SYNTHESIS OF NEW [1,3]DIAZAHETEROCYCLO[2′,1′:2,3]-[1,3,5]THIADIAZINO[4,5-*f*]PURINE RING SYSTEMS

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A simple method for preparation of the title ring systems **3a**–**3d** starting from 7-chloromethyl-8-chloro-1,3-dimethyl-7*H*-purine-2,6(1*H*,3*H*)-dione (**1**) and cyclic isothioureas **2** is described. First, alkylation of the mercapto group of compound **2** took place to give 7-isothiuronium derivative **5**, which in turn cyclized to the final product **3** in alkaline medium.
Key words: Annelation reactions; [1,3,5]Thiadiazino[4,5-*f*]purinediones.

In continuation of our previous papers dealing with [*f*]-fused purine derivatives[1–3] our attention has now been paid to polycyclic diazaheterocyclo-thiadiazino-purinediones. To prepare these new heterocyclic systems we made use of cyclization reactions between 7-chloromethyl-8-chloropurinedione and cyclic isothioureas. Since the reactants dispose of two reaction centres each, it was of interest to know which one of the two most probable fusions with the [*f*]-bond of the purine skeleton will occur.

Reaction of 7-chloromethyl-8-chloro-1,3-dimethyl-7*H*-purine- 2,6-(1*H*,3*H*)-dione (**1**, refs[4–6]) with cyclic isothioureas **2** in alkaline medium, afforded [1,3]diazaheterocyclo[2′,1′:2,3][1,3,5]thiadiazino[4,5-*f*]purinediones **3** but not [1,3]diazaheterocyclo-[1′,2′:5,6][1,3,5]thiadiazino[2,3-*f*]purinediones **4** (Scheme 1). Tetracyclic compounds **3a**, **3b** and particularly pentacyclic compounds **3c**, **3d** are slightly soluble in commonly used solvents.

Reaction course of the above-mentioned cyclization giving compound **3b** was studied in detail. The starting material **1** reacted with 3,4,5,6-tetrahydropyrimidine-2-thiol (**2b**) under reflux in ethanol in the absence of alkaline reagents to afford the intermediate **5b**, which after isolation cyclized to the final product **3b** on mild heating in an aqueous-

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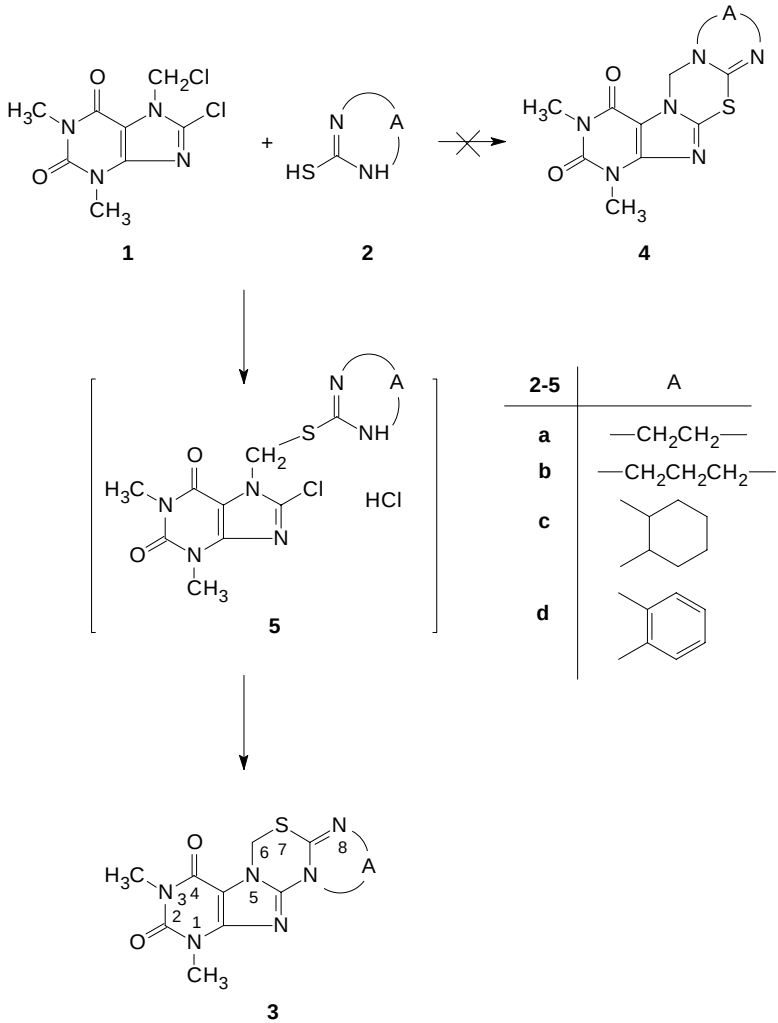
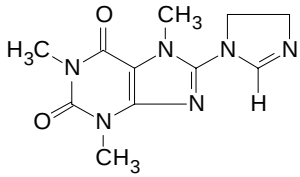
alkaline medium. This reaction course was supported by the ^{1}H NMR signals for N-7-CH_2 of the intermediate **5b** and the starting material **1** (δ = 6.01 s, 2 H and 6.10 s, 2 H, respectively). Provided the nucleophilic replacement of sulfur in **2b** took place to yield 8-(cyclic isothiuronio)-7-chloromethyl derivative, the signals for N-7-CH_2 of the former and also of the starting material would virtually be identical. The UV spectrum of compound **3b** showed an absorption band at λ_{max} = 300 nm characteristic of 1,3-dimethyl-7*H*-purine-2,6(1*H*,3*H*)-dione derivatives with an sp^3-hybridized nitrogen in position 8 (ref.[8]).



SCHEME 1

Desulfuration of compound **3a** with Raney nickel producing 8-(4,5-dihydroimidazol-1-yl)-1,3,7-trimethyl-7*H*-purine-2,6(1*H*,3*H*)-dione **6** provided an unambiguous proof for structure **3**. ^{1}H NMR spectrum of compound **6** revealed singlets of three methyl groups at δ = 3.35, 3.48 and 3.91, one singlet for H–C(=N)–N of the imidazoline moiety at δ = 7.52 and two triplets of methylene groups at δ = 3.62 and 4.08. The presence of three methyl groups, two methylene groups and one hydrogen at C-2′ of the imidazoline grouping was also corroborated by the ^{13}C NMR spectrum signals at δ_c = 27.8, 29.7, 32.4, 47.5, 55.8 and 150.1, respectively.



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Should the *S*-alkylation of cyclic isothiourea **2** followed by cyclization give rise to the polycyclic compound **4**, then its desulfuration could not give a compound with three methyl groups.

EXPERIMENTAL

The melting points were determined with a hot stage microscope Boetius and are uncorrected. Samples for analyses were dried over P_4O_{10} at 60 °C and 30 Pa for 8–10 h. The mass spectra were measured with a Varian MS 902 S using the electron impact ionization technique (100–210 °C, 70 eV). The ^{1}H and ^{13}C NMR spectra were obtained on a Jeol FX-100 (for compounds **3b**–**3d** and **5b**) and on a Bruker AM-300 (for compounds **3a**, **6**) spectrometers. The working frequency was 100 and 300.13 MHz for ^{1}H, and 25.05 and 75.46 MHz for ^{13}C, respectively. The chemical shifts (δ) are reported in ppm, using TMS as internal reference. The IR spectra ($\tilde{\nu}$, cm^{-1}, KBr technique) were taken with a Perkin–Elmer, model 457 and the UV spectra (λ_{max} in nm, ε in m^2 mol^{-1}) with a Specord M-40 UV-VIS (Zeiss, Jena) spectrophotometers. The TLC was carried out on plates SILUFOL UV_{254} (Kavalier, Votice, Czech Republic) in chloroform–methanol (9 : 1).

1,3-Dimethyl-2,4-dioxo-1,2,3,4,9,10-hexahydro-6*H*-imidazo[2′,1′: 2,3][1,3,5]thiadiazino-[4,5-*f*]purine (**3a**)

A stirred mixture of 7-chloromethyl-8-chloro derivative **1** (refs[4–6]; 2.66 g, 10 mmol) and 4,5-dihydro-1*H*-imidazole-2-thiol (**2a**; 1.1 g, 10.6 mmol) in dimethylformamide (40 ml) was heated to 60 °C. After 10 min, triethylamine (3.5 ml, 25 mmol) in ethanol (24 ml) was added in one portion to this solution from which the product began to separate. The mixture was stirred for another 10 min, then water (20 ml) was added, the product was filtered off and crystallized from acetic acid. Yield 2.30 g (78%), m.p. 326–329 °C. For $C_{11}H_{12}N_6O_2S$ (292.3) calculated: 45.19% C, 4.14% H, 28.79% N, 10.97% S; found: 45.10% C, 4.18% H, 28.78% N, 10.83% S. Mass spectrum (*m/z*): 292 (M^+). UV spectrum (dioxane): 301 (4.39). IR spectrum: 1 460, 1 530, 1 560, 1 610, 1 660, 1 710, 2 970. ^{1}H NMR spectrum (CF_3CO_2D): 3.59 s, 3 H (N-3-CH_3); 3.76 s, 3 H (N-1-CH_3); 4.46 t, 2 H (H-10); 4.78 t,

2 H (H-9); 5.96 s, 2 H (H-6). ^{13}C NMR spectrum (CF_3CO_2D): 30.5 (N-3-CH_3); 32.3 (N-1-CH_3); 43.3 (C-6); 47.7 (C-10); 49.4 (C-9); 107.2 (C-4a); 145.4 (C-11a); 150.8 (12a); 154.6 (C-2); 157.7 (C-4); 168.9 (C-7a).

1,3-Dimethyl-2,4-dioxo-1,2,3,4,9,10-hexahydro-6*H*,11*H*-pyrimido[2′,1′:2,3][1,3,5]thiadiazino-[4,5-*f*]purine (**3b**)

Method A. 3,4,5,6-Tetrahydropyrimidine-2-thiol (**2b**; 1.22 g, 10.6 mmol) was allowed to react with compound **1** (2.66 g, 10 mmol) as described for compound **3a**. The crude product was recrystallized from ethanol. Yield 2.15 g (70%), m.p. 225–227 °C.

Method B. Potassium hydroxide (2.04 g, 36 mmol) in water (20 ml) was added dropwise during 5 min to the solution of chloride **5b** (3.80 g, 10 mmol) in water (30 ml) stirred at 50 °C. The pH value of the solution was adjusted at 7 with acetic acid, the separated product was filtered off and recrystallized from ethanol. Yield 1.54 g (50%), m.p. 224–227 °C. For $C_{12}H_{14}N_6O_2S$ (306.3) calculated: 47.04% C, 4.60% H, 27.43% N, 10.46% S; found: 47.12% C, 4.56% H, 27.13% N, 10.56% S. Mass spectrum (*m/z*): 306 (M^+). UV spectrum (methanol): 266 (4.44), 300 (4.27). IR spectrum: 1 451, 1 522, 1 619, 1 670, 1 713, 2 960. ^{1}H NMR spectrum ($(CD_3)_2SO$): 2.11 m, 2 H (H-10); 3.39 s, 3 H (N-3-CH_3); 3.56 s, 3 H (N-1-CH_3); 3.67 t, 2 H (H-11); 4.08 t, 2 H (H-9); 5.70 s, 2 H (H-6). ^{13}C NMR ($(CD_3)_2SO$): 20.6 (C-10); 27.4 (N-3-CH_3); 29.6 (N-1-CH_3); 41.2, 44.4, 45.3 (C-6); 102.5 (12a); 141.7, 143.8, 141.7, 147.1, 147.6, 153.4.

1,3-Dimethyl-2,4-dioxo-1,2,3,4,8a,9,10,11,12,12a-decahydro-6*H*-benzimidazo[2′,1′:2,3][1,3,5]-thiadiazino[4,5-*f*]purine (**3c**)

A mixture of compound **1** (5.32 g, 20 mmol), 3a,4,5,6,7,7a-hexahydro-3*H*-benzimidazole-2-thiol[7] (**2c**; 3.20 g, 20.5 mmol), dimethylformamide (80 ml) and sodium methoxide (1.30 g, 24 mmol) was heated at 65 °C for 20 min; then another portion of sodium methoxide (1.30 g, 24 mmol) was added and stirring was continued at this temperature for 1 h. The solution obtained was filtered and dimethylformamide distilled off at reduced pressure. The resulting oil was dissolved in chloroform (30 ml), washed with water, dried (Na_2SO_4) and purified by column chromatography (silica gel, 50 : 1, 150–350 mesh, chloroform–methanol 10 : 1). Yield 4.30 g (62%), m.p. (ethanol) 240–243 °C. For $C_{15}H_{18}N_6O_2S$ (346.4) calculated: 52.00% C, 5.23% H, 24.26% N, 9.25% S; found: 51.86% C, 5.20% H, 24.39% N, 9.01% S. Mass spectrum (*m/z*): 346 (M^+). UV spectrum (methanol): 227 (4.25), 302 (4.09). IR spectrum: 1 525, 1 570, 1 610, 1 650, 1 708, 2 970. ^{1}H NMR spectrum ($CDCl_3$): 1.2–2.8 m, 10 H, (CH_2,CH); 3.39 s, 3 H, (N-3-CH_3); 3.54 s, 3 H,(N-1-CH_3); 5.44 s, 2 H, (H-6). ^{13}C NMR spectrum ($CDCl_3$): 24.3, 27.7, 29.4, 29.9, 30.4, 40.8, 69.2, 72.0, 102.9, 147.9, 151.5, 154.3, 156.1.

1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-6*H*-benzimidazo[2′,1′: 2,3]thiadiazino[4,5-*f*]purine (**3d**)

Powdered potassium carbonate (5.80 g, 42 mmol) was added to a stirred mixture of compound **1** (5.32 g, 20 mmol) and benzimidazole-2-thiol (**2d**; 3.10 g, 20.6 mmol) in dimethylformamide (50 ml) at 50 °C during 20 min. Water (20 ml) was added to the solidified mixture and stirring was continued at 60 °C for another 30 min. The cooled mixture was poured into water (250 ml, 0 °C) and the precipitated product was recrystallized from acetic acid (500 ml). Yield 4.50 g (66%), m.p. 335–337 °C. For $C_{15}H_{12}N_6O_2S$ (340.3) calculated: 52.93% C, 3.55% H, 24.69% N, 9.42% S; found: 52.64% C, 3.48% H, 24.90% N, 9.42% S. Mass spectrum (*m/z*): 340 (M^+). UV spectrum (dioxane): 285 (4.11). IR spectrum: 1 530, 1 565, 1 615, 1 650, 1 698. ^{1}H NMR spectrum (CF_3CO_2D): 3.65 s, 3 H (N-3-CH_3); 3.90 s, 3 H (N-1-CH_3); 6.25 s, 2 H (H-6); 8.73–7.84 m, 4 H (arom.). ^{13}C NMR spectrum (CF_3CO_2D): 30.4

(N-3-CH_3); 32.2 (N-1-CH_3); 44.2 (C-6); 116.0, 117.0, 131.1, 131.5 (arom.); 107.5, 142.3, 150.0, 154.7, 158.2 (C-7a, purine ring).

8-Chloro-1,3-dimethyl-7-[(3′,4′,5′,6′-tetrahydropyrimidin-2′-yl)thiomethyl]-7*H*-purine-2,6(1*H*,3*H*)-dione Hydrochloride (**5b**)

3,4,5,6-Tetrahydropyrimidine-2-thiol (**2b**; 1.28 g, 11 mmol) was added to a solution of compound **1** (2.66 g, 10 mmol) in ethanol (50 ml) and the mixture was refluxed for 1 h. The product crystallizing from the cooled mixture was filtered off and washed with acetone (10 ml). Yield 2.80 g (74%), m.p. 264–268 °C. For $C_{12}H_{16}Cl_2N_6O_2S$ (379.3) calculated: 38.00% C, 4.25% H, 18.70% Cl, 22.16% N, 8.45% S; found: 38.22% C, 4.49% H, 18.49% Cl, 22.03% N, 8.69% S. ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.84, 3.30, 3.85 m, 6 H (CH_2); 3.24 s, 3 H (N-1-CH_3); 3.40 s, 3 H (N-3-CH_3); 6.01 s, 2 H (CH_2S).

8-(4,5-Dihydroimidazol-1-yl)-1,3,7-trimethyl-7H-purine-2,6(1*H*,3*H*)-dione (**6**)

Raney nickel (3.3 g) was added to a stirred mixture of compound **3a** (292 mg, 1.0 mmol) in dioxane (90 ml). The mixture was refluxed for 1.5 h, the catalyst was filtered off, the filtrate was concentrated under reduced pressure and the glassy residue was recrystallized from methanol (4.5 ml); after standing in refrigerator for several days, the crystals were filtered off and dried under reduced pressure. Yield 150 mg (58%), m.p. 272–275 °C. For $C_{11}H_{14}N_6O_2$ (262.27) calculated: 50.38% C, 5.38% H, 32.04% N; found: 50.16% C, 5.49% H, 31.87% N. Mass spectrum (*m/z*): 262 (M^+). ^{1}H NMR spectrum ($(CD_3)_2SO$): 3.35 s, 3 H (N-1-CH_3); 3.48 s, 3 H (N-3-CH_3); 3.62 t, 2 H (H-4′); 3.91 s, 3 H (N-7-CH_3); 4.08 t, 2 H (H-5′); 7.52 s, 1 H (H-2′). ^{13}C NMR spectrum ($(CD_3)_2SO$): 27.8 (N-1-CH_3); 29.7 (N-3-CH_3); 32.4 (N-7-CH_3); 47.5 (C-4′); 55.8 (C-5′); 102.0 (C-5); 148.0 (C-8); 150.1 (C-2′); 150.8 (C-4); 152.9 (C-2); 154.0 (C-6).

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