ISOLATION OF NEW CHLORINATED REGIOISOMERS OF MONO *N*-SUBSTITUTED URACIL DERIVATIVES AND SYNTHESIS OF 3-SUBSTITUTED 8-PHENYLPYRIMIDO-[5,4-*e*]-1,2,4-TRIAZINE-5,7(6*H*,8*H*)-DIONES¶

Tomohisa Nagamatsu,*[a] Hirofumi Yamasaki,[a] and Fumio Yoneda[b]

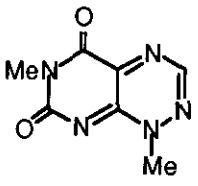
[a]Faculty of Pharmaceutical Sciences, Okayama University, Tsushima, Okayama 700, Japan and [b]Faculty of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606, Japan

Abstract ---- A variety of fervenulin type products, 3-substituted 8-phenylpyrimido[5,4-*e*]-1,2,4-triazine-5,7(6*H*,8*H*)-diones (**18a-i**), were synthesized by nitrosative or nitrative cyclization of the aldehyde hydrazones (**17a-i**) derived from 6-(1-methylhydrazino)-1-phenyluracil (**16**) with aliphatic as well as aromatic aldehydes. The compound (**16**) was prepared by the reaction of 6-chloro-1-phenyluracil (**8**) with methylhydrazine. In addition, not only the precursor of **16**, 6-chloro-1-phenyluracil (**8**), but also other new chlorinated regioisomers of mono *N*-substituted pyrimidine (**9**) and uracil (**14**) were isolated and characterized by the reductive dechlorination of them.

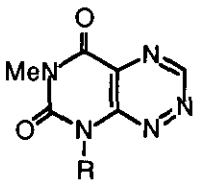
During the last several decades there has been considerable interest in the synthesis[1] and

¶This contribution is dedicated to Prof. Alan R. Katritzky on the occasion of his 65th birthday.

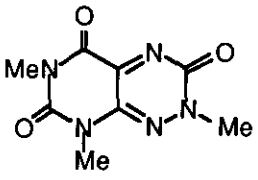
biological evaluation[2] of 7-azapteridines (pyrimido[5,4-*e*]-1,2,4-triazine derivatives), since the *N*-methyl derivatives of pyrimido[5,4-*e*]-1,2,4-triazine-5,7-dione are the natural occurring antibiotics toxoflavin (xanthothricin) (**1**),[3] reumycin (**2a**),[4] and fervenulin (planomycin) (**2b**),[5] and the antibiotic MSD-92 (**3**)[6] is 2,6,8-trimethylpyrimido[5,4-*e*]-1,2,4-triazine-3,5,7(2*H*,6*H*,8*H*)-trione. We have previously reported the convenient syntheses of toxoflavin,[7] reumycin,[7a,8] fervenulin,[7c,d,8a,9] and their analogs.[10] As part of our recent studies on the synthesis and antiviral evaluation of 7-azapteridine analogs,[11] we herein report not only the facile synthesis of 3-substituted 8-phenylpyrimido[5,4-*e*]-1,2,4-triazine-5,7(6*H*,8*H*)-diones (fervenulin type compounds) but also the synthesis of novel chlorinated regioisomers of mono *N*-substituted uracils prepared by the reaction of mono *N*-substituted barbituric acids with phosphoryl chloride.



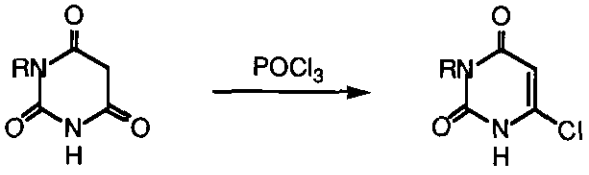
1: toxoflavin



2a: R = H: reumycin
b: R = Me: fervenulin



3: MSD-92



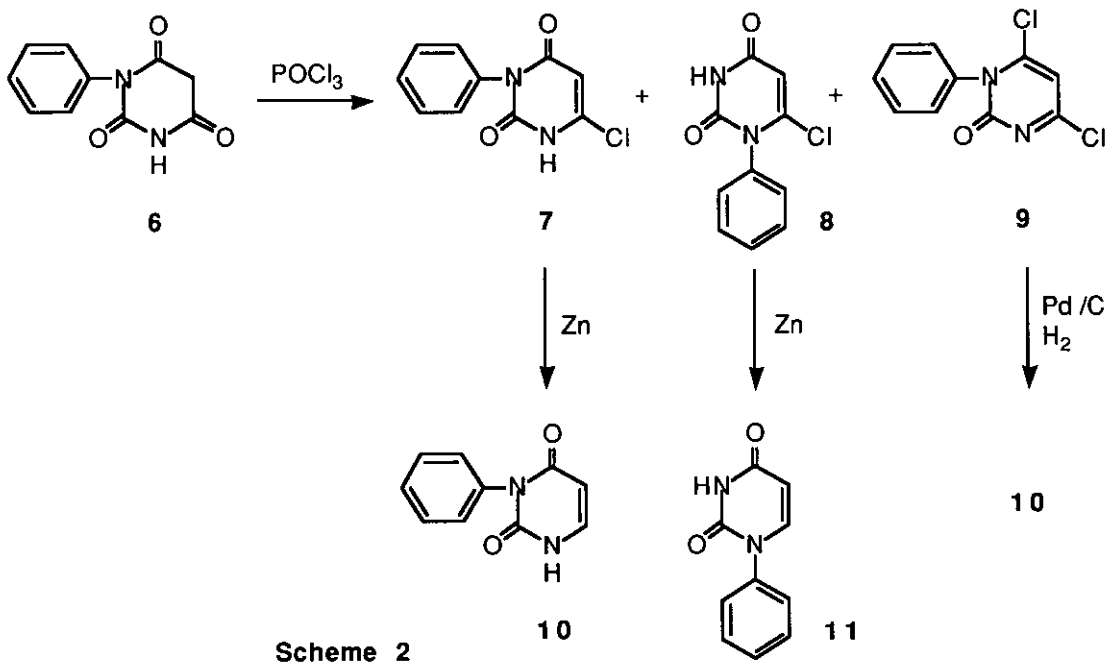
4 R = Me, Et, CH_2Ph, Ph **5**

Scheme 1

The mono *N*-substituted chlorouracils (**5**) are key compounds for the preparation of pyrimido-[5,4-*e*]-1,2,4-triazine-5,7(6*H*,8*H*)-diones as described in the former report.[11] Although the synthesis of the chlorouracils (**5**) has been previously accomplished by chlorination of mono *N*-substituted barbituric acids (**4**) with phosphoryl chloride (**Scheme 1**), only one monochloro-

uracil (3-*N*-substituted 6-chlorouracil) (**5**) was isolated in case of R = Me,[12] CH_2Ph,[13] and Ph.[13] However, the chlorination of 1-ethylbarbituric acid (**4**; R = Et) afforded the two regioisomers of 6-chloro-1- and 6-chloro-3-ethyluracil.[14] Therefore, the first purpose of our study was focused on the isolation of other chlorinated regioisomers of uracils, and we reinvestigated the chlorination of 1-phenyl- and 1-benzylbarbituric acid (**4**; R = Ph and CH_2Ph) with phosphoryl chloride. As a result of the chlorination, two monochlorinated regioisomers and a dichloro compound were isolated newly in this study.

Goldner *et al.* reported[13] that heating 1-phenylbarbituric acid (**6**) with phosphoryl chloride at reflux gave only 6-chloro-3-phenyluracil (**7**). In the same reaction, we now isolated other two products such as 6-chloro-1-phenyluracil (**8**) and 4,6-dichloro-1-phenylpyrimidin-2(1*H*)-one (**9**) in yield of 46% and 7%, respectively, with **7** (38%) as shown in **Scheme 2**. The structures of products were determined on the basis of the following evidences. In the ^{1}H-nmr spectrum of **8**, the meta coupling (J = 1.74 Hz) between the NH proton (δ 11.71, br d, exchangeable with deuterium oxide) at the 3-position and the proton (δ 6.06, d, changed to singlet after addition of deuterium oxide) at the 5-position was observed. In the EI-mass spectrometry, the product (**8**)



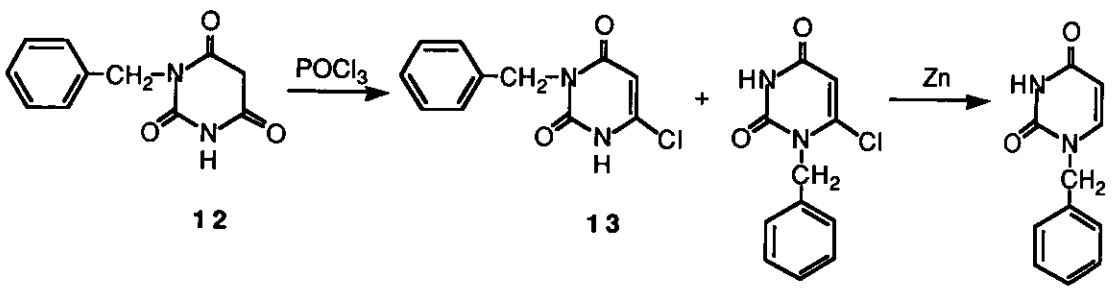
6 **7** **8** **9** **10** **10** **11**

Scheme 2

showed the parent ion (*m/z* 222, 25%) and M+2 ion (8%), which suggested that one chlorine atom may be contained in the molecule, whereas the product (**9**) showed the parent ion (*m/z* 240, 27%) and M+2 ion (18%), which suggested that two chlorine atoms may be contained in the molecule. In the case of the latter, although M+4 was not observed, the presence of two chlorine atoms was supported by the evidence of M+2 of *ca.* 67% intensity against the parent ion peak due to the stable isotope of two ^{37}Cl.

To establish the position of chloro group for the above chlorinated compounds, the reductive dechlorination of them was undertaken. Namely, heating 6-chloro-3-phenyluracil (**7**) with zinc dust in a mixture of 25% aqueous ammonia and ethanol at 90 °C in a sealed glass tube gave 3-phenyluracil (**10**) in 81% yield, while 6-chloro-1-phenyluracil (**8**) gave 1-phenyluracil (**11**) in 75% yield in the same reaction conditions. The structures of **10** and **11** were determined from the spectral data, and the ultimate proof was provided by a comparison of authentic compounds[15,16] prepared by another unambiguous route, respectively. On the other hand, it was difficult to produce 1-phenylpyrimidin-2(1*H*)-one by the reductive dechlorination of 4,6-dichloro-1-phenylpyrimidin-2(1*H*)-one (**9**) with zinc dust. However, **9** was dechlorinated by hydrogenation over 10% palladium charcoal catalyst in a mixture of 10% aqueous sodium hydroxide and ethanol to yield the 3-phenyluracil (**10**), which was identical to that obtained from the reaction of **7** with zinc dust as described above. In the ^{1}H-nmr spectrum of **11**, the meta coupling (J = 2.03 Hz) between the NH proton (δ 11.43, br d, exchangeable with deuterium oxide) at the 3-position and the proton (δ 5.66, dd, $J_{5,6}$ = 7.89 Hz, changed to doublet after addition of deuterium oxide) at the 5-position was also observed similarly to that of **8**, and the proton born on the 6-position of **11** by the dechlorination located at δ 7.70 as a doublet ($J_{5,6}$ = 7.89 Hz).

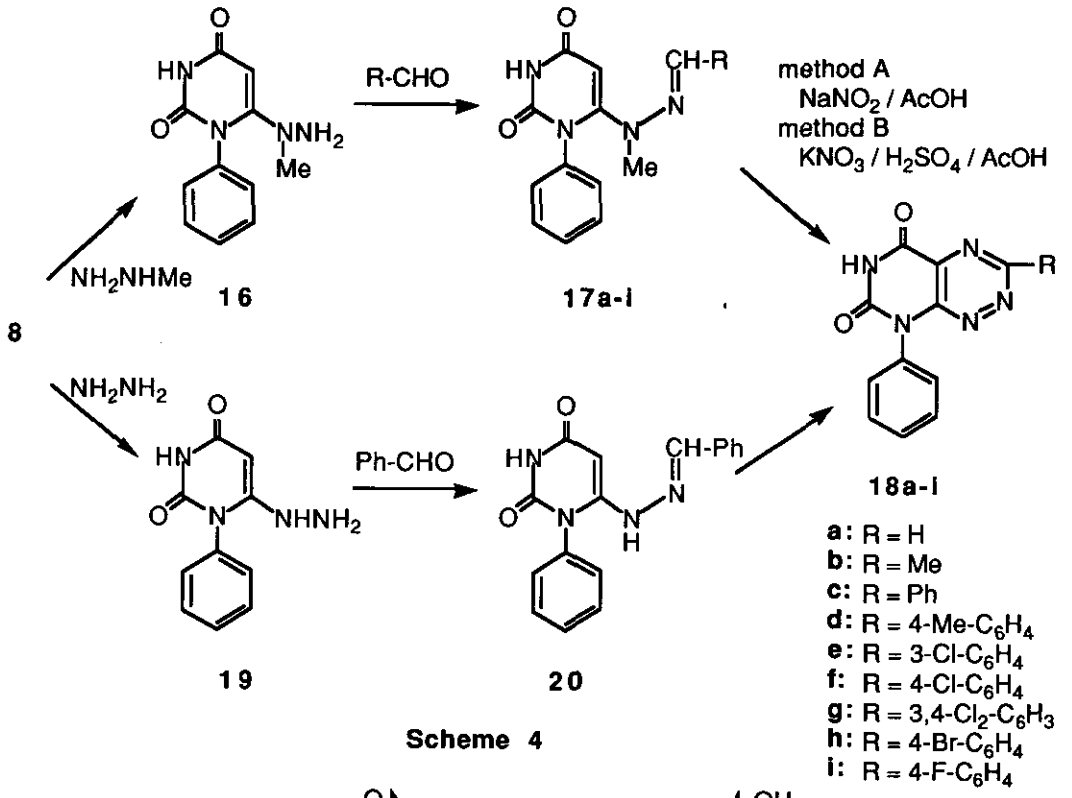
In a similar manner as above, the chlorination was also applied to 1-benzylbarbituric acid (**12**) (**Scheme 3**). Namely, heating **12** with phosphoryl chloride at reflux gave 6-chloro-3-benzyluracil (**13**) and 6-chloro-1-benzyluracil (**14**) in yield of 45% and 32%, respectively. The structure of **13** was determined by a comparison of the melting point of authentic sample[13] reported by Goldner *et al.* They obtained only one chlorinated product (**13**) in the same reaction. On the other hand, the structure of **14** obtained newly was unequivocally established on the basis of following facts. In the ^{1}H-nmr spectrum of **14**, the meta coupling (J = 1.75 Hz) between the



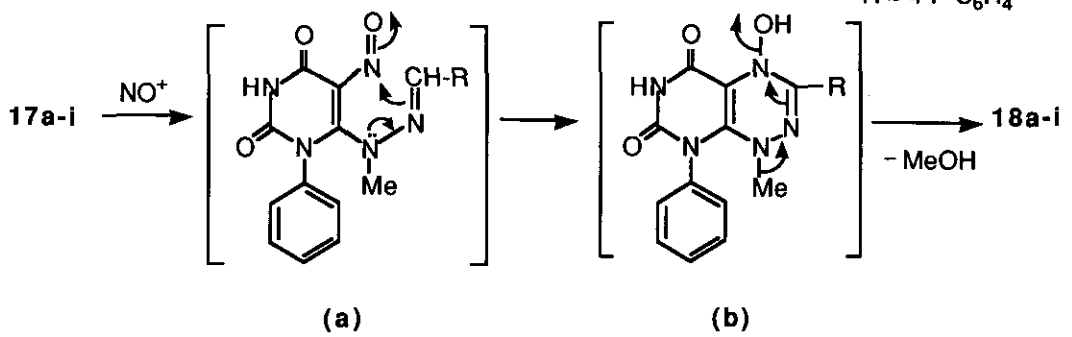
Scheme 3

protons at the 3-position (δ 11.72, br d) and the 5-position (δ 5.99, d) was also observed in a similar manner as **8**. In the FAB-mass spectrometry, the product (**14**) showed molecular ion peaks at 237 (MH^+) and 239 (MH+2), which suggested that one chlorine atom may be contained in the molecule. Moreover, the structure of **14** was confirmed by the derivation to 1-benzyluracil (**15**), which was identical to that prepared by another unambiguous route.[17] Namely, the product (**15**) (71% yield) was prepared by the reaction of **14** with zinc dust in the same reaction conditions as described above, and showed the ortho coupling (J = 7.87 Hz) between the protons at the 5-position (δ 5.59, dd) and the 6-position (δ 7.75, d) and the meta coupling (J = 2.01 Hz) between the protons at the 3-position (δ 11.32, br d) and the 5-position in a similar manner as **11** in the ^{1}H-nmr spectrum.

Now, the 6-chloro-1-phenyluracil (**8**), which served as the starting material for the preparation of 8-phenylpyrimido[5,4-*e*]-1,2,4-triazine-5,7(6*H*,8*H*)-dione ring, was derived to 6-(1-methylhydrazino)-1-phenyluracil (**16**) by heating with methylhydrazine in ethanol (**Scheme 4**). Next the key intermediates, the aldehyde hydrazones (**17a-i**) of **16**, were prepared by treatment of **16** with aliphatic as well as aromatic aldehydes in ethanol at room temperature in good yields as shown in **Table 1**. The hydrazones (**17a-i**) thus obtained were treated with excess sodium nitrite in acetic acid at 5-7 °C to afford the corresponding 3-substituted 8-phenylpyrimido[5,4-*e*]-1,2,4-triazine-5,7(6*H*,8*H*)-diones (**18a-i**) in moderate yields as shown in column A of **Table 2**. The structures of **17a-i** and **18a-i** were assigned on the basis of elemental analyses, satisfactory spectral data (**Table 3**), and the expected mechanism of the reaction. It is noteworthy that the above nitrosative cyclization of **17a-i** was always accompanied by



Scheme 4



Scheme 5

demethylation from the *N*-methylhydrazone moiety. A plausible mechanism for the formation of **18a-i** is outlined in **Scheme 5**. The first step in the proposed mechanism involves the nitrosation on the carbon at the 5-position of **17a-i** to give the nitroso compounds (**a**), followed by intramolecular nucleophilic attack of the electron-rich-α-carbon of the hydrazone moiety to the nitroso group to form the cyclized hydroxylamine intermediates (**b**), which are then

Table 1. Yields and Analytical Data for 6-(2-Alkylidene- and 2-Benzylidene-1-methylhydrazino)-1-phenyluracils (**17a-i**)

Compd No.	R	Yield (%)	Mp (°C)[a]	Ir ν_{max}^{KBr} cm^{-1} C=O	NH	Formula	Analysis (%) Calcd (Found) C	H	N
17a	H	91	205-207	1690	3025	$C_{12}H_{12}N_4O_2$	59.01	4.95	22.94
				1710			(59.18	5.22	23.07)
17b	Me	89	224-226	1670	3050	$C_{13}H_{14}N_4O_2$	60.46	5.46	21.69
				1695			(60.39	5.43	21.78)
17c	Ph	93	213-215	1640	3000	$C_{18}H_{16}N_4O_2$	67.49	5.03	17.49
				1700			(67.26	5.02	17.28)
17d	4-Me-C_6H_4	89	233-235	1660	3020	$C_{19}H_{18}N_4O_2$	68.25	5.43	16.76
				1715			(68.41	5.50	16.48)
17e	3-Cl-C_6H_4	94	204-206	1650	3000	$C_{18}H_{15}N_4O_2Cl$	60.94	4.26	15.79
				1705			(60.98	4.16	15.22)
17f	4-Cl-C_6H_4	90	230-232	1665	3020	$C_{18}H_{15}N_4O_2Cl$	60.94	4.26	15.79
				1715			(61.01	4.22	15.52)
17g	3,4-Cl_2-C_6H_3	91	251-253	1650	3020	$C_{18}H_{14}N_4O_2Cl_2$	55.54	3.63	14.39
				1700			(55.47	3.60	14.29)
17h	4-Br-C_6H_4	87	224-226	1660	3030	$C_{18}H_{15}N_4O_2Br$	54.15	3.79	14.03
				1700			(54.00	3.70	13.94)
17i	4-F-C_6H_4	85	235-237	1645	2980	$C_{18}H_{15}N_4O_2F$	63.90	4.47	16.56
				1700			(64.11	4.41	16.38)

[a]All compounds were recrystallized from ethanol and were obtained as colorless needles.

converted into the corresponding fervenulin type products (**18a-i**) with elimination of the methanol. In addition, the direct cyclizations of **17a-i** were also achieved by nitration. Thus, stirring of **17a-i** with an excess of potassium nitrate in acetic acid containing sulfuric acid at 95 °C for 3-4 h and cooling of the reaction solution yielded the desired products (**18a-i**) in moderate yields as shown in column B of **Table 2**. This reaction may be rationalized in terms of nitration on the carbon at the 5-position of **17a-i** to give the nitro compounds, followed by intramolecular cyclization and elimination of the methanol with loss of oxygen to afford **18a-i** in an analogous manner as noted above.

In order to establish the structures of **18a-i** another unambiguous synthetic route was also attempted as indicated in **Scheme 4**. The synthesis was worked up in a similar manner as

Table 2. Yields and Analytical Data for 8-Phenylpyrimido[5,4-*e*]-1,2,4-triazine-5,7(6*H*,8*H*)-dione (**18a**) and Its 3-Substituted Derivatives (**18b-i**)

Compd No.	R	Yield[a] (%) A	B	Mp (°C)[b]	Ir ν_{max}^{KBr} cm^{-1} C=O	NH	Formula	Analysis (%) Calcd (Found) C	H	N
18a	H	50	48	135-137	1730	3460	$C_{11}H_7N_5O_2$	54.77	2.93	29.03
								(55.03	3.21	29.19)
18b	Me	48	53	145-147	1720	3450	$C_{12}H_9N_5O_2 \cdot 2/3H_2O$	53.93	3.90	26.21
								(53.95	3.86	26.26)
18c	Ph	63	55	317-319	1700	3450	$C_{17}H_{11}N_5O_2$	64.35	3.49	22.07
								(64.15	3.73	22.07)
18d	4-Me-C_6H_4	57	61	301-303	1720	3450	$C_{18}H_{13}N_5O_2$	65.25	3.95	21.14
								(65.01	3.91	21.07)
18e	3-Cl-C_6H_4	65	57	311-313	1720	3460	$C_{17}H_{10}N_5O_2Cl$	58.05	2.87	19.91
								(57.75	2.81	19.65)
18f	4-Cl-C_6H_4	55	51	299-301	1720	3450	$C_{17}H_{10}N_5O_2Cl$	58.05	2.87	19.91
								(67.97	2.93	19.77)
18g	3,4-Cl_2-C_6H_3	53	60	295-297	1720	3420	$C_{17}H_9N_5O_2Cl_2$	52.87	2.35	18.13
								(52.68	2.29	17.85)
18h	4-Br-C_6H_4	61	67	290-292	1720	3450	$C_{17}H_{10}N_5O_2Br$	51.54	2.54	17.68
								(51.25	2.44	17.52)
18i	4-F-C_6H_4	54	57	313-315	1700	3450	$C_{17}H_{10}N_5O_2F$	60.90	3.01	20.89
								(61.06	2.81	21.01)

[a]The yields in column A and B were obtained by the nitrosative cyclization and the nitrative cyclization, respectively, of **17a-i**. [b]All products were recrystallized from 40% aqueous dioxane and were obtained as dark yellow needles or powder.

above except for using anhydrous hydrazine instead of methylhydrazine as follows. Heating 6-chloro-1-phenyluracil (**8**) with anhydrous hydrazine in ethanol to yield 6-hydrazino-1-phenyluracil (**19**) in 83% yield, followed by treatment of benzaldehyde in ethanol at room temperature gave the desired 6-(2-benzylidenehydrazino)-1-phenyluracil (**20**) in 68% yield. Then, the intermediate (**20**) was reacted with sodium nitrite in acetic acid at 5 - 7 °C to obtain the nitrosative intramolecular cyclization compound, 3,8-diphenylpyrimido[5,4-*e*]-1,2,4-triazine-5,7-dione (**18c**) in 44% yield, which was identical with the above product prepared by the cyclization of **17c** in all spectra. In the ^{1}H-nmr spectra of **16**, **17a-i**, and **20**, the meta

Table 3. Nmr Spectral Data for **17a-i** and **18a-i** and Uv Absorption Spectral Data for **18a-i**

Compd No.	Uv: $\lambda_{max}^{dioxane}$ nm (ε)	^{1}H-Nmr (DMSO-d_6 / TMS) at 60 MHz: δ (ppm), J (Hz)
17a		2.71 (3H, s, Me), 5.38 (1H, d, $J_{3,5}$ = 1.74, changed to singlet after addition of deuterium oxide, 5-H), 6.17 and 6.42 (each 1H, each d, J_{gem} = 9.60, N=CH_2), 7.35 (5H, s, Ph-H), 11.24 (1H, d, $J_{3,5}$ = 1.74, exchangeable with deuterium oxide, NH)
17b		1.68 (3H, d, J = 5.28, C-Me), 2.73 (3H, s, N-Me), 5.33 (1H, d, $J_{3,5}$ = 1.80, changed to singlet after addition of deuterium oxide, 5-H), 6.83 (1H, q, J = 5.28, N=CH), 7.34 (5H, br s, Ph-H), 11.14 (1H, d, $J_{3,5}$ = 1.80, exchangeable with deuterium oxide, NH)
17c[a]		3.00 (3H, s, Me), 5.46 (1H, d, $J_{3,5}$ = 2.06, changed to singlet after addition of deuterium oxide, 5-H), 7.21-7.44 (10H, m, 2 x Ph-H), 7.52 (1H, s, N=CH), 11.26 (1H, d, $J_{3,5}$ = 2.06, exchangeable with deuterium oxide, NH)
17d		2.29 (3H, s, C-Me), 2.99 (3H, s, N-Me), 5.47 (1H, d, $J_{3,5}$ = 1.80, changed to singlet after addition of deuterium oxide, 5-H), 7.14-7.26 (9H, m, Ph-H and Ar-H), 7.49 (1H, s, N=CH), 11.18 (1H, d, $J_{3,5}$ = 1.80, exchangeable with deuterium oxide, NH)
17e		3.05 (3H, s, Me), 5.49 (1H, d, $J_{3,5}$ = 1.80, changed to singlet after addition of deuterium oxide, 5-H), 7.35 (9H, m, Ph-H and Ar-H), 7.51 (1H, s, N=CH), 11.28 (1H, d, $J_{3,5}$ = 1.80, exchangeable with deuterium oxide, NH)
17f[a]		3.01 (3H, s, Me), 5.47 (1H, d, $J_{3,5}$ = 1.98, changed to singlet after addition of deuterium oxide, 5-H), 7.33-7.41 (9H, m, Ph-H and Ar-H), 7.50 (1H, s, N=CH), 11.28 (1H, d, $J_{3,5}$ = 1.98, exchangeable with deuterium oxide, NH)
17g		3.06 (3H, s, Me), 5.50 (1H, d, $J_{3,5}$ = 1.80, changed to singlet after addition of deuterium oxide, 5-H), 7.10-7.70 (8H, m, Ph-H and Ar-H), 7.53 (1H, s, N=CH), 11.29 (1H, d, $J_{3,5}$ = 1.80, exchangeable with deuterium oxide, NH)
17h		3.02 (3H, s, Me), 5.48 (1H, d, $J_{3,5}$ = 1.80, changed to singlet after addition of deuterium oxide, 5-H), 7.20-7.60 (9H, m, Ph-H and Ar-H), 7.84 (1H, s, N=CH), 11.23 (1H, d, $J_{3,5}$ = 1.80, exchangeable with deuterium oxide, NH)
17i		3.01 (3H, s, Me), 5.49 (1H, d, $J_{3,5}$ = 1.74, changed to singlet after addition of deuterium oxide, 5-H), 7.22-7.70 (9H, m, Ph-H and Ar-H), 7.53 (1H, s, N=CH), 11.27 (1H, d, $J_{3,5}$ = 1.74, exchangeable with deuterium oxide, NH)
18a	275 (16190) 365 (2470)	6.95-7.74 (6H, m, 3-H and Ph-H), 12.30 (1H, br s, exchangeable with deuterium oxide, NH)
18b	283 (15740) 370 (2170)	2.83 (3H, s, Me), 7.17-7.81 (5H, m, Ph-H), 12.30 (1H, br s, exchangeable with deuterium oxide, NH)

18c	282 (22600) 371 (2870)	7.40-7.78 (8H, m, C-Ph-*m,p*H and N-Ph-*o,m,p*H), 8.27-8.59 (2H, m, C-Ph-*o*H), 12.41 (1H, br, exchangeable with deuterium oxide, NH)
18d	281 (21670) 373 (2680)	2.49 (3H, s, Me), 7.43 (2H, d, J_{AB} = 8.16, Ar-*m*H), 7.54 (5H, s, Ph-H), 8.29 (2H, d, J_{AB} = 8.16, Ar-*o*H), 12.19 (1H, br s, exchangeable with deuterium oxide, NH)
18e	282 (27510) 364 (5120)	7.31-7.82 (7H, m, Ph-*o,m,p*H and Ar-*m,p*H), 8.36 (2H, m,Ar-*o*H), 12.47 (1H, s, exchangeable with deuterium oxide, NH)
18f	282 (25020) 371 (3080)	6.98-7.94 (5H, m, Ph-H), 7.52 (2H, d, J_{AB} = 8.82, Ar-*m*H), 8.40 (2H, d, J_{AB} = 8.82, Ar-*o*H), 12.19 (1H, br s, exchangeable with deuterium oxide, NH)
18g[a]	281 (26120) 372 (3150)	7.40-7.46 (2H, m, Ph-H), 7.52-7.63 (3H, m, Ph-H), 7.88 (1H, d, $J_{5',6'}$ = 8.22, Ar-5'-H), 8.37 (1H, dd, $J_{5',6'}$ = 8.22, $J_{2',6'}$ = 2.09, Ar-6'-H), 8.49 (1H, d, $J_{2',6'}$ = 2.09, Ar-2'-H), 12.46 (1H, br s, exchangeable with deuterium oxide, NH)
18h	284 (27540) 370 (3960)	7.24-7.95 (5H, m, Ph-H), 7.82 (2H, d, J_{AB} = 8.82, Ar-*m*H), 8.34 (2H, d, J_{AB} = 8.82, Ar-*o*H), 12.31 (1H, br s, exchangeable with deuterium oxide, NH)
18i	282 (23460) 364 (4370)	6.90-7.80 (7H, m, Ph-*o,m,p*H and Ar-*m,p*H), 8.45 (2H, m, Ar-*o*H), 12.46 (1H, br s, exchangeable with deuterium oxide, NH)

[a]Run at 200 MHz.

coupling (J = 1.7 - 2.1 Hz) between the protons at 3- and 5-position of the uracil ring was also observed, respectively. The ultraviolet spectra of **18a-i** in ethanol showed two maximum absorption bands at *ca.* 280 nm and 370 nm and were all qualitatively similar.

Thus, the present methodology provided a facile convenient route to the preparation of biologically significant fervenulin analogs, 3-substituted 8-phenylpyrimido[5,4-*e*]-1,2,4-triazine-5,7(6*H*,8*H*)-diones (**18a-i**). In addition, not only the key compound, 6-chloro-1-phenyluracil (**8**), for the preparation of **18a-i**, but also other new chlorinated compounds (**9**) and (**14**) were isolated and characterized by the reductive dechlorination of them in this project.

EXPERIMENTAL

All melting points were taken using a Yanagimoto micro melting points apparatus and are uncorrected. Microanalyses were performed with a Yanagimoto MT-2 CHN elemental analyser. Infrared (ir) spectra were taken on a JASCO IRA-102 spectrophotometer. Nuclear magnetic

resonance (^{1}H-nmr) spectra were recorded on a Hitachi FT-NMR R-1500 (60 MHz), a Varian VXR-200 (200 MHz) or a Varian VXR-500 (500 MHz) instrument. Chemical shifts are given in δ (ppm) relative to tetramethylsilane and coupling constants (J) are given in hertz (Hz). Mass spectra (ms) were obtained using a VG-70SE spectrometer with FAB ionization or a JEOL JMS 01SG-2 instrument by direct insertion at 75 eV. Reactions were monitored by analytical thin-layer chromatography (tlc) performed on tlc plates, Kiesel gel 60 F_{254} precoated, layer thickness 0.25 mm (Merck) and spots were detected under ultraviolet (uv) irradiation at 254 and 360 nm. The solvent systems used were A (benzene / ethanol, 4 : 3 v/v) and B (ethyl acetate). Column chromatography was done on Kiesel gel 60 (70-230 mesh ASTM, Merck) and the developing solvents were as described below.

Chlorination of 1-Phenylbarbituric acid (6). Formation of 6-Chloro-3-phenyluracil (7), 6-Chloro-1-phenyluracil (8), and 4,6-Dichloro-1-phenylpyrimidin-2(1*H*)-one (9).

To a kneading solid of 1-phenylbarbituric acid (**6**)[18] (20.4 g, 0.1 mol) with water (5 ml) was added dropwise phosphoryl chloride (110 ml, 1.2 mol), and the mixture was heated under reflux with stirring for 2 h. After reaction, the resulting solution was concentrated to dryness *in vacuo*, and ice-water was poured into the residue to afford the mixed solid of three components, which was filtered by suction and washed with cold water. The solid was added to the saturated aqueous sodium bicarbonate (*ca.* 900 ml), and then the mixture was stirred at room temperature for 7 h to isolate the first product (**8**) (R_f = 0.72, A), which was filtered by suction, washed with cold water, and recrystallized from ethanol. The solution of other two components dissolved in the saturated aqueous sodium bicarbonate was acidified (pH *ca.* 1) with concentrated hydrochloric acid to crop them as solid. The two products collected as mixture were separated by column chromatography on silica gel with dichloromethane eluent to afford the second product (**9**) (R_f = 0.79, A) and the third product (**7**) (R_f = 0.60, A), individually.

Recrystallization of **7** from ethanol gave colorless needles (8.5 g, 38%), mp 268-270 °C[13]; ir (potassium bromide): 3100 (NH), 1725 and 1630 (C=O) cm^{-1}; EI-ms *m/z* (rel. int.): 224 (M+2, 9%), 222 (M^+, 24%), 179 (M^+ - CONH, 20%), 144 (100%), 116 (14%), 77 (36%); ^{1}H-nmr (200 MHz, DMSO-

d_6): δ 6.00 (1H, s, 5-H), 7.20-7.26 (2H, m, Ph-H), 7.38-7.47 (3H, m, Ph-H), 12.50 (1H, s, exchangeable with deuterium oxide, NH); *Anal.* Calcd for $C_{10}H_7N_2O_2Cl$: C, 53.95; H, 3.17; N, 12.58. Found: C, 54.17; H, 3.15; N, 12.53.

Recrystallization of **8** from ethanol gave colorless powder (10.2 g, 46%), mp 260-262 °C; ir (potassium bromide): 3060 (NH), 1720 and 1705 (C=O) cm^{-1}; EI-ms *m/z* (rel. int.): 224 (M+2, 8%), 222 (M^+, 25%), 119 (M^+ - NHCOCH=CCl, 100%), 91 (24%), 77 (4%); ^{1}H-nmr (60 MHz, DMSO-d_6): δ 6.06 (1H, d, $J_{3,5}$ = 1.74 Hz, changed to singlet after addition of deuterium oxide, 5-H), 7.47 (5H, s, Ph-H), 11.71 (1H, br d, exchangeable with deuterium oxide, NH); *Anal.* Calcd for $C_{10}H_7N_2O_2Cl$: C, 53.95; H, 3.17; N, 12.58. Found: C, 53.88; H, 3.13; N, 12.42.

Recrystallization of **9** from ethanol gave colorless needles (1.69 g, 7%), mp 127-129 °C; ir (potassium bromide): 1690 (C=O) cm^{-1}; EI-ms *m/z* (rel. int.): 242 (M+2, 18%), 240 (M^+, 27%), 205 (M^+ - Cl, 100%), 138 (26%), 119 (18%), 93 (46%), 77 (75%); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 6.81 (1H, s, 5-H), 7.50 (5H, m, Ph-H); *Anal.* Calcd for $C_{10}H_6N_2OCl_2$: C, 49.82; H, 2.51; N, 11.62. Found: C, 49.91; H, 2.48; N, 11.78.

3-Phenyluracil (10).

A suspension of **7** (2 g, 9 mmol) with zinc dust (6 g) in a mixture of 25% aqueous ammonia (40 ml) and ethanol (10 ml) was heated at 90 °C in a sealed glass tube with stirring for 3 h. After cooling, the settled zinc dust was removed by filtration and the filtrate was neutralized with 10% aqueous hydrochloric acid. The deposited crystals (R_f = 0.50, A) were collected by filtration, washed with cold water, and recrystallized from ethanol to afford **10** (1.37 g, 81%) as colorless needles, mp 243-245 °C[15]; ir (potassium bromide): 3230 (NH), 1735 and 1690 (C=O) cm^{-1}; EI-ms *m/z* (rel. int.): 188 (M^+, 57%), 119 (M^+ - NHCH=CHCO, 100%), 91 (M^+ - CONHCH=CHCO, 23%), 77 (5%); ^{1}H-nmr (500 MHz, DMSO-d_6): δ 5.68 (1H, d, $J_{5,6}$ = 7.50 Hz, 5-H), 7.21 (2H, m, Ph-H), 7.36-7.48 (3H, m, Ph-H), 7.53 (1H, dd, $J_{5,6}$ = 7.50 Hz, $J_{1,6}$ = 5.00 Hz, changed to doublet after addition of deuterium oxide, 6-H), 11.23 (1H, d, $J_{1,6}$ = 5.00 Hz, exchangeable with deuterium oxide, NH); *Anal.* Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.28; N, 14.89. Found: C, 63.61; H, 4.20; N, 14.76.

1-Phenyluracil (11).

A suspension of **8** (2 g, 9 mmol) with zinc dust (6 g) in a mixture of 25% aqueous ammonia (10 ml) and ethanol (40 ml) was heated at 90 °C in a sealed tube with stirring for 3 h. After the same work-up as noted above, recrystallization of the crude crystals (R_f = 0.55, A) from ethanol afforded **11** (1.27 g, 75%) as colorless needles, mp 244-246 °C[16]; ir (potassium bromide): 3050 (NH), 1740 and 1695 (C=O) cm^{-1}; ^{1}H-nmr (500 MHz, DMSO-d_6): δ 5.66 (1H, dd, $J_{5,6}$ = 7.89 Hz, $J_{3,5}$ = 2.03 Hz, changed to doublet after addition of deuterium oxide, 5-H), 7.42 (3H, m, Ph-H), 7.48 (2H, m, Ph-H), 7.70 (1H, d, $J_{5,6}$ = 7.89 Hz, 6-H), 11.43 (1H, br d, exchangeable with deuterium oxide, NH); *Anal.* Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.28; N, 14.89. Found: C, 63.54; H, 4.26; N, 14.64.

Dechlorination of 4,6-Dichloro-1-phenylpyrimidin-2(1*H*)-one (9) by Hydrogenation over Palladium Charcoal Catalyst.

To a solution of **9** (300 mg, 1.25 mmol) in a mixture of 10% aqueous sodium hydroxide (5 ml) and ethanol (25 ml) was added a suspension of 10% palladium charcoal (60 mg) in ethanol (5 ml), and then the mixture was hydrogenated at room temperature and atmospheric pressure. The reaction was monitored by analytical tlc until the disappearance of the compound (**9**) (R_f = 0.79, A). After reaction, the palladium charcoal was removed by filtration, and the filtrate was poured into ice-water (100 ml) and neutralized with 10% aqueous hydrochloric acid. After that, the solution was extracted with ethyl acetate (3 x 30 ml), and the combined organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residue was purified by recrystallization from ethanol to afford **10** (134 mg, 57%), which was identical with the above product prepared by the dechlorination of **7** with zinc dust in all spectra.

Chlorination of 1-Benzylbarbituric acid (12). Formation of 6-Chloro-3-benzyluracil (13) and 6-Chloro-1-benzyluracil (14).

To a kneading solid of 1-benzylbarbituric acid (**12**)[18] (10.3 g, 0.05 mol) with water (2.5 ml) was added dropwise phosphoryl chloride (55 ml, 0.6 mol), and the mixture was heated under reflux with stirring for 2 h. After evaporation of excess phosphoryl chloride *in vacuo*, the residue was poured into ice-water (100 ml). The resulting solution was extracted with dichloromethane

(3 x 30 ml), the combined organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The two products included in the residue were separated by column chromatography on silica gel with dichloromethane eluent to afford the first product (**14**) (R_f = 0.70, A) and the second product (**13**) (R_f = 0.65, A), individually.

Recrystallization of **13** from ethanol gave colorless needles (5.3 g, 45%), mp 208-210 °C[13]; ir (potassium bromide): 3100 (NH), 1730 and 1710 (C=O) cm^{-1}; FAB-ms *m/z*: 239 (MH+2), 237 (MH^+); ^{1}H-nmr (60 MHz, DMSO-d_6): δ 4.92 (2H, s, CH_2), 5.95 (1H, s, 5-H), 7.29 (5H, s, Ph-H), 12.50 (1H, s, exchangeable with deuterium oxide, NH); *Anal.* Calcd for $C_{11}H_9N_2O_2Cl$: C, 55.83; H, 3.83; N, 11.84. Found: C, 55.94; H, 4.02; N, 11.71.

Recrystallization of **14** from ethanol gave colorless needles (3.8 g, 32%), mp 159-161 °C; ir (potassium bromide): 3050 (NH), 1730 and 1710 (C=O) cm^{-1}; FAB-ms *m/z*: 239 (MH+2), 237 (MH^+); ^{1}H-nmr (60 MHz, DMSO-d_6): δ 5.17 (2H, s, CH_2), 5.99 (1H, d, $J_{3,5}$ = 1.75 Hz, changed to singlet after addition of deuterium oxide, 5-H), 7.31 (5H, s, Ph-H), 11.72 (1H, br d, exchangeable with deuterium oxide, NH); *Anal.* Calcd for $C_{11}H_9N_2O_2Cl$: C, 55.83; H, 3.83; N, 11.84. Found: C, 55.77; H, 3.91; N, 11.71.

1-Benzyluracil (15).

A suspension of **14** (1.5 g, 6.3 mmol) with zinc dust (6 g) in a mixture of 25% aqueous ammonia (10 ml) and ethanol (40 ml) was heated at 90 °C in a sealed glass tube with stirring for 4 h. After cooling, the settled zinc dust was removed by filtration and the filtrate was neutralized with 10% aqueous hydrochloric acid. The deposited crystals (R_f = 0.63, A) were collected by filtration, washed with cold water, and recrystallized from ethanol to afford **15** (0.86 g, 71%) as colorless needles, mp 177-179 °C[17]; ir (potassium bromide): 3030 (NH), 1705 and 1670 (C=O) cm^{-1}; ^{1}H-nmr (500 MHz, DMSO-d_6): δ 4.86 (2H, s, CH_2), 5.59 (1H, dd, $J_{5,6}$ = 7.87 Hz, $J_{3,5}$ = 2.01 Hz, changed to doublet after addition of deuterium oxide, 5-H), 7.29 (3H, m, Ph-H), 7.35 (2H, m, Ph-H), 7.75 (1H, d, $J_{5,6}$ = 7.87 Hz, 6-H), 11.32 (1H, br d, exchangeable with deuterium oxide, NH); *Anal.* Calcd for $C_{10}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.68; H, 5.00; N, 13.82.

6-(1-Methylhydrazino)-1-phenyluracil (16).

A mixture of **8** (40 g, 0.18 mol) and methylhydrazine (28.5 ml, 0.54 mol) in dry ethanol (250 ml) was heated under reflux for 1 h. After cooling, the precipitated crystals (R_f = 0.46, A) were collected by filtration, washed with dry ethanol, and recrystallized from dry ethanol to afford the pure product (**16**) (32.2 g, 77%) as colorless columns, mp 206-208 °C; ir (potassium bromide): 3170 and 3150 (NH_2), 3070 (NH), 1705 and 1675 (C=O) cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 2.61 (3H, s, Me), 4.13 (2H, s, exchangeable with deuterium oxide, NH_2), 5.24 (1H, d, $J_{3,5}$ = 1.80 Hz, changed to singlet after addition of deuterium oxide, 5-H), 7.33 (5H, br s, Ph-H), 10.88 (1H, $J_{3,5}$ = 1.80 Hz, exchangeable with deuterium oxide, NH); *Anal.* Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 56.70; H, 5.26; N, 24.06.

General Procedure for Preparation of 6-(2-Alkylidene- and 2-Benzylidene-1-methylhydrazino)-1-phenyluracils (17a-i).

A mixture of **16** (4.64 g, 20 mmol) with appropriate aldehydes (40 mmol) in dry ethanol (100 ml) was stirred at room temperature for 1.5-2 h. Then, the resulting crystals were collected by filtration, washed with ethanol, dried, and recrystallized from ethanol to afford the corresponding pure products (**17a**: R_f= 0.57, A; **17b**: R_f= 0.59, A; **17c**: R_f= 0.65, A; **17d**: R_f= 0.66, A; **17e**: R_f= 0.67, A; **17f**: R_f= 0.65, A; **17g**: R_f= 0.65, A; **17h**: R_f= 0.66, A; **17i**: R_f= 0.66, A) (**Tables 1** and **3**).

General Procedure for Preparation of 3-Substituted 8-Phenylpyrimido[5,4-*e*]-1,2,4-triazine-5,7(6*H*,8*H*)-diones (18a-i).

Method A (Nitrosative Cyclization):

Sodium nitrite (3.1 g, 45 mmol) was added in portions to a stirred solution of **17a-i** (15 mmol) in acetic acid (50 ml) under cooling at 5-7 °C. The reaction mixture was then stirred at room temperature for 6 h, whereupon crystals of the products (**18a-i**) deposited gradually. The crystals were collected by filtration, washed with cold water, dried, and recrystallized from 40% dioxane to afford the corresponding pure products (**18a**: R_f= 0.58, B; **18b**: R_f= 0.60, B; **18c**: R_f= 0.62, B; **18d**: R_f= 0.63, B; **18e**: R_f= 0.63, B; **18f**: R_f= 0.62, B; **18g**: R_f= 0.63, B; **18h**: R_f= 0.64, B; **18i**: R_f= 0.63, B) (**Table 2** and **3**).

Method B (Nitrative Cyclization):

A stirred mixture of **17a-i** (10 mmol) and potassium nitrate (1.3 g, 13 mmol) in acetic acid (50 ml) was treated with concentrated sulfuric acid (0.5 g, 5.1 mmol) drop by drop at room temperature, and then the mixture was heated at 95 °C for 3-4 h. After cooling at room temperature, the precipitated crystals were collected by filtration, washed with cold water, dried, and recrystallized from 40% dioxane to afford the corresponding pure products (**18a-i**) (**Table 2** and **3**).

6-Hydrazino-1-phenyluracil (19).

A mixture of **8** (11.1 g, 50 mmol) and anhydrous hydrazine (4.8 ml, 150 mmol) in dry ethanol (100 ml) was heated under reflux for 1 h. After cooling, the precipitated crystals (R_f = 0.42, A) were collected by filtration, washed with dry ethanol, and recrystallized from dry ethanol to afford the pure product **19** (9.1 g, 83%) as colorless prisms, mp 218-220 °C; ir (potassium bromide): 3340 and 3200 (NH_2), 3070 (NH), 1770 and 1660 (C=O) cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 4.10 (2H, br, exchangeable with deuterium oxide, NH_2), 5.07 (1H, s, 5-H), 6.60 (1H, br, exchangeable with deuterium oxide, 6-NH), 7.13-7.71 (5H, m, Ph-H), 10.47 (1H, br, exchangeable with deuterium oxide, 3-NH); *Anal.* Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.67. Found: C,54.78; H, 4.85; N, 25.51.

6-(2-Benzylidenehydrazino)-1-phenyluracil (20).

A mixture of **19** (4.36 g, 20 mmol) with benzaldehyde (4.25 ml, 40 mmol) in dry ethanol (100 ml) was stirred at room temperature for 2 h. Then, the resulting crystals (R_f = 0.72, A) were collected by filtration, washed with ethanol, dried, and recrystallized from ethanol to afford the corresponding pure product (**20**) (4.2 g, 68%), mp 229-231 °C; ir (potassium bromide): 3160 and 3040 (NH), 1705 and 1665 (C=O) cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): δ 5.48 (1H, d, $J_{3,5}$ = 1.80 Hz, changed to singlet after addition of deuterium oxide, 5-H), 7.27-7.96 (10H, m, 2 x Ph-H), 9.19 (1H, s, N=CH), 9.22 (1H, s, exchangeable with deuterium oxide, 6-NH), 10.76 (1H, d, $J_{3,5}$ = 1.80 Hz, exchangeable with deuterium oxide, 3-NH); *Anal.* Calcd for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.48; H, 4.72; N, 18.20.

3,8-Diphenylpyrimido[5,4-*e*]-1,2,4-triazine-5,7(6*H*,8*H*)-dione (18c) Prepared by Nitrosative Cyclization of 20.

Sodium nitrite (3.1 g, 45 mmol) was added in portions to a stirred solution of **20** (4.6 g, 15 mmol) in acetic acid (50 ml) under cooling at 5-7 °C. The reaction mixture was then stirred at room temperature for 6 h, whereupon crystals of the product (**18c**) deposited gradually. The crystals were collected by filtration, washed with cold water, dried, and recrystallized from 40% dioxane to afford the corresponding pure product (**18c**) (2.0 g, 44%), which was identical with the above product prepared by the cyclization of **17c** in all spectra.

ACKNOWLEDGMENTS

We thank Mr. A. Iwadoh for mass spectral measurements (FAB-ms) and the staff of the SC-nmr Laboratory of Okayama University for 200 and 500 MHz proton nmr experiments. We are also grateful to Dr. N. Akimoto of the Mass Spectral Analyses Room of the Faculty of Pharmaceutical Sciences, Kyoto University, for mass spectral measurements (EI-ms).

REFERENCES

1. (a) W. Pfleiderer and K. H. Schündehütte, *Liebigs Ann. Chem.*, 1958, **615**, 42; (b) G. D. Daves, Jr., R. K. Robins, and C. C. Cheng, *J. Am. Chem. Soc.*, 1961, **83**, 3904; (c) G. D. Daves, Jr., R. K. Robins, and C. C. Cheng, *J. Am. Chem. Soc.*, 1962, **84**, 1724; (d) T. K. Liao, F. Baiocchi, and C. C. Cheng, *J. Org. Chem.*, 1966, **31**, 900; (e) F. Yoneda, K. Shinomura, and S. Nishigaki, *Tetrahydron Lett.*, 1971, 851; (f) E. C. Taylor and F. Sowinsky, *J. Org. Chem.*, 1975, **40**, 2321.
2. (a) S. M. Navashin, I. N. Fomina, T. G. Terent'eva, and L. A. Shtegel'man, *Aktual. Vop. Sovrem. Onkol. (Moscow)*, 1973, 273; (b) V. K. Akimenko, N. P. Golovchenko, and T. G. Terent'eva, *Antibiotiki (Moscow)*, 1974, **19**, 1101; (c) V. K. Akimenko, N. P. Golovchenko, and A. G. Medentsev, *Mikrobiologiya (Moscow)*, 1974, **43**, 839; (d) G. G. Egorenko, L. A. Shtegel'man, V. N. Solov'ev, E. K. Berezina, V. V. Berezhinskaya, M. A. Bykova, G. V. Dolgova, and A. A. Firsov, *Antibiotiki (Moscow)*, 1976, **21**, 178; (e) S. M. Navashin, L. P. Ivanitskaya, T. G. Terent'eva, and L. V. Egorov, *Farmatsiya (Moscow)*, 1981, **30**, 55; (f) A. A. Firsov, S. V. Geodakyan, M. R. Lichinitser, and V. Ya. Shutka, *Antibiot. Med. Biotekhnol (Moscow)*, 1985, **30**, 604.

3. R. A. Machlowitz, W. P. Fisher, B. S. McKay, A. A. Tytell, and J. Charney, *Antibiot. Chemother.*, 1954, **4**, 259.

4. S. E. Esipov, M. N. Kolosov, and L. A. Saburova, *J. Antibiot.*, 1973, **26**, 537.

5. K. Tanabe, Y. Asahi, M. Nishikawa, T. Shima, Y. Kuwada, T. Kanzawa, and K. Ogata, *Takeda Kenkyusho Nempo.*, 1963, **22**, 133 (*Chem. Abstr.*, 1964, **60**, 13242).

6. E. C. Taylor and F. Sowinsky, *J. Am. Chem. Soc.*, 1969, **91**, 2143.

7. (a) F. Yoneda and T. Nagamatsu, *Chem. Pharm. Bull.*, 1975, **23**, 2001; (b) F. Yoneda and T. Nagamatsu, *Synthesis*, 1975, 177; (c) F. Yoneda, T. Nagamatsu, and k. Shinomura, *J. Chem. Soc., Perkin Trans. 1*, 1976, 713; (d) F. Yoneda, Y. Sakuma, T. Nagamatsu, and S. Mizumoto, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2398.

8. (a) F. Yoneda and T. Nagamatsu, *Tetrahedron Lett.*, 1973, 1577; (b) F. Yoneda and T. Nagamatsu, *J. Am. Chem. Soc.*, 1973, **95**, 5735; (c) F. Yoneda, M. Kawamura, T. Nagamatsu, K. Kuretani, A. Hoshi, and M. Iigo, *Heterocycles*, 1976, **4**, 1503.

9. (a) F. Yoneda and T. Nagamatsu, *J. Heterocycl. Chem.*, 1974, **11**, 271; (b) F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 2884; (c) Y. Sakuma, S. Matsumoto, T. Nagamatsu, and F. Yoneda, *Chem. Pharm. Bull.*, 1976, **24**, 338.

10. (a) F. Yoneda, T. Nagamatsu, and M. Ichiba, *J. Heterocycl. Chem.*, 1974, **11**, 83; (b) F. Yoneda, T. Nagamatsu, K. Ogiwara, M. Kanahori, S. Nishigaki, and E. C. Taylor, *Chem. Pharm. Bull.*, 1978, **26**, 367.

11. T. Nagamatsu, H. Yamasaki, T. Hirota, M. Yamato, Y. Kido, M. Shibata, and F. Yoneda, *Chem. Pharm. Bull.*, 1993, **41**, 362.

12. G. Nübel and W. Pfleiderer, *Chem. Ber.*, 1962, **95**, 1605.

13. H. Goldner, G. Dietz, and E. Carstens, *Liebigs Ann. Chem.*, 1966, **691**, 142.

14. K. K. Gauri, *Arch. Pharm.*, 1973, **306**, 622.

15. C. W. Whitehead, *J. Am. Chem. Soc.*, 1952, **74**, 4267.

16. G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 1958, 157.

17. T. B. Johnson and A. W. Joyce, *J. Am. Chem. Soc.*, 1916, **38**, 1385.

18. G. Brückman and S. D. Isaacs, *J. Am. Chem. Soc.*, 1949, **71**, 390.

Received, 7th October, 1993