine (*cis-***5***)*: A solution of 0.5 g (2 mmol) of *cis*-2-(3-phenylthioureido)cyclopentyl cyanide in 80 mL of absolute methanol was refluxed for 3 h. The solvent was removed by a rotatory evaporator and the solid residue recrystallized from MeOH–MeCN to give 0.39 g (78%) of solid *cis*-**5** (mp 231–2°C). MS *m/e*: M^+ 245; λ_{max} (H_2O): 269, 242; IR (KBr disk) ν_{max}: 1670 (C=N), 1564 (δ NH), 1346 (NHCSNH), 3170, 3460 (NH); IR ($CHCl_3$) ν_{max}: 1664 (C=N) 1535 (δ NH), 1348 (NHCSNH), 3226, 3408 (NH). Anal. calcd. for $C_{13}H_{15}N_3S$: C 63.63, H 6.16, N 17.13, S 13.07; found: C 63.78, H 6.45, N 16.85, S 13.18.

cis-*1,2,3,4a,5,6,7,7a-Octahydro-4-oxo-2-thiooxocyclopenta[*d*]-pyrimidine (*cis-***8***)*: (a) From phenyliminopyrimidine *cis*-**5**. The phenyliminopyrimidine *cis*-**5** (0.37 g, 1.5 mmol) was dissolved with gentle heating in 30 mL of MeOH and 10 mL of MeCN. 40 mL of distilled water and 15 mL of 1M HCl were further added. The solution was left at ambient temperature for 75 min and then evaporated to dryness until HCl was completely removed in vacuo. Recrystallization from MeOH–petroleum ether afforded 0.180 g (80%) of solid (mp 198–9°C, lit. mp 206–208°C(11)); MS *m/e*: M^+ 170; IR (KBr disk) ν_{max}: 1693 (CO), 1362 (NHCSNH), 3182, 3460w (NH). Anal. calcd. for $C_7H_{10}N_2OS$: C 49.39; H 5.92; N 16.46; S 18.91; found C 49.50; H 6.03; N 16.77; S 18.91.

(b) From cyclization of *cis*-2-thioureidocyclopentanecarboxylic acid (*cis*-**6**). The acid *cis*-**6** (0.150 g) was dissolved in 8 mL of MeCN and 4 mL of MeOH. 12 mL of 1 M HCl were added and the mixture left at room temperature for 20 h. The solvent removed and the dry residue recrystallized from MeCN and petroleum ether to yield 0.085 g (63%) of

Table 4. Pseudo-first-order rate constants (s^{-1}) for the formation and breakdown of 4-imino-2-thiooxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]pyrimidine *cis*-**2** in aqueous KOH and ionic strength 1.0 M (KCl) at 25°C.

$[OH^-]$ (mol/dm^{-3})	10^3 k_{obs} for formation	10^4 k_{obs} for breakdown
0.00031[a]	2.48	2.00
0.001	8.07	2.24
0.002	12.3	2.23
0.004	25.8	2.23
0.006	35.2	2.22
0.0064	43.4	2.21
0.007	48.2	2.11
0.0074	52.3	2.17
0.008	44.0	2.03
0.01	54.0	2.17
0.012	68.0	2.48
0.014	72.2	—
0.016	83.9	—
0.0174	92.0	—
0.02	87.1	—
0.024	107	—
0.032	141	—
0.04	164	—
0.1	—	3.90

[a]Experiment conducted at pH 10.49 in carbonate buffer 70% base.

solid *cis*-**8** (mp 197–199°C) identical with the above product according to spectral data and mixed mp.

cis-*2-Thioureidocyclopentanecarboxylic acid (*cis-***6***)*: (a) 0.31 g of phenyliminopyrimidine *cis*-**5** were dissolved by gentle heating in 20 mL of MeOH. 20 mL of aqueous 1 M KOH were added and the solution left at room temperature for 12 h. Most of the MeOH in the solution was removed on a rotary evaporator and the alkaline solution extracted twice with 20 mL portions of ether. The organic layers were dried and the solvent removed to yield an reddish-brown oil identified as aniline: M^+ 93; same IR and UV spectra as that of an authentic sample. The aqueous layer was neutralized with 2 equivalents of cationite Dowex 50x8 in H^+ form. The solution (pH two to three) was evaporated and the residue recrystallized twice from MeCN with addition of petroleum ether to yield 0.045 g (19%) of *cis*-**6** (mp 155–157°C). MS *m/e*: M^+ 188. λ_{max} (H_2O): 230 (log ϵ = 3.9), 280 (log ϵ = 3.1). IR (KBr disk) ν_{max}: 1635, 1560 (delta NH) 1703 (COOH), 3186, 3300, 3350 (NH,OH). Solution resulted a single spot on TLC and no admixtures were observable in the ^1H NMR spectrum. (b) 0.095 g of *cis*-**8** were dissolved in five mL of MeOH by gently heating and 10 mL of 1 M aqueous KOH added. Similar work up yielded 0.097 g of raw *cis*-**6** identical (according to ^1H NMR) to the product obtained in (a).

Kinetic measurements

The rates were measured under pseudo first order conditions in the thermostated cell compartment of a Unicam SP 800 spectrophotometer. The reactions were initiated by injecting 20 to 80 μL of a 10^{-2} to 10^{-3} M stock solution of the substrate in MeCN, to the preheated KOH solution of ionic strength 1 M (KCl). The conversion of *cis*-**1** into *cis*-**2** was monitored by the increase of absorption at 267 nm while the degradation of the latter was monitored by the decrease at the same wavelength. Pseudo-first-order rate constants (k_{obs}) were calculated by the least squares procedure from plots of either ln ($A_t - A_{inf}$) or ln ($A_{inf} - A_t$) (as appropriate) versus time, where A_{inf} was the absorbance after ten half-lives.

Equilibrium between the *cis* nitrile 1 and *cis* iminopyrimidine 2

Under the conditions of the rate experiments a solution of the *cis* nitrile **1** in MeCN was added to the preheated at 25.0°C KOH solution so that the final concentration of **2** was 7–8 × 10^{-5} M. When maximum absorption at 267 nm (λ_{max} (H_2O) of *cis*-**2**) was reached, the solution in the cell was acidified with a predetermined amount of HCl so that its final concentration was ca. 0.1 M and the spectrum of the solution taken immediately. The ratio [*cis*-**2**]:[*cis*-**1**] was determined from the ratio of the absorbances at the two wave lengths as well as the known extinction coefficients at these wavelengths of the two compounds in HCl solutions. Making the solution alkaline after the measurement restored the pre-acidification spectrum by better than 5%.

Product analysis

The course of the alkaline hydrolysis of *cis*-**1** was also followed by ^1H NMR in order to identify the products. For these large scale experiments the substrate was dissolved in an appropriate amount of MeCN so that when added to the KOH solution, the final concentration of MeCN equalled that in the kinetic experiment. After being kept at 25°C for the appropriate period of time, aliquots were acidified and extracted with dichloromethane, the solvent removed and the composition determined by ^1H NMR.

Determination of p*K*-values

(*a*) *cis*-Amide **3**. A solution (20 μL) of the amide (0.01 M) in MeCN was added to a 25.0°C (2.7 cm^{-1}) preheated solution of KOH (0.002 to 1 M, I = 1 M (KCl)) in a UV cell, and the absorbance measured at 255 nm. The pK was obtained by a nonlinear regression fit of the equation

$$K = (A_{AH} - A)[H^+]/(A - A_{A^-})$$

where A is the absorbance, A_{AH} and A_{A^-} the limiting absorbances at low and high basicity respectively. $[H^+]$ was assumed equal to antilog(14 – log $[OH^-]$).

(*b*) *cis*-Iminopyrimidine **2**. The compound was isolated as a solid as described above and as a solution prepared in MeOH which was kept cooled in ice/water. Aliquots (10 μL) were injected into UV cells containing 25.0°C preheated 0.1 M buffer solutions (formate, acetate, and phosphate) with I = 1 M (KCl). The absorbances were measured at 295 nm and the p*K* was calculated as above using the pH-values measured by means of a Radiometer pHM 84 Research pH-meter with a GK 2401 electrode.

Acknowledgements

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