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[*f*]-Fused Purine-2,6-diones: Synthesis of New [1,3,5]- and [1,3,6]-Thiadiazepino-[3,2-*f*]-purine Ring Systems**

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Summary. 6-Phenyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,8,9-hexahydro-[1,3,5]-thiadiazepino-[3,2-f]-purine (**5**) was obtained by a three-step synthesis from 8-mercapto-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (**1**) and 2-(benzoylamino)-ethyl chloride (**2**) *via* 8-(benzoylaminoethylthio)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (**3**) and its chloromido derivative **4**. The analogous 9-phenyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-[1,3,6]-thiadiazepino-[3,2-f]-purine (**7**) was synthesized either from compound **1** and N-(2-chloroethyl)-benzimido chloride *via* N-(chloroethyl)-S-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-7*H*-purin-8-yl)-benzothioimide (**6**), or alternatively from 7-(2-benzoylaminoethyl)-8-bromo-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (**9**), its 8-mercapto derivative **10** and the corresponding chloroimido compound **11** being the intermediates.

Keywords. [1,3,5]- and [1,3,6]-Thiadiazepino-[3,2-f]-purines; Intramolecular alkylation.

[*f*]-Anellierte Purin-2,6-dione. Synthese von neuen [1,3,5]- und [1,3,6]-thiadiazepino-[3,2-*f*]-purinringsystemen

Zusammenfassung. 6-Phenyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,8,9-hexahydro-[1,3,5]-thiadiazepino-[3,2-*f*]-purin (**5**) wurde in drei Stufen aus 8-Mercapto-1,3-dimethyl-3,7-dihydro-1*H*-purin-2,6-dion (**1**) und 2-(Benzoylamino)-ethylchlorid (**2**) *via* 8-(2-Benzoylaminoethylthio)-1,3-dimethyl-3,7-dihydro-1*H*-purin-2,6-dion (**3**) und sein entsprechendes Chlorimid-Derivat **4** dargestellt. Das analoge 9-Phenyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-[1,3,6]-thiadiazepino-[3,2-*f*]-purin (**7**) wurde entweder aus Verbindung **1** und N-(2-Chlorethyl)-benzimidochlorid *via* N-(Chlorethyl)-S-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-7*H*-purin-8-yl)-benzothioimid (**6**) oder aus 7-(2-Benzoylaminoethyl)-8-brom-1,3-dimethyl-3,7-dihydro-1*H*-purin-2,6-dion (**9**), seinem 8-Mercapto-Analogen **10** und dem entsprechenden Chlorimid-Derivat **11** erhalten.

Introduction

So far, only one paper concerning fusion of a thiadiazepine ring system has been reported for 7-phenyl-6,7-dihydro-5*H*-thiadiazepino-[5,6,7-*g*,*h*]-purin-7-ol [1].

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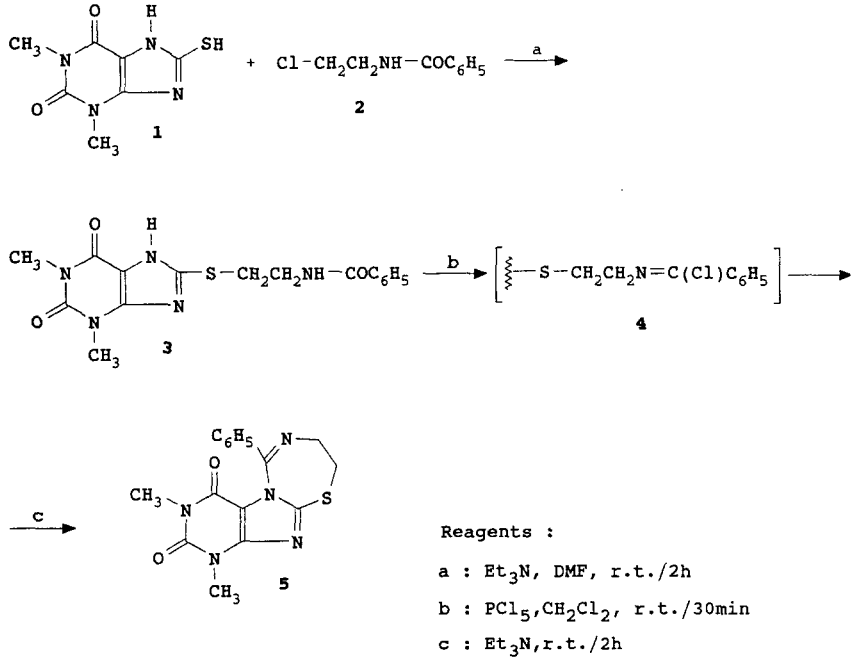
This compound was, however, obtained as a by-product when preparing 6-(benzoylaminomethylthio)-9*H*-purine from 6-mercapto-9*H*-purine and benzoylaminomethyl chloride.

In continuation of our studies searching for new fused heterocyclo-[*f*]-purines [2–5] as potentially active pharmaceuticals, we described the synthesis of hitherto unpublished heterocycles with thiadiazepine moiety fused to the [*f*]-bond of the purine skeleton, interesting from the preparation point of view. This paper presents synthetic routes leading to [1,3,5]-thiadiazepino-[3,2-*f*]- and [1,3,6]-thiadiazepino-[3,2-*f*]-purines as new ring systems, starting from 8-mercapto-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (**1**) functionalized either in position 7 or 8, or alternatively from the 8-bromo analogue derivatized in position 7.

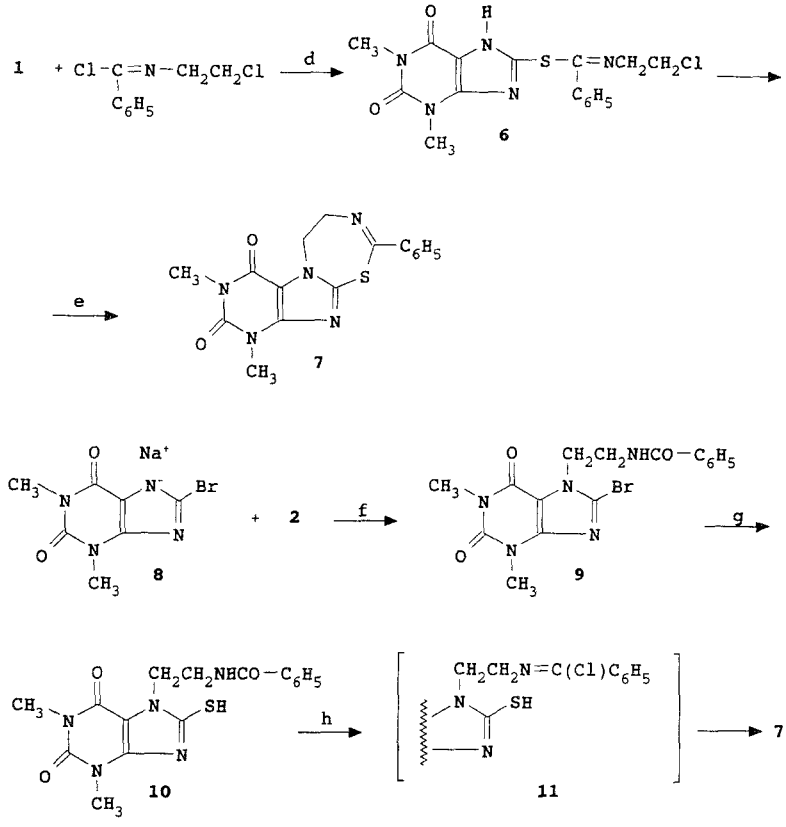
Results and Discussion

The [1,3,5]-ring system represented by 6-phenyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,8,9-hexahydro-[1,3,5]-thiadiazepino-[3,2-*f*]-purine (**5**) was synthesized as follows (Scheme 1): compound **1** was reacted with 2-(benzoylamino)-ethyl chloride (**2**) in ethanol or dimethylformamide in the presence of triethylamine as a hydrogen chloride trapping reagent to give 8-(2-benzoylaminoethylthio)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (**3**). The alkylation reagent **2** was obtained according to Ref. [6] by benzoylation of 2-chloroethylammonium chloride. The intermediate **3**, treated with phosphorus pentachloride in dichloromethane or chloroform, afforded N-{2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-7*H*-purin-8-ylthio)-ethyl}-benzimido chloride (**4**), which underwent intramolecular organic base-catalyzed alkylation to yield the tricyclic [1,3,5]-thiadiazepine **5**.



Scheme 1

The [1,3,6]-ring system represented by 9-phenyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-[1,3,6]-thiadiazepino-[3,2-*f*]-purine (**7**) was prepared by two synthetic routes (Scheme 2). The first one started from the triethylammonium salt of compound **1**, which was functionalized to N-(2-chloroethyl)-S-(1,3-dimethyl-2,6-dioxo-1,2,3,4-tetrahydro-7*H*-purin-8-yl)-benzothioamide (**6**) with N-(2-chloroethyl)-benzimido chloride. The latter was obtained from compound **2** and phosphorus pentachloride according to [6]. Intramolecular alkylation of the intermediate **6** with triethylamine in dimethylformamide furnished the tricyclic [1,3,6]-thiadiazepine **7**.



Scheme 2

Alternatively, the sodium salt of 8-bromo-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (**8**), produced according to [3], was alkylated with reagent **2** in dimethylformamide to give 7-(2-benzamidoethyl)-8-bromo-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (**9**). Bromine in position 8 of the latter was replaced by a mercapto group (nucleophilic substitution with sodium hydrogen sulfide in dimethylformamide) to afford the intermediate **10**, which was cyclized with phosphorus pentachloride to the final tricyclic compound **7** *via* the corresponding benzimidochloride **11**. In

contrast to the above mentioned cyclization methods of the third ring requiring triethylamine, this cyclodehydrochlorination can be accomplished merely by heating at *ca.* 60 °C (reflux in chloroform).

Attempts to prepare analogous tricyclic derivatives with methyl or ethyl instead of phenyl in position 6 or 9 failed. All three methods presented gave tarry products in the last step, *i.e.* on reaction of the corresponding amides with phosphorus pentachloride.

Both final products, **5** and **7**, differ from each other by their stability against moisture. Compound **5** had to be crystallized from perfectly dry solvents and thus prevented from decomposition to compound **3**, especially in mild acid media (*e.g.* acetic acid). Due to good solubility of compounds **3** and **5** in chlorinated solvents and their markedly different polarity, compound **3** can be easily separated by column chromatography on silica gel. It is worth nothing that the final product **7** is quite stable in aqueous solution, but less soluble in chlorinated solvents and lower alcohols than compound **5**.

The ^{13}C NMR spectra of compounds **5** and **7** reveal five singlets at 141–154 ppm attributable to carbons of the purine ring system (C-2, C-4, C-10a, C-11a, and the endocyclic ketimine group in the thiadiazepine molecule moiety, *i.e.* C-6 of compound **5** or C-9 of compound **7**). The differences in chemical shifts of carbons C-8 and C-9 of compound **5** and C-6 and C-7 of compound **7**, associated with the shielding effect of sulfur or the sp^2 and sp^3 hybridisation of nitrogen, were found to be significant ($\delta = 49.1$, 39.7, and 46.6, 51.7 ppm, respectively).

Experimental

Melting points are uncorrected. Samples for analyses were dried over P_2O_5 at 100 °C/30 Pa for 8 h. Mass spectra were measured with a Varian MS 902 S apparatus at 70 eV ionizing energy; UV and IR spectra were taken with the respective Zeiss Specord M-40 UV-Vis and Perkin-El-mer model 457 spectrophotometers. NMR spectra were recorded with a Jeol FX-100 instrument operating at 100 MHz (^1H) and 25.05 MHz (^{13}C); tetramethylsilane served as internal reference. The reaction course and the purity of compounds were monitored by TLC on Silufol UV_{254} sheets (Kavalier, Votice, Czech Republic) in chloroform:methanol = 9:1.

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

A hot solution of N-(2-chloroethyl)-benzamide (Ref. [6]) (**2**, 9.6 g, 52 mmol) in ethanol (69 ml) was poured into a stirred suspension of 8-mercapto-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (Ref. [7]) (**1**, 10.6 g, 50 mmol) in ethanol (200 ml) and triethylamine (7.4 ml, 53 mmol) previously dissolved at 60 °C. After refluxing for 2 h, cold water (25 ml) was added and the stirred solution was allowed to crystallize at room temperature. The separated crystals were filtered off and recrystallized from acetic acid:ethanol = 2:1. Yield: 9.0 g (50%); m.p.: 265–268 °C; anal.: calcd. for $C_{16}H_{17}N_5O_3S$ (359.4): C 53.46, H 4.76, N 19.48, S 8.92; found: C 53.40, H 4.53, N 19.31, S 8.70.

6-Phenyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,8,9-hexahydro-[1,3,5]-thiadiazepino-[3,2-f]-purine (**5**)

Finely powdered phosphorus pentachloride (5.3 g, 25 mmol) was added to a stirred suspension of the intermediate **3** (9.0 g, 25 mmol) in dichloromethane (80 ml). To the yellow solution formed within 30 min stirring at room temperature, triethylamine (7.0 ml, 50 mmol) was dropped during 2 h. Phosphorus

oxychloride resulting from this reaction was decomposed by addition of ammonium hydroxide (9.0 ml, 60 mmol) at −5 °C. The separated solid was filtered off, and the organic layer was washed with water (2 × 20 ml) and evaporated to dryness under reduced pressure. Ethanol (80 ml) was added to the solid residue and the triturated solid was filtered off. Yield: 6.0 g (70%); m.p.: 220–224 °C (after recrystallization from chloroform–2-propanol: 224–226 °C); anal.: calcd. for $C_{16}H_{15}N_5O_2S$ (341.4): C 56.28, H 4.43, N 20.51, S 9.30; found: C 56.17, H 4.32, N 20.91, S 9.06. MS, *m/z*(relative intensity): 343(24), 342(35), 341(55, M^+), 257(5), 240(18), 239(100), 211(9), 182(14), 164(8), 154(13), 153(32), 141(11), 130(10), 104(13), 103(25), 99(12); UV (methanol): 251, 312 nm; IR (KBr): 1539, 1600, 1635, 1670, 1710, 2960 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.23$ (s, 3H, N-3–CH_3), 3.64 (s, 3H, N-1–CH_3), 3.67 and 4.25 (m, 4H, H-8, H-9), 7.38–7.80 (m, 5H, H-arom); ^{13}C NMR ($CDCl_3$): $\delta = 28.2$ (q), 30.1 (q), 39.7 (t), 49.1 (t), 108.8 (s), 2 × 127.5 (d), 2 × 128.7 (d), 131.9 (d), 134.2 (s), 148.5 (s), 151.2 (s), 152.4 (s), 152.8 (s).

N-(2-Chloroethyl)-S-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-7H-purin-8-yl)benzothioimide (**6**)

Triethylamine (2.4 ml, 30 mmol) was poured to a stirred suspension of compound **1** (6.3 g, 30 mmol) in dimethylformamide (45 ml). N-(2-Chloroethyl)-benzimido chloride (6.0 g, 30 mmol) was added to the cooled solution at 0–5 °C during 5 min and the mixture was stirred at ambient temperature for 30 min during which triethylammonium chloride separated. Water (50 ml) was then added and the separated product was filtered off and crystallized from ethanol. Yield: 9.1 g (80%); m.p.: 194–196 °C; anal.: calcd. for $C_{16}H_{16}ClN_5O_2S$ (377.1): C 50.92, H 4.28, N 18.57, Cl 9.40, S 8.48; found: C 51.08, H 4.20, N 18.39, Cl 10.97, S 8.27.

7-(2-Benzamidoethyl)-8-bromo-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (**10**)

The intermediate **9** (14.0 g, 33 mmol), sodium hydrogen sulfide (3.5 g, 46 mmol) and dimethylformamide (75 ml) were stirred and heated at 60–80 °C for 2 h during which the green colour of the mixture turned to yellow. Water (150 ml) and acetic acid (2 ml) were then poured to the hot mixture which was left standing for *ca.* 15 h and the separated crystals were filtered off. Yield: 11.7 g (94%); m.p.: 296–300 °C; anal.: calcd. for $C_{16}H_{17}N_5O_3S$ (359.1): C 53.47, H 4.77, N 19.50, S 8.90; found: C 53.15, H 5.03, N 19.77, S 9.15.

9-Phenyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-[1,3,6]-thiadiazepino-[3,2-f]purine (**7**)

Method A: Potassium carbonate (2.0 g, 14 mmol) was added to the stirred solution of the intermediate **6** (7.5 g, 20 mmol) at 60 °C in dimethylformamide (40 ml). During the stirring (1 h) the mixture first cleared up and then the cyclization product began to separate. Water (50 ml) was poured to the cooled mixture and the product was filtered off. Yield: 3.8 g (55%) of the product recrystallized from chloroform–diethyl ether, m.p.: 248–251 °C.

Method B: About one tenth of the finely powdered phosphorus pentachloride (totally 5.0 g, 24 mmol) was added to a stirred suspension of the intermediate **10** in chloroform (70 ml) at room temperature. After about 1 min, a vigorous reaction occurred during which the chloroform began to boil and hydrogen chloride was liberated. When this process ceased, further phosphorus pentachloride was added at such a rate as to keep the mixture refluxing. Stirring and refluxing was continued for 1 h; at the end, the mixture solidified from separated cyclization product. Diethyl ether (70 ml) was added to the cooled mixture, the product was filtered off, suspended in water (150 ml) to which potassium carbonate (2.3 g) was added and stirred for 20 min. Finally, the product was filtered off and crystallized from ethanol. Yield: 3.9 g (47%); m.p.: 252–254 °C; anal.: calcd. for $C_{16}H_{15}N_5O_2S$ (341.4): C 56.28, H 4.43, N 20.51, S 9.39; found: C 56.49, H 4.62, N 20.19, S 9.08. MS, *m/z*(relative intensity): 341(1, M^+), 326(5), 253(8), 239(14), 209(7), 164(10), 152(11), 149(18), 148(12), 122(20), 121(11), 117(12), 106(10),

105(100), 103(12). UV (methanol): 221, 321 nm; IR (KBr): 1530, 1600, 1660, 1705, 2970 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.20$ (s, 3H, N-3–CH_3), 3.35 (s, 3H, N-1–CH_3), 3.38 and 4.41 (m, 4H, H-6, H-7), 7.30–7.70 (m, 5H, H-arom); ^{13}C NMR (*DMSO*-d_6): $\delta = 28.0$ (q), 29.8 (q), 46.6 (t), 51.7 (t), 107.6 (s), 2 × 129.0 (d), 2 × 130.1 (d), 135.3 (d), 138.5 (s), 141.7 (s), 147.9 (s), 151.4 (s), 152.0 (s), 154.2 (s).

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