A NEW SYNTHESIS OF PYRIMIDO[4,5-b]QUINOLINE-2,4(1H,3H)-DIONE (5-DEAZAALLOXAZINE) DERIVATIVES

Keitaro Senge,* Kayoko Shimizu, and Sadao Nishigaki
Pharmaceutical Institute, School of Medicine, Keio University, Shinanomachi, Shinjuku-ku, Tokyo 160, Japan
Fumio Yoneda
Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi, Kumamoto 862, Japan

Treatment of 6-anilino-1,3-dimethyluracils with dimethylformamide dimethylacetal afforded the corresponding 1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-diones (1,3-dimethyl-5-deazaalloxazines).

We wish to report a new synthesis of 1,3-dimethylpyrimido-[4,5-b]quinoline-2,4(1H,3H)-dione (1,3-dimethyl-5-deazaalloxazine) derivatives (IVa-e) by a treatment of 6-anilino-1,3-dimethyluracils (IIa-e) with dimethylformamide dimethylacetal.

The starting materials, (IIa-e), were prepared by the nucleophilic displacement of 6-chloro-1,3-dimethyluracil (I) with the respective anilines according to the reported procedure (Table I).

Heating of (IIa) with excess dimethylformamide dimethylacetal at 95°C for 1.5 hr afforded 1,3-dimethylpyrimido[4,5-b]quinoline-
2,4(1H,3H)-dione (IVa), which was isolated by concentration of the reaction mixture and addition of ethanol. In complete analogy with the above result, the reaction of other 6-anilino-1,3-dimethyluracils (IIb-e) with dimethylformamide dimethylacetal provided the corresponding pyrimido[4,5-b]quinoline derivatives (IVb-e) (Table II). The structures of (IVa-e) were confirmed by the satisfactory spectral data and elemental analyses.  

Scheme
Table I  6-Anilino-1,3-dimethyluracils

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
<th>Mp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>H</td>
<td>190-192&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>87</td>
</tr>
<tr>
<td>IIb</td>
<td>OMe</td>
<td>188-190&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>91</td>
</tr>
<tr>
<td>IIc</td>
<td>Br</td>
<td>217-219&lt;sup&gt;a&lt;/sup&gt;</td>
<td>97</td>
</tr>
<tr>
<td>IID</td>
<td>Cl</td>
<td>210-212&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td>81</td>
</tr>
<tr>
<td>IIE</td>
<td>NO₂</td>
<td>270-272&lt;sup&gt;e&lt;/sup&gt;</td>
<td>48</td>
</tr>
</tbody>
</table>

<sup>a</sup>) Recrystallized from EtOH.
<sup>b</sup>) Lit. mp 186.5-187°.
<sup>c</sup>) Lit. mp 243°.
<sup>d</sup>) Lit. mp 212-214°.
<sup>e</sup>) Recrystallized from DMF.

Table II  1,3-Dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-diones<sup>a</sup>

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
<th>Mp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVA</td>
<td>H</td>
<td>211-212</td>
<td>60</td>
</tr>
<tr>
<td>IVB</td>
<td>OMe</td>
<td>273-274</td>
<td>63</td>
</tr>
<tr>
<td>IVC</td>
<td>Br</td>
<td>275</td>
<td>56</td>
</tr>
<tr>
<td>IVD</td>
<td>Cl</td>
<td>270</td>
<td>62</td>
</tr>
<tr>
<td>IVE</td>
<td>NO₂</td>
<td>&gt;300</td>
<td>35</td>
</tr>
</tbody>
</table>

<sup>a</sup>) All compounds were recrystallized from DMF.
As depicted in the Scheme, the new pyrimido[4,5-b]quinoline synthesis is presumably initiated by the formation of 5-N,N-di-methylaminomethylene intermediate (III), which possesses an aza-hexatriene-type structure. This could undergo intramolecular cyclization through valence isomerization and subsequent aromatization by elimination of dimethylamine. Recently, this type of intramolecular cycloaddition of azahexatrienes has been demonstrated in the preparation of purines,\(^5,6\) pteridines,\(^6,7\) and pyrazolo[3,4-d]pyrimidines.\(^5,8\)

REFERENCES AND NOTES
1 W. Pfleiderer and K.H. Schündehütte, Annalen, 1958, 613, 158.
2 H. Goldner, G. Dietz, and E. Carstens, Annalen, 1966, 694, 142:
As one exception, the compound (IIe) was prepared by the fusion of (I) with p-nitroaniline at 180° for 3 hr.
3 For example, the spectral data for compound (IVa) are as follows.
\[\text{MS (m/e): 241 (M^+), IR } \text{cm}^{-1}: 1650 (C=O), 1705 (C=O), \text{NMR(DMSO-\text{d}_6)} \]
\[\text{δ: 3.33 (3H, s, N-Me), 3.63 (3H, s, N-Me), 7.33-8.33 (4H, m, C}_6\text{H}_4), \]
9.40 (1H, s, C^5-H).

Received, 22nd June, 1977