The Synthesis of 6-R-[1(Methylthio)-2,3,4,9-Tetrahydro-1H- β -Carbolin-1-yl] Cyanamides by the Interaction of Tryptamines with N-Cyanoimido-S, S-Dimethyldithiocarbonate

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Abstract: It is studied the interaction of 5-substituted tryptamines with N-cyanoimido-S,S-dimethyldithiocarbonates. It is established that the reaction proceeds exhaustively under reflux in ethanol for 10-15 hours with elimination of one molecule of methylmercaptan, further cyclization passes not through the expected cleavage of the second molecule of methylmercaptan formation (6-R-2,3,4,9-tetrahydro-1H- β -carbolin-1-ylidene)cyanamides, and the accession of the hydrogen atom located at the carbon atom of the indole ring to the nitrogen atom of the imide groups and the carbon-carbon bond formation and the yield previously undescribed 6-R-[1(methylthio)-2,3,4,9-tetrahydro-1H- β -carbolin-1-yl] cyanamides.

Key words: Tetrahydro- β -carbolines, tryptamine, N-cyanoimido-S,S-dimethyldithiocarbonate, 6-R-[1(methylthio)-2,3,4,9-tetrahydro-1H- β -carbolin-1-yl] cyanamide.

1. Introduction

Indefatigable interest to development of new approaches to synthesis of various derivatives of tetrahydro- β -carbolines is caused by well-known biological activity of the natural and synthetic compounds containing pharmaceutical activity indoles and tetrahydropyridines fragments [1, 2]. In particular β -carbolines (including tetrahydro- β -carbolines) show antiinsurane, antipanic, antituberculosis and antitumor activity and stressprotective properties, therefore, are successfully used in the treatment of stress, depression [3-7].

In this connection, tetrahydro- β -carbolines are a perspective class of substances for the further research of medical products. Therefore creation of new

approaches which would allow expanding possibilities of designing of derivatives of it of some compounds is actual.

In nature, a fragment of tetrahydro- β - carboline is the basis of some simple indole alkaloids (tryptoline, pinoline, tetrahydroharman, tetrahydrogarmin) in monoterpene indole alkaloids this fragment condensed with a carbo- and heterocycles (ajmalicine, akuamidine, vincarine, vincamine, erwin, nitrarin, yohimbine, reserpine) [8, 9]. However, with few exceptions [10-14], virtually nothing is known about psychopharmacology unannulation tetrahydro- β -carbolines. At the same time there is evidence [15-20] on the pharmacological activity of annulation tetrahydro- β -carbolines. In this regard, getting new multifunctional tetrahydro- β -carbolines is of interest in terms of their research pharmacological properties, on the other hand, the presence of several

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functional groups will allow annelated other heterocycles to fragment tetrahydro- β -carboline.

2. Experiments

2.1 Materials

All solvents and chemicals used in this work were analytical grade and used without purification.

2.2 Characterization

Control over the individuality of the reagents and the obtained compounds, as well as the progress of the reaction was monitored by TLC on Silufol UV-254. As eluent was used chloroform; the manifestation of chromatograms were in UV light and iodine vapor. ^1H NMR spectra were recorded on the instrument Bruker AC-300 (300 MHz); internal standard, TMS, solvents, deuterodimethylsulfoxide. Mass-spectra were removed on the device LKB 9000 with the input of the substance directly in the ionizing source, the energy of ionizing electrons 70 EV.

2.3 General Method for the Synthesis of 6-R-[1-(Methylthio)-2,3,4,9-Tetrahydro-1H- β -Carbolin-1-yl] Cyanamides 4a-d.

A mixture of 1 mmol of the corresponding 5-R-tryptamine 1a-d and 1.6 g (1.1 mmol) N-cyanoimido-S,S-dimethyldithiocarbonate in 20 ml of ethanol is refluxed for 10-15 hours (control - TLC). The solvent was evaporated, the precipitate was filtered and recrystallized from THF. Received 6-R-[1-(methylthio)-2,3,4,9-tetrahydro-1H- β -carbolin-1-yl]cyanamides 4 a-d.

[1-(methylthio)-2,3,4,9-tetrahydro-1H- β -carbolin-1-yl]cyanamide 4a. Yield 95%, mp 171-172 °C. MS (EI, 70 ev) m/z , %: 258 (20, M+); 143 (100); 130 (65); 115 (5); 103 (5); 77 (5). ^1H NMR (300 MHz, DMSO- d_6) δ : 2.50 (3H, s, SCH₃); 2.90-3.00 (2H, m, CH₂); 3.50-3.60 (2H, m, CH₂N); 6.98 (1H, ddd J = 8.1 Hz, 6.9 Hz, 1.1 Hz 6-H or 7-H.); 7.12; (1H, ddd J = 8.1 Hz, 6.9 Hz, 1.1 Hz 6-H, or 7-H.); 7.36 (1H, d, J = 8.3 Hz, 1.1 Hz 5-H or 8-H); 7.56 (1H, d J = 8.3 Hz, 1.1 Hz 5-H or 8-H); 7.18 (1H, s,

NH_{pyrid.}); 8.44 (1H, br s, NH); 10.86 (1H, br s, NH_{indol.}). Analysis: calc. for C₁₃H₁₄N₄S: C 60.44, H 5.46, N 21.69, S 12.41. Found. C 60.54, H 5.49, N 21.60, S 12.48.

[6-fluoro-1-(methylthio)-2,3,4,9-tetrahydro-1H- β -carbolin-1-yl]cyanamide 4b. Yield 74%, mp 164-165 °C. MS (EI, 70 ev) m/z , %: 276 (20, M+); 161 (100); 148 (65); 115 (5); 103 (5); 95 (5). ^1H NMR (300 MHz, DMSO- d_6) δ : 2.46 (3H, s, SCH₃); 2.86-2.96 (2H, m, CH₂); 3.50-3.66 (2H, m, CH₂N); 7.02 (1H, s, 5-H.); 7.36 (1H, J = 8.3 Hz, 6-H или 8-H); 7.50 (1H, J = 8.1 Hz, 6-H или 8-H); 7.24 (1H, s, NH_{pyrid.}); 8.42 (1H, br s, NH); 10.92 (1H, br s, NH_{indol.}). Analysis: calc. for C₁₃H₁₃FN₄S: C 56.51, H 4.74, N 20.27, S 11.60. Found. C 56.60, H 4.79, N 20.20, S 11.68.

[6-chloro-1-(methylthio)-2,3,4,9-tetrahydro-1H- β -carbolin-1-yl]cyanamide 4c. Yield 68%, mp 161-162 °C. MS (EI, 70 ev) m/z , %: 293 (20, M+); 178 (100); 165 (65); 115 (5); 138 (5); 112 (5). ^1H NMR (300 MHz, DMSO- d_6) δ : 2.48 (3H, s, SCH₃); 2.90-2.96 (2H, m, CH₂); 3.52-3.68 (2H, m, CH₂N); 7.14 (1H, s, 5-H.); 7.42 (1H, d, J = 8.3 Hz, 6-H or 8-H); 7.54 (1H, d, J = 8.1 Hz, 6-H or 8-H); 7.28 (1H, s, NH_{pyrid.}); 8.46 (1H, br s, NH); 10.88 (1H, br s, NH_{indol.}). Analysis: calc. for C₁₃H₁₃ClN₄S: C 53.41, H 4.44, N 19.26, S 10.87. Found. C 53.35, H 4.50, N 19.15, S 10.93.

[6-methoxy-1-(methylthio)-2, 3, 4,9-tetrahydro-1H-carbolin-1-yl] cyanamide 4d. Yield 87%, mp 173-174 °C. MS (EI, 70 ev) m/z , %: 288 (20, M+); 173 (100); 160 (65); 115 (5); 133 (5); 110 (5). ^1H NMR (300 MHz, DMSO- d_6) δ : 2.48 (3H, s, SCH₃); 2.92-3.00 (2H, m, CH₂); 3.46-3.68 (2H, m, CH₂N); 3.82 (3H, s, OCH₃); 7.08 (1H, s, 5-H.); 7.42 (1H, d, J = 8.3 Hz, 6-H or 8-H); 7.52 (1H, d, J = 8.1 Hz, 6-H or 8-H); 7.18 (1H, s, NH_{pyrid.}); 8.42 (1H, br s, NH); 10.90 (1H, br s, NH_{indol.}). Analysis: calc. for C₁₄H₁₆N₄OS: C 58.39, H 5.56, N 19.66, S 11.17. Found. C 58.30, H 5.60, N 19.45, S 11.10.

3. Results and Discussion

3.1 Synthesis and Characterization

One of widespread methods of synthesis

tetrahydro-β-carbolines cycle is interaction tryptamine with various cyclization agents. Wide enough application reaction of Pictet-Spengler in which basis interaction tryptamines with carbonyl compounds lies in particular has found [21, 22]. In the given work in quality of cyclization agent has been chosen N-cyanoimido-S,S-dimethyldithiocarbonate. Given the reactivity of the starting compounds can be assumed that the interaction of tryptamine ([2-(1*H*-indol-3-yl)ethyl]amine) with N-cyanoimido-S,S-dimethyldithiocarbonates should occur with the removal of two molecules of methylmercaptan. It is established that for all tryptamines 1 reaction easily passes at a boiling in ethanol and comes to the end during 10-15 h. Obviously, interaction begins with amino group

The structure of 6-R-[1(methylthio)-2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl] cyanamides 4a-d was proved by ^1H NMR spectroscopy and mass spectrometry. In ^1H NMR spectrum of these compounds there are signals of three protons methylmercapto-group in the form of singlets in the region of 2.46-2.50 ppm, two broadened singlet protons of amino-groups and NH-protons indoles fragment in the areas of 8.28-8.46, and 10.86-10.92 ppm. The signal of the protons of amino-groups hydropyridines fragment is shifted into the weak field in the district 7.14-7.28 ppm, due to the influence of neighboring groups. Chemical shifts of aromatic protons and four protons of two methylene groups are shown in the relevant areas for these protons.

Mass spectrometric investigation showed that they give molecular ion peaks of low intensity ($I = 20\%$).

tryptamines attack methylthio group of reagent, with elimination molecules of methylmercaptan that gives intermediate 2-methyl-*N*-cyano-*N*-[2-(1*H*-indol-3-yl)ethyl] imidothiocarbamates 2. As we established, further cyclization passes not at the expense of expected elimination the second molecule of methylmercaptan and formations (6-R-2,3,4,9-tetrahydro-1*H*-β-carbolin-1-ylidene)cyan amide 3A or its tautomer (6-R-4,9-dihydro-3*H*-β-carboline-1-yl) cyanamide 3B, in summary joining of atom hydrogen at carbon atom being indole cycles to atom of nitrogen imido groups and short circuits carbon-carbon bond. Thus with the yield reaching 95%, have been received 6-R-[1(methylthio)-2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl] cyanamides 4a-4d.

Maximum intensity ($I = 100\%$) have the fragment ions formed by the removal of the neutral molecule methyl *N*-cyanoimidothiocarbamate. Observed as intense peaks ($I = 80\%$) indolylmethyl cations. All this implies greater stability compared to the indoles ring with hydropyridines.

Proceeding from structure of compounds 4, it is possible to assume possibility elimination of second molecule of methyl mercaptan, at the expense of atom of hydrogen endo-cycles or exo-cycles amino groups that should lead 4,9-dihydro-3*H*-β-carbolin-1-ylcyanamide 3b or it tautomer 3a, accordingly. However, the elimination of the second mercapto-groups not occur even in harsh conditions: by reflux compounds 4 in alcohols (methanol, ethanol and butanol) with the addition of triethylamine as a catalyst, in dioxane in the presence

of triethylamine, prolonged reflux (> 50 h.) in DMF leads to resinification of the reaction mass.

3.2 Virtual Screening

For all received compounds virtual screening by means of program PASS developed in IBMKh the Russian Academy of Medical Science (Moscow <http://www.pharmaexpert.ru/PASSOnline/>) is carried out. Computer forecasting has foretold with the probability exceeding 70% that compound 4a will 5-hydroxytryptamine release stimulant, antihypoxic, compound 4b, 5-hydroxytryptamine release stimulant, antineurotic, compound 4c, antineurotic, phobic disorders treatment, compound 4d, 5-hydroxytryptamine release stimulant.

4. Conclusions

It is established that the interaction of tryptamines with N-cyanoimido-S,S-dimethyldithiocarbonates in boiling ethanol proceeds of abnormally with elimination one molecule of methylmercaptan, further cyclization passes not through the expected cleavage of the second molecule of methyl mercaptan, and the accession of the hydrogen atom located on the carbon atom of the indole ring to the nitrogen atom of the imide group and a circuit carbon-carbon bond formation with polyfunctional 6-R-[1(methylthio)-2,3,4,9-tetrahydro-1H-β-carbolin-1-yl] cyanamides, not (6-R-2,3,4,9-tetrahydro-1H-β-carbolin-1-ylidene) cyanamides.

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784 **The synthesis of 6-R-[1(Methylthio)-2,3,4,9-Tetrahydro-1H- β -Carbolin-1-yl]Cyanamides by the Interaction of Tryptamines with N-Cyanoimido-S,S-Dimethyldithiocarbonate**

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