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7,8-Disubstituted [1,3]-Thiazino-[2,3-f]-purine Derivatives

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Summary. 7-Cyanomethyl-8-ethoxycarbonylmethylthio- (**3a**), 7-cyanomethyl-8-cyanomethylthio- (**3b**), and 7-ethoxycarbonylmethyl-8-ethoxycarbonylmethylthio-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (**3c**) afforded 7-amino-8-ethoxycarbonyl-(**5**), 7-amino-8-cyano- (**6**), and 8-ethoxycarbonyl-7-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-6*H*-[1,3]-thiazino-[2,3-f]-purine (**7**), respectively, on intramolecular Claisen-type condensation.

Keywords. Intramolecular cyclocondensation; [1,3]-Thiazino-[2,3-f]-purines; 7,8-Disubstituted purine-2,6-diones.

7,8-Disubstituierte [1,3]-Thiazino-[2,3-f]-purinderivate

Zusammenfassung. 7-Cyanomethyl-8-ethoxycarbonylmethylthio- (**3a**), 7-Cyanomethyl-8-cyanomethylthio- (**3b**) und 7-Ethoxycarbonylmethyl-8-ethoxycarbonylmethylthio-1,3-dimethyl-3,7-dihydro-1*H*-purin-2,6-dion (**3c**) liefern bei einer intramolekularen Claisen-Kondensation die 7-Amino-8-ethoxycarbonyl- (**5**), 7-Amino-8-cyano- (**6**), und 8-Ethoxycarbonyl-7-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-6*H*-[1,3]-thiazino-[2,3-f]-purine (**7**).

Introduction

Purines annelated in the [f] position represent an interesting synthetic problem due to their potential pharmacological effects [1–5]. In continuation of our preceding investigations concerning new condensed heterocyclo-[f]-purines [6–8] we wish to present a new method leading to the [1,3]-thiazino-[2,3-f]-purine ring system.

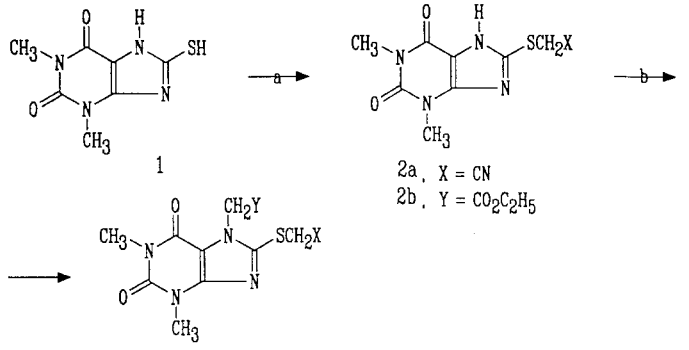
The known 1,3-dimethyl-2,4-dioxo-1,2,3,4,7,8-hexahydro-6*H*-[1,3]-thiazino-[2,3-f]-purine can be synthesized from 8-mercapto-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione and 1-bromo-3-chloropropane [9], or alternatively from 8-bromo-7-(γ-bromopropyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione and sodium sulfide [10]. Reported has also been a series of 7-hydroxy-[1,3]-thiazino-[2,3-f]-purine derivatives obtained via 8-substituted 7-(2,3-epoxypropyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-diones [11].

The above-mentioned heterocyclic ring system has not been obtained by a Claisen-type intramolecular cyclocondensation as yet. This paper refers to the

preparation of a [1,3]-thiazino-[2,3-f]-purine skeleton by Dieckmann condensation of 7-ethoxycarbonylmethyl-8-ethoxycarbonylmethylthio-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (**3c**), the Thorpe-Ziegler reaction with 7-cyanomethyl-8-cyanomethyltio derivative **3b**, or the mixed intramolecular condensation of 7-cyanomethyl-8-ethoxycarbonylmethylthio derivative **3a**.

Results and Discussion

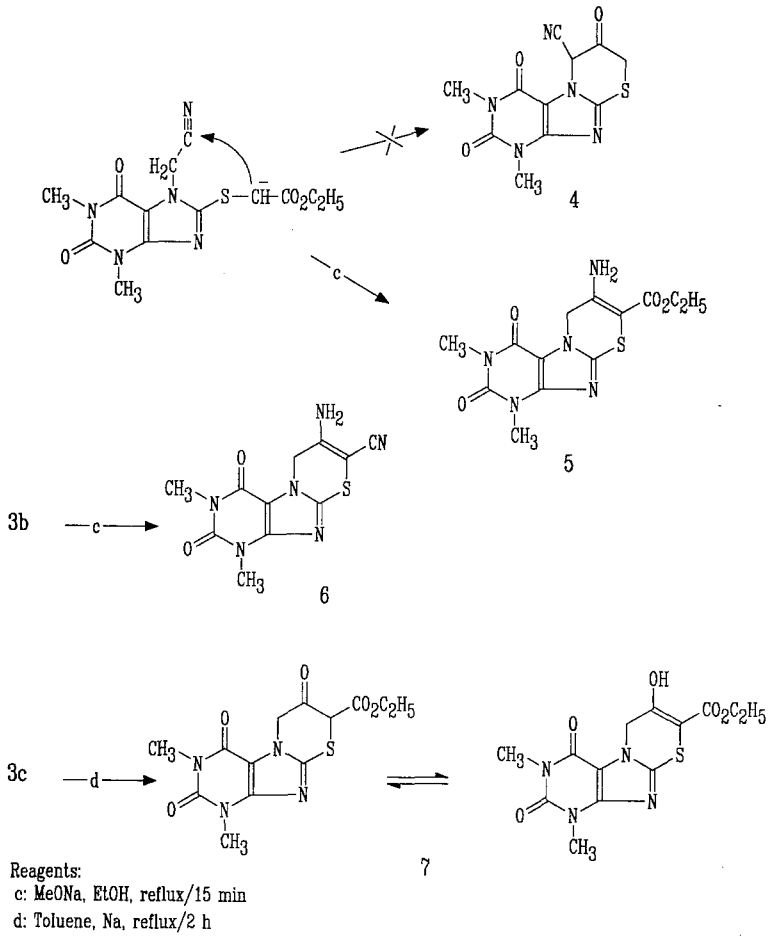
The double-functionalized dialkyl derivatives **3** required for this project were prepared from 8-mercapto-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (**1**) and its derivative **2**. The asymmetrically substituted compounds **3** (i.e. $X \neq Y$) can be obtained by a successive alkylation of compound **1** through **2** only; initially, the mercapto group in position 8 was alkylated to afford the 8-methylthio derivative **2** (cf. the reaction of **1** with propargyl bromide [12]) and then the functionalized alkyl entered position N-7 of compound **2**. The successive alkylation i.e. isolation of the intermediate **2** is also favoured with substitution $X = Y$ leading to compounds **3b**, **3c**. An excess of the alkylating agent led to alkylation at both centres of compound **1** to yield the double functionalized dialkyl derivatives **3b** and **3c**. These are, however, considerably more contaminated with by-products, when compared with those prepared by a stepwise alkylation (Scheme 1).



Scheme 1

Intramolecular Claisen-type condensation with compound **3a** can furnish either 6-cyano-1,3-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-6*H*-[1,3]-thiazino-[2,3-f]-purine (**4**), or 7-amino-8-ethoxycarbonyl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-6*H*-[1,3]-thiazino-[2,3-f]-purine (**5**). As known, the mixed Claisen-type condensation of carboxylates with nitriles produced exclusively β-ketonitriles R^1–CO–CH(R^2)–CN. Considering this fact, one can expect formation of a fused purine **4** when reacting the intermediate **3a**. As found, the annelated purine **5** resulted from this reaction as evidenced by the presence of ^{1}H- and ^{13}C-NMR signals of ethyl ester and amino groups. Compound **5** can only be formed when accepting the presumption that compound **3a** attacked as a carbanion in the 8-S–$CH_2CO_2C_2H_5$ grouping the

nitrile group at C-7. We presume that this carbanion is stabilized by the resonance effect of 3d orbitals of sulfur (Scheme 2).

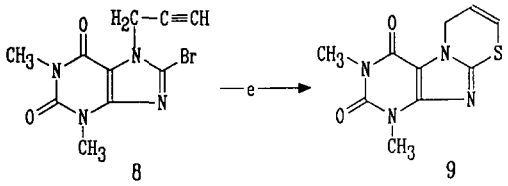


Scheme 2

An analogous reaction of bis-cyanomethyl derivative **3b** and bis-ethoxycarbonylmethyl derivative **3c** afforded 7-amino-8-cyano-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-6*H*-[1,3]-thiazino-[2,3-f]-purine (**6**) and 8-ethoxycarbonyl-7-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-6*H*-[1,3]-thiazino-[2,3-f]-purine (**7**), respectively. Formation of carbanions is anticipated, also with these reactions namely at the 8-S–CH_2CN and 8-S–$CH_2CO_2C_2H_5$ groupings of the respective compounds **3b** and **3c**. While compounds **5** and **6** occurred in an amino and not imino form in solutions substance **7** exhibited an equilibrated oxo-enol tautomerism. This equilibrium was ascertained from the ^{13}C-NMR spectra of compound **7** showing, apart from singlets characterizing the enol form (88.2, C-8; 150.8, C-7), signals indicative of an oxo group (50.9, d, C-8; 203.2, s, C-7). These positions are in good agreement with data published [13] for the respective oxo and enol groups of 3-ethoxycarbonyl-4-oxo-2,3,4,5-tetrahydrothiophene.

1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-6*H*-[1,3]-thiazino-[2,3-f]-purine (**9**) without substituents at the thiazine ring, hitherto not reported, was synthesized

for spectral comparison with final compounds **5**–**7** from 8-bromo-1,3-dimethyl-7-propargyl-3,7-dihydro-1*H*-purine-2,6-dione (**8**) [7] and sodium hydrosulfide. Displacement of bromine for the mercapto group took place in the first phase to give the 8-mercapto-7-propargyl derivative. The latter underwent an intramolecular nucleophilic addition of the mercapto group to the C≡C bond resulting in the [1,3]thiazine ring (Scheme 3).



Scheme 3

Experimental Part

The melting points are uncorrected, samples for analyses were dried over phosphorus pentoxide at 100 °C/65 Pa during 8 h. The ^1H and ^{13}C NMR spectra recorded with a Jeol FX-100 spectrometer operating at 100 and 25.05 MHz, respectively, are relative to tetramethylsilane. The UV spectra were measured with a Specord M-40 spectrophotometer.

8-Cyanomethylthio-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (**2a**)

Chloroacetonitrile (0.76 g, 10 mmol) diluted with dimethylformamide (5 ml) was added to the solution of compound **1** (2.12 g, 10 mmol) dissolved in dimethylformamide (15 ml) and triethylamine (1.7 ml, 12 mmol) and the mixture was heated at 40 °C with stirring for 10 min. Water (20 ml) was poured into the cooled mixture to dissolve the triethylammonium chloride and to precipitate the reaction product, which was filtered off and crystallized from a suitable solvent. Yield 1.76 g (70%); m.p. 259–262 °C (dimethylformamide). Anal. calcd. for $C_9H_9N_5O_2S$ (251.2): C 43.01, H 3.61, N 27.87, S 12.76; found: 43.18, H 3.64, N 27.93, S 12.98.

8-Ethoxycarbonylmethylthio-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (**2b**)

This was likewise prepared from ethyl chloroacetate (1.23 g, 10 mmol) and compound **1** (2.12 g, 10 mmol). Yield 1.97 g (66%); m.p. 201–204 °C (ethanol). Anal. calcd. for $C_{11}H_{14}N_4O_4S$ (298.3); C 44.28, H 4.74, N 18.78, S 10.75; found: C 44.10, H 4.52, N 18.84, S 10.70.

7-Cyanomethyl-8-ethoxycarbonylmethylthio-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (**3a**)

Sodium hydride (0.35 g, 14 mmol) was stepwise carefully added to the functionalized derivative **2b** (2.98 g, 10 mmol) in dry dimethylformamide (30 ml). Chloroacetonitrile (0.91 g, 12 mmol) was added immediately after the evolution of hydrogen ceased and the mixture was stirred at 40 °C for 30 min. Ethanol (40 ml) was added to the stirred mixture and the crystalline precipitate was filtered off and recrystalized from a suitable solvent. Yield 2.87 (85%); m.p. 138–139 °C (ethanol). Anal. calcd. for $C_{13}H_{15}N_5O_4S$ (337.3): C 46.28, H 4.48, N 20.76, S 9.51; found: C 46.12, H 4.13, N 20.96, S 9.32.

7-Cyanomethyl-8-cyanomethylthio-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (**3b**)

The reaction of **2a** (2.51 g, 10 mmol) and chloroacetonitrile (0.91 g, 12 mmol) according to the procedure described for the synthesis of **3a** yielded 1.83 g (63%) of **3b**; m.p. 191–193 °C (ethanol). Anal. calcd. for $C_{11}H_{10}N_6O_2S$ (290.3): C 45.50, H 3.47, N 28.95, S 11.05; found: C 45.42, H 3.45, N 28.80, S 10.80.

7-Ethoxycarbonylmethyl-8-ethoxycarbonylmethylthio-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (**3c**)

The reaction of **2b** (2.98 g, 10 mmol) and ethyl chloroacetate (1.47 g, 12 mmol) according to the procedure described for the synthesis of **3a** yielded 3.38 g (88%) of **3c**; m.p. 148–149 °C (ethanol). Anal. calcd. for $C_{15}H_{20}N_4O_6S$ (384.4): C 46.86, H 5.24, N 14.57, S 8.34; found: C 46.80, H 5.20, N 14.53, S 8.27.

7-Amino-8-ethoxycarbonyl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-6H-[1,3]-thiazino-[2,3-f]-purine (**5**)

Dry sodium methoxide (0.50 g, 1 mmol) was added to a stirred solution of 7-cyanomethyl-8-ethoxycarbonylmethylthio derivative **3a** (10.46 g, 31 mmol) in ethanol (160 ml) and the mixture was refluxed for 15 min. The product precipitated on cooling was crystallized from a convenient solvent. Yield 6.27 g (60%); m.p. 273–275 °C (dimethylformamide). Anal. calcd. for $C_{13}H_{15}N_5O_4S$ (337.3): C 46.28, H 4.48, N 20.76, S 9.50; found: C 46.02, H 4.31, N 21.01, S 9.45. UV (dioxane): 294 nm ($\log \varepsilon$ 4.24). ^{1}H NMR (Me_2SO-d_6): $\delta = 1.23$ (t, $J = 7.0$ Hz, $CH_2\mathbf{CH_3}$), 3.21 (s, N-3 $-CH_3$), 3.37 (s, N-1 $-CH_3$), 4.17 (q, $J = 7.0$ Hz, $\mathbf{CH_2}CH_3$), 5.14 (s, H-6), 8.12 (br s, NH_2). ^{13}C NMR (Me_2SO-d_6): $\delta = 14.2$ ($CH_2\mathbf{CH_3}$), 27.4 (N-1 $-CH_3$), 29.4 (N-3 $-CH_3$), 46.1 (C-6), 60.1 ($\mathbf{CH_2}CH_3$), 77.5 (C-8), 106.2 (C-4a), 147.2 and 148.7 (C-9a, C-10a), 150.7 (C-2), 151.7 (C-7), 153.2 (C-4), 164.7 ($\mathbf{CO_2}C_2H_5$).

7-Amino-8-cyano-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-6H-[1,3]-thiazino-[2,3-f]-purine (**6**)

This was synthesized similar to **5** starting with 7-cyanomethyl-8-cyanomethylthio derivative **3b** (9.00 g, 31 mmol). Yield 4.50 g (50%); m.p. 293–296 °C (decomp.) (dimethylformamide). Anal. calcd. for $C_{11}H_{10}N_6O_2S$ (290.3): C 45.50, H 3.47, N 28.95, S 11.04; found: C 45.90, H 3.52, N 28.23, S 10.93. UV (dioxane): 275 (4.28), 314 nm ($\log \varepsilon$ 3.72). ^{1}H NMR (Me_2SO-d_6): $\delta = 3.21$ (s, N-3 $-CH_3$), 3.38 (s, N-1 $-CH_3$), 5.14 (s, H-6), 7.74 (br s, NH_2). ^{13}C NMR (Me_2SO-d_6): $\delta = 27.4$ (N-1 $-CH_3$), 29.4 (N-3 $-CH_3$), 46.7 (C-6), 107.0 (C-4a), 116.4 (C-8), 145.6 and 148.6 (C-9a, C-10a), 150.7 (C-2), 151.7 (C-7), 153.3 (C-4), 155.7 (C≡N).

8-Ethoxycarbonyl-7-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-6H-[1,3]-thiazino-[2,3-f]-purine (**7**)

Sodium wire (0.30 g, 1.2 mmol) was added to a lukewarm solution of 7-ethoxycarbonylmethyl-8-ethoxycarbonylmethylthio derivative **3c** (3.90 g, 10 mmol) dissolved in hot toluene (40 ml). The mixture was refluxed for 2 h and ethanol (20 ml) was then added to the gently cooled solution. The precipitated product was filtered off, dissolved in water (30 ml), filtered and acidified with acetic acid (1 ml). The precipitate was crystallized from acetic acid : ethanol (2 : 1). Yield 1.93 g (57%); m.p. 188–191 °C. Anal. calcd. for $C_{13}H_{14}N_4O_5S$ (338.3): C 46.14, H 4.17, N 16.56, S 9.47; found: C 45.92, H 4.01, N 16.40, S 9.33. UV (dioxane): 234 (4.29), 278 (4.17), 320 nm ($\log \varepsilon$ 3.56). ^{1}H NMR (Me_2SO-d_6): $\delta = 1.28$ (t, $J = 7.0$ Hz, $CH_2\mathbf{CH_3}$), 3.21 (s, N-3 $-CH_3$), 3.38 (s, N-1 $-CH_3$), 4.31 (q, $J = 7.0$ Hz, $\mathbf{CH_2}CH_3$), 5.19 (s, H-6). ^{13}C NMR (Me_2SO-d_6): $\delta = 13.7$ ($CH_2\mathbf{CH_3}$), 27.5 (N-1 $-CH_3$), 29.8 (N-3 $-CH_3$), 48.2 (C-6), 50.9 (oxo-7, C-8), 61.7 ($\mathbf{CH_2}CH_3$), 88.2 (enol-7, C-8), 107.2 (C-4a), 143.7 and 148.4 (C-9a, C-10a), 150.4 (C-2), 150.8 (enol-7, C-7), 153.3 (C-4), 169.6 ($\mathbf{CO_2}C_2H_5$), 203.2 (oxo-7, C-7).

1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-6H-[1,3]thiazino-[2,3-f]-purine (**9**)

Sodium hydrogen sulfide (0.8 g, 14 mmol) was added to a stirred solution of 8-bromo-7-propargyl derivative **8** (3.0 g, 10 mmol) in dimethylformamide (20 ml). The mixture was heated to 125 °C during 2 h in a nitrogen atmosphere. Acetic acid (1 ml) and water (20 ml) were added to the mixture cooled to room temperature, the precipitated product was filtered off and crystallized from the mixture dioxane : ethanol (1 : 1). yield 1.30 g (52%); m.p. 247–248 °C. Anal. calcd. for $C_{10}H_{10}N_4O_2S$ (250.3): C 47.98, H 4.02, N 22.38, S 12.81; found: C 47.90, H 4.14, N 22.09, S 12.77. UV (methanol): 209 (4.45), 248 (4.09), 309 nm (log ε 3.99). ^{1}H NMR ($CDCl_3$): $\delta = 3.37$ (s, N-3 $-CH_3$), 3.54 (s, N-1 $-CH_3$), 5.16 (dd, H-6), 5.99 (td, $J = 3.5$ Hz, H-7), 6.30 (td, $J = 10.0$ Hz, 2.0 Hz, H-8). ^{13}C NMR ($CDCl_3$): $\delta = 27.9$ (N-3 $-CH_3$), 29.8 (N-1 $-CH_3$), 45.1 (C-6), 107.1 (C-4a), 115.1 and 116.0 (C-7, C-8), 142.5 (C-9a), 148.7 (C-10a), 151.4 (C-2), 154.3 (C-4).

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