Synthesis and Properties of 1,3-Dimethyl-6-azalumazines (Isofervenulins)

FUMIO YONEDA, TOMOHISA NAGAMATSU,16) KAZUKO OGIWARA, MICHIKO KANAHORI, SADAO NISHIGAKI,19)
and EDWARD C. TAYLOR16)

Pharmaceutical Sciences, Kumamoto University,16) Pharmaceutical Institute, School of Medicine, Keio University19) and Department of Chemistry, Princeton University16)

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A new synthesis of 1,3-dimethyl-6-azalumazines (isofervenulins) is described. The reaction of 6-amino-1,3-dimethyl-5-nitrosourea (I) with acid hydrazides in refluxing aprotic solvents such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO) or sulfolane affords the corresponding 1,3-dimethyl-6-azalumazines (II) along with by-products, 2,4,9,11-tetramethyl-8-azapurino[7,8-f]-6-azaperidine-1,3,10,12[2H,4H,9H,11H]-tetrones (III). These 8-azapurino[7,8-f]-6-azaperidines were alternatively prepared by the condensation of II with 6-amino-1,3-dimethyluracil in refluxing DMF. Compounds II were converted into 8-substituted theophyllines (V) by reductive ring contraction with sodium dithionite in formic acid.

Keywords—6-azaperidine; 6-azalumazine; 8-azapurino[7,8-f]6-azaperidine; ring contraction; theophylline

The antibiotic tosoflavin4,3) and fervenulin4–11) derivatives of the pyrimido[5,4-e]-astriazone (7-azaperidine) ring system, are of interest because of their close structural similarity to the naturally-occurring and physiologically active pteridines and purines, and because of their demonstrated antimicrobial activity. The isomeric pyrimido[4,5-e]-astriazone (6-azaperidine) system has also become of interest12–20) because of antiviral activity discovered in

1) Location: a) 5-1, Os-kommachi, Kumamoto, 862, Japan; b) 35, Shinanomachi, Shinjuku-ku, Tokyo, 160, Japan; c) Princeton, New Jersey 08540, U.S.A.
this series.\textsuperscript{24,25} For example, 7-ethylmercapto-1,3-dimethyl-6-azalumazine inhibited influenza A PR 8-virus and vaccinia virus.\textsuperscript{24} 

\begin{center}
\begin{tabular}{c c c}
\text{toxoflavin} & \text{fervenulin} & \text{isofervenulin (IIa)} \\
\end{tabular}
\end{center}

\begin{equation}
\begin{array}{c}
\text{CH_3} \\
\text{O} \\
\text{N} \overset{\text{N=N}}{\text{N}} \\
\text{N} \\
\text{CH_3}
\end{array} \quad \text{CH_3} \\
\begin{array}{c}
\text{O} \\
\text{CH_3}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{NH}_3
\end{array} \quad \text{NH}_2\text{NHCOR} \quad \begin{array}{c}
\text{O} \\
\text{CH_3}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{N=O}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{CH_3}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{CH_3}
\end{array} \quad \begin{array}{c}
\text{N=O}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{CH_3}
\end{array} \quad \begin{array}{c}
\text{N} \\
\text{NH}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{CH_3}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{N=O}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{CH_3}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{I} \\
\text{II}
\end{array} \quad \begin{array}{c}
\text{III}
\end{array} \quad \begin{array}{c}
\text{IV}
\end{array}
\end{equation}

\text{Chart 1}

We now report a simple, one-step 6-azalumazine synthesis which consists of treatment of 6-amino-1,3-dimethyl-5-nitrosouracil (I) with acid hydrazides.\textsuperscript{26} For example, heating I with a stoichiometric amount of formylhydrazine in dimethylformamide (DMF) afforded 1,3-dimethyl-6-azalumazine (isofervenulin) (IIa)\textsuperscript{23} in about 15\% yield, along with a small amount of 2,4,9,11-tetramethyl-8-azapurino[7, 8-f]-6-azapteridine-1,3,10,12(3H,4H,9H,11H)-tetrone (IIIa). When dimethylsulfoxide (DMSO) or sulfolane was employed as solvent, the main product was 1,3,7,9-tetramethylpyrimido[5,4-g]pteridine-2,4,6,8(1H,3H,7H,9H)-tetrone (IV). Formation of IV by partial thermal denitrosation of I, followed by condensation between the resulting 1,3-dimethyl-6-aminouracil and unchanged I, is well-known.\textsuperscript{27} Condensation of I with several other acid hydrazides under similar conditions gave 7-substituted 1,3-dimethyl-6-azalumazines (IIc—g) along with the corresponding 8-azapurino[7,8-f]-6-azapteridines (IIIc—g). However, condensation of I with acetylhydrazide in DMF or DMSO gave only the insoluble 8-azapurino[7, 8-f]-6-azapteridine (IIIb) along with a trace of IV.

It is known that under certain conditions 6-amino-5-nitroso-pyrimidines undergo reactions characteristic of oximes rather than nitroso compounds;\textsuperscript{28—30} this also appears to be the case in the above condensation of I with acid hydrazides, and is apparently favored by the use of aprotic solvents. For example, fusion of I with acid hydrazides, or the use of acetic acid as solvent, led only to the symmetrical IV.

\textsuperscript{26} A part of this work was reported at the fourth international symposium on pteridines, Toba, 1969; see F. Yoneda, K. Ogwara, M. Kanahori, S. Nishigaki, and E.C. Taylor in “Chemistry and Biology of Pteridines,” ed. by K. Iwai, M. Akino, M. Goto, and Y. Iwanami, International Academic Printing Co., Ltd., Tokyo, 1970, pp. 145—153.


\textsuperscript{29} W. Pfileiderer and F.E. Kempter, \textit{Angew. Chem.}, 79, 234 (1967).

\textsuperscript{30} W. Pfileiderer and F.E. Kempter, \textit{Angew. Chem.}, 79, 234 (1967).
Representative examples are given in Table I. Yields of products differ according to slight changes in reaction conditions and it was difficult to obtain constant yields. Separation of the reaction products was easily achieved by concentration of the reaction mixture to a

**Table I.** Preparation of 1,3-Dimethyl-6-azalumazines (Isofervenulins) (II) and 8-Azaapurino[7,8-f]-6-azapteridines (III) from I and Acid Hydrazides

<table>
<thead>
<tr>
<th>Substituent (R)</th>
<th>Solvent</th>
<th>Time (hr)</th>
<th>Temp (°C)</th>
<th>Yield (%) of II</th>
<th>Yield (%) of III</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>DMF</td>
<td>6</td>
<td>170</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Me</td>
<td>DMF</td>
<td>6</td>
<td>170</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>Ph</td>
<td>DMF</td>
<td>10</td>
<td>200</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>DMSO</td>
<td>2</td>
<td>200</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Sulfolane</td>
<td>5</td>
<td>250</td>
<td></td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>2-Furyl</td>
<td>DMF</td>
<td>12</td>
<td>170</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>DMSO</td>
<td>2</td>
<td>200</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>2-Thienyl</td>
<td>DMF</td>
<td>8</td>
<td>170</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>DMSO</td>
<td>2</td>
<td>200</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>3-Pyridyl</td>
<td>Sulfolane</td>
<td>2</td>
<td>250</td>
<td>36</td>
<td>14</td>
</tr>
<tr>
<td>4-Pyridyl</td>
<td>DMF</td>
<td>3</td>
<td>170</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Sulfolane</td>
<td>1</td>
<td>250</td>
<td>44</td>
<td>5</td>
</tr>
</tbody>
</table>

**Table II.** UV Absorptions of Isofervenulins (II)

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>(\lambda_{max}) nm (log (\varepsilon))</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>H</td>
<td>239.6 (4.28), 311.5 (3.85)</td>
</tr>
<tr>
<td>IIc</td>
<td>Ph</td>
<td>246.5 (4.46), 351.0 (4.25)</td>
</tr>
<tr>
<td>IIc</td>
<td>2-Furyl</td>
<td>244.0 (4.41), 351.0 (4.42)</td>
</tr>
<tr>
<td>IIe</td>
<td>2-Thienyl</td>
<td>246.3 (4.50), 354.0 (4.54)</td>
</tr>
<tr>
<td>IIg</td>
<td>3-Pyridyl</td>
<td>240.0 (4.43), 327.0 (4.10)</td>
</tr>
<tr>
<td>IIh</td>
<td>4-Pyridyl</td>
<td>234.5 (4.62), 324.0 (4.24)</td>
</tr>
<tr>
<td>Fervenulin</td>
<td></td>
<td>238 (4.27), 340 (3.62)</td>
</tr>
<tr>
<td>1,3-Dimethylumazine</td>
<td></td>
<td>236 (4.19), 331 (3.88)</td>
</tr>
</tbody>
</table>

\(\lambda_{max}\) Measured at pH 6.0. Ph = phenyl

![Chart 2](chart2.png)
small volume, cooling to precipitate the insoluble by-product (III), and dilution of the filtrate with methanol.

Table II gives ultraviolet absorption data for 1,3-dimethyl-6-azalamazine derivatives, as well as for fervenulin31) and 1,3-dimethylllumazine.31) It is interesting to note that introduction of nitrogen into the 6-position of 1,3-dimethylllumazine shifts the longest absorption band from 331 nm to 311.5 nm. On the other hand, introduction of nitrogen into the 7-position (compare 1,3-dimethylllumazine with fervenulin) results in a red shift to 340 nm.

The most intense peak in the mass spectrum (MS) of 1,3-dimethyl-6-azalamazine and its 7-substituted derivatives (II) is at m/e 81. The second most intense peak is the molecular ion except in the case of the 7-phenyl derivative (see Fig. 2). Initial expulsion of nitrogen is the predominant and most characteristic mode of decomposition of a 1,3-dimethyl-6-azalamazine molecular ion. Although no metastable peaks are observed, several common patterns permit some generalization about the fragmentation mechanism, and this is illustrated in Chart 2. Only the 7-unsubstituted derivative (isofervenulin) is exceptional; here HCN is

Fig. 1. Mass Spectrum of 1,3-Dimethyl-6-azalamazine (IIa)

Fig. 2. Mass Spectrum of 1,3-Dimethyl-7-phenyl-6-azalamazine (IIc)

initially lost. Fig. 1 and 2 show the mass spectra of isofervenulin (IIa) and its 7-phenyl derivative (IIc).

The assigned structures of by-products (III) as 2,4,9,11-tetramethyl-8-azapurino[7,8-f]-6-azapteridine-1,3,10,12(2H,4H,9H,11H)-tetrone were derived on the basis of elemental analyses, molecular weights as determined by mass spectrometry, the presence of N–H absorption (3180 cm⁻¹ region) in their infrared spectra, the presence of four N-methyl groups in their nuclear magnetic resonance (NMR) spectra and by consideration of their probable mode of formation. The reaction presumably is initiated by nucleophilic attack of 6-amino-1,3-dimethyluracil (formed by denitrosation of I) on the electron deficient N-5 of the preformed

1,3-dimethyl-6-azalumazines (II).\textsuperscript{32}) Intramolecular cyclization of the resulting adduct and subsequent dehydrogenation would then yield III.

To confirm this, we have examined the condensation of II with 6-amino-1,3-dimethyluracil; for example, refluxing IIc with 6-amino-1,3-dimethyluracil in DMF gave IIIc in 70% yield.

Treatment of the above isofervenulin derivatives (II) with sodium dithionite in formic acid gave 8-substituted theophyllines (V), whose structures were established by comparison with authentic samples prepared by an alternative route.\textsuperscript{33})

\textsuperscript{32}) Fig. 3 and 4 show $\pi$-electron distributions of 1,3-dimethyl-6-azalumazine, and frontier electron distributions and superdelocalizabilities for reaction with nucleophiles calculated by a simple LCAO-MO method. The parameters used in these calculations are shown in Fig. 5. As can be seen from Figs 3 and 4, the most reactive site of II for nucleophilic addition is N-5.

The ring contraction observed in the conversion of isofervenulins to 8-substituted theophyllines is best rationalized by assuming initial reductive nitrogen-nitrogen bond cleavage to a 5-amino-6-amidinouracil, followed by intramolecular cyclization with elimination of ammonia. A remarkable solvent effect was noted during these reductive studies; heating of the above isofervenulins with sodium dithionite in DMSO resulted solely in the formation of IV.

![Chart 4](image)

**Experimental**

1,3-Dimethyl-6-azalumazine (Isofervulin) (IIa)—A mixture of I (0.9 g, 0.005 mol) and formylhydrazine (0.3 g, 0.005 mol) in DMF (25 ml) was heated under mild reflux for 6 hr. The reaction mixture was evaporated to dryness and the residue was recrystallized from benzene to remove the less soluble 8-azapurino[7,8-f]-6-azaperidine (IIIa) as a yellow microcrystalline powder, MS m/e: 346 (M+). The filtrate

**Table III.** 7-Substituted 1,3-Dimethyl-6-azalumazines (Isofervenulins)

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>mp (°C)</th>
<th>Recrystn. solvent</th>
<th>MS m/e (M+)</th>
<th>Formula</th>
<th>Analysis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>IIa</td>
<td>H</td>
<td>199–200</td>
<td>MeOH</td>
<td>193</td>
<td>C₂H₃N₅O₂</td>
<td>43.52</td>
</tr>
<tr>
<td>IIc</td>
<td>Ph</td>
<td>239–240</td>
<td>MeOH or Benzene</td>
<td>269</td>
<td>C₁₂H₁₃N₅O₂</td>
<td>57.98</td>
</tr>
<tr>
<td>IIId</td>
<td>2-Furyl</td>
<td>275–276</td>
<td>MeOH or CHC₁₃</td>
<td>259</td>
<td>C₁₁H₁₂N₅O₃</td>
<td>50.96</td>
</tr>
<tr>
<td>IIe</td>
<td>2-Thieryl</td>
<td>249–250</td>
<td>MeOH or CHCl₃</td>
<td>275</td>
<td>C₁₃H₁₄N₅O₃S</td>
<td>47.99</td>
</tr>
<tr>
<td>IIIf</td>
<td>3-Pyridyl</td>
<td>245</td>
<td>EtOH</td>
<td>270</td>
<td>C₁₂H₁₄N₅O₂</td>
<td>53.33</td>
</tr>
<tr>
<td>IIIfa</td>
<td>4-Pyridyl</td>
<td>292–295</td>
<td>EtOH</td>
<td>270</td>
<td>C₁₃H₁₄N₅O₂</td>
<td>53.33</td>
</tr>
</tbody>
</table>

34) All melting points were uncorrected. NMR spectra were determined with a JEOL JNM 3H-60 spectrometer (tetramethylsilane as internal standard). Identity of compounds was confirmed by comparison of infrared (IR) spectra (Nujol mulls) with a JASCO IR-1A spectrophotometer.
was evaporated to dryness and the residue was recrystallized from methanol to give isorfenulnin (IIa), mp 209—210° (lit.²⁹ 212°). NMR (DMSO-d₆) δ: 3.35 (s, N-Me), 3.49 (s, N-Me) and 9.66 (s, C-7 H).

When this reaction was carried out in DMSO or sulfolane at 200° for 2 hr, 1,3,7,9-tetramethylpyrimido-[5,4-e]pteridine-2,4,6,8(1H,3H,7H,9H)-tetrones (IV),³⁷ mp>360°, was obtained almost exclusively in 30% yield.

7-Substituted 1,3-Dimethyl-6-azalazines (IIc—g). General Procedure—A mixture of I (1.8 g, 0.01 mol) and an acid hydrazide (0.01 mol) in DMF (45 ml), DMSO (40 ml) or sulfolane (20 ml) was heated under the conditions indicated in Table I. The reaction mixture was concentrated to a small volume and cooled to precipitate the less soluble by-product, the 8-azapurino[7,8-f]-6-azapteridine (III). The filtrate was diluted with methanol and allowed to stand overnight to separate the corresponding 1,3-dimethyl-6-azalazine (II). These products were recrystallized from appropriate solvents.

Alternative Synthesis of 8-Azapurino[7,8-f]-6-azapteridines (III). General Procedure—A mixture of a 1,3-dimethyl-6-azalazine (II) (0.01 mol) and 6-amino-1,3-dimethyluracil (0.01 mol) in DMF (50 ml) was refluxed for 10 hr, and the reaction mixture was concentrated to a small volume. The crystals thus separated were filtered off and recrystallized from appropriate solvents to give III as yellow crystals in 60—70% yields.

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>mp (°C)</th>
<th>Recrystn. solvent</th>
<th>MS m/e (M+</th>
<th>Formula</th>
<th>Analysis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIa</td>
<td>H</td>
<td>&gt;330</td>
<td>MeOH</td>
<td>346</td>
<td>C₁₃H₁₄N₅O₄</td>
<td>Calcd.: C 45.08, H 4.08, N 32.36, H 4.12</td>
</tr>
<tr>
<td>IIIb</td>
<td>Me</td>
<td>&gt;330</td>
<td>CHCl₃</td>
<td>360</td>
<td>C₁₃H₁₄N₅O₄</td>
<td>Calcd.: C 46.66, H 4.48, N 31.10, H 4.43</td>
</tr>
<tr>
<td>IIIc</td>
<td>Ph</td>
<td>&gt;330</td>
<td>CHCl₃</td>
<td>422</td>
<td>C₁₃H₁₄N₅O₄</td>
<td>Calcd.: C 54.02, H 4.30, N 26.53, H 53.93, H 4.35</td>
</tr>
<tr>
<td>IIId</td>
<td>2-Furyl</td>
<td>&gt;330</td>
<td>CHCl₃</td>
<td>412</td>
<td>C₁₃H₁₄N₅O₄</td>
<td>Calcd.: C 49.51, H 3.91, N 27.18, H 49.52, H 3.90</td>
</tr>
<tr>
<td>IIIe</td>
<td>2-Thienyl</td>
<td>&gt;330</td>
<td>CHCl₃</td>
<td>428</td>
<td>C₁₃H₁₄N₅O₄S</td>
<td>Calcd.: C 47.68, H 3.76, N 26.14, H 48.00, H 4.12</td>
</tr>
<tr>
<td>IIIf</td>
<td>3-Pyridyl</td>
<td>&gt;330</td>
<td>DMF</td>
<td>423</td>
<td>C₁₃H₁₄N₅O₄</td>
<td>Calcd.: C 51.06, H 4.05, N 29.78, H 50.94, H 4.03</td>
</tr>
<tr>
<td>IIIg</td>
<td>4-Pyridyl</td>
<td>&gt;330</td>
<td>DMF</td>
<td>423</td>
<td>C₁₃H₁₄N₅O₄</td>
<td>Calcd.: C 47.68, H 3.76, N 26.14, H 48.00, H 4.12</td>
</tr>
</tbody>
</table>

Conversion of 1,3-Dimethyl-6-azalazines (II) into Theophyllines (V). General Procedure—A mixture of II (0.002 mol) and Na₅S₃O₇ (5.2 g, 0.03 mol) in 90% HCOOH (30 ml) was heated as indicated in Table V. After cooling, the precipitated crystals were filtered off, washed with H₂O and recrystallized from DMF to give the corresponding 8-substituted theophyllines (V), which were in all respects identical with authentic samples prepared by an alternative route.³⁹

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Substituent (R)</th>
<th>Reaction Time (hr)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Formula</th>
<th>Analysis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vc</td>
<td>Ph</td>
<td>15</td>
<td>180</td>
<td>50</td>
<td>&gt;330</td>
<td>C₁₉H₁₄N₅O₄</td>
<td>Calcd.: C 60.93, H 4.72, N 21.87, H 60.77, H 4.59</td>
</tr>
<tr>
<td>Vd</td>
<td>2-Furyl</td>
<td>7</td>
<td>160</td>
<td>38</td>
<td>&gt;330</td>
<td>C₁₉H₁₄N₅O₄</td>
<td>Calcd.: C 53.66, H 4.09, N 22.76, H 53.72, H 4.15</td>
</tr>
<tr>
<td>Vf</td>
<td>3-Pyridyl</td>
<td>6</td>
<td>180</td>
<td>56</td>
<td>&gt;330</td>
<td>C₁₉H₁₄N₅O₄</td>
<td>Calcd.: C 56.02, H 4.31, N 27.23, H 56.13, H 4.33</td>
</tr>
<tr>
<td>Vg</td>
<td>4-Pyridyl</td>
<td>6</td>
<td>180</td>
<td>68</td>
<td>&gt;330</td>
<td>C₁₉H₁₄N₅O₄</td>
<td>Calcd.: C 56.02, H 4.31, N 27.23, H 56.20, H 4.27</td>
</tr>
</tbody>
</table>