

SYNTHESIS OF 4,6-DISUBSTITUTED THIENO[2,3-*d*]PYRIMIDINES FROM 4,6-DICHLORO-2-METHYLTHIOPYRIMIDINE-5-CARBALDEHYDE

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Abstract. Treatment of 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde (**1**) with (1*H*-benzimidazol-2-yl)methanethiol afforded 6-(1*H*-benzimidazol-2-yl)-4-chloro-2-methylthiothieno[2,3-*d*]pyrimidine (**2**). Reaction of **1** with ethyl mercaptoacetate depending on its amount gave ethyl (4-chloro-2-methylthio-5-formylpyrimidin-6-ylthio)acetate (**4**) or 4,6-bis(ethoxycarbonylmethylthio)pyrimidine-5-carbaldehyde (**5**). Heating **4**, **5** in dimethyl sulfoxide or ethanol in the presence of base afforded ethyl 4-oxo-3,4-dihydro- (**6**) and 4-ethoxycarbonylmethylthiothieno[2,3-*d*]pyrimidine-6-carboxylates (**7**), respectively. 4-Dialkylamino-6-chloro-2-methylthiopyrimidine-5-carbaldehydes (**8a,b**) obtained from **1** and dialkylamines, underwent the displacement/cyclisation reaction with ethyl mercaptoacetate to give the appropriate ethyl thieno[2,3-*d*]pyrimidine-6-carboxylates (**9a,b**), which were converted to the corresponding acids **10a,b**, hydrazides **11a,b** and (thieno[2,3-*d*]pyrimidin-6-yl)methanols **12a,b**.

Introduction

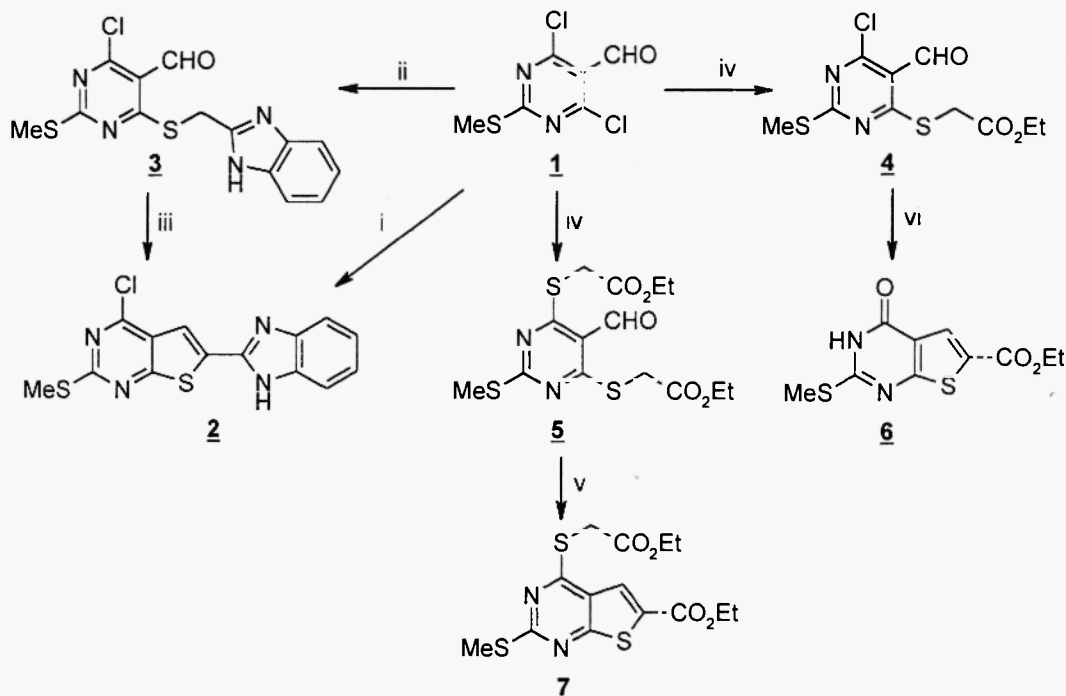
Thieno[2,3-*d*]pyrimidines and tri- and tetracyclic compounds containing the thienopyrimidine system are a subject of chemical and biological studies due to their interesting pharmacological properties. Such derivatives inhibit platelet aggregation (1, 2), show antihypertensive (3, 4), antiinflammatory (5, 6), anticancer (7), antiviral (8) activities and are potential antifolates (9, 10). To the best of our knowledge, however, there are only few literature reports about the synthesis of thieno[2,3-*d*]pyrimidines from pyrimidine-5-carbaldehydes (11,12). Moreover, a survey on thieno[2,3-*d*]pyrimidine-6-carboxylates revealed that chemical properties of these compounds have been studied insufficiently. In this context and as continuation of our studies in the synthesis of the thieno[2,3-*d*]pyrimidine moiety containing heterocycles (13-16) it was of interest to study the interaction of the easily available 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde **1** (17) with (1*H*-benzimidazol-2-yl)methanethiol (18) and ethyl mercaptoacetate, and to prepare new 4,6-disubstituted 2-methylthiothieno[2,3-*d*]pyrimidine derivatives with potential biological activity. The work was also stimulated by the reports that similar derivatives of thienopyrimidines exhibit the valuable pharmacological properties (19, 20).

Results and Discussion

Treatment of carbaldehyde **1** with one equivalent of (benzimidazol-2-yl)methanethiol at 50°C in DMF gave 6-(benzimidazol-2-yl)thienopyrimidine **2** (Scheme 1). The formation of thienopyrimidine **2** was a rather

unexpected result, because such type of cyclisation usually requires the presence of base. To prove the reaction pathway and the structure of **2**, we tried to obtain the reaction intermediate. Performing the reaction at room temperature allowed to isolate the benzimidazolymethylthio derivative **3**, which appeared to be rather unstable. Already under the crystallization conditions it partially underwent cyclocondensation to give thienopyrimidine **2**. Full conversion of **3** into **2** was achieved by heating **3** in 2-propanol for 4 h.

Scheme 1

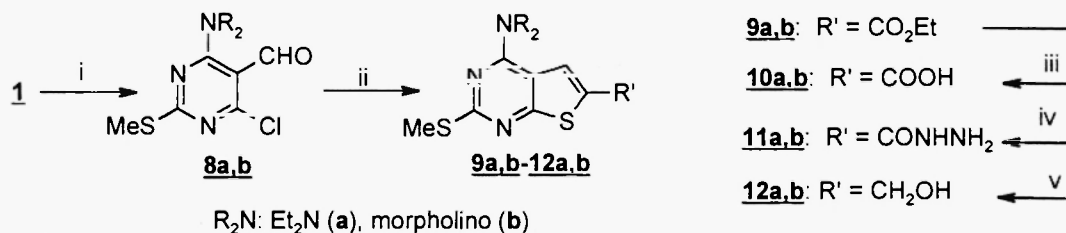


Reagents and conditions: i - (benzimidazol-2-yl)methanethiol, DMF, 50°, ii - (benzimidazol-2-yl)methanethiol, Me₂CHOH, r.t.; iii - Me₂CHOH, Δ; iv - HSCH₂CO₂Et, Et₃N, EtOH, r.t.; v - EtOH, Et₃N, 50°; vi - K₂CO₃, DMSO, 50°;

In the reaction of **1** with ethyl mercaptoacetate at room temperature in the presence of triethylamine the replacement of one or two chloro atoms depending on the amount of ethyl mercaptoacetate took place and the appropriate compounds **4**, **5** were formed. Carbaldehydes **4** and **5** under basic conditions underwent a cyclodehydration reaction at 50 °C to give thienopyrimidines **6**, **7**. Nevertheless, it should be noted that the cyclodehydration reaction of **4** was accompanied by hydrolysis at the position 4 to give 4-oxothienopyrimidine **6**. To synthesise some 4-(substituted amino)-2-methylthiothieno[2,3-d]pyrimidine-6-carboxylic acids esters **9a,b** and compounds derived from them, the reaction of **1** with diethylamine or morpholine and subsequent tandem displacement/annulation of the obtained 4-dialkylaminopyrimidines **8a,b** with ethyl mercaptoacetate were carried out (Scheme 2). Esters **9a,b** were hydrolysed with ethanolic KOH at room temperature to the corresponding acids **10a,b**. To our surprise the ester group in compounds **9a,b** appeared to be rather inert towards the nitrogen nucleophiles. We did not succeed to obtain the corresponding amides by the reaction of esters **9a,b** with diethylamine, aniline or 4-methoxyaniline. Only the prolonged reflux of esters **9a,b** with an excess of hydrazine hydrate in ethanol gave hydrazides **11a,b**.

Reduction of esters **9a,b** with lithium aluminium hydride afforded the corresponding (thienopyrimidin-6-yl)methanols **12a,b** in good yields.

Scheme 2



Reagents and conditions: i - R₂NH, MeOH, r.t.; ii - HSCH₂CO₂Et, Et₃N, EtOH, Δ; iii - KOH, EtOH, H₂O, r.t.; iv - N₂H₄ · H₂O, EtOH, Δ; v - LiAlH₄, Et₂O.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were run in Nujol mulls on a Perkin-Elmer FT spectrophotometer Spectrum BX II. ¹³C NMR spectra were recorded on Tesla 587A spectrometer, ¹H NMR spectra - on Tesla 587A or Bruker AC-300 spectrometers using tetramethylsilane as internal standard. Chemical shifts are expressed in δ, ppm. Mass spectrum of compound **2** was measured on a Kratos MS 30 spectrometer using an ionising energy of 70 eV and introduction by direct insertion probe. All reactions and purity of the synthesized compounds were monitored by TLC using Silica gel 60 F₂₅₄ aluminium plates (Merck). Visualization was accomplished by UV light.

6-(1H-Benzimidazol-2-yl)-4-chloro-2-methylthiothieno[2,3-d]pyrimidine (2). Method A. A solution of **1** (1.36 g, 6.1 mmol) and (1H-benzimidazol-2-yl)methanethiole (1 g, 6.1 mmol) in 20 ml DMF was heated at 50°C for 4 h. After cooling to room temperature the precipitate was filtered off and recrystallised to give 1.06 g (52%) of **2**, mp 290-292°C (from DMF).

Method B. A solution of **3** (0.11 g, 0.3 mmol) in 5 ml of 2-propanol was refluxed under stirring for 4 h. After cooling to room temperature the precipitate was filtered off and recrystallised from DMF to give 0.05 g (50%) of **2**, mp 290-292 °C (from DMF). IR: 3364 cm⁻¹ (NH). ¹H NMR (300 MHz, DMSO-d₆): 2.63 (3H, s, SCH₃), 7.20-7.44 (2H, m, 5'- and 6'-H), 7.52-7.75 (2H, m, 4'- and 7'-H), 8.04 (1H, s, 5-H), 13.34 (1H, br.s, NH). MS, *m/z* (%): 332 (M⁺, 100). Anal. calcd. for C₁₄H₉ClN₄S₂: C 50.52; H 2.73, N 16.83. Found: C 50.40; H 2.70; N 16.72.

4-(1H-Benzimidazol-2-yl)methylthio-6-chloro-2-methylthiopyrimidine-5-carbaldehyde (3).

A mixture of **1** (0.22 g, 1 mmol) and (1H-benzimidazol-2-yl)methanethiol (0.16 g, 1 mmol) in 10 ml of 2-propanol was kept for 4 days at ambient temperature. Then the reaction mixture was concentrated without heating on a rotary evaporator to 3 ml. The precipitate was filtered off and washed with a small amount of 2-propanol to give 0.11 g (32%) of **3**, mp 180°C (dec.). Compound **3** was used for the synthesis of **2** without further purification. IR: 1672 (CO), 3332 cm⁻¹ (NH). ¹H NMR (80 MHz, DMSO-d₆): 2.41 (3H, s, SCH₃), 5.01 (2H, s, SCH₂), 7.16-7.45 (2H, m, 5'- and 6'-H), 7.48-7.75 (2H, m, 4'- and 7'-H), 10.36 (1H, s, CHO).

Ethyl (4-chloro-5-formyl-2-methylthiopyrimidin-6-ylthio)acetate (4). To a solution of **1** (1 g, 4.5 mmol) and ethyl mercaptoacetate (0.54 g, 4.5 mmol) in 5 ml of ethanol triethylamine (0.45 g, 4.5 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 20 min. The precipitate was

filtered off, washed with water and recrystallised to give 0.64 g (46%) of **4**, mp 96-98 °C (from 2-propanol). IR: 1670, 1721 cm⁻¹ (CO). ¹H NMR (80 MHz, CDCl₃): 1.29 (3H, t, *J* = 6 Hz, CH₂CH₃), 2.60 (3H, s, SCH₃), 3.91 (2H, s, SCH₂), 4.22 (2H, q, *J* = 6 Hz, CH₂CH₃), 10.43 (1H, s, CHO). ¹³C NMR (20.082 MHz, CDCl₃): 14.05 (SCH₃), 14.3 (CH₃), 32.9 (SCH₂), 61.7 (OCH₂), 117.9 (C₅), 162.9 (C₄), 168.1 (CO), 172.2 (C₂), 175.1 (C₆), 187.4 (CHO). Anal. Calcd. for C₁₀H₁₁ClN₂O₃S₂: C 39.15; H 3.61, N 9.13. Found: C 39.49; H 3.21; N 9.27.

4,6-Bis(ethoxycarbonylmethylthio)-2-methylthiopyrimidine-5-carbaldehyde (5) was synthesised according to the procedure described for compound **4** with a difference that 2 equivalents of each of ethyl mercaptoacetate and triethylamine were used. The reaction time 30 min. Yield 55%, mp 80-82 °C (from 2-propanol). IR: 1677, 1738 cm⁻¹ (CO). ¹H NMR (80 MHz, CDCl₃): 1.27 (6H, t, *J* = 6 Hz, CH₂CH₃), 2.53 (3H, s, SCH₃), 3.93 (4H, s, SCH₂), 4.21 (4H, q, *J* = 6 Hz, CH₂CH₃), 10.37 (1H, s, CHO). Anal. Calcd. for C₁₄H₁₈N₂O₅S₃: C 43.06; H 4.65, N 7.17. Found: C 43.35; H 4.58; N 7.45.

Ethyl 2-methylthio-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylate (6). A mixture of **4** (0.3 g, 0.98 mmol), 10 ml DMSO and K₂CO₃ (0.08 g, 0.58 mmol) was stirred at 50 °C for 11 h. The precipitate was filtered off and recrystallised to give 0.13 g (50%) of **6**, mp 198-200 °C (from DMF-water). IR: 1679, 1715 cm⁻¹ (CO). ¹H NMR (80 MHz, DMSO-*d*₆): 1.34 (3H, t, *J* = 7 Hz, CH₂CH₃), 2.58 (3H, s, SCH₃), 4.33 (2H, q, *J* = 7 Hz, CH₂CH₃), 7.87 (1H, s, 5-H). Anal. Calcd. for C₁₀H₁₀N₂O₃S₂: C 44.43; H 3.73; N 10.36. Found: C 44.59; H 4.02; N 10.17.

Ethyl 4-ethoxycarbonylmethylthio-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylate (7). To a mixture of **5** (1 g, 2.56 mmol) in 15 ml of ethanol triethylamine (0.26 g, 2.57 mmol) was added dropwise. The reaction mixture was stirred at 50 °C for 3 h. The precipitate was filtered off, washed with water and recrystallised to give 0.7 g (73%) of **7**, m.p. 96-99 °C (from 2-propanol). IR: 1715, 1736 cm⁻¹ (CO). ¹H NMR (80 MHz, CDCl₃): 1.31 (3H, t, *J* = 6 Hz, CH₂CH₃), 1.42 (3H, t, *J* = 6 Hz, CH₂CH₃), 2.62 (3H, s, SCH₃), 4.10 (2H, s, SCH₂), 4.25 (2H, q, *J* = 6 Hz, CH₂CH₃), 4.43 (2H, q, *J* = 6 Hz, CH₂CH₃), 7.95 (1H, s, 5-H). ¹³C NMR (20.082 MHz, CDCl₃): 14.05 (SCH₃), 14.2 (2CH₃), 31.6 (SCH₂), 61.9 (2OCH₂), 123.6 (C_{4a}), 124.6 (C₆), 130.5 (C₅), 161.6 (2CO), 164.15 (C₂), 167.98 (C_{7a}), 168.9 (C₄). Anal. Calcd. for C₁₄H₁₆N₂O₄S₃: C 45.14; H 4.33; N 7.52. Found: C 45.40; H 4.17; N 7.45.

4-Dialkylamino-6-chloro-2-methylthiopyrimidine-5-carbaldehydes (8a,b). To a mixture of **1** (2 g, 9 mmol) in 20 ml of methanol the corresponding amine (17.9 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature, the precipitate was filtered off, washed with water. The filtrate was concentrated to 1/3 of the initial volume and poured to water. The precipitate was filtered off, combined with the earlier obtained and recrystallised to give compounds **8a,b**.

8a: Yield 74%, (yellow oil). The reaction time 50 min. Compound **8a** without further purification was used in the next step. IR: 1674 cm⁻¹ (CO). ¹H NMR (80 MHz, CDCl₃): 1.25 (6H, t, *J* = 7.6 Hz, CH₃), 2.47 (3H, s, SCH₃), 3.53 (4H, q, *J* = 7.6 Hz, NCH₂), 10.18 (1H, s, CHO).

8b: Yield 75%, mp 132-133 °C (from 2-propanol). The reaction time 2.5 h. IR: 1669 cm⁻¹ (CO). ¹H NMR (80 MHz, CDCl₃): 2.52 (3H, s, SCH₃), 3.52-3.92 (8H, m, NCH₂, OCH₂), 10.20 (1H, s, CHO). Anal. Calcd. for C₁₀H₁₂ClN₃O₂S: C 43.88; H 4.42; N 15.35. Found: C 43.84; H 4.20; N 15.51.

Ethyl 4-dialkylamino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylates (9a,b). To a mixture of the corresponding aldehyde **8a,b** (3 mmol) and ethyl mercaptoacetate (0.4 g, 3.3 mmol) in 10 ml of ethanol

triethylamine (0.61 g, 6 mmol) was added dropwise. The reaction mixture was refluxed for 10 h (for the synthesis of **9a**) or 6 h (for the synthesis of **9b**). After cooling to room temperature the precipitate was filtered off and recrystallised to give compounds **9a,b**.

9a: Yield 64%, mp 118-119 °C (from 2-propanol). IR: 1706 cm⁻¹ (CO). ¹H NMR (80 MHz, CDCl₃): 1.33 (6H, t, *J* = 7 Hz, CH₃), 1.39 (3H, t, *J* = 6 Hz, CH₃), 2.55 (3H, s, SCH₃), 3.76 (4H, q, *J* = 7 Hz, NCH₂), 4.37 (2H, q, *J* = 6 Hz, CH₂CH₃), 7.98 (1H, s, 5-H). Anal.Calcd. for C₁₄H₁₉N₃O₂S₂: C 51.67; H 5.88; N 12.91. Found: C 51.37; H 6.15; N 12.96.

9b: Yield 58%, mp 112-113 °C (from 2-propanol). IR: 1711 cm⁻¹ (CO). ¹H NMR (80 MHz, CDCl₃): 1.41 (3H, t, *J* = 6 Hz, CH₃), 2.57 (3H, s, SCH₃), 3.85-4.10 (8H, m, NCH₂, OCH₂), 4.39 (2H, q, *J* = 6 Hz, CH₂CH₃), 7.99 (1H, s, 5-H). ¹³C (20.082 MHz, CDCl₃): 14.2 (SCH₃), 14.3 (CH₃), 46.8 (2NCH₂), 61.6 (OCH₂), 66.4 (2CH₂O), 112.6 (C_{4a}), 125.5 (C₆), 127.15 (C₅), 157.75 (C₄), 162.1 (CO), 168.7 (C₂), 172.15 (C_{7a}). Anal.Calcd. for C₁₄H₁₇N₃O₃S₂: C 49.54; H 5.05; N 12.38. Found: C 49.31; H 5.16; N 12.28.

4-Dialkylamino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic acids (10a,b**)**. To a solution of KOH (0.1 g, 1.8 mmol) in 5 ml of ethanol and 2.5 ml H₂O the corresponding ester **9a,b** (0.6 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 16 h (for the synthesis of **10a**) or 4.5 h (for the synthesis of **10b**), then concentrated to 1/3 of the initial volume and acidified to pH = 2 with 10% hydrochloric acid. The precipitate was filtered off, washed with water and recrystallised to give compounds **10a,b**.

10a: Yield 55%, mp 220 °C (dec.) (from 2-propanol). IR: 1675 (CO), 3050 cm⁻¹ (OH). ¹H NMR (80 MHz, DMSO-*d*₆): 1.27 (6H, t, *J* = 7.6 Hz, CH₃), 2.52 (3H, s, SCH₃), 3.77 (4H, q, *J* = 7.6 Hz, NCH₂), 7.94 (1H, s, 5-H). Anal.Calcd. for C₁₂H₁₅N₃O₂S₂: C 48.46; H 5.08; N 14.13. Found: C 48.77; H 5.10; N 14.24.

10b: Yield 55%, mp > 255 °C (dec.) (from dioxane/2-propanol). IR: 1670 (CO), 3426 cm⁻¹ (OH). ¹H NMR (80 MHz, DMSO-*d*₆): 2.52 (3H, s, SCH₃), 3.79-3.94 (8H, m, NCH₂, OCH₂), 8.12 (1H, s, 5-H). ¹³C (20.082 MHz, DMSO-*d*₆): 13.7 (SCH₃), 46.1 (2NCH₂), 65.6 (2CH₂O), 112.3 (C_{4a}), 125.8 (C₆), 127.8 (C₅), 157.1 (C₄), 162.9 (CO), 167.6 (C₂), 171.1 (C_{7a}). Anal.Calcd. for C₁₂H₁₃N₃O₃S₂: C 46.29; H 4.21; N 13.49. Found: C 46.55; H 4.29; N 13.48.

Hydrazides of 4-dialkylamino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic acids (11a,b**)**. A mixture of the corresponding ester **9a,b** (0.9 mmol) and 99% hydrazine hydrate (0.9 g, 17.8 mmol) in 5 ml of ethanol was refluxed under stirring for 24 h (for the synthesis of **11a**) or 4 h (for the synthesis of **11b**). After cooling the precipitate was filtered off, washed with water and recrystallised to give compounds **11a,b**.

11a: Yield 84%, mp 170-172 °C (from ethanol). IR: 1602 (CO), 3178 cm⁻¹ (NH, NH₂). ¹H NMR (80 MHz, CDCl₃): 1.33 (6H, t, *J* = 7.6 Hz, CH₃), 2.57 (3H, s, SCH₃), 3.71-3.8 (6H, m, NCH₂, NH₂), 7.83 (1H, br.s, NH), 7.87 (1H, s, 5-H). Anal.Calcd. for C₁₂H₁₇N₅O₂S₂: C 46.28; H 5.50; N 22.49. Found: C 46.51; H 5.42; N 22.63.

11b: Yield 59%, mp 235-236.5 °C (from dioxane). IR 1649 (CO), 3313 cm⁻¹ (NH). ¹H NMR (80 MHz, CF₃COOD): 2.36 (3H, s, SCH₃), 3.84-4.04 (8H, m, NCH₂, OCH₂), 8.03 (1H, s, 5-H). Anal.Calcd. for C₁₂H₁₅N₅O₂S₂: C 44.29; H 4.65; N 21.52. Found: C 44.57; H 4.81; N 21.49.

(4-Dialkylamino-2-methylthiothieno[2,3-*d*]pyrimidin-6-yl)methanols (12a,b**)**. To a stirred mixture of LiAlH₄ (0.03 g, 0.79 mmol) in 15 ml of anhydrous diethyl ether the corresponding ester **9a,b** (1 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 5 h (for the synthesis of **12a**) or

refluxed for 5 h (for the synthesis of **12b**). Then water was added dropwise to the reaction mixture and an organic layer separated. Aqueous layer was extracted with chloroform (3x30 ml). Organic layers were combined, dried with Na₂SO₄ and evaporated to dryness. The residue was recrystallised to give compounds **12a,b**.

12a: Yield 71%, mp 124.5-125.5°C (from hexane/benzene). IR: 3246 cm⁻¹ (OH). ¹H NMR (80 MHz, CDCl₃): 1.29 (6H, t, *J* = 7 Hz, CH₃), 2.55 (3H, s, SCH₃), 3.40 (4H, q, *J* = 7 Hz, NCH₂), 4.82 (2H, s, CH₂), 7.05 (1H, s, 5-H). Anal. Calcd. for C₁₂H₁₇N₃OS₂: C 50.86; H 6.05; N 14.83. Found: C 50.99; H 5.89; N 14.69.

12b: Yield 74%, mp 130-132°C (from ethyl acetate). IR: 3399 cm⁻¹ (OH). ¹H NMR (80 MHz, CDCl₃): 2.55 (3H, s, SCH₃), 3.72-3.95 (8H, m, NCH₂, OCH₂), 4.84 (2H, s, CH₂), 7.09 (1H, s, 5-H). ¹³C (20.082 MHz, CDCl₃): 14.1 (SCH₃), 46.8 (2NCH₂), 60.3 (CH₂), 66.45 (2CH₂O), 112.7 (C_{4a}), 116.9 (C₅), 138.3 (C₆), 157.1 (C₄), 165.3 (C₂), 169.97 (C_{7a}). Anal. Calcd. for C₁₂H₁₅N₃O₂S₂: C 48.46; H 5.08; N 14.13. Found: C 48.62; H 5.15; N 14.07.

References

- (1) K. Kikugawa, M. Ichino, *Chem. Pharm. Bull.*, **21**, 1151 (1973).
- (2) F. Ishikawa, A. Kosasayama, H. Yamaguchi, Y. Watanabe, J. Saegusa, S. Shibamura, K. Sakuma, S. Ashida, Y. Abiko, *J. Med. Chem.*, **24**, 376 (1981).
- (3) R.K. Russel, J.B. Press, R.A. Rampulla, J. J. McNally, R. Falotico, J. A. Keiser, D. A. Bright, A. Tobia, *J. Med. Chem.*, **31**, 1786 (1988).
- (4) R. K. Russel, R. A. Rampulla, C. E. van Nieveit, D. H. Klaubert, *J. Heterocycl. Chem.*, **27**, 1761 (1990).
- (5) M. Modica, M. Santagati, A. Santagati, V. Cutuli, N. Mangano, A. Caruso, *Pharmazie*, **55**, 500 (2000).
- (6) Panico, V. Cardile, A. Santagati, B. Gentile, *Farmaco*, **56**, 959 (2001).
- (7) J. Katada, K. Iijima, M. Muramatsu, M. Takami, E. Yasuda, M. Hayashi, M. Hattori, Y. Hayashi, *Biorg. Med. Chem. Letters*, **9**, 797 (1999).
- (8) M. A. El-Sherbenyl, M. B. El-Ashmawy, H. I. El-Emam, F. A. Badria, *Eur. J. Med. Chem. Chim. Ther.*, **30**, 445 (1995).
- (9) E. C. Taylor, H. H. Patel, G. Sabitha, R. Chaudhari, *Heterocycles*, **43**, 349 (1996).
- (10) Rosowsky, A. T. Papoulis, S. F. Queener, *J. Med. Chem.*, **40**, 3694 (1997).
- (11) K. Hirota, M. Shirahashi, S. Senda, M. Yogo, *J. Heterocycl. Chem.*, **27**, 717 (1990).
- (12) J. Clark, M. S. Shahhet, D. Korakas, G. Varvounis, *J. Heterocycl. Chem.*, **30**, 1065 (1993).
- (13) S. Tumkevicius, *Liebigs Ann. Chem.*, 1703 (1995);
- (14) S. Tumkevicius, R. Pupeikyte, *J. Chem. Res. (S)*, 286 (1995);
- (15) S. Tumkevicius, A. Kaminskas, J. Kulbokaite, *J. Chem. Res. (S)*, 287 (2000);
- (16) S. Tumkevicius, L. A. Agrofoglio, A. Kaminskas, G. Urbelis, T. A. Zevaco, O. Walter, *Tetrahedron Letters*, **43**, 695 (2002).
- (17) A. A. Santilli, D. H. Kim, S. V. Wanser, *J. Heterocycl. Chem.*, **8**, 445 (1971).
- (18) P. Fiodorov, R. P. Mamedov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1626 (1962).
- (19) O. Stewart, P. A. Bhatia, C. M. McCarty, M. V. Patel, M. A. Staeger, D. L. Arendsen, I. W. Gunawardana, L. M. Melcher, G. Zhu, S. A. Boyd, D. G. Fry, B. L. Cool, L. Kifle, K. Lartey, K. C. Marsh, A. J. Kempf-Grote, P. Kilgannon, W. Wisdom, J. Meyer, W. M. Galattin, G. F. Okasinski, *J. Med. Chem.*, **44**, 988 (2001).
- (20) G. Zhu, D. L. Arendsen, I. W. Gunawardana, S. A. Boyd, A. O. Stewart, D. G. Fry, B. L. Cool, L. Kifle, V. Schaefer, J. Meuth, K. C. Marsh, A. J. Kempf-Grote, P. Kilgannon, W. M. Galattin, G. F. Okasinski, *J. Med. Chem.*, **44**, 3469 (2001).

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