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Different Behaviour of Fervenulin 4-Oxide and 1,3-Dimethyllumazine 5-Oxide towards Nucleophiles

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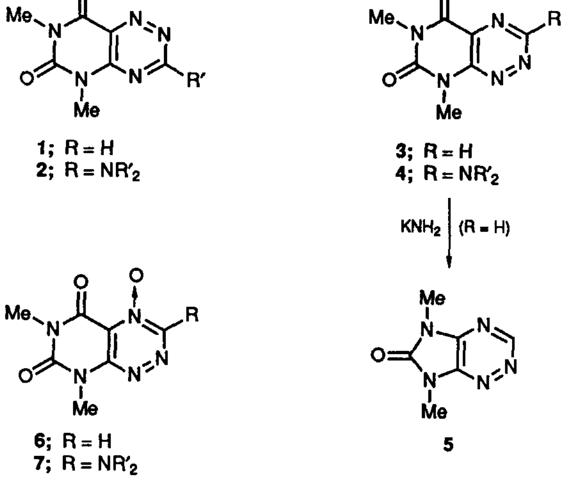
Fervenulin 4-oxide reacts with secondary amines and carbanions to give derivatives of 1,3-dimethyl-5-nitroso-6-hydrazinouracil **9** and **10**; under similar conditions 1,3-dimethyllumazine 5-oxide reacts with piperidine and morpholine to give products **14** in high yield, by nucleophilic substitution of hydrogen at C(6).

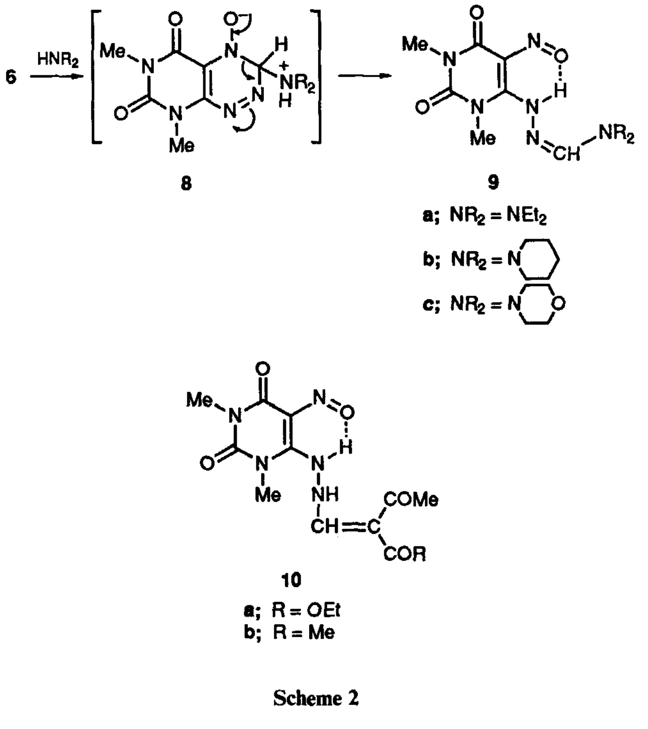
Recently we have shown that 5,7-dimethylpyrimido[4,5-*e*]-1,2,4-triazine-6,8-dione (isofervenulin) **1** is easily aminated with liquid ammonia and alkylamines in the presence of permanganate anions to afford the corresponding 3-amino derivatives **2**.[1] Contrary to this the natural antibiotic fervenulin **3** remains unchanged under the same conditions, but with stronger nucleophiles (*e.g.* KNH_2) it is converted into 5,7-dimethylimidazo[4,5-*e*]-1,2,4-triazine-6-one **5** (Scheme 1).[1] In the present work our aim was to change the direction of nucleophilic attack on the fervenulin molecule in order to obtain previously unknown 3-aminofervenulins. We thus decided to use fervenulin 4-oxide **6** in the reaction with nucleophiles. Until now the only observed instance of interaction of **6** with nucleophilic reagents was its conversion to compound **5** on refluxing with concentrated aqueous potassium hydroxide.[2] Nevertheless we hoped that in the case of milder nucleophiles, such as alkylamines, the reaction would result in the formation of the amines **4** or their *N*-oxides **7**.

Compound **6** was found to react with alkylamines at room temperature giving rise to bright yellow substances, in high yield, which proved to be amidrazones **9** (Scheme 2).† Thus in accordance with our expectation the alkylamines are indeed joined to C(3) of fervenulin 4-oxide but the initially formed σ-complex **8** is evidently unstable and rearranges to **9** in order to become aromatized. The addition to the reaction mixture of an oxidant $[Ag(C_5H_5N)_2MnO_4]$[3] only accelerates the formation of compounds **9** and does not lead to the desired 3-aminofervenulins.

The reaction of fervenulin 4-oxide with *C*-nucleophiles (ethyl acetoacetate and acetylacetone in the presence of diethylamine



Scheme 1



Scheme 2

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† *Typical procedure*: a suspension of **6** (0.21 g, 1 mmol) in alkylamine (40 ml diethylamine, 2 ml other amines) was stirred at room temperature for 10–90 min until it dissolved fully. The orange solution was then evaporated and the dry residue extracted with 20 ml of chloroform. Chromatography on Al_2O_3 (chloroform) followed by recrystallization from ethanol afforded a 75–79% yield of **9** as yellow–orange needles. Compound **9a** m.p. 159–161 °C (decomp.); **9b** m.p. 156–157 °C (decomp.); **9c** m.p. 154–155 °C (decomp.).

All compounds **9** gave analytical and spectral data in agreement with their structures. For **9a**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.23 (t, *J* 7.1 Hz, 3H, Me—CH_2'), 1.30 (t, *J* 7.1 Hz, 3H, Me—CH_2''), 3.36 [s, 3H, Me—N(3)], 3.39 (q, *J* 7.1 Hz, 4H, $2CH_2$), 3.40 [s, 3H, Me—N(1)], 7.90 (d, *J* 2.0 Hz, 1H, —CH=), 15.05 (d, *J* 2.0 Hz, 1H, NH); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.38 (qt, *J* 128.1 and 3.3 Hz, Me'), 14.35 (qt, *J* 127.0 and 2.8 Hz, Me''), 28.36 [q, *J* 141.9 Hz, Me—N(1)], 31.95 [q, *J* 141.9 Hz, Me—N(3)], 41.95 (tm, *J* 138.6 Hz, CH_2—N'), 47.54 (tm, *J* 138.6 Hz, CH_2—N''), 140.37 [s, C(5)], 143.41 [q, *J* 2.2 Hz, C(6)], 150.27 (qq, *J* 2.2 Hz, C(2)], 156.14 (dq, *J* 181.1 and 4.1 Hz, —CH=), 160.06 [q, *J* 2.8 Hz, C(4)]; IR ($CHCl_3$) ν/cm^{-1} 1675, 1710 (CO); UV λ_{max}/nm (lg ε) (MeOH) 259 (4.33), 384 (3.64); *m*/*z* 282 (M^+).

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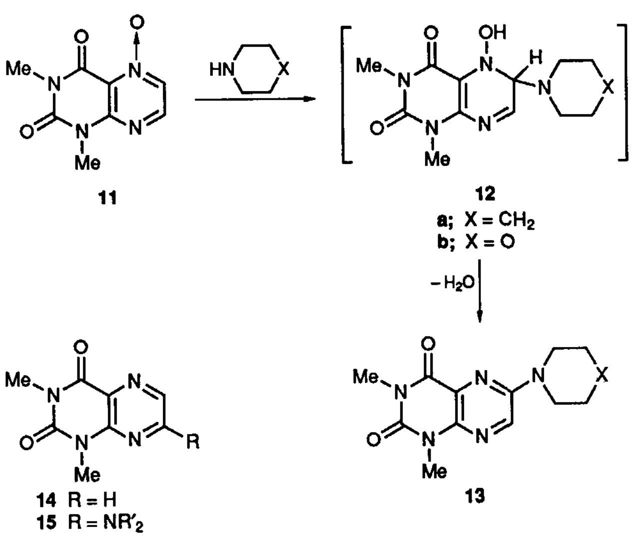

Scheme 3

were used) proceeds in the same way and produces compounds **10**.‡

It was further established that 1,3-dimethyllumazine 5-oxide **11**,[4] a structural deaza analogue of **6**, behaves differently under the action of nucleophiles. Treatment of **11** with an excess of piperidine or morpholine affords the 6-piperidino(morpholino)-1,3-dimethyllumazines **13** in almost quantitative yield (Scheme 3).§ This is the first case of nucleophilic substitution of the hydrogen atom at C(6) of the lumazine system. As demonstrated earlier 1,3-dimethyllumazine **14** undergoes oxidative amination with ammonia and alkylamines at C(7), giving rise to the corresponding 7-amino derivatives in moderate yields.[5]

The structure of compounds **13** was proven by the independent synthesis of **13a** by addition of piperidine to the known 1,3-dimethyl-6-chlorolumazine.[6]

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‡ Diethylamine (0.52 ml, 2 mmol) was added to a stirred suspension of **6** (0.21 g, 1 mmol) in ethyl acetoacetate (10 ml). After 5–7 min at 20 °C an orange precipitate of **10a** had formed. The mixture was stirred at room temperature for 15 min and filtered. Recrystallization from ethanol gave 0.27 g (65%) of the product **10a** as bright yellow crystals, m.p. 162–164 °C (decomp.). For **10b**: time of reaction 80 min, yield 10%, m.p. 165–167 °C (decomp.).

Both compounds **10** gave satisfactory analytical and spectral data. For **10a**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.35 (t, *J* 7.1 Hz, 3H, *Me*—CH_2), 2.48 (s, 3H, COMe), 3.26 [s, 3H, Me—N(3)], 3.49 [s, 3H, Me—N(1)], 4.24 (q, *J* 7.1 Hz, 2H, CH_2), 8.44 (d, *J* 11.6 Hz, 1H, —CH=), 14.83 (d, *J* 11.6 Hz, 1H, NH); IR ($CHCl_3$) ν/cm^{-1} 1655–1680 (CO), 2600–3400 (NH).

§ *Typical procedure*: a solution of **11** (0.21 g, 1 mmol) in alkylamine (50 ml) was stirred at room temperature for 2 h. The mixture was then evaporated and the dry residue extracted with 30 ml of chloroform. Chromatography on Al_2O_3 (chloroform) followed by recrystallization from ethanol afforded a 90–92% yield of product **13** as bright yellow needles. Compound **13a** m.p. 166–168 °C; **13b** m.p. 189–191 °C.

Spectral data for **13a**: ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.62 (s, 6H, β- and γ-CH_2 piperidino), 3.45 [s, 3H, Me—N(3)], 3.57 [pseudosinglet, 7H, Me—N(1) and α-CH_2 piperidino], 8.2 [s, 1H, H(7)]; IR ($CHCl_3$) ν/cm^{-1} 1660, 1700 (CO); UV λ_{max}/nm (lg ε) (MeOH) 240 (4.14), 283 (4.38), 418 (3.71). For **13b**: ^{1}H NMR (80 MHz, $CHCl_3$) δ 3.42 [s, 3H, Me—N(3)], 3.57 [pseudosinglet, 7H, Me—N(1) and 2CH_2 morpholino], 3.78 (m, 4H, 2CH_2 morpholino), 8.2 [s, 1H, H(7)]; IR ($CHCl_3$) ν/cm^{-1} 1670, 1700 (CO); UV λ_{max}/nm (lg ε) (MeOH) 241 (4.25), 280 (4.18), 347 (3.45), 406 (3.51).