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Pyrimido[4,5-c]pyridazines related to an antibiotic fervenulin were prepared by two routes: one involving the reaction of 6-hydrazino-1,3-dimethyl(or 3-methyl)uracil with phenacyl bromides, and the other involving the reaction of 6-benzylidenehydrazino-1,3-dimethyluracils with dimethylformamide dimethylacetal.

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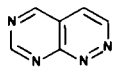
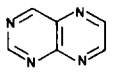
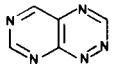
Pyrimido[4,5-c]pyridazines are of biological interest not only as isomers of pteridine but as 4-deazalogs of pyrimido[5,4-e]-*as*-triazine; however, not much effort has been devoted on the synthesis of this ring system. Previous methods for the preparation of this heterocycle involve the ring closure of either suitably substituted pyrimidine derivatives (2-3) or the appropriate pyridazine precursors (4-6). We now wish to report two new synthetic approaches to pyrimido[4,5-c]pyridazines related to fervenulin (6,8-dimethylpyrimido[5,4-e]-*as*-triazine-5,7-(6*H*,8*H*)dione) (7): one involving the reaction of 6-hydrazino-1,3-dimethyl(or 3-methyl)uracil with phenacyl bromides, and the other involving the reaction of 6-benzylidenehydrazino-1,3-dimethyluracils with dimethylformamide dimethylacetal.



Pyrimido[4,5-c]-pyridazine



Pteridine



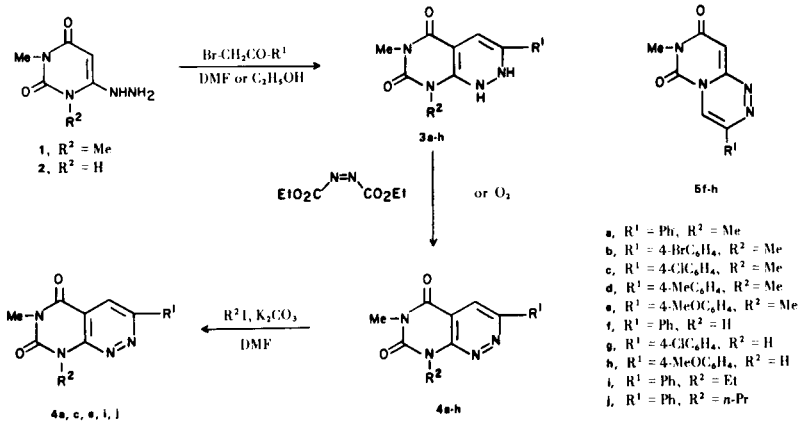
Pyrimido[5,4-e]-*as*-triazine

Reaction of 6-Hydrazino-1,3-dimethyl(or 3-methyl)uracil with Phenacyl Bromides.

Refluxing 6-hydrazino-1,3-dimethyluracil (**1**) (8) with the appropriate phenacyl bromides in dimethylformamide for 1 hour afforded the corresponding 3-aryl-6,8-dimethylpyrimido[4,5-c]pyridazine-5,7(6*H*,8*H*)diones (3-aryl-4-deazafervenulins: **4a-e**) in 32-41% yields. The structures of **4a-e** were assigned by spectral data as well as elemental analyses, and established by their unequivocal alternative synthesis (*vide infra*). Analogously, treatment of 6-hydrazino-3-methyluracil (**2**) (9) with the phenacyl bromides in dimethylformamide under the conditions described above provided the respective 3-aryl-6-methylpyrimido[4,5-c]pyridazine-5,7(6*H*,8*H*)diones (3-aryl-8-desmethyl-4-deazafervenulins: **4f-h**) in similar yields. Alkylation of **4f-h** with alkyl iodide and potassium carbonate in dimethylformamide gave the desired 8-alkylated pyrimido[4,5-c]pyridazines, **4a**, **4c**, **4e**, and **4i-j**, which excluded the possibility of pyrimido[4,3-c]-*as*-triazines (**5f-h**) as alternative structures for **4f-h**.

As depicted in the Scheme I, this new pyrimido[4,5-c]-pyridazine synthesis presumably proceeds by the initial formation of 3-aryl-6,8-dimethyl(or 6-methyl)pyrimido-[4,5-c]pyridazine-5,7(1*H*,2*H*,6*H*,8*H*)diones (**3a-h**) and subsequent spontaneous air oxidation. In fact, these dihydro derivatives were isolated when the above reaction was carried out under mild conditions. Thus, refluxing **1** or **2** with the appropriate phenacyl bromides in ethanol for 1 hour yielded the corresponding **3a-f** as major products (32-50% yields) and **4a-f** as minor products (2-10% yields), respectively. The compounds **3a-f** were readily separated out from the reaction mixture, while the compounds **4a-f** were isolated by evaporation of the filtrate. The

Scheme I

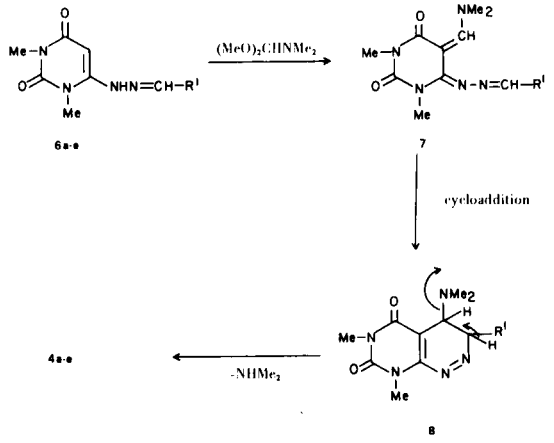


structures of these dihydro derivatives (10) were supported by ir spectra, the presence of a secondary amino stretching absorption band at 3240-3290 cm^{-1}, as well as molecular weight determination by mass spectrometry, and confirmed by their quantitative oxidation to **4a-f** with diethyl azodicarboxylate (11) in refluxing chloroform for 5 minutes (12).

Reaction of 6-Benzylidenehydrazino-1,3-dimethyluracils with Dimethylformamide Dimethylacetal.

Heating the 6-benzylidenehydrazino-1,3-dimethyluracils (**6a-e**) (13) with an excess of dimethylformamide dimethylacetal under reflux for 1 hour gave 30-37% yields of the expected pyrimido[4,5-*c*]pyridazines **4a-e**, which were identical with the samples prepared by the above methods. As shown in the Scheme II, this reaction

Scheme II



is probably initiated by the formation of a 5-*N*,*N*-dimethylaminomethylene intermediate (**7**), which possesses a diazahexatriene-type structure. This could undergo valence isomerization and subsequent aromatization of **8** by loss of dimethylamine. Recently, this type of cyclization of azahexatrienes has been demonstrated in the synthesis of purines (14-15), pyrazolo[3,4-*d*]pyrimidines (14,16), pteridines (15,17), and pyrimido[4,5-*b*]quinolines (18). It should be noted that the Vilsmeier reagent (dimethylformamide-phosphorus oxychloride) under various conditions was not effective for the cyclization of **6a-e** to **4a-e**.

Besides the isolation of **4a-e**, this reaction also provided unexpected results. Namely, *e.g.*, evaporation of the filtrate which removed **4a** and addition of chilled ethanol caused the separation of 2-benzyl-5,7-dimethyl-3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)dione (**11**) (20% yield), which was identical with an authentic sample (13,16). The formation of **11** can be best explained by the mechanism shown in the Scheme III. Thus, the initial nucleophilic attack of the enamine activated position 5 of **6a** on the anil carbon of another molecule of **6a** would

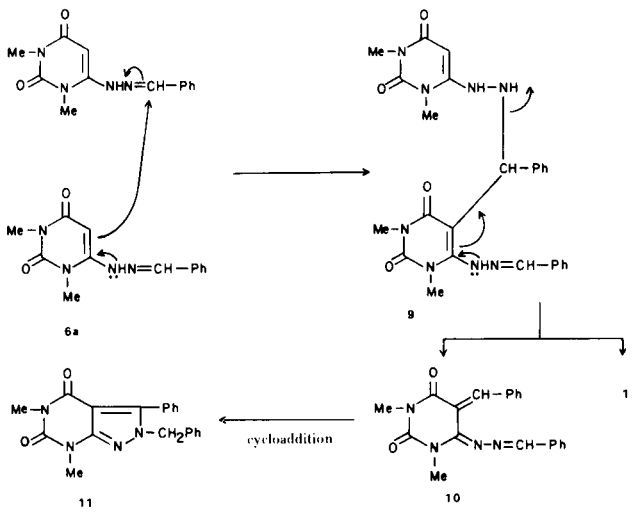
Table I

Pyrimido[4,5-*c*]pyridazine Derivatives

Compounds	M.p. (°C) (a)	Yield (%) (b)				Recrystallization solvent (c)	Calcd. (%)			Formula	Found (%)		
		A	B	C	D		C	H	N		C	H	N
3a		0	33			DMF-ethanol	62.21	5.22	20.73	$C_{14}H_{14}N_4O_2$	61.91	5.08	20.68
3b		0	50			DMF-ethanol	48.15	3.76	16.05	$C_{14}H_{13}BrN_4O_2$	48.02	3.69	16.20
3c		0	45			DMF-ethanol	55.17	4.31	18.39	$C_{14}H_{13}ClN_4O_2$	55.15	4.23	18.68
3d		0	36			Ethanol	63.36	5.67	19.71	$C_{15}H_{16}N_4O_2$	63.56	5.74	19.77
3e		0	32			Ethanol	59.99	5.37	18.66	$C_{15}H_{16}N_4O_3$	59.97	5.22	18.77
3f		0	43			DMF-ethanol	60.93	4.72	21.87	$C_{13}H_{12}N_4O_2$	60.58	4.82	21.96
4a	255-256	41	9	30	63	Ethanol	62.68	4.51	20.89	$C_{14}H_{12}N_4O_2$	62.44	4.50	21.10
4b	297-298	34	2	36		Ethanol	48.43	3.20	16.14	$C_{14}H_{11}BrN_4O_2$	48.25	3.17	16.30
4c	264-265	40	2	37	78	Ethanol	55.54	3.67	18.51	$C_{14}H_{11}ClN_4O_2$	55.49	3.69	18.30
4d	257-260	32	10	32		Ethanol	63.82	5.00	19.85	$C_{15}H_{14}N_4O_2$	63.73	5.02	19.85
4e	244-245	37	8	30	50	Ethanol	60.39	4.73	18.78	$C_{15}H_{14}N_4O_3$	60.18	4.75	18.86
4f	> 300	43	9			DMF-ethanol	61.41	3.96	22.04	$C_{13}H_{10}N_4O_2$	61.15	4.06	22.29
4g	> 300	35				DMF	54.06	3.14	19.42	$C_{13}H_9ClN_4O_2$	54.27	3.26	19.69
4h	280 dec.	35				DMF	59.15	4.26	19.71	$C_{14}H_{12}N_4O_3$	59.08	4.43	19.89
4i	173-175				72	Ethanol	63.82	5.00	19.85	$C_{15}H_{14}N_4O_2$	63.53	4.87	20.12
4j	164-165				74	Ethanol	64.85	5.44	18.91	$C_{16}H_{16}N_4O_2$	64.59	5.44	19.09

(a) Compounds **3a-f** underwent thermal oxidation to give **4a-f**. (b) A, **1** (or **2**) with phenacyl bromides in dimethylformamide; B, **1** (or **2**) with phenacyl bromides in ethanol; C, **6a-e** with dimethylformamide dimethylacetal; D, alkylation of **4f-h**. (c) DMF, dimethylformamide.

Scheme III



yield the dimeric intermediate (**9**). Following carbon-nitrogen bond cleavage could give both the 5-benzylidene intermediate **10** and **1**. Thus formed, **10**, possessing diazahexatriene type structure, would undergo intramolecular cyclization to provide **11**. We have recently described that the condensation of **6a** with benzaldehyde gives **11** under reflux in dimethylformamide (16).

The pyrimido[4,5-c]pyridazine derivatives prepared in this study are listed in Table I.

EXPERIMENTAL

Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Nmr spectra were determined with a Varian T-60 spectrometer at 60 MHz (tetramethylsilane as internal standard in deuteriodimethylsulfoxide) and uv spectra were recorded on a Hitachi 124 spectrophotometer (ethanol in 1 cm quartz cell). Identity of compounds was confirmed by comparison of ir spectra (Nujol mulls) with a Japan Spectroscopic Co. Ltd., Model IR-E spectrophotometer.

Reaction of 6-Hydrazino-1,3-dimethyl(or 3-methyl)uracil with Phanacyl Bromides in Dimethylformamide.

A mixture of 6-hydrazino-1,3-dimethyluracil (**1**) (8) or 6-hydrazino-3-methyluracil (**2**) (9) (0.001 mole) and the appropriate phenacyl bromides (0.001 mole) in dimethylformamide (3 ml.) was refluxed for 1 hour. The reaction mixture was evaporated *in vacuo* and the residue was covered with ethanol. The insoluble crystals were filtered off and recrystallized to give the corresponding 3-aryl-6,8-dimethyl(or 6-methyl)pyrimido[4,5-c]pyridazine-5,7-(6*H*,8*H*)diones (**4a-h**).

Compound **4a**.

This compound had ms: m/e 268 (M^+); nmr: δ 3.33 (3H, s, N-Me), 3.76 (3H, s, N-Me), 7.46-8.33 (5H, m, Ph), 8.50 (1H, s, C^4-H); uv λ max nm (log ε): 255 sh (4.01), 270 (4.05), 350 (3.22); ir: 1660, 1705 cm^{-1} (CO).

Compound **4f**.

This compound had ms: 254 (M^+); nmr: δ 3.30 (3H, s, N-Me), 7.33-8.33 (5H, m, Ph), 8.43 (1H, s, C^4-H), 12.53 (1H, br, NH exchangeable with deuterium oxide); ir: 1650, 1725 (CO), 3160 cm^{-1} (NH).

Reaciton of 6-Hydrazino-1,3-dimethyl(or 3-methyl)uracil with Phenacyl Bromides in Ethanol.

A mixture of **1** or **2** (0.001 mole) and the appropriate phenacyl bromides (0.001 mole) in ethanol (10 ml.) was refluxed for 1 hour. After cooling, the precipitates were filtered and recrystallized to give the corresponding 3-aryl-6,8-dimethyl(or 6-methyl)-pyrimido[4,5-c]pyridazine-5,7(1*H*,2*H*,6*H*,8*H*)diones (**3a-f**).

Compound **3a**.

This compound had ms: m/e 270 (M^+); nmr: (19); uv λ max nm (log ε): 257 (3.92), 345 (3.47); ir: 1640, 1675 (CO), 3290 cm^{-1} (NH).

Compound **3f**.

This compound had ms: m/e 256 (M^+); nmr: (19); ir: 1635, 1695 (CO), 3240 cm^{-1} (NH).

The filtrate which removed **3a-f** was evaporated *in vacuo* and the residue was triturated with ethanol. The insoluble crystals were filtered off and recrystallized to afford the respective **4a-f**, which were identical with the samples prepared by the above method.

Oxidation of **3a-f** to **4a-f** with Diethyl Azodicarboxylate.

A suspension of the appropriate **3a-f** (0.001 mole) and diethyl azodicarboxylate (0.174 g., 0.001 mole) in dry chloroform (5 ml.) was refluxed for 5 minutes. The reaction mixture was evaporated *in vacuo* and the residue was triturated with ethanol. The insoluble crystals were filtered off to give quantitative yields of the desired **4a-f**, identical with the samples prepared by the above methods.

Alkylation of **4f-h**.

A mixture of the respective **4f-h** (0.001 mole) and the alkyl iodide (0.003 mole) in dimethylformamide (5 ml.) containing potassium carbonate (0.207 g., 0.0015 mole) was refluxed for 1 hour. The reaction mixture was evaporated *in vacuo* and the residue was covered with water. The insoluble crystals were filtered off and recrystallized to give the corresponding 8-alkyl-3-aryl-6-methylpyrimido[4,5-c]pyridazine-5,7(6*H*,8*H*)diones **4a**, **4c**, **4e** and **4i-j**.

6-Benzylidenehydrazino-1,3-dimethyluracils (**6a-e**).

6-Benzylidenehydrazino-1,3-dimethyluracils (**6a**, **6c**, and **6e**) were prepared previously (13). Other derivatives (**6b** and **6d**) were obtained according to the reported procedure (13).

Compound **6b**.

This compound had m.p. 275-276° (90% from a mixture of ethanol and dimethylformamide).

Anal. Calcd. for $C_{13}H_{13}BrN_4O_2$: C, 46.30; H, 3.86; N, 16.62. Found: C, 46.29; H, 3.88; N, 16.72.

Compound **6d**.

This compound had m.p. 252° (94% from dimethylformamide).

Anal. Calcd. for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.74; H, 5.89; N, 20.88.

Reaction of 6-Benzylidenehydrazino-1,3-dimethyluracils with Dimethylformamide Dimethylacetal.

A mixture of the uracils **6a-e** (0.001 mole) and dimethyl-

formamide dimethylacetal (3 ml.) was refluxed at 160° for 1 hour. The reaction mixture was evaporated *in vacuo* and the residue was triturated with ethanol. The insoluble crystals were filtered off and recrystallized to yield the corresponding products **4a-e**, identical with the samples prepared by the above methods.

The filtrate which removed **4a** was again evaporated *in vacuo* and the residue was covered with chilled ethanol. The precipitated crystals were filtered off and recrystallized from ethanol to give 2-benzyl-5,7-dimethyl-3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6-(5*H*,7*H*)dione (**11**) (0.07 g., 20%), which was identical with an authentic sample (13,16).

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(10) None of these compounds were obtained in the reaction of **1** or **2** with phenacyl bromides in dimethylformamide.

(11) Diethyl azodicarboxylate has been known as a strong hydrogen acceptor: For example, F. Yoneda, K. Suzuki and Y. Nitta, *J. Am. Chem. Soc.*, **88**, 2328 (1966); C. Temple, C. L. Kussner and J. A. Montgomery, *J. Org. Chem.*, **34**, 3161 (1969); F. Yoneda, M. Higuchi, K. Senga, K. Shimizu and S. Nishigaki, *Heterocycles*, **4**, 1759 (1976).

(12) Oxidation of **3a-f** to **4a-f** was also achieved in quantitative yields by reflux with dimethylformamide for 1 hour. Prolonged heating of **3a-f** in ethanol also gave **4 a-f**, albeit in low yields.

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(15) F. Yoneda, M. Higuchi and M. Kawamura, *Heterocycles*, **4**, 1659 (1976).

(16) F. Yoneda, T. Nagamatsu, T. Nagamura and K. Senga, *J. Chem. Soc., Perkin Trans. I*, 765 (1977).

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(18) K. Senga, K. Shimizu, S. Nishigaki and F. Yoneda, *Heterocycles*, **6**, 1361 (1977).

(19) The nmr spectrum could not be determined due to its limited solubility.