A New Synthesis of Pyrimido[5,4-*e*]-*as*-triazine 4-Oxides and Their Ring Transformation to Pyrrolo[3,2-*d*]pyrimidines

Sadao Nishigaki, Hashime Kanazawa, Yukako Kanamori, Misuzu Ichiba and Keitaro Senga*

Pharmaceutical Institute, School of Medicine, Keio University, 35, Shinanomachi, Shinjuku-ku, Tokyo 160, Japan

Received April 19, 1982

A new synthesis of certain pyrimido[5,4-*e*]-*as*-triazine 4-oxides and their ring transformation to pyrrolo-[3,2-*d*]pyrimidines by the 1,3-dipolar cycloaddition reaction is described. Thus, reaction of 6-hydrazino-1,3-dimethyluracil (**1**) with triethyl orthoformate gave 6-ethoxymethylenehydrazino-1,3-dimethyluracil (**2**). Treatment of **2** with arylamines gave 6-arylaminomethylenehydrazino-1,3-dimethyluracils (**3a-e**). Nitrosative cyclization of **3a-e** with sodium nitrite afforded 3-arylaminofervenulin 4-oxides (**6a-e**). Reaction of **6a-e** with acetylenic esters yielded 7-alkoxycarbonyl-6-arylamino-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**15a-e** and **16**).

J. Heterocyclic Chem., **19**, 1309 (1982).

Pyrimido[5,4-*e*]-*as*-triazines (1) and pyrrolo[3,2-*d*]pyrimidines (2) have aroused recent attention from chemical and biological view points since they can be regarded as 7-azapteridines and 9-deazapurines, respectively. We have recently described that the reaction of 6-hydrazino-1,3-dimethyl-5-nitrosouracil with various one-carbon reagents affords normally inaccessible pyrimido[5,4-*e*]-*as*-triazine 4-oxides (3) and whose 1,3-dipolar cycloaddition reaction with acetylenic esters results in the ring transformation of the *as*-triazine nucleus to give pyrrolo[3,2-*d*]pyrimidines (4). In connection with these findings and our program directed toward the development of potential pteridine and purine antagonists, we now wish to report a new, alternate synthesis of certain pyrimido[5,4-*e*]-*as*-triazine 4-oxides as well as their conversion into pyrrolo[3,2-*d*]-pyrimidines.

Refluxing of 6-hydrazino-1,3-dimethyluracil (**1**) (5) with triethyl orthoformate for 1 hour gave 6-ethoxymethylene-hydrazino-1,3-dimethyluracil (**2**) in 60% yield. Fusion of **2** with the appropriate excess arylamines at 185° for 15 minutes afforded the corresponding 6-arylaminomethyl-enehydrazino-1,3-dimethyluracils (**3a-e**) in 38-62% yields (Table I).

Treatment of the appropriate **3a-e** with excess sodium nitrite in the presence of acetic acid at 5° for 1 hour yielded the corresponding 3-arylaminofervenulin 4-oxides (**6a-e**) in 50-68% yields (Table II). The structures of **6a-e** were supported by the satisfactory analytical and spectral data, particularly the presence of their strong parent ions and remarkable M-16 ions in their mass spectra, and confirmed by the fact that the reduction of **6a** with sodium dithionite in water gives 3-anilinofervenulin (**7**), which is

Table I

6-Arylaminomethylenehydrazino-1,3-dimethyluracils (**3a-e**)

Compound Number	Substituent R	Mp (°C)	Recrystallization Solvent	Yield (%)	Calcd. (%) C	H	N	Formula	Found (%) C	H	N
3a	H	186-187	ethanol	47	57.13	5.53	25.63	$C_{13}H_{15}N_5O_2$	57.18	5.40	25.68
3b	Br	213-214	ethanol-DMF	38	44.31	4.01	19.89	$C_{13}H_{14}BrN_5O_2$	44.36	3.95	19.88
3c	Cl	204-206	ethanol-DMF	62	50.71	4.59	22.77	$C_{13}H_{14}ClN_5O_2$	50.53	4.47	22.79
3d	Me	160-162	ethanol	61	58.52	5.96	24.38	$C_{14}H_{17}N_5O_2$	58.66	5.96	24.64
3e	OMe	175-177	ethanol	53	55.43	5.65	23.09	$C_{14}H_{17}N_5O_3$	55.19	5.56	22.91

Table II

3-Arylaminofervenulin 4-Oxides (**6a-e**)

Compound Number	Substituent R	Mp (°C)	Recrystallization Solvent	Yield (%)	Calcd. (%) C	H	N	Formula	Found (%) C	H	N
6a	H	272-273	DMF	62	52.00	4.03	27.99	$C_{13}H_{12}N_6O_3$	51.84	4.08	27.90
6b	Br	282-283	DMF	50	41.16	2.93	22.17	$C_{13}H_{11}BrN_6O_3$	41.35	2.93	22.45
6c	Cl	287-289	DMF	64	46.62	3.31	25.21	$C_{13}H_{11}ClN_6O_3$	46.54	3.21	25.03
6d	Me	272-274	DMF	68	53.50	4.49	26.74	$C_{14}H_{14}N_6O_3$	53.66	4.56	27.04
6e	OMe	265-266	DMF	57	50.91	4.27	25.45	$C_{14}H_{14}N_6O_4$	50.89	4.17	25.27

identical with the product obtained by the reaction of 3-chlorofervenulin (**8**) (3) with aniline.

The ring annelation of **3a-e** to **6a-e** presumably involves the initial formation of the 5-nitrosouracil (**4**), followed by cyclization to the cyclic hydroxylamine (**5**), and subsequent dehydrogenation with excess nitrous acid. The formation of *N*-oxides was rather unexpected since the nitrosative cyclization of hydrazones of **1** has been reported to give 3-substituted fervenulins by the dehydrative process (6). The preferential formation of the *N*-oxides could be explained by participation of the intramolecular hydrogen bonding of **5**, where the cyclic hydroxylamine is more susceptible toward dehydrogenation than dehydration (Scheme I).

Generally, pyrimido[5,4-*e*]-*as*-triazine 4-oxides could not be obtained by the conventional peroxy acid oxidation. In fact, attempted oxidation of **7a** with trifluoroperacetic acid did not give the 4-oxides **6a** but the 2-oxide (**9**) in 95% yield. Although the structure of **9** is isomeric with that of the 1-oxide, the possibility of the latter was eliminated by taking into account the steric hindrance of the peri methyl group at the position 8. The *N*-oxidation of 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione has also been found to give the corresponding 2-oxide exclusively (7).

Refluxing of the *N*-oxides **6a-e** with 1.5 equivalents of dimethyl acetylenedicarboxylate (DMAD) in dimethylformamide for 1 hour gave the 6-arylamino-7-methoxy-

Scheme I

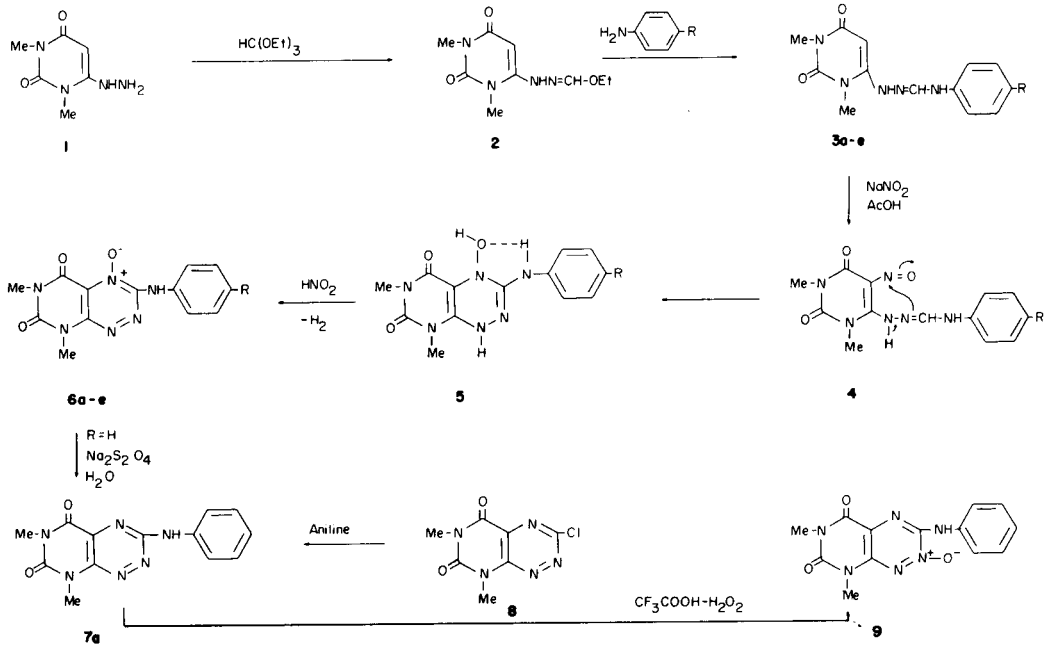


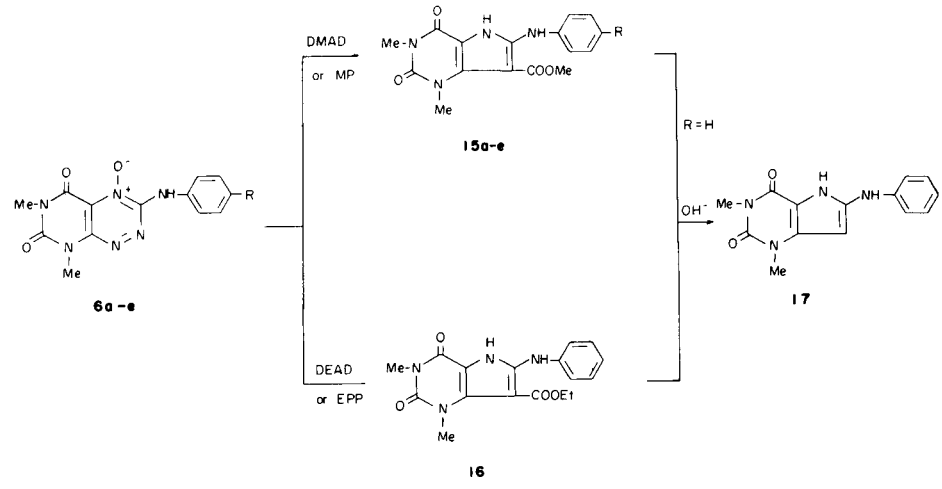
Table III

7-Alkoxycarbonyl-6-arylamino-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**15a-e** and **16**)

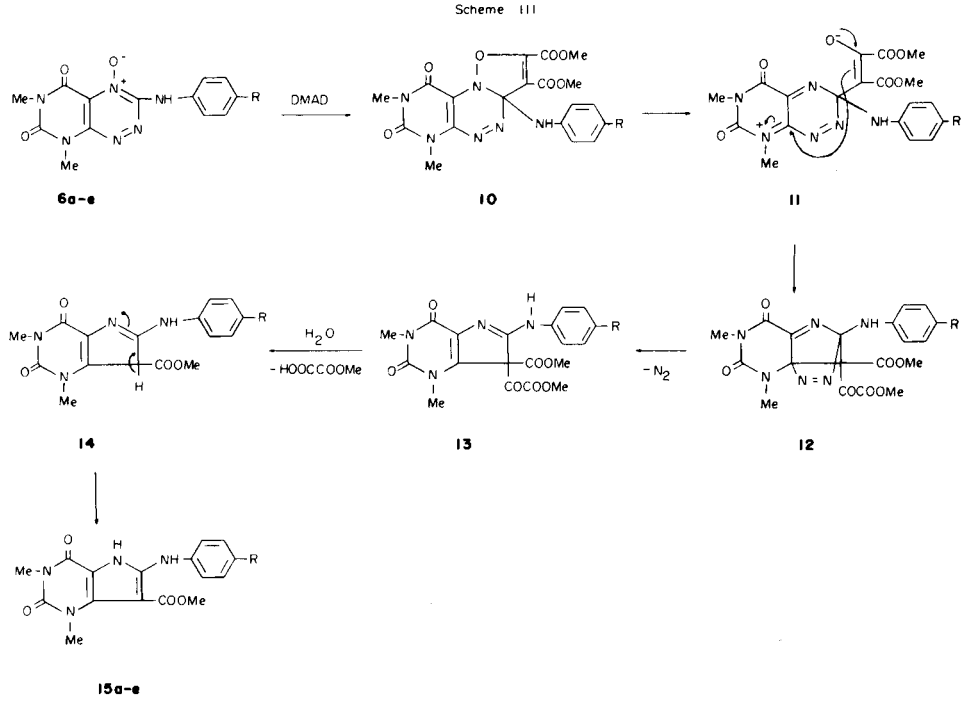
Compound Number	Substituent R	Mp (°C)	Recrystallization Solvent	Yield (%)	Calcd. (%) C	H	N	Formula	Found (%) C	H	N
15a	H	278-280	ethanol-DMF	62 (a), 12 (b)	58.53	4.91	17.07	$C_{16}H_{16}N_4O_4$	58.48	4.82	16.94
15b	Br	259-261	ethanol-DMF	61 (a)	47.17	3.71	13.77	$C_{16}H_{15}BrN_4O_4$	46.80	3.58	13.70
15c	Cl	252-253	ethanol	63 (a)	52.95	4.17	15.45	$C_{16}H_{15}ClN_4O_4$	52.65	4.26	15.27
15d	Me	237-239	ethanol	61 (a)	59.64	5.30	16.37	$C_{17}H_{18}N_4O_4$	59.39	5.13	16.48
15e	OMe	259-261	ethanol	25 (a)	56.98	5.06	15.64	$C_{17}H_{18}N_4O_5$	56.76	4.78	15.29
16		218-220	ethanol-DMF	37 (c), 3 (d)	59.64	5.30	16.37	$C_{17}H_{18}N_4O_4$	59.53	5.27	16.63

(a) Yield by DMAD. (b) Yield by MP. (c) Yield by DEAD. (d) Yield by EPP.

Scheme II



Scheme III



carbonylpyrrolo[3,2-*d*]pyrimidine (**15a-e**) in 25-63% yields. The compound **15a** was alternately prepared by treatment of **7a** with methyl propiolate (MP) albeit in low yield (12%). Moreover, the reaction of **7a** with diethyl acetylenedicarboxylate (DEAD) or ethyl phenylpropiolate (EPP) gave the 7-ethoxycarbonyl derivative (**16**) in 37 and 3% yields, respectively. Heating of **15a** and **16** with 5% sodium hydroxide resulted in the hydrolytic decarboxylation of the alkoxycarbonyl group to yield the 6-anilinopyrrolo[3,2-*d*]pyrimidine (**17**) in 86 and 83% yields, respectively (Table III) (Scheme II).

The ring transformation of pyrimido[5,4-*e*]-*as*-triazine to pyrrolo[3,2-*d*]pyrimidine, *e.g.*, in the case of DMAD (8), can be best explained by assuming the initial formation of the adduct (**10**) by the 1,3-dipolar cycloaddition reaction. The cleavage of the isoxazoline ring to (**11**), followed by the intramolecular cyclization to (**12**), and subsequent extrusion of nitrogen would yield the intermediate (**13**). The conversion of **13** into the final product **15a-e** probably occurs by liberation of the methoxalyl group *via* (**14**) as monomethyl oxalate owing to the moisture (Scheme III).

EXPERIMENTAL

Melting points were taken on a Yanaco micro-hot-stage melting point apparatus and are uncorrected. The nmr spectra were determined with a Varian T-60 spectrometer at 60 MHz using tetramethylsilane as internal standard.

6-Ethoxymethylenehydrazino-1,3-dimethyluracil (**2**).

A mixture of 6-hydrazino-1,3-dimethyluracil (**1**) (5) (6.8 g, 0.04 mole) and triethyl orthoformate (60 ml) was refluxed for 2 hours. The reaction mixture was evaporated *in vacuo* and the residue was triturated with ethanol to give **2** (5.4 g, 60%), mp 172-173°.

Anal. Calcd. for $C_9H_{14}N_4O_3$: C, 47.78; H, 6.24; N, 24.77. Found: C, 47.73; H, 6.22; N, 25.08.

6-Arylaminomethylenehydrazino-1,3-dimethyluracils (**3a-e**) (Table I).

A mixture of **2** (2.26 g, 0.01 mole) and the appropriate arylamine (0.02 mole) was fused at 185° for 15 minutes. After cooling, the reaction mixture was triturated with ethanol and the insoluble material was filtered. Recrystallization from the appropriate solvent afforded the corresponding **3a-e**.

3-Arylaminofervenulin 4-Oxides (3-Arylamino-6,8-dimethylpyrimido-[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione 4-Oxides (**6a-e**)) (Table II).

To a mixture of the appropriate **3** (0.002 mole) and sodium nitrite (0.41 g, 0.006 mole), acetic acid (5 ml) was added dropwise at 0-5° with stirring. After stirring for 1 hour at the same temperature, the precipitates were filtered, washed with chilled ethanol, and recrystallized from dimethylformamide to give the corresponding **6a-e**.

Compound **6a**.

This compound had nmr (deuteriotrifluoroacetic acid): δ 3.83 (s, 3H, N-Me), 4.00 (s, 3H,N-Me), 7.53-8.67 (m, 5H, Ph).

3-Anilinofervenulin (3-Anilino-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (**7**)).

Method A.

A suspension of **6a** (0.046 g, 0.00015 mole) in water (10 ml) containing sodium dithionite (0.13 g, 0.00075 mole) was heated at 95° for 5 hours. The precipitates were filtered, washed well with hot water and recrystallized from ethanol to give **7** (0.04 g, 92%), mp 245-248°.

Anal. Calcd. for $C_{13}H_{12}N_6O_2$: C, 54.92; H, 4.26; N, 29.57. Found: C, 54.69; H, 4.29; N, 29.44.

Method B.

A suspension of 3-chlorofervenulin (**8**) (3) (0.23 g, 0.001 mole) in ethanol (10 ml) containing aniline (0.09 g, 0.001 mole) was refluxed for 1 hour. After cooling, the precipitates were filtered, and recrystallized from ethanol to give **7** (0.22 g, 77%), which is identical with the compound obtained by the Method A.

Acknowledgement.

The authors are grateful to Mr. Katsuhiko Nagahara of Kitasato University for nmr spectra and microanalyses. The authors also thank Dr. Kenji Ishii, Dr. Kazuki Saito, and Mr. Kazuyoshi Chiba of this school for mass spectra.

REFERENCES AND NOTES

(1) For a survey of methods for the synthesis of pyrimido[5,4-*e*]-*as*-triazines, see D. J. Brown and R. K. Lynn, "Chemistry and Biology of Pteridines", W. Pfleiderer, ed, Walter de Gruyter, New York, NY, 1975, pp 575-601.

(2) For a survey of methods for the synthesis of pyrrolo[3,2-*d*]pyrimidines, see V. Amarnath and R. Madhav, *Synthesis*, 837 (1974).

(3) M. Ichiba, S. Nishigaki, and K. Senga, *J. Org. Chem.*, **43**, 469 (1978).

(4) K. Senga, M. Ichiba, and S. Nishigaki, *ibid.*, **44**, 3830 (1979).

(5) W. Pfleiderer and K.-H. Schündehütte, *Ann. Chem.*, **612**, 158 (1958).

(6) G. Blankenhorn and W. Pfleiderer, *Chem. Ber.*, **105**, 3334 (1972).

(7) M. Ichiba, S. Nishigaki, and K. Senga, *J. Org. Chem.*, "submitted". A. D. Broom and D. G. Bartholomew also reported that the reaction of 1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione with trifluoroperacetic acid did not give the desired *N*-oxide; *J. Org. Chem.*, **41**, 3027 (1976).

(8) The reaction of **15a** with other acetylenic esters would proceed *via* the similar mechanism shown in the Scheme III.

3-Anilinofervenulin 2-Oxide (3-Anilino-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione 2-Oxide (**9**)).

To a solution of **7** (0.43 g, 0.0015 mole) in trifluoroacetic acid (5 ml), 30% hydrogen peroxide (3 ml) was added dropwise with stirring at room temperature. After stirring for 24 hours at the same temperature, the reaction mixture was diluted with water (100 ml). The precipitates were filtered, washed with water, and recrystallized from dimethylformamide to give **9** (0.43 g, 95%), mp >300°.

Anal. Calcd. for $C_{13}H_{12}N_6O_3$: C, 52.00; H, 4.03; N, 27.99. Found: C, 52.36; H, 4.07; N, 28.11.

7-Alkoxycarbonyl-6-arylamino-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**15a-e** and **16**).

A mixture of the appropriate **6a-e** (0.001 mole) and acetylenic esters (0.0015 mole) in dimethylformamide (7 ml) was refluxed for 1 hour. The reaction mixture was evaporated *in vacuo* and the residue was extracted with boiling ethanol. The ethanol extracts were evaporated *in vacuo* and the residue was recrystallized to give the corresponding **15a-e** and **16**.

Compound **15a**.

This compound had nmr (deuteriotrifluoroacetic acid): δ 3.57 (s, 3H, Me), 3.90 (s, 3H, Me), 4.07 (s, 3H,Me), 7.40 (broad s, 5H, Ph).

6-Anilino-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**17**).

A suspension of **15a** or **16** (0.0003 mole) in 5% sodium hydroxide (10 ml) was heated at 95° for 1 hour. After cooling, the precipitates were filtered and recrystallized from a mixture of dimethylformamide and ethanol gave **17** (86% from **15a**, 83% from **16**), mp >300°.

Anal. Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.39; H, 5.03; N, 20.43.