Pyrimidines. XXXIII [1]. Synthesis and Properties of New Fervenulin Derivatives

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Dedicated to the memory of Professor Nicholas Alexandrou

A series of new 3-substituted fervenulin (6,8-dimethylpyrimido[5,4-*e*]-1,2,4-triazine-5,7-dione) (**1**) derivatives have been synthesized by modifying the 3-alkyl- and aralkyl side-chains. Brominations of 3-methyl-**15**, 3-ethyl-**16**- and 3-benzylfervenulin (**17**) led to mono- and dibromo derivatives **22**, **23**, **25-27**, which are prone to various nucleophilic displacement reactions **24**, **28-35**. Periodate oxidation and ozonolysis, respectively, of 3-styrylfervenulin (**20**) afforded fervenulin-3-carboxaldehyde (**36**) which was transformed to a folic acid analog (**39**). Potassium permanganate oxidation of 3-alkylfervenulins **15-19** afforded only ring-contraction to 3-alkyl-5,7-dimethylimidazo[4,5-*e*]-1,2,4-triazin-6-ones **42-46** which are also formed as mixtures with its 2,4a-dihydro derivatives **47-50** on treatment with ethanolic sodium hydroxide. Fervenulin-3-carboxylic acid (**55**) can be converted to the corresponding acid chloride **58** which reacts with amines to fervenulin-3-carboxamides **59**, **64-67** and/or 2,4a-dihydro-5,7-dimethylimidazo[4,5-*e*]-1,2,4-triazin-6-one-biscarboxamides **60-64**.

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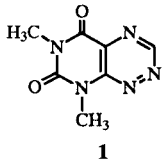
Introduction.

The heterocyclic pyrimido[5,4-*e*]-1,2,4-triazine ring-system has attracted some attention from a chemical and biochemical point of view due to the fact that various naturally occurring derivatives like fervenulin (Planomycin) (**1**) [2,3], toxoflavin (Xanthothricin) (**2**) [4-6] and 2-methylfervenulone (MSD 92) (**3**) [7,8] show interesting biological activities which can be considered as lead substances for future investigations. Since we have performed in 1958 [9] with the synthesis of 6,8-dimethylpyrimido[5,4-*e*]-1,2,4-triazine-5,7-dione (**1**) the first derivative of this new heterocyclic ring-system even before the substance was isolated from *Streptomyces fervens* [3] and named fervenulin and due to its structural relationship to the pteridines, further synthetic efforts have recently been undertaken to increase our knowledge about this class of substances.



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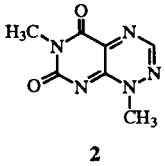

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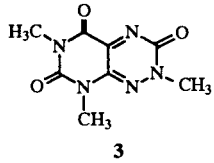
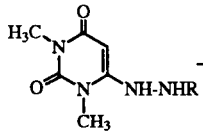


3

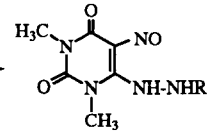
The first synthetic approach cyclizing 4-acylhydrazino-5-amino-1,3-dimethyluracils and followed by dehydration [9] has been varied to a large extent [10-27] whereas the annelation of the pyrimidine ring onto the 1,2,4-triazine nucleus has only been practised in rare cases [28]. We could furthermore show that aldehydrohydrazones of 4-hydrazino-1,3-dimethyluracil form directly 3-substituted fervenulins during nitrosation preferentially with isoamylnitrite in methanolic hydrogen chloride and slightly elevated temperature [29,30] whereby aromatic and heteroaromatic hydrazones gave much better results than applying this method to the aliphatic counterpart [31,32]. In the present paper various functional groups have been introduced into the 3-position of **1** by modifying the corresponding alkyl side-chains and getting excess to new types of fervenulin derivatives.

Synthesis.

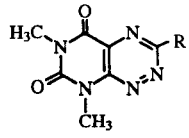
The synthesis of various 3-alkylfervenulins **15-19** was performed by the classical approach [9] starting from 4-hydrazino-1,3-dimethyluracil (**4**) which was acylated in the normal manner at the hydrazino group to **5-9** subsequently followed by nitrosation at the 5-position yielding **10-14** and reductive cyclization with final air oxidation to the yellow fervenulin derivatives **15-19**. In order to check the C-H activity of the alkyl side-chains **15** was condensed with benzaldehyde in the presence of zinc chloride at 160° to give in 63% yield 3-styrylfervenulin (**20**) which was identical with the product synthesized by Yoneda *et al.* [31] by a different route. The stereochemistry of the side-chain in **20** is clearly *trans* due to a 16 Hz coupling of the vicinal protons. Treatment of **20** with bromine afforded the 3-(1,2-dibromo-2-phenyl)ethylfervenulin (**21**) in 90% yield.



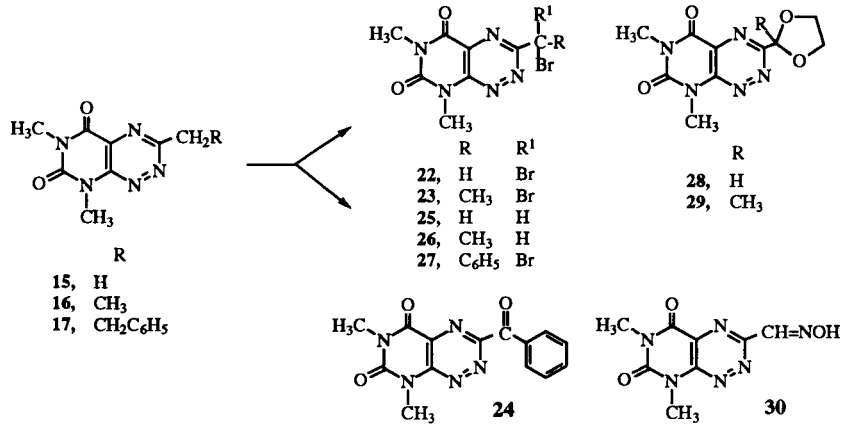
R	
4,	H
5,	$COCH_3$
6,	$COCH_2CH_3$
7,	$COCH_2C_6H_5$
8,	$COCH(CH_3)_2$
9,	$COC(CH_3)_3$



R	
10,	$COCH_3$
11,	$COCH_2CH_3$
12,	$COCH_2C_6H_5$
13,	$COCH(CH_3)_2$
14,	$COC(CH_3)_3$

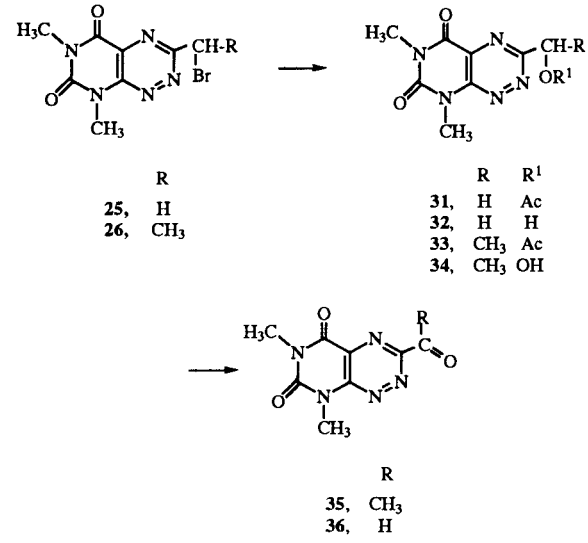


R	
15,	CH_3
16,	CH_2CH_3
17,	$CH_2C_6H_5$
18,	$CH(CH_3)_2$
19,	$C(CH_3)_3$
20,	$CH{=}CH\text{-}C_6H_5$
21,	$CHBrCHBrC_6H_5$

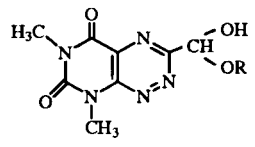


Brominations were performed with **15-17** showing that 3-methylfervenulin (**15**) reacts with bromine in acetic acid in excellent yield to the 3-dibromomethyl derivative **22** whereas 3-ethylfervenulin (**16**) led to a complex mixture of substances of which the 3-(1,1-dibromoethyl)- and the 3-(1,1,2-tribromoethyl)fervenulin are considered as the main components from the nmr spectra but their separation and purification was not successful. The 3-benzylfervenulin (**17**), however, reacted in the expected manner yielding the 3-(1-bromobenzyl)fervenulin (**27**) in 54% yield and the corresponding 3-benzoyl derivative **24** which is derived by hydrolysis from its precursor 3-(1,1-dibromobenzyl)fervenulin. Treatment of **15** with *N*-bromosuccinimide (NBS)/azoisobutyronitrile (AIBN) in carbon tetrachloride was less successful and gave only 8% of 3-bromomethyl-**25** and 7% of **22**. Compound **16** however, reacted under these conditions much better forming 3-(1-bromoethyl)-**26** in 59% and the 3-(1,1-dibromoethyl)fervenulin (**23**) in 10% isolated yield.

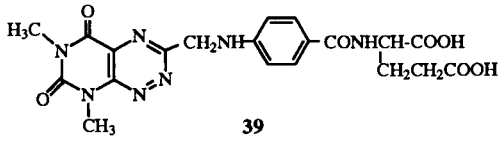
The bromoalkylfervenulins have also been used as starting materials of various nucleophilic displacement reactions. 3-Dibromomethyl-**22** and 3-(1,1-dibromoethyl)fervenulin (**23**) reacted with glycol to the corresponding dioxolanes **28** and **29** and treatment of **22** with hydroxylamine afforded fervenulin-3-carbaldoxime (**30**) in good yield. All attempts to hydrolyse **22** and **30**, respectively, under different reaction conditions to the fervenulin-3-carboxaldehyde (**36**) failed. On treatment of **22** with silver acetate did not produce the expected 3-diacetoxymethyl derivate but in low yield fervenulin (**1**) derived probably *via* the intermediarily formed 3-carboxaldehyde, its subsequent oxidation to fervenulin-3-carboxylic acid (**55**) followed by decarboxylation. The best method to prepare compound **25** is so far by the reduction of **22** by stannous bromide since the direct bromination of **15** always afforded mixtures of the mono- and dibromomethyl derivatives. The reaction of **25** with silver acetate worked well to give 3-acetoxymethylfervenulin (**31**) and its hydrolysis formed the 3-hydroxymethyl derivative **32**. In a similar manner **26** reacted to **33** and **34**, respectively. Chromic acid oxidation of **34** afforded 3-acetylfervenulin (**35**) in 63% yield but the same reaction conditions converted **32** into fervenulin (**1**) as the result of extensive oxidation to fervenulin-3-carboxylic acid (**55**) and subsequent decarboxylation. Mild oxidation of **32** with active manganese dioxide in chloroform allowed for the first time the synthesis of fervenulin-3-carboxaldehyde (**36**) in 19% yield together with ethylfervenulin-3-carboxylate (**57**) which is seen as the oxidation product of the fervenulin-3-carboxaldehydeethylhemiacetal (**38**) formed from **36** with ethanol as an added stabilizer for chloroform.



Improved methods for the synthesis of fervenulin-3-carboxaldehyde (**36**) were found in the periodate oxidation of 3-styrylfervenulin (**20**) in the presence of osmium tetroxide and ozonolysis of the same starting material, respectively, leading to 85 and 88% yield. The carboxaldehyde **36** could not be obtained in free form since the strongly π-deficient 1,2,4-triazine moiety forces the carbonyl group to form a covalent hydrate **37**. Similarly recrystallization of **36** from



R
37, H
38, Et

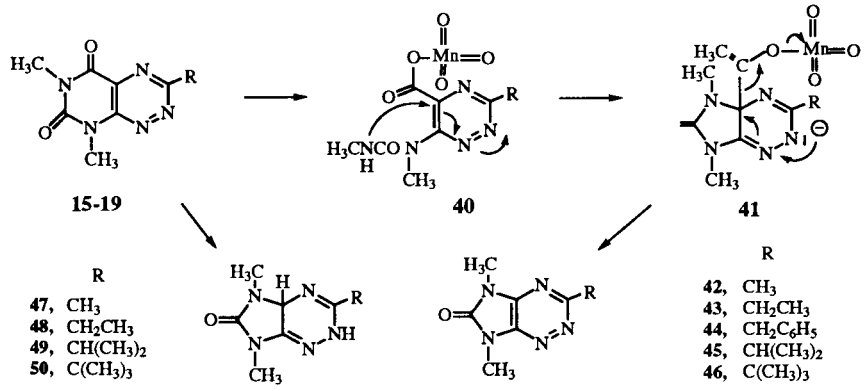


39

ethanol led to 3-(1-ethoxy-1-hydroxymethyl)fervenulin (**38**) and heating in glycol afforded in 63% yield the cyclic acetal **28**. The high reactivity of the carboxaldehyde group was furthermore proven by reaction with *p*-aminobenzoyl-glutamic acid to the corresponding Schiff's base which was reduced without isolation with dimethylaminoborane to the folic acid analog **39** in good yield.

Treatment of the 3-alkylfervenulins by ethanolic sodium hydroxide under reflux afforded an analogous ring-contraction to **42**, **43**, **45** and **46**, also found by Yoneda *et al.* [33,34] but in these cases also the corresponding 3-alkyl-2,4a-dihydro-5,7-dimethyl[4,5-*e*]-1,2,4-triazin-6-ones **47-50** were isolated derived by decarboxylation of the corresponding 4a-carboxylic acid precursors which are very unstable and lose carbon dioxide very easily since all attempts to isolate these intermediates under mild conditions failed. The structures of the 2,4a-dihydro derivatives **47-50** were assigned from ^{1}H-nmr spectra showing one exchangeable proton at low field and a characteristic singlet signal at about 4.4 ppm as well as from the ^{13}C-nmr spectra which reveal a signal at 66 ppm typical for a sp^3 hybridized C-atom.

Under these aspects we also became interested in the investigations of Clark and Morton [35] who claimed a ring-opening during treatment of fervenulin and its 3-methyl derivative with primary amines by a nucleophilic attack in position 7 leading to 1,2,4-triazin-6-yl-urea derivatives **51,52**. We found,



15-19

40

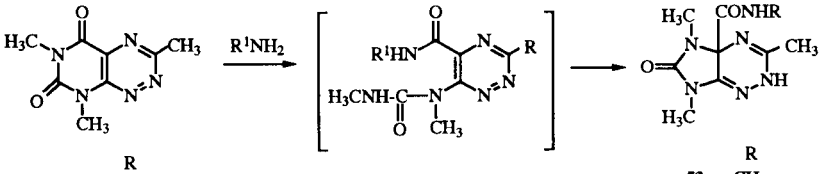
41

R
47, CH_3
48, CH_2CH_3
49, $CH(CH_3)_2$
50, $C(CH_3)_3$

R
42, CH_3
43, CH_2CH_3
44, $CH_2C_6H_5$
45, $CH(CH_3)_2$
46, $C(CH_3)_3$

Another series of investigations was directed towards the synthesis of fervenulin-3-carboxylic acid (**40**) and its derivatives. Attempts to oxidise the 3-alkylfervenulin **15-18** with aqueous potassium permanganate did not proceed in the expected manner but led to a more drastic structural change of the nucleus in forming the corresponding 3-alkyl-5,7-dimethylimidazo[4,5-*e*]-1,2,4-triazin-6-ones **42-45**. We assume that this ring contraction is initiated by a nucleophilic attack of the permanganate ion at the C(5)=O position leading under ring opening to **40** which cyclizes by ipso-attack at C(5) of the triazine ring to form **41** and followed by oxidative decarboxylation.

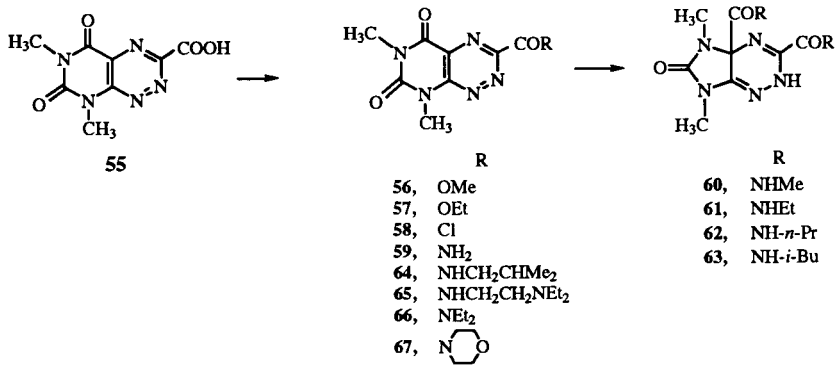
however, that 3-methylfervenulin (**15**) reacts with methanolic methylamine already at room temperature to 2,4a-dihydro-3,5,7-trimethylimidazo[4,5-*e*]-1,2,4-triazin-6-on-4a-*N*-methylcarboxamide (**53**) the structure of which was again proven by ^{1}H- and ^{13}C-nmr spectral studies. In this case the mechanism for the formation of **53** can not differentiate between a nucleophilic attack of methylamine at position 5 or 7 since both routes lead to the same end-product. Applying ethylamine, however, the 4a-*N*-ethylcarboxamide **54** is formed showing that the ring-contraction of the 1,3-dimethyl-uracil- into the 1,3-dimethylimidazolone-ring is undoubtedly initiated by C(5)-N(6)-amide-bond scission.



R
1, H
15, CH_3

R R^1
51, H CH_3
52, CH_3 CH_3

R
53, CH_3
54, CH_2CH_3



Finally we synthesized fervenulin-3-carboxylic acid (**55**) by mild oxidation of 3-styrylfervenulin (**20**) by permanganate in pyridine/water at 0-20° in 77% yield. Compound **55** is a relatively strong acid which precipitated from the reaction solution, after filtration of manganese dioxide, and acidification to *p*H 0. It is also very sensitive to decarboxylation as anticipated and is converted into fervenulin (**1**) on boiling in water. Esterification of **55** with methanol and ethanol, respectively, under H^+-catalysis afforded the corresponding methyl **56** and ethyl carboxylates **57**.

The synthesis of various 3-carbamoylfervenulins was achieved by conversion of **55** with thionyl chloride into fervenulin-3-carboxyl chloride (**58**) which was not isolated but used *in situ* by treatment with the appropriate amines. Reaction with ammonia at room temperature led in 1 hour to fervenulin-3-carboxamide (**59**) in 79% yield but methylamine and ethylamine, respectively, under the same conditions resulted in displacement in the side-chain as well as ring-contraction to form 2,4a-dihydro-5,7-dimethylimidazo-[4,5-*e*]-1,2,4-triazin-6-one-3,4a-bis-*N*-methylcarboxamide (**60**) and its 3,4a-bis-*N*-ethylcarboxamide derivative **61**. The same interconversions with *n*-propylamine and *i*-butylamine afforded much longer reaction times and led in 16 hours to the 3,4a-bis-*N*-*n*-propylcarboxamide **62** in 73% yield and to the *i*-butyl derivative **63** in 5 days with 59% yield. Shorter treatment of **58** with various primary and secondary amines allow the syntheses of fervenuline-3-carboxamides as

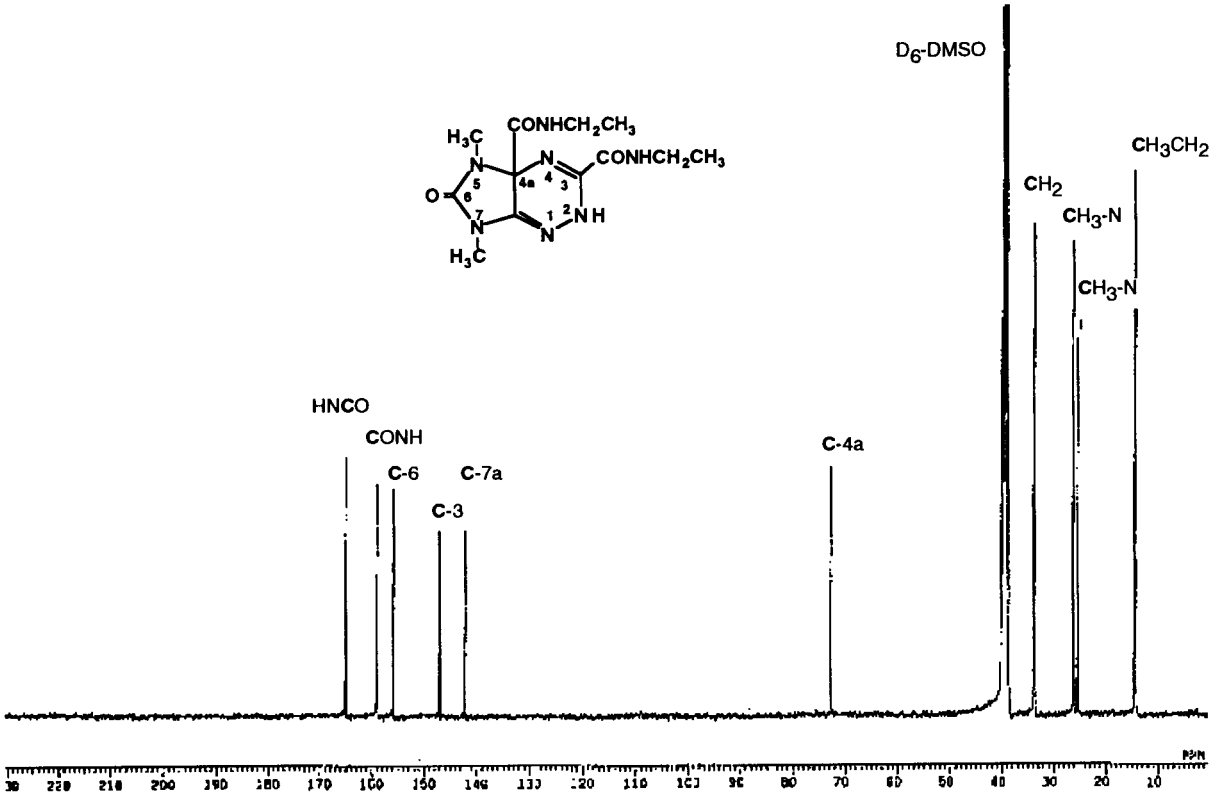


Figure 1. The ^{13}C-nmr spectrum of 2,4a-dihydro-5,7-dimethylimidazo[4,5-*e*]-1,2,4-triazin-6-one-3,4a-bis-*N*-ethylcarboxamide (**61**).

Table 1

UV Absorption Spectra of Fervenulin Derivatives

	pK_a in H_2O	UV Absorption Spectra λ_{max} (nm)			log ε			pH	Molecular Form
1		238	274	348	4.29	3.19	3.66	MeOH	o
15	0.4		286	355		3.85	2.79	-2.0	+
		238	(270)	348	4.30	(3.23)	3.65	6.0	o
16		239	(272)	348	4.30	(3.25)	3.67	MeOH	o
17		243	(280)	349	4.34	(3.36)	3.61	MeOH	o
18		237	(270)	345	4.31	(3.22)	3.65	MeOH	o
19	-1.3	251	292	359	4.23	3.44	3.31	-4.0	+
		238	(270)	346	4.37	(3.21)	3.70	4.0	o
20		225	313	390	4.01	4.51	3.51	MeOH	o
21	-5.0		267	359		4.28	3.44	-6.8	+
		251		353	4.34		3.62	4.0	o
22		252		350	4.30		3.61	5.0	o
23		251		353	4.34		3.62	5.0	o
24			268	343		4.26	3.64	5.0	o
25		248		348	4.30		3.63	MeOH	o
26		247		350	4.27		3.59	MeOH	o
27		251		351	4.28		3.61	5.0	o
28		242	(284)	344	4.32	(3.17)	3.63	6.0	o
29		242	280	346	4.31	3.21	3.61	6.0	o
30			267	368		4.30	3.57	6.0	o
31		240	(274)	345	4.29	(3.20)	3.62	MeOH	o
32		239	274	346	4.33	3.22	3.65	6.0	o
33		240	(274)	347	4.31	(3.19)	3.62	6.0	o
34		239	274	346	4.33	3.22	3.65	6.0	o
35		262	(281)	344	4.17	(4.00)	3.63	6.0	o
36		240	(274)	344	4.25	(3.13)	3.58	MeOH	o
39		239	288	346	4.32	4.31	3.67	5.0	o
55	-2.6		262	346		4.18	3.54	-4.3	+
	2.04		258	343		4.21	3.61	0.0	o
			248	344		4.26	3.63	5.0	-
56	-3.32		263	348		4.18	3.52	-5.5	+
			259	344		4.22	3.60	3.0	o
57	-3.61		263	348		4.18	3.52	-5.5	+
			258	343		4.23	3.58	3.0	o
59	-4.21		261	348		4.34	3.72	-5.5	+
			256	344		4.40	3.76	3.0	o
64			256	345		4.31	3.60	MeOH	o
65			256	343		4.30	3.62	MeOH	o
66	-3.30		258	347		4.18	3.57	-5.5	+
			248	350		4.30	3.59	3.0	o
67			247	348		4.30	3.60	MeOH	o

demonstrated with *i*-butylamine, 2-diethylaminoethylamine, diethylamine and morpholine yielding **64-67**. The structures of the imidazo[4,5-*e*]-1,2,4-triazin-6-one derivatives **60-63** are depicted again from the ^{13}C-nmr spectra (Figure 1) showing the C(4a) signal in the region of 70 ppm and have unambiguously proven by an X-ray structural determination of the 3,4a-bis-*N*-ethylcarboxamide derivative **61** (Figure 2).

Physical Properties.

Determinations of the basic pK_a value of various fervenulin derivatives established the weak basicity expected from the nature of the ring system belonging to the π-electron-deficient nitrogen-heterocycles. In accordance with this electronic behaviour is also the relative strong acidity of fervenulin-3-carboxylic acid (**55**) showing an acidic pK_a of 2.04. The uv spectra of the fervenulin derivatives (Table 1) look very similar and the substituents in 3 position do not alter the character of the spectrum significantly. 3-Styrylfervenulin (**20**), however, shows a strong bathochromic shift as expectyed from the extended chromophoric π-system.

The imidazo[4,5-*e*]-1,2,4-triazine derivatives **42-46** coincide also in their spectral properties and absorb at 288 ±1 nm. The simple 2,4a-dihydro derivatives **47-50**, **53** and **54** show a hypsochromic shift. In the corresponding 3-carboxamides (**60-63**) is the long wavelength band shifted to the red by about the same value of 20 nm.

The ^1H nmr spectra are relatively simple and the various signals which are listed in the experimental agree in all details with the proposed structures.

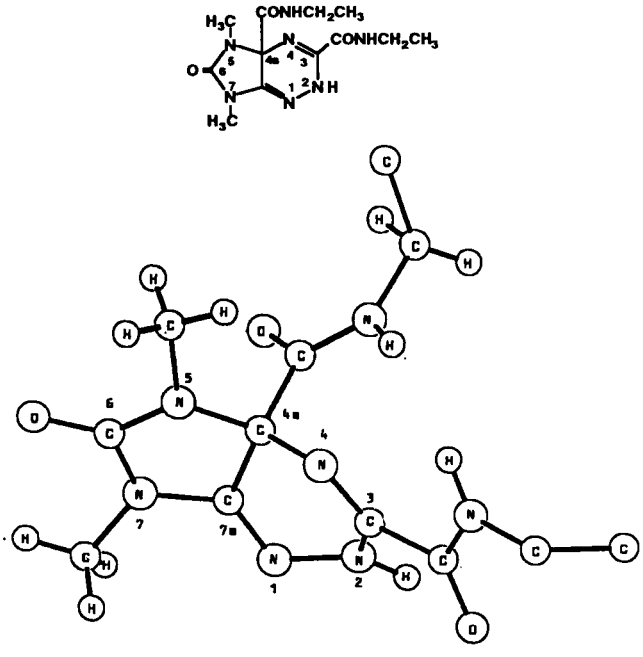


Figure 2. X-ray structure of **61**.

Table 2
UV Absorption Spectra of Imidazo[4,5-*e*]-1,2,4-triazine Derivatives

	pK_a in H_2O	UV Absorption Spectra λ_{max} (nm)		log ε		*p*H	Molecular Form
42	2.11	(248)	276	(2.46)	3.96	0.0	+
		(248)	289	(3.50)	4.01	5.0	o
43	2.32		276		3.97	0.0	+
		(250)	289	(3.54)	4.03	5.0	o
44	1.55		276		4.02	0.0	+
			287		4.03	5.0	o
45	2.36		276		3.97	0.0	+
		(248)	288	(3.55)	4.04	5.0	o
46		(244)	287	(3.47)	4.01	MeOH	o
47			267		3.39	MeOH	o
48		(224)	267	(3.80)	3.44	MeOH	o
49		(224)	269	(3.79)	3.48	MeOH	o
50		(225)	263	(3.76)	3.39	MeOH	o
53	2.63		286		3.81	0.0	+
			270		3.69	5.0	o
54		(223)	272	(3.85)	3.37	MeOH	o
60	-1.3		322		3.51	-4.0	+
		(229)	309	(3.96)	3.13	4.0	o
61		(228)	306	(4.03)	3.21	6.0	o
62		(230)	308	(4.04)	3.21	6.0	o
63		(232)	307	(4.06)	3.32	6.0	o

EXPERIMENTAL

Melting points were determined on a Gallenkamp hot stage apparatus and are uncorrected. The ^1H nmr spectra were recorded on a 250 MHz Bruker WM 250 and the ^{13}C nmr spectra on a Jeol JNM-GX 400 spectrometer in δ (ppm) and with tetramethylsilane as internal standard. The uv spectra were obtained on a Kontron, Uvikon 820 and a Perkin-Elmer, Lambda 5 spectrometer recording + = monocation, o = neutral form and - = monoanion in λ_{max} and log ε; ( ) shoulder. The pK_a determinations were performed by the spectrophotometric method [36]. The X-ray analysis of compound **62** was done on a Syntex P3 diffractometer with monocline crystals of space group $P2_1/c$. The lattice parameters are a = 7.839 (1), b = 9.948 (1), c = 21.136 (3) Å, β = 106.84 (1)°. Scan technique ω2Θ; data collected $4.0 < 2\Theta > 52°$; radiation by graphite-monochromated MoKα (λ = 71,069 pm). Reflexions collected 3505. The H-atoms were calculated in idealized geometry and refined isotropically. The tlc was performed on precoated silica gel sheets F 1500/LS 254 and precoated cellulose sheets F 1440/LS 254 from Schleicher & Schüll. Detection uv light 254 and 366 nm. Preparative tlc was undertaken on glass plates (40 x 20 x 0.2 cm) with silica gel 60 F 254 of Merck. Elemental analyses were determined on a Heraeus microanalyser model CHN-O-Rapid by the Microanalytical Laboratory of the Department of Chemistry, Konstanz University.

6,8-Dimethylpyrimido[5,4-*e*]-1,2,4-triazine-5,7-dione (Fervenulin) (**1**).

a) A solution of 3-dibromomethylfervenulin (**22**) (0.1 g, 0.27 mmole) in acetic acid (15 ml) was treated with silver acetate (0.2 g) first at room temperature for 30 minutes and then under reflux for 6 hours. Water (30 ml) was added and boling continued for 1 hour. After filtration was evaporated, the residue extracted by chloroform, washed with sodium bicarbonate solution and the organic layer dried over sodium sulfate. Isolation and purification was done by preparative tlc on silica gel with toluene/ethyl acetate 1:1 to give a yellowish solid (8 mg, 9%), mp 177°, Lit [9] mp 178-179°.

b) To a solution of 3-hydroxymethylfervenulin (**32**) (0.1 g, 0.45 mmole) in acetic acid (10 ml) were added dropwise with stirring, chromium trioxide (0.045 g) in a mixture of water (3 ml) and acetic acid (8 ml) at room temperature. After 22 hours more chromium trioxide (0.03 g) in water (1 ml)/acetic acid (5 ml) was added, stirred for 4 hours and then refluxed for another 4 hours. The mixture was poured onto ice, extracted with chloroform followed by work-up analogous to the preceding procedure yielding a yellowish solid (0.06 g, 69%), mp 177°.

c) A solution of fervenulin-3-carboxylic acid (**56**) (0.05 g, 0.2 mmole) in water (5 ml) was refluxed for 18 hours. Evaporation to dryness and purification by preparative tlc in toluene/ethyl acetate 1:1 yields a yellowish solid (0.034 g, 89%), mp 177°.

1,3-Dimethyl-6-propionylaminouracil (**6**).

A suspension of 6-hydrazino-1,3-dimethyluracil (**4**) [37] (1.0 g, 5.9 mmoles) in ethanol (15 ml) was treated with propionic anhydride (6.8 ml, 0.053 mole) by stirring at room temperature. After 40 minutes the precipitate was collected, the filtrate concentrated and then diluted with ether to give a second crop. Recrystallization from ethanol gave colorless crystals (0.853 g, 64%), mp 240-242°; uv (methanol): 267 (4.26).

Anal. Calcd. for $C_9H_{14}N_4O_3$: C, 47.78; H, 6.24; N, 24.76. Found: C, 47.49; H, 6.01; N, 24.80.

1,3-Dimethyl-6-phenacetylhydrazinouracil (**7**).

A suspension of **4** [37] (1.0 g, 5.9 mmoles) in ethanol (30 ml) was treated by phenylacetic anhydride (16 g, 0.063 mole) in ethanol (50 ml) by fast dropwise addition with stirring. After 90 minutes the precipitate was filtered off (1.3 g, 77%).

Recrystallization from ethanol gave colorless needles, mp 249-251° dec; uv (methanol): 265 (4.25).

Anal. Calcd. for $C_{14}H_{16}N_4O_3$: C, 58,33; H, 5.59; N, 19.43. Found: C, 58.24; H, 5.77; N, 19.14.

6-Isobutyroylhydrazino-1,3-dimethyluracil (**8**).

To a suspension of **4** [37] (4.0 g, 0.024 mole) in ethanol (60 ml) was added isobutyric anhydride (36 ml, 0.22 mole) dropwise with stirring at room temperature. After 15 hours the chromatographically pure precipitate was collected and dried (4.92 g, 87%). Recrystallization from ethanol gave colorless needles, mp 271-273°; uv (methanol): 265 (4.28).

Anal. Calcd. for $C_{10}H_{16}N_4O_3$: C, 49.99; H, 6.71; N, 23.32. Found: C, 49.92; H, 6.77; N, 23.07.

1,3-Dimethyl-6-pivaloylhydrazinouracil (**9**).

A suspension of **4** [37] (1.0 g, 5.9 mmoles) in ethanol (15 ml) was treated with pivalic anhydride (11 ml, 0.054 mole) for 20 hours at room temperature with stirring. The colorless precipitate was filtered off, washed and dried at 100° (1.12 g, 75%), mp 251-253°; uv (methanol): 266 (4.27).

Anal. Calcd. for $C_{11}H_{18}N_4O_3$: C, 51.96; H, 7.13; N, 22.03. Found: C, 51.93; H, 7.03; N, 21.98.

General Procedure for the Nitrosation of 6-Acylhydrazinouracils.

To a suspension of the appropriate 6-acylhydrazino-1,3-dimethyluracil (2.5 mmoles) in ethanol (12 ml) was added isoamyl nitrite and then a drop of concentrated hydrochloric acid. After sirring for 1 hour at room temperature the yellow precipitate was collected, washed and dried at 100°. Analytical samples are obtained by recrystallisation from ethanol.

1,3-Dimethyl-5-nitroso-6-propionylhydrazinouracil (**11**).

From **6** (0.565 g) were obtained yellow crystals (0.57 g, 89%), mp 172-175° dec; uv (methanol): 237 (4.34), 370 (3.60).

Anal. Calcd. for $C_9H_{13}N_5O_4$: C, 42.35; H, 5.13; N, 27.44. Found: C, 42.41; H, 5.12; N, 27.47.

1,3-Dimethyl-5-nitroso-6-phenacetylhydrazinouracil (**12**).

From **7** (0.72 g) were obtained yellow crystals (0.71 g, 92%), mp 197-199° dec; uv (methanol): 238 (4.41), 365 (3.68).

Anal. Calcd. for $C_{14}H_{15}N_5O_4$: C, 52.99; H, 4.76; N, 22.07. Found: C, 52.92; H, 4.76; N, 21.84.

6-Isobutyroylhydrazino-1,3-dimethyl-5-nitrosouracil (**13**).

From **8** (0.6 g) were obtained yellow crystals (0.61 g, 91%), mp 180-183°; uv (methanol): 236 (4.40), 364 (3.66).

Anal. Calcd. for $C_{10}H_{15}N_5O_4$: C, 44.61; H, 5.62; N, 26.01. Found: C, 44.61; H, 5.54; C, 25.82.

1,3-Dimethyl-5-nitroso-6-pivaloylhydrazinouracil (**14**).

From **9** (0.636 g) were obtained yellow crystals (0.7 g, 99%), mp 168-170°; uv (methanol): 238 (4.33), 370 (3.63).

Anal. Calcd. for $C_{11}H_{17}N_5O_4$: C, 46.64; H, 6.05; N, 24.72. Found: C, 46.68; H, 5.78; N, 24.79.

General Synthesis of 3-Alkyl-1,3-dimethylfervenulins.

6-Acylhydrazino-1,3-dimethyl-5-nitrosouracil (0.05 mole) **11-14** was dissolved in a mixture of water (450 ml) and ethanol (150 ml) by heating to 80°, then a solution of $Na_2S_2O_4$ (0.05 mole) in water (150 ml) added dropwise and followed by boiling under reflux for 4 hours. After cooling it was extracted with chloroform. Then the organic layer was separated, dried over sodium sulfate, evaporated and the residue purified by column chromatography on silica gel. The main product fraction was evaporated and dried in a vacuum dessicator.

3-Ethylfervenulin (**16**).

From **11** (12.75 g) was obtained after chromatography in toluene/ethyl acetate 19:1 a yellow solid (6.63 g, 60%), mp 95°, Lit [37] 88-89°; ^{1}H nmr (deuteriochloroform): δ 3.86 (s, 3H, (N-Me(8)), 3.53 (s, 3H, N-Me (6)), 3.31 (q, 2H, CH_2), 1.46 (t, 3H, CH_3).

3-Benzylfervenulin (**17**).

From **12** (15.85 g) was obtained after chromatography in toluene/acetonitrile 15:1 a yellow solid (5.66 g, 40%), mp 193°, Lit [29] 196°; ^{1}H nmr (deuteriochloroform): δ 7.43-7.20 (m, 5H, arom), 4.60 (s, 2H, CH_2), 3.84 (s, 3H, N-Me(8)), 3.52 (s, 3H, N-Me(6)).

3-Isopropylfervenulin (**18**).

From **13** (13.45 g) was obtained after chromatography in toluene/ethyl acetate 15:1 a yellow solid (5.05 g, 43%), mp 170-171°, Lit [29] 173-174°; ^{1}H nmr (deuteriochloroform): δ 3.86 (s, 3H, N-Me(8)), 3.68-3.54 (m, 1H, C-H), 3.53 (s, 3H, N-Me(6)), 1.47 (d, 6H, C-Me).

3-*tert*-Butylfervenulin (**19**).

From **14** (14.15 g) was obtained after chromatography in toluene/ethyl acetate 19:1 a yellow solid (3.1 g, 25%), mp 198-199°; ^{1}H nmr (deuteriochloroform): δ 3.86 (s, 3H, N-Me(8)), 3.53 (s, 3H, N-Me(6)), 1.54 (s, 9H, C-CH_3).

Anal. Calcd. for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.09. Found: C, 53.11; H, 6.15; N, 27.97.

3-Styrylfervenulin (**20**).

A mixture of 3-methylfervenulin (**15**) (4.0 g, 0.019 mole), zinc chloride (0.8 g) and benzaldehyde (8 ml, 0.8 mole) was heated in an oil bath to 160° with stirring. After 2 and 4 hours, respectively, more benzaldehyde (8 ml) was added and heating continued up to 24 hours. It was diluted with 2*N* hydrochloric acid (40 ml) and then the excess benzaldehyde removed by steam distillation. The residue was dissolved in water (600 ml), neutralised by sodium bicarbonate and then extracted with chloroform. The organic layer was dried over sodium sulfate, evaporated and the crude product purified by silica gel column chromatography in toluene/ethyl acetate 15:1-10:1-5:1. Evaporation of the main fraction gave a yellow solid (3.52 g, 63%), mp 275-277° dec; Lit [31,38] 263°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 8.0-6.88 (m, 7H, C_6H_5CH=CH), 3.68 (s, 3H, N-Me(8)), 3.65 (s, 3H, N-Me(6)).

3-(1,2-Dibromo-2-phenylethyl)fervenulin (**21**).

A solution of **20** (0.6 g, 2 mmoles) in chloroform (180 ml) was cooled to 0° and then with stirring, bromine (0.1 ml) was added. After 3 and 6 hours, respectively, the same amount of bromine was added and stirred for a total of 7.5 hours. The solution was evaporated to dryness and the residue purified by silica gel column chromatography with toluene/ethyl acetate 19:1 to give a yellow solid (0.831 g, 90%), mp 201°; ^{1}H nmr (deuteriochloroform): δ 7.60-7.41 (m, 5H, arom), 6.10 (d, 1H, J = 12 Hz, H-C), 6.01 (d, 1H, J = 12 Hz, H-C), 3.93 (s, 2H, N-Me(8)), 3.57 (s, 3H, N-Me(6)).

Anal. Calcd. for $C_{15}H_{13}Br_2N_5O_2$: C, 39.59; H, 2.88; N, 15.39. Found: C, 39.17; H, 2.95; N, 14.96.

3-Dibromomethylfervenulin (**22**).

a) A solution of 3-methylfervenulin (**15**) (0.5 g, 2.4 mmoles) in acetic acid (20 ml) was heated under reflux and then 4 portions of bromine (0.2 ml in 1 ml of acetic acid) was added during a period of 8 hours. After cooling and evaporation, the residue dissolved in chloroform (35 ml) and extracted twice with water. The organic layer was dried over sodium sulfate, evaporated and the resulting solid purified by silica gel column chromatography in toluene/ethyl acetate 15:1 to give **22** (0.727 g, 83%), mp 198-200° dec, and traces of **25**; ^{1}H nmr (deuteriochloroform): δ 6.98 (s, 1H, H-C), 3.90 (s, 3H, N-Me(8)), 3.54 (s, 3H, N-Me(6)).

Anal. Calcd. for $C_8H_7Br_2N_5O_2$: C, 26.33; H, 1.93; N, 19.19. Found: C, 26.36; H, 1.91; N, 19.13.

b) A suspension of **15** (1 g, 4.8 mmoles) in dry carbon tetrachloride (70 ml) was treated with *N*-bromosuccinimide (1.71 g, 10 mmoles) and azoisobutyronitrile (25 mg) for 41 hours under reflux. The insoluble material was filtered off, washed with carbon tetrachloride and the filtrates evaporated. The residue was put on preparative silica gel plates and developed with toluene/ethyl acetate 1:1 to give two main bands. After elution and evaporation compound **22** was obtained (0.12 g, 7%), mp 200° dec, and **25** (0.11 g, 8%), mp 105-107°.

3-(1,1-Dibromoethyl)fervenulin (**23**) and 3-(1-Bromoethyl)fervenulin (**26**).

A mixture of 3-ethyl-fervenulin (**16**) (4.0 g, 0.018 mole), *N*-bromosuccinimide (3.3 g) and azoisobutyronitrile (0.1 g) were heated in carbon tetrachloride under reflux for 3 hours. Then the same amounts of *N*-bromosuccinimide and azoisobutyronitrile were added and heating continued for 2 hours. The precipitate was filtered off, washed with carbon tetrachloride and the united filtrates evaporated. The residue was separated by silica gel column chromatography in toluene/ethyl acetate 19:1 to give **23** (0.65 g, 10%), mp 137-140° and **26** (3.13 g, 59%), mp 169-170°.

Compound **23** had ^{1}H nmr (deuteriochloroform): δ 3.91 (s, 3H, N-Me(8)), 3.55 (s, 3H, N-Me(6)), 3.14 (s, 3H, C-Me).

Anal. Calcd. for $C_9H_9BrN_5O_2$: C, 28.52; H, 2.39; N, 18.48. Found: C, 28.68; H, 2.34; N, 18.49.

Compound **26** had ^{1}H nmr (deuteriochloroform): δ 5.61 (q, 1H, H-C), 3.88 (s, 3H, N-Me(8)), 3.53 (s, 3H, N-Me(6)), 2.24 (d, 3H, C-Me).

Anal. Calcd. for $C_9H_{10}BrN_5O_2$: C, 36.02; H, 3.36; N, 23.34. Found: C, 36.43; H, 3.36; N, 23.08.

3-Benzoylfervenulin (**24**) and 3-(1-Bromobenzyl)fervenulin (**27**).

To a hot solution of 3-benzylfervenulin (**17**) (3.0 g, 0.01 moles) in acetic acid (120 ml) was added bromine (0.54 ml) in acetic acid (2 ml) dropwise. After 3 hours of heating under reflux again bromine (0.6 ml) in acetic acid (2 ml) was added and boiling continued for 2 hours. After cooling it was evaporated to dryness, the residue dissolved in chloroform and extracted with water. The organic phase was dried over sodium sulfate, evaporated and the residue separated by silica gel column chromatography with toluene/ethyl acetate 19:1 to give as the first fraction **27** (2.08 g, 54%), mp 72-74° and as the slower moving fraction **24** (1.0 g, 32%), mp 221° dec.

Compound **24** had ^{1}H nmr (deuteriochloroform): δ 7.98-7.43 (m, 5H, arom), 3.91 (s, 3H, N-Me(8)), 3.52 (s, 3H, N-Me(6)).

Anal. Calcd. for $C_{14}H_{11}N_5O_3$: C, 56.57; H, 3.73; N, 23.56. Found: C, 56.21; H, 3.78; N, 23.30.

Compound **27** had ^{1}H nmr (deuteriochloroform): δ 7.82-7.32 (m, 5H, arom), 6.51 (s, 1H, H-C), 3.86 (s, 3H, N-Me(8)), 3.53 (s, 3H, N-Me(6)).

Anal. Calcd. for $C_{14}H_{12}BrN_5O_2$: C, 46.43; H, 3.34; N, 19.34. Found: C, 46.72; H, 3.58; N, 18.83.

3-Bromomethylfervenulin (**25**).

A solution of **22** (0.1 g, 0.27 mmole) in acetic acid (10 ml) was treated with tin (34 mg) and hydrobromic acid (0.3 ml, 48%) by boiling for 8 hours. The mixture was diluted with water (150 ml), neutralized with calcium carbonate, filtered and then extracted with chloroform several times. The united extracts were dried over sodium sulfate, evaporated and purified by chromatography on preparative silica gel plates with toluene/ethyl acetate 1:1 to give **25** (29 mg, 34%), mp 105-107°; ^{1}H nmr (deuteriochloroform): δ 4.92 (s, 2H, CH_2), 3.88 (s, 2H, N-Me(8)), 3.54 (s, 3H, N-Me(6)).

Anal. Calcd. for $C_8H_8BrN_5O_2$: C, 36.10; H, 3.04; N, 26.32. Found: C, 36.01; H, 2.98; N, 26.25.

3-(1,3-Dioxolan-2-yl)fervenulin (**28**).

a) A solution of **22** (0.2 g, 0.55 mmole) in 1,2-ethanediol was refluxed for 70 minutes. After cooling and evaporation, the residue was treated with water and then extracted with chloroform. The organic layer was dried over sodium sulfate, evaporated and the residue purified by silica gel chromatography on preparative plates (40 x 20 x 0.2 cm) with chloroform/methanol 19:1. The main band gave **28** (27 mg, 19%), mp 235° dec.

b) A mixture of 3-formylfervenulin (**36**) (0.1 g, 0.45 mmole), *p*-toluensulfonic acid (15 mg, 0.08 mmole) and 1,2-ethanediol (0.06 ml, 1.07 mmoles) were heated under reflux in chloroform for 5 hours. It was diluted with chloroform, washed with a saturated aqueous solution of sodium bicarbonate and water and after drying, the organic phase evaporated to dryness. The residue was recrystallized from ethanol to give **28** (0.076 g, 63%), mp 235° dec; ^{1}H nmr (deuteriochloroform): δ 6.37 (s, 1H, H-C), 4.40 (m, 2H, CH_2), 4.15 (m, 2H, CH_2), 3.86 (s, 3H, N-Me(8)), 3.52 (s, 3H, N-Me(6)).

Anal. Calcd. for $C_{10}H_{11}N_5O_4$: C, 45.29; H, 4.18; N, 26.40. Found: C, 45.21; H, 4.18; N, 26.51.

3-(1,3-Dioxolan-2-methyl-2-yl)fervenulin (**29**).

A solution of **23** (0.2 g, 0.53 mmole) in 1,2-ethanediol (20 ml) was heated under reflux for 2 hours. After cooling it was evaporated, the residue treated with water and then extracted with chloroform. The organic layer was dried over sodium sulfate, again evaporated and the residue purified by silica gel chromatography on preparative plates with toluene/ethyl acetate 1:1 to give a yellow solid (0.07 g, 48%), mp 193-194°; ^{1}H nmr (deuteriochloroform): δ 4.23 (m, 4H, CH_2), 3.87 (s, 3H, N-Me(8)), 3.52 (s, 3H, N-Me(6)).

Anal. Calcd. for $C_{11}H_{13}N_5O_4$: C, 47.31; H, 4.69; N, 25.08. Found: C, 46.99; H, 4.62; N, 24.88.

Fervenulin-3-carboxaldoxime (**30**).

A mixture of **22** (0.1 g, 0.27 mmole), hydroxylamine hydrochloride (0.186 g, 2.68 mmoles) and sodium carbonate (0.142 g, 1.34 mmoles) were heated in ethanol (30 ml) under reflux for 9 hours. After cooling, dilution with water, and extraction with chloroform, the organic phase dried over sodium sulfate and again evaporated. The residue was purified by silica gel chromatography on preparative plates (40 x 20 x 0.2 cm) with toluene/acetonitrile 1:1. The main band was eluted to give a

yellow solid (0.04 g, 62%), mp 247-248° dec; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 12.36 (s, 1H, HO-N), 8.44 (s, 1H, H-C), 3.67 (s, 3H, N-Me(8)), 3.33 (s, 3H, N-Me(6)).

Anal. Calcd. for $C_8H_8N_6O$: C, 40.68; H, 3.41; N, 35.58. Found: C, 40.83; H, 3.45; N, 35.25.

3-Acetoxymethylfervenulin (**31**).

A solution of **25** (0.05 g, 0.17 mmole) in acetic acid (5 ml) was treated under excess of light with silver acetate (0.032 g, 0.19 mmole) first by stirring at room temperature and then by boiling for 3 hours. After cooling and filtering, the filtrate evaporated and the residue purified by silica gel chromatography on a preparative plate (20 x 20 x 0.2 cm) with toluene/ethyl acetate 1:1. The main band was eluted and gave a solid (0.038 g, 82%), mp 92-95°; ^{1}H nmr (deuteriochloroform): δ 5.57 (s, 2H, CH_2), 3.87 (s, 3H, N-Me(8)), 3.53 (s, 3H, N-Me(6)), 2.18 (s, 3H, MeCO).

Anal. Calcd. for $C_{10}H_{11}N_5O_2$: C, 55.32; H, 5.11; N, 32.26. Found: C, 55.18; H, 5.06; N, 32.38.

3-Hydroxymethylfervenulin (**32**).

A solution of **25** (0.4 g, 1.4 mmoles) in acetic acid (40 ml) was treated with silver acetate (0.256 g, 1.5 mmoles) analogous to the preceding procedure. Compound **31** was obtained by chromatography in form of a yellow oil which was treated with half concentrated methanolic ammonia overnight. After evaporation the residue was purified by silica gel column chromatography first with chloroform and then with chloroform/methanol 50:1 to give a yellow solid (0.193 g, 62%), mp 150-152° dec; ^{1}H nmr (deuteriochloroform): δ 5.18 (s, 2H, CH_2), 3.36 (bs, 1H, H-O), 3.88 (s, 3H, N-Me(8)), 3.53 (s, 3H, N-Me(6)).

Anal. Calcd. for $C_8H_9N_5O_3$: C, 43.05; H, 4.06; N, 31.38. Found: C, 43.13; H, 3.99; N, 30.72.

3-(1-Acetoxyethyl)fervenulin (**33**).

A solution of **26** (0.5 g, 1.7 mmoles) in acetic acid (50 ml) was treated under excess of light with silver acetate (0.31 g, 1.9 mmoles) first with stirring at room temperature and then by boiling for 2 hours. The precipitate was filtered off, the filtrate evaporated and the resulting oil crystallized by ether to give yellow crystals (0.46 g, 99%), mp 103-106°; ^{1}H nmr (deuteriochloroform): δ 6.14 (q, 1H, H-C), 3.87 (s, 3H, N-Me(8)), 3.53 (s, 3H, N-Me(6)), 2.15 (s, 3H, MeCO), 1.76 (d, 3H, C-Me).

Anal. Calcd. for $C_{11}H_{13}N_5O_4$: C, 47.31; H, 4.69; N, 25.08. Found: C, 47.46; H, 4.69; N, 24.66.

3-(1-Hydroxyethyl)fervenulin (**34**).

The preceding procedure was repeated with **26** (3.2 g, 0.011 mole), silver acetate (2 g, 0.012 mole) in acetic acid (320 ml). Compound **33** was treated with methanolic ammonia (30 ml) at room temperature overnight. Evaporation and crystallization of the residue from ethanol gave a yellow solid (1.22 g, 48%), mp 145-147°; ^{1}H nmr (deuteriochloroform): δ 5.34 (m, 1H, H-C), 3.88 (s, 3H, N-Me(8)), 3.55 (s, 1H, H-O), 3.53 (s, 3H, N-Me(6)), 1.69 (d, 3H, C-Me).

Anal. Calcd. for $C_9H_{11}N_5O_3$: C, 45.57; H, 4.67; N, 29.52. Found: C, 45.65; H, 4.69; N, 29.13.

3-Acetylfervenulin (**35**).

A solution of **34** (0.1 g, 0.42 mmole) in acetic acid (10 ml) was treated with chromium trioxide (0.042 g, 0.042 mmole) dissolved in water (1.5 ml) and acetic acid (7.2 ml) by dropwise addition with stirring at room temperature. After 20 hours more chromium trioxide (21 mg) was added and stirring continued for another day. The mixture was then diluted with ice-water (100 ml) and extracted with chloroform. The organic phase was dried over sodium sulfate, evaporated and the residue purified by silica gel chromatography with toluene/ethyl acetate 1:1 to give a yellow solid (0.062 g, 63%), mp 152-153°; ^{1}H nmr (deuteriochloroform): δ 3.93 (s, 3H, N-Me), 3.55 (s, 3H, N-Me (6)), 2.91 (s, 3H, MeCO).

Anal. Calcd. for $C_9H_9N_5O_3$: C, 45.96; H, 3.86; N, 29.78. Found: C, 46.09; H, 3.86; N, 29.23.

3-Formylfervenulin (**36**).

a) A suspension of 3-styrylfervenulin (**20**) (0.2 g, 0.68 mmole) in dioxane (48 ml) and water (16 ml) was treated with osmium tetroxide (0.1 g) and vigorous stirring at room temperature for 15 minutes. Then sodium periodate (0.3 g) was added and after 7 hours more sodium periodate (0.28 g) and stirred for one day. The reaction mxture was then evaporated and the residue put onto a silica gel column for chromatography with chloroform/methanol 19:1 to give a yellow solid (0.128 g, 85%), mp 82-88° dec.

b) A suspension of **20** (2 g, 6.7 mmoles) in absolute methanol (300 ml) and absolute chloroform (400 ml) was cooled to -40° and then ozone (3 g) injected whereby a clear solution was obtained. After concentrating in vacuum to a small volume $Na_2S_2O_4$ (1 g) in water (20 ml) was added and stirred overnight. The solution was then extracted with chloroform, the organic phase dried over sodium sulfate, again evaporated and the residue purified by silica gel column chromatography with chloroform/methanol 19:1 to give a yellow powder (1.31 g, 88%), mp 82-88° dec; ^{1}H nmr (deuteriochloroform): δ 10.36 (s, 1H, CHO), 3.95 (s, 3H, N-Me(8)), 3.55 (s, 3H, N-Me(6)).

Anal. Calcd. for $C_8H_7N_5O_3$ x H_2O: C, 40.18; H, 3.79; N, 29.28. Found: C, 40.27; H, 3.90; N, 29.32.

3-(1-Ethoxy-1-hydroxymethyl)fervenulin (**38**).

Recrystallization of compound **36** (0.2 g, 0.9 mmole) from ethanol (5.8 ml) gave yellow crystals which were dried in a vacuum dessicator (0.126 g, 52%), mp 97-100°; ^{1}H nmr (deuteriochloroform): δ 6.01 (d, 1H, H-C), 4.27 (d, 1H, H-O), 4.08 (m, 1H, CH_2), 3.88 (s, 3H, N-Me(8)), 3.70 (m, 2H, CH_2), 3.53 (s, 3H, N-Me(6)), 1.25 (t, 3H, C-Me).

Anal. Calcd. for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 44.79; H, 4.85; N, 26.21.

N-(Fervenulin-3-ylmethyl)-4-aminobenzoyl-L-glutamic Acid (**39**).

A mixture of **36** (0.5 g, 2.3 mmoles) and *N*-(4-aminobenzoyl-L-glutamic acid (1.2 g, 4.5 mmoles) was stirred in acetic acid (50 ml) at room temperature for 5 hours. The dimethylaminoborane (0.23 g, 3.9 mmoles) were added and stirring continued overnight. The reaction mixture was evaporated and the residue recrystallized from water/ethanol 3:1 with charcoal to give yellow crystals (0.8 g, 76%), mp 131°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 12.3 (bs, 2H, COOH), 8.10 (d, 1H, H-N), 7.62 (d, 2H, phenyl), 7.21 (t, 1H, *H*-NCH_2), 6.67 (d, 2H, phenyl), 4.80 (d, 2H, CH_2-NH), 4.33 (m, 1H, H-C), 3.63 (s, 3H, N-Me(8)), 3.28 (s, 3H, N-Me(6)), 2.32-1.89 (m, 4H, CH_2CH_2).

Anal. Calcd. for $C_{20}H_{21}N_7O_7$ x H_2O: C, 49.08; H, 4.74; N, 20.03. Found: C, 49.12; H, 4.68; N, 19.96.

3,5,7-Trimethylimidazo[4,5-*e*]-1,2,4-triazin-6-one (**42**).

a) A solution of **15** (0.5 g, 2.4 mmoles) in water (50 ml) was heated in a boiling water-bath and then potassium permanganate

(0.5 g, 2.8 mmoles) added gradually with stirring. After heating for 6 hours the manganese dioxide was filtered off and the filtrate acidified by acetic acid. The reaction solution was extracted with chloroform, the organic layer separated and dried over sodium sulfate, followed by evaporation. The residue was recrystallized from ethanol to give colorless crystals (0.3 g, 69%), mp 110°.

b) A solution of **47** (20 mg, 0.11 mmole) in water (5 ml) was treated with potassium permanganate (24 mg, 0.15 mmole) at room temperature with stirring for 1 hour. The manganese dioxide was filtered off, washed with water and the filtrate then extracted with chloroform. The extract was dried over sodium sulfate and evaporated to give a chromatographically pure solid (18.3 mg, 92%), mp 110°; ^{1}H nmr (deuteriochloroform): δ 3.53 (s, 3H, N-Me(7)), 3.44 (s, 3H, N-Me(5)), 2.71 (s, 3H, C-Me).

Anal. Calcd. for $C_7H_9N_5O$: C, 46.92; H, 5.06; N, 39.08. Found: C, 46.85; H, 5.08; N, 38.68.

3-Ethyl-5,7-dimethylimidazo[4,5-*e*]-1,2,4-triazin-6-one (**43**).

A hot solution of **16** (0.5 g, 2.3 mmoles) in water (50 ml) was treated gradually with potassium permanganate (0.5 g, 2.8 mmoles) in a boling water-bath for 6 hours. The manganese dioxide was filtered off, washed with water and the filtrate acidified by acetic acid then was extracted by chloroform. The extract was dried over sodium sulfate and evaporated to give a chromatographically pure colorless solid (0.254 g, 58%), mp 72-73°; ^{1}H nmr (deuteriochloroform): δ 3.49 (s, 3H, N-Me(7)), 3.42 (s, 3H, N-Me(5)), 2.95 (q, 2H, CH_2), 1.32 (t, 3H, Me).

Anal. Calcd. for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.77; H, 5.53; N, 35.90.

3-Benzyl-5,7-dimethylimidazo[4,5-*e*]-1,2,4-triazin-6-one (**44**).

Compound **17** was allowed to react as described in the procedure for **43** (0.5 g, 1.8 mmoles) in water (90 ml)/acetone (50 ml). Purification was accomplished by preparative silica gel chromatography on plates with toluene/ethyl acetate 1:1 to give a colorless solid (77 mg, 17%), mp 103-106°; ^{1}H nmr (deuteriochloroform): δ 7.32-7.11 (m, 5H, phenyl), 4.20 (s, 2H, CH_2), 3.43 (s, 3H, N-Me(7)), 3.33 (s, 3H, N-Me(5)).

Anal. Calcd. for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 60.87; H, 5.19; N, 26.96.

5,7-Dimethyl-3-isopropylimidazo[4,5-*e*]-1,2,4-triazin-6-one (**45**).

Compound **18** was allowed to react as described in the procedure for **43** (0.5 g, 2.1 mmoles) in water (50 ml)/dioxane (50 ml). Purification was accomplished by silica gel column chromatography in toluene/ethyl acetate 15:1-10:1 to give a colorless solid (0.05 g, 12%), mp 141-142°; ^{1}H nmr (deuteriochloroform): δ 3.51 (s, 3H, N-Me(7)), 3.44 (s, 3H, N-Me(5)), 3.26 (m, 1H, H-C), 1.33 (d, 6H, CMe_2).

Anal. Calcd. for $C_9H_{13}N_5O$: C, 52.16; H, 6.32; N, 33.79. Found: C, 52.58; H, 6.47; N, 33.53.

3-*tert*-Butyl-5,7-dimethylimidazo[4,5-*e*]-1,2,6-triazin-6-one (**46**).

A solution of **19** (0.5 g, 2 mmoles) in ethanolic sodium hydroxide (10%, 30 ml) was boiled under reflux for 1 hour. It was acidified by acetic acid, evaporated and the residue was extracted with hot ethyl acetate several times. The extract was again evaporated and the resulting solid was separated and purified on preparative silica gel plates with toluene/acetonitrile 1:1 to give two main bands of **46** (R_f = 0.75, 48 mg, 11%), mp 75-77° and of **50** (R_f = 0.47, 0.124 g, 28%); ^{1}H mnr (deuteriochloroform): δ 3.52 (s, 3H, N-Me(7)), 3.45 (s, 3H, N-Me(5)), 1.42 (s, 9H, CMe_3).

Anal. Calcd. for $C_{10}H_{15}N_5O$: C, 54.28; H, 6.83; N, 31.65. Found: C, 54.29; H, 6.94; N, 31.06.

2,4a-Dihydro-3,5,7-trimethylimidazo[4,5-*e*]-1,2,6-triazin-6-one (**47**).

Compound **15** was allowed to react as described in the procedure for **46** (0.5 g, 2.4 mmoles) and isolation on preparative silica gel plates in chloroform/methanol 9:1 to give **42** (0.103 g, 24%) and **47** (75 mg, 17%), mp 154-158°; ^{1}H nmr (deuteriochloroform): δ 7.68 (bs, 1H, H-N), 4.45 (s, 1H, H-C(4a)), 3.10 (s, 3H, N-Me(7)), 3.02 (s, 3H, N-Me(5)), 2.10 (s, 3H, Me(3)); ^{13}C nmr (deuteriochloroform): 165.9 (C-6), 154.1 (C-3), 143.0 (C-7a), 66.2 (C-4a), 28.1 (CH_3), 26.3 (CH_3).

Anal. Calcd. for $C_7H_{11}N_5O$: C, 46.40; H, 6.12; N, 38.65. Found: C, 46.56; H, 6.17; N, 38.87.

2,4a-Dihydro-3-ethyl-5,7-dimethylimidazo[4,5-*e*]-1,2,6-triazin-6-one (**48**).

Compound **16** was allowed to react as described in the procedure for **46** (0.5 g, 2.3 mmoles) and isolation on preparative silica gel plates in chloroform/methanol 9:1 to give **43** (88 mg, 20%) and **48** (113 mg, 26%), mp 108-110°; ^{1}H nmr (deuteriochloroform): δ 7.87 (s, 1H, H-N), 4.43 (s, 1H, H-C(4a)), 3.10 (s, 3H, N-Me(7)), 3.00 (s, 1H, N-Me(5)), 2.35 (q, 2H, CH_2), 1.19 (t, 3H, C-Me).

Anal. Calcd. for $C_8H_{13}N_5O$: C, 49.21; H, 6.71; N, 35.87. Found: C, 48.97; H, 6.60; N, 35.57.

2,4a-Dihydro-3-isopropyl-5,7-dimethylimidazo[4,5-*e*]-1,2,4-triazin-6-one (**49**).

Compound **18** was allowed to react as described in the procedure for **46** (0.5 g, 2.1 mmoles) and chromatographic isolation on preparative silica gel plates in toluene/acetonitrile 1:1 to give **45** (43 mg, 10%) and **49** (0.12 g, 27%), mp 116-120°; ^{1}H nmr (deuteriochloroform): δ 7.63 (bs, 1H, H-N), 4.41 (s, 1H, H-C(4a)), 3.11 (s, 3H, N-Me(7)), 3.02 (s, 3H, N-Me(5)), 2.58 (m, 1H, *H*-CMe_2), 1.20 (d, 6H, CMe_2).

Anal. Calcd. for $C_6H_{15}N_5O$: C, 51.66; H, 7.23; N, 33.47. Found: C, 51.73; H, 7.22; N, 33.03.

3-*tert*-Butyl-2,4a-dihydro-5,7-dimethylimidazo[4,5-*e*]-1,2,4-triazin-6-one (**50**).

Compound **50** was also obtained from **19** (0.124 g, 28%) as described in the procedure for **46**, mp 159-163°; ^{1}H nmr (deuteriochloroform): δ 7.79 (bs, 1H, H-N), 4.38 (s, 1H, H-C(4a)), 3.11 (s, 3H, N-Me(7)), 3.02 (s, 1H, N-Me(5)), 1.23 (s, 9H, CMe_3).

Anal. Calcd. for $C_{15}H_{17}N_5O$: C, 53.79; H, 7.67; N, 31.37. Found: C, 53.82; H, 7.65; N, 30.95.

2,4a-Dihydro-3,5,7-trimethylimidazo[4,5-*e*]-1,2,4-triazin-6-one-4a-*N*-methylcarboxamide (**53**).

A solution of **15** (2.07 g, 0.01 mole) in dry methanol (120 ml) was treated with methanolic methylamine (44%, 20 ml) at room temperature for 4 hours. After evaporation a chromatographically pure solid was obtained which gave upon recrystallization from water colorless crystals (1.78 g, 67%), mp 235-237°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.50 (s, 1H, H-N), 7.69 (bs, 1H, H-NMe), 2.88 (s, 3H, N-Me(7)), 2.70 (s, 3H, N-Me(5)), 2.54 (d, 3H, HN-*Me*), 2.04 (2, 3H, C-Me); ^{13}C nmr (dimethyl sulfoxide-d_6): 166.1 (CO), 165.2 (C-6), 154.1 (C-3), 141.9 (C-7a), 72.7 (C-4a).

Anal. Calcd. for $C_9H_{14}N_6O_2$ x H_2O: C, 42.18; H, 6.26; N, 32.79. Found: C, 42.30; H, 6.20; N, 32.97.

2,4a-Dihydro-3,5,7-trimethylimidazo[4,5-*e*]-1,2,4-triazin-6-one-4a-*N*-ethylcarboxamide (**54**).

A yellow solution of **15** (1.04 g, 5 mmoles) in aqueous ethylamine (70%, 20 ml) was stirred at room tempertature for 2 hours and became colorless after about 15 minutes. It was evaporated and the residue was recrystallized from a little water to give colorless crystals (0.72 g, 53%); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.51 (s, 1H, H-N), 7.80 (t, 1H, *H*-NCH$_2$), 3.03 (m, 2H, CH$_2$), 2.87 (s, 3H, N-Me(7)), 2.72 (s, 3H, N-Me(5)), 2.04 (s, 3H, C-Me), 0.94 (t, 3H, CH$_2$C*H*$_3$).

Anal. Calcd. for $C_{10}H_{16}N_6O_2$ x H_2O: C, 44.32; H, 6.71; 31.09. Found: C, 44.36; H, 6.71; N, 31.37.

Fervenulin-3-carboxylic Acid (**55**).

A suspension of 3-styrylfervenulin (**20**) (3.0 g, 0.01 mole) in a mixture of pyridine (600 ml) and water (600 ml) was cooled to 0° and potassium permanganate (4 g, 0.025 mole) added gradually with stirring. While stirring overnight the mixture warmed up to room temperature, then the manganese dioxide was filtered off and the filtrate evaporated in vacuum at room temperature to dryness. The residue was dissolved in water at a slightly elevated temperature, filtered from a little insoluble material, acidified to *p*H 0, again evaporated and the residue recrystallized from ethanol/water 3:1 (200 ml) after dyring to give in a vacuum dessicator over phosphorus pentoxide a yellowish crystal powder (1.77 g, 77%), mp 188-190° dec; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 3.70 (s, 3H, N-Me(8)), 3.34 (s, 3H, N-Me(6)).

Anal. Calcd. for $C_8H_7N_5O_4$ x H_2O: C, 37.65; H, 3.55; N, 27.45. Found: C, 37.55; H, 3.63; N, 27.28.

Methyl Fervenulin-3-carboxylate (**56**).

A suspension of **55** (0.1 g, 0.4 mmole) in methanol (40 ml) was treated with hydrogen chloride acid gas until a clear solution was obtained. After boiling for 1 hour it was evaporated, and the residue dissolved in chloroform when washed with sodium bicarbonate solution, the organic phase dried over sodium sulfate, evaporated and the residue recrystallzed from a little methanol to give yellow crystals (34 mg, 34%), mp 164-165°; ^{1}H nmr (deuteriochloroform): δ 4.10 (s, 3H, O-Me), 3.93 (s, 3H, N-Me(8)), 3.54 (s, 3H, N-Me(6)).

Anal. Calcd. for $C_9H_9N_5O_4$: C, 43.03; H, 3.61; N, 27.88. Found: C, 43.18; H, 3.72; N, 27.74.

Ethyl Fervenulin-3-carboxylate (**57**).

To a mixture of **55** (0.41 g, 1.6 mmoles) in dry ethanol (80 ml) was added concentrated sulfuric acid (0.1 ml) and then heated under reflux for 2 hours. The solution was diluted with chloroform (80 ml), treated with a saturated sodium bicarbonate-solution (100 ml), the phases separated and the water layer extracted with chloroform. The united chloroform extracts were dried over sodium sulfate, evaporated and the residue purified by silica gel column chromatography in toluene/ethyl acetate 15:1-10:1 to give a yellow solid (0.38 g, 90%), mp 84-86°; ^{1}H nmr (deuteriochloroform): δ 4.57 (q, 2H, OCH$_2$), 3.92 (s, 3H, N-Me(8)), 3.54 (s, 3H, N-Me(6)), 1.46 (t, 3H, CH$_2$-*Me*).

Anal. Calcd. for $C_{10}H_{11}N_5O_4$: C, 45.29; H, 4.18; N, 26.40. Found: C, 45.36; H, 4.29; N, 26.28.

Fervenulin-3-carboxamide (**59**).

A mixture of **55** (0.204 g, 0.8 mmole) and thionyl chloride (10 ml) was heated under reflux for 1 hour and then evaporated. The residue was dissolved in dioxane (15 ml) and dry ammonia gas bubbled through the solution for 1 hour whereby a precipitate separated. It was again evaporated and the residue recrystallized from ethanol/water 3:1 (130 ml) to give a yellow crystal powder which was dried at 100° (0.15 g, 79%), mp >300°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.55 (bs, 1H, H-N), 8.12 (bs, 1H, H-N), 3.70 (s, 3H, N-Me), 3.34 (s, 3H, N-Me).

Anal. Calcd. for $C_8H_8N_6O_3$: 40.68; H, 3.41; N, 35.58. Found: C, 40.51; H, 3.36; N, 35.40.

2,4a-Dihydro-5,7-dimethylimidazo[4,5-*e*]-1,2,4-triazin-6-one-3,4a-bis-*N*-methylcarboxamide (**60**).

Fervenulin-3-carboxylic acid (**55**) (0.204 g, 0.8 mmole) was refluxed with thionyl chloride (10 ml) for 1 hour to form **58**. It was evaporated and the residue treated in dry methanol (10 ml) with methanolic methylamine (60%, 2 ml) for 1 hour at room temperature. After evaporation the residue was recrystallized from ethanol/water 5:1 (4 ml) to give colorless crystals (0.136 g, 58%), mp 238-240°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 11.37 (s, 1H, H-N), 8.67 (m, 1H, *H*-NMe), 7.93 (m, 1H, *H*-NMe), 2.91 (s, 3H, N-Me(7)), 2.79 (s, 3H, N-Me(5)), 2.76 (d, 3H, CH$_3$-NH), 2.56 (d, 3H, C*H*$_3$-NH).

Anal. Calcd. for $C_{10}H_{15}N_7O_3$ x 0.75 H_2O: C, 40.75; H, 5.64; N, 33.26. Found: C, 40.95; H, 5.19; N, 33.68.

2,4a-Dihydro-5,7-dimethylimidazo[4,5-e]-1,2,4-triazin-6-one-3,4a-bis-*N*-ethylcarboxamide (**61**).

Compound **55** (0.41 g, 1.6 mmoles) was allowed t o react with thionyl chloride forming first **58** and then as described for **60**, the reaction with ethylamine in dioxane. The crude reaction product was purified by silica gel column chromatography in chloroform to give a colorless solid (0.34 g, 69%), mp 217-220°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 11.32 (s, 1H, H-N), 8.73 (t, 1H, *H*-NCH$_2$), 7.97 (t, 1H, *H*-NCH$_2$), 3.36-2.97 (m, 4H, C-CH$_2$), 2.92 (s, 3H, N-Me(7)), 2.83 (s, 3H, N-Me(5)), 1.11 (t, 3H, C*H*$_3$CH$_2$), 0.96 (t, 3H, C*H*$_3$CH$_2$).

Anal. Calcd. for $C_{12}H_{19}N_7O_3$: C, 46.60; H, 6.19; N, 31.70. Found: C, 46.69; H, 6.25; N, 31.86.

2,4a-Dihydro-5,7-dimethylimidazo[4,5-*e*]-1,2,4-triazin-6-one-3,4a-bis-*N*-*n*-propylcarboxamide (**62**).

Comound **55** (0.41 g, 1.6 mmoles) was allowed to react with thionyl chloride to give **58** which when treated with *n*-propylamine (1 ml) in dioxane (20 ml) with stirring at room temperature for 16 hours provided **62**. Chromatographic purification with toluene/acetonitrile 1:1 and recrystallization from ethanol gave colorless crystals (0.39 g, 73%), mp 154-156°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 11.35 (s, 1H, H-N), 8.75 (t, 2H, *H*-NCH$_2$), 7.92 (t, 2H, *H*-NCH$_2$), 3.29-2.96 (m, 4H, C*H*$_2$CH$_2$CH$_3$), 2.92 (s, 3H, N-Me(7)), 2.84 (s, 3H, N-Me(5)), 1.52 (m, 2H, C*H*$_2$CH$_3$), 1.35 (m, 2H, C*H*$_2$CH$_3$), 0.86 (t, 3H, C*H*$_3$CH$_2$), 0.72 (t, 3H, C*H*$_3$CH$_2$).

Anal. Calcd. for $C_{14}H_{23}N_7O_3$: C, 49.84; H, 6.87; N, 29.06. Found: C, 49.75; H, 6.81; N, 29.05.

2,4a-Dihydro-5,7-dimethylimidazo[4,5-*e*]-1,2,4-triazin-6-one-3,4a-bis-*N*-isobutylcarboxamide (**63**).

Compound **55** (0.51 g, 2 mmoles) was allowed to react with thionyl chloride to give **58**. Compound **58** in dioxane (25 ml)

and isobutylamine (2.5 ml) gave the product by heating under reflux for 20 hours. Chromatographic isolation by toluene/acetonitrile 1:1 gave a colorless solid (0.43 (59%), mp 166-168°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 11.38 (s, 1H, H-N), 8.80 (t, 1H, *H*-NCH$_2$), 7.91 (t, 1H, *H*-NCH$_2$), 3.07-3.00 (m, 2H, CH$_2$), 2.92 (s, 3H, N-Me(7)), 2.85 (s, 3H, N-Me(5)), 2.76-2.66 (m, 2H, CH$_2$), 1.82 (m, 1H, H-C), 1.63 (m, 1H, H-C), 0.86 (d, 6H, C-Me), 0.72 (d, 6H, C-Me).

Anal. Calcd. for $C_{16}H_{27}N_7O_3$: C, 52.59; H, 7.45; N, 26.83. Found: C, 52.69; H, 7.44; N, 26.37.

Fervenulin-3-*N*-isobutylcarboxamide (**64**).

Compound **55** (0.1 g, 0.4 mmole) was allowed to react with thionyl chloride to give **58**. Compound **58** upon treatment with isobutylamine (0.3 g) in dry dioxane (5 ml) at room temperature for 3 hours gave the crude product. Chromatographic work-up on a preparative silica gel plate gave a yellow solid (72 mg, 60%), mp 117-122° dec; ^{1}H nmr (deuteriochloroform): δ 7.93 (t, 1H, H-N), 3.92 (s, 3H, N-Me(8)), 3.55 (s, 3H, N-Me(6)), 3.88 (m, 2H, CH$_2$), 1.95 (m, 1H, H-C), 0.98 (d, 6H, HC*Me*$_2$).

Anal. Calcd. for $C_{12}H_{16}N_6O_3$ x 0.5 H_2O: C, 47.84; H, 5.69; N, 27.89. Found: C, 47.84; H, 5.85; N, 27.70.

Fervenulin-3-*N*-(2-diethylaminoethyl)carboxamide (**65**).

Compound **55** (0.1 g, 0.4 mmole) with thionyl chloride as described for **60** provided **58** which in dioxane (5 ml) and 2-diethylaminoethylamine (0.36 g, 2.5 mmoles) at room temperature and stirring for 3 hours provided the crude product. After evaporation and dilution with water (10 ml) and extraction with chloroform, the organic phase was dried over sodium sulfate, filtered, evaporated and the resulting syrup treated with a little ether to form a yellow solid (52 mg, 39%), mp 159-161°; ^{1}H nmr (deuteriochloroform): δ 8.36 (t, 1H, H-N), 3.91 (s, 3H, N-Me(8)), 3.57 (m, 2H, C*H*$_2$-NH), 3.53 (s, 3H, N-Me(6)), 2.68 (t, 2H, C*H*$_2$NEt$_2$), 2.57 (q, 4H, C*H*$_2$CH$_3$), 1.02 (t, 6H, CH$_2$C*H*$_3$).

Anal. Calcd. for $C_{14}H_{21}N_7O_3$: C, 50.14; H, 6.31; N, 29.24. Found: C, 49.98; H, 6.32; N, 28.96.

Fervenulin-3-*N,N*-diethylcarboxamide (**66**).

Compound **55** (0.21 g, 0.8 mmole) treated as described for **64**, then allowed to react in dioxane (10 ml) with diethylamine (0.5 ml) with stirring at room temperature for 2 hours afforded crude **66**. Chromatographic isolation on silica gel with toluene/ethyl acetate 10:1-1:1 gave a yellow solid (0.153 g, 58%), mp 138-140° dec; ^{1}H nmr (deuteriochloroform): δ 3.88 (s, 3H, N-Me(8)), 3.61 (q, 2H, CH$_2$), 3.54 (s, 3H, N-Me(6)), 3.23 (q, 2H, CH$_2$), 1.27 (t, 3H, C-CH$_3$), 1.19 (t, 3H, C-CH$_3$).

Anal. Calcd. for $C_{12}H_{16}N_6O_3$: C, 49.31; H, 5.52; N, 28.75. Found: C, 49.15; H, 5.69; N, 28.77.

Fervenulin-3-carboxmorpholide (**67**).

Compound **55** (0.1 g, 0.4 mmole) treated as described for **64**, then allowed to react in dry dioxane (5 ml) with morpholine (0.25 ml) with stirring at room temperature for 75 minutes provided the solution which upon evaporation and recrystallization of the residue from ethanol/water 5:1 (9 ml) gave yellow crystals (86 mg, 71%), mp 253-254°; ^{1}H nmr (deuteriochloroform): δ 3.87-3.83 (m, 4H, OCH$_2$), 3.86 (s, 3H, N-Me(8)), 3.80-3.67 (m, 2H, NCH$_2$), 3.40 (m, 2H, NCH$_2$).

Anal. Calcd. for $C_{12}H_{14}N_6O_4$: C, 47.06; H, 4.61; N, 27.44. Found: C, 47.14; H, 4.63; N, 27.15.

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