SYNTHESIS AND PROPERTIES OF PARTIALLY HYDROGENATED ETHYL ([3,4']BIPYRIDIN-6'-YLSULFANYL) ACETATES

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Ethyl 2'-hydroxy-1',2',3',4'-tetrahydro[3,4']bipyridine-3'-carboxylate **3** and the corresponding ethyl 1',4'-dihydro[3,4']bipyridine-3'-carboxylate **4** as potential cardiovascular agents have been prepared by alkylation of 2'-hydroxy-1',2',3',4'-tetrahydro[3,4']bipyridine-6'-thiolate **1** or betaine **2** with ethyl bromoacetate. The treatment of [3,4']bipyridine **4** with KOH/H₂O gave diethyl 3-amino-4-(pyridin-3-yl)-4,7-dihydrothieno[2,3-*b*]-pyridine-2,5-dicarboxylate **5**, but subsequent treatment of the remaining reaction mixture with acetic acid excess gave ethyl 3-oxo-7-(pyridin-3-yl)-2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine-6-carboxylate **7** – the product of intramolecular acylation. Compounds **4**, **5** and **7** have been prepared using the one-pot synthesis method. Alkylation of [3,4']bipyridine **4** with iodomethane gave 1',4'-dihydro[3,4']bipyridin-1-ium iodide **8**.

Key words: [3,4']bipyridine, piperidinium pyridine-6-thiolate, 7H-thiazolo[3,2-*a*]pyridine, thieno[2,3-*b*]pyridine, [3,4']bipyridin-1-ium iodide.

INTRODUCTION

6-Alkylsulfanyl-1,4-dihydropyridines (DHPs) display antihypertensive and vasodilating [1–3], hepatoprotective [4], antioxidant [5], and antiradical [6] activities, however, the biological activities of these compounds in comparison with DHPs not containing sulfur atom are still insufficiently studied.

On the other hand, [3,4']bipyridines are of interest as cardiogenic agents [7] for more than 25 years. Among them milrinone, phosphodiesterase III inhibitor, is non-catecholamine, non-glycoside drug that is not associated with β -adrenergic receptors or plasma catecholamine concentrations [8–10]. Recently compounds and pharmaceutical compositions for treatment of myosin heavy chain mediated diseases, and in particular, heart failure, have been found in series of 3-acetyl-6-benzoylsulfanyl-1,4-DHPs [11]. The potential cardiogenics – 1',4'-dihydro[3,4']bipyridines bearing carbamoylmethylsulfanyl substituent in position 6' appeared to be not enough soluble and lipophilic [12].

To improve cardiovascular activity of the low-toxic 4-aryl-5-cyano-2-methyl-6-methylsulfanyl-1,4-DHP-3-carboxylates [3], lipophilicity was optimized by introducing another ester group in the 1,4-DHP molecule [13], which is in agreement with general observations for DHPs series [14].

Partially hydrogenated ethyl (5'-ethoxycarbonyl[3,4']bipyridin-6'-ylsulfanyl) acetates bearing two ester groups could be interesting from this point of view as potential cardiogenics.

EXPERIMENTAL

Melting points were determined on a *Boetius* apparatus and were used uncorrected. IR spectra were recorded on a *Perkin-Elmer 580 B* spectrometer

(in nujol) and peak positions $\nu_{\max}$ were measured in cm^{-1} . NMR spectra were recorded on a *Varian Mercury 200* spectrometer using hexamethyldisiloxane (HMDSO) as internal standard. The course of the reactions and the individuality of substances were monitored by TLC on Kieselgel 60 F Merck plates with dichloromethane – hexane – acetone (2:1:1) as eluent. Synthesis of piperidinium 1',2',3',4'-tetrahydrobipyridine-6'-thiolate **1** (yield 72%) and betaine **2** (yield 80%) is described in [12]. Compounds were recrystallized from ethanol.

Ethyl 5'-cyano-6'-ethoxycarbonylmethylsulfanyl-2'-hydroxy-2'-phenyl-1',2',3',4'-tetrahydro[3,4]bipyridine-3'-carboxylate (3**)**

Mixture of piperidinium 1',2',3',4'-tetrahydrobipyridine-6'-thiolate **1** [12] (4.67 g, 10 mmol) and ethyl bromoacetate (1.10 ml, 10 mmol) in 20 ml of ethanol was shortly heated until dissolution, stirred for 30 min at ambient temperature, and water (2 ml) was added. The precipitate was filtered, washed with ethanol (5 ml) and water (20 ml) to give 3.83 g (82%) of compound **3** as colourless powder; mp 172–174 °C. IR spectrum, ν , cm^{-1} : 1700, 1738 (C=O); 2201 (C≡N); 3282, 3456 (NH, OH); ^1H NMR spectrum (DMSO- d_6 ; δ , ppm): 0.40 and 3.35 (5H, t and q, $J = 7.0$ Hz, 3'-COOEt); 1.17 and 4.11 (5H, t and q, $J = 7.0$ Hz, 6'-SCH₂COOEt); 2.90 and 4.12 (2H, d and d, $J = 12.1$ Hz, 3'-H and 4'-H); 3.86 and 3.97 (2H, d and d, $J = 15.7$ Hz, SCH₂); 6.49 (1H, s, OH); 7.27–8.40 (9H, m, 2'-C₆H₅ and 2-, 4-, 5- and 6-H); 8.08 (1H, s, NH). Found, %: C 61.30; H 5.44; N 8.83; S 6.72. Calculated for C₂₄H₂₅N₃O₅S, %: C 61.66; H 5.39; N 8.99; S 6.86.

One-pot reactions of betaine **2** with ethyl bromoacetate, potassium hydroxide and acetic acid

To the suspension of betaine **2** [12] (3.63 g, 10 mmol) in 10 ml of ethanol, piperidine (1.0 ml, 10 mmol) and ethyl bromoacetate (1.10 ml, 10 mmol) were added, the mixture was shortly heated until dissolution, stirred for 30 min at ambient temperature, and water (20 ml) was added. The reaction mixture was treated with 10 ml of 2 *N* potassium hydroxide solution, refluxed for 5 min, cooled to ~ 0 °C and precipitate was filtered, washed with ethanol (5 ml) and water (20 ml) to give 0.55 g (12%) of **diethyl 3-amino-6-phenyl-4-(pyridin-3-yl)-4,7-dihydrothieno[2,3-*b*]pyridine-2,5-dicarboxylate (5)** as slightly yellow powder; mp 200–203 °C. IR spectrum, ν , cm^{-1} : 1650, 1660 (C=O); 3320, 3460 (NH, NH₂); ¹H NMR spectrum (DMSO-*d*₆; δ , ppm): 0.63 and 3.61 (5H, t and q, *J* = 7.0 Hz, 5-COOEt); 1.13 and 4.05 (5H, t and q, *J* = 7.0 Hz, 2-COOEt); 5.16 (1H, s, 4-H); 6.38 (2H, s, NH₂); 7.24–8.60 (9H, m, 6-C₆H₅ and 4-C₅H₄N); 10.05 (1H, s, NH). Found, %: C 63.70; H 5.27; N 9.20; S 7.28. Calculated for C₂₄H₂₃N₃O₄S, %: C 64.13; H 5.16; N 9.35; S 7.13.

The remaining reaction mixture was refluxed for 5 min with 2 ml of acetic acid, cooled to ~ 10 °C and precipitate was filtered, washed with ethanol (5 ml) and water (20 ml) to give 1.05 g (23%) of **ethyl 5'-cyano-6'-ethoxycarbonylmethylsulfanyl-2'-phenyl-1',4'-dihydro-[3,4']bipyridine-3'-carboxylate (4)** as slightly yellow powder; mp 128–129 °C. IR spectrum, ν , cm^{-1} : 1684, 1735 (C=O); 2198 (C≡N); 3148, 3240 (NH); ¹H NMR spectrum (DMSO-*d*₆; δ , ppm): 0.65 and 3.65 (5H, t and q, *J* = 7.0 Hz, 3'-COOEt); 1.14 and 4.07 (5H, t and q, *J* = 7.0 Hz, 6'-SCH₂COOEt); 3.79 and 4.05 (2H, d and d, *J* = 15.3 Hz, SCH₂); 4.58 (1H, s, 4'-H); 7.27–8.46 (9H, m, 2'-C₆H₅ and 2-, 4-, 5- and 6-H); 9.98 (1H, s, NH). Found, %: C 63.90; H 5.14; N 9.27; S 7.18. Calculated for C₂₄H₂₃N₃O₄S, %: C 64.13; H 5.16; N 9.35; S 7.13.

The remaining second filtrate was refluxed for 5 h with 2 ml of acetic acid, cooled to ~ 10 °C and precipitate was filtered, washed with ethanol (5 ml) to give 0.20 g (5%) of **ethyl 8-cyano-3-oxo-5-phenyl-7-(pyridin-3-yl)-2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine-6-carboxylate (7)** as slightly yellow powder; mp 168–170 °C [15]. IR spectrum, ν , cm^{-1} : 1672, 1757 (C=O); 2206 (C≡N); ¹H NMR spectrum (DMSO-*d*₆; δ , ppm): 0.53 and 3.52 (5H, t and q, *J* = 7.0 Hz, 6-COOEt); 3.97 and 4.04 (2H, d and d, *J* = 17.2 Hz, 2-CH₂); 4.80 (1H, s, 7-H); 7.24–8.54 (9H, m, 5-C₆H₅ and 7-C₅H₄N).

Treatment of pure ethyl 5'-cyano-6'-ethoxycarbonylmethylsulfanyl-2'-phenyl-1',4'-dihydro[3,4']bipyridine-3'-carboxylate (4) with KOH

Mixture of carboxylate **4** (0.31 g, 0.69 mmol) and KOH (0.04 g, 0.71 mmol) in 10 ml of absolute ethanol was refluxed for 5 min, cooled to ~ 10 °C and precipitate was filtered, washed with ethanol (2 ml) and water (10 ml) to give 0.24 g (79%) of **diethyl 4,7-dihydrothieno[2,3-*b*]pyridine-2,5-dicarboxylate (5)**.

5'-Cyano-3'-ethoxycarbonyl-6'-ethoxycarbonylmethylsulfanyl-1-methyl-2'-phenyl-1',4'-dihydro[3,4']bipyridin-1-ium iodide (8)

Mixture of 1',4'-dihydro-[3,4']bipyridine-3'-carboxylate **4** (0.23 g, 0.5 mmol) and iodomethane (0.62 ml, 10 mmol) in 10 ml of acetone was refluxed for 5 h, the reaction mixture was evaporated to dry and treated with 10 ml of ethanol. The precipitated crystals were filtered to give 0.22 g (74%) of **1-methyl-1',4'-**

dihydro[3,4']bipyridin-1-ium iodide 8 as yellow powder; mp 95–98 °C. IR spectrum, ν , cm^{-1} : 1635, 1676, 1720 (C=O); 2201 (C $\equiv$ N); 3250 (NH). ^1H NMR spectrum (DMSO- d_6 ; δ , ppm): 0.64 and 3.66 (5H, t and q, J = 7.0 Hz, 3'-COOEt); 1.15 and 4.09 (5H, t and q, J = 7.0 Hz, 6'-SCH $_2$ COOEt); 3.82 and 4.08 (2H, d and d, J = 15.3 Hz, SCH $_2$); 4.35 (3H, s, 1-Me); 4.90 (1H, s, 4'-H); 7.32–8.87 (9H, m, 2'-C $_6$ H $_5$ and 4-C $_6$ H $_4$ N); 10.16 (1H, s, NH). Found, %: C 50.31; H 4.16; N 6.87. Calculated for C $_{25}$ H $_{26}$ IN $_3$ O $_4$ S, %: C 50.77; H 4.43; N 7.10.

RESULTS AND DISCUSSION

In continuation of search for biologically active compounds, we have synthesized new [3,4']bipyridines – ethyl 6'-ethoxycarbonylmethylsulfanyl-1',2',3',4'-tetrahydro-[3,4']bipyridine-3'-carboxylate **3**, the corresponding 1',4'-dihydro[3,4']bipyridine **4** and investigated their transformations by treatment with KOH, acetic acid and iodomethane.

Piperidinium 5'-cyano-3'-ethoxycarbonyl-2'-hydroxy-2'-phenyl-1',2',3',4'-tetrahydro[3,4']bipyridine-6'-thiolate (**1**) has been obtained by three-component condensation of ethyl benzoylacetate, 3-pyridinecarboxaldehyde, 2-cyanothioacetamide and piperidine with 72% yield [12]. It is worth to mention that application of N-methylmorpholine instead of piperidine leads to the corresponding 1',4'-dihydrobipyridine-6'-thiolate [16]. Alkylation of 2'-hydroxy-1',2',3',4'-tetrahydro[3,4']bipyridine-6'-thiolate **1** bearing many nucleophilic reaction centres (O, S, N(1), N(1') and C(5')) under mild reaction conditions with ethyl bromoacetate proceeds preferably at the sulfur atom giving rise to ethyl 5'-cyano-6'-ethoxycarbonylmethylsulfanyl-2'-hydroxy-2'-phenyl-1',2',3',4'-tetrahydro[3,4']bipyridine-3'-carboxylate (**3**).

Usually, the corresponding 1,4-dihydropyridines are easily prepared by dehydration of 2-hydroxy-1,2,3,4-tetrahydropyridines, but treatment of 2'-hydroxy-1',2',3',4'-tetrahydro[3,4']bipyridine **3** with HCl/EtOH similarly as mentioned in [17] leads to the complicated reaction mixture, which contains products of ring cleavage and hydrolysis. By treatment of bipyridine **3** with KOH/H $_2$ O, the desired 6-hydroxy-4,5,6,7-tetrahydrothieno[2,3-*b*]pyridine **6** was not isolated from the complicated reaction mixture.

Alkylation of betaine **2** [12] (prepared by treatment of 1',2',3',4'-tetrahydrobipyridine-6'-thiolate **1** with HCl/EtOH) with ethyl bromoacetate in the presence of stoichiometric amount of piperidine gave crude ethyl 6'-ethoxycarbonylmethylsulfanyl-1',4'-dihydro[3,4']bipyridine-3'-carboxylate **4** which did not crystallize from reaction mixture. The treatment of the latter with KOH/H $_2$ O gave the desired diethyl 3-amino-6-phenyl-4-(pyridin-3-yl)-4,7-dihydrothieno[2,3-*b*]pyridine-2,5-dicarboxylate (**5**) with 12% yield (79% yield of compound **5** was reached, when pure 1',4'-dihydrobipyridine **4** was used), but subsequent treatment of the remaining reaction mixture with acetic acid gave pure 1',4'-dihydrobipyridine **4** (5 min reflux) and the product of intramolecular acylation – ethyl 8-cyano-3-oxo-5-phenyl-7-(pyridin-3-yl)-2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine-6-carboxylate (**7**) (5 h reflux). By treatment of ethyl 1',4'-dihydro[3,4']bipyridine-3'-carboxylate **4** with iodomethane in dry acetone, dihydro[3,4']bipyridinium salt **8** was formed. The low yield of 1',4'-dihydrobipyridine **4** (complicated isolation) in the case when betaine **2** was treated with stoichiometric amount of ethyl bromoacetate is, obviously, explained by competitive alkylation both at S atom and N(1) atom of the pyridine ring.

The structures of the synthesized compounds were confirmed by spectroscopic methods. In the IR spectra, the characteristic absorption bands of C≡N group are observed for 1',2',3',4'-tetrahydrobipyridine **3**, 1',4'-dihydrobipyridines **4**, **8** and 7H-thiazolo[3,2-*a*]pyridine **7** at 2198–2206 cm⁻¹. Absorption bands of C=O groups of the compounds **3-5** and **7** are in agreement with the type of conjugation of C=O groups. The doublets in the ¹H NMR spectrum of compound **3** with $J_{3,4} = 12.1$ Hz according to [18] confirm *trans*-diaxial configuration of the 3'-H and 4'-H protons. In the case of 1',4'-dihydrobipyridines **4**, **8**, 4,7-dihydrothieno[2,3-*b*]pyridine **5** and 7H-thiazolo[3,2-*a*]pyridine **7**, the characteristic 4'-H, 4-H or 7-H proton signals at 4.58–5.18 ppm are observed.

CONCLUSIONS

Ethyl 5'-cyano-6'-ethoxycarbonylmethylsulfanyl-2'-hydroxy-2'-phenyl-1',2',3',4'-tetrahydro[3,4']bipyridine-3'-carboxylate (**3**) and the corresponding ethyl 1',4'-dihydro[3,4']bipyridine-3'-carboxylate (**4**) as potential cardiovascular agents have been prepared by alkylation of 2'-hydroxy-1',2',3',4'-tetrahydro[3,4']bipyridine-6'-thiolate **1** or betaine **2** with ethyl bromoacetate. The treatment of ethyl 5'-cyano-6'-ethoxycarbonylmethylsulfanyl-2'-phenyl-1',4'-dihydro[3,4']bipyridine-3'-carboxylate (**4**) with KOH/H₂O gave diethyl 3-amino-6-phenyl-4-(pyridin-3-yl)-4,7-dihydrothieno[2,3-*b*]pyridine-2,5-dicarboxylate (**5**), but subsequent treatment of the remaining reaction mixture with acetic acid excess gave ethyl 8-cyano-3-oxo-5-phenyl-7-(pyridin-3-yl)-2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine-6-carboxylate (**7**) – the product of intramolecular acylation. Compounds **4**, **5** and **7** have been prepared by making use of one-pot synthesis method. Alkylation of [3,4']bipyridine **4** with iodomethane gave 1',4'-dihydro[3,4']bipyridin-1-ium iodide **8**.

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DAĻĒJI HIDRĒTO ([3,4']BIPIRIDĪN-6'-ILSULFANIL)ETIĶSKĀBES ETILESTERU SINTĒZE UN ĪPAŠĪBAS

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K O P S A V I L K U M S

5'-Ciano-6'-etoksikarbonilmetilsulfanil-2'-fenil-2'-hidroksi-1',2',3',4'-tetrahydro-[3,4']bipiridīn-3'-karbonskābes etilesteris (**3**) un atbilstošais 1',4'-dihidro[3,4']bipiridīn-3'-karbonskābes etilesteris (**4**) kā potenciāli kardiovaskulārie aģenti iegūti, alkilējot 2'-hidroksi-1',2',3',4'-tetrahydro[3,4']bipiridīn-6'-tiolātu (**1**) vai betaīnu **2** ar brometiķskābes etilesteri. Iedarbojoties uz 5'-ciano-6'-etoksikarbonilmetilsulfanil-2'-fenil-1',4'-dihidro[3,4']bipiridīn-3'-karbonskābes etilesteri (**4**) ar KOH/H₂O, iegūts 3-amino-6-fenil-4-(piridīn-3-il)-4,7-dihidrotiēno[2,3-*b*]-piridīn-2,5-dikarbonskābes dietilesteris (**5**), bet reakcijas atlikumu vārot 5 stundas etiķskābē, iegūts 8-ciano-5-fenil-3-okso-7-(piridīn-3-il)-2,3-dihidro-7H-tiazolo[3,2-*a*]piridīn-6-karbonskābes etilesteris (**7**), kas ir savienojuma **4** iekšmolekulārās acilēšanas produkts. Savienojumi **4**, **5** un **7** iegūti, lietojot vienreaktora sintēzes metodi. Alkilējot [3,4']bipiridīnu (**4**) ar jodmetānu, iegūts attiecīgais 5'-ciano-3'-etoksikarbonil-6'-etoksikarbonilmetilsulfanil-2'-fenil-1-metil-1',4'-dihidro[3,4']bipiridīn-1-ija jodīds (**8**).