Saturated Heterocycles, 248 [1]. Synthesis of 2,4-Dioxo and 4-Oxo-2-thioxo Derivatives of Octahydrocyclopenta[*d*]pyrimidines

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Unsubstituted and 1-benzyl-substituted *cis*-cyclopenta[*d*]pyrimidine-2,4-diones and *cis*-2-thioxocyclopenta[*d*]pyrimidin-4-ones **9a,b** and **10a,b** were prepared from the corresponding *cis*-2-amino-1-cyclopentanecarboxylates **3** and **5** with potassium cyanate and thiocyanate. It was found that the *cis* derivatives **7a-h** readily underwent ring closure, resulting in 3-substituted *cis*-2,4-cyclopenta[*d*]pyrimidinediones and *cis*-2-thioxocyclopenta[*d*]pyrimidin-4-ones **11a-d** and **12a-d**, whereas the *trans* counterparts **8a-d** failed to cyclize, but gave hydrolysed amino acid derivatives **13a,b** and **14**. This difference in the reactivities of the *cis* and *trans* isomers is a further example of the difficulty of preparing cyclopentane *trans*-fused six-membered 1,3-heterocycles by ring closure.

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Introduction.

Although six-membered saturated 1,3-heterocycles and their benzene ring-fused derivatives have been studied thoroughly, much less attention has been paid to the bicyclic saturated derivatives [2]. Because of the theoretical and pharmacological importance of the saturated carbocycle-fused heterocycles, the synthesis and conformational study of saturated or partially saturated six-membered 1,3-heterocycles *cis*- or *trans*-fused with 5-, 6-, 7- or 8-membered alicycles have comprised one of our main research topics [3,4].

The synthesis and stereochemical aspects have been thoroughly studied for the cyclohexane-, cyclohexene-, norbornane- and norbornene-*diexo*- and *diendo*-fused derivatives, among them pyrimidine-2,4-diones and 2-thioxo-4-pyrimidinones, but few *cis*-fused cyclopentane derivatives have been prepared [2-7].

The unsubstituted perhydroquinazoline-2,4-diones have been obtained *via* the reactions of the appropriate ethyl 2-amino-1-cyclohexanecarboxylate hydrochloride and potassium cyanate, yielding the urea esters, which were smoothly cyclized without purification in boiling xylene [8,9], but in the cyclization of ethyl *trans*-2-amino-1-cyclohexanecarboxylate hydrochloride, a partial *trans* → *cis* isomerization took place, resulting in a *cis-trans* mixture of quinazolinedione [9].

The parent cyclohexane-fused 2-thioxopyrimidin-4-ones were prepared by reacting the corresponding amino ester hydrochlorides with potassium thiocyanate [10], or from alicyclic ethyl 2-isothiocyanato-1-carboxylates, obtained by the reaction of amino esters and thiophosgene with ammonia [11].

A number of 3-aryl-substituted perhydroquinazoline-2,4-diones and 2-thioxo-4-ones were prepared from the corresponding amino acids with isocyanate or isothiocyanate and acidic ring closure of the resulting urea adducts [12,13].

The 3-aryl-substituted perhydroquinazoline-2,4-diones have also been prepared through ring enlargements of the urea derivatives obtained by reaction of the appropriate *cis* azetidinones and aryl isocyanates. On heating in polyphosphoric acid, the cyclopentane- and cyclohexane-fused *cis* azetidinones underwent transamidation with ring enlargement to yield the *cis*- and *trans*-fused pyrimidinediones [14]. In the transamidation, the attack of the more nucleophilic nitrogen on the carbonyl group of the strained four-membered ring gives the cyclopentane *cis*-fused derivatives with retention, whereas the analogous reaction of the *cis* cyclohexane derivatives takes place with inversion and results in the thermodynamically favoured *trans* isomer [7].

Our present aim was to prepare cyclopentane-condensed *N*-substituted and unsubstituted pyrimidine-2,4-diones and 2-thioxo-4-pyrimidinones and to compare the attempted ring closure reactions of *cis*- and *trans*-2-amino-1-cyclopentanecarboxylic acid derivatives.

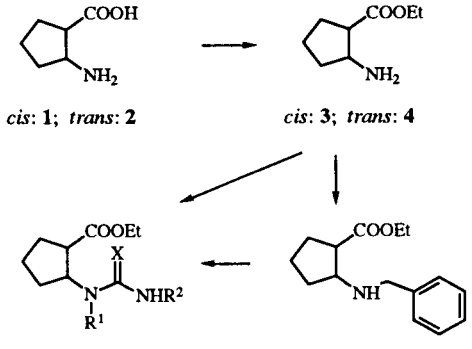
Results and Discussion.

cis-2-Amino-1-cyclopentanecarboxylic acid **1** was prepared from cyclopentene by chlorosulfonyl isocyanate addition and ring opening of the resulting azetidinone with hydrochloric acid [15]. The *trans* isomer **2** was obtained by ammonia addition to 1-cyclopentene-1-carboxylic acid [16]. The amino acids were transformed to the amino ester hydrochlorides **3** and **4**. The amino esters were reacted

with benzaldehyde to give the imines, which were reduced, without isolation, by sodium borohydride to furnish the *N*-benzylamino esters **5** and **6** (Scheme 1) [17].

The urea and thiourea derivatives **7a-h** and **8a-d** were prepared by the reactions of the amino esters **3-6** with the corresponding isocyanate or isothiocyanate in toluene (Scheme 1).

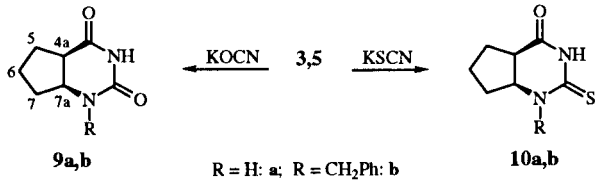
Scheme 1



	a	b	c	d	e	f	g	h
R^1	H	CH_2Ph	H	CH_2Ph	H	CH_2Ph	H	CH_2Ph
X	O	O	S	S	O	O	S	S
R^2	Ph	Ph	Ph	Ph	Me	Me	Me	Me

Unsubstituted and 1-benzyl-substituted *cis*-cyclopenta[*d*]pyrimidine-2,4-diones **9a,b** were prepared by refluxing a mixture of the *cis* amino ester **3** or **5** and potassium cyanate in water, while *cis*-2-thioxocyclopenta[*d*]-pyrimidin-4-ones **10a,b** were obtained by stirring a mixture of the corresponding amino ester and potassium thiocyanate in acetone, with subsequent filtration and evaporation, and refluxing of the residue in xylene (Scheme 2). The yields were only moderate.

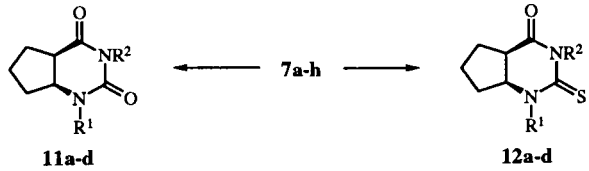
Scheme 2



9a,b R = H: **a**; R = CH_2Ph: **b** **10a,b**

The *cis*-fused derivatives **11** and **12** were obtained by refluxing the urea or thiourea derivative **7a-h** in dilute hydrochloric acid. However, the same ring closure for the *N*-benzyl derivatives gave a mixture of hydrolysed amino acid derivative and ring-closed product. Therefore, these *N*-benzyl derivatives were cyclized to pyrimidinones **11** and **12** by refluxing in ethanol containing 22% dry hydrogen chloride (Scheme 3). Both the urea or thiourea derivatives and the 3-substituted pyrimidinone derivative **11** and **12** were formed in good yields. It was found that the amino esters are more suitable starting materials than the amino acids, due to the better solubility of the intermediates. In these reactions the yields were higher.

Scheme 3

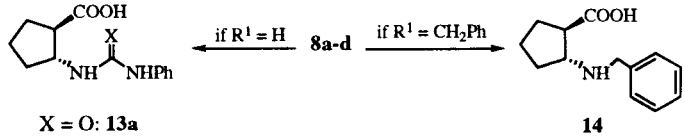


11a-d **12a-d**

	a	b	c	d
R^1	H	CH_2Ph	H	CH_2Ph
R^2	Ph	Ph	Me	Me

The attempted ring-closure reactions of the *trans*-fused urea and thiourea derivatives **8a-d** to pyrimidinones, by refluxing in dilute hydrochloric acid (22%) or in ethanol containing 22% dry hydrogen chloride, did not result in cyclized products. For the *N*-unsubstituted derivatives, the products were the corresponding urea or thiourea derivative of *trans*-2-amino-1-cyclopentanecarboxylic acid **13a** and **13b**. The *N*-benzyl derivatives **8b** and **8d** under the same conditions gave the *N*-benzyl-*trans*-2-amino-1-cyclopentanecarboxylic acid **14** (Scheme 4). Besides the spectroscopic evidence, the structures of **13a,b** and **14** were proved by synthesis, starting from the corresponding *trans*-2-aminocyclopentane-1-carboxylic acid **1**.

Scheme 4



X = O: **13a**
X = S: **13b**

14

It is noteworthy that in the ring closures of the 1,2-disubstituted 1,3-difunctional cyclohexane, cycloheptane and cyclooctane derivative no appreciable differences were found in the reactivities of the *cis* and *trans* isomers in the formation of six-membered 1,3-heterocycles fused with carbocycles [7]. In contrast, very striking differences were observed in the cyclization reactivities of the *cis* and *trans* 1,2-disubstituted 1,3-difunctional cyclopentane derivatives, such as 1,3-amino alcohols, or in case of the *cis* and *trans*-2-hydroxy-1-cyclopentanecarboxamides or *cis*- and *trans*-2-amino-1-cyclopentanecarboxylic acids. While the *cis* isomers react readily, their *trans* counterparts do not undergo ring closure in most cases [7].

For example, *trans*-2-hydroxy-1-cyclopentanecarboxamide could not be cyclized with aldehydes or ketones to the corresponding cyclopentane-fused 1,3-oxazin-4-ones [18]. This permitted a facile isomer separation [19,20]. *trans*-2-Amino-1-cyclopentanecarboxylic acid or carboxamide could not be cyclized to the corresponding *trans*-fused dihydropyrimidinone; instead, a slow racemization took place and the *cis*-fused pyrimidinone was formed [2].

Kinetic studies on $N \rightarrow O$ acyl migrations afforded results in agreement with the above observations and on the stereoisomers and positional isomers of 1,3-amino-alcohols, *i.e.* the $N \rightarrow O$ acyl migration of *cis*- and *trans*-2-aminomethyl-1-cyclopentanol derivatives and *cis*- and *trans*-2-hydroxymethyl-1-cyclopentylamine quantitatively confirmed the above differences [21,22]. The ring-chain tautomerism of tetrahydro-1,3-oxazines is very sensitive to the stability differences, the substituents and the ring-fusion effect. It also reveals a considerable stability difference in favour of the cyclopentane-*cis*-fused isomers [23-25].

In spite of these appreciable differences in the ability of the *cis* and *trans* isomers to undergo ring closure, the ring closures of *trans*-1,2-disubstituted 1,2- and 1,3-difunctional cyclopentane derivatives to cyclopentane *trans*-fused six-membered 1,3-heterocycles were successfully performed in some cases, *e.g.* with cyclopentane *trans*-fused 1,3-oxazin-2-ones, 2-thiones [26], 2-imino derivatives [27], and *N*-substituted tetrahydro-1,3-oxazines, where the possibility of ring-chain tautomerism is excluded [28], and dihydrothiazines [29,30] were synthesized without difficulty.

The above differences and similarities indicate a considerable difference in the stabilities of *cis* and *trans* cyclopentane-fused heterocycles as compared with the higher homologues. Such differences are especially striking when the formation of the heterocycles proceeds through an equilibrium reaction [7].

The differences demonstrated in the present experiments also gave a clear indication of the different reactivities in ring closure reactions of the *cis* and *trans* 1,2-disubstituted 1,3-difunctional cyclopentane derivatives and may serve as supporting evidence concerning the not too widely known features of the ring closure abilities of the *cis*- and *trans*-1,2-disubstituted-1,3-difunctional cyclopentane derivatives of both theoretical and preparative importance.

The characteristic ir frequencies and the ^{1}H- and ^{13}C-nmr chemical shifts are given in Tables 1 and 2, respectively. The spectral data are self-explanatory and require only a few additional comments.

The *cis* and *trans* configurations of **5** and **6** are supported [31a] by the smaller sum of the cyclopentane-carbon shifts for the former ($\Sigma\delta$ C-4a,5-7,7a [31d] is 190.0 ppm for **5**, and 198.4 ppm for **6**).

Table 1

Characteristic IR Frequencies (cm^{-1} in Potassium Bromide) and ^{1}H-NMR Data (Chemical Shifts in ppm[a] and Coupling Constants in Hz) in Deuteriochloroform Solution[b] at 250 MHz of Compounds **5**, **6**, **9a,b**, **10a,b**, **11a-d**, **12a-d**, **13a,b** and **14** [c]

Compound	νNH band [d] broad or diffuse	Amide-I band [e]	N(CX)N band [f]	H-4a *qa* (1H) [g]	H-7a *qa* (1H) [h]	NH br (1H) [i]	NCH_2 2 x *d* (2 x 1H) [j]		CH_2(5-7) *m's* (6H)
5	3334	1728	1183	2.92	3.30	2.34	3.76	3.80	1.4-2.1
6	3320	1728	1186	2.60	3.33	~1.8 [k]	3.75	3.80	1.4-2.1 [k]
9a	3600-2750	1717	~1700 [l]	2.86	4.00	5.45		–	1.7-2.3
9b	3250-2750	1700	1681	2.87	3.62	8.41	4.32	5.06	1.4-2.0
10a	3250-2750	1693	1145	2.90	4.10	7.15		–	1.7-2.3
10b	3220	1690	1247	2.88	3.77	8.62	4.75	5.74	1.5-2.4
11a	3230	1728	1684	3.00	4.06	5.40		–	1.7-2.4
11b	–	1715	1673	3.01	3.67	–	4.39	4.99	1.5-2.4
11c	3260	1722	1650	2.80	3.80	7.65		–	1.5-2.1
11d	–	1706	1666	2.84	3.56	–	4.34	5.01	1.4-2.3
12a	3170	1710	1220	3.03	4.03	9.81		–	1.6-2.2
12b	–	1710	1226	3.09	3.90	–	5.00	5.85	1.6-2.5
12c	3242	1670	1356	2.93	3.89	9.62		–	1.5-2.2
12d	–	1699	1381	2.85	3.74	–	4.88	5.32	1.5-2.5
13a	3346, 3280	1721	1610	2.50	4.13	6.29 [m]		–	1.4-2.0
13b	3350-2800	1722	1540	2.40	4.75	7.85		–	1.4-2.2
14	3200-2400	1665	–	3.05	3.94	?	4.25	4.31	1.7-2.3

[a] δ_{TMS} = 0 ppm. [b] Solvent: DMSO-d_6 (**11c**, **12a,c**, **13a,b**), deuterium oxide (**14**). [c] Assignments were supported by 2D-COSY and 2D-HSC measurements for **5** and **6**. Further signals, IR: $\gamma C_{Ar}H$ and $\gamma C_{Ar}C_{Ar}$, (phenyl): 748 ±17 and 700 ±7; ^{1}H-nmr: CH_3(OEt), *t*, J: 7.1 (3H): 1.27 (**5**), 1.24 (**6**), OCH_2, *qa* (**5**, **6**): 4.14, NCH_3, *s* (3H): 2.97 (**11c**), 3.25 (**11d**), 3.39 (**12c**), 3.66 (**12d**), ArH (*N*-benzyl), ~*s* (5H): ~7.35 (**9b**, **10b**, **11b** [n], **d**, **12d**) ~7.5 (**14**), *m* (5H): 7.1-7.4 (**5**, **6**), 7.3-7.6 [o] (**12b**); *N*-phenyl group, ArH-2',6', *d* (2H): 7.17 (**11a,b**), 7.10 (**12a**), 7.35 (**13a**), 7.42 (**13b**), ArH-3',5', *t* (2H): 7.45 (**11a,b**), 7.35 [n] (**12a**), 7.20 (**13a**), 7.30 (**13b**), ArH-4', *t* (1H): 7.40 (**11a**), 6.87 (**13a**), 7.07 (**13b**), OH, br (1H): ~12.2 (**13a,b**). [d] With a strong maximum superimposed on the diffuse band at about 3240 (**9a**) and 3182 (**10a**). [e] Ester νC=O (**5**, **6**), acid νC=O (**13a,b**, **14**). [f] Carbamide/thiocarbamide group, ester νC-O (**5**, **6**). [g] J ≈ 8, coalesced signal, half-width ~25 (**10a**, **11a,c**, **12a,b**, **14**), *dt* (J: 8.1 ±0.3, 3.2 ±0.3 (**9b**, **10b**, **11b,d**, **12d**). [h] J: 6.5 (**5**), 7.2 ±0.2 (**6**, **9b**, **14**), ~8 (**11b,d**), coalesced signal, half-width ~12 (**9a**, **10a**, **11a,c**, **12a,c**), ~25 (**12b**), *dt*, J: 10.8, 7.8 (**12d**), *qi* (J: 7.3, **13a**), very broad signal (**13b**). [i] Amine group (**5**, **6**), CHNH-type amide group (**9a**, **10a**, **11a,c**, **12a,c**, **13a,b**). Imide-NH, broad *s* (1H): 7.63 (**9a**), 8.31 (**10a**), PhNH, *s* (1H): 8.30 (**13a**), 9.78 (**13b**). [j] AB-type multiplet, J: 13.2 (**5**, **6**, **14**), 15.0 (**9b**, **10b**, **11b,d**, **12b,d**). [k] Coalesced signals. [l] Shoulder on the amide-I band. [m] Doublet, J: 7.5. [n] In overlap with the ArH-4' signal of the *N*-phenyl group. Intensity: 6H (**11b**), 3H (**12a**). [o] Intensity: 10H (coalesced signal of the two phenyl groups).

Table 2

^{13}C-NMR Chemical Shifts (ppm) [a] of Compounds **5, 6, 9a,b, 10a,b, 11a-d, 12a-d, 13a,b** and **14** in Deuteriochloroform Solution [b] at 125.7 MHz [c]

Compound	C=X [d] (Pos 2)	C=O (Pos 4)	CH-4a	CH_2(5)	CH_2(6)	CH_2(7)	CH-7a	NCH_2[e]	C-1'	C-2', 6'	C-3', 5'	C-4'
									N-benzyl or *N*-phenyl group [f]			
5	–	174.5	47.5	27.4	22.2	31.6	61.3	52.2	140.5	128.0	128.2	126.7
6	–	175.6	50.9	28.6	23.4	33.1	62.6	52.4	140.2	128.0	128.3	126.8
9a	152.6	172.3	43.6	28.3	22.1	34.0	53.5	–	–	–	–	–
9b	151.9	172.3	43.0	26.4	21.4	30.7	57.5	49.5	136.8	128.1	128.8	127.9
10a	178.2	168.3	42.5	28.4	22.1	33.6	56.8	–	–	–	–	–
10b	177.4	168.1	43.1	26.5	21.3	30.3	61.0	56.6	135.1	128.4	129.5	128.7
11a	153.4	172.1	44.9	28.8	22.0	34.2	52.3	–	135.1	129.1	128.8	128.4
11b	152.9	172.0	44.2	27.0	21.5	31.0	56.8	51.0	136.6 [g]	129.1 [h]	128.6	128.1 [i]
11c	152.9	172.2	43.5	28.1	21.7	32.8	50.9	26.5	–	–	–	–
11d	153.2	172.1	43.6	27.3	21.6	30.9	56.5	51.0	137.5	129.1	128.4	128.1
12a	179.8	169.1	43.0	27.9	21.4	32.1	54.4	–	139.3	129.4	128.0	127.3
12b	180.6	168.6	43.4	26.2	20.6	29.5	59.6	57.8	135.8.	128.9 [h]	128.2	127.9
12c	179.8	169.3	43.0	28.1	21.6	32.0	54.0	32.5	–	–	–	–
12d	180.9	169.1	43.2	27.1	21.0	29.6	59.5	58.4	136.4	129.2	128.4	128.1
13a	154.8	175.9	50.2	28.2	22.9	33.0	54.4	–	140.3	117.6	128.6	121.0
13b	179.9	175.8	49.2	28.4	23.0	32.3	58.4 [l]	–	139.5	122.6 [l]	128.4	123.8
14 [m]	–	179.9	50.2	32.3 [h]	26.1	32.3 [h]	63.2	52.9	133.3	132.0	132.4 [k]	132.4 [k]

[a] δ_{TMS} = 0 ppm; Further signals, NMe: 28.6 (**11d**), 35.5 (**12**). Me(Et): 14.2 (**5**, **6**), OCH_2: 60.0 (**5**), 60.2 (**6**). [b] Solvent DMSO-d_6 for **11c**, **12a,c** and **13a,b**, deuterium oxide for **14**. [c] Assignments were supported by DEPT (except for **11c** and **12a**), and for **5** and **6** also by 2D-HSC measurements. [d] X = O, for **10a,b**, **12a-d** and **13b** X = S. [e] *N*-benzyl group, NCH_3 group for **11c** and **12c**. [f] Phenyl for **11a**, **12a** and **13a,b**. The assignments of C-2',6' and C-3',5' lines may be interchanged. Phenyl lines for **11b** and **12b**: C-1': 137.3 [g] and 140.5, C-2',3',5',6': 129.1 [h] and 129.3 (**11b**) and 128.1 and 128.9 [h] (**12b**) C-4': 128.5 [i] and 127.9 [k]. [g,i] Interchangeable assignments. [h,k] Two overlapping lines. [l] Broadened lines due to hindered rotation of the thiourea group. [m] Hydrochloride salt.

Instead of the amide-I frequency (1650-1684 cm^{-1}) of the carbamide group in **11a-d,** a significantly lower group frequency (1220-1381 cm^{-1}) was observed, as expected [32], for the thioureas **12a-d.**

Likewise, in the ^{13}C-nmr spectra of the latter compounds the characteristic high shifts of the thiooxo groups [31b] were observed (179.8-180.9 ppm) instead of the signal of the NHCONH groups in the interval 152.9-153.4 ppm.

The benzyl substitution follows in a straightforward way from the nmr signals of the NCH_2Ph group, and the 1-position from the β-effect [31c,33] on the C-7a shifts, as illustrated by comparing the pairs **a-b** for **9-12** and the pairs **c-d** for **11** and **12**.

Table 3

Physical and Analytical Data on Compounds **5-14**

Compound	Yield (%)	Mp (°C)	Formula (Mw)	Calcd./Found C (%)	H (%)	N (%)
5	85	oil	$C_{15}H_{21}NO_2$	72.84	8.56	5.66
			(247.34)	–	–	–
6	76	oil	$C_{15}H_{21}NO_2$	72.84	8.56	5.66
			(247.34)	–	–	–
7a	66	115-119	$C_{15}H_{20}N_2O_3$	65.20	7.30	10.14
		[a]	(276.34)	65.41	7.22	10.58
7b	95	117-121	$C_{22}H_{26}N_2O_3$	72.11	7.15	7.64
		[b]	(366.47)	71.58	7.63	7.61
7c	50	66-69	$C_{15}H_{20}N_2O_2S$	61.62	6.89	9.58
		[a]	(292.40)	61.82	6.76	9.68
7d	87	107-111	$C_{22}H_{26}N_2O_2S$	69.08	6.85	7.32
		[b]	(382.53)	69.61	6.52	7.05
7e	67	87-92	$C_{10}H_{18}N_2O_3$	56.06	8.47	13.07
		[a]	(214.27)	56.47	8.29	13.41
7f	94	162-165	$C_{17}H_{24}N_2O_3$	67.08	7.95	9.20
		[b]	(304.39)	67.30	7.63	8.87
7g	66	oil	$C_{10}H_{18}N_2O_2S$	52.15	7.88	12.16
			(230.33)	–	–	–
7h	94	126-128	$C_{17}H_{24}N_2O_2S$	63.72	7.55	8.74
		[b]	(320.46)	63.56	7.76	8.52

Table 3 (continued)

Compound	Yield (%)	Mp (°C)	Formula (Mw)	Calcd./Found C (%)	H (%)	N (%)
8a	85	91-92	$C_{15}H_{20}N_2O_3$	65.20	7.30	10.14
		[a]	(276.34)	65.32	7.28	10.42
8b	81	85-87	$C_{22}H_{26}N_2O_3$	72.11	7.15	7.64
		[b]	(366.47)	71.53	7.35	7.58
8c	83	70-73	$C_{15}H_{20}N_2O_2S$	61.62	6.89	9.58
		[a]	(292.40)	61.71	6.74	9.91
8d	93	oil	$C_{22}H_{26}N_2O_2S$	69.08	6.85	7.32
			(382.53)	69.53	6.68	7.11
9a	30	219-221	$C_7H_{10}N_2O_2$	54.54	6.54	18.17
		[c] [d]	(154.17)	54.23	6.49	18.08
9b	41	140-143	$C_{14}H_{16}N_2O_2$	68.83	6.60	11.47
		[c]	(244.29)	68.65	6.51	11.39
10a	50	201-203	$C_7H_{10}N_2OS$	49.39	5.92	16.46
		[c] [e]	(170.24)	49.30	5.45	16.35
10b	48	111-114	$C_{14}H_{16}N_2OS$	64.59	6.19	10.76
		[c]	(260.36)	64.42	6.09	10.67
11a	73	249-252	$C_{13}H_{14}N_2O_2$	67.81	6.13	12.17
		[f] [g]	(230.27)	68.44	6.20	12.17
11b	75	oil	$C_{20}H_{20}N_2O_2$	74.98	6.29	8.74
			(320.40)	–	–	–
11c	62	154-157	$C_8H_{12}N_2O_2$	57.13	7.19	16.66
		[f]	(168.20)	57.10	7.02	16.56
11d	74	oil	$C_{15}H_{18}N_2O_2$	69.74	7.02	10.84
			(258.32)	–	–	–
12a	69	285-287	$C_{13}H_{14}N_2OS$	63.39	5.73	11.37
		[f]	(246.33)	63.26	5.58	11.26
12b	75	174-177	$C_{20}H_{20}N_2OS$	71.4	5.99	8.33
		[f]	(336.46)	70.87	6.04	8.40
12c	65	134-137	$C_8H_{12}N_2OS$	52.15	6.56	15.20
		[f]	(184.26)	52.72	6.75	15.48
12d	72	oil	$C_{15}H_{18}N_2OS$	65.66	6.61	10.21
			(274.39)	–	–	–
13a	92	203-205	$C_{13}H_{16}N_2O_3$	62.89	6.50	11.28
		[h]	(248.28)	62.73	6.54	11.52
13b	89	142-144	$C_{13}H_{16}N_2O_2S$	59.07	6.10	10.60
		[h]	(264.35)	58.89	6.13	10.56
14	59	146-149	$C_{13}H_{18}ClNO_2$	61.05	7.09	5.48
		[i]	(255.74)	61.50	7.57	5.83

[a] From diethyl ether/diisopropyl ether. [b] From diisopropyl ether. [c] From ethyl acetate. [d] Lit mp [9] 222-225°. [e] Lit mp [10] 205-208°. [f] From diethyl ether/methanol. [g] Lit mp [14] 255-257°. [h] From ethyl acetate/diethyl ether. [i] From acetone/diethyl ether.

EXPERIMENTAL

The ir spectra were measured in potassium bromide pellets on an Opus 2.0 computer software-controlled Bruker IFS-55 FT spectrometer.

The ^1H and ^{13}C-nmr spectra were recorded in deuteriochloroform or hexadeuteriodimethyl sulfoxide solution in 5 mm tubes at room temperature on a Bruker WM-250 FT spectrometer at 500.13 (^1H) and 125.76 MHz (^{13}C), respectively, using the ^2H signal of the solvent as the lock and TMS as internal standard. COSY and two-dimensional heteronuclear shift correlation (2D-HSC) measurements were carried out with the standard software written for the Bruker DRX spectrometers. DEPT spectra [34] were run in a standard way [35], using only the $\theta = 135°$ pulse to separate CH/CH_3 and CH_2 lines phased "up and down", respectively.

Melting points were determined with a Kofler apparatus and the values are not corrected. The physical and analytical data on the compounds prepared are listed in Tables 3 and 4.

The *cis*- and *trans*-2-amino-1-cyclopentanecarboxylic acids **1** and **2** and their esters **3** and **4** were prepared according to the literature methods [15,16].

Ethyl *cis*- and *trans*-2-Benzylamino-1-cyclopentanecarboxylates **5** and **6**.

Benzaldehyde (5.4 g, 50.9 mmoles) was added in one portion to amino esters **3** or **4** (8.0 g, 50.9 mmoles) dissolved in 150 ml of dry ethanol. After stirring for 2 hours at room temperature, the solution was evaporated and stirred again with ethanol for 1 hour. Sodium borohydride (7.7 g, 203.6 mmoles) was added in 4 portions to the stirred solution with ice-cooling. The mixture was stirred for a further 3 hours at room temperature and the excess of sodium borohydride was decomposed with 18% hydrochloric acid solution. After the solution had been clarified, the reaction

mixture was evaporated to half volume and made alkaline with saturated sodium carbonate solution. The product was extracted with chloroform, and the combined organic phase was dried (sodium sulfate) and evaporated, to give an oily product which was purified by flash chromatography (toluene:methanol = 9:1).

Urea and Thiourea Derivatives **7a-h** and **8a-d.**

Methyl or phenyl isocyanate or isothiocyanate (10.0 mmoles) was added to the appropriate amino ester (9.5 mmoles) dissolved in 30 ml of toluene. The solution was evaporated after standing for 12 hours at room temperature. The crystalline products were filtered and recrystallized. The oily product was purified by flash chromatography (toluene:methanol = 19:1).

cis-1,2,3,4a,5,6,7,7a-Octahydrocyclopenta[*d*]pyrimidine-2,4-dione **9a** and *cis*-1-Benzyl-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]pyrimidine-2,4-dione **9b**.

A mixture of *cis* amino ester hydrochlorides **3** or **5** (4.13 mmoles) and powdered potassium cyanate (10 mmoles) was refluxed in water (30 ml) for 5 hours. After cooling, the white crystalline product that formed was filtered and recrystallized.

cis-2-Thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]pyrimidin-4-one **10a** and *cis*-1-Benzyl-2-thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]pyrimidin-4-one **10b**.

A mixture of the *cis* amino ester hydrochloride **3** or **5** (4.65 mmoles) and powdered potassium thiocyanate (11 mmoles) was stirred in acetone (20 ml) for 1 hour at room temperature. After filtration of the suspension, the filtrate was evaporated, and the residue was refluxed in xylene (20 ml) for 10 hours. The solution was evaporated to dryness and the crystalline product obtained was filtered and recrystallized.

cis-3-Phenyl- or 3-Methyl-1,2,3,4a,5,6,7,7a-octahydrocyclopenta-[*d*]pyrimidine-2,4-diones **11a,c** and *cis*-3-Phenyl- or 3-Methyl-2-thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]pyrimidin-4-ones **12a,c.**

The appropriate urea or thiourea derivative **7** (10 mmoles) was refluxed in 30 ml of 22% hydrochloric acid solution for 12 hours. After standing overnight, the crystalline product obtained was separated by filtration and recrystallized.

cis-1-Benzyl-3-phenyl- or 3-Methyl-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]pyrimidine-2,4-diones **11b,d** and *cis*-1-Benzyl-3-phenyl- or 3-Methyl-2-thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]pyrimidin-4-ones **12b,d.**

The appropriate benzyl-substituted urea or thiourea derivative **7** (10 mmoles) was refluxed in ethanol containing 22% dry hydrogen chloride for 12 hours. After standing overnight, the crystalline product obtained was separated by filtration and recrystallized from a mixture of diethyl ether and methanol. If an oily product was obtained, it was extracted with chloroform, dried with sodium sulfate, filtered, evaporated and purified by flash chromatography, using a mixture of toluene:methanol = 19:1.

Attempted Ring Closures of **8a,b**.

Urea or thiourea derivative **8a** or **8c** (10 mmoles) was refluxed in 30 ml of 22% hydrochloric acid solution for 12 hours. After standing overnight, the precipitated crystalline product **13a,b** was separated by filtration and recrystallized.

Urea Derivatives **13a,b**.

Phenyl isocyanate or isothiocyanate (3.3 mmoles) was added to the *trans* amino acid **2** (3.1 mmoles) dissolved in 30 ml of toluene. The mixture was evaporated after stirring for 12 hours at room temperature. The crystalline product **13a,b** was filtered and recrystallized.

N-Benzyl-*trans*-2-amino-1-cyclopentanecarboxylic Acid **14**.

The appropriate benzyl-substituted urea or thiourea derivative **8b** or **8d** (10 mmoles) was refluxed in 25 ml of ethanol containing 22% dry hydrogen chloride for 12 hours. After evaporation, the starting material was recovered. This residue was refluxed in 20 ml of 22% hydrochloric acid solution for 12 hours. After evaporation, the crystalline product **14** was recrystallized.

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