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Synthesis and Properties of 2,3,4,8-Tetrahydro-2,4-dioxopyrido[2,3-*d*]pyrimidines (5-Deazalumazines) and Their Bis-compounds

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Ethyl 2,3,4,8-tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylates (IV) and their bis-compounds (VI) were synthesized by the condensation of 6-alkyl- or 6-aryl-amino-3-methyluracils (II) and appropriate ethyl 3-chloro-2-formylprop-2-enoates (III) in dimethylformamide. Hydrolysis of the esters IV and VI with base resulted in a novel rearrangement of a substituent (R^2) at the 7-position onto the 6-substituent to give the corresponding 6-acyl-1,2,3,4,7,8-hexahydro-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidines (VII) and their bis-compounds (X). The mechanism of the rearrangement is discussed.

Keywords——2,3,4,8-tetrahydro-2,4-dioxopyrido[2,3-*d*]pyrimidine; ethyl 3-chloro-2-formylprop-2-enoate; bis(3-methyluracil-6-ylamino)alkane; bis(2,3,4,8-tetrahydro-2,4-dioxopyrido[2,3-*d*]pyrimidin-8-yl)alkane; 1,2,3,4,7,8-hexahydro-2,4,7-trioxopyrido[2,3-*d*]pyrimidine; bis(1,2,3,4,7,8-hexahydro-2,4,7-trioxopyrido[2,3-*d*]pyrimidin-8-yl)alkane; hydrolysis; rearrangement; 5-deazalumazine

2,3,4,8-Tetrahydro-2,4-dioxopyrido[2,3-*d*]pyrimidines (IV), which are structural analogues of the pteridine precursor (6,7-dimethyl-8-D-ribityllumazine) of riboflavin in certain micro-organisms,[1] would be expected to act as specific inhibitors[2] of the enzyme riboflavin synthetase. Actually, it has been shown that some derivatives of type IV act as inhibitors in the earlier stages of the biosynthesis of riboflavin.[3] In a previous communication[4] we reported a convenient synthesis of 2,3,4,8-tetrahydro-2,4-dioxopyrido[2,3-*d*]pyrimidines (IV) by condensation of 6-substituted-aminouracils (II) with appropriate 3-chloro-2-alkenals (III). In the present paper we describe the synthesis of previously unknown ethyl 2,3,4,8-tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylates (IV) and their bis-compounds (VI) by an application of the above synthetic methodology. We also present a novel base-catalyzed rearrangement of these compounds into 6-acyl-1,2,3,4,7,8-hexahydro-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidines (VII) and their bis-compounds (X).

Synthesis of Ethyl 2,3,4,8-Tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylates (IV) and Their Bis-compounds (VI)

The ethyl esters IVa—i were synthesized by condensation of 6-alkyl- or 6-aryl-amino-3-methyluracils (II)[5] and the appropriate ethyl 3-chloro-2-formylprop-2-enoates (III)[6] in dimethylformamide (Chart 1) (Table I). Similarly, bis(6-ethoxycarbonyl-2,3,4,8-tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidin-8-yl)alkanes (VIa—d) were prepared by using bis(3-methyluracil-6-ylamino)alkanes (Va—d) instead of the compounds II in the above synthesis (Table III). The requisite precursors of the bis-compounds VI, bis(3-methyluracil-6-ylamino)alkanes (Va—d) were prepared by condensation of 6-chloro-3-methyluracil (I) and α,ω-diaminoalkanes (Table II). The structural assignments of IV, V, and VI were based on the results of elemental analyses and nuclear magnetic resonance (NMR) spectroscopy. In the ^{1}H-NMR spectra (in CF_3CO_2H) of IV and VI, the characteristic signals of the C^5 protons appeared at $\delta = 9.57$—9.80 ppm (Tables I and III).

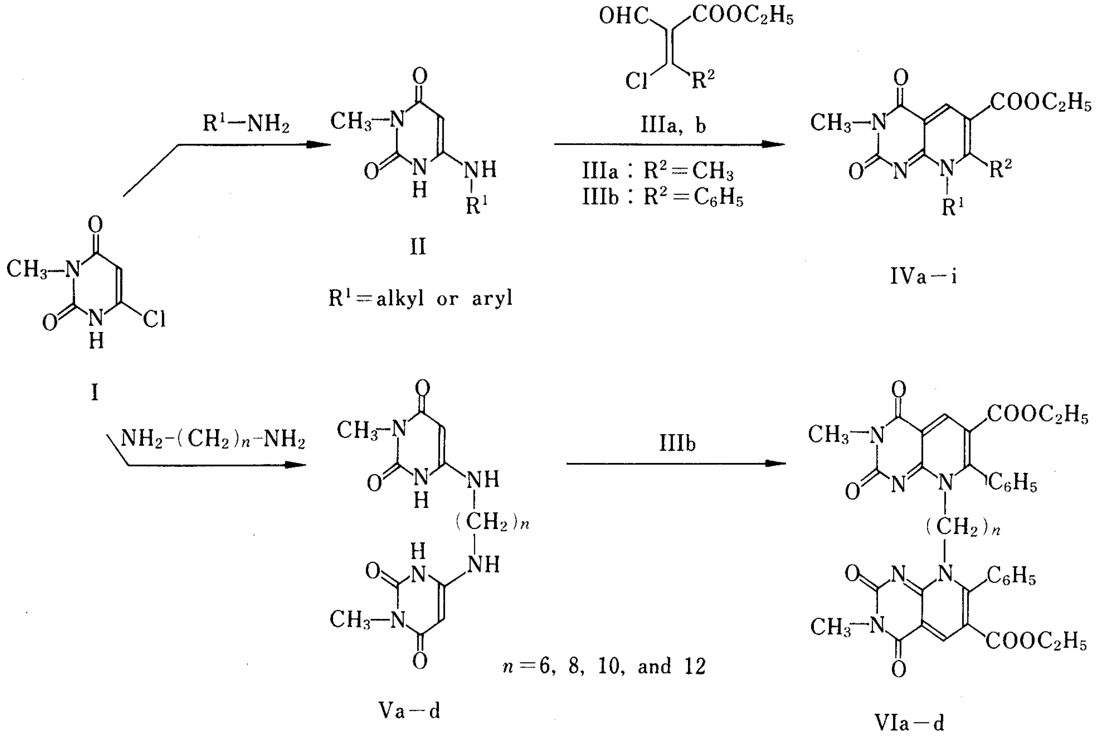

Chart 1

Rearrangement of Ethyl 2,3,4,8-Tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylate (IV) and Their Bis-compounds (VI) into 6-Acyl- or 6-Benzimidoyl-1,2,3,4,7,8-hexahydro-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidines (VII and VIII) and Their Bis-compounds (X) by Bases

Treatment of IV with a 5% ethanol solution of potassium hydroxide at room temperature unexpectedly gave VIIa—i, which are isomerization products. That is, R^2 at the 7-position of the esters IV was rearranged onto the 6-substituent of the products VII (Chart 2) (Table IV). Similarly, treatment of the esters IV with amines in dimethylformamide under heating and reflux gave the isomerized 6-benzimidoyl-1,2,3,4,7,8-hexahydro-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidines (VIII) (Table V). In the ^{1}H-NMR spectra, the characteristic signals of the C^5 protons of VII and VIII, which appeared t δ 8.30—9.55 ppm, were located at δ 0.02—1.09 ppm higher field compared with the corresponding signals of IV. The signals of the ethyl protons of the C^6-ethoxycarbonyl groups of IV were absent in the spectra of VII and VIII.[7] The reaction of the compounds VII with 2,4-dinitrophenylhydrazine produced the corresponding 2,4-dinitrophenylhydrazones. Further examples are shown in Chart 2. Heating of 6-benzoyl-1,2,3,4,7,8-hexahydro-3,8-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (VIIb) with benzylamine in dimethylformamide under reflux gave the 6-(*N*-benzyl-benzimidoyl)-1,2,3,4,7,8-hexahydro-3,8-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (VIIIa), which was converted into the starting material VIIb by heating of VIIIa in 50% aqueous potassium hydroxide. Similarly, the reaction of VIIb, g and urea in acetic acid gave the corresponding 6-benzimidoyl-1,2,3,4,7,8-hexahydro-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidines (IXa, b) which were readily converted into the starting VIIb, g on treatment of IXa, b with 50% aqueous potassium hydroxide (Table V). These reactions mean that the C^6-acyl carbonyl group of VII has little tendency to adopt the enol form. Furthermore, similar novel rearrangements were observed in the reactions of the bis-compounds VI with base. Namely, the treatment of the bis-compounds (VIa—d) with a 5% ethanol solution of potassium hydroxide at room temperature gave the corresponding bis(6-benzoyl-1,2,3,4,7,8-hexahydro-

Table I. Ethyl 2,3,4,8-Tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylates (IV)

Compd. No.	R^1	R^2	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (CF_3COOH/TMS) δ (H–C-5) (ppm)
IVa	CH_3	CH_3	80	225	$C_{13}H_{15}N_3O_4$	56.31	5.45	15.16	9.59
						(56.11	5.25	14.96)	
IVb	CH_3	C_6H_5	81	194	$C_{18}H_{17}N_3O_4$	63.71	5.05	12.38	9.60
						(63.51	5.26	12.25)	
IVc	n-C_4H_9	CH_3	88	214	$C_{16}H_{21}N_3O_4$	60.17	6.63	13.16	9.57
						(59.93	6.57	12.87)	
IVd	n-C_4H_9	C_6H_5	91	152	$C_{21}H_{23}N_3O_4$	66.12	6.08	11.02	9.68
						(66.03	6.02	10.85)	
IVe	n-C_8H_{17}	C_6H_5	90	107	$C_{25}H_{31}N_3O_4$	68.63	7.14	9.61	9.65
						(68.31	6.92	9.71)	
IVf	C_6H_5	CH_3	75	275	$C_{18}H_{17}N_3O_4$	63.71	5.05	12.38	9.69
						(63.66	5.18	12.53)	
IVg	C_6H_5	C_6H_5	91	224	$C_{23}H_{19}N_3O_4$	68.81	4.77	10.47	9.77
						(68.50	5.00	10.45)	
IVh	4-CH_3–C_6H_4	C_6H_5	88	264	$C_{24}H_{21}N_3O_4$	69.38	5.10	10.12	9.80
						(69.77	4.73	10.17)	
IVi	4-Cl–C_6H_4	C_6H_5	89	325	$C_{23}H_{18}ClN_3O_4$	63.38	4.16	9.64	9.80
						(63.57	3.96	9.87)	

a) All compounds were recrystallized from methanol and were obtained as pale yellow needles.

Table II. Bis(3-methyluracil-6-ylamino)alkanes (V)

Compd. No.	*n*	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
Va	6	58	>330	$C_{16}H_{24}N_6O_4$	52.73	6.64	23.06
					(52.52	6.54	23.34)
Vb	8	58	>330	$C_{18}H_{28}N_6O_4$	55.08	7.19	21.42
					(54.72	7.38	21.21)
Vc	10	32	>315	$C_{20}H_{32}N_6O_4$	57.12	7.67	19.99
					(57.34	7.70	19.69)
Vd	12	64	>305	$C_{22}H_{36}N_6O_4$	58.90	8.09	18.74
					(58.81	8.34	18.57)

a) All compounds were recrystallized from acetic acid and were obtained as colorless powders.

3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidin-8-yl)alkanes (Xa—d) (Chart 3) (Table VI).

The formation of VII can be rationalized as shown in Chart 4. The initial step in the base-catalyzed reaction probably involves nucleophilic attack of the hydroxide ion at the C^7-position of IV to form the intermediate A. Subsequently, ring-fission between C^7 and the N^8-position, followed by ring-rotation along the 5 : 6-bond axis and recyclization between the C^6-ethoxycarbonyl group of IV and the N^8-position, would ultimately yield VII with elimination of the ethoxide ion. The rearrangement of the bis-compounds VI into X may be presumed to follow a similar pathway.

The possibility of migration of the N^8-R^1 group to the N^1-position in the case of reaction of IV with base has been excluded as follows (Chart 5). Namely, the reaction of 6-amino-1,3-

Table III. Bis(6-ethoxycarbonyl-2,3,4,8-tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidin-8-yl)alkanes (VI)

Compd. No.	*n*	Yield (%)	mp[a)] (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (CF$_3$COOH/TMS) δ (H-C-5) (ppm)
VIa	6	90	298	$C_{40}H_{40}N_6O_8$	65.56	5.50	11.47	9.70
					(65.21	5.39	11.69)	
VIb	8	92	295	$C_{42}H_{44}N_6O_8$	66.30	5.83	11.05	9.66
					(66.04	5.54	10.96)	
VIc	10	89	294	$C_{44}H_{48}N_6O_8$	66.99	6.13	10.65	9.65
					(66.95	6.10	10.67)	
VId	12	92	292	$C_{46}H_{52}N_6O_8$	67.63	6.42	10.29	9.70
					(67.46	6.37	10.20)	

a) All compounds were recrystallized from methanol and were obtained as yellow powders.

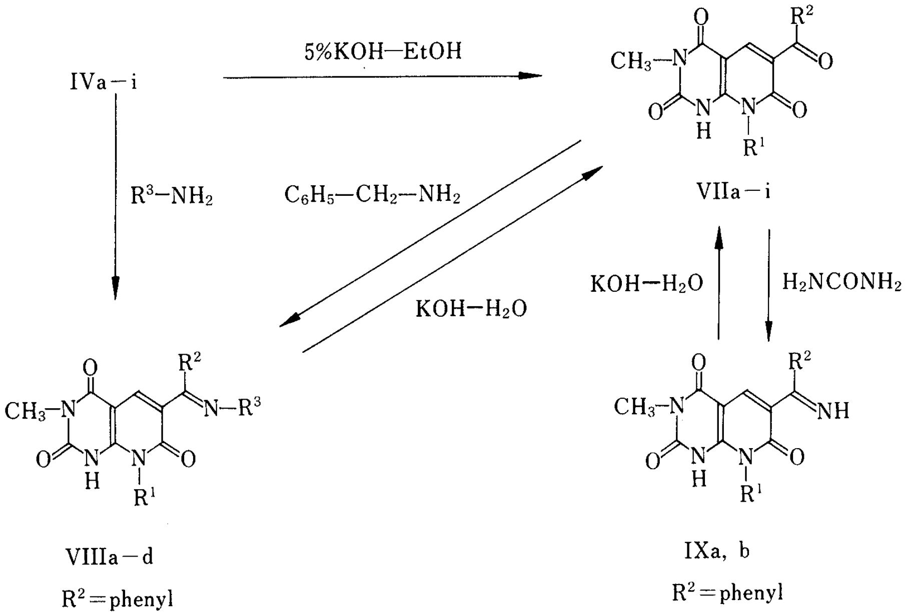

Chart 2

dimethyluracil (XI) and ethyl 3-chloro-2-formyl-3-phenylprop-2-enoate (IIIb) in dimethylformamide afforded ethyl 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-7-phenylpyrido[2,3-*d*]-pyrimidine-6-carboxylate (XII). Hydrolysis of XII with conc. hydrochloric acid gave 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-7-phenylpyrido[2,3-*d*]pyrimidine-6-carboxylic acid (XIII). We compared this compound XIII with 6-benzoyl-1,2,3,4,7,8-hexahydro-3,8-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (VIIb), and as shown in Table IV and experiments, VIIb was not identical with XIII. On the other hand, treatment of the compound XIII with thionyl chloride gave 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-7-phenylpyrido[2,3-*d*]-pyrimidine-6-carbonyl chloride (XIV), which was treated with benzylamine to give 6-(*N*-benzylcarbamoyl)-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-7-phenylpyrido[2,3-*d*]-pyrimidine (XV).

Hydrolysis of Ethyl 2,3,4,8-Tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylates (IV) and Their Bis-compounds (VI) by Acid

Treatment of the esters (IVa—i) and their bis-compounds (VIa—d) with conc. hydro-

TABLE IV. 6-Acyl-1,2,3,4,7,8-hexahydro-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidines (VII)

Compd. No.	R^1	R^2	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (CF_3COOH/TMS) δ (H–C-5) (ppm)
VIIa	CH_3	CH_3	85	296	$C_{11}H_{11}N_3O_4$	53.01	4.45	16.86	9.47
						(53.09	4.19	16.54)	
VIIb	CH_3	C_6H_5	90	285	$C_{16}H_{13}N_3O_4$	61.73	4.21	13.50	8.79
						(61.59	4.30	13.32)	
VIIc	n-C_4H_9	CH_3	83	254	$C_{14}H_{17}N_3O_4$	57.72	5.88	14.43	9.55
						(57.86	5.86	14.27)	
VIId	n-C_4H_9	C_6H_5	89	264	$C_{19}H_{19}N_3O_4$	64.58	5.42	11.89	8.90
						(64.50	5.27	11.52)	
VIIe	n-C_8H_{17}	C_6H_5	87	220	$C_{23}H_{27}N_3O_4$	67.46	6.65	10.26	8.91
						(67.64	6.68	10.31)	
VIIf	C_6H_5	CH_3	82	290	$C_{16}H_{13}N_3O_4$	61.73	4.21	13.50	9.35
						(61.60	4.24	13.77)	
VIIg	C_6H_5	C_6H_5	86	312	$C_{21}H_{15}N_3O_4$	67.55	4.05	11.26	8.82
						(67.18	4.12	11.17)	
VIIh	4-CH_3–C_6H_4	C_6H_5	85	295	$C_{22}H_{17}N_3O_4$	68.21	4.42	10.85	8.77
						(68.11	4.41	10.63)	
VIIi	4-Cl–C_6H_4	C_6H_5	84	325	$C_{21}H_{14}ClN_3O_4$	61.85	3.46	10.30	8.71
						(62.02	3.50	10.41)	

[a] All compounds were recrystallized from methanol or acetic acid and were obtained as colorless powders.

TABLE V. 6-Benzimidoyl-1,2,3,4,7,8-hexahydro-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidines (VIII and IX)

Compd. No.	R^1	R^3	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (CF_3COOH/TMS) δ (H–C-5) (ppm)
VIIIa	CH_3	$CH_2C_6H_5$	87	>330	$C_{23}H_{20}N_4O_3$	68.99	5.03	13.99	8.32
						(69.04	4.97	14.07)	
VIIIb	CH_3	$CH(CH_3)C_6H_5$(*R*)	80	>330	$C_{24}H_{22}N_4O_3$	69.55	5.35	13.52	8.30
						(69.45	5.41	13.41)	
VIIIc	CH_3	$CH(CH_3)C_6H_5$(*S*)	81	>330	$C_{24}H_{22}N_4O_3$	69.55	5.35	13.52	8.30
						(69.66	5.32	13.67)	
VIIId	C_6H_5	$CH_2C_6H_5$	79	>330	$C_{28}H_{22}N_4O_3$	72.71	4.79	12.12	8.54
						(72.45	4.87	12.14)	
IXa	CH_3		85	>330	$C_{16}H_{14}N_4O_3$	61.93	4.55	18.06	8.82
						(62.17	4.45	18.27)	
IXb	C_6H_5		87	>330	$C_{21}H_{16}N_4O_3$	67.73	4.33	15.05	8.94
						(67.98	4.26	14.82)	

[a] All compounds were recrystallized from methanol or acetic acid and were obtained as yellow needles.

chloric acid afforded the corresponding acids (XVIa—i) and bis(6-carboxy-2,3,4,8-tetrahydro-3-methyl-2,4-dioxo-7-phenylpyrido[2,3-*d*]pyrimidin-8-yl)alkanes (XVIIa—d) (Chart 6) (Tables VII and VIII).

Experimental

All melting points were determined on a Yanagimoto hot-stage apparatus, and are uncorrected. The identity of

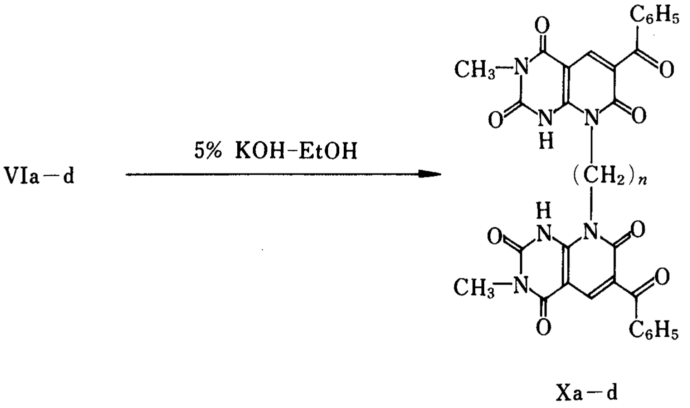

Chart 3

Table VI. Bis(6-benzoyl-1,2,3,4,7,8-hexahydro-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidin-8-yl)alkanes (X)

Compd. No.	n	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (CF$_3$COOH/TMS) δ (H–C-5) (ppm)
Xa	6	80	330	$C_{36}H_{32}N_6O_8$	63.90 (64.16	4.77 4.99	12.42 12.42)	8.86
Xb	8	79	295	$C_{38}H_{36}N_6O_8$	64.76 (64.47	5.15 5.22	11.93 11.65)	8.97
Xc	10	83	294	$C_{40}H_{40}N_6O_8$	65.56 (65.31	5.50 5.45	11.47 11.49)	8.96
Xd	12	81	292	$C_{42}H_{44}N_6O_8$	66.30 (66.49	5.83 5.51	11.05 11.22)	8.88

a) All compounds were recrystallized from methanol or acetic acid and were obtained as colorless powders.

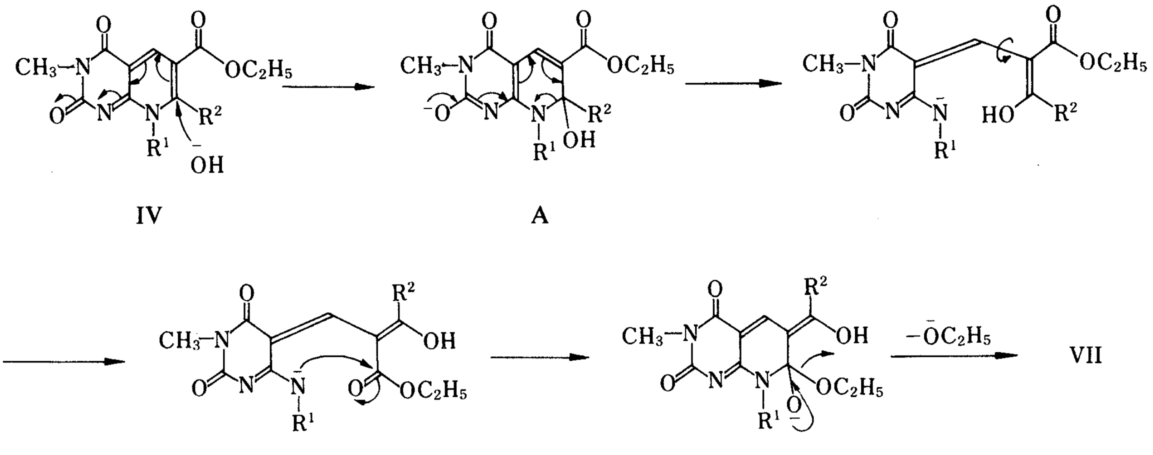

Chart 4

compounds was confirmed by comparison of infrared spectra (Nujol mulls) using a JASCO IRA-1 spectrometer. ^{1}H-NMR spectra were taken on a Hitachi R-24B 60 MHz spectrometer with tetramethylsilane (TMS) as an internal standard.

Ethyl 2,3,4,8-Tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylates (IVa—i). General Procedure——A mixture of a 6-alkyl- or 6-aryl-amino-3-methyluracil (II) (2 mmol) and the appropriate 3-substituted

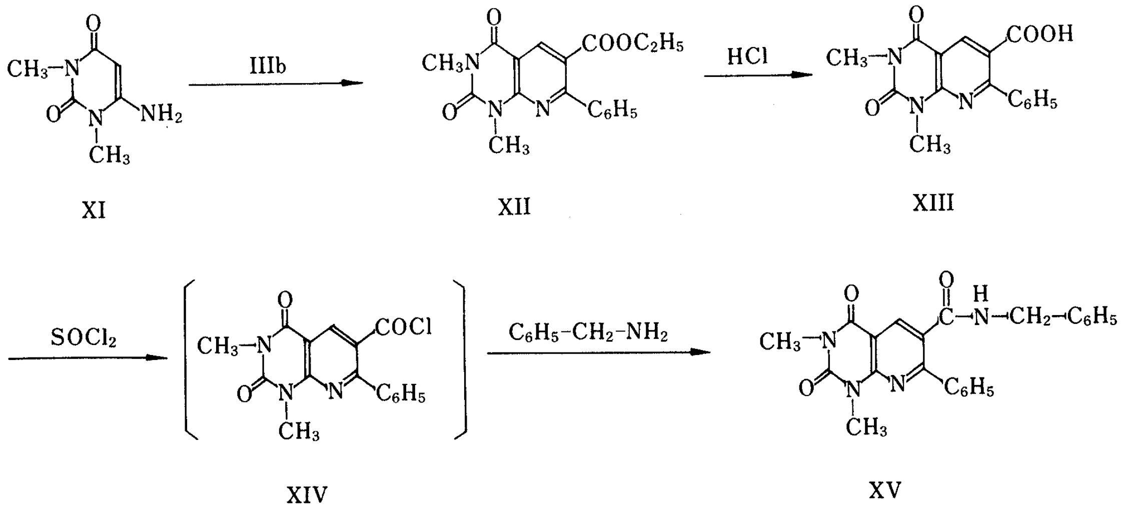

Chart 5

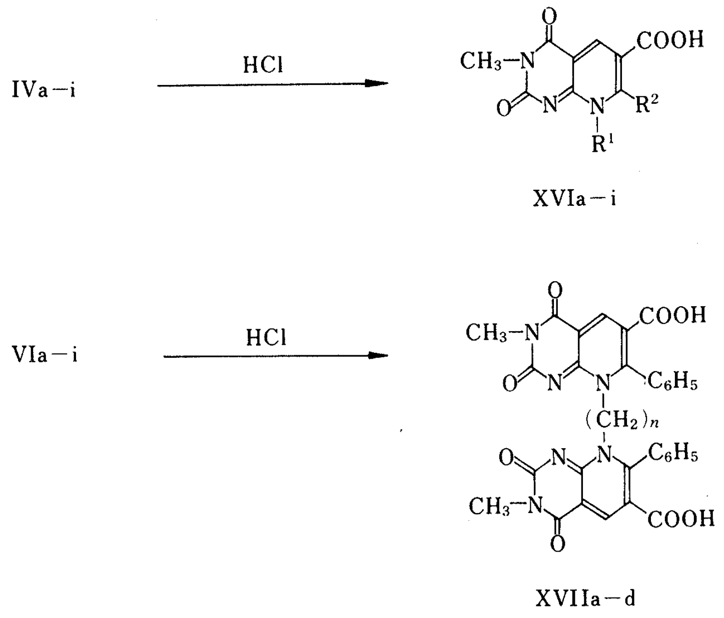

Chart 6

ethyl 3-chloro-2-formylprop-2-enoate (III) (2.5 mmol) in dimethylformamide (3 ml) was heated under stirring at 85—100 °C for 2—3 h. Cooling and concentration of the solution *in vacuo* gave the corresponding IVa—i (Table I).

Bis(3-methyluracil-6-ylamino)alkanes (Va—d). General Procedure——A mixture of 6-chloro-3-methyluracil (I) (6.8 mmol) and the appropriate α,ω-diaminoalkane (3.4 mmol) in *n*-butanol (20 ml) was heated under reflux for 8 h. Cooling and concentration of the solution *in vacuo* gave the corresponding Va—d (Table II).

Bis(6-ethoxycarbonyl-2,3,4,8-tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidin-8-yl)alkanes (VIa—d). General Procedure——A mixture of a bis(3-methyluracil-6-ylamino)alkane (V) (2 mmol) and ethyl 3-chloro-2-formyl-3-phenylprop-2-enoate (IIIb) (5 mmol) in dimethylformamide (10 ml) was heated under stirring at 85—100 °C for 5—6 h. Cooling and concentration of the solution *in vacuo* gave the corresponding VIa—d (Table III).

Rearrangement of Ethyl 2,3,4,8-Tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylates (IV) by Bases. General Procedure——1) A solution of IV (1 mmol) in a 5% ethanol solution of potassium hydroxide (40 ml) was stirred at room temperature for 12 h. The solution was neutralized with dilute hydrochloric acid followed by concentration of the mixture *in vacuo* to give the corresponding 6-acyl-1,2,3,4,7,8-hexahydro-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (VIIa—i) (Table IV). These compounds were converted to the 2,4-dinitrophenylhydrazones by reaction with 2,4-dinitrophenylhydrazine in 2 N HCl solution. For example, 2,4-dinitrophenylhy-

TABLE VII. 2,3,4,8-Tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylic Acids (XVI)

Compd. No.	R^1	R^2	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found)			^{1}H-NMR (CF_3COOH/TMS) δ (H-C-5) (ppm)
						C	H	N	
XVIa	CH_3	CH_3	87	308	$C_{11}H_{11}N_3O_4$	53.01	4.45	18.86	9.70
						(53.15	4.52	17.05)	
XVIb	CH_3	C_6H_5	98	312	$C_{16}H_{13}N_3O_4$	61.73	4.21	13.50	9.79
						(61.93	4.25	13.33)	
XVIc	n-C_4H_9	CH_3	91	272	$C_{14}H_{17}N_3O_4$	57.72	5.88	14.43	9.70
						(57.55	5.88	14.19)	
XVId	n-C_4H_9	C_6H_5	92	273	$C_{19}H_{19}N_3O_4$	64.58	5.42	11.89	9.77
						(64.27	5.32	11.71)	
XVIe	n-C_8H_{17}	C_6H_5	90	233	$C_{23}H_{27}N_3O_4$	67.46	6.65	10.26	9.76
						(67.66	6.51	10.51)	
XVIf	C_6H_5	CH_3	89	320	$C_{16}H_{13}N_3O_4$	61.73	4.21	13.50	9.85
						(61.53	4.09	13.70)	
XVIg	C_6H_5	C_6H_5	97	309	$C_{21}H_{15}N_3O_4$	67.55	4.05	11.26	9.88
						(67.69	4.16	11.18)	
XVIh	4-CH_3-C_6H_4	C_6H_5	89	295	$C_{22}H_{17}N_3O_4$	68.21	4.42	10.85	9.90
						(67.86	4.38	10.54)	
XVIi	4-Cl-C_6H_4	C_6H_5	93	289	$C_{21}H_{14}ClN_3O_4$	61.85	3.46	10.30	9.90
						(61.73	3.23	10.36)	

a) All compounds were recrystallized from acetic acid and were obtained as pale yellow powders.

TABLE VIII. Bis(6-carboxy-2,3,4,8-tetrahydro-3-methyl-2,4-dioxo-7-phenylpyrido[2,3-*d*]pyrimidin-8-yl)alkanes (XVII)

Compd. No.	n	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found)			^{1}H-NMR (CF_3COOH/TMS) δ (H-C-5) (ppm)
					C	H	N	
XVIIa	6	90	298	$C_{36}H_{32}N_6O_8$	63.90	4.77	12.42	9.87
					(63.65	4.66	12.38)	
XVIIb	8	92	295	$C_{38}H_{36}N_6O_8$	64.76	5.15	11.93	9.79
					(64.73	5.05	11.72)	
XVIIc	10	89	294	$C_{40}H_{40}N_6O_8$	65.56	5.50	11.47	9.80
					(65.20	5.86	11.73)	
XVIId	12	92	292	$C_{42}H_{44}N_6O_8$	66.30	5.83	11.05	9.75
					(66.43	5.92	11.08)	

a) All compounds were recrystallized from acetic acid and were obtained as pale yellow powders.

drazone of VIIa: mp 330 °C (from ethanol), orange powder, *Anal.* Calcd for $C_{17}H_{15}N_7O_7$: C, 47.55; H, 3.52; N, 22.84. Found: C, 47.50; H, 3.71; N, 22.69.

2) A mixture of IV (1.5 mmol) and an amine (3 mmol) in dimethylformamide (10 ml) was heated under reflux for 10 h. Concentration of the solution and dilution of the residue with methanol gave the corresponding 6-benzimidoyl-1,2,3,4,7,8-hexahydro-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (VIIIa—d) (Table V).

Reaction of 6-Benzoyl-1,2,3,4,7,8-hexahydro-3,8-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (VIIb) with Benzylamine——A mixture of VIIb (1.5 mmol) and benzylamine (3 mmol) in dimethylformamide (10 ml) was heated under reflux. The mixture was concentrated *in vacuo* and the residue was recrystallized from methanol to give 6-(*N*-benzyl-benzimidoyl)-1,2,3,4,7,8-hexahydro-3,8-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (VIIIa) in 95% yield.

Reaction of 6-Acyl-1,2,3,4,7,8-hexahydro-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidines (VIIb, g) with Urea.

General Procedure——A mixture of VIIb, g (1.5 mmol) and urea (3 mmol) in acetic acid (10 ml) was heated under reflux for 10 h. Concentration of the mixture *in vacuo* and washing of the residue with water gave the corresponding 6-benzimidoyl-1,2,3,4,7,8-hexahydro-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (IXa, b) (Table V).

Reaction of 6-(*N*-Benzyl-benzimidoyl)-1,2,3,4,7,8-hexahydro-3,8-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (VIIIa) and 6-Benzimidoyl-1,2,3,4,7,8-hexahydro-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidines (IXa, b) with Alkali——A mixture of VIIIa (1.5 mmol) or IXa, b (1.5 mmol) and 50% aqueous potassium hydroxide (10 ml) was heated under reflux for 20 min. The mixture was neutralized with hydrochloric acid and concentrated to dryness *in vacuo*, followed by washing of the residue with water to give the corresponding VIIb or VIIg in 80—90% yield.

Rearrangement of Bis(6-ethoxycarbonyl-2,3,4,8-tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidin-8-yl)-alkanes (VIa—d) by Base. General Procedure——A solution of VI (1 mmol) in a 5% ethanol solution of potassium hydroxide (80 ml) was stirred at room temperature for 12 h. The solution was neutralized with dilute hydrochloric acid followed by concentration of the mixture *in vacuo* to give the corresponding bis(6-benzoyl-1,2,3,4,7,8-hexahydro-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidin-8-yl)alkane (Xa—d) (Table VI).

Ethyl 1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-7-phenylpyrido[2,3-*d*]pyrimidin-6-carboxylate (XII)——A mixture of 6-amino-1,3-dimethyluracil (XI) (4 mmol) and ethyl 3-chloro-2-formyl-3-phenylprop-2-enoate (IIIb) (4 mmol) in dimethylformamide (5 ml) was heated at 80—100 °C for 5 h. Concentration of the mixture *in vacuo* and recrystallization of the residue from methanol gave XII (85%) as yellow prisms, mp 155—157 °C. IR $\nu_{\max}^{\text{Nujol}}\,\text{cm}^{-1}$ (C=O): 1720 (sh), 1700, 1656, 1600. ^{1}H-NMR (CF_3COOH) δ: 1.28 (3H, t, $J=8$ Hz, C^6–$COOCH_2C\underline{H}_3$), 3.67 (3H, s, N^3–CH_3), 3.96 (3H, s, N^1–CH_3), 4.41 (2H, q, $J=8$ Hz, C^6–$COOC\underline{H}_2CH_3$), 7.57 (5H, s, Ar-H), 9.17 (1H, s, C^5–H). *Anal.* Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.41; H, 5.07; N, 12.35.

1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-7-phenylpyrido[2,3-*d*]pyrimidine-6-carboxylic Acid (XIII)——A mixture of ethyl 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-7-phenylpyrido[2,3-*d*]pyrimidine-6-carboxylate (XII) (1.5 mmol), conc. hydrochloric acid (10 ml), and acetic acid (3 ml) was heated under reflux for 5 h. Concentration of the mixture *in vacuo* and recrystallization of the residue from acetic acid gave the acid (XIII) (91%) as colorless prisms, mp 229—231 °C. IR $\nu_{\max}^{\text{Nujol}}\,\text{cm}^{-1}$ (C=O): 1720 (sh), 1710, 1632, 1610. ^{1}H-NMR (CF_3COOH) δ: 3.69 (3H, s, N^3–CH_3), 3.96 (3H, s, N^1–CH_3), 7.40—7.88 (5H, m, Ar-H), 9.31 (1H, s, C^5–H). *Anal.* Calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 62.01; H, 4.26; N, 13.62.

1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-7-phenylpyrido[2,3-*d*]pyrimidine-6-carbonyl Chloride (XIV) and 6-(*N*-Benzylcarbamoyl)-1,2,3,4-tetrahydro-1,3-dimethyl-2,4,-dioxo-7-phenylpyrido[2,3-*d*]pyrimidine (XV)——A mixture of 1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-7-phenylpyrido[2,3-*d*]pyrimidine-6-carboxylic acid (XIII) (0.5 mmol) and thionyl chloride (3 ml) was heated with stirring at 80 °C for 5 h. The mixture was diluted with ethyl ether to precipitate crystals, and then the ethyl ether solution, which included thionyl chloride, was removed by decantation. The product (XIV) was used for the next reaction without further purification because of its instability. IR $\nu_{\max}^{\text{Nujol}}\,\text{cm}^{-1}$ (C=O) for XIV: 1793, 1726, 1678, 1615. Benzylamine (0.5 ml) was added in portions to a suspension of the above compound XIV in ethyl ether (10 ml) with stirring and ice-cooling. The mixture was stirred for 1 h to afford crystals, which were collected by filtration and washed with ethyl ether. Recrystallization of the crystals from methanol gave the pure product (XV) (51%) as colorless needles, mp 190—192 °C. IR $\nu_{\max}^{\text{Nujol}}\,\text{cm}^{-1}$ (C=O): 1720, 1672, 1653, 1620. ^{1}H-NMR (CF_3COOH) δ: 3.62 (3H, s, N^3–CH_3), 3.96 (3H, s, N^1–CH_3), 4.57 (2H, d, $J=7.5$ Hz, –CH_2–), 6.93—7.80 (10H, m, Ar-H), 8.94 (1H, s, C^5–H). *Anal.* Calcd for $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99. Found: C, 69.12; H, 5.03; N, 14.17.

Hydrolysis of Ethyl 2,3,4,8-Tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylates (IVa—i) by Acid. General Procedure——A solution of IV (3 mmol) in conc. hydrochloric acid (10 ml) was heated under reflux for 3 h, then cooled to obtain the corresponding 2,3,4,8-tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylic acids (XVIa—i). Concentration of the mother liquor *in vacuo* and recrystallization of the residue from acetic acid gave a further, smaller crop of the same product (Table VII).

Hydrolysis of Bis(6-ethoxycarbonyl-2,3,4,8-tetrahydro-3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidin-8-yl)alkanes (VIa—d) by Acid. General Procedure——A solution of VI (3 mmol) in conc. hydrochloric acid (20 ml) was heated under reflux for 3 h, then cooled to yield the corresponding bis(6-carboxy-2,3,4,8-tetrahydro-3-methyl-2,4-dioxo-7-phenylpyrido[2,3-*d*]pyrimidin-8-yl)alkanes (XVIIa—d) (Table VIII).

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7) For example, ^{1}H-NMR (CF_3COOH), IVa: δ 1.56 (3H, t, J=8 Hz, C^6-$COOCH_2C\underline{H}_3$), 3.30 (3H, s, C^7–CH_3), 3.65 (3H, s, N^3–CH_3), 4.40 (3H, s, N^8–CH_3), 4.67 (2H, q, J=8 Hz, C^6–$COOC\underline{H}_2CH_3$), 9.59 (1H, s, C^5–H); VIIa: δ 2.97 (3H, s, C^6–$COCH_3$), 3.62 (3H, s, N^3–CH_3), 4.08 (3H, s, N^8–CH_3), 9.47 (1H, s, C^5–H).