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Synthesis of Isofervenulin and 2-Methylisofervenulone[1]

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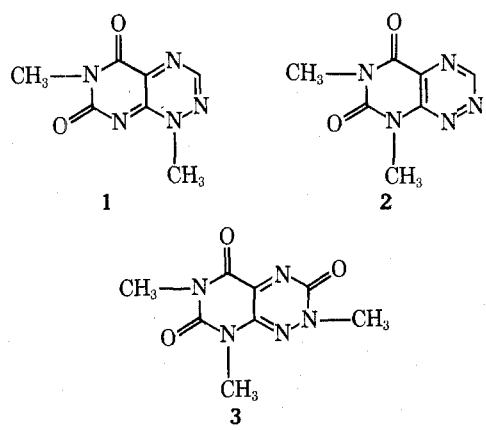
Syntheses of 5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8(5*H*,7*H*)-dione (isofervenulin, **13**) and 2,5,7-trimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (2-methylisofervenulone, **10**) are described from a common intermediate, 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (**4**). Although these compounds are ring isomers of the naturally occurring antibiotics fervenulin (**2**) and 2-methylfervenulone (MSD-92, **3**), neither exhibited antibiotic activity.

Derivatives of the pyrimido[4,5-*e*]-*as*-triazine (6-azapteridine) ring system have received considerable recent attention,[2] primarily because of their demonstrated antiviral activity,[3] and as a consequence of their close structural relationship to the pteridines and their isomeric relationship with the pyrimido[5,4-*e*]-*as*-triazine ring system present in the naturally occurring antibiotics toxoflavin (**1**), fervenulin (**2**), and 2-methylfervenulone (MSD-92, **3**).[4] We report in the present paper the synthesis of 5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8(5*H*,7*H*)-dione (isofervenulin, **13**) and 2,5,7-trimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (2-methylisofervenulone, **10**). Both of these compounds are of considerable potential interest as ring isomers of the antibiotics **2** and **3**, respectively.



1

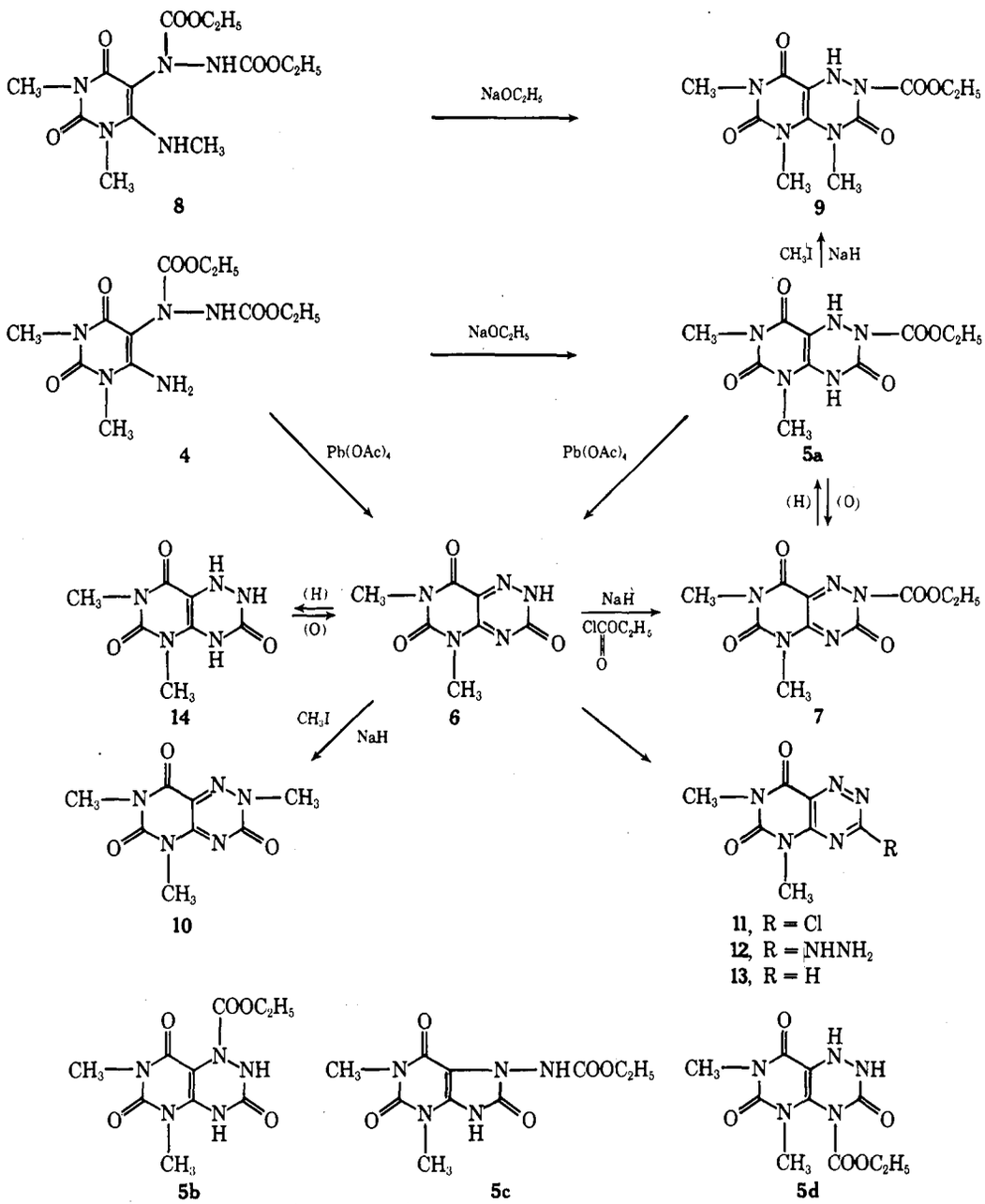
2

3

We have recently reported[5] a new method for C-5 functionalization of a variety of 6-amino- and 6-hydrazinopyrimidines which involves Michael addition to diethyl azodicarboxylate. This gives rise to a 5-(1,2-dicarbethoxyhydrazino) derivative which can then be converted (a) to a 5-carbethoxyamino derivative by Raney nickel reduction, or (b) to derivatives of the pyrimido[5,4-*e*]-*as*-triazine ring system (in the case of 6-hydrazino-substituted pyrimidines) by a variety of cyclization procedures.[4] We have now found that 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (**4**), readily available in high yield from 1,3-dimethyl-6-aminouracil and diethyl azodicarboxylate,[5] can be smoothly cyclized with sodium ethoxide in ethanol to **5a**, a derivative of the isomeric pyrimido[4,5-*e*]-*as*-triazine ring system. Although it might have been expected that base-catalyzed intramolecular cyclization of **4** would have led to compound **5b** or **5c**, we present below convincing evidence that the structure of this intramolecular cyclization product of **4** possesses structure **5a**, in which the carbethoxy group is attached to N-2 of the pyrimidotriazine ring.

Thus, compound **5a** could be dehydrogenated with either phosphorus oxychloride or thionyl chloride to 2-carbethoxy-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**7**), which could then be reconverted to **5a** by catalytic reduction. This simple sequence of interconversions thus serves to eliminate both structures **5b** and **5c** from consideration. It seems reasonable to suggest that the 1-carbethoxy derivative **5b** is probably the initial product of intramolecular cyclization of **4**, but that a subsequent intramolecular acyl transfer of the carbethoxy group from N-1 to N-2 then ensues. Steric hindrance at N-1 in compound **5b** may well be responsible for this unidirectional rearrangement. The structure of **5a** was further confirmed as follows. Treatment with sodium hydride followed by addition of methyl iodide gave 2-carbethoxy-1,4-dihydro-4,5,7-trimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**9**), whose structure was then firmly established by its independent synthesis by base-catalyzed cycli-

Scheme I



zation of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-methylaminouracil (8). This sequence of reactions eliminates the final alternative structure **5d**, which is implausible in any event on both mechanistic and steric grounds.

Compound **5a** was then converted in a single step with lead tetraacetate to 5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione[6] (*isofervenulone*, **6**), which could alternately be prepared directly from **4** by treatment with lead tetraacetate, although somewhat more vigorous conditions were required. To complete this series of interrelationships, **7** was obtained independently from **6** by reaction with ethyl chloroformate in the presence of sodium hydride. 2-Methylisofervenulone (**10**) was then prepared, by a reaction analogous to the conversion of **6** to **7**, by methylation of **6** with methyl iodide in the presence of sodium hydride.

Isofervenulin (**13**) was readily prepared from isofervenulone (**6**) by chlorination with phosphorus oxychloride in the presence of diethylaniline to **11**, conversion to the substituted hydrazine **12** with alcoholic hydrazine hydrate, and then "oxidative reduction" of **12** with aqueous mercuric oxide. It is interesting to note that although isofervenulone (**6**) could be smoothly reduced to dihydroisofervenulone (**14**), we were able to confirm previous observations[2a] that **11** could not be reductively dehydrohalogenated without destruction of the ring system. All of the reactions discussed above are summarized in Scheme I.

Neither isofervenulin (**13**) nor 2-methylisofervenulone (**10**) exhibited any in vitro antibiotic activity, which thus appears to be restricted to the [5,4-*e*] series.

Experimental Section

2-Carbethoxy-1,4-dihydro-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (5a). To a solution of sodium ethoxide, prepared from 11.98 g (0.521 mol) of sodium and 300 ml of absolute ethanol, was added at room temperature 34.25 g (0.101 mol) of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (**4**) hemihydrate.[5] Stirring and heating to reflux produced complete solution followed by separation of a colorless solid. After 1 hr, the mixture was cooled in an ice bath, and 89.3 ml of 5.83 *M* (0.52 mol) alcoholic hydrogen chloride was added in small portions with continued cooling and stirring. The mixture was

then heated to reflux and filtered, and the inorganic material was extracted with a second 500-ml portion of hot ethanol. The combined extracts were concentrated to dryness and the product was washed with ether and recrystallized by solution in 650 ml of boiling ethanol, repeated filtration, concentration to one-fourth of the original volume, and cooling, yield 21.75 g (76%) of colorless crystals, mp 228–229° dec. The analytical sample was recrystallized from acetonitrile.

Anal. Calcd for $C_{10}H_{13}N_5O_5$: C, 42.40; H, 4.63; N, 24.72. Found: C, 42.33; H, 4.62; N, 24.43.

5,7-Dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (6). Method A. To a stirred solution of 16.46 g (0.049 mol) of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (**4**) hemihydrate in 35 ml of glacial acetic acid, kept under a slight positive pressure of nitrogen, was added during 1 hr 22.15 g (0.05 mol) of lead tetraacetate in small portions. The reaction mixture was kept in an oil bath maintained at 75–80° during the reaction period. After the addition of each portion of the oxidant, a strong initial lavender coloration appeared which gradually faded to a pale yellow. The product began to separate from solution toward the end of the addition period, and after stirring for 1 hr, the mixture was cooled and filtered. The mother liquors were treated with 17.0 ml of 5.83 *M* alcoholic hydrogen chloride, and the precipitated solid was collected by filtration and extracted with 50 ml of hot ethanol. The combined filtrate and extract were concentrated to dryness, and the combined solids were recrystallized from water to give 6.83 g (67%) of **6**, mp 287–289° dec (lit.[2a] mp 284–285° dec).

Anal. Calcd for $C_7H_7N_5O_3$: C, 40.18; H, 3.38; N, 33.48. Found: C, 40.15; H, 3.42; N, 33.55.

Method B. A stirred suspension of 2.89 g (0.01 mol) of 2-carbethoxy-1,4-dihydro-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**5a**) in 25 ml of glacial acetic acid was treated with 4.87 g (0.011 mol) of lead tetraacetate, added portionwise over a period of 10 min. During this period the reaction temperature rose from 26 to 33°, and the product began to separate. After stirring for 1 hr, the product was filtered and the mother liquors were partially concentrated and cooled to give an additional quantity of product. The combined solids were washed with cold water and recrystallized from water to give 1.39 g (66%) of **6**, mp 287–289° dec, identical in every respect with the product prepared by method A.

2-Carbethoxy-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (7). Method A. A mixture of 8.5 g of 2-carbethoxy-1,4-dihydro-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**5a**) and 300 ml of thionyl chloride was heated under reflux for 1 hr. The resulting clear solution was then concentrated under reduced pressure to remove excess thionyl chloride, and the residual solid was dissolved in 75 ml of chloroform, 25 ml of water was added, and sodium bicarbonate was added in small portions to pH 7. The aqueous phase was separated and extracted with chloroform, and the combined chloroform extracts were washed with water, dried, and concentrated to dryness. The residual oil was crystallized by treatment with benzene and then recrystallized from benzene to give 5.36 g (63%) of **7**, mp 124–125° dec.

Anal. Calcd for $C_{10}N_{11}N_5O_5$: C, 42.71; H, 3.94; N, 24.90. Found: C, 42.64; H, 3.86; N, 24.90.

Method B. A mixture of 1.0 g of **5a**, 25 ml of phosphorus oxychloride, and 1 g of diethylaniline was heated under reflux for 15 min and then worked up as described above to give 0.45 g (45%), mp (after recrystallization from methanol) 124–125° dec, identical with the material obtained by method A.

Method C. To an ice-cooled solution of 4.19 g (0.02 mol) of 5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**6**) in 25 ml of DMF was added 1.20 g (0.025 mol) of a 50% dispersion of sodium hydride in mineral oil, and the mixture was stirred for 15 min. The resulting gray-green, gelatinous suspension of the sodium salt of **6** was then treated with 3.26 g (0.03 mol) of ethyl chloroformate. A vigorous reaction ensued, accompanied by the immediate separation of sodium chloride. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was extracted with 50 ml of chloroform; the extract was washed with three 25-ml portions of water, dried ($MgSO_4$), and concentrated to dryness. The residual solid was separated from 1.19 g of unreacted starting material by extraction with two 25-ml portions of hot benzene. The combined extracts were concentrated and the crystalline residue was washed with a small amount of cold ethanol and dried, yield 2.55 g (45%) of **7**, mp 124–125° dec, identical with the material prepared by methods A and B above.

Catalytic reduction of **6** in absolute ethanol, using 10% Pd/C as catalyst, resulted in quantitative reconversion to **5a**, mp 228–229° dec.

2-Carbethoxy-1,4-dihydro-4,5,7-trimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (9). Method A. A solution of 1.60 g (0.005 mol) of 2-carbethoxy-1,4-dihydro-5,7-dimethylpyrimido[4,5-*e*0-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**5a**) in 10 ml of DMF was stirred for 15 min with 0.31 g of a 53% dispersion of sodium hydride in mineral oil, and then treated with 4.3 g (0.028 mol) of methyl iodide. The reaction mixture was heated under reflux for 1 hr and filtered, and the filtrate was concentrated under reduced pressure to dryness. The residue was dissolved in chloroform, washed with water, dried ($MgSO_4$), and concentrated, and the residual crystals (1.21 g) were recrystallized from ethanol to give 1.15 g (77%) of **9**, mp 191–192° dec.

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.43; H, 5.09; N, 23.56. Found: C, 44.61; H, 5.17; N, 23.35.

Method B. A solution of 17.2 g (0.05 mol) of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-methylaminouracil (**8**) in 150 ml of absolute ethanol containing 2.4 g (0.104 mol) of sodium was heated under reflux for 1 hr, cooled, and acidified to Congo Red by the addition of alcoholic hydrogen chloride. The mixture was then filtered, the collected solid was extracted with two 50-ml portions of boiling ethanol, and the combined filtrate and extracts were evaporated under reduced pressure. Trituration of the residue with ether gave a solid, which was recrystallized first from ethanol–ether (1:1) and then from a small amount of ethanol to give 3.60 g (24%) of **9**, mp 191–192° dec. This material was identical with a sample of **9** prepared by method A.

2,5,7-Trimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,-7*H*)-trione (2-Methylisofervenulone, 10). To an ice-cooled solution of 4.19 g (0.02 mol) of 5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**6**) in 35 ml of DMF was added with stirring 1.20 g (0.025 mol) of a 50% dispersion of sodium hydride in mineral oil, and the mixture was stirred for 30 min. The slurry of the sodium salt of **6** was then treated with 14.2 g (0.10 mol) of methyl iodide; the mixture was heated under reflux for 30 min and concentrated to dryness, and the residue was partitioned between 100 ml of chloroform and 25 ml of water. The chloroform extract was dried ($MgSO_4$) and concentrated, and the residue was recrystallized from ethanol to give 3.89 g (87%) of **10**, mp 184–185° dec.

Anal. Calcd for $C_8H_9N_5O_3$: C, 43.05; H, 4.06; N, 31.38. Found: C, 42.96; H, 4.27; N, 31.42.

3-Chloro-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8(5*H*,7*H*)-dione (11). To a stirred solution of 3.74 g (0.025 mol) of diethylaniline in 50 ml of phosphorus oxychloride was added 5.22 g (0.025 mol) of 5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**6**), and the mixture was heated in an oil bath under reflux for 15 min. The product gradually separated from the solution during this period. Excess phosphorus oxychloride was then removed by distillation under reduced pressure, the residue was stirred with crushed ice and filtered, and the collected solid was washed well with ethanol and ether, yield, 5.55 g (96%). The analytical sample was prepared by sublimation (200°, 1.5 mm) followed by recrystallization from acetonitrile, and melted at 252–253° (lit.[2a] mp 251–253°).

Anal. Calcd for $C_7H_6ClN_5O_2$: C, 36.94; H, 2.65; N, 30.77; Cl, 15.58. Found: C, 36.65; H, 2.55; N, 30.71; Cl, 15.37.

3-Hydrazino-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8(5*H*,7*H*)-dione (12). To a warm (50°) solution of 0.454 g (0.002 mol) of 3-chloro-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8-(5*H*,7*H*)-dione (**11**) in 100 ml of ethanol was added 0.236 g (0.004 mol) of 85% hydrazine hydrate. The reaction mixture turned deep orange, and bronze-colored plates began to separate almost immediately. The mixture was cooled and filtered, and the collected solid was washed with ethanol followed by ether to give 0.425 g (95%) of **12**, mp 253–255° dec. The analytical sample was prepared by recrystallization from ethanol without change in the melting point.

Anal. Calcd for $C_7H_9N_7O_2$: C, 37.66; H, 4.06; N, 43.93. Found: C, 37.52; H, 4.16; N, 43.75.

5,7-Dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8(5*H*,7*H*)-dione (Isofervenulin, 13). A solution of 1.11 g (0.005 mol) of 3-hydrazino-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8(5*H*,7*H*)-dione (**12**) and 1.63 g (0.0075 mol) of yellow mercuric oxide in 250 ml of water was stirred vigorously for 48 hr and then centrifuged. The supernatant liquid was filtered through a mat of Hy-flo, while the collected solid above was extracted with 100 ml of hot ethanol, and the extract was filtered through Hy-flo. The combined filtrates were then concentrated to a small volume, cooled and filtered, and

the yellow solid thus collected recrystallized from ethanol to give 0.43 g (44%) of **13**, mp 211.5–212°.

Anal. Calcd for $C_7H_7N_5O_2$: C, 43.52; H, 3.65; N, 36.26. Found: C, 43.53; H, 3.61; N, 36.12.

1,4-Dihydro-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (14). A solution of 1.04 g of 5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**6**) in 100 ml of glacial acetic acid was hydrogenated in the presence of 0.2 g of 10% Pd/C catalyst at 50 psi of hydrogen. The uptake of hydrogen was rapid, and reduction was complete in 3 min. The mixture was filtered, the filtrate was evaporated to dryness, and the residual solid was triturated with ether and then filtered. Recrystallization from acetic acid then gave 0.59 g of colorless crystals, mp 264–265° dec. This compound is probably a solvate with acetic acid, since prolonged drying under reduced pressure at 110° raised the melting point to 326–328° dec. The analytical sample was recrystallized from water without change in the melting point.

Anal. Calcd for $C_7H_9N_5O_3$: C, 39.80; H, 4.30; N, 33.16. Found: C, 39.86; H, 4.30; N, 32.98.

Repeated recrystallization of **14** from water led to air oxidation and the separation of starting material (**6**), mp 287–289° dec, in quantitative yield.

Registry No.—**4**, 18969-87-4; **5a**, 54632-24-5; **6**, 7271-90-1; **7**, 54632-25-6; **8**, 49810-14-2; **9**, 54632-26-7; **10**, 26154-55-2; **11**, 54632-27-8; **12**, 18969-88-5; **13**, 16044-79-4; **14**, 54632-28-9.

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(6) This compound had been prepared independently by the condensation of 1,3-dimethylalloxan with *S*-methylisothiosemicarbazide, followed by hydrolysis, as an intermediate in an unsuccessful attempt to synthesize isofervenulin (*ref 2a*).

Pteridines. XXXIV. Synthesis of 8-Hydroxy-7(8*H*)-pteridinones (Pteridine Hydroxamic Acids)[1,2]

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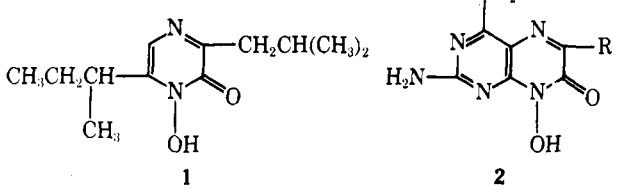
A series of 2,4-diamino-6-substituted 8-hydroxy-7(8*H*)-pteridinones (pteridine hydroxamic acids) (**2**) has been prepared from 2,4-diamino-6-substituted pteridine 8-oxides (**5**) by chlorination in glacial acetic acid, followed by cleavage of the resulting pteridine hydroxamic acid anhydrides (**13**) with ethanolic HCl. An alternative but less satisfactory route to 2,4-diamino-6-methyl-8-hydroxy-7(8*H*)-pteridinone (**2a**) involved condensation of pyruvohydroxamoyl chloride (**6**) with aminomalononitrile (**3**) tosylate to give 2-amino-3-cyano-5-methyl-6-chloropyrazine 1-oxide (**7**), hydrolysis to the pyrazine hydroxamic acid **9**, and cyclization with guanidine.

The striking antibacterial activity of the naturally occurring pyrazine antibiotic aspergillic acid (**1**)[3-5] has stimulated work on the preparation of numerous analogs, among them being hydroxamic acids of pyridine,[6] pyrimidine,[7] quinoline,[8] and quinazoline.[9] By far the greatest efforts, however, have been concentrated on the synthesis of variously substituted pyrazine hydroxamic acids,[10] and in some instances the in vitro antibacterial activity of these synthetic analogs has actually exceeded that of aspergillic acid itself. Despite the incorporation of a pyrazine ring within the pteridine nucleus, and the broad spectrum of biological activities associated with pteridine derivatives, there are no reports of the preparation of pteridine analogs of aspergillic acid.[11] We describe in the present paper the synthesis and properties of a number of 8-hydroxy-7(8*H*)-pteridinones (pteridine hydroxamic acids) of structure **2**.



1 **2**

These compounds should be of considerable potential pharmacological interest, not only because of their obvious structural relationship to **1**, but also because of their similarity to the clinically important 2,4-diamino-6-substituted pteridines.[12]

We have recently described the condensation of aminomalononitrile (**3**) with α-keto aldoximes to give 2-amino-3-cyano-5-substituted pyrazine 1-oxides[13] (**4**), which were then cyclized with guanidine to give 2,4-diamino-6-substituted pteridine 8-oxides (**5**). For the purpose of preparing pyrazine, and subsequently pteridine, hydroxamic acids, this general reaction sequence requires as a modification the condensation of **3** with an α-keto hydroxamic acid (see Scheme I). Similar conversions were briefly explored by Ramsey and Spring,[10c] who reported that the action of pyruvohydroxamic acid bisulfite with aminoacetone led in moderate yield to 1-hydroxy-3,6-dimethyl-2(1*H*)-pyrazinone. In spite of this encouraging precedent, we were unable to bring about condensation of aminomalononitrile (**3**) either with pyruvohydroxamic acid or its bisulfite derivative; no reaction could be detected at room temperature, and a rapid conversion to ammonium tosylate and a number of unidentified noncrystalline materials occurred at temperatures exceeding 40°. This approach was therefore abandoned, and a second potential synthetic route to the desired pteridine hydroxamic acids was explored as follows.

Chlorination of oximinoacetone in benzene solution,[14] or preferably nitrosation of chloroacetone,[15] gave pyruvohydroxamoyl chloride (**6**), which, in contrast to pyruvohy-