Synthesis of Fervenulin 4-Oxide and Its Conversion to the Antibiotics Fervenulin and 2-Methylfervenulone[1]

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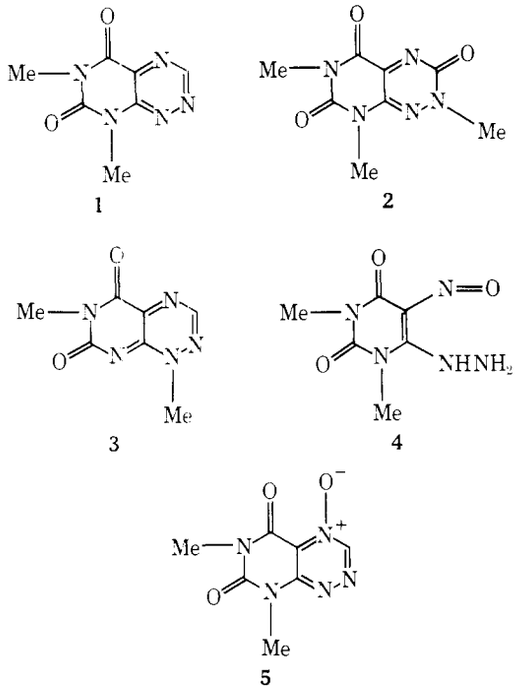
Normally inaccessible fervenulin 4-oxide (**5**) was synthesized in a single step by the reaction of 1,3-dimethyl-6-hydrazino-5-nitrosouracil (**4**) with one-carbon reagents (dimethylformamide–phosphorus oxychloride, dimethylformamide–dimethyl sulfate, formic acid, and triethyl orthoformate). Compound **5** was found to be a versatile intermediate for the synthesis of antibiotics fervenulin (**1**) and 2-methylfervenulone (MSD-92) (**2**). Namely, the antibiotic **1** could be synthesized in the highest yield when **5** was treated with sodium hydrosulfite in water. The antibiotic **2** was synthesized most conveniently by the following three steps: treatment of **5** with dimethylformamide–phosphorus oxychloride afforded 3-chloro-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (**14**), followed by acid hydrolysis to fervenulone (**15**), and subsequent alkylation with methyl iodide in dimethylformamide containing potassium carbonate. Some derivatives related to **1** or **5** were also prepared from **4** or **5**.

In recent years considerable chemical and medicinal interest has been focused on the pyrimido[5,4-*e*]-*as*-triazine (7-azapteridine) ring system primarily because of the attractive biological activities displayed by the antibiotics fervenulin (**1**), 2-methylfervenulone (MSD-92) (**2**), and toxoflavin (**3**).[2] In connection with our recent studies on the synthesis of purines[3] and pteridines[4] from 6-amino-1,3-dimethyl-5-nitrosouracil, we have now examined the reaction of readily available 1,3-dimethyl-6-hydrazino-5-nitrosouracil (**4**)[5] with various one-carbon reagents (dimethylformamide–phosphorus oxychloride, dimethylformamide–dimethyl sulfate,[6] formic acid, and triethyl orthoformate) and have found that the respective product is surprisingly fervenulin 4-oxide (**5**), which is a versatile intermediate for the synthesis of pyrimido[5,4-*e*]-*as*-triazine derivatives including the antibiotics **1** and **2**.



The 4-oxide **5** seems to be less accessible by the conventional peroxy acid oxidation since the π-electron distribution of **1** calculated by the Hückel LCAO–MO method indicates that the most reactive site for the oxidation is position 1.[7] In fact, the oxidation of **1** with trifluoroperacetic acid has been shown to give fervenulin 1-oxide.[8] Recently, Yoneda et al.[7] reported the synthesis of 3-substituted fervenulin 4-oxides by the nitrosative cyclization of 6-alkylidene(or benzylidene)hydrazino-1,3-dimethyluracils in the presence of diethyl azodicarboxylate. However, the preparation of **5** itself has not been described. We now wish to report four new one-step syntheses of **5** and its successful conversion to the antibiotics **1** and **2** as well as to some derivatives related to **1**.

Fervenulin 4-Oxide. Treatment of **4** with a mixture of dimethylformamide and phosphorus oxychloride (Vilsmeier reagent) at 0 °C followed by stirring at room temperature for 30 min gave **5** in 72% yield (method A). The structure of **5** was assigned by the satisfactory elemental analysis and spectral data. The mass spectrum showed a strong parent ion at *m/e* 209 and a remarkable $M^+ - 16$ ion due to the presence of *N*-oxide. The NMR spectrum revealed the presence of two *N*-methyl groups (δ 3.45 and 3.80) and a single aromatic proton (δ 10.30). The structure of **5** was finally corroborated by its successful reduction to the antibiotic **1** (vide infra). The formation of **5** presumably proceeds through the *N,N*-dimethylaminomethylenehydrazino intermediate **6**, followed by cyclization, and subsequent aromatization by loss of dimethylamine.[9] There seem to be no previous instances in which the Vilsmeier reagent has been used for the synthesis of heterocyclic *N*-oxides. Method A was found to be greatly dependent on the reaction temperature. When this reaction was attempted without cooling, the product obtained was not **5** but *v*-triazolo[4,5-*d*]pyrimidine derivatives (**9**),[10] which arise from the intramolecular dehydrative cyclization of **4**. In analogy with method A, treatment of **4** with dimethylformamide–dimethyl sulfate complex[6] (a modified Vilsmeier reagent) at room temperature for 2 h afforded a 43% yield of **5**, probably via the same intermediate with that of method A (method B). Refluxing **4** with formic acid for 30 min also provided a 54% yield of **5**, presumably formed via the dehydrative cyclization of a formylhydrazino intermediate **7** (method C). Furthermore, heating **4** with triethyl orthoformate at 90 °C for 30 min caused the separation of **5** in 71% yield (method D). This method appears to have greater scope than those of methods A, B, and C, and constitutes a general synthetic route to fervenulin 4-oxide derivatives. For example, the reaction of **4** with triethyl orthoacetate or triethyl orthopropionate under the conditions described above furnished the corresponding 3-alkylfervenulin 4-oxides, **10**[7] and **11**, in high yields. The condensation of **4** with ortho esters may be involved with the intermediacy of α-ethoxyalkylidenehydrazino derivative **8**, which undergoes cyclization by the elimination of ethanol. In general, the proposed intermediates, **6**, **7**, and **8**, described in the above reactions can exist in either nitroso or oxime forms; however, these cyclizations may be facilitated by the nucleophilicity of the latter. The partici-

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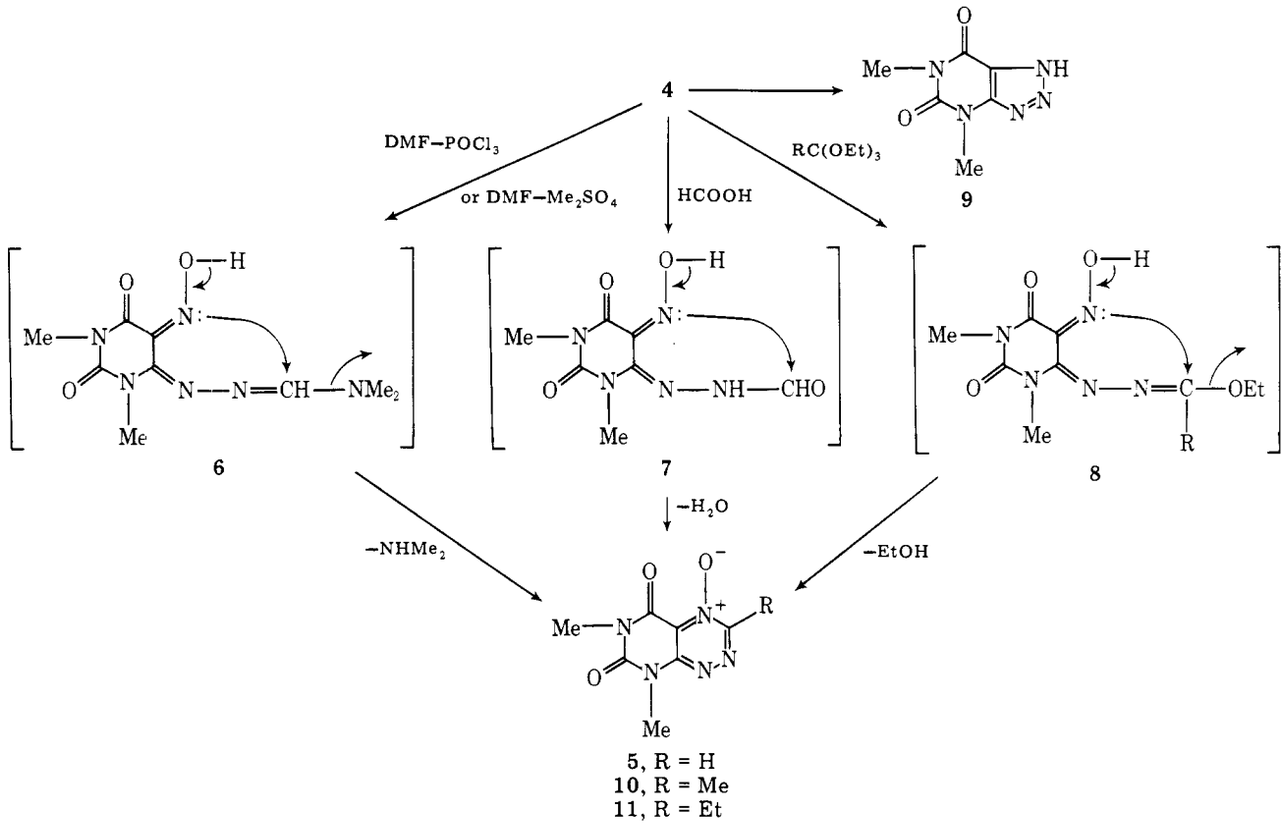
Scheme I



pation of oxime groups as nucleophiles has been well documented[11] (Scheme I).

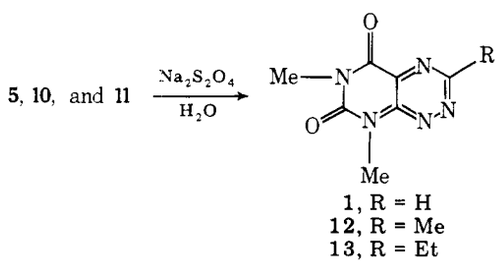
Fervenulin and 2-Methylfervenulone. The total syntheses of antibiotics fervenulin (**1**)[5,8,12–16] and 2-methylfervenulone (MSD-92) (**2**)[15] have been accomplished. We have now examined a new synthetic approach to these antibiotics starting with fervenulin 4-oxide (**5**) obtained above.

Antibiotic **1** could be obtained in an excellent yield by the reduction of **5** with aqueous sodium hydrosulfite at room temperature. Compound **1** thus obtained was identical in all respects with the authentic sample prepared by the reported procedure.[5] Analogously, compounds **10** and **11** were converted to the corresponding 3-alkylfervenulins, **12** and **13**. The deoxygenation of *N*-oxide function of **5** to **1** was also achieved by the prolonged heating with dimethylformamide in less satisfactory yield (Scheme II).

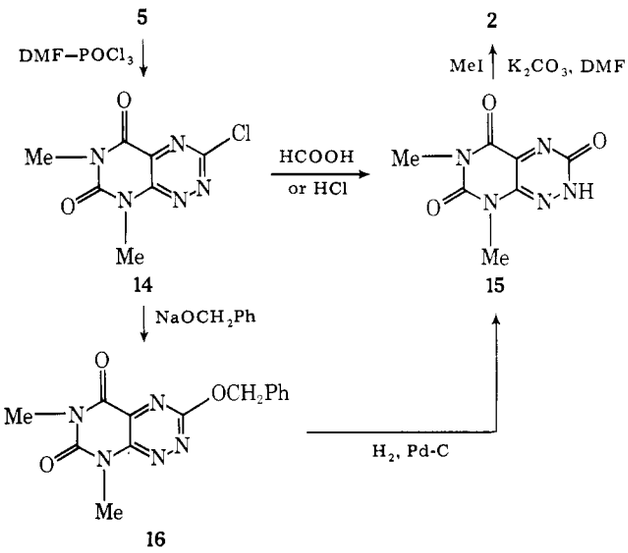
Antibiotic **2** was prepared most conveniently by three steps starting with **5** as described below. Treatment of **5** with a mixture of dimethylformamide and phosphorus oxychloride at 50 °C afforded the chloro derivative **14**[15] in 84% yield. Heating **14** with either formic acid[17] at reflux or 2 N hydrochloric acid at 90 °C gave fervenulone (**15**),[15] the precursor of **2**, in 89 and 51% yield, respectively. Compound **15** could also be obtained from **14** by the indirect route. Thus the nucleophilic displacement of chloride from **14** with sodium benzyloxide gave the benzyloxy derivative **16**, and the subsequent removal of the benzyl group by catalytic reduction with palladium charcoal provided **15** in 50% yield. The final alkylation was accomplished in almost quantitative yield by the reaction of **15** with methyl iodide in dimethylformamide containing potassium carbonate. The spectral data (IR, NMR, MS, and UV) of the synthetic compound and those of the authentic sample described in the literature[18] proved to be identical (Scheme III).

In connection with **15**, we also attempted the direct synthesis of **15** from **5** since various heterocyclic *N*-oxides have been known to react with nucleophiles to give α-hydroxy compounds.[19] However, these attempts were found to be unsuccessful. Thus, treatment of **5** with tosyl chloride in

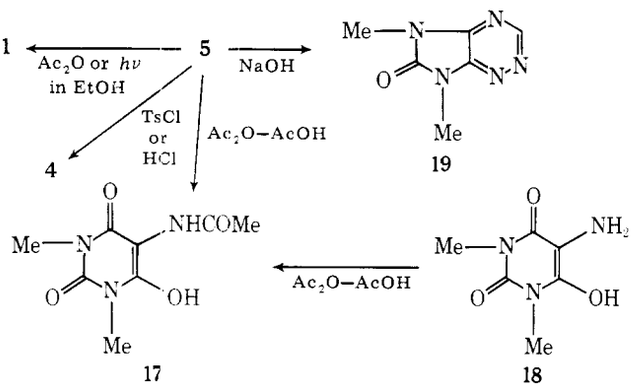
Scheme II



Scheme III



Scheme IV



chloroform caused the ring cleavage of the *as*-triazine nucleus to give the starting material (**4**), which was alternatively obtained by the action of methanolic hydrochloric acid on **5**. Refluxing **5** with acetic anhydride gave only **1**. Treatment of **5** with a mixture of acetic anhydride and acetic acid furnished 5-acetylamino-1,3-dimethylbarbituric acid (**17**), which was identical with the sample prepared by the acetylation of 5-amino-1,3-dimethylbarbituric acid (**18**)[20] with a mixture of acetic anhydride and acetic acid.[21] In contrast to the acids, treatment of **5** with 0.5% sodium hydroxide resulted in the deoxygenation of the *N*-oxide group and ring contraction of the pyrimidine moiety to give a new class of azapurine, imidazo[4,5-*e*]-*as*-triazine derivative (**19**), in 40% yield.[22] The structure of **19** was supported by the elemental analysis and spectral data. In particular the IR spectrum revealed a characteristic carbonyl band at 1750 cm^{-1},[23] and the NMR spectrum showed the presence of two *N*-methyl groups (δ 3.31 and 3.40) and a single aromatic proton (δ 10.23). The mechanism of this ring contraction probably involves a benzylic acid type rearrangement which has been discussed in the conversion of a certain pyrimido[5,4-*g*]pteridine 5-oxide to an imidazo[4,5-*b*]pyrazine by the action of sodium hydroxide.[24] The photoirradiation of **5** in ethanol provided only **1** in 54% yield and no rearrangement of the *N*-oxide group was observed (Scheme IV).

Experimental Section

Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Japan Spectroscopic Co., Ltd. Model IR-E spectrophotometer from samples mulled in Nujol. NMR spectra were determined at 60 MHz with a Varian T-60 spectrometer using tetramethylsilane as the internal standard. UV spectra were recorded on a Hitachi 124 spectrophotometer. Mass spectra were performed on a JMS D100 EI spectrometer by a direct inlet system at 75 eV.

6,8-Dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione 4-Oxide (Fervenulin 4-Oxide (5)). Method A. The suspension of 1,3-dimethyl-6-hydrazino-5-nitrosouracil (**4**)[5] (0.199 g, 0.001 mol) in dry DMF (3 mL) was stirred at 0 °C while the Vilsmeier reagent prepared from dry DMF (0.29 g, 0.004 mol) and $POCl_3$ (0.153 g, 0.001 mol) was added dropwise. When the addition was complete the reaction mixture was allowed to warm to room temperature and stirred for 30 min. The resulting solution was diluted with EtOH (2 mL) and evaporated in vacuo. The residue was poured onto ice–water and the precipitated solid was filtered. Recrystallization from EtOH gave **5** (0.15 g, 72%): mp 179—180 °C; IR 1715, 1660 cm^{-1} (CO); NMR ($CDCl_3$) δ 3.45 (s, 3 H, NCH_3), 3.80 (s, 3 H, NCH_3), 10.30 (s, 1 H, C^3H); UV λ_{max} (EtOH) 240 nm (log ϵ 4.10), 304 (3.21), 323 sh (2.78); MS *m/e* 209 (M^+), 193 ($M^+ - 16$).

Anal. Calcd for $C_7H_7N_5O_3$: C, 40.19; H, 3.37; N, 33.48. Found: C, 39.92; H, 3.41; N, 33.76.

When this reaction was carried out without cooling, 4,6-dimethyl-*v*-triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**9**) (0.1 g, 55%), mp 259—260 °C (lit.[10] mp 260 °C), identical (IR) with an authentic sample,[10] was obtained after evaporation of the reaction mixture, followed by recrystallization of the residue from H_2O.

Method B. A mixture of **4** (0.199 g, 0.001 mol) and dimethylformamide–dimethyl sulfate complex[6] (0.6 g, 0.003 mol) was stirred at room temperature for 2 h. The resulting solution was diluted with EtOH (1 mL) and the precipitates were filtered. Recrystallization from EtOH afforded **5** (0.09 g, 43%), mp 179—180 °C, identical with a sample of **5** prepared by method A.

Method C. A mixture of **4** (0.199 g, 0.001 mol) and HCOOH (3 mL) was refluxed for 30 min and the reaction mixture was evaporated in vacuo. The residue was recrystallized from EtOH to give **5** (0.11 g, 54%), mp 179—180 °C, identical in all respects with the material prepared as described above.

Method D. A suspension of **4** (0.199 g, 0.001 mol) in triethyl orthoformate (3 mL) was heated at 90 °C for 30 min. After cooling the reaction mixture, the precipitated solid was filtered and recrystallized from EtOH to give **5** (0.148 g, 71%), mp 179–180 °C, identical with the material prepared by methods A, B, and C.

3-Alkyl-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione 4-Oxides (3-Alkylfervenulin 4-Oxides (10 and 11)). General Procedure. A mixture of **4** (0.199 g, 0.001 mol) and the respective ortho esters (2 mL) was heated for 30 min at 90 °C. The resulting solution was evaporated in vacuo and the residue was recrystallized from an appropriate solvent to give the corresponding fervenulin 4-oxides (**10** and **11**).

Compound **10:** recrystallized from EtOH (0.17 g, 76%); mp 137–138 °C (lit.[7] mp 138 °C); IR 1715, 1660 cm^{-1} (CO); MS *m/e* 223 (M^+), 207 ($M^+ - 16$). Anal. Calcd for $C_8H_9N_5O_3$: C, 43.05; H, 4.06; N, 31.38. Found: C, 43.06; H, 4.06; N, 31.65.

Compound **11:** recrystallized from EtOAc (0.2 g, 85%); mp 145.5–147 °C; IR 1725, 1670 cm^{-1} (CO); MS *m/e* 237 (M^+), 221 ($M^+ - 16$). Anal. Calcd for $C_9H_{11}N_5O_3$: C, 45.57; H, 4.67; N, 29.53. Found: C, 45.22; H, 4.62; N, 29.27.

6,8-Dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (Fervenulin (1)). Method A. A mixture of **5** (0.209 g, 0.001 mol) and $Na_2S_2O_4$ (0.522 g, 0.003 mol) in H_2O (3 mL) was stirred at room temperature for 1 h. The resulting clear solution was extracted with $CHCl_3$ (three 5-mL portions). The $CHCl_3$ extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was recrystallized from C_6H_6 to give **1** (0.17 g, 90%): mp 177–178 °C (lit.[5] mp 178–179 °C); IR 1725, 1670 cm^{-1} (CO); NMR ($CDCl_3$) δ 3.60 (s, 3 H, NCH_3), 3.93 (s, 3 H, NCH_3), 9.47 (s, 1 H, C^3H); UV λ_{max} (EtOH) 237 nm (log ϵ 3.97), 275 sh (2.99), 343 (3.16); MS *m/e* 193 (M^+).

Anal. Calcd for $C_7H_7N_5O_2$: C, 43.52; H, 3.65; N, 36.26. Found: C, 43.33; H, 3.61; N, 36.19.

Method B. A mixture of **5** (0.104 g, 0.0005 mol) in dry DMF (3 mL) was refluxed for 8 h and the reaction mixture was concentrated in vacuo. The residue was recrystallized from C_6H_6 to give **1** (0.06 g, 60%), mp 177–178 °C, identical with a sample of **1** prepared by method A. Treatment of **5** (0.104 g, 0.0005 mol) with Ac_2O (3 mL) under the same conditions afforded **1** (0.02 g, 21%).

Method C. A solution of **5** (0.209 g, 0.001 mol) in EtOH (400 mL) was irradiated with a 100-W high-pressure mercury lamp surrounded by a water-cooled Pyrex filter at room temperature for 20 min. The reaction mixture was evaporated in vacuo and the residue was recrystallized from C_6H_6 to afford **1** (0.104 g, 54%), mp 177–178 °C, identical with the material prepared by methods A and B.

3-Alkyl-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7-(6*H*,8*H*)-diones (3-Alkylfervenulins (12 and 13)). General Procedure. A mixture of **10** or **11** (0.001 mol) and $Na_2S_2O_4$ (0.522 g, 0.003 mol) in H_2O (3 mL) was treated as described in method A of **1.**

Compound **12:** recrystallized from *n*-hexane (0.176 g, 85%), mp 112–113 °C (lit.[8] mp 127 °C); IR 1725, 1670 cm^{-1} (CO); MS *m/e* 207 (M^+). Anal. Calcd for $C_8H_9N_5O_2$: C, 46.37; H, 4.38; N, 33.80. Found: C, 46.69; H, 4.46; N, 34.15.

Compound **13:** recrystallized from *n*-hexane (0.12 g, 55%), mp 88–89 °C; IR 1730, 1685 cm^{-1} (CO); MS *m/e* 221 (M^+). Anal. Calcd for $C_9H_{11}N_5O_2$: C, 48.86; H, 5.01; N, 31.66. Found: C, 48.55; H, 4.93; N, 31.64.

3-Chloro-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (14). A mixture of **5** (0.209 g, 0.001 mol) and $POCl_3$ (0.6 mL) in dry DMF (3 mL) was stirred at 50 °C for 2 h. The reaction mixture was evaporated in vacuo and the residue was covered with ice–water. The precipitates were filtered and recrystallized from EtOH to yield **14** (0.19 g, 84%), mp 147 °C (lit.[15] mp 146–147 °C); IR 1740, 1675 cm^{-1} (CO); MS *m/e* 227 (M^+), 229 ($M^+ + 2$).

Anal. Calcd for $C_7H_6ClN_5O_2$: C, 36.93; H, 2.66; N, 30.77. Found: C, 37.06; H, 2.72; N, 30.98.

6,8-Dimethyl-3-hydroxyprimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (Fervenulone (15)). Method A. A mixture of **14** (0.227 g, 0.001 mol) and HCOOH (5 mL) was refluxed for 1 h. The reaction mixture was evaporated in vacuo, and the residue was filtered by the addition of EtOH. The mass was recrystallized from EtOH and the crystals were dried (P_2O_5) in vacuo for 2 h at 120 °C to give the

anhydrous **15** (0.186 g, 89%), mp 256–258 °C (lit.[15] mp 260–261 °C); IR 1710, 1660 cm^{-1} (CO); MS *m/e* 209 (M^+).

Anal. Calcd for $C_7H_7N_5O_3$: C, 40.19; H, 3.37; N, 33.48. Found: C, 39.89; H, 3.78; N, 33.40.

Method B. A mixture of **14** (0.227 g, 0.001 mol) and 2 N HCl (3 mL) at 90 °C for 30 min. The resulting solution was neutralized with 4% NaOH and allowed to stand overnight at room temperature. The precipitates were filtered and recrystallized from EtOH. The crystals were dried under the conditions described above to yield **15** (0.107 g, 51%), mp 256–258 °C, identical with a sample prepared by method A.

Method C. A solution of 3-benzyloxy-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione **16** (1.196 g, 0.004 mol) in EtOH (100 mL) containing 10% Pd–C (1 g) was hydrogenated at room temperature and at atmospheric pressure. Hydrogenation was stopped when the theoretical volume (90 mL) of H_2 gas was consumed. The solution was filtered and the filtrate was evaporated to dryness in vacuo. The residue was treated as described in method A to give **15** (0.418 g, 50%), mp 256–258 °C, identical with the material prepared by methods A and B.

3-Benzyloxy-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (16). A suspension of **14** (2.27 g, 0.01 mol) in absolute benzyl alcohol (10 mL) dissolving metallic Na (0.24 g, 0.01 g-atom) was stirred at room temperature for 3 h. The precipitates were filtered, washed with H_2O, and recrystallized from EtOH to give **16** (2.24 g, 75%), mp 185–187 °C; IR 1735, 1675 cm^{-1} (CO); MS *m/e* 299 (M^+).

Anal. Calcd for $C_{14}H_{13}N_5O_3$: C, 56.18; H, 4.38; N, 23.40. Found: C, 55.82; H, 4.51; N, 23.07.

2,6,8-Trimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione (2-Methylfervenulone, MSD-92 (2)). A mixture of **15** (0.209 g, 0.001 mol), methyl iodide (0.28 g, 0.002 mol), and K_2CO_3 (0.07 g, 0.0005 mol) in dry DMF (10 mL) was stirred at 50 °C for 3 h. The solution was evaporated in vacuo and the residue was covered with EtOAc (3 mL). The insoluble solid was filtered off and the filtrate was again evaporated in vacuo. The residue was recrystallized from EtOH and the separated solid was dried at 120 °C in vacuo (P_2O_5) for 2 h to give the anhydrous **2** (0.212 g, 95%) as yellow crystals: mp 180–181 °C (lit.[15] mp 181–182 °C, lit.[18] mp 183–183.5 °C); IR 1730, 1665 cm^{-1} (CO); NMR ($CDCl_3$) δ 3.52 (s, 3 H, NCH_3), 3.54 (s, 3 H, NCH_3), 3.93 (s, 3 H, NCH_3); UV λ_{max} (H_2O) 240 nm (log ϵ 4.27), 280 (3.30), 415 (3.45); λ_{max} (MeOH) 218 nm (log ϵ 4.10), 285 (3.86), 415 (2.95); MS *m/e* 223 (M^+).

Anal. Calcd for $C_8H_9N_5O_3$: C, 43.05; H, 4.06; N, 31.38. Found: C, 43.12; H, 4.29; N, 31.72.

5-Acetylamino-1,3-dimethylbarbituric Acid (17). Method A. A solution of **5** (0.209 g, 0.001 mol) in a mixture of Ac_2O (2 mL) and AcOH (2 mL) was refluxed for 1 h. The reaction mixture was evaporated in vacuo and the residue was recrystallized from EtOH to give **17** (0.107 g, 50%), mp 230–231 °C; MS *m/e* 213 (M^+).

Anal. Calcd for $C_8H_{11}N_3O_4$: C, 45.07; H, 5.20; N, 19.71. Found: C, 44.89; H, 5.08; N, 19.76.

Method B. A solution of 5-amino-1,3-dimethylbarbituric acid **18**[20] (0.171 g, 0.001 mol) and a mixture of Ac_2O (2 mL) and AcOH (2 mL) was refluxed for 1 h and the reaction mixture was treated as described above to give **17** (0.1 g, 47%), mp 230–231 °C, identical with a material prepared by method A.

5,7-Dimethylimidazo[4,5-*e*]-*as*-triazine-6(7*H*)-one (19). A mixture of **5** (0.209 g, 0.001 mol) and 0.5% NaOH (10 mL) was heated at 90 °C for 1 h. The resulting solution was acidified (pH 4) by the addition of AcOH and the precipitated solid was filtered. Recrystallization from EtOH gave **19** (0.066 g, 40%), mp 146–147 °C; IR 1750 cm^{-1} (CO); NMR (Me_2SO-d_6) δ 3.31 (s, 3 H, NCH_3), 3.40 (s, 3 H, NCH_3), 10.23 (s, 1 H, C^3H); MS *m/e* 165 (M^+).

Anal. Calcd for $C_6H_7N_5O$: C, 43.63; H, 4.27; N, 42.41. Found: C, 43.55; H, 4.31; N, 42.05.

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Registry No.—**1**, 483-57-8; **2**, 22712-32-9; **4**, 40012-15-5; **5**, 62758-20-7; **10**, 60026-36-0; **11**, 63069-55-6; **12**, 25696-97-3; **13**, 64235-46-7; **14**, 18969-84-1; **15**, 18969-83-0; **16**, 64235-47-8; **17**, 64235-48-9; **18**, 54632-31-4; **19**, 64216-10-0; benzyl alcohol, 100-51-6.

References and Notes

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(9) In a preliminary communication,[1a] it was speculated that the reaction proceeds via the nucleophilic attack of the oxime group of **4** on the Vilsmeier reagent; however, the initial formation of intermediate **6** seems to be favorable since the nucleophilicity of the hydrazino group is greater than that of the oxime group.
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