[\textit{f}]-Fused Purine-2,6-diones: Synthesis of New \([1,3,5]\)- and \([1,3,6]\)-Thiadiazepino-
[3,2-\textit{f}]-purine Ring Systems\textsuperscript{**}

D. Hesek\textsuperscript{1} and A. Rybár\textsuperscript{2,*}

\textsuperscript{1} Drug Research Institute, SK-90001 Modra, Slovakia
\textsuperscript{2} Institute of Chemistry, Slovak Academy of Sciences, SK-84238 Bratislava, Slovakia

\textbf{Summary.} 6-Phenyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,8,9-hexahydro-[1,3,5]-thiadiazepino-[3,2-\textit{f}]-purine (5) was obtained by a three-step synthesis from 8-mercapto-1,3-dimethyl-3,7-dihydro-1\textit{H}-purine-2,6-dione (1) and 2-(benzoylamino)-ethyl chloride (2) via 8-(benzoylaminoethylthio)-1,3-dimethyl-3,7-dihydro-1\textit{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-\textit{f}]-purine (7) was synthesized either from compound 1 and N-(2-chloroethyl)-benzimidochloride via N-(chloroethyl)-S-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-7\textit{H}-purin-8-yl)-benzothioimid (6), or alternatively from 7-(2-benzoylaminoethyl)-8-bromo-1,3-dimethyl-3,7-dihydro-1\textit{H}-purine-2,6-dione (9), its 8-mercaptop derivative 10 and the corresponding chlorimidom compound 11 being the intermediates.

\textbf{Keywords.} \([1,3,5]\)- and \([1,3,6]\)-Thiadiazepino-[3,2-\textit{f}]-purines; Intramolecular alkylation.

[\textit{f}]-Anellierte Purin-2,6-dione. Synthese von neuen \([1,3,5]\)- und \([1,3,6]\)-thiadiazepino-
[3,2-\textit{f}]-purinringsystemen

\textbf{Zusammenfassung.} 6-Phenyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,8,9-hexahydro-[1,3,5]-thiadiazepino-
[3,2-\textit{f}]-purin (5) wurde in drei Stufen aus 8-Mercapto-1,3-dimethyl-3,7-dihydro-1\textit{H}-purin-2,6-dion (1) und 2-(Benzoylamino)-ethylchlorid (2) via 8-(2-Benzoylaminoethylthio)-1,3-dimethyl-3,7-dihydro-1\textit{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-\textit{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\textit{H}-purin-8-yl)-benzothioimid (6) oder aus 7-(2-Benzoylaminoethyl)-8-bromo-1,3-dimethyl-3,7-dihydro-1\textit{H}-purin-2,6-dion (9), seinem 8-Mercapto-Analogen 10 und dem entsprechenden Chlorimid-Derivat 11 erhalten.

\textbf{Introduction}

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

\textsuperscript{**} Part of this paper was presented as a preliminary report at the Congress of Czech and Slovak Chemical Societies, Olomouc, Czech Republic, September 13–16, 1993
This compound was, however, obtained as a by-product when preparing 6-(benzoylaminomethylthio)-9H-purine from 6-mercapto-9H-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-mercaptop-1,3-dimethyl-3,7-dihydro-1H-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-(benzoylarnino)-ethyl chloride (2) in ethanol or dimethylformamide in the presence of triethylamine as a hydrogen chloride trapping reagent to give 8-(2-benzoylaminomethylthio)-1,3-dimethyl-3,7-dihydro-1H-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-7H-purin-8-ylthio)-ethyl}-benzamido chloride (4), which underwent intramolecular organic base-catalyzed alkylation to yield the tricyclic [1,3,5]-thiadiazepine 5.

\[
\begin{align*}
\text{CH}_3 \quad \text{N} & \quad \text{SH} \\
\text{O} & \quad \text{CH}_3 \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{Cl-CH}_2\text{CH}_2\text{NH-COC}_6\text{H}_5 & \quad \overset{\text{a}}{\rightarrow} \\
\text{CH}_3 \quad \text{N} & \quad \text{SH} \\
\text{O} & \quad \text{CH}_3 \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 \quad \text{N} & \quad \text{S} \quad \text{SH} \\
\text{O} & \quad \text{CH}_3 \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{Cl-CH}_2\text{CH}_2\text{NH-COC}_6\text{H}_5 & \quad \overset{\text{b}}{\rightarrow} \\
\text{CH}_3 \quad \text{N} & \quad \text{S} \quad \text{CH}_2\text{CH}_2\text{NH-COC}_6\text{H}_5 \\
\text{O} & \quad \text{CH}_3 \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 \quad \text{N} & \quad \text{S} \quad \text{CH}_2\text{CH}_2\text{NH-COC}_6\text{H}_5 \\
\text{O} & \quad \text{CH}_3 \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

Reagents:
\[
\begin{align*}
\text{a} & : \text{Et}_3\text{N, DMF, r.t./2h} \\
\text{b} & : \text{PCl}_5, \text{CH}_2\text{Cl}_2, \text{r.t./30min} \\
\text{c} & : \text{Et}_3\text{N, r.t./2h} \\
\end{align*}
\]

Scheme 1