Synthesis of 3,7-disubstituted 9-methylthiopyrimido [5,4-f][1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines

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Synthesis of a series of 3,7-disubstituted 9-methylthio-pyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines by the reaction of the corresponding 7-chloropyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines with water, sodium methoxide and various primary or secondary amines is described.

Key words: pyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines, nucleophilic substitution, amines

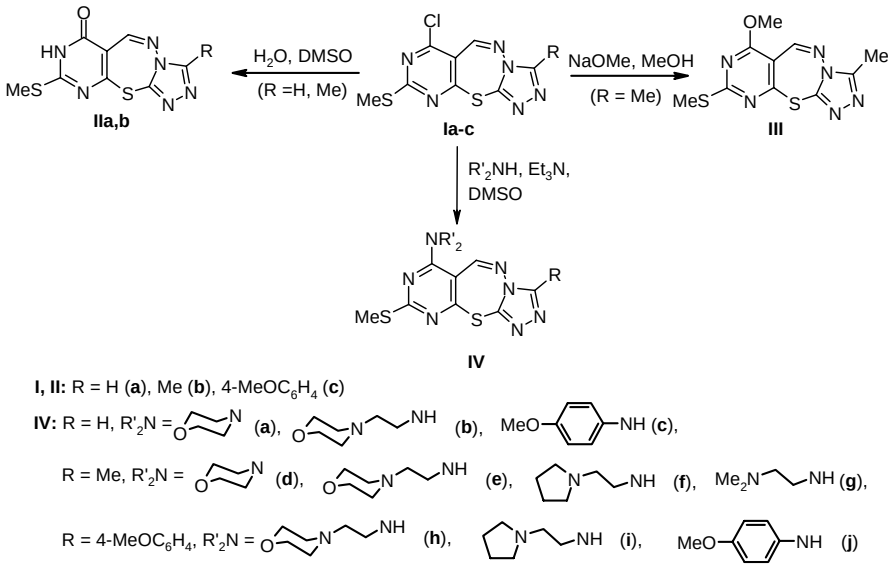
INTRODUCTION

Recently reported data on the naturally occuring antitumor pyrrolo[2,1-*c*]benzodiazepine antibiotics and their heterocyclic analogues indicate that their cytotoxic and antitumor activity arises due to formation of covalent adducts between the azomethine group of the diazepine moiety and C(2)-amino group of a guanine residue within the minor groove of duplex DNA [1–5]. In paper [6] we described the synthesis of a new heterosystem, pyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine, which can be considered to some extent as a structural analogue of the mentioned antibiotics. In this context and continuing our studies on the synthesis of pyrimidine nucleus containing heterocycles fused with seven-membered rings [7–9], it was of interest to study the interaction of some representatives of this pyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazepine with certain nucleophiles and to synthesise new derivatives for biological evaluation.

RESULTS AND DISCUSSION

The 3-substituted 7-chloro-9-methylthiopyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines (**I a–c**) studied have been synthesised by the cyclocondensation reaction of 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde with the corresponding 3-substituted 4-amino-1,2,4-triazole-5-thiones [6].

Scheme



During recording the ^{1}H NMR spectra of compound **Ia** in DMSO-d$_6$ solutions at different tem-

peratures we have found that at higher temperatures a singlet for C(6)-H irreversibly moved upfield about 0.2 ppm. We assumed that nucleophilic substitution reaction of **Ia** with water present in dimethyl sulfoxide took place. To prove this observation, reaction of **I a, b** with water in dimethyl sulfoxide at 80 °C was carried out. The isolated products according to the results of the ^{1}H NMR, IR spectra and elemental analyses appeared to be the corresponding 7-oxo derivative **II a, b** (Scheme). Reaction of **Ib** with the equimolar amount of sodium methoxide in methanol resulted in the formation of several products (according to TLC). Only 7-methoxy derivative **III** was isolated from the reaction mixture in a 21% yield. Introduction of (dialkylamino)alkylamino groups into the molecules was also of considerable interest, because polycyclic aromatic or heteroaromatic systems with flexible basic side chains are potential antitumor agents with DNA-intercalative properties [10–12]. The reaction of **I a–c** with various primary and secondary amines in dimethyl sulfoxide at 60 °C proceeded under formation of the corresponding 7-substituted amino derivatives **IV a–j**.

The spectral characteristics and analytical data were in accordance with the structures of the synthesised pyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines **II–IV**.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were run in Nujol mulls or in KBr discs on Spectrum BX II FT-IR spectrophotometer (Perkin–Elmer). ^{1}H-NMR spectra were recorded with a TESLA BS 587A spectrometer (80 MHz) using tetramethylsilane as internal standard. All reactions and purity of the synthesized compounds were monitored by TLC using Silica gel 60 F_{254} aluminium plates (Merck). Visualization was accomplished by UV light.

3-Substituted 7-chloro-9-methylthiopyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines (**I a–c**) were synthesised according to the procedure described in [6].

***3-Substituted 9-methylthio-7,8-dihydropyrimido[5,4-f][1,2,4]triazolo[3,4-b][1,3,4]thiadiazepin-7-ones* (II a, b).** To a solution of the corresponding compound **I a, b** (0.56 mmol) in DMSO (3 ml) water (0.01 ml, 0.56 mmol) was added. The reaction mixture was heated under stirring at 80 °C for 3 h. After cooling to room temperature the precipitate was filtered off and recrystallized.

IIa: Yield 54%, m. p. 248–250 °C (from 2-propanol). IR (cm^{-1}): 3299 (NH), 1618 (CO). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.65 (3H, s, SCH_3), 3.37 (1H, br. s, NH exchangeable with D_2O), 8.39 (1H, s, C_6-H), 8.98 (1H, s, C_3-H). Elemental analysis data: found, %: C 35.86; H 2.17; N 31.36; formula $C_8H_6N_6OS_2$; calculated, %: C 36.08; H 2.27; N 31.56.

IIb: Yield 57%, m. p. 267–269 °C (from 2-propanol-DMSO). IR (cm^{-1}): 3390 (NH), 1695 (CO). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.44 (3H, s, CH_3), 2.58 (3H, s, SCH_3), 5.28 (1H, br. s, NH exchangeable with D_2O), 8.23 (s, 1H, C_6-H). Elemental analysis data: found, %: C 38.78; H 2.87; N 29.67; formula $C_9H_8N_6OS_2$; calculated, %: C 38.58; H 2.88; N 29.98.

***7-Methoxy-3-methyl-9-methylthiopyrimido[5,4-f][1,2,4]triazolo[3,4-b][1,3,4]thia-diazepine* (III).** A solution of sodium methoxide in methanol, prepared from sodium (0.013 g, 0.56 mmol) and anhydrous methanol (5 ml), was added dropwise to a solution of the corresponding compound **IIb** (0.167 g, 0.56 mmol) in anhydrous methanol (10 ml). The suspension was stirred at room temperature for 2–4 h. The precipitate was filtered off and recrystallized from a mixture of 2-propanol-DMSO to give 0.035 g (21%) of compound III, m. p. 183–185 °C. ^{1}H NMR (DMSO-d_6, δ, ppm): 2.44 (3H, s, CH_3), 2.62 (3H, s, SCH_3), 4.08 (3H, s, OCH_3), 8.45 (1H, s, C_6-H). Elemental analysis data: found, %: C 41.18; H 3.68; N 28.79; formula $C_{10}H_{10}N_6OS_2$; calculated, %: C 40.81; H 3.42; N 28.55.

***3-Substituted 7-(Substituted amino)-9-methylthiopyrimido[5,4-f][1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines* (IV a–j).** *Typical procedure.* A mixture of the corresponding compound **I a–c** (0.7 mmol), corresponding amine (0.7 mmol), triethylamine (0.073 g, 0.1 ml, 0.7 mmol) and DMSO (3 ml) was heated at 60 °C for 4 h and cooled to room temperature. The precipitate was filtered off and recrystallized to give compounds **IV a–f**.

IVa: Yield 68%, m. p. 236–236.5 °C (from n-butanol). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.51 (3H, s, SCH_3), 3.32–3.40 [8H, m, $N(CH_2)_4O$], 8.21 (1H, s, C_6-H), 9.01 (1H, s, C_3-H). Elemental analysis data: found, %: C 43.08; H 3.86; N 29.15; formula $C_{12}H_{13}N_7OS_2$; calculated, %: C 42.97; H 3.91; N 29.23.

IVb: Yield 65%, m. p. 203–205 °C (from 2-propanol-DMSO). IR (cm^{-1}): 3300 (NH). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.52 (3H, s, SCH_3), 2.70–2.82 [8H, m, $N(CH_2)_2$ $N(CH_2)_2$], 3.51–3.58 [4H, m, $(CH_2)_2O$], 6.06 (1H, s, NH exchangeable with D_2O), 8.01 (1H, s, C_6-H), 9.05 (1H, s, C_3-H). Elemental analysis data: found, %: C 44.87; H 4.97; N 29.40; formula $C_{14}H_{18}N_8OS_2$; calculated, %: C 44.43; H 4.79; N 29.61.

IVc: Yield 66%, m. p. 165–166 °C (from 2-propanol-DMSO). IR (cm^{-1}): 3247 (NH). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.43 (3H, s, SCH_3), 3.78 (3H, s, OCH_3), 6.97 (2H, d, J = 10,4 Hz, ArH), 7.48 (2H, d, J = 8,8 Hz, ArH), 8.43 (1H, s, C_6-H), 9.12 (1H, s,

C_3-H), 9.81 (1H, s, NH exchangeable with D_2O). Elemental analysis data: found, %: C 48.48; H 3.20; N 26.04; formula $C_{15}H_{13}N_7OS_2$; calculated, %: C 48.50.; H 3.53.; N 26.40.

IVd: Yield 72%, m. p. 202–203 °C (from 2-propanol-DMSO). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.42 (3H, s, CH_3), 2.51 (3H, s, SCH_3), 3.61–3.69 [8H, m, $N(CH_2)_4O$], 8.13 (1H, s, C_6-H). Elemental analysis data: found, %: C 44.85; H 4.52; N 28.09; formula $C_{13}H_{15}N_7OS_2$; calculated, %: C 44.69; H 4.33; N 28.06.

IVe: Yield 60%, m. p. 236–238 °C (from 2-propanol). IR (cm^{-1}): 3220 (NH). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.49 (3H, s, CH_3), 2.51 (3H, s, SCH_3), 2.60–2.68 [8H, m, $N(CH_2)_2N(CH_2)_2$], 3.60–3.68 [4H, m, $(CH_2)_2O$], 6.11 (1H, br. s, NH exchangeable with D_2O), 7.90 (1H, s, C_6-H). Elemental analysis data: found, %: C 46.26; H 5.28; N 28.35; formula $C_{15}H_{20}N_8OS_2$; calculated, %: C 45.90; H 5.14; N 28.55.

IVf: Yield 68%, m. p. 199–200 °C (from toluene). IR (cm^{-1}): 3243 (NH). ^{1}H NMR ($CDCl_3$, δ, ppm): 1.81 (4H, s, $2CH_2$), 2.48 (3H, s, CH_3), 2.51 (3H, s, SCH_3), 3.59–3.67 [8H, m, $N(CH_2)_2N(CH_2)_2$], 6.28 (1H, br. s, NH exchangeable with D_2O), 7.93 (1H, s, C_6-H). Elemental analysis data: found, %: C 47.73; H 5.05; N 29.58; formula $C_{15}H_{20}N_8S_2$; calculated, %: C 47.85; H 5.35; N 29.76.

IVg: Yield 20%, m. p. 213–214.5 °C (from methanol). IR (cm^{-1}): 3368 (NH). ^{1}H NMR ($CDCl_3$, δ, ppm): 2.28 [6H, s, $N(CH_3)_2$], 2.51 (3H, s, SCH_3), 2.49 (3H, s, CH_3), 3.58 [4H, m, $N(CH_2)_2N$], 6.16 (1H, br. s, NH exchangeable with D_2O), 8.19 (1H, s, C_6-H). Elemental analysis data: found, %: C 44.57; H 5.16; N 31.79; formula $C_{13}H_{18}N_8S_2$; calculated, %: C 44.55; H 5.18; N 31.97.

IVh: Yield 62%, m. p. 225–227 °C (from octane-ethyl acetate). IR (cm^{-1}): 3204 (NH). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.54 (3H, s, SCH_3), 3.30–3.38 [8H, m, $N(CH_2)_2N(CH_2)_2$], 3.82–3.88 [4H, m, $(CH_2)_2O$], 3.87 (3H, s, OCH_3), 7.54 (2H, d, J = 8.8 Hz, ArH), 7.77 (2H, d, J = 8.8 Hz, ArH), 8.55 (1H, s, NH exchangeable with D_2O), 8.56 (1H, s, C_6-H). Elemental analysis data: found, %: C 52.35; H 4.81; N 23.02; formula $C_{21}H_{24}N_8O_2S_2$; calculated, %: C 52.05; H 4.99; N 23.12.

IVi: Yield 40%, m. p. 189–190 °C (from 2-propanol-DMSO). IR (cm^{-1}): 3247 (NH). ^{1}H NMR ($CDCl_3$, δ, ppm): 1.70 (4H, s, $2CH_2$), 2.55 (3H, s, SCH_3), 3.40–3.49 [8H, m, $N(CH_2)_2N(CH_2)_2$], 3.85 (3H, s, OCH_3), 7.46 (2H, d, J = 8 Hz, ArH), 7.68 (2H, d, J = 8.8 Hz, ArH), 8.53 (1H, s, NH exchangeable with D_2O), 8.56 (1H, s, C_6-H). Elemental analysis data: found, %: C 54.02; H 5.05; N 24.03; formula $C_{21}H_{24}N_8OS_2$; calculated, %: C 53.83; H 5.16; N 23.91

IVj: Yield 77%, m. p. 224–226 °C (from n-butanol-DMSO). IR (cm^{-1}): 3196 (NH). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.42 (3H, s, SCH_3), 3.78 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.89 (2H, d, J = 8.8 Hz, ArH), 7.09 (2H, d, J = 8.8 Hz, ArH), 7.47 (2H, d, J = 8.8 Hz, ArH), 8.02 (2H, d, J = 8.8 Hz, ArH), 8.52 (1H, s, C_6-H), 9.80 (1H, s, NH exchangeable with D_2O). Elemental analysis data: found, %: C 55.45; H 3.92; N 20.35; formula $C_{22}H_{19}N_7O_2S_2$; calculated, %: C, 55.33; H 4.01; N, 20.53.

CONCLUSION

Nucleophilic substitution of 7-chloro-9-metylthio-3-substituted pyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazepines with water, sodium methoxide and amines has been shown to proceed with the formation of the corresponding 3,7-disubstituted 9-methylthiopyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazepines.

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3,7-DIPAKEISTŲ-9-METILTIOPIRIMIDO[5,4-*F*)[1,2,4]TRIAZOLO[3,4-*B*][1,3,4]-TIADIAZEPINŲ SINTEZĖ

S a n t r a u k a

Reaguojant 7-chloro-9-metiltiopirimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]tiadiazepinams su vandeniu, natrio metanoliatu ir pirminiais bei antriniais aminais susintetinti atitinkami 3,7-dipakeisti 9-metiltiopirimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]tiadiazepinai.