A New Synthesis of Pyrimido[4,5-*e*]-*as*-triazine 4-Oxides by Nitrosative Cyclization of Aldehyde Uracil-6-ylhydrazones in the Presence of Diethyl Azodiformate

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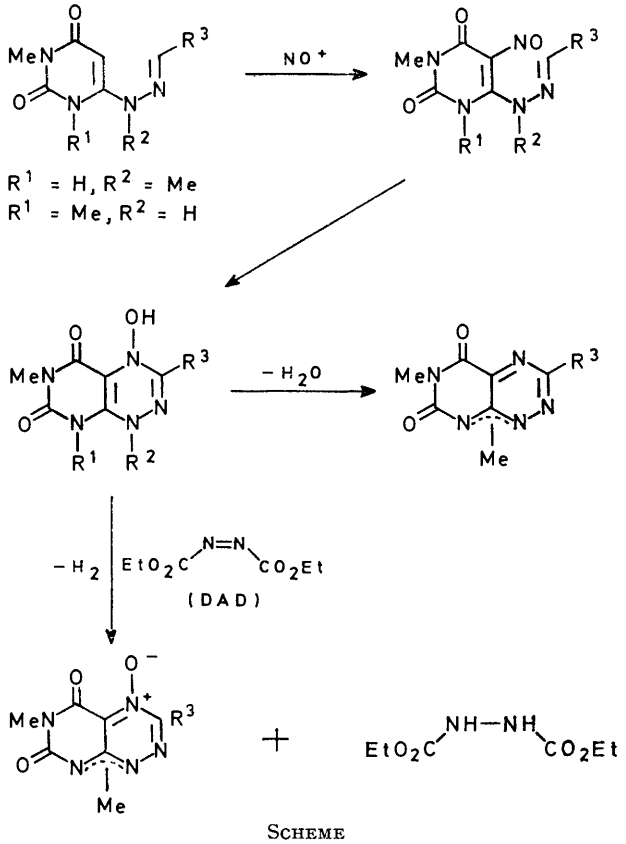
The nitrosative cyclization of the aldehyde uracil-6-ylhydrazones in the presence of diethyl azodiformate gives the corresponding pyrimido[5,4-*e*]-*as*-triazine 4-oxides; several toxoflavin and fervenulin 4-oxides were prepared by this method. The compounds showed characteristic u.v. spectra.

NITROSATION of the aldehyde 3-methyluracil-6-ylhydrazones results in simultaneous cyclization to give pyrimido[5,4-*e*]-*as*-triazine derivatives, *e.g.* toxoflavin [1] and fervenulin.[2] The process may involve intermediate hydroxylamines, which give the pyrimido[5,4-*e*]-*as*-triazines by intramolecular dehydration. We considered that dehydrogenation of the intermediates should lead to pyrimido[5,4-*e*]-*as*-triazine 4-oxides (Scheme), and therefore examined the utility of diethyl azodiformate (DAD),



SCHEME

a strong hydrogen-abstracting agent, as a reagent for the exclusive formation of the 4-oxides.[3]

Treatment of the *N*-methyl-*N*-(3-methyluracil-1-yl)-hydrazones (Ib—k) [4] in acetic acid with saturated aqueous sodium nitrite in the presence of a slight excess of DAD afforded the corresponding toxoflavin 4-oxides (IIb—k) as the exclusive products (see Table 1). Toxoflavin 4-oxide (IIa) itself was synthesized without isolation of the corresponding formaldehyde hydrazone (Ia),

TABLE 1
Toxoflavin 4-oxides

Product	M.p. (°C)	Yield (%)	Product	M.p. (°C)	Yield (%)
(IIa) [4]	189	64	(IIg) [4]	191	73
(IIb) [a]	168	75	(IIh) [b]	>315	80
(IIc) [4]	204	66	(IIi) [4]	233	80
(IId) [4]	221	80	(IIj) [4]	209	75
(IIe) [4]	207	85	(IIk) [4]	210	71
(IIf) [4]	230	85			

[a] Found: C, 43.1; H, 3.85; N, 31.35. $C_8H_9N_5O_3$ requires C, 43.05; H, 4.05; N, 31.4%. [b] Found: C, 54.9; H, 4.85; N, 25.45. $C_{15}H_{16}N_6P_3$ requires C, 54.85; H, 4.9; N, 25.6%.

which was prepared *in situ* from aqueous formaldehyde and 3-methyl-6-(1-methylhydrazino)uracil, because of its instability. Diethyl hydrazodiformate was isolated from the mother liquor. In this connection, the nitrosation of (Ic) in the presence of nitrosobenzene instead of DAD also gave 3-phenyltoxoflavin 4-oxide (IIc), albeit in less satisfactory yield.

The structures of compounds (IIa—k) were demonstrated by elemental analyses, the presence of the strong parent ions and pronounced $M-16$ ions in their mass spectra (see later), and the formation of the corresponding toxoflavins (III) [1] by reduction with sodium dithionite in water.

DAD was also used for the preparation of the fervenulin 4-oxides (Va—g). For example, treatment of acetaldehyde 1,3-dimethyluracil-6-ylhydrazone (IVa) [2] in acetic acid with saturated aqueous sodium nitrite in the presence of a slight excess of DAD caused separation of 3-methylfervenulin 4-oxide (Va). Similarly, other aldehyde hydrazones (IVb—g) [5] gave the corresponding 3-substituted fervenulin 4-oxides (Vb—g) exclusively (see Table 2).

The mass spectra of the products (V) revealed strong parent and $M-16$ ions, and an $M-17$ ion in the case of (Va). Saha and Pfleiderer [6] reported that pronounced $M-17$ as well as $M-16$ ions can be observed in the mass spectra of pteridine *N*-oxides having alkyl and aryl substituents in the position next to the *N*-oxide group. However, $M-17$ ions were not observed in the spectra of fervenulin 4-oxides other than (Va) or of toxoflavin 4-oxides having the same 3-substituents. Treatment of

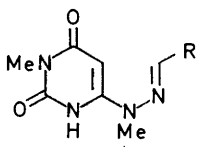
[1] F. Yoneda, K. Shinomura, and S. Nishigaki, *Tetrahedron Letters*, 1971, 851.
[2] G. Blankenhorn and W. Pfleiderer, *Chem. Ber.*, 1972, **105**, 3334.
[3] Preliminary report, F. Yoneda, S. Nishigaki, and K. Shinomura, *Chem. and Pharm. Bull.* (*Japan*), 1971, **19**, 2647.
[4] F. Yoneda and T. Nagamatsu, *Chem. and Pharm. Bull.* (*Japan*), 1975, **23**, 2001.
[5] F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Japan*, 1975, **48**, 1484.
[6] S. K. Saha and W. Pfleiderer, *Tetrahedron Letters*, 1973, 1441.

the 4-oxides (V) with sodium dithionite in water gave the corresponding fervenulins (VI), also obtained by fusion or by refluxing the 4-oxides in dimethylformamide.

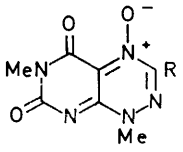
We consider this oxidative cyclization involving hydrogen abstraction as possessing considerable potential for the syntheses of other heterocycle *N*-oxides. Moreover, the foregoing pyrimido[5,4-*e*]-*as*-triazine 4-oxides cannot be obtained by conventional peroxyacid oxidation.

The Figure shows the π-electron distributions of toxoflavin and fervenulin calculated by the Hückel LCAO–MO method. The most reactive site of toxoflavin for peroxyacid oxidation is position 8 and that of fervenulin is position 1 if steric hindrance is neglected. In fact, Blankenhorn and Pfleiderer [2] report that the oxidation of fervenulin derivatives with trifluoroperacetic acid led to 1-oxides.[2] Toxoflavin derivatives are unstable towards acetic acid and other nucleophilic reagents, undergoing 1-demethylation.[7] Compounds (II) are not oxidised by *m*-chloroperbenzoic acid in chloroform. This is ascribed to the lack of π-electron density at position 4 as well as to steric hindrance at position 8.

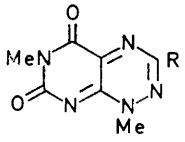
U.v. absorption maxima for the toxoflavin and fervenulin 4-oxides are presented and compared with those of the corresponding toxoflavins and fervenulins in Tables 3 and 4. In the toxoflavin series, the spectra of (II) and (III) were very similar except for a small red shift in going from (II) to (III). In the fervenulin series, the spectral relationship between (V) and (VI) varied according to the nature of the 3-substituent. However the spectrum of fervenulin 4-oxides having a electron-releasing substituent, such as (Vf and g), were similar to those of the fervenulins (VIf and g).



(I)

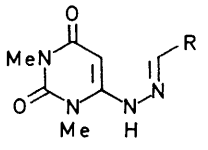


(II)

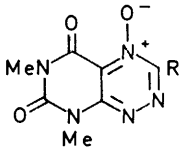


(III)

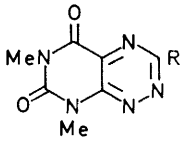
a; R = H
b; R = Me
c; R = Ph
d; R = 4-ClC$_6$H$_4$
e; R = 3,4-Cl$_2$C$_6$H$_3$
f; R = 4-MeO·C$_6$H$_4$
g; R = 3,4-(MeO)$_2$C$_6$H$_3$
h; R = 4-Me$_2$N·C$_6$H$_4$
i; R = 3,4-CH$_2$O$_2$·C$_6$H$_3$
j; R = PhCH:CH
k; R = 3-pyridyl



(IV)



(V)



(VI)

a; R = Me
b; R = Ph
c; R = 4-ClC$_6$H$_4$
d; R = 3,4-Cl$_2$C$_6$H$_3$
e; R = 4-NO$_2$·C$_6$H$_4$
f; R = 4-MeO·C$_6$H$_4$
g; R = 4-Me$_2$N·C$_6$H$_4$

TABLE 2
Fervenulin 4-oxides

Product	M.p. (°C)	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
(Va)	138	40	43.1	3.9	31.15	$C_8H_9N_5O_3$	43.05	4.05	31.4
(Vb)	229 (decomp.)	60	54.7	3.9	24.5	$C_{13}H_{11}N_5O_3$	54.75	3.9	24.55
(Vc)	257	80	48.85	3.05	22.05	$C_{13}H_{10}ClN_5O_3$	48.85	3.15	21.9
(Vd)	222	85	43.85	2.55	19.55	$C_{13}H_9Cl_2N_5O_3$	44.1	2.55	19.8
(Ve)	330	50	47.35	3.2	25.55	$C_{13}H_{10}N_6O_5$	47.25	3.05	25.45
(Vf)	256	45	53.4	4.2	21.9	$C_{14}H_{13}N_5O_4$	53.35	4.15	22.2
(Vg)	305 (decomp.)	42	54.65	4.9	25.75	$C_{15}H_{16}N_6O_3$	54.85	4.9	25.6

EXPERIMENTAL

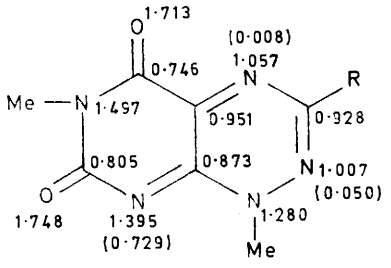
M.p.s (corrected) were determined with a Mettler FP-1 apparatus.

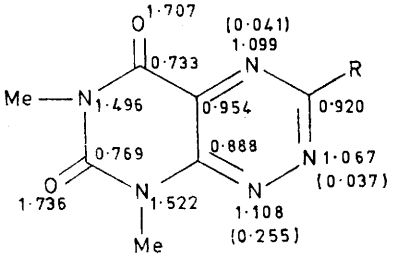
Aldehyde *N*-methyl-*N*-(3-methyluracil-6-yl)hydrazones [4] and 1,3-dimethyluracil-6-ylhydrazones [5] were synthesized by reported procedures.

Toxoflavin 4-Oxide (IIa)—A mixture of 3-methyl-6-(1-methylhydrazino)uracil (2 g, 0.012 mol) and 37%

[7] F. Yoneda and Y. Nagamatsu, *J. Amer. Chem. Soc.*, 1973, **95**, 5735.

formaldehyde (1.4 g, 0.017 mol) in acetic acid (20 ml) was stirred at 5 °C for 10 min. To this solution DAD (3 g, 0.017 mol) was added, followed by saturated aqueous sodium nitrite (1.2 g, 0.017 mol), dropwise with continuous cooling at 5 °C. The solution was then stirred at room temperature for 2 h. The crystals which separated were filtered off and the filtrate was diluted with ethanol (40 ml) and stored in a refrigerator; more crystals of (IIa) separated gradually. The combined crystals were recrystallized from ethanol or dioxan to give yellow *needles* (1.6 g), m.p. 189°.





π-Electron densities and frontier electron densities (in parentheses) of toxoflavin and fervenulin ring systems calculated by Hückel LCAO–MO method. The parameters of the coulomb and resonance integrals for substituent groups are as follows: for =N–, $a_X = 0.6$, $a_r = 0.1$, $l = 1$; for –N<, $a_X = 1$, $a_r = 0.1$, $l = 1$; for =O, $a_X = 2$, $a_r = 0.2$, $l = 1.4$; a_X is the coulomb integral of the substituent X: $\alpha_X = \alpha + a_X\beta$; a_r is the coulomb integral of the carbon atom adjacent to X: $\alpha_{adj} = \alpha + a_r\beta$; l is the resonance integral between that carbon atom and X: $\beta_{C-X} = l\beta$

3-*Substituted Toxoflavin* 4-*Oxides* (IIb—k). *General Procedure.*—To a stirred solution of the hydrazone (Ib—k) (0.008 mol) and DAD (0.01 mol) in acetic acid (40 ml) was added drop by drop saturated aqueous sodium nitrite (0.01 mol) with cooling at 5 °C. The mixture was stirred at room temperature for 2 h and then treated as above to give yellow or orange needles of the respective *toxoflavin* 4-*oxide* (IIb—k), which were recrystallized from ethanol or dioxan.

TABLE 3

U.v. spectra of toxoflavin 4-oxides (II) and toxoflavins (III) in dioxan

	$\lambda_{max.}$/nm (log ε)		$\lambda_{max.}$/nm (log ε)
(IIa)	264 (4.29), 321 (3.65), 412 (3.37)		
(IIb)	264 (4.35), 324 (3.65), 420 (3.41)		
(IIc)	290 (4.48), 431 (3.47)	(IIIc)	295 (4.49), 433 (3.47)
(IId)	298 (4.53), 435 (3.49)	(IIId)	300 (4.54), 436 (3.49)
(IIe)	295 (4.51), 432 (3.47)	(IIIe)	301 (4.48), 434 (3.44)
(IIf)	304 (4.55), 450 (3.44)	(IIIf)	308 (4.54), 456 (3.40)
(IIh)	266 (3.20), 357 (4.53)	(IIIh)	263 (3.85), 359 (4.55)
(IIk)	291 (4.46), 431 (3.48)		

TABLE 4

U.v. spectra of fervenulin 4-oxides (V) and fervenulins (VI) in dioxan

	$\lambda_{max.}$/nm (log ε)		$\lambda_{max.}$/nm (log ε)
(Va) †	240 (4.38), 301 (3.71), 361 (3.56)	(VIa) †	240 (4.32), 350 (3.64)
(Vb)	268 (4.34), 283 (4.36), 380 (3.47)	(VIb)	278 (4.45), 375 (3.55)
(Vc)	265 (4.37), 292 (4.44), 385 (3.47)	(VIc)	288 (4.39), 377 (3.44)
(Vd)	262 (4.39), 300 (4.37), 389 (3.37)	(VId)	288 (4.48), 377 (3.57)
(Ve)	271 (4.24), 308 (4.31), 375sh (3.54)	(VIe)	309 (4.38), 362sh (3.09)
(Vf)	305 (4.49), 401 (3.37)	(VIf)	303 (4.51), 397 (3.54)
(Vg)	358 (4.55), 439 (3.39)	(VIg)	353 (4.61), 437 (3.21)

† In ethanol.

3-*Substituted Fervenulin* 4-*Oxides* (Va—g). *General Procedure.*—To a stirred solution of the hydrazone (IVa—g) (0.008 mol) and DAD (0.01 mol) in acetic acid (40 ml) was added dropwise saturated aqueous sodium nitrite (0.01 mol) with cooling at 5 °C. The mixture was further stirred at 5 °C for 3—20 h until crystals were precipitated. The crystals were filtered off and washed with ether. The filtrate was diluted with ether to precipitate more crystals of (V). The combined crystals were recrystallized from dioxan to give pale yellow *needles*.

3-*Substituted Fervenulins* (VI—g) *by Thermal Deoxygenation.*—A solution of the 4-oxide (Va—g) (0.05 mol) in dimethylformamide (20 ml) was refluxed for 1 h., then evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol to give the fervenulin (VIa—g) in quantitative yield.

[5/1107 *Received, 6th June,* 1975]