SYNTHESIS OF PYRIMIDO[4,5-c]PYRIDAZINE DERIVATIVES

Sadao Nishigaki, Misuzu Ichiba, Junko Sato, Keitaro Senga,* Mitsuko Noguchi,+ and Fumio Yoneda+

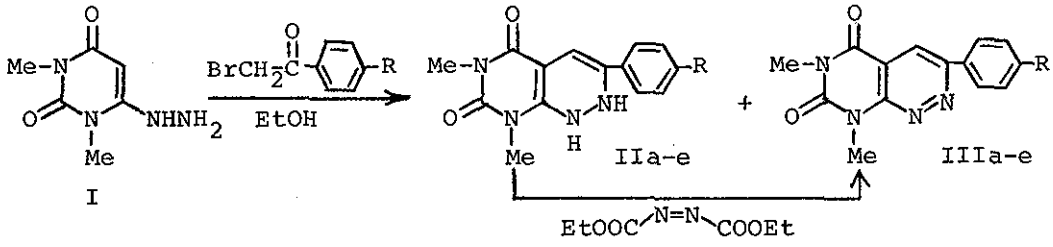
Pharmaceutical Institute, School of Medicine, Keio University, 35, Shinanomachi, Shinjuku-ku, Tokyo 160, Japan and +Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1, Oe-honmachi, Kumamoto 862, Japan

Treatment of 6-hydrazino-1,3-dimethyluracil (I) with phenacyl bromides afforded the corresponding 3-aryl-6,8-dimethylpyrimido[4,5-c]pyridazine-5,7(1H,2H,6H,8H)-diones (IIa-e) and 3-aryl-6,8-dimethylpyrimido[4,5-c]pyridazine-5,7(6H,8H)-diones (IIIa-e), respectively. The oxidation of II with diethyl azodicarboxylate provided III. The reaction of 6-benzylidene-1,3-dimethyluracils with dimethylformamide dimethylacetal also gave III.

Pyrimido[4,5-c]pyridazines are of interest since they are closely related to the biologically important pteridines and pyrimido[5,4-e]-as-triazines; however, the synthesis of this ring system has not been widely investigated.[1] We now present two new synthetic methods of pyrimido[4,5-c]pyridazines related to an antibiotic fervenulin.[2]

Method A Refluxing 6-hydrazino-1,3-dimethyluracil (I)[3] with the appropriate phenacyl bromides in ethanol for 1 hr afforded the corresponding 3-aryl-6,8-dimethylpyrimido[4,5-c]pyridazine-5,7(1H, 2H,6H,8H)-diones (IIa-e) as major products and 3-aryl-6,8-dimethylpyrimido[4,5-c]pyridazine-5,7(6H,8H)-diones (3-aryl-4-deazafervenulins)(IIIa-e) as minor products. The compounds IIa-e were separated out from the reaction mixture, while the compounds IIIa-e were isolated by evaporation of the filtrate. The dihydro derivatives IIa-e were relatively stable, however, their oxidation with diethyl azodicarboxylate[4] in refluxing chloroform for 5 min gave IIIa-e in quantitative yields[5] (Scheme I)(Table). The structures of these products were confirmed by the satisfactory spectral data and elemental analyses.[6]

Scheme I



Method B Heating of the 6-benzylidenehydrazino-1,3-dimethyluracils (IVa-e)[7] with dimethylformamide dimethylacetal at 160° for 1 hr resulted in the formation of the corresponding pyrimido[4,5-c]-pyridazines IIIa-e, which were identical with the samples prepared by Method A. This reaction is presumably initiated by the formation of 5-N,N-dimethylaminomethylene intermediate, which possesses a diazahexatriene-type structure. This could undergo valence isomerization and subsequent aromatization by elimination of dimethylamine

(Scheme II)(Table). Recently, this type of cyclization of azahexatrienes has been demonstrated in the preparation of purines,[8,9] pyrazolo[3,4-d]pyrimidines,[8,10] pteridines,[9,11] and pyrimido[4,5-b]quinolines.[12] It is noted that the Vilsmeier reagent under various conditions was not effective for the cyclization of IVa-e to IIIa-e.

Scheme II

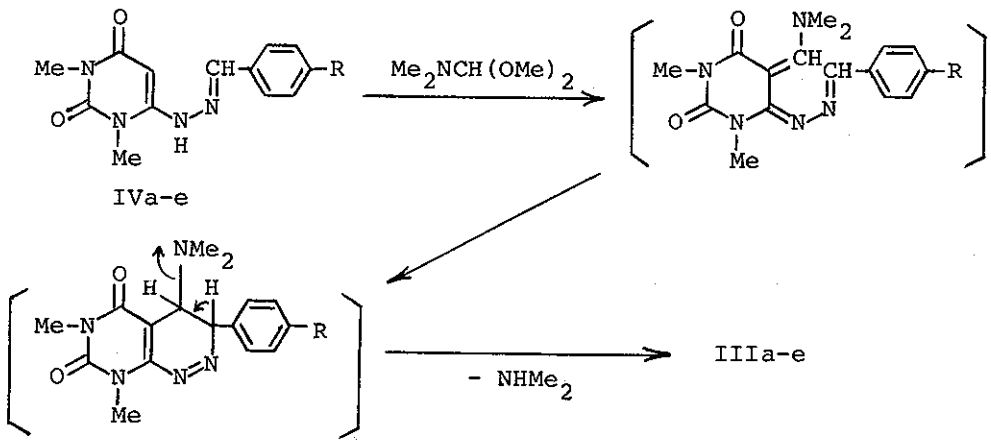


Table Pyrimido[4,5-c]pyridazines

Compd. No.	R	Recrystn. solvent	Mp (°C)	Yield(%) Method A	Method B
IIa	H	EtOH-DMF	___ a	33	—
IIb	Br	EtOH-DMF	___ a	50	—
IIc	Cl	EtOH-DMF	___ a	45	—
IId	Me	EtOH	___ a	36	—
IIe	OMe	EtOH	___ a	32	—
IIIa	H	EtOH	255-256	9	30
IIIb	Br	EtOH	297-298	2	36
IIIc	Cl	EtOH	264-265	2	37
IIId	Me	EtOH	257-260	10	32
IIIe	OMe	EtOH	244-245	8	30

a) The compounds IIa-e underwent thermal oxidation to give IIIa-e.

EXPERIMENTAL

Reaction of 6-Hydrazino-1,3-dimethyluracil (I) with Phenacyl bromides. A mixture of 6-hydrazino-1,3-dimethyluracil (I)[3] (0.001 mol) and the respective phenacyl bromides (0.001 mol) in EtOH (10 ml) was refluxed for 1 hr. After cooling, the precipitates were filtered and recrystallized to give the corresponding 3-aryl-6,8-dimethylpyrimido[4,5-c]pyridazine-5,7(1H,2H,6H,8H)-diones (IIa-e). The filtrate was evaporated in vacuo to dryness and the residue was triturated with EtOH. The insoluble material was filtered and recrystallized to give the corresponding 3-aryl-6,8-dimethylpyrimido[4,5-c]pyridazine-5,7(6H,8H)-diones (IIIa-e)(Table; Method A).

Oxidation of IIa-e with Diethyl azodicarboxylate. A mixture of the respective IIa-e (0.001 mol) and diethyl azodicarboxylate (0.001 mol) in dry $CHCl_3$ (5 ml) was refluxed for 5 min. The reaction mixture was evaporated in vacuo to dryness. The residue was triturated with EtOH and the insoluble material was recrystallized to give the corresponding products IIIa-e.

Reaction of 6-Benzylidenehydrazino-1,3-dimethyluracils (IVa-e) with Dimethylformamide dimethylacetal. A mixture of the appropriate 6-benzylidenehydrazino-1,3-dimethyluracils (IVa-e)[7] (0.001 mol) and dimethylformamide dimethylacetal (3 ml) was heated at 160° for 1 hr. The reaction mixture was evaporated in vacuo to dryness and the residue was covered with EtOH. The insoluble material was filtered and recrystallized to yield the corresponding products IIIa-e (Table; Method B).

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2 Fervenulin (6,8-dimethylpyrimido[5,4-e]-as-triazine-5,7(6H,8H)-dione) is an antibiotic isolated from culture of Streptomyces fervens n. Sp., which possesses an interesting spectrum of biological activities: T.E. Eble, E.C. Olson, C.M. Large, and J.W. Shell, Antibiot. Annu., 1959-1960, 227.

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4 It is well known that diethyl azodicarboxylate is a strong hydrogen acceptor: For example, F. Yoneda, K. Suzuki, and Y. Nitta, J. Am. Chem. Soc., 1966, 88, 2328; C. Temple, C.L. Kussner, and J.A. Montgomery, J. Org. Chem., 1969, 34, 3161.

5 Prolonged heating of IIa-e in ethanol also gave IIIa-e, albeit in low yields.

6 For example, the spectral data for compounds IIa and IIIa are as follows. IIa: MS(m/e); 270(M^+), IR ν_{max}^{Nujol} cm^{-1}; 1640(C=O), 1675(C=O), 3300(NH), UV λ_{max}^{EtOH} nm(log ε); 257(3.92), 345(3.47). The NMR spectrum could not be determined due to its limited solubility. IIIa: MS(m/e); 268(M^+), IR ν_{max}^{Nujol} cm^{-1}; 1660(C=O), 1705(C=O), UV λ_{max}^{EtOH} nm(log ε); 255sh(4.01), 270(4.05), 350 (3.22), NMR(DMSO-d_6) δ: 3.33(3H, s, N-Me), 3.76(3H, s, N-Me), 7.46-8.33(5H, m, C_6H_5), 8.50(1H, s, C^4-H).

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