tert-BUTYLCYCLOPENTANE DERIVATIVES. PART 8.[1] SYNTHESIS OF *tert*-BUTYLCYCLOPENTANE-FUSED PYRIMIDIN-4-ONES [#]

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Abstract - In the reactions of ethyl (1*R**,2*S**,4*S**)-2-amino-4-*tert*-butyl-1-cyclopentanecarboxylate (**4**) or (1*R**,3*S**,5*S**)-3-*tert*-butyl-6-azabicyclo[3.2.0]heptan-7-one (**2**) or (1*R**,2*S**,4*S**)-2-amino-4-*tert*-butyl-1-cyclopentanecarboxamide (**6**) with imidates or triethyl orthobenzoate, *tert*-butylcyclopentane-fused dihydropyrimidin-4-ones (**7a-e**) were prepared. The azetidinone (**2**) with lactim ethers furnished pyrrolo-, pyrido- and azepino[1,2-*a*]pyrimidin-4-ones (**8-10**) in ring-enlargement reactions. Ethyl (1*R**,2*S**,4*S**)-2-amino-4-*tert*-butyl-1-cyclopentanecarboxylate (**4**) and ethyl (1*R**,2*S**,4*S**)-2-benzylamino-4-*tert*-butyl-1-cyclopentanecarboxylate (**5**) and potassium cyanate or phenyl isocyanate or potassium thiocyanate or phenyl isothiocyanate, yielded pyrimidine-2,4-diones or 2-thioxopyrimidin-4-ones (**11-22**).

INTRODUCTION

In the course of a systematic study of the synthesis, stereochemistry and reactions of stereoisomeric alicycle-fused 1,3-heterocycles such as 1,3-oxazines, 1,3-thiazines and pyrimidinones,[2,3] a number of comparative investigations (*e g* nmr, ms, polarographic, *etc.*) of the isomers and homologues and pharmacological testing of numerous related series have also been performed.

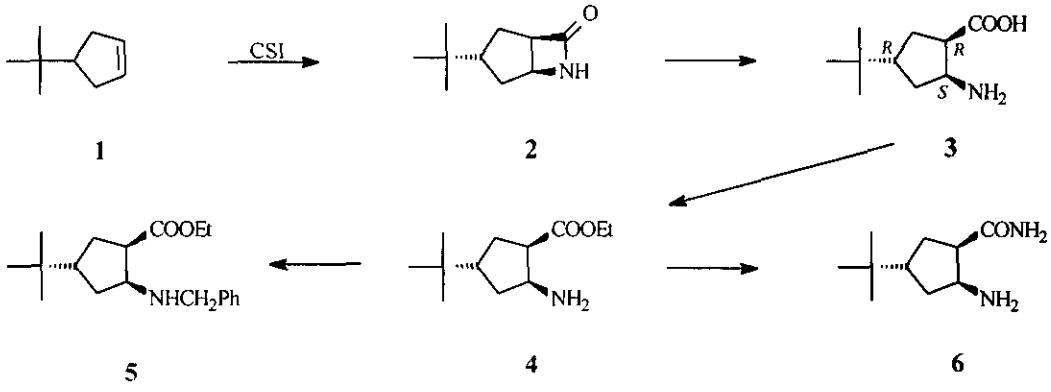
The reactions of 1,2-disubstituted 1,3-bifunctional cycloalkane derivatives depend both on the *cis* or *trans* arrangement of the functional groups and on the further substituents on the cycloalkane ring.[2-5] We recently reported on the synthesis, stereochemistry[6] and ring-chain tautomerism[7] of *tert*-butylcyclopentane-fused 1,3-oxazines and thiazines. In a continuation of these studies, our present aim was to investigate the synthesis and stereochemistry of *tert*-butylcyclopentane-fused pyrimidinones.

RESULTS

Chlorosulphonyl isocyanate (CSI) addition to 4-*tert*-butyl-1-cyclopentene (**1**) resulted in the azetidinone (**2**) in a stereospecific reaction.[7] The reaction of the azetidinone (**2**) with hydrochloric acid furnished

Dedicated to the memory of **Professor Yoshio Ban**

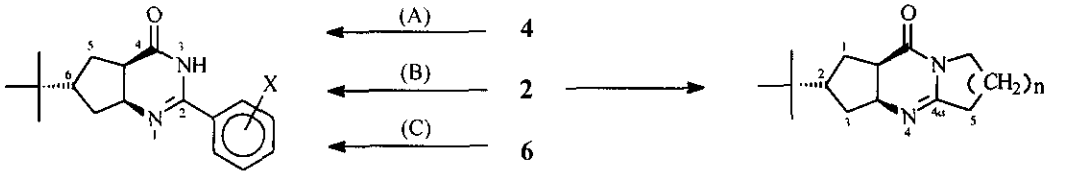
(1*R**,2*S**,4*S**)-4-*tert*-butyl-2-amino-1-cyclopentanecarboxylic acid (**3**).[7,8] The amino carboxylic acid (**3**), a *tert*-butyl-substituted analogue of cispentacin, a naturally occurring antibiotic, was isolated[9-12] from *Bacillus cereus* and *Streptomyces setonii*. Recent investigations revealed that cispentacin has a marked protective effect against *Candida albicans* and *Cryptococcus neoformans* in mice.[9-14]



Scheme 1

Esterification of **3** resulted in **4**,which was transformed to the *N*-benzylamino ester (**5**) with benzaldehyde and subsequent reduction with sodium borohydride. Ammonolysis of the ester (**4**) furnished the carboxamide (**6**) (Scheme 1).

Some of the cycloalkane-fused dihydropyrimidin-4-ones, and especially the cyclopentane *cis*-fused derivatives, have remarkably strong analgetic and anti-inflammatory activities.[15] We therefore prepared the analogous *tert*-butyl-substituted derivatives (**7**). The 2-phenyl-substituted pyrimidinone (**7a**) was obtained by reaction of the amino ester (**4**) or the azetidinone (**2**) with ethyl benzimidate, or in the reaction of the carboxamide (**6**) with triethyl orthobenzoate. For the preparation of other derivatives, reaction of amino acid (**4**) with substituted benzimidates proved to be the best method, resulting in compounds (**7b-7e**) in 62-72% yield (Scheme 2).



X = **7a** H; **7b** *p*Cl; **7c** *m*Cl; **7d** *p*Br; **7e** *p*CH_3

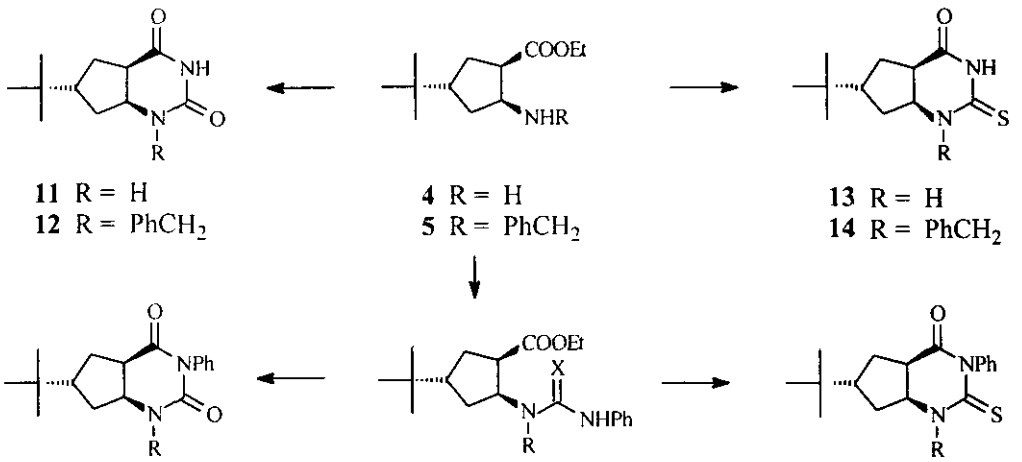
8 n = 1; **9** n = 2; **10** n = 3

Scheme 2

When the azetidinone (**2**) was melted with a twofold excess of butyro-, valero- or caprolactim ether at 110-140 °C for 5 h, the desired tricycles (**8-10**) were formed. The first step in the reaction is the splitting-off of methanol, resulting in an amidine intermediate which, after transamidation,[16] yields the ring-enlargement products (**8-10**) (Scheme 2).

Several cycloalkane-fused pyrimidinediones have earlier been prepared from 2-amino-1-cycloalkanecarboxylic acids by reaction with isocyanates and subsequent treatment with hydrochloric acid, or by acylation of azetidinones and subsequent heating with polyphosphoric acid, or from substituted 2-amino-1-cycloalkanecarboxamides with carbonyldiimidazole.[2,17,18] Faster cyclization reactions and higher yields were observed when the ethyl esters of the amino acids were used.

A 5 h reflux of a mixture of the amino ester hydrochloride (**4**) and potassium cyanate gave the pyrimidinedione (**11**). A longer reaction time was required with the *N*-benzyl derivative (**5**) as starting compound, in the presence of hydrochloric acid, resulting in **12**. The amino ester hydrochlorides (**4**) and (**5**) reacted readily with potassium thiocyanate to give **13** and **14**, respectively (Scheme 3).



11 R = H
12 R = $PhCH_2$

4 R = H
5 R = $PhCH_2$

13 R = H
14 R = $PhCH_2$

19 R = H
20 R = $PhCH_2$

15 R = H, X = O
16 R = H, X = S
17 R = $PhCH_2$, X = O
18 R = $PhCH_2$, X = S

21 R = H
22 R = $PhCH_2$

Scheme 3

Reaction of the amino esters (**4**) and (**5**) with phenyl isocyanate or phenyl isothiocyanate furnished the urea and thiourea derivatives (**15-18**) at room temperature. On refluxing with hydrochloric acid, the *N*-unsubstituted derivatives (**15**) and (**16**) were transformed to pyrimidinones (**19**) and (**21**) in good yields. For *N*-benzyl-substituted derivatives, the same ring closure gave multicomponent mixtures in aqueous solution, whereas when the reaction was performed in ethanol containing dry hydrogen chloride, the ring closure proceeded smoothly, resulting in the pyrimidinones (**20**) and (**22**), respectively (Scheme 3).

Table 1.Charasteristic ir frequencies (cm^{-1}, in KBr) and ^1H-nmr data (chemical shifts in δ, $\delta_{TMS} = 0$ ppm and coupling constants in Hz) in $CDCl_3$ solution[a] at 250 MHz on compounds **7a-e**, **8-14** and **19-22**.[b]

Com-pound	νNH band	νC=O band	νC=X band[c]	$\gamma C_{Ar}H$ band	$\gamma C_{Ar}C_{Ar}$ band	CH_3 *s*(9H)	CH_2(Pos. 5,7), H-6 1-4 *m*(5H)[d]	H-4a *m*(1H)[e]	H-7a *m*(1H)	ArH or NCH_2 1-2 *m*(2-10H)[f]	NH br(1H)
7a	3210	1693	1657	776	690	0.87	1 8 - 2.1	2 75[g]	4.25[h]	7.45[i] 7.79[j]	8.90
7b	3230	1691	1648	835	—	0.87	1 8 - 2.1	2 75[g]	4.25[h]	7.41 7 77	9 25
7c	3240	1690	1655	797	702	0 87	1.8 - 2.1	2 75[g]	4.26[h]	7.3 - 7 5[k] 7 70[j] 7 86[l]	9 65
7d	3235	1692	1648	833	—	0 87	1.8 - 2.1	2 75[g]	4.25[h]	7 58 7 70	9 20
7e	~3200	1703	1649	828	—	0.86	1.8 - 2.1	2.72[g]	4.24[h]	7 24 7 67	8 80
8	—	1692	1692	—	—	0 86	1.7 - 2 1	~2 65	4.10[h]	3.74	—
9	—	1679	1650	—	—	0.85	1.7 - 2 0	2.68[g]	3.98[h]	3.55 ~3.9	—
10	—	1679	1655	—	—	0.86	1.5 - 2 0	~2 6	3.93[h]	3.65 4.12	—
11	~3210	1740	1690	—	—	0.82	1 45 - 2.05	2 67[g]	3.80[h]	—	7 38[m]
12	3190	1716	1675	728	700	0.71	1.25 - 1 75[n] 2.05[o]	2.90[h]	3.68[g]	7 35	10.3
13	3185	1684	1590	—	—	0.82	1.5 - 2.25	2.80[h]	3.95[g]	—	9.45[m]
14	3200	1709	1516	738	698	0.75	1 4 - 1 75[i] ~1 9[o] 2.35[o]	2.90[h]	3.78[g]	7.35	8.7
19	3230	1728	1684	768	695	0 86	1.6 - 2.2	2.92[g]	3 98[h]	7.13[j] ~7.4[i]	7 8
20	—	1712	1674	753	692	0 78	~1 7[i] ~1.95[o] 2.35[o]	3.02[h]	3 70[g]	7.10[i] 7.25 - 7.45[p]	—
21	3172	1709	1567	742	692	0.86	~1.65[o] 1 9 - 2.2	3.05[g]	4 10[h]	7 10[j] ~7.35[i]	9.8
22	—	1712	1499	752	692	0.76	~1.55[o] ~1 75[n] ~2 0[o] ~2 4[o]	3.05[h]	3 80[g]	~7.1[o,r] 7.25 - 7 5[p]	—

[a] Solvent DMSO-d_6 for **11-13**, **19** and **21**. [b] Assignments were supported by DNOE (**7d**) and 2D-HSC measurements (**9**, **10**) Further signals. CH_2 (benzyl), 2x*d* (*AB*-type spectrum) 4.42 and 4 69 (**12**, *J* 15 2), 4 79 and 5.65 (**14**, *J*: 4 7), 4 41 and 4 95 (**20**, *J*· 14.8), 5 01 and 5 69 (**22**, *J* 14.8), [c] X· N(**7a-e**, **8-10**), O(**11**, **12**, **19**, **20**) or S(**13**, **14**, **21**, **22**), the νC=O and νC=N bands are coalesced for **8**,[d] Intensity· 7H(**8**), 9H(**9**), 11H(**10**) coalesced with the signal of inner CH_2 groups (1, 2 or 3) in the terminal heteroring, [e] Coalesced with the CH_2 signal vicinal to the C(sp^2) atom of the terminal heteroring for **8** and **10** (intensity. 3H). The corresponding CH_2 signal of **9** appears at 2 55 *m*(2H), [f] *AA' BB'* -type multiplet for **7b**, **d**, **e** , 2x~*d*(2x2H), *J* 8 5 (**7b**), 8 7 (**7d**), 8 1 (**7e**), singlet-like signal of 5H intensity for **12** and **14**, NCH_2 signal, *t* for **8** (*J* 7.0), 2x*m* (2x1H) for **9** and 2x*d*(2x1H) for **10** (J 14 and 8 or 7), [g] Quartet-like signal, *J*. 6 7 (**7c**), 8 0 (**11**), 7.5 (**12**), 7 4 (**13**), 8 4 (**14**), 7 2 (**20**), ~8 (**22**), with coalesced lines for **7a**,**b**,**d**,**e**, **9**, **19** and **21**: [h] Triplet-like signal, *J*. 6 (**10**), 8 (**12**), 7.2 (**14**), 5 (**21**), with coalesced lines, half signal width ~15 Hz for **7a-e**, **8**, **9**, **11**, **13**, **19**, **20** and **22**, [i, k, n, o, p] *m*, Intensity 3H, 2H, 4H, 1H, 9H, [j] *dd*, 2H(**7a**, **19**, **21**), 1H(**7c**, **20**), [l] *t* (1H), *J* ~2, [m] Amide NH (Pos 1), imide or thioimide NH (Pos 3). 9 90 (**11**) and 10 9 (**13**), [r] Broad

Table 2. ^{13}C-nmr chemical shifts (δ_{TMS} = 0 ppm) in $CDCl_3$ solution[a] at 63 MHz of compounds **7a-e**, **8-14** and **19-22**[b,c]

Compound	CH_3 *t*-butyl	C_q *t*-butyl	C-2	C-4	C-4a	C-5	C-6	C-7	C-7a	C-1'	C-2',6'	C-3',5'	C-4'
			cyclopenta[*d*]pyrimidine moiety							phenyl group[d]			
7a	27.1	32.0	149.2	174.1	42.3	30.4	47.3	35.9	61.2	133.7	126.4	128.7	130.9
7b	27.2	32.1	148.2	174.3	42.3	30.6	47.5	36.0	61.3	132.0	127.8	128.8	137.0
7c	27.1	32.1	148.1	174.4	42.1	30.5	47.4	35.9	61.2	135.2[e]	126.9	134.6[e]	130.7
7d	27.2	32.1	148.2	174.2	42.3	30.6	47.5	36.0	61.3	132.5	128.0	131.8	125.1
7e	27.2	32.1	149.0	174.1	42.4	30.5	47.4	36.0	61.1	130.8	129.2	126.2	141.1
8	27.2	31.9	156.4	171.0	42.1	31.0[e]	47.7	36.2	61.8	31.1[e]	10.0	44.2	—
9	27.0	31.9	151.9	172.1	43.0	30.4	47.2	35.9	59.0	31.5	22.2	19.9	40.3
10	27.0	32.0	156.7	172.0	42.4	30.3	47.3	36.0	59.1	36.7	28.9[e]	25.9	29.1[e]
11	27.2	31.9	153.0	173.1	43.1	29.8	46.7	34.6	52.3	—	—	—	—
12	26.9	31.8[f]	152.1	172.0	43.7	28.3	46.0	31.8[f]	56.6	137.9	127.8	128.6	127.3
13	27.2	31.8	177.7	169.2	41.9	29.9	46.9	34.0	55.5	—	—	—	—
14	26.8	31.9	176.8	167.3	43.9	28.6	45.9	31.3	59.5	135.3	128.0	128.8	128.2
19	27.2	32.0	153.0	172.5	44.0	30.0	46.7	34.5	51.4	136.5	129.5	128.7	127.7
20[g]	26.8	31.9[f]	152.6	171.0	44.8	29.1	46.0	31.9[f]	55.5	136.0	128.2	125.5	127.7
21	27.1	31.9	180.5	169.3	43.3	29.9	46.8	33.9	54.8	139.5	129.7	128.4	127.6
22[g]	26.7	32.1	180.4	168.1	44.5	28.9	45.5	31.0	58.6	135.6	128.0	128.7[f]	128.7[f]

[a] Solvent DMSO-d_6 for **11-13**, **19** and **21**; [b] Assignments were supported by DEPT (**8-10**, **12**, **14** and **19**) and 2D-HSC measurements (**9**, **10**). Further signals: CH_3 (tolyl in **7e**): 21.2; NCH_2: 41.0 (**10**), 48.5 (**12**), 55.9 (**14**); [c] The numbering in the heading refers to that given for compounds of type **7** in Scheme 2; [d] The line pairs C-2',6' and C-3',5' are separated for **7c**, the counterpart of the line at 126.9 ppm appears at 124.4; C-5': 129.7 (interchangeable with C-4' line at 130.7). Methylene groups in terminal heteroring in Pos. 5, 6, 7, 8 (cf. numbering in Scheme 3) for **8-10**; [e] Interchangeable assignments; [f] Overlapping lines; [g] The C-1', C-3',5' and C-4' lines for the second phenyl group in **20**: 136.7, 128.8 and 128.0. The C-2',6' lines of the two phenyl substituents are coalesced. For **22** C-1' (*N*-phenyl) 140.3. Due to signal overlap, instead of the expected 6 lines for C-2'-6' in the two aromatic rings, only two lines are observed for **22**

Spectroscopic Studies

The ^{1}H- and ^{13}C-nmr data on **7-14** and **19-22** are listed in Tables 1 and 2, and are consistent with the expected structures. The spectral data are self-explanatory and only the following points need to be noted. To prove the assignments of ^{13}C-nmr lines, DEPT measurements were executed in a few cases. Due to the more complex structure of **9** and **10**, the ^{1}H-nmr assignments were also confirmed via 2D-HSC experiments. In one case (for **7d**), the *cis* position of the *tert*-butyl group and the hydrogens in positions 4a and 7a was proved by DNOE measurements. On saturation of one of the H-4a, H-7a or methyl signals, the intensities of the two other hydrogen signals were observed to be enhanced, supporting the sterically close arrangement. The rotation of the N(3)-phenyl group about the N-C-1'(Ar) bond in **20** and **22** is restricted, as shown by the separation and broadening of an aromatic ^{1}H-nmr signal of 1H intensity. Similar hindered rotation is not present in the 1-unsubstituted analogues (**19**) and (**21**).

EXPERIMENTAL

Ir spectra were run in KBr discs on a Bruker IFS-113v vacuum optic FT-spectrophotometer controlled by an Aspect 2000 computer. ^{1}H- and ^{13}C-nmr spectra were recorded in $CDCl_3$ solution in 5 tubes at room temperature, on a Bruker WM-250 FT spectrometer controlled by an Aspect 2000 computer at 250.13 (^{1}H) and 62.89 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters were as follows: spectral width 5 and 15 kHz, pulse width 1 and 5 μs (*ca.* 20° and 30° flip angle), acquisition time 1.64 and 0.42 s, number of scans 16 or 32 (^{1}H) and 0.2-2.5 K (^{13}C), computer memory 16 and 32 K. Lorentzian exponential multiplication for signal-to-noise enhancement (line broadening 0.7 and 1.0 Hz), and for the ^{13}C-nmr spectra complete proton noise decoupling (~ 3W) was applied.

The standard Bruker microprogram "DNOEMULT.AU" to generate NOE was used with a selective pre-irradiation time of 5 s and a decoupling power (CW mode) of *ca.* 30-40 mW; number of scans 64-256, dummy scans 4-8, pulse width 5.0 μs (90°) and 16 K data points for ca. 2 kHz spectral width. A line broadening of 1.0 Hz was applied to diminish residual dispersion signals in the difference spectra.

DEPT[19] spectra were run in a standard way,[20] using only the $\Theta = 135°$ pulse to separate CH/CH_3 and CH_2 lines phased "up and down", respectively. Typical acquisition data were: number of scans 128-12 K, relaxation delay for protons 3 s, 90° pulse widths 10.8 and 22.8 μs for ^{13}C and ^{1}H, respectively. The estimated value for J (C, H) resulted in a 3.7 ms delay for polarization.

The 2D-HSC spectra were obtained by using the standard BRUKER pulse program "XHCORRD.AU". Data points: 4 K (^{13}C domain), increments: 64-256, digital resolution: better than 5 Hz/point (^{1}H domain), transients: 256, relaxation delay: 3 s. All C-H correlations were found by using a value of J (C, H) = 135 Hz for calculation of the delay.

Melting points were determined on a Kofler apparatus and are uncorrected. Compounds **1-5** were prepared as described elsewhere.[6,7] The physical and analytical data on the compounds prepared are listed in Table 3.

Ethyl (1*R,2*S**,4*S**)-2-benzylamino-4-*tert*-butyl-1-cyclopentanecarboxylate (5).** Benzaldehyde (2.12 g, 20 mmol) was added in one portion to amino ester (**4**) (4.23 g, 20 mmol) dissolved in methanol (50 ml). After stirring for 2 h at room temperature, $NaBH_4$ (2.27 g, 60 mmol) was added in small portions to the stirred solution with ice-cooling. The mixture was stirred for a further 3 h at room temperature and the excess of $NaBH_4$ was decomposed with 5% AcOH solution. After the solution had clarified, the reaction mixture was evaporated to half volume and extracted with chloroform (3x30 ml). The combined organic phase was dried (Na_2SO_4) and evaporated to give a yellow oil, which was purified as the hydrochloride. The base liberated for spectroscopic examination was a colourless oil.

(1*R,2*S**,4*S**)-2-Amino-4-*tert*-butyl-1-cyclopentanecarboxamide (6).** Ethyl 4-*tert*-butyl-2-amino-1-cyclopentanecarboxylate (**4**) (3.20 g, 15 mmol) was dissolved in methanol (50 ml) containing 40 wt% ammonia. After standing for a week at room temperature, the solution was evaporated to dryness and the residue was treated with ether. The pale-yellow crystalline product was filtered off and recrystallized.

(4*aR,6*R**,7*aS**)-6-*tert*-Butyl-2-phenyl-3,4*a*,5,6,7,7*a*-hexahydro-4*H*-cyclopenta[*d*]pyrimidin-4-one (7a)**

Method A: The amino ester (**4**) (0.40 g, 1.88 mmol) and ethyl benzimidate (0.28 g, 1.88 mmol) were dissolved in 20 ml of ethanol and the mixture was refluxed with one drop of glacial acetic acid as a catalyst for 8 h. After evaporation, a white crystalline product was obtained.

Method B: A mixture of azetidinone (**1**) (0.30 g, 1.79 mmol) and ethyl benzimidate (0.27 g, 1.79 mmol) was heated at 140 °C on an oil bath for 10 h. The yellow oily product crystallized on standing overnight at room temperature.

Method C: A mixture of amide (**6**) (0.20 g, 1.08 mmol) and triethyl orthobenzoate (0.92 g, 4.10 mmol) was heated at 100 °C on an oil bath for 6 h and a crystalline product was obtained on standing for a few hours.

(2*R,3*aS**,9*aR**)-2-*tert*-Butyl-1,2,3,3*a*,5,6,7,9*a*-octahydrocyclopenta[*d*]pyrrolo[1,2-*a*]pyrimidin-9-one (8), (2*R**,3*aS**,10*aR**)-2-*tert*-butyl-2,3,3*a*,5,6,7,8,10*a*-octahydrocyclopenta[*d*]pyrido[1,2-*a*]pyrimidin-10(1*H*)-one (9) and (2*R**,3*aS**,11*aR**)-2-*tert*-butyl-1,2,3,3*a*,5,6,7,8,9,11*a*-decahydrocyclopenta[*d*]azepino[1,2-*a*]pyrimidin-11-one (10).** A mixture of the azetidinone (**1**) (0.40 g, 2.39 mmol) and a lactim ether (4.78 mmol, **8**: butyro-, **9**: capro-, **10**: valerolactim ether) was heated on an oil bath (**8**: 110 °C, **9**: 130 °C, **10**: 140 °C) for 5 h. The product was dissolved in ether and treated with charcoal. After filtration, the solvent was evaporated to give a yellow oil, which was purified as the hydrochloride. The bases liberated for purposes of spectroscopic examination were pale-yellow oils.

(4*aR,6*R**,7*aS**)-6-*tert*-Butyl-1,2,3,4*a*,5,6,7,7*a*-octahydrocyclopenta[*d*]pyrimidine-2,4-dione (11).** A mixture of amino ester hydrochloride (**4**) (0.30 g, 1.2 mmol) and potassium cyanate (0.12 g, 1.48 mmol) was refluxed in water (20 ml) for 5 h and the white crystalline product that precipitated was filtered off and recrystallized.

Table 3. Analytical data on compounds (**5-22**)

Com-poud	Yield[a] (%)	Mp (°C)	Formula	Analysis C(%) Calcd	C(%) Found	H(%) Calcd	H(%) Found	N(%) Calcd	N(%) Found
5	75	144-147[c]	$C_{19}H_{30}NO_2Cl$	67.14	66.84	8.90	8.81	4.12	4.15
6	69	142-145[d]	$C_{10}H_{20}N_2O$	65.18	64.71	10.94	11.40	15.20	15.28
7a	81(A),45(B),71(C)	171-173[e]	$C_{17}H_{22}N_2O$	75.52	75.09	8.20	8.20	10.36	10.32
7b	65(A)	188-190[e]	$C_{17}H_{21}N_2OCl$	66.99	66.76	6.94	7.12	9.19	9.08
7c	62(A)	140-142[f]	$C_{17}H_{21}N_2OCl$	66.99	66.54	6.94	7.21	9.19	9.60
7d	72(A)	203-205[f]	$C_{17}H_{21}N_2OBr$	58.46	58.91	6.06	6.43	8.02	7.87
7e	70(A)	163-165[e]	$C_{18}H_{24}N_2O$	76.02	76 29	8.51	8.21	9.85	9.56
8[b]	65	213-216[g]	$C_{14}H_{23}N_2OCl$	62.09	62.37	8.56	8.91	10.34	10.74
9[b]	62	231-233[g]	$C_{15}H_{25}N_2OCl$	63.25	63.71	8.85	9.45	9.83	9.36
10[b]	67	260-262[g]	$C_{16}H_{27}N_2OCl$	64.30	63.86	9.11	8.96	9.37	9.19
11	59	252-254[f]	$C_{11}H_{18}N_2O_2$	62.83	62.36	8.63	8.90	13.32	13.44
12	62	179-181[h]	$C_{18}H_{24}N_2O_2$	71.97	71.82	8.05	8.49	9.33	8.89
13	35	211-212[e]	$C_{11}H_{18}N_2OS$	58.37	58.56	8.02	8.31	12.38	12.11
14	58	174-177[e]	$C_{18}H_{24}N_2OS$	68.32	68.59	7.64	7.96	8.85	8.92
15	90	oil	$C_{19}H_{28}N_2O_3$						
16	92	123-125[i]	$C_{19}H_{28}N_2O_2S$	65.48	65.52	8.10	8.01	8.04	8.26
17	86	133-136[f]	$C_{26}H_{34}N_2O_3$	73.90	74.34	8.11	8.59	6.63	7.08
18	86	116-119[f]	$C_{26}H_{34}N_2O_2S$	71.20	71.31	7.81	8.20	6.39	6.71
19	73	264-267[i]	$C_{17}H_{22}N_2O_2$	71.30	71.18	7.74	8.16	9.78	10.18
20	86	118-120[f]	$C_{24}H_{28}N_2O_2$	76.56	76 08	7.50	7.97	7.44	7.65
21	72	270-272[k]	$C_{17}H_{22}N_2OS$	67.51	67 31	7.33	7.58	9.26	9.08
22	70	76-78[f]	$C_{24}H_{28}N_2OS$	73.43	73.88	7.19	7.56	7.14	7.32

[a] Methods used in parentheses; [b] Hydrochloride; Solvents for recrystallization: [c] Diisopropyl ether/hexane; [d] Ethyl acetate/ethanol; [e] Diisopropyl ether/ethyl acetate; [f] Ethyl acetate; [g] Acetone/diisopropyl ether; [h] Methanol; [i] Ethyl acetate/chloroform; [j] Chloroform; [k] DMF

(4*aR,6*R**,7*aS**)-1-Benzyl-6-*tert*-butyl-1,2,3,4*a*,5,6,7,7*a*-octahydrocyclopenta[*d*]pyrimidine-2,4-dione (12)**. A mixture of the amino ester hydrochloride (**5**) (0.90 g, 2.65 mmol) and potassium cyanate (0.30 g, 3.70 mmol) was refluxed in water (20 ml) for 5 h. The precipitated product was filtered off and dissolved in ethanol (20 ml) containing 22% dry hydrogen chloride. After refluxing for 6 h and standing overnight at room temperature, the white crystalline product was separated.

(4*aR,6*R**,7*aS**)-6-*tert*-Butyl-2-thioxo-1,2,3,4*a*,5,6,7,7*a*-octahydrocyclopenta[*d*]pyrimidin-4-one (13) and (4*aR**,6*R**,7*aS**)-1-benzyl-6-*tert*-butyl-2-thioxo-1,2,3,4*a*,5,6,7,7*a*-octahydrocyclopenta[*d*]pyrimidin-4-one (14)**. A mixture of the amino ester hydrochloride (**4**) or (**5**) (1.6 mmol) and potassium thiocyanate (0.12 g, 1.23 mmol) was stirred in acetone (10 ml) for 1 h at room temperature. After filtration of the suspension, the filtrate was evaporated and xylene (10 ml) was added to the residue. The mixture was refluxed for 10 h, and was then evaporated to dryness.

Urea and thiourea derivatives (15-18). Phenyl isocyanate or phenyl isothiocyanate (1.55 mmol) was added to amino ester (**4**) or (**5**) (1.44 mmol) dissolved in benzene (30 ml). The solution was evaporated after standing for 1 day at room temperature and the crystalline product obtained was washed with hexane. For **15**, an oily product was obtained, which was transformed to **19** without further purification.

(4*aR,6*R**,7*aS**)-6-*tert*-Butyl-3-phenyl-1,2,3,4*a*,5,6,7,7*a*-octahydrocyclopenta[*d*]pyrimidine-2,4-dione (19).** The urea (**15**) (0.40 g, 1.20 mmol) was refluxed for 6 h in 10% hydrochloric acid (20 ml). The crystalline product was separated by filtration.

(4*aR,6*R**,7*aS**)-1-Benzyl-6-*tert*-butyl-3-phenyl-1,2,3,4*a*,5,6,7,7*a*-octahydrocyclopenta[*d*]pyrimidine-2,4-dione (20)**. The urea (**16**) (0.60 g, 1.39 mmol) was refluxed in ethanol (20 ml) containing 22% dry hydrogen chloride for 6 h. After evaporation of the solution to dryness, the residue was made alkaline with saturated $NaHCO_3$ solution and extracted with chloroform. The combined organic phase was dried (Na_2SO_4) and evaporated.

(4*aR,6*R**,7*aS**)-6-*tert*-Butyl-3-phenyl-2-thioxo-1,2,3,4*a*,5,6,7,7*a*-octahydrocyclopenta[*d*]pyrimidin-4-one (21)**. The reaction was performed with thiourea (**17**) as described for **19**.

(4*aR,6*R**,7*aS**)-1-Benzyl-6-*tert*-butyl-3-phenyl-2-thioxo-1,2,3,4*a*,5,6,7,7*a*-octahydrocyclopenta[*d*]pyrimidin-4-one (22)**. The reaction was performed with thiourea (**18**) as described for **20**.

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