

Synthesis of (2*S*,4*S*)-2-Substituted-3-(3-Sulfanylpropanoyl)-6-Oxohexahydropyrimidine-4-Carboxylic Acids as Potential Antihypertensive Drugs

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Abstract

Proceeding from natural amino acid *L*-asparagine and commercially available aldehydes a stereoselective synthesis was developed of (2*S*,4*S*)-2-alkyl(aryl)-3-(3-sulfanylpropanoyl)-6-oxohexahydropyrimidine-4-carboxylic acids, potential antihypertensive drugs, inhibitors of the angiotensin converting enzyme.

Keywords

6-Oxohexahydropyrimidine-4-Carboxylic Acids, Inhibitors of the Angiotensin Converting Enzyme

1. Introduction

Efficient antihypertensive drugs function as inhibitors of the angiotensin converting enzyme (ACE). This enzyme is involved in the regulator system rennin-angiotensin-aldosterone, and the distortion of its operation results in the majority of hypertensive human diseases [1]-[3]. The first of the drugs from this series was *captopril*, (*S*)-*N*-(3-sulfanyl-2-methyl-1-oxopropyl)-*L*-proline [4]. The later research on development of antihypertensive substances, ACE inhibitors, was directed to the replacement of the natural amino acid *L*-proline in the captopril molecule by synthetic cyclic amino acids of the heterocyclic series, among them derivatives of 1,3-oxazolidine [5], 1,3-thiazolidine [6], piperidine [7], quinazoline [8], indole [9], and azepine [10]. In the series of the saturated pyrimidine derivatives the only example of the inhibitor activity with respect to ACE is known to be shown by 3-(3-sulfanylpropanoyl)-6-oxohexahydropyrimidine-4-carboxylic acid [11].

It was found by the analysis of published data that sodium (potassium) salts of 2-substituted 6-oxohexahydropyrimidine-4-carboxylic acids formed in the reaction of the natural amino acid *L*-asparagine with carbonyl compounds in alkaline medium. This reaction was investigated mainly by an example of derivatives of isobutyric, trimethylacetic, and benzoic aldehydes [12]-[16]. The process was found to occur with a high stereoselectivity giving prevalingly the spatial isomer with (2*R*,4*S*)-configuration of the substituents in the pyrimidine ring.

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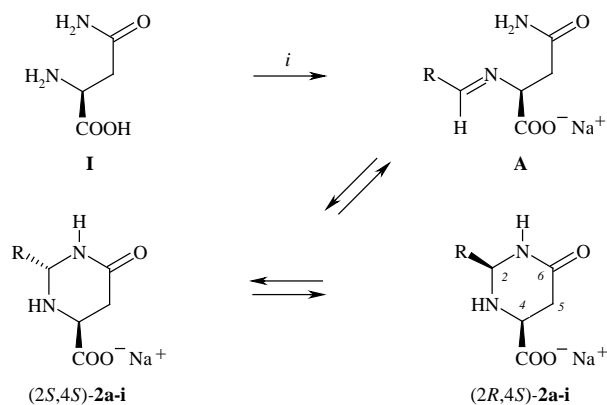
The derivatives of 6-oxohexahydropyrimidine-4-carboxylic acids are used as key intermediates in the synthesis of β -amino acids [12] [13], in the asymmetric cycloaddition reactions [14], in liposomal microencapsulation of biopreparations [15].

2. Results and Discussion

The goal of this study is the search for new and synthetically accessible potential antihypertensive substances, ACE inhibitors, compounds where the cyclic amino acid fragment is a derivative of pyrimidine-4-carboxylic acid.

Compounds **2a-i** were obtained in 70% - 90% yields after maintaining *L*-asparagine, an appropriate aliphatic or aromatic aldehyde, and equivalent quantity of sodium hydroxide in methanol solution for 10 - 12 h at 25°C (see **Scheme 1** and **Table 1**).

The first objects of our investigation were the condensation products of *L*-asparagine with a series of aliphatic aldehydes, compounds **2a-f**. The cyclic pyrimidine structure of these compounds is unquestionable, as shows the appearance in the ^1H NMR spectra of the typical *ABX* system due to the diastereotopic character of H-5 and H-4 protons, of the signals of H-2 atom in the region 4.2 - 4.5 ppm, and in the ^{13}C NMR spectra, of the signal of sp^3 -hybridized C-2 atom in the region 65 - 70 ppm. In the spectra of all obtained compounds **2a-f** two sets of resonance signals from (2*R*,4*S*)- and (2*S*,4*S*)-stereoisomeric forms of the pyrimidine ring are observed. The assignment of the stereoisomeric forms of compounds **2a-f** is based on the formerly established criteria and rules ob-



Scheme 1. *i*: RCH=O , NaOH/MeOH , 25°C, 10 - 12 h. R = Me (**a**), Et (**b**), Bu (**c**), *i*-Pr (**d**), *i*-Bu (**e**), $\text{CH}_2\text{CH}_2\text{Ph}$ (**f**), R = XC_6H_4 , X = H (**g**), 4-Cl (**h**), 4-MeO (**i**).

Table 1. Characteristics of compounds **2a-i**.

Compound	$[\alpha]_D^{25}$ in MeOH	Tautomeric composition in D_2O , (%)		
		Form A	Form (2 <i>R</i> ,4 <i>S</i>)	Form (2 <i>S</i> ,4 <i>S</i>)
2a	-89.1, <i>c</i> 1.31	—	95	5
2b	-91.2, <i>c</i> 1.50	—	93	7
2c	-70.1, <i>c</i> 1.50	—	90	10
2d	-97.7, <i>c</i> 1.40	—	93	7
2e	-77.2, <i>c</i> 1.53	—	87	13
2f	-69.5, <i>c</i> 1.50	—	92	8
2g	-60.2, <i>c</i> 2.01	13	68	19
2h	-35.1, <i>c</i> 2.02	51	40	9
2i	-37.2, <i>c</i> 1.70	18	66	16

tained at the use of ^1H and ^{13}C NMR spectroscopy [13]-[15], and also on the data of X-ray diffraction analysis [13] [16]. In keeping with the comparison of the ^1H and ^{13}C NMR spectra of compounds **2a-f** to the analogous spectral characteristics published in [13]-[16] the (2*R*,4*S*)-configuration was assigned to the main isomer. In the ^1H NMR spectrum of this stereoisomer the protons H-5 and H-4 are characterized by larger spin-spin coupling constant ($J_{AB} = 17$ Hz, $J_{AX} + J_{BX} = 16$ Hz), and the signals of H-5 and H-4 protons are considerably shifted up-field than the analogous signals of the stereoisomer with (2*S*,4*S*)-configuration. The corresponding coupling constant in the latter isomer is smaller ($J_{AB} = 15$ Hz, $J_{AX} + J_{BX} = 13$ Hz).

The position of the configurational equilibrium of compounds **2a-f** is shifted to a large extent to (2*R*,4*S*)-stereoisomer, therefore it is impossible to obtain a clear correlation between the logarithms of the constant of the configurational equilibrium and the Taft steric constants of alkyl substituents. The largest fraction of the minor (2*S*,4*S*)-isomer (13%) was observed in the D_2O solution of compound **2e**, isovaleric aldehyde derivative.

In the ^1H and ^{13}C NMR spectra in D_2O of the *L*-asparagine condensation products with aromatic aldehydes (compounds **2g-i**) alongside the signals of two configuration isomers of the pyrimidine form signals appear of a linear form **A**. Not entering into details of the previously found by us [17] spectral distinctions between the cyclic and linear forms of compounds **2g-i** we only mention that the typical signs of the latter in the ^1H NMR spectrum is a significant downfield shift of the protons of CH_2CH group as compared with analogous signals H-5 and H-4 of cyclic forms, the appearance of the proton signal of the azomethine group at 8.25 - 8.35 ppm, and in the ^{13}C NMR spectrum, of the downfield signal at 165 ppm ($\text{C}=\text{N}$).

By an example of compound **2g**, the condensation product of *L*-asparagine with benzaldehyde, we studied the dependence of the position of the tautomeric equilibrium on the nature of the applied solvent (see **Table 2**). In the crystalline state compound **2g** exists in the cyclic pyrimidine (2*R*,4*S*)-form as confirmed by the solid state ^{13}C NMR spectrum [17]. In all solvents the coexistence of tautomeric forms was observed, and in going to aprotic polar solvents (DMSO-D_6 and DMF-D_7) the fraction of the linear form **A** significantly increased.

Hence the products of *L*-asparagine condensation with acetic, propionic, valeric, isobutyric, isovaleric, and hydrocinnamic aldehydes in alkaline medium have the cyclic pyrimidine structure, and in D_2O solutions they are present as two cyclic spatial stereoisomers with a significant prevalence of the (2*R*,4*S*)-form. In neither case the appearance in the solutions of the linear imine form **A** was observed. In this respect compounds **2a-f** fundamentally differ from the condensation products of *L*-asparagine with a series of aromatic aldehydes **2g-i** where the occurrence of the ring-chain tautomerism has been found and alongside two pyrimidine stereoisomers a linear form exists in solutions.

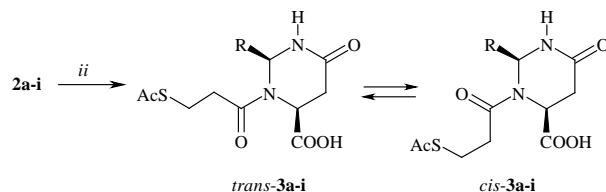
The acylation of 2-substituted 6-oxohexahydropyrimidine-4-carboxylic acids results in the formation of optically pure *N*-acyl derivatives with (2*S*,4*S*)-configuration of the substituents at the pyrimidine ring [13]-[16]. In some studies the ability was demonstrated of (2*S*,4*S*)-3-acyl-2-substituted-6-oxohexahydropyrimidine-4-carboxylic acids to the conformational *cis,trans*-isomerization in solutions due to effect of the hindered rotation relative to $\text{C}-\text{N}$ bond of the amide fragment [13] [15] [18].

It was found that acylation of compounds **2a-i** with 3-(acetylthio)propionyl chloride proceeded in acetone and completed in 10-12 h with the formation of 3-(3-acetylsulfanypropionyl)-2-alkyl(aryl)-6-oxohexahydropyrimidine-4-carboxylic acids **3a-i** (see **Scheme 2** and **Table 3**).

The acylation products **3a-i** possess the (2*S*,4*S*)-configuration of the substituents of the pyrimidine ring, in their solutions in DMSO-D_6 , in keeping with the data of ^1H and ^{13}C NMR spectra, the presence of two *cis, trans*-conformers has been found in the ratio ~3:2. It was confirmed by the coalescence of doubled signals at the re-

Table 2. Tautomeric composition (%) of compound **2g** in various solvents 48 h after dissolution.

Solvent	Form A	Form (2 <i>R</i> ,4 <i>S</i>)	Form (2 <i>S</i> ,4 <i>S</i>)
Solid phase	–	100	–
D_2O	13	68	19
Pyridine- D_5	40	48	12
DMSO-D_6	45	44	11
DMF-D_7	51	40	9



Scheme 2. *ii*: $\text{AcSCH}_2\text{CH}_2\text{COCl}/\text{Me}_2\text{CO}$, $\text{C}_5\text{H}_5\text{N}$, $5^\circ\text{C} - 10^\circ\text{C}$, 10 - 12 h. R = Me (**a**), Et (**b**), Bu (**c**), *i*-Pr (**d**), *i*-Bu (**e**), $\text{CH}_2\text{CH}_2\text{Ph}$ (**f**), R = XC_6H_4 , X = H (**g**), 4-Cl (**h**), 4-MeO (**i**).

Table 3. Characteristics of compounds **3a-i**.

Compound	$[\alpha]_D^{25}$ in DMF	mp, $^\circ\text{C}$	Yield, %
3a	-52.1, <i>c</i> 1.00	73 - 75	45
3b	-87.2, <i>c</i> 1.20	121 - 123	52
3c	-115.8, <i>c</i> 1.10	92 - 94	56
3d	-114.8, <i>c</i> 1.10	133 - 135	65
3e	-109.4, <i>c</i> 1.15	119 - 121	65
3f	-57.4, <i>c</i> 1.10	125 - 127	68
3g	+52.1, <i>c</i> 1.00	88 - 91	53
3h	+19.4, <i>c</i> 1.10	93 - 95	56
3i	+35.1, <i>c</i> 1.20	78 - 81	62

gistering ^1H NMR spectra in $\text{DMSO}-\text{D}_6$ at higher temperature ($\sim 80^\circ\text{C} - 85^\circ\text{C}$). Proceeding from the comparison of the ^1H and ^{13}C NMR spectra of compounds **3a-i** with the published [13]-[16] spectral characteristics of 3-alkanoyl-2-substituted 6-oxohexahydropyrimidine-4-carboxylic acids the *trans*-configuration was ascribed to the main isomer. This conformer is characterized by the downfield shift of H-4 and H-2 signals in the ^1H NMR spectrum compared the analogous signals of the minor *cis*-isomer. The position of the conformational equilibrium is governed by the nature of the applied solvent, and in going from CDCl_3 to polar solvents, as show the data for compounds **3a-i**, the stability of the more polar *cis*-conformer increases.

The removal of S-acetyl protection in compounds **3a-i** occurs in the ammonia solution within several hours at room temperature and leads to the formation of (2*S*,4*S*)-2-alkyl(aryl)-3-sulfanylpropanoyl-6-oxohexahydropyrimidine-4-carboxylic acids **4a-i** in 50% - 65% yields (see **Scheme 3** and **Table 4**). In the ^1H NMR spectra in $\text{DMSO}-\text{D}_6$ of compounds **4a-i** a triplet signal is observed from the proton of the SH group in the region 1.45 - 2.10 ppm. Like in compounds **3a-i**, in the solutions of products **4a-i** *cis*- and *trans*-conformers are present due to the effect of the hindered amide rotation.

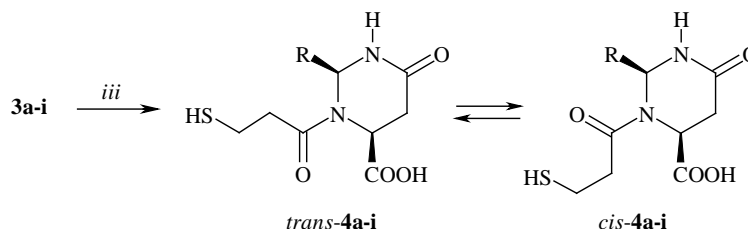
3. Experimental

^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker AV-400 at operating frequencies 400 and 100 MHz respectively (internal reference HMDS). The stereoisomeric composition of obtained compounds was estimated by the integration of the appropriate signals in the ^1H NMR spectra. The specific optical rotation was measured on a polarimeter P-161M at the wavelength of the plane-polarized light 589 nm. Elemental analysis of newly obtained compounds was carried out on a CHN Analyzer Hewlett Packard 185B. The purity of prepared compounds was checked by TLC on Silufol UV-254 plates, eluent benzene-acetone, 1:1.

Compounds **2a-i** are white or light yellow amorphous hygroscopic powders, mp $>250^\circ\text{C}$. Spectral characteristics of compounds **2a-i**, **3a-i**, and **4a-i** were described previously [19]. 3-(Acetylsulfanyl)propanoyl chloride was obtained by the method [20].

4. Conclusions

Hence we developed a three-stage stereoselective synthesis from *L*-asparagine of previously unknown (2*S*,4*S*)-



Scheme 3. iii: NH₃(aq.), 25°C, 5 - 10 h. R = Me (**a**), Et (**b**), Bu (**c**), *i*-Pr (**d**), *i*-Bu (**e**), CH₂CH₂Ph (**f**), R = XC₆H₄, X = H (**g**), 4-Cl (**h**), 4-MeO (**i**).

Table 4. Characteristics of compounds **4a-i**.

Compound	$[\alpha]_D^{25}$ in MeOH	mp., °C	Yield, %
4a	-48.6, <i>c</i> 1.30	189 - 191	66
4b	-76.5, <i>c</i> 1.37	165 - 168	58
4c	-84.2, <i>c</i> 1.15	122 - 125	50
4d	-95.7, <i>c</i> 1.10	184 - 186	65
4e	-122.8, <i>c</i> 1.20	162 - 164	60
4f	-80.1, <i>c</i> 1.00	132 - 134	54
4g	+13.7, <i>c</i> 1.00	120 - 123	55
4h	+22.4, <i>c</i> 1.00	202 - 204	58
4i	+28.7, <i>c</i> 1.10	148 - 151	65

3-(3-sulfanylanoyl)-2-alkyl(aryl)-6-oxohexahydropyrimidine-4-carboxylic acids **4a-i**, potential antihypertensive drugs, ACE inhibitors [21]; the compounds obtained are structural analogs of the known antihypertensive drug *methiaprilo*, (2*S*,6*S*)-1-[(3-acetylsulfanylanoyl)-6-methylpipecolinic acid [7]. However unlike *methiaprilo* whose production requires difficultly available synthetic (2*S*,6*S*)-6-methylpipecolinic acid [22], the stereoselective synthesis of compounds **4a-i** is underlain by natural or commercially available reagents. Besides, by varying the structure of the initial aldehyde component the developed procedure makes it possible to introduce in the position 2 of pyrimidine ring substituents of diverse nature, length, and branching.

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