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Preparation of cycloalkane-fused dihydropyrimidin-4(3*H*)-one enantiomers †

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Abstract

Racemic *cis*-2-amino-1-cyclopentane- or -cyclohexane-1-carboxylic acid was reacted with (*R*)-α-methylbenzylamine to form homochiral amides **3**, **4** and **8**, **9**. The ring closures of **3**, **4** and **8**, **9** with aryl imidates resulted in cyclopentane *cis*-fused and cyclohexane *cis*- and *trans*-fused dihydropyrimidin-4-one enantiomers with loss of the N-substituent. The absolute configurations were determined by hydrolysis of **5**, **6** and **10–13** to the corresponding amino acids.

In the past two decades, increased attention has been directed towards the synthesis of cycloalkane-fused saturated heterocycles,[1] but the methods applied have mostly involved racemic compounds. However, besides their stereochemical and pharmacological interest,[2–4] these heterocycles can also be used for enantioselective syntheses.[5,6]

The aim of the present work was the preparation of the enantiomers of 2-aryl-substituted cycloalkane-fused dihydropyrimidin-4(3*H*)-ones, and determination of their absolute configurations. These compounds possess pronounced pharmacological activity; as an example, (±)-2-(*m*-chlorophenyl)-3,4a,5,6,7,7a-hexahydrocyclopenta[*d*]pyrimidin-4(3*H*)-one (CHINOIN-143) has a strong anti-inflammatory effect.[7] CHINOIN-143 had been earlier resolved via diastereomeric salt formation in two-phase systems by using half an equivalent of dibenzoyltartaric acid.[8] The anti-inflammatory activity of the (−)-enantiomer was twice that of the racemic mixture.[7] The absolute configurations of the enantiomers were not determined.

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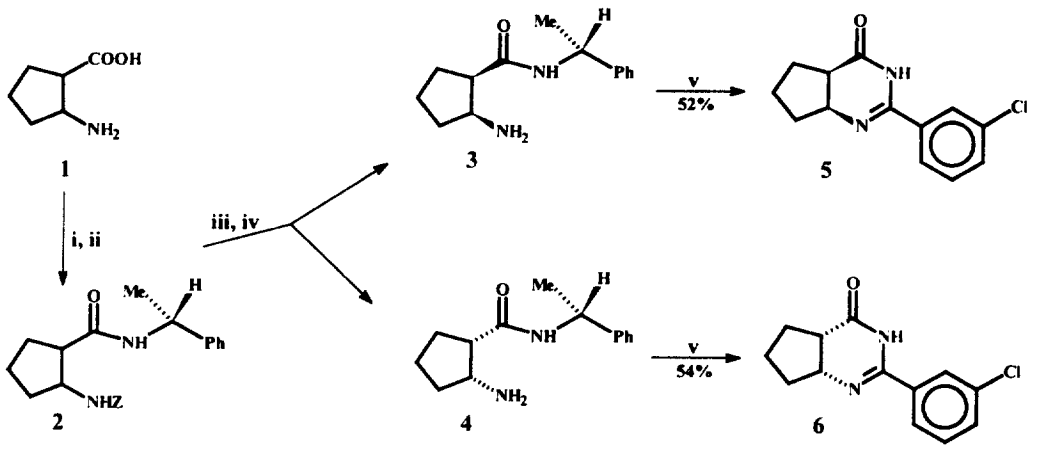
1. Results and discussion

The pathways for the syntheses of the desired cyclopentane-fused dihydropyrimidin-4-ones **5** and **6** are shown in Scheme 1. After protection of the racemic *cis*-2-amino-1-cyclopentanecarboxylic acid **1**, the Z-amino acid was treated with isobutyl chloroformate, and the resulting anhydride was reacted with (+)-(*R*)-α-methylbenzylamine, resulting in **2**.[9] The protecting group of **2** was removed by treatment with hydrogen bromide. The separation of racemic *cis*-2-amino-1-cyclopentanecarboxylic acid was accomplished by the procedure applied by Goodman et al. to Boc-*trans*-2-amino-1-cyclopentanecarboxylic acid.[10] The diastereomers **3** and **4** were separated by flash chromatography.

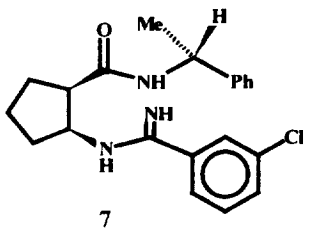


Scheme 1. i: 10% aq. NaOH, $PhCH_2OCOCl$ (yield: 95%); ii: TEA, ClCOO*i*Bu, THF/−10°C, then (+)-(*R*)-$H_2NCH(Me)Ph$/−10°C, 5 h (yield: 81%); iii: cc. AcOH, HBr, 1 h, then 20% aq. NaOH (yield: 89%); iv: flash chromatography (MeOH:EtOAc=4:1); v: ethyl *m*-chlorobenzimidate, cat. H^+/EtOH, reflux for 5 days

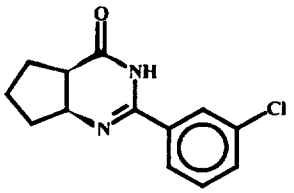
When **3** and **4** were heated with ethyl *m*-chlorobenzimidate in ethanol in the presence of a catalytic amount of acetic acid, **5** and **6** were obtained in high enantiomeric purity.

Racemic 2-(*m*-chlorophenyl)-3,4a,5,6,7,7a-hexahydrocyclopenta[*d*]pyrimidin-4(3*H*)-one and its analogues were synthesized by reaction of the corresponding β-amino acid or its derivatives with ethyl benzimidates, by reaction of orthoesters with 2-amino-1-cycloalkanecarboxamides, or by ring enlargement of cycloalkane-fused azetidinones with imidates.[1,11] In the reactions of the β-amino acid derivatives with benzimidates, the first step is the formation of an amidine intermediate; the subsequent nucleophilic attack of the imino group of the amidine on the carbonyl group results in the desired pyrimidin-4(3*H*)-ones. The same mechanism was found in the ring enlargement of cycloalkane-fused azetidinones on reaction with benzimidates.[12] In the reaction of **3**, the intermediate amidine **7** was isolated (mp: 218–221°C).

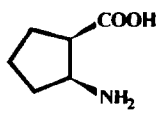
The absolute configurations of the prepared compounds were determined by hydrolysis of **5** and **6** to the corresponding amino acid, which was identified by HPLC.[13–17] It is interesting that the absolute configuration of the enantiomer with the higher anti-inflammatory activity corresponds to that of cispentacin [(1*R*,2*S*)-2-amino-1-cyclopentanecarboxylic acid], an antibiotic isolated from *Bacillus cereus* and *Streptomyces setonii*[18–22] and enantioselectively prepared earlier.[23–25]



7

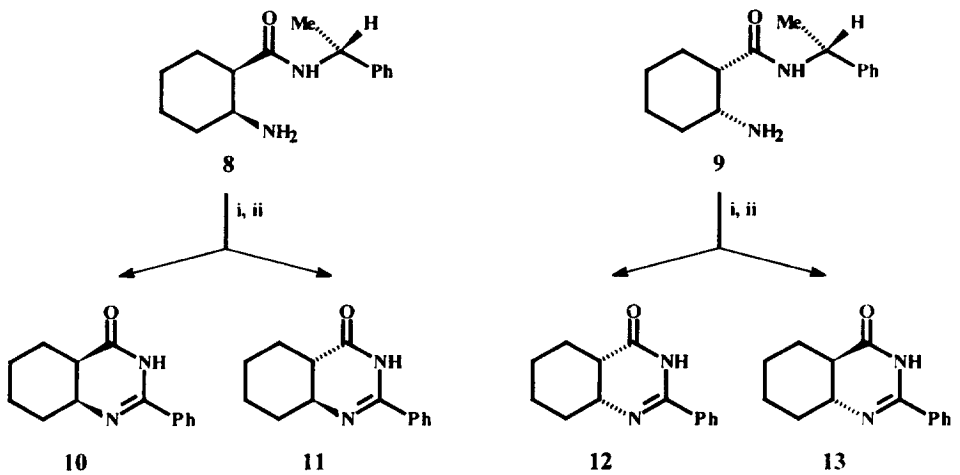


(-)-CHINOIN 143



cispentacin

In the ring-closure reaction of the cyclohexane-fused homologue, C-1 epimerization was observed (Scheme 2). Separation of the epimers **10**, **11** and **12**, **13** resulted in all four possible enantiomers. It is noteworthy that *cis*→*trans* isomerization is also possible for the cyclopentane derivatives, but the *trans* isomer (in accordance with earlier observations on *trans*-1,2-disubstituted 1,3-difunctional cyclopentane derivatives) does not undergo hetero-ring formation.[1]



Scheme 2. i: Ethyl benzimidate, cat. H^+/EtOH, 5 days; ii: flash chromatography (hexane:EtOAc=6:4)

The yields of the cyclohexane-fused pyrimidin-4(3*H*)-ones were relatively low, probably in consequence of their ring opening to afford amidines[26] in the course of the separation of the isomers on a silica gel column. The absolute configurations of the prepared compounds were determined by hydrolysis of **10–13** to the corresponding amino acids, which were identified by HPLC.[13–17]

2. Experimental

The NMR spectra were recorded on a BRUKER AVANCE DRX 400 spectrometer, using a '5 mm inverse Z gradient' probehead. The samples were dissolved in $CDCl_3$ containing 0.03% TMS as a reference. The number of scans was usually 64 for ^1H and 2K for ^{13}C spectra. All NMR measurements were carried out at 300 K.

HPLC measurements were performed on a Waters system consisting of an M-600 low-pressure gradient pump, an M-996 photodiode array detector and a Millenium 2010 Chromatography Manager data system (Waters Chromatography, Division of Millipore, Milford, MA, USA). The column used for indirect separation was a Vydac 218TP54 C_{18} column (250×4.6 mm I.D.), 5 μm particle size (The Separations Group, Hesperia, CA, USA), and for direct separation a CHIRAL-AGP column (100×4.0

mm I.D.), 5 μm particle size (ChromTech AB, HŠgersten, Sweden), and a cellulose triacetate column (250×10 mm I.D.), 10 μm particle size (Merck, Darmstadt, Germany).

GC measurements were performed on a Crompack CP-9002 system consisting of a Flame Ionization Detector 901A and Maestro II Chromatography data system (Chrompack International B.V., Middelburg, The Netherlands). The column used for direct separation was a CHIRASIL-DEX CB column (2500×0.25 mm I.D.). Optical rotation values were obtained with a Perkin–Elmer 341 polarimeter.

Melting points were determined on a Kofler apparatus and are uncorrected.

2.1. *Chemicals and reagents*

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylisothiocyanate (GITC) was purchased from Aldrich (Steinheim, Germany); trifluoroacetic acid (TFA), NaH_2PO_4 and NaOH of analytical reagent grade and HPLC-grade methanol, ethanol and 2-propanol were obtained from Merck (Darmstadt, Germany). A 0.1% aqueous solution of TFA was prepared with Milli-Q water purified further by filtering on a 0.45 μm Millipore filter, type HV (Molsheim, France). A 0.01 M NaH_2PO_4 buffer (pH=5.0) was prepared with Milli-Q water. A Radelkis OP/20811 pH meter (Budapest, Hungary) equipped with a combined glass–calomel electrode was employed for pH measurements. The mobile phases were prepared by mixing a 0.1% aqueous solution of TFA or 0.01 M NaH_2PO_4 buffer or water with methanol, ethanol or 2-propanol. The eluent was degassed in an ultrasonic bath, and during the analysis helium gas was bubbled through the solution.

2.2. cis-*2-Benzyloxycarbonylamino-1-cycloalkanecarbonyl-(+)-(*R*)-α-methylbenzylamines*

A quantity (20 mmol) of *cis*-2-benzyloxycarbonylamino-1-cyclopentane- or -cyclohexanecarboxylic acid was dissolved in dry THF (70 ml) and the solution was cooled to −10°C. Triethylamine (2.02 g, 20 mmol) and isobutyl chloroformate (2.73 g, 20 mmol) were added with vigorous stirring; after stirring for another 10 minutes, (+)-(*R*)-α-methylbenzylamine (2.42 g, 20 mmol) dissolved in THF (20 ml) was added dropwise at −10°C. Stirring was continued for 5 hrs, and the mixture was then allowed to stand overnight at room temperature. After evaporation of the THF, the residue was dissolved in $CHCl_3$ (200 ml) and extracted with a 5% solution of aqueous HCl (2×50 ml) and a 5% solution of NaOH (1×50 ml). The organic phase was dried over Na_2SO_4 and evaporated. The crude products were used for the preparation of **3**, **4**, **8** and **9** without further purification.[10]

2.3. *[(1*R,2S*)- and (1*S,2R*)-*cis*-2-Amino-1-cyclopentanecarbonyl]-(+)-(*R*)-α-methylbenzylamine (3 and 4), [(1*R,2S*)- and (1*S,2R*)-*cis*-2-amino-1-cyclohexanecarbonyl]-(+)-(*R*)-α-methylbenzylamine (8 and 9)*

Five equivalents of HBr, as a 20% solution in glacial acetic acid, was added to a diastereomeric mixture of 2-Z-amino-1-carboxamides (10 mmol) and the mixture was stirred for 50 minutes at room temperature. The clarified solution was extracted with diethyl ether (2×60 ml). The aqueous phase was made alkaline with a 20% solution of NaOH and extracted with $CHCl_3$ (3×50 ml). The organic phase was dried over Na_2SO_4 and evaporated, yielding the products as yellow oils. The diastereomeric mixtures were separated by flash chromatography ($CHCl_3$:MeOH=4:1) and the separated diastereomers were obtained as pale-yellow crystalline products.

The fast-eluting isomer **3** [1.11 g, 48%; $[\alpha]_D^{20}$ = +108 (c=0.1, MeOH); ee>99%]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.35 (m, 5H, Ph), 7.20 (bd, 1H, *J*=6.4 Hz, NH), 5.10 (m, 1H, PhCHN), 3.47 (m,

1H, H–C2), 2.59 (m, 1H, H–C1), 1.52–1.96 (m, 6H, 3×CH_2), 1.47 (d, 3H, *J*=6.9 Hz, Me). Analysis: calculated for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06; found: C, 72.12; H, 8.49; N, 12.15.

The slow-eluting isomer **4** [0.95 g, 41%; $[\alpha]_D^{20}$ = +124 (c=0.1, MeOH); ee>99%]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.33 (m, 5H, Ph), 7.16 (bd, 1H, *J*=6.4 Hz, NH), 5.14 (m, 1H, PhCHN), 3.51 (m, 1H, H–C2), 2.53 (m, 1H, H–C1), 1.50–2.00 (m, 6H, 3×CH_2), 1.48 (d, 3H, *J*=6.9 Hz, Me). Analysis: calculated for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06; found: C, 72.16; H, 8.79; N, 12.46.

The fast-eluting isomer **8** [1.06 g, 43%; $[\alpha]_D^{20}$ = +80 (c=0.1, MeOH); ee>99%]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (bd, 1H, *J*=6.8 Hz, NH), 7.20–7.34 (m, 5H, Ph), 5.11 (m, 1H, PhCHN), 3.29 (m, 1H, H–C2), 2.38 (m, 1H, H–C1), 1.33–1.87 (m, 8H, 4×CH_2), 1.45 (d, 3H, *J*=6.9 Hz, Me). Analysis: calculated for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37; found: C, 73.29; H, 8.69; N, 11.35.

The slow-eluting isomer **9** [0.98 g, 40%; $[\alpha]_D^{20}$ = +95 (c=0.1, MeOH); ee>99%]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (bd, 1H, *J*=6.5 Hz, NH), 7.20–7.31 (m, 5H, Ph), 5.12 (m, 1H, PhCHN), 3.28 (m, 1H, H–C2), 2.35 (m, 1H, H–C1), 1.34–1.91 (m, 8H, 4×CH_2), 1.45 (d, 3H, *J*=6.9 Hz, Me). Analysis: calculated for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37; found: C, 73.32; H, 8.88; N, 11.53.

To determine the enantiomeric purity, **3**, **4** and **8**, **9** were derivatized with GITC and subsequently separated by HPLC on a Vydac column (a 0.1% aqueous solution of TFA:methanol=45:55 v/v; flow rate, 0.8 ml/min; detection at 250 nm).

2.4. (−)-(4aR,7aS)- and (+)-(4aS,7aR)-2-(m-Chlorophenyl)-3,4a,5,6,7,7a-hexahydrocyclopenta[d]-pyrimidin-4(3H)-one (5 and 6)

To a solution of **3** or **4** (1.00 g, 4.3 mmol) in 40 ml of dry ethanol, ethyl *m*-chlorobenzimidate (0.47 g, 4.3 mmol) and one drop of glacial acetic acid were added and the mixture was refluxed for 6 days. The solution was then evaporated to dryness, and the residue was dissolved in 50 ml of 3% aqueous HCl solution and extracted with $CHCl_3$ (2×20 ml). The aqueous phase was made alkaline with saturated $NaHCO_3$ solution and extracted with $CHCl_3$ (3×30 ml). The combined organic phase was dried (Na_2SO_4), and evaporated, and the crystalline residue was recrystallized from isopropyl ether.

Compound **5** (0.56 g, 52%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (bs, 1H, NH), 7.36–7.82 (m, 4H, *m*ClPh), 4.28 (m, 1H, H–C7a), 2.75 (m, 1H, H–C4a), 1.64–2.27 (m, 6H, 3×CH_2). Analysis: calculated for $C_{13}H_{13}ClN_2O$: C, 62.78; H, 5.27; N, 11.26; found: C, 62.39; H, 5.43; N, 11.41; mp: 120–122°C (lit.[7]: 117–118°C); $[\alpha]_D^{20}$ = −55 (c=1.0, n HCl, lit.[7]: −54); ee>98%.

Compound **6** (0.58 g, 54%): the ^{1}H NMR spectrum of **6** was identical to that of **5**. Analysis: calculated for $C_{13}H_{13}ClN_2O$: C, 62.78; H, 5.27; N, 11.26; found: C, 62.48; H, 5.52; N, 11.12; mp: 122–123°C (lit.[7]: 117–118°C); $[\alpha]_D^{20}$ = +54 (c=1.0, n HCl, lit.[7]: +54); ee>98%.

To determine the enantiomeric purity, direct separation of **5** and **6** was performed on a CHIRAL-AGP column (2-propanol:NaH_2PO_4 (0.01 M, pH=5.0) 3:97 v/v; flow rate, 0.9 ml/min; detection at 246 nm).

2.5. (−)-(4aR,8aS)- and (+)-(4aS,8aS)-2-Phenyl-3,4,4a,5,6,7,8,8a-octahydroquinazolin-4(3H)-one (10 and 11), (+)-(4aS,8aR)- and (−)-(4aR,8aR)-2-phenyl-3,4,4a,5,6,7,8,8a-octahydroquinazolin-4(3H)-one (12 and 13)

The reaction was performed on **8** or **9** (1.20 g, 4.9 mmol) and ethyl benzimidate (0.73 g, 4.9 mmol), as described for **5** and **6**. The diastereomeric mixtures obtained were separated on a silica gel column by flash chromatography (hexane:EtOAc=6:4) and the separated diastereomers were recrystallized from isopropyl ether.

Compound **10** (0.30 g, 27%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (bs, 1H, NH), 7.42–7.78 (m, 5H, Ph), 3.90 (m, 1H, H–C8a), 2.69 (m, 1H, H–C4a), 1.44–2.11 (m, 8H, 4×CH_2). Analysis: calculated for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27; found: C, 73.81; H, 7.15; N, 12.08; mp: 170–172°C; $[\alpha]_D^{20}$ = −75 (c=0.1, MeOH); ee>98%.

Compound **11** (0.15 g, 13%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (bs, 1H, NH), 7.41–7.78 (m, 5H, Ph), 3.24 (m, 1H, H–C8a), 2.40 (overlapping m, 1H, H–C4a), 1.27–2.40 (m, 8H, 4×CH_2). Analysis: calculated for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27; found: C, 73.54; H, 7.02; N, 12.43; mp: 200–202°C; $[\alpha]_D^{20}$ = +107 (c=0.1, MeOH); ee>98%.

Compound **12** (0.32 g, 29%): the ^{1}H NMR spectrum of **12** was identical to that of **10**. Analysis: calculated for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27; found: C, 73.78; H, 7.13; N, 12.21; mp: 172–174°C; $[\alpha]_D^{20}$ = +76 (c=0.1, MeOH); ee>98%.

Compound **13** (0.19 g, 17%): the ^{1}H NMR spectrum of **13** was identical with that of **11**. Analysis: calculated for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27; found: C, 73.75; H, 7.27; N, 12.45; mp: 200–203°C; $[\alpha]_D^{20}$ = −106 (c=0.1, MeOH); ee>98%.

To determine the enantiomeric purity, direct separation of **10** and **12** was performed by GC on a CHIRASIL-DEX CB column (170°C, 80 kPa), and that of **11** and **13** by HPLC on a cellulose triacetate column (ethanol:water=75:25 v/v; flow rate, 0.8 ml/min; temperature, 50°C; detection at 246 nm).

2.6. General method for the hydrolysis, derivatization and absolute configuration determination

A quantity (0.5 mg) of **5**, **6** or **10–13** was dissolved in 100 μl methanol, and 200 μl aqueous NaOH solution (5 M) was added to each solution. The compounds were hydrolysed at 40°C for 6 days. The reaction was stopped by adding aqueous HCl solution (2 M) until pH≤7 was reached. 1 mg/ml solutions of **1**, cispentacin, (±)-*cis*- and (±)-*trans*-2-amino-1-cyclohexanecarboxylic acid (*cis*- and *trans*-ACHC), the 1*R*,2*S* and 1*S*,2*S* enantiomers of ACHC and 100 μl of solutions of each hydrolysed compound were used for derivatization with GITC by the method of Nimura et al.[22]

The absolute configurations of **5**, **6** and **10–13** were determined by comparison of the spectra and chromatograms of the GITC derivatives of **5**, **6** (Vydac, a 0.1% aqueous solution of TFA:methanol=57.5:42.5 v/v; flow rate, 0.8 ml/min; detection at 250 nm) and **10–13** (Vydac, a 0.1% aqueous solution of TFA:methanol=50:50 v/v; flow rate, 0.8 ml/min; detection at 250 nm), with those of the GITC derivatives of cispentacin, and the 1*R*,2*S* and 1*S*,2*S* enantiomers of ACHC.[23]

Acknowledgements

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